JOC Article

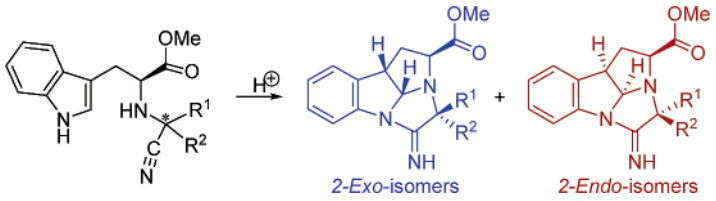
Novel Domino Cyclization of Tryptophan-Derived Amino Nitriles: Scope and Stereoselectivity

Juan A. González-Vera, M. Teresa García-López, and Rosario Herranz*

Instituto de Química Médica (CSIC), Juan de la Cierva 3, E-28006 Madrid, Spain

rosario@iqm.csic.es

Received July 12, 2005



The scope and stereoselectivity of the acid-promoted cyclization of new tryptophan-based α-amino nitriles derived from either ketones or aldehydes to novel hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo-[1,2-*a*]indoles is described. This cyclization involves the generation of two or three stereogenic centers. The time and stereoselectivity of this reaction mostly depended on both the steric volume of the substituents at the amino nitrile and its stereochemistry. Unhindered amino nitriles gave exclusively 2-exo-isomers, while hindered amino nitriles, which required higher reaction times, provided also these isomers under kinetic control. Under thermodynamic control, the 2-endo-isomer was the main reaction product, except for the benzaldehyde-derived α-amino nitriles, where a favorable electronic interaction between the phenyl and methoxycarbonyl groups in a relative cis-disposition might be responsible of the formation of the 2-exo-isomer as the only cyclization product.

Introduction

We have recently communicated the stereospecific synthesis of compounds that contain the novel indole-based tetraheterocyclic system of 1,2,4,5,10b,10c-hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole (Figure 1, **A**), via an acid-promoted domino cyclization of an α-amino nitrile derived from tryptophan and cyclohexanone[1] (Scheme 1, **a**). This novel ring system could be considered as a hybrid of the 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]-indole (**B**) and the 2,3,9,9a-tetrahydroimidazo[1,2-*a*]indole (**C**), both present in a growing class of indole alkaloids. Thus, the 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole is present in physostigmine[2] (**1**), flustramines,[3] urochordamines,[4] mollenines,[5] in the numerous group of fused piperazine derivatives (among others: ardeemins[6] (**2**), amauromine,[7] roquefortines,[8] leptosins,[9] brevianamide E,[10] or okaramines[11]), and as a modified tryptophan residue in several peptides such as himastatin,[12] chloptosin,[13] and the *Bacillus subtilis* pheromone ComX[14] (**3**). The tetrahydroimidazo[1,2-*a*]indole is present in tryptoquivalines,[15] asperlicins[16] (**4**), fiscalins[17] (**5**), fumiquinazolines,[18] and kapakahines, which have an additional *peri*-fused piperidone ring.[19]

* Corresponding author. Phone: (+34) 91-5622900. Fax: (+34) 91-5644853.

(1) González-Vera, J. A.; García-López, M. T.; Herranz, R. *Org. Lett.* **2004**, *6*, 2641−2644.

(2) (a) Takano, S.; Ogasawara, K. *The Alkaloids. Chemistry and Pharmacology*; Brosi, A., Ed.; Academic Press: San Diego, CA, 1989; Vol. 36, pp 225−251. (b) Pharmacology review: Greig, N. H.; Pei, X.-F.; Soncrant, T. T.; Ingram, D. K.; Brossi, A. *Med. Res. Rev*. **1995**, *15*, 3−31.

(3) Carle, J. S.; Christophersen, C. *J. Org. Chem*. **1980**, *45*, 1586−1589.

(4) Tsukamoto, S.; Hirota, H.; Kato, H.; Fusetani, N. *Tetrahedron Lett.* **1993**, *34*, 4819−4822.

(5) Wang, H.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod*. **1998**, *61*, 804−807.

(6) Hochlowski, J. E.; Mullally, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiot.* **1993**, *46*, 380−386.

(7) Takase, S.; Kawai, Y.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron* **1985**, *41*, 3037−3048.

(8) (a) Ohmomo, S.; Sato, T.; Utagawa, T.; Abe, M. *Agric. Biol. Chem.* **1975**, *39*, 1333−1334. (b) Scott, P. M.; Merrien, M.-A.; Polonsky, J. *Experientia* **1976**, *32*, 140−141. (c) Scott, P. M.; Kennedy, P. C. *J. Agric. Food Chem*. **1976**, *24*, 865−868. (d) Ohmomo, S.; Utagawa, S.; Abe, M. *Agric. Biol. Chem*. **1977**, *41*, 2097−2098.

