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A Novel One-Pot Approach of Hexahydropyrrolo[2,3-*b*]indole Nucleus by a cascade addition/cyclization strategy: Synthesis of (±)-Esermethole

Simone Lucarini, Francesca Bartoccini, Flavia Battistoni, Giuseppe Diamantini, Giovanni Piersanti,* Marika Righi, and Gilberto Spadoni

Department of Drug and Health Sciences, University of Urbino "Carlo Bo", Piazza del Rinascimento 6, 61029 Urbino (PU), Italy

giovanni.piersanti@uniurb.it

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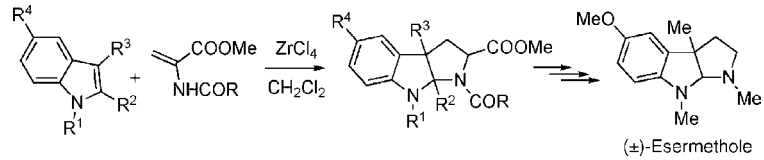
ABSTRACT



A practical and efficient synthesis of 3-substituted hexahydropyrrolo[2,3-*b*]indole is described. The addition/cyclization of 3-substituted indoles with α,β-dehydroamino esters in the presence of a Lewis acid provides hexahydropyrrolo[2,3-*b*]indole adducts in good yields and stereoselectivities. This approach has been applied to the concise synthesis of esermethole employing an appropriately substituted indole and an *N*-acyl dehydroamino ester.

The hexahydropyrrolo[2,3-*b*]indole[1] framework (**1**) having a quaternary center at the C-3a site occurs frequently in many alkaloids isolated from a variety of natural sources.[2] The best known members of this group are alkaloids found in seeds of the African calabar bean *Physostigma Venenosum*, such as (−-)-physostigmine (**2**).[3] Some other representative examples include flustramine B (**5**),[4] (−)-pseudophrynaminol (**6**),[5] and polycyclic minfiensine compounds[6] (Figure 1). Various biological activities are associated with 3a-substituted pyrrolidinoindolines as exemplified by (−)-physostigmine (**2**) and (−)-phenserine (**3**), which are used to treat glaucoma and Alzheimer's disease.[7]

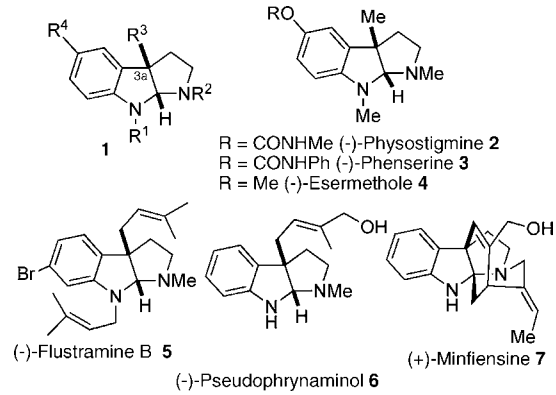


Figure 1. Representative hexahydropyrrolo[2,3-*b*]indole alkaloids having a quaternary center at C3a.

(1) For recent reviews, see: (a) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (b) Schmidt, M. A.; Movassaghi, M. *Synlett* **2008**, 313.

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The unique structural arrays and interesting biological activities displayed by these alkaloids makes them a particularly appealing target for total synthetic efforts as well as the design of new reaction methods that enable the simple and rapid construction of many of these complex alkaloids. The construction of the hexahydropyrrolo[2,3-*b*]indole structural motif has been classically carried out by electrophilic attack on a tryptophan or tryptamine (**8**) unit at the indole C-3 position, followed by cyclization onto the resulting C-2 iminium ion by the side-chain nitrogen (Figure 2, biomimetic

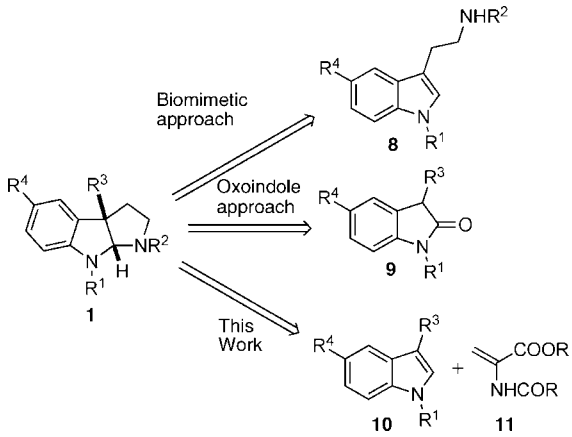


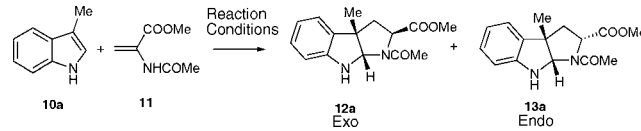
Figure 2. Retrosynthetic approaches.

approach).[8] Although this retrosynthetic disconnection has been realized, it is highly sensitive to the nature of the electrophile and the indole substrate. Yields are often poor, versatility is low, and many total syntheses have adopted less direct solutions for the construction of this skeleton. Alternatively, the hexahydropyrrolo[2,3-*b*]indole core can be attained through alkylation of a suitable 2-oxoindole (**9**) followed by a sequence of functional group interconversions that allows the final cyclization under reductive conditions.[9] (Figure 2, oxoindole approach).

