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Mechanistic Insights into the Stereocontrolled Synthesis of Hexahydropyrrolo[2,3-*b*]indoles by Electrophilic Activation of Tryptophan Derivatives

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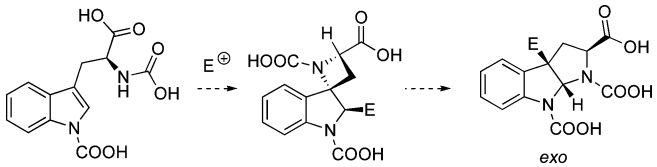
ABSTRACT



A three-step mechanism involving the formation and rearrangement of an intermediate with indoline–azetidine spirocyclic core structure was shown by DFT computations to account for the electrophilic cyclization of tryptophan derivatives to hexahydropyrrolo[2,3-*b*]indoles. The corresponding 3a-bromo derivatives have been obtained in high yields and synthetically useful *exolendo* ratios.

The hexahydropyrrolo[2,3-*b*]indole[1] skeleton is found embedded in a number of biologically active alkaloids, such as ardeemins,[2] okaramines,[3] sporidesmins,[4] brevianamides,[5] gypsetins,[6] roquefortines,[7] and leptosins[8] (Figure 1). The construction of this structural motif has been classically carried out by treatment of N-protected tryptophan esters with electrophilic reagents. Presumably, activation of the indole C2−C3 bond by the electrophile followed by nucleophilic attack of the tryptophan amine group results in the formation of the hexahydropyrrolo[2,3-*b*]indole core, usually as a mixture of diastereoisomers. Hino and co-workers observed that N_α-methoxycarbonyl L-tryptophan methyl ester undergoes cyclization in strong acidic media to give a mixture of

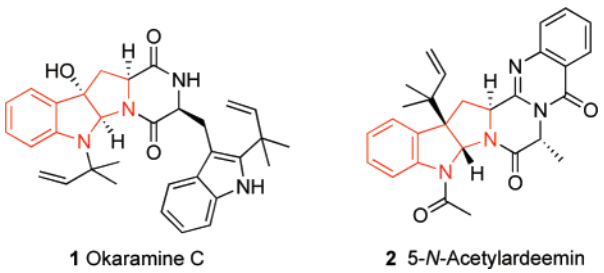


Figure 1. Relevant biologically active alkaloids containing a hexahydropyrrolo[2,3-*b*]indole motif.

(1) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151.
(2) Hochlowski, J. E.; Mullaly, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiot.* **1993**, *46*, 380.
(3) (a) Furutsuka, K.; Hayashi, H.; Shiono, Y. *J. Nat. Prod.* **1992**, *62*, 315. (b) Roe, J. M.; Webster, A. B.; Ganesan, A. *Org. Lett.* **2003**, *5*, 2825.
(4) Francis, E.; Rahman, R.; Safe, S.; Taylor, A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 470.
(5) Birch, A. J.; Wright, J. J. *J. Chem. Soc., Chem. Commun.* **1969**, 644.
(6) Schkeryantz, J.; Woo, J.; Siliphaivanh, P.; Depew, K.; Danishefsky, S. *J. Am. Chem. Soc.* **1999**, *121*, 11964.
(7) (a) Ohmomo, S.; Utagawa, S.; Abe, M. *Agric. Biol. Chem* **1977**, *41*, 2097. (b) Scott, P. M.; Kennedy, B. P. C. *J. Agric. Food Chem.* **1976**, *24*, 868.
(8) Takahashi, C.; Numata, A.; Matsumura, E.; Minoura, K.; Eto, H.; Shingu, T.; Ito, T.; Hasegawa, T. *J. Antibiot.* **1994**, *47*, 1242.