(9) Takahashi, C.; Numata, A.; Matsumura, E.; Minoura, K.; Eto, H.; Shingu, T.; Ito, T.; Hasegawa, T. *J. Antibiot*. **1994**, *47*, 1242−1249.

(10) (a) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329−2344. (b) Birch, A. J.; Russell, R. A. *Tetrahedron* **1972**, *28*, 2999−3008.

(11) (a) Hayashi, H.; Furutsuka, K.; Shiono, Y. *J. Nat. Prod*. **1999**, *62*, 315−317. (b) Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci. Biotechnol. Biochem*. **2000**, *64*, 103−110.

(12) Kamenecka, T. M.; Danishefsky, S. J. *Chem.−Eur. J*. **2001**, *7*, 41−63.

(13) Umezawa, K.; Ikeda, Y.; Uchihata, Y.; Naganawa, H.; Kondo, S. *J. Org. Chem*. **2000**, *65*, 459−463.

(14) Nokada, M.; Sato, I.; Cho, S. J.; Iwata, H.; Nishio, T.; Dubnau, D.; Sakagami, Y. *Nat. Chem. Biol*. **2005**, *1*, 23−24.

10.1021/jo051441+ CCC: $30.25
Published on Web 09/29/2005

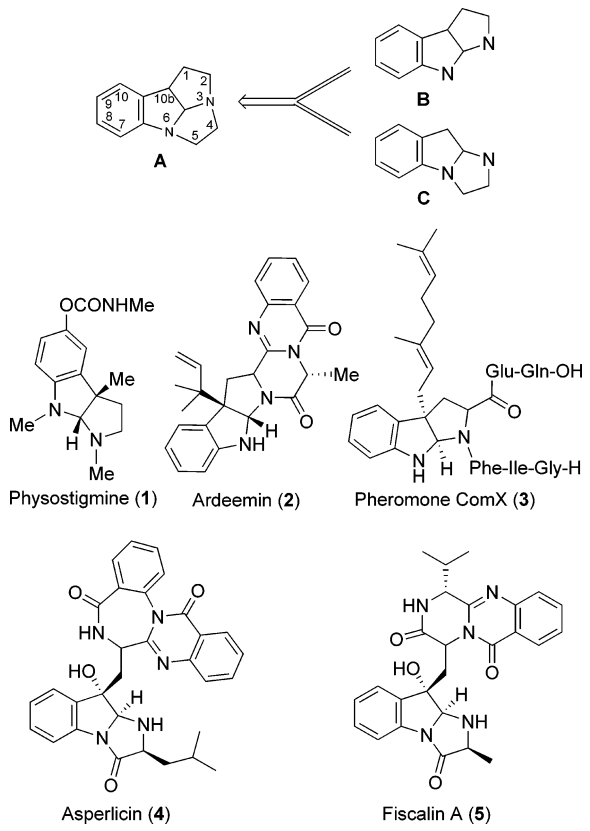
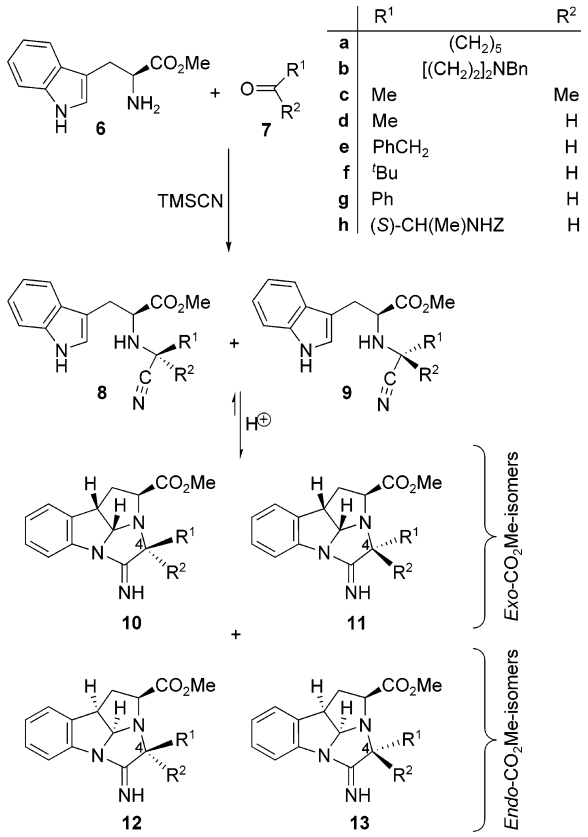


FIGURE 1. Examples of hexahydropyrrolo[2,3-*b*]indole and tetrahydroimidazo[1,2-*a*]indole alkaloids.