Recently, we have reported the Michael-type Friedel−Crafts (FC) alkylations of various 3-unsubstituted indoles with acylated α,*β*-dehydroamino esters for the preparation of tryptophan and related amino acid derivatives.[10] To extend the methodology developed, we now describe a conceptually different approach to the hexahydropyrrolo[2,3-*b*]indole core, in which the tricyclic pyrrolidinoindoline ring system is constructed in a single-step one-pot reaction by reacting readily available 3-substituted indoles (**10**) and N-acylated α,*β*-dehydroamino esters (**11**) through the domino addition−cyclization approach outlined in Figure 2. Besides the simplicity of employing commercially or readily available precursors, this novel and concise approach to the pyrrolidinoindoline core structure potentially could allow a wide variety of substituents to be incorporated at C-3a, including those not readily introduced through other methods. Interestingly, the proposed pyrroloindoline ring formation involves a two step reaction: carbon−carbon bond formation that leads to dearomatization of the indolyl system with concomitant formation of a quaternary stereocenter and subsequent carbon−nitrogen bond formation. Both reactions occur under the influence of the same Lewis acid.

We report herein the first examples of Lewis acid mediated diastereoselective one-pot pyrrolidinoindoline formation from 3-substituted indoles and α-amidoacrylates and application of this methodology for the synthesis of (±)-esermethole. To achieve this goal, we first examined the addition of 3-methylindole (**10a**) to commercially available *N*-acetamidoacrylate (**11**) in the presence of ethylaluminum dichloride; the desired tricyclic hexahydropyrroloindole **12** was obtained in good yield and high *exo*-diastereoselectivity (Table 1, entry 1). We then examined the effect of the Lewis acid on the reaction, starting from metal salts that in previous studies allowed **11** to behave as an electron-deficient olefin in the FC alkylation. The best results in terms of yield and selectivity were obtained by employing 2 equiv of zirconium chloride with respect to the electrophile (Table 1, entry 2).

Table 1. Optimization of Reaction Conditions



entry	solvent	MX_n (2 equiv)	yield[a] (%) (*exo*/*endo*)[b]
1	CH_2Cl_2	$EtAlCl_2$	63 (9/1)
2	CH_2Cl_2	$ZrCl_4$	75 (9/1)
3	CH_2Cl_2	$TiCl_4$	58 (8/1)
4	*i*PrOH	$ZrCl_4$	n.r.
5	CH_3CN	$ZrCl_4$	16 (8/1)
6	dioxane	$ZrCl_4$	10 (8/1)
7	toluene	$ZrCl_4$	11 (9/1)
8[c]	CH_2Cl_2	$ZrCl_4$	65 (9/1)
9[d]	CH_2Cl_2	$ZrCl_4$	n.r.
10[e]	CH_2Cl_2	$ZrCl_4$	71 (9/1)
11[f]	CH_2Cl_2	$ZrCl_4$	55 (9/1)

[a] Isolated yield. [b] Determined by HPLC. [c] The reaction was conducted at 40 °C. [d] Catalytic amount of $ZrCl_4$; [e] 2.4 equiv of $ZrCl_4$; [f] 0.8 equiv of DHA.