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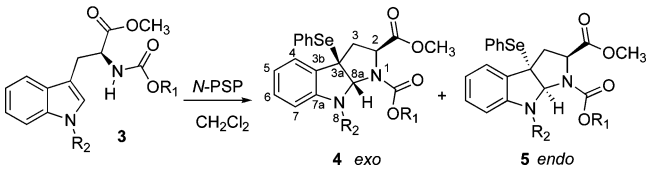
hexahydropyrroloindoles, which can be trapped by acylation at the indole nitrogen.[9] Dimethyl dioxirane (DMDO) has been utilized for the preparation of 3a-hydroxypyrroloindoles with good stereoselectivities.[10] More interestingly, *N*-phenylselenophthalimide (*N*-PSP)[11] effects selenocyclization to give 3a-(phenylselenyl)hexahydropyrrolo[2,3-*b*]indoles in high yields and diastereoselectivities. These seleno intermediates have been successfully exploited in the total syntheses of okaramine C[12] **1** and 5-*N*-acetylardeemin[13] **2** (Figure 1).

First described by Danishefsky and co-workers in 1994,[14] the reaction of tryptophan methyl esters with *N*-PSP has been studied by Crich, who showed the dependence of the reaction outcome with the protecting groups used.[15] The selenocyclization reaction affords a mixture of diastereomeric hexahydropyrrolo[2,3-*b*]indoles, corresponding to the *exo*-**4** and *endo*-**5** C2 acyl systems.[16] As shown in Table 1, an important bias exists in favor of the *exo* product, which is considered kinetically favored. Under basic equilibrating conditions, the *exo* products undergo epimerization at the C2 position to give the thermodynamic *endo* products.[1] This striking thermodynamic bias for the *endo* isomer has been attributed to torsional interactions around the bicyclo[3.3.0]octane nucleus.[17] Table 1 summarizes the reaction conditions and *exo*/*endo* ratios reported.

Danishefsky and co-workers have proposed that the diastereoselectivity obtained in this process could stem from two equilibrating pre-*endo* and pre-*exo* arrangements of the side chain in the intermediate selenonium ions,[13] with the former undergoing greater destabilization by steric contacts. Being involved in a project directed toward the synthesis of natural products containing the hexahydropyrrolo[2,3-*b*]-indole core, we decided to carry out a computational study on this mechanistic hypothesis in order to better understand the sources of selectivity, optimize the reaction conditions, and determine the reaction scope with regard to other electrophilic species. The model system depicted as **R** in Scheme 1 was selected as surrogate of the protected tryptophan **3** reacting with the simplified electrophile $MeSe^+$.

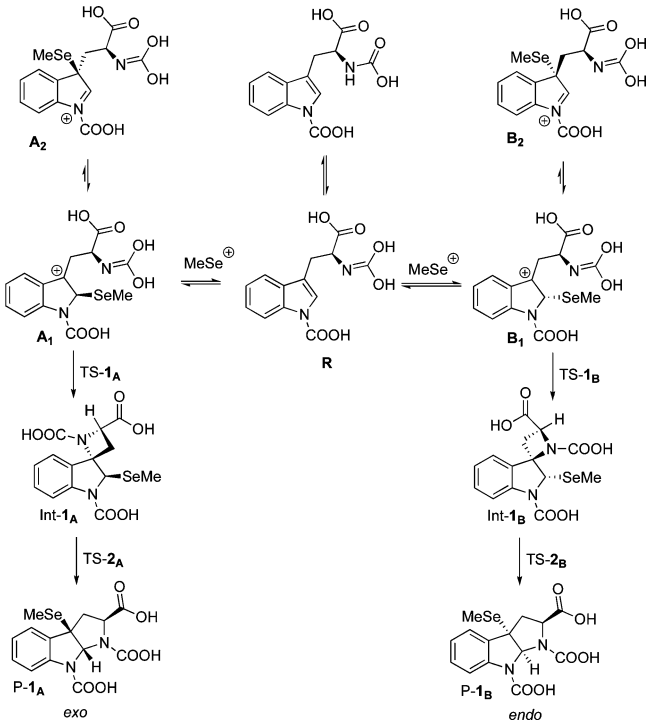
Table 1. Selenocyclization of Tryptophan Derivatives



entry	R_1	R_2	conditions[a]	yield (%)	*exo*/*endo* ratio
1	*t*-Bu	Boc	A	65	9:1[15]
2	Me	Cbz	A	76	12:1[15]
3	Me	CO_2Me	A	83	11:1[15]
4	Me	SO_2Ph	A	40	>98:2[15]
5	*t*-Bu	Boc	B	93	18:2[13]
6	Bn	Boc	B	93	>98:2[12]

[a] Conditions: A: 1.5 equiv of *N*-PSP, 0.1 equiv of PTSA; B: 1.5 equiv of *N*-PSP, 1.0 equiv of PPTS.