SCHEME 1. Synthesis of Hexahydropyrrolo-[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole Derivatives



The recurrent presence of indole-based heterocycles in natural products and in diverse compounds of therapeutic interest, along with the novelty of the aforementioned tetracyclic ring system, have pushed us to study, and report herein, the scope and stereoselectivity of the cyclization of tryptophan-based α-amino nitriles derived from other ketones, different from cyclohexanone (**7a**), and aldehydes. Among the ketones, we selected *N*-benzyl-4-piperidone and acetone (Scheme 1, **7b** and **7c**, respectively), while among the aldehydes, aliphatic ones of variable steric volume [acetaldehyde (**7d**), phenylacetaldehyde (**7e**), and pivalaldehyde (**7f**)] and benzaldehyde (**7g**) were selected. Furthermore, *N*-Z-L-alaninal (**7h**) was also included, as a model, to explore the synthesis of amino acid-derived hexahydropyrrolo[1′,2′,3′:1,9a,9]-imidazo[1,2-*a*]indoles as intermediates in the preparation of fused piperazine derivatives, which could be analogues of the aforementioned pyrazino[1′,2′:1,5]pyrrolo[2,3-*b*]-indole-containing natural products.[6−11]

Results and Discussion

Similar to the reaction recently described for the synthesis of the α-amino nitrile **8a**,[20] the reaction of tryptophan methyl ester (**6**) with the ketones **7b** and **7c**, followed by in situ $Yb(OTf)_3$-promoted addition of TMSCN, yielded the corresponding amino nitriles **8b** and **8c**, respectively. The application of this methodology to the reaction of **6** with the aldehydes **7d**−**h** produced epimeric mixtures of the amino nitriles **8** and **9** in an ∼2:1 ratio, except for the phenylacetaldehyde and pivalaldehyde derivatives **8**,**9e** and **8**,**9f**, which were obtained in an ∼3:2 ratio. These epimeric mixtures were resolved by radial chromatography, except for the pivalaldehyde derivatives **8f** and **9f**, which could not be chromatographically resolved, but were kinetically resolved in the subsequent reaction of cyclization (within 24 h of reaction, **9f** cyclized completely, while 70% of **8f** was recovered unchanged). The cyclization was carried out by treating a CH_2Cl_2 solution of the corresponding amino nitrile with a 50% sample of 85% H_3PO_4, except for the alanine derivatives **8h** and **9h**, which were treated with neat TFA, due to the instability of the Z-protecting group in H_3PO_4. In the major and less reactive epimer

(15) (a) Yamazaki, M.; Fujimoto, H.; Okuyama, E. *Tetrahedron Lett.* **1976**, *17*, 2861−2864. (b) Fujimoto, H.; Negishi, E.; Yamaguchi, K.; Nishi, N.; Yamazaki, M. *Chem. Pharm. Bull.* **1996**, *44*, 1843−1848.

(16) (a) Chang, R. S.; Lotti, V. J.; Monaghan, R. L.; Birnbaum, J.; Stapley, E. O.; Goetz, M. A.; Albers-Schonberg, G.; Patchett, A. A.; Liesch, J. M.; Hensens, O. D.; Springer, J. P. *Science* **1985**, *230*, 177−179. (b) Liesch, J. M.; Hensens, O. D.; Zink, D. L.; Goetz, M. A. *J. Antibiot.* **1988**, *41*, 878−881.

(17) Wong, S. M.; Musza, L. L.; Kydd, G. C.; Kullnig, R.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1993**, *46*, 545−553.

(18) (a) Numata, A.; Takahashi, C.; Matsushita, T.; Miyamoto, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Inoue, M.; Ohishi, H.; Shingu, T. *Tetrahedron Lett.* **1992**, *33*, 1621−1624. (b) Belofsky, G. N.; Anguera, M.; Jensen, P. R.; Fenical, W.; Kock, M. *Chem.−Eur. J.* **2000**, *6*, 1355−1360.

(19) (a) Nakao, Y.; Yeung, B. K.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Am. Chem. Soc.* **1995**, *117*, 8271−8272. (b) Yeung, B. K.; Nakao, Y.; Kinnel, R. B.; Carney, J. R.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Org. Chem.* **1996**, *61*, 7168−7173. (c) Nakao, Y.; Kuo, J.; Yoshida, W. Y.; Kelly, M.; Scheuer, P. J. *Org. Lett.* **2003**, *5*, 1387−1390.

(20) González-Vera, J. A.; García-López, M. T.; Herranz, R. *J. Org. Chem.* **2005**, *70*, 3660−3666.