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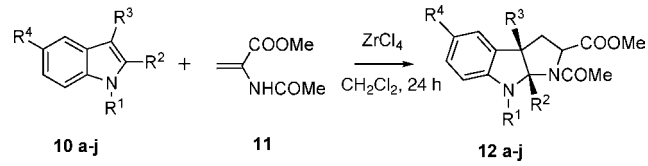
No reactivity was observed when the reaction was carried out using catalytic amounts or less than 1 equiv of the Lewis acid (Table 1, entry 9). Low conversion was observed when 1 equiv was used. To further optimize the process, examination of the reaction medium led to the selection of dichloromethane as the best solvent. Reactions performed in ethereal solvents such as THF, ether, dioxane, methyl *tert*-butyl ether (MTBE), and 1,2-dimethoxyethane (DME) generally afforded worse results in terms of reaction yield and diastereoselectivity, and no reaction occurred in polar solvents such as DMF, CH_3CN, or water. Less promising results were also obtained in nonpolar solvents such as 1,2-dichloroethane (DCE), chloroform, and toluene. These results are consistent with previous reports that nonpolar and noncoordinating solvents are generally optimal in these types of reaction systems. The reaction temperature also has an important effect on the reaction. In general, lowering the temperature resulted in a decreased reaction rate but slightly increased the yield (Table 1, entry 8). The reaction proceeds with high *exo*-selectivity.[11] At this point, it is difficult to offer a mechanistic proposal to rationalize this stereochemical preference in light of a known thermodynamic bias for the *endo*-diastereomer. However, the reaction of tryptophan or tryptamine with a number of electrophiles has shown a similar stereochemical outcome.[8] It is also evident that the preference of ester substituent for the *exo*- over the *endo* position holds under acidic reaction conditions ($ZrCl_4$ in CH_2Cl_2), as *endo*-**13a** undergoes inversion. Clearly, *exo*-**12a** becomes the more stable *endo* form upon treatment with sodium *tert*-butoxide in DMF at 80 °C for 16 h. Thus, the use of $ZrCl_4$ (2 equiv) and a 1:1.1 ratio of indole/*N*-acetamidoacrylate in CH_2Cl_2 at room temperature for 24 h became our standard conditions.

Having established the optimal conditions for the tandem addition/cyclization reaction, the generality of the reaction was then examined in detail using various substituted indoles (Table 2). The corresponding 3-substituted hexahydropyrrolo[2,3-*b*]indoles were obtained, albeit in lower yields and diastereoselectivities (entries 1−8). When 1,3-dimethyl indole was prepared and treated with *N*-acetamidoacrylate, the reaction occurred demonstrating that the H atom on the N atom is not crucial for the cascade reaction. However, *N*-acetyl, *N*-sulfonyl, and *N*-BOC-indole did not afford the desired products, clearly showing the importance of the nucleophility of the indole. The size of the 3-alkyl group plays an important role in the reaction (entries 2, 4, and 8). While acceptable yields were obtained with cyclopentyl in this position, the reaction did not proceed with the more bulky γ-prenyl substituent.[12] This was not unexpected as the dehydroamino acid was likely coordinated to the bulky zirconium metal during the reaction and would try to minimize steric interactions by steering the large substituent away from the metal. Translation of these conditions to the reaction with 3-vinylindole, however, was not possible. This more electron-rich olefin was in fact found to be much more sensitive to the acidic catalyst, resulting mainly in decomposition and giving a very poor product yield. The alkylation reaction was also highly regio- and chemoselective. Indeed, although N- and C2-electrophilic substitution of 3-substituted indoles have been reported,[13] neither N- nor C2-adducts were detected under the reaction conditions utilized. Suitably encouraged by these results, we commenced our investigation using 2,3-disubstituted indoles. Gratifyingly, the domino reaction occurred and the corresponding 2,3-disubstituted hexahydropyrrolo[2,3-*b*]indoles were obtained in satisfactory yields and diastereselectivities both with 2,3-dimethylindole and cyclopentane-fused indole. These are notable results because the direct C3-functionalization of 2,3-disubstituted indoles represents a great synthetic challenge. Moreover, it represents an easy approach to C2-substituted hexahydropyrrolo[2,3-*b*]indole analogues, difficult to obtain by the oxyindole approach and never reported by biomimetic or other approaches.

To illustrate the synthetic utility of this methodology and further confirm the relative stereochemistry of this reaction, we undertook the total synthesis of (±)-esermethole, the

Table 2. Scope of the Reaction



10 a-j 11 12 a-j

		indole				
entry		R^1	R^2	R^3	R^4	yield[a] (%) (*exo*/*endo*)[b]
1	a	H	H	CH_3	H	75 (9/1)
2	b	CH_3	H	CH_3	H	46 (6/1)
3	c	H	CH_3	CH_3	H	72 (4/1)[c]
4	d	H	$CH_2CH_2CH_2$		H	69 (7/1)[c]
5	e	H	H	CH_3	Br	45 (3/1)
6	f	H	H	CH_3	OCH_3	84 (4/1)
7	g	CH_3	H	CH_3	OCH_3	68 (3/1)
8	h	H	H	cyclopentyl	H	62 (6/1)
9	i	H	H	C_6H_5	H	trace
10	j	H	H	$CH{=}CH_2$	H	n.r.

[a] Isolated yield. [b] Determined by HPLC. [c] *Exo*/*endo* ratio was determined by ^1H NMR.

(9) (a) Matsuura, T.; Overman, L. E.; Poon, D. *J. Am. Chem. Soc.* **1998**, *120*, 6500. (b) Overman, J. L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702. (c) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677. (d) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043. (e) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590. (f) Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem.—Eur. J.* **2007**, *13*, 961.