Scheme 1. Computed Reaction Profile for the Selenocyclization Reaction of **R**, a Model System of **3**



Density functional theory[18] was employed throughout this study. Geometry optimizations and frequency calculations were performed with the B3LYP functional.[19] The LANLDZ ECP[20] and its associated basis functions were used for Se and Br, whereas the 6-31G(d) basis set was assigned to the remaining atoms. Solvent effects were included through the PCM[21] model with CH_2Cl_2 parameters. All of these calcula-

(9) Taniguchi, M.; Hino, T. *Tetrahedron* **1981**, *37*, 1487.

(10) (a) Kameneka, T. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2995. (b) Kameneka, T. M.; Danishefsky, S. J. *Chem.—Eur. J.* **2001**, *7*, 41. (c) May, J.; Fournier, P.; Pellicelli, J.; Patrick, B.; Perrin, D. *J. Org. Chem.* **2005**, *70*, 8424. (d) May, J.; Patrick, B.; Perrin, D. *Synlett* **2006**, 3403.

(11) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

(12) (a) Hewitt, P. R.; Cleator, E.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 2417. (b) Ley, S. V.; Cleator, E.; Hewitt, P. R. *Org. Biomol. Chem.* **2003**, *1*, 3492.

(13) Depew, M. K.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953.

(14) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143.

(15) Crich, D.; Huang, X. *J. Org. Chem.* **1999**, *64*, 7218.

(16) The *exo*/*endo* ratio is readily established by ^1H NMR due to the characteristic methyl ester resonance of both diastereoisomers. The *endo* isomer shows a remarkably upfield signal at δ ~3.1 ppm, whereas the *exo* isomer shows a more common resonance at δ ~3.7 ppm.

(17) (a) Chan, C. O.; Cooksey, C. J.; Crich, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 777. (b) Crich, D.; Brunko, M.; Natarajan, S.; Teo, B. K.; Tocher, D. A. *Tetrahedron* **1995**, *51*, 2215.

(18) Hohenberg, P.; Kohn, W. *Phys. Rev. A* **1964**, *136*, B864.

(19) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

(20) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284.

tions were performed with the Gaussian03 package.[22] Long-range dispersion interactions were also included through an energy refinement step with the double hybrid B2PLYP functional[23] in conjunction with a basis set of triple-ζ quality with polarization functions (TZVP)[24] for all of the atoms.[25] The latter single-point energy refinement was performed with the Orca package.[26]