TABLE 1. Stereoselectivity of the Cyclization of Tryptophan-Derived α-Amino Nitriles

	starting α-amino nitrile[a]			time	pyrroloimidazoindole (%)[b]		
entry	No.	R^1	R^2	(h)	**10**	**11**	**13**
1	**8a**[c]	$(CH_2)_5$		1	100[c]		0
2	**8a**[c]	$(CH_2)_5$		192	100[c]		0
3	**8b**[c]	$[(CH_2)_2]_2NBn$		3	74[c]		26
4	**8b**[c]	$[(CH_2)_2]_2NBn$		192	19[c]		81
5	**8c**[c]	Me	Me	1	95[c]		0
6	**8d**	Me	H	2	71	0	0
7	**9d**	Me	H	2	0	72	0
8	**9d**	Me	H	24	100	0	0
9	**8e**	$PhCH_2$	H	24	72	0	21
10	**8e**	$PhCH_2$	H	96	64	0	34
11	**8e**	$PhCH_2$	H	360	25	0	72
12	**9e**	$PhCH_2$	H	10	96	0	0
13	**9e**	$PhCH_2$	H	24	90	0	7
14	**9e**	$PhCH_2$	H	360	26	0	74
15	**8f**	^{t}Bu	H	24	7	0	6
16	**8f**	^{t}Bu	H	48	7	0	13
17	**8f**	^{t}Bu	H	192	25	0	72
18	**8f**	^{t}Bu	H	360	13	0	84
19	**8f**+**9f**	^{t}Bu	H	24	41[d]	0	7[d]
20	**8g**	Ph	H	2	100	0	0
21	**8g**	Ph	H	24	100	0	0
22	**8g**	Ph	H	192	80	0	0
23	**9g**	Ph	H	2	100	0	0
24	**8h**	(*S*)-CH(Me)-NHZ	H	3	18	0	12
25	**8h**	(*S*)-CH(Me)-NHZ	H	144	0	0	48[e]
26	**9h**	(*S*)-CH(Me)-NHZ	H	3	70	0	0

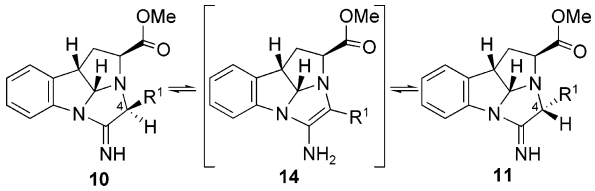
[a] The **8**/**9** ratio was determined as ∼2:1 by ^{1}H NMR or HPLC analysis of the crude amino nitrile mixture, except for **8**,**9e** and **8**,**9f**, where it was determined as ∼3:2. [b] Isolated yields (%), except for entries 8−10, 13, 15−17, and 24, where the ratio was determined in the HPLC analysis of the reaction mixture. [c] As $R^1 = R^2$, **8** = **9** and **10** = **11**. [d] 70% of **8f** was recovered. [e] This low yield was due to the partial replacement (38%) of the Z protecting group of **13h** by a trifluoroacetyl group.

8h the TFA treatment produced, in addition to the cyclization to its tautomer **13h** (48%), partial replacement of the Z group of this cyclized compound by a trifluoroacetyl group (38%).

The literature precedents on the synthesis of tetrahydropyrrolo[2,3-*b*]indoles have demonstrated the high preference for cis versus trans fusion in the pyrroloindole junction and that the 2-endo-carboxylate isomers are thermodynamically more stable, while the 2-exo-isomers are the kinetically controlled products.[21] Bearing in mind these precedents, two stereoisomers might be expected from the cyclization of the amino nitriles derived from symmetrical ketones (**8a**−**c**), while in the case of the amino nitriles derived from aldehydes (**8** and **9d**−**h**), due to the additional stereogenic center generated at position 4, the four stereosisomers **10**−**13**, shown in Scheme 1, might be formed. As shown in Table 1, the results depended mostly upon the steric volume of the amino nitrile R^1 and R^2 substituents and upon the reaction time. Thus, in the ketone derivatives **8a** and **8c** (entries 1, 2, and 5), independent on the reaction time, the cyclization was stereospecific toward the respective 2-exo-isomer **10a** and **10c**. However, in the *N*-benzyl-4-piperidone derivative **8b**, the results depended on the reaction time. Thus,

(21) (a) Taniguchi, M.; Hino, T. *Tetrahedron* **1981**, *37*, 1487−1494. (b) Caballero, E.; Avendaño, C.; Menéndez, J. C. *Tetrahedron: Asymmetry* **1998**, *9*, 967−981. (c) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953−11963 and references therein. (d) Crich, D.; Huang, X. *J. Org. Chem*. **1999**, *64*, 7218−7223 and references therein.

SCHEME 2. Epimerization Mechanism



within 3 h of reaction (entry 3), the 2-exo-isomer **10b** was the major reaction product in a 3:1 ratio, while after 8 days (entry 4) the thermodynamic-controlled product **13b** was major in a **10b**/**13b** ratio of 1:4.