(10) Angelini, E.; Balsamini, C.; Bartoccini, F.; Lucarini, S.; Piersanti, G. *J. Org. Chem.* **2008**, *73*, 5654.

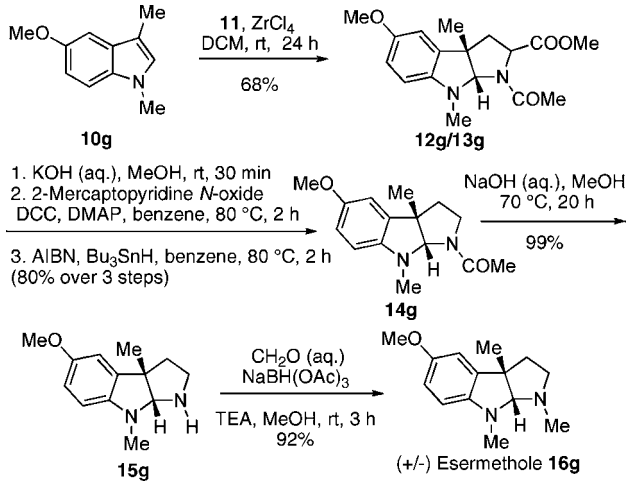
(11) The *exo*/*endo* ratio is readily established by ^1H NMR due to the characteristic methyl ester resonance of both diastereoisomers. The *endo*-isomer shows a remarkably upfield signal at δ 3.1 ppm, whereas the *exo*-isomer shows a more common resonance at δ <3.7 ppm.

(12) For a comprehensive review on selective catalytic indole functionalization, see: Bandini, M.; Eichholzer, A. *Angew Chem. Int. Ed.* **2009**, *48*, 9608. For specific examples, see: (a) Lin, Y. D.; Kao, J. Q.; Chen, C. T. *Org. Lett.* **2007**, *9*, 5195. (b) Leitch, S.; Addison-Jones, J.; McCluskey, A. *Tetrahedron Lett.* **2005**, *46*, 2915.

(13) For an interesting report on C-3a-prenylated pyrroloindoles, see: Lindel, T.; Bräuchle, L.; Golz, G.; Böhrer, P. *Org. Lett.* **2007**, *9*, 283.

penultimate intermediate to physostigmine and phenserine.[2b] By reacting 5-methoxy-3-methyl-*N*-methylindole (**10g**), readily available in one step from 4-methoxy-*N*-methylaniline and chloroacetone,[14] under standard reaction conditions, it was possible to prepare tricycles **12g**/**13g** in multigram quantities (Scheme 1). Under optimal reaction conditions, treatment

Scheme 1. Synthesis of Esermethole



of esters **12g**/**13g** with a mixture of methanol and aqueous potassium hydroxide at room temperature for 1 h provided the corresponding carboxylic acid in 92% yield. Decarboxylation was achieved by the Barton reaction through sequential conversion to the thiohydroxamic ester, followed by treatment with Bu_3SnH in benzene, to afford tricycle **14g** in almost quantitative yield. At this point, strong acidic conditions for the removal of the acetyl group of **14g** led to decomposition, whereas a methanolic solution of amide **14g** and sodium hydroxide at 80 °C for 16 h afforded the desired amine **15g** in 99% yield. N-Methylation of the secondary amine group using formalin and sodium triacetoxyborohydride provided racemic esermethole in 87% yield. The spectral data of the compound obtained were identical with the reported data for esermethole.[15]

In summary, we have demonstrated a one-pot, novel, and simple approach to the hexahydropyrrolo[2,3-*b*]indole nucleus using a tandem addition/cyclization reaction of three substituted indoles and dehydroamino acids. The tandem reaction was general with respect to indoles and provided the desired products bearing a chiral quaternary center at C3 in good yield. This chemistry allows the formation of both the carbon−carbon bond and the carbon−nitrogen bond of the hexahydropyrrolo[2,3-*b*]indole substructure and offers the shortest synthesis of these alkaloids from commercial materials. It is to be noted that this synthetic strategy requires only minor variations to be adapted for the synthesis of hexahydropyrrolo[2,3-*b*]indoles, which differ mainly by a substituent at the C-3a position. The application of this chemistry for the concise synthesis of racemic esermethole is also described. Further investigations of the scope and synthetic utility of this chemistry are underway, and the results will be reported in due course.

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Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Underwood, R.; Prasad, K.; Repic, O.; Hardtmann, G. E. *Synth. Commun.* **1992**, *22*, 343.

(15) Selected previous syntheses of esermethole: (a) Reddy, V. J.; Douglas, C. J. *Org. Lett.* **2010 12**, 952. (b) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874. (c) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (d) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049. (e) Pallavicini, M.; Valoti, E.; Villa, L.; Resta, I. *Tetrahedron: Asymmetry* **1994**, *5*, 363.