In keeping with the textbook explanation, the first step in this mechanism is seemingly the activation of the C2−C3 bond of **R** by the electrophilic species, with formation of a charged three-membered ring that is subsequently opened by the nucleophile. For the case at hand, the activation step is likely not diastereoselective since the steric cluttering upon selenonium ion formation is similar on both faces of the indole side chain due to its considerable flexibility. The good diastereomeric ratios (dr) of the selenocyclization reactions (Table 1) argue against the activation step being rate-limiting since low dr should be expected in that case. The mechanistic proposal by Danishefsky involves the attack of the carbamate N lone pair to the C2 position of the electrophile-activated intermediate. All attempts to locate this transition structure and its associated cyclic intermediate were unsuccessful. These calculations, in turn, suggest that the carbamate lone pair is very compromised in its conjugation with the carbonyl group and lacks the nucleophilicity required for an effective attack. Since these cyclization reactions are performed under acid catalysis (pTSA or PPTS), we instead considered likely the involvement of the carbamate keto−enol equilibrium, thus leaving the N lone pair in the enol form isolated from the carbonyl group and enhancing its nucleophilic character. In fact, when this tautomer is proposed as the reactive species of the tryptophan model system **R**, the nucleophilic attack does take place, but the reaction mechanism detours considerably from the direct attack of the carbamate nitrogen to C2 (see Scheme 1). The electrophilic selenium activates the indole ring in a first step that occurs with neither facial nor positional selectivity, in clear contrast with the textbook hypothesis summoned initially (vide supra). For the very unsymmetrical indole C2−C3 bond, the activation occurs by $MeSe^+$ attacking either the C2 or the C3 positions, with formation of a benzyl carbenium ion or an iminium ion, respectively (see $\mathbf{A_1}$−$\mathbf{A_2}$ and $\mathbf{B_1}$−$\mathbf{B_2}$ species in Scheme 1). These four species are dynamically exchanging in fast equilibrium processes. Actually, it is remarkable that only the benzyl carbenium ions are active regarding the seleno-cyclization reaction, whereas $\mathbf{A_2}$ and $\mathbf{B_2}$ are unproductive species. Since the carbamate nitrogen captures the benzyl carbenium ions, the attack occurs on C3 instead of C2, thus forming a spirocyclic intermediate (Int-$\mathbf{1_A}$ and Int-$\mathbf{1_B}$). Subsequently, a concerted double rearrangement of the N and the Se atoms with ring expansion of the azetidine to the final fused pyrrol unit was located.[27]

The formation of the azetidine is the rate-limiting step with an activation barrier of ca. 23 kcal/mol (see Table 2). There is about 1 kcal/mol difference in activation energy favoring TS-$\mathbf{1_A}$ over TS-$\mathbf{1_B}$, which we surmise is the source of the final *exo*/*endo* selectivity. Danishefsky's finding that the *exo* adduct is the kinetic product in the rearrangement of **3** (Table 1) is in good agreement with our calculations.

Table 2. Relative Free Energies in Solution (CH_2Cl_2) for the Seleno- and Bromocyclization Mechanisms[a]

		selenocyclization	bromocyclization
exo	$\mathbf{A_1}$	0.00	0.00
	$\mathbf{A_2}$	1.61	−2.30
	TS-$\mathbf{1_A}$	23.14	15.69
	Int-$\mathbf{1_A}$	11.56	−0.41
	TS-$\mathbf{2_A}$	19.01	18.29
	P-$\mathbf{1_A}$	−5.83	−15.11
endo	$\mathbf{B_1}$	−3.81	−10.13
	$\mathbf{B_2}$	−4.12	−3.10
	TS-$\mathbf{1_B}$	24.16	16.17
	Int-$\mathbf{1_B}$	11.86	0.22
	TS-$\mathbf{2_B}$	20.33	19.76
	P-$\mathbf{1_B}$	−6.37	−15.74

[a] Relative free energies in kcal/mol.

After thorough inspection of these two transition structures, we concluded that there are no obvious structural features responsible for the difference in activation energies. Both transition structures exhibit similar geometries (bond lengths, angles, and dihedrals); in fact, the energy difference between both transition structures is only ∼0.5 kcal/mol in the gas phase, which means that half of the energy difference

(21) (a) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027. (b) Mineva, T.; Russo, N.; Sicilia, E. *J. Comput. Chem.* **1998**, *19*, 290.

(22) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(23) Grimme and co-workers have demonstrated that intramolecular long-range dispersion is very important to obtain an accurate electronic description of molecules in general and oligopeptides in particular (Schwabe, T.; Grimme, S. *Phys. Chem. Chem. Phys.* **2007**, *9*, 3397). They introduced long-range dispersion by perturbative methods (Grimme, S. *J. Chem. Phys.* **2006**, *124*, 034108) and developed a semiempirical scheme to further improve the latter functionals (Grimme, S. *J. Comput. Chem.* **2004**, *25*, 1463). In particular, the double hybrid B2PLYP functional with dispersion corrections included semiempirically has proved to yield errors considerably smaller than those of the venerable B3LYP for the G3 set.

(24) Schaefer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571.