With respect to the aldehyde derivatives, the cyclization of each isolated acetaldehyde-derived epimer **8d** and **9d** was completely stereoselective toward the corresponding 2-exo-isomer **10d** and **11d**, respectively, with retention of the stereochemistry at the α-amino nitrile chiral center. This result allowed the assignment of the absolute configuration at that chiral center of **8d** and **9d** by correlation. In the other amino nitriles **8**,**9e**−**h**, that configuration was tentatively assigned by comparison of their respective ^{1}H NMR and HPLC data with those of **8d** and **9d**. Thus, in the major isomers **8** (*S*), the Trp 2-H, 3-H, and indole protons 1-H and 2-H appeared at a higher field than in the corresponding (*R*)-epimers **9**. Furthermore, the major isomers **8** showed higher t_R (Novapak C_{18}) than the minor ones **9**.

Interestingly, both isolated acetaldehyde-derived epimers **10d** and **11d** exchanged slowly, and at room temperature in $CDCl_3$ solution, the equilibrium of this exchange was achieved after 94 days with a **10d**/**11d** ratio of 4:1. Under the acid medium of the cyclization reaction, after 24 h, the epimerization of **11d** to **10d** was complete (Table 1, entry 8). As shown in Scheme 2, this epimerization must proceed through the enamine tautomer **14d**, although this isomer was not detected, probably due to its short lifetime. In the case of the other aldehyde derivatives bearing higher volume groups (**8**,**9e**−**h**), the epimer **11**, with the R^1 group toward the endo-face, was not obtained, and neither this isomer nor the corresponding enamine tautomer **14** was detected in the reaction mixture.

In most cases of the aldehyde-derived amino nitriles (**8** and **9d**−**f** and **h**), the steric volume of the R^1 substituents and their configuration affected their cyclization reaction time, and this had an important influence on the stereoselectivity. Thus, the (*R*)-amino nitriles **9**, after the shorter reaction times required for their complete conversion (entries 7, 12, 19, and 26), yielded exclusively the kinetic controlled 2-exo-isomers **10** (or **11d** in the case of the acetaldehyde derivatives). However, the increase in the reaction time in more constrained amino nitriles favored the formation of the 2-endo-isomer, such as in the phenylacetaldehyde derivative **9e**, where after 15 days, isomer **13e** was the major isomer in a 3:1 ratio (entry 14). The (*S*)-amino nitriles **8**, which, except for the acetaldehyde and benzaldehyde derivatives **8d** and **8g**, required considerable higher reaction times, also gave the 2-exo-isomer **10** as major product of short reaction times (entries 9, 15, and 24), although with low % of cyclization. However, within higher reaction times, the thermodynamic controlled 2-endo-isomer **13** was the main reaction product (entries 11, 18, and 25), except for the acetalde-

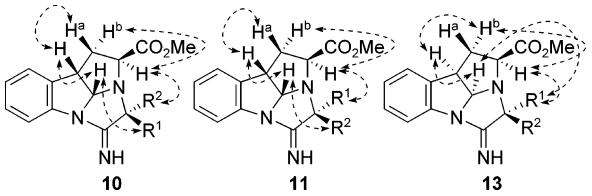


FIGURE 2. NOE effects observed in the ^{1}H NOESY 1D spectra.

hyde- and benzaldehyde-derived amino nitriles, which gave only the 2-exo-isomer (**10d** and **10g**, respectively). Interestingly, the epimer of **13** at position 4, **12**, was not obtained in any case.

We also studied the configurational stability of the 2-exo-hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indoles **10a**−**c** and **10d**−**g**. At room temperature in CH_3CN solution, conditions of the HPLC analysis, samples of all of these compounds remained unaltered after more than 15 days. After 8 days under the cyclization reaction conditions (a solution of each compound in CH_2Cl_2 was stirred at room temperature with a 50% of 85% H_3PO_4), the ketone derivatives **10a**−**c** and the acetaldehyde and benzaldehyde derivatives **10d** and **10g** retained their 2-exo-configuration. However, the phenylacetaldehyde and pivalaldehyde derivatives **10e** and **10f** isomerized slowly to the 2-endo-isomers **13e** and **13f**, which after 20 days reached a **10/13** ratio of 1:4 and 2:3, respectively. In all cases, traces of the corresponding amino nitriles **8** and **9**, in a time-independent ratio (3−10%), were detected in the HPLC analysis of the reaction mixtures. This indicated that, in the acid medium, the α-amino nitriles were in equilibrium with their respective pyrroloimidazoindole derivatives, and, therefore, the cyclization could be considered as an acid-promoted tautomerization reaction. Interestingly, the 2-exo (**10**) to 2-endo (**13**) isomerization requires both the opening of the fused pyrroloimidazo system and the epimerization at position 4. Although we have not identified any intermediate of this isomerization, we think that it is more probable that the epimerization happens at the pyrroloimidazoindol state, via an enamine intermediate similar to **14**, than at the amino nitrile state. In our previous wide experience in amino acid-derived α-amino nitriles,[20] we have not observed epimerizations, in either basic or acid media.

The configurational assignment of the hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indoles **10**−**13** was based on the NOE effects observed in their ^{1}H NOESY 1D spectra, shown in Figure 2. Furthermore, as has been previously described for tetrahydropyrrolo[2,3-*b*]indole derivatives,[21a,d] the endo-isomers **13** showed an upfield shift of the MeO signal in their ^{1}H NMR spectra, appearing at 3.02−3.29 ppm, and their coupling constant between 2-H and the 1-endo-H (H^a) was 0−2.5 Hz. Additionally, comparatively, the 2-exo-isomers **10** were significantly more levorotatory than their respective 2-endo-isomers **13**.[21d]

The overall results of the above cyclization and configuration stability studies show that the 2-*exo*-methoxycarbonyl tautomer **10** was the most stable in the benzaldehyde derivatives (**g**) and in the less hindered compounds (those derived from cyclohexanone (**a**), acetone (**c**), and acetaldehyde (**d**)), while in those more

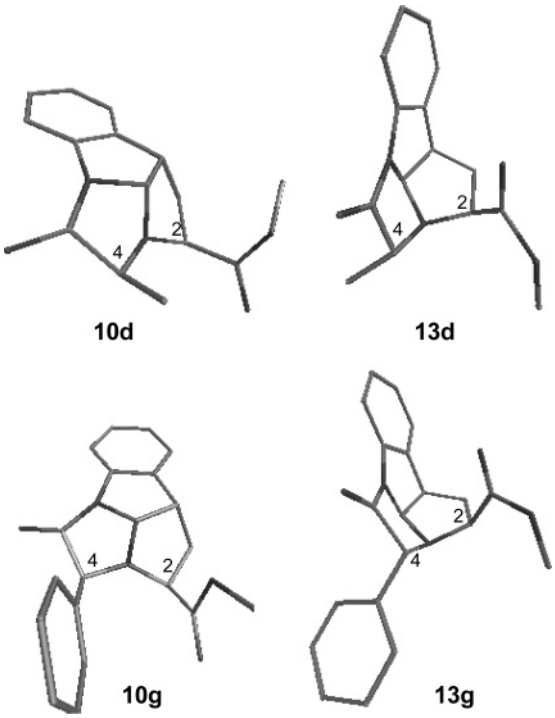


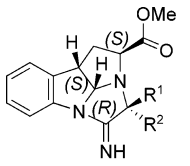
FIGURE 3. Chem 3D models of the 2-methoxycarbonyl-exo- and -endo-isomers of the pyrroloimidazoindol derivatives of acetaldehyde (**10d** and **13d**) and benzaldehyde (**10g** and **13g**).

hindered compounds, such as those derived from *N*-benzyl-4-piperidone (**b**), phenylacetaldehyde (**e**), pivalaldehyde (**f**), and *N*-Z-alaninal (**h**), the 2-*endo*-methoxycarbonyl isomer was the most stable. In the case of the aldehyde derivatives, the results could be explained in terms of the 3D molecular models for the four pyrroloimidazoindoles **10**−**13**. Thus, in any case, the 2-endo-isomer **12** would be the less stable, as both the methoxycarbonyl and the R^1 moieties would project toward the more constrained concave endo-face. The relative stability between **10**, **11**, and **13** would depend mostly on the steric volume of the R^1 substituent, which, except for very small groups as Me (acetaldehyde derivatives (**d**)), would have a high preference for an orientation toward the less hindered exo-face of the pyrroloimidazoindol framework, as in **10** or **13**. Finally, with the increase in volume of R^1, a destabilizing steric interaction of this group with the 2-methoxycarbonyl moiety, in a relative cis-disposition in the 2-exo-isomer **10**, would displace the equilibrium toward the 2-endo-isomer **13**, in which those groups would be in a relative trans-disposition. Although the steric volume of the phenyl group is higher than that of the phenylmethyl group,[22] the higher stability of the exo-tautomer **10g** versus the endo **13g** might be attributed to a possible nonbonding secondary orbital interaction, possibly of the π-stacking type,[23] between the ester moiety and the 4-phenyl group, which would adopt a parallel cis-disposition, as shown in Figure 3.

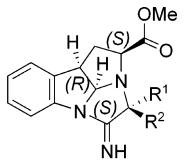
In the case of the ketone derivatives (**a**−**c**), the stabilization of the 2-endo-isomer in the *N*-benzyl-4-

(22) MacPhee, J. A.; Panaye, A.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 3553−3562.
(23) Crich, D.; Chan, C.; Davies, J. W.; Natarajan, S.; Vinter, J. G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2233−2240.