(25) To make the perturbative part more affordable given the large basis functions employed, the resolution of the identity (RI) was used as implemented in the Orca program: (a) Weigend, F.; Häser, M. *Theor. Chem. Acc.* **1997**, *97*, 331. (b) Weigend, F.; Köhn, A.; Hättig, C. *J. Chem. Phys.* **2002**, *116*, 3175.

(26) See http://www.thch.uni-bonn.de/tc/orca/.

(27) Similar ring expansions on indole motifs can be found in recent literature: (a) Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1444. (b) Baran, P. S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 14028.

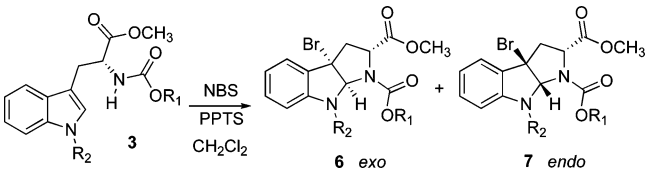
between TS-$\mathbf{1_A}$ and TS-$\mathbf{1_B}$ corresponds to solvation effects. The rearrangement to the final products preserves the chiral information created in the cyclization reaction. The spiranic intermediate formed must have a kinetically insignificant lifetime since it is only 7−8 kcal/mol lower in energy than the subsequent transition structures (Table 2). Ring expansion is probably the driving force for the double concerted rearrangement and the source of such a low-energy barrier.

The cyclization reaction of tryptophan derivatives has been typically performed with selenium electrophiles such as *N*-PSP, but the latter mechanistic proposal might also be compatible with reaction conditions using more popular electrophiles such as NBS. We therefore considered the development of the bromocyclization as an alternative to the selenocyclization since the formed 3a-bromohexahydropyrrolo[2,3-*b*]indole motif can be also synthetically useful.[28] In fact, the mechanistic path computed for the activation with the electrophilic bromine (Table 2) closely resembles the one depicted in Scheme 1.

Differences are limited to the following: (a) the rate-limiting step is not the intermediate spirocyclic ring formation, but the concerted rearrangement with ring expansion (see Table 2); and (b) the rate-limiting transition structures exhibit barriers considerably lower (ca. 4−5 kcal/mol) than those of the selenocyclization. The lower activation energy at the rate-limiting step should allow the use of shorter reaction times or milder thermal activation conditions. For the experimental validation of the computational suggestion, protected tryptophan **3** of the D series was treated with 1 equiv of NBS and 1 equiv of PPTS in CH_2Cl_2. The results, listed in Table 3, confirm the feasibility of the bromocyclization reaction and the predominance of the *exo* diastereomer.

In summary, a mechanistic proposal for formation of the hexahydropyrrolo[2,3-*b*]indole skeleton by electrophilic activation of tryptophan derivatives is suggested based on DFT computations. It comprises three steps: indol C2−C3 activation by the electrophile to give diastereomeric carbenium ions, followed by their capture by the carbamate nitrogen with formation of spirocyclic skeletons, and last, double concerted rearrangement of the electrophile and the azetidine nitrogen to give the hexahydropyrrolo[2,3-*b*]indole core. Using an electrophilic halogen species, versatile 3a-bromo derivatives are obtained efficiently in high *exo*/*endo* diastereomeric ratios.

Table 3. Bromocyclization of Tryptophan Derivatives



3	R_1	R_2	yield (%)	*exo*/*endo* ratio[a]
a	*t*-Bu	Boc	85	24:1
b	Bn	Boc	87	ND
c	Me	Boc	90	30:1
d	*t*-Bu	$PhSO_2$	65	>98:2
e	Bn	$PhSO_2$	72	ND
f	Me	$PhSO_2$	83	ND

[a] The diastereomeric ratio is provided only when the NMR signals do not overlap. ND: not determined.

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Supporting Information Available: Experimental information and data for all new compounds. SCF energies, Cartesian coordinates, free energies, and number of imaginary frequencies for all the computed stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Movassaghi, M.; Schmidt, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3725.