TABLE 2. Analytical Data of the Hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole Derivatives 10b−h, 11d, and 13b−i



10 and **11**

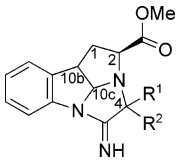


13

compd[a]	R^1	R^2	formula[b]	yield (%)	ESI-MS [M + 1]	$[\alpha]^{20}_D$	RP HPLC[c] t_R (min)	RP HPLC[c] (A:B)
10b	$[(CH_2)_2]_2N-Bn$		$C_{25}H_{28}N_4O_2$	94	417.3	−158.45 (*c* 1.1, MeOH)	2.68	(25:75)
13b	$[(CH_2)_2]_2N-Bn$		$C_{25}H_{28}N_4O_2$	81	417.3	−14.76 (*c* 1.1, MeOH)	2.81	(25:75)
10c	Me	Me	$C_{16}H_{19}N_3O_2$	95	286.2	−133.92 (*c* 1.1, MeOH)	2.00	(25:75)
10d	Me	H	$C_{15}H_{17}N_3O_2$	71	272.1	−127.69 (*c* 1.3, MeOH)	2.17	(25:75)
11d	H	Me	$C_{15}H_{17}N_3O_2$	72	272.1	−104.86 (*c* 0.9, MeOH)	2.36	(25:75)
10e	$PhCH_2$	H	$C_{21}H_{21}N_3O_2$	96	348.3	−114.29 (*c* 1.0, MeOH)	2.07	(50:50)
13e	$PhCH_2$	H	$C_{21}H_{21}N_3O_2$	74	348.3	−5.31 (*c* 0.4, MeOH)	2.49	(50:50)
10f	^{t}Bu	H	$C_{18}H_{23}N_3O_2$	86	314.3	−148.31 (*c* 1, MeOH)	2.02	(50:50)
13f	^{t}Bu	H	$C_{18}H_{23}N_3O_2$	84	314.3	+12.04 (*c* 1, MeOH)	2.31	(50:50)
10g	Ph	H	$C_{20}H_{19}N_3O_2$	100	334.2	−98.41 (*c* 0.9, MeOH)	2.02	(50:50)
10h	(*S*)-CH(Me)NHZ	H	$C_{24}H_{26}N_4O_4$	70	435.3	−119.07 (*c* 1.3, MeOH)	10.25	(30:70)
13h	(*S*)-CH(Me)NHZ	H	$C_{24}H_{26}N_4O_4$	48	435.3	+15.02 (*c* 0.8, MeOH)	8.16	(30:70)
13i[d]	(*S*)-CH(Me)NHCOCF$_3$	H	$C_{18}H_{19}F_3N_4O_3$	34	397.0	−13.72 (*c* 0.7, MeOH)	3.44	(30:70)

[a] Foams. [b] Satisfactory analysis for C, H, N. [c] Novapak C_{18} (3.9 × 150 mm, 4 μm). A = CH_3CN, B = 0.05% TFA in H_2O. [d] Resulting from the partial replacement of the Z-protecting group of **13h** by a trifluoroacelyl group.

TABLE 3. Significant ^{1}H NMR Data of the Hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole Derivatives 10b−h, 11d, and 13b−i[a]



compd	1-H	2-H	7-H	8-H	9-H	10-H	10b-H	10c-H	OMe	R^1	R^2	$J_{1,2}$	$J_{1,10b}$	$J_{10b,10c}$
10b	2.12, 2.48	3.23	7.36	7.23	7.02	7.14	3.80	5.84	3.65	1.72−2.19, 2.53−2.73, 3.50, 7.21−7.31		6 and 11.5	0 and 8	7
13b	2.13, 2.76−2.85	4.01	7.42	7.20	6.94	7.08	3.81	5.65	3.02	1.44−2.16, 2.45, 2.76−2.85, 3.47, 3.53		0 and 9	0 and 8.5	7.5
10c	2.15, 2.37	3.21	7.37	7.23	7.02	7.15	3.79	5.84	3.67	1.54	1.25	6 and 12	0 and 8	7
10d	2.15, 2.45	3.18	7.36	7.23	7.04	7.17	3.78	5.86	3.69	1.53	3.74	6 and 11.5	0 and 8	7
11d	2.04, 2.28	3.09	7.36	7.20	6.99	7.13	3.76	5.66	3.65	1.24	4.15	6 and 11.5	0 and 8	7
10e	2.10, 2.49	3.15−3.22	7.40	7.23	7.04	7.16	3.77	5.71	3.52	3.07, 3.15−3.22	3.90	6 and 12	0 and 8	7
13e	2.25, 2.62	3.96	7.37	7.21	7.00	7.14	3.78	5.59	3.13	3.05, 3.12	4.10	0 and 8	0 and 8.5	7.5
10f	2.08, 2.49	3.19	7.44	7.23	7.03	7.14	3.76	5.73	3.67	1.12	3.27	6 and 11.5	1 and 8	7
13f	2.18, 2.65	4.06	7.46	7.22	6.99	7.12	3.77	5.64	3.16	1.10	3.31	2.5 and 8.5	2 and 7.5	7.5
10g	2.23, 2.53	3.44	7.64	7.20−7.49	7.09	7.20−7.49	3.70−3.75	5.67	3.75	7.20−7.49	4.92	6 and 11	0 and 8	7
10h	2.21, 2.42	3.28	7.39	7.24	7.06	7.17	3.79	5.71	3.64	1.36, 4.10, 5.98	3.71	6 and 11.5	0 and 8	7.5
13h	2.15, 2.56	4.09	7.29−7.36	7.22	7.04	7.15	3.71	5.67	3.29	1.34, 4.16, 5.35	3.83	4 and 8	4 and 8	7.5
13i	2.10, 2.59	4.15	7.17−7.20	7.26	7.07	7.17−7.20	3.70	5.65	3.40	1.39, 4.38, 8.00	3.93	5 and 8	5 and 8	7.5

[a] Spectra registered at 400 or 500 MHz in $CDCl_3$, assigned with the help of COSY spectra.

piperidone derivatives (**b**), with respect to the cyclohexanone (**a**) and acetone (**c**) derivatives, might also be due to the increase in steric hindrance, but some stabilizing electronic interaction of the *N*-benzyl group with the aromatic part of the pyrroloimidazoindol system cannot be ruled out.

Studies on the synthesis of hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole derivatives with an additional

fused piperazine ring from the alanine derivatives **10h** and **13h**, via *N*-Z removal followed by lactamization, are in progress and will be communicated in due time.

The hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole derivatives herein described **10**−**13** were evaluated as cytotoxics in human lung carcinoma (A549) and human colon carcinoma (HT-29) cell lines. However, none of them showed significant cytotoxicity at concentrations below 10^{-6} M.

In conclusion, the results herein described show the wide scope of the acid-promoted domino cyclization of tryptophan-based α-amino nitriles derived from either ketones or aldehydes to hexahydropyrrolo[1′,2′,3′:1,9a,9]-imidazo[1,2-*a*]indoles. The reaction time and the stereoselectivity mostly depended on both the steric volume of the substituents at the amino nitrile and its stereochemistry. Unhindered α-amino nitriles gave exclusively the isomer with the 2-CO_2Me group toward the exo-face (**10**) as the kinetic and thermodynamic controlled product, while more hindered α-amino nitriles, which required higher conversion times, under kinetic control, gave also the 2-exo-isomer, but under thermodynamic control, provided the 2-endo-isomer **13** as main reaction product. The absolute preference of the 2-exo-stereochemistry of the benzaldehyde derivative **10g** versus the 2-endo **13g** might be due to some stabilizing electronic interaction between the 4-phenyl and the 2-methoxycarbonyl groups in a relative parallel cis-disposition.

Experimental Section

Acid-Promoted Cyclization of α-Amino Nitriles 8 and 9. Method A: Synthesis of the Hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole Derivatives 10b−g, 11d, and 13b−g. H_3PO_4 (85%, 3 mL) was added to a solution of the corresponding Trp-derived α-amino nitrile (**8b**−**g** and **9d**−**g**) (1.5 mmol) in CH_2Cl_2 (6 mL), and the mixture was stirred at room temperature for a variable time, as specified in Table 1. Afterward, the reaction mixture was sequentially poured into ice, neutralized with NH_4OH, 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 30−100% gradient of EtOAc in hexane as eluant. Significant analytical and ^{1}H NMR spectroscopic data of the resulting hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole derivatives **10b**−**g**, **12d**, and **13b**−**g** are summarized in the Tables 2 and 3. ^{13}C NMR spectroscopic data are summarized in Table 4 of the Supporting Information.

Acid-Promoted Cyclization of α-Amino Nitriles 8 and 9. Method B: Synthesis of the Hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole Derivatives 10h, 13h, and 13i. The corresponding α-amino nitriles **8h** and **9h** (1.5 mmol) were dissolved in neat TFA (2 mL), and the solution was stirred at room temperature for a variable time, as specified in Table 1. Afterward, the reaction mixture was processed and purified as above for method A. Amino nitrile **9h** gave exclusively the tautomer **10h**, while **8h** gave a mixture of the tautomer **13h** and the analogue with a trifluoroacetyl group replacing the Z-protecting group **13i**, which were resolved in the chromatographic purification. Significant analytical and ^{1}H NMR spectroscopic data of the resulting hexahydropyrrolo[1′,2′,3′:1,9a,9]-imidazo[1,2-*a*]indole derivatives **10h**, **13h**, and **13i** are summarized in the Tables 2 and 3, respectively. ^{13}C NMR spectroscopic data are summarized in Table 4 of the Supporting Information.

Acknowledgment. This work was supported by CICYT (SAF2000-0147). The antitumoral evaluation was carried out by the company Pharma Mar, S. A.

Supporting Information Available: General methods, experimental procedure for the synthesis, characterization data of α-amino nitriles **8** and **9**, and the ^{13}C NMR data of the pyrroloimidazoindol derivatives **10**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051441+