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[2,3-b]indole core of leptosins D-F based on  
nucleophilic substitution reaction on indole  
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SYNTHESIS OF 3a-(INDOL-3-YL)-1,2,3,3a,8,8a-HEXAHYDROPIRROLO-  
[2,3-*b*]INDOLE CORE OF LEPTOSINS D-F BASED ON NUCLEOPHILIC  
SUBSTITUTION REACTION ON INDOLE NUCLEUS<sup>1</sup>

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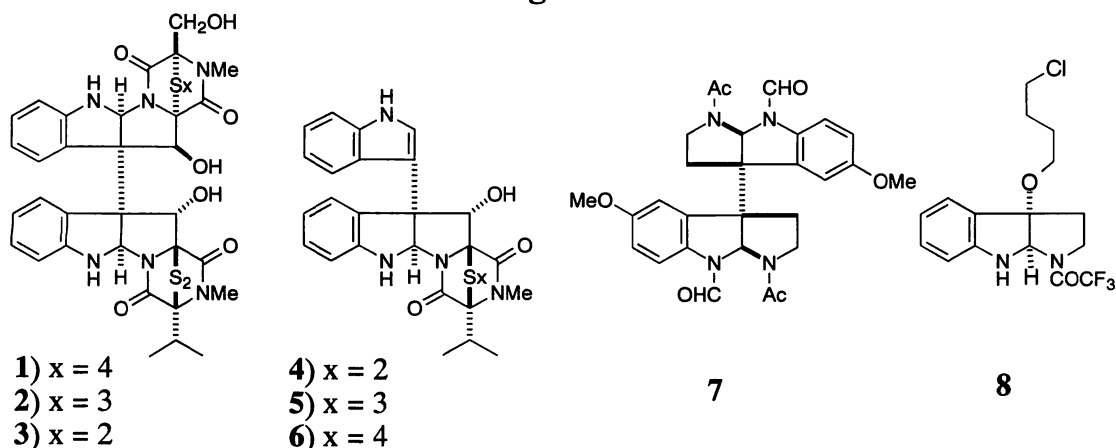
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**Abstract** — A simple and convenient synthetic methodology for 3a-(indol-3-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole, the core structure of leptosins D-F is developed by applying nucleophilic substitution reaction of 1-hydroxytryptamines.

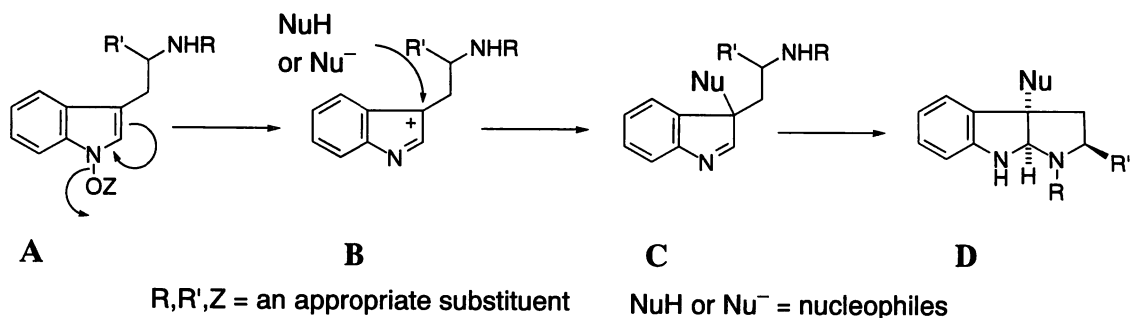
Leptosins A-C<sup>2,3</sup> (**1**–**3**, Figure 1) and D-F<sup>3</sup> (**4**–**6**) were isolated from the culture of a strain of *Leptosphaeria* sp. as cytotoxic substances against the P-388 lymphocytic leukemia cell line comparable to that of mytomycin C. Thusfar, only one group reported a synthetic study directed toward them.<sup>4</sup>

As for the biosynthesis of these types of compounds, we have proposed an intermediacy of 1-hydroxytryptamines (**A**) and/or -tryptophans (**A**) in our 1-hydroxyindole hypothesis<sup>5</sup> as shown in general formula in Scheme 1. If we assume the 1-hydroxy group departs after being transformed to a good leaving group, an indolyl cation<sup>6</sup> (**B**) is generated and then it can be trapped with various nucleophiles to give imine<sup>6</sup> (**C**). Subsequent cyclization of *Nb*-nucleophile on the side chain results in the formation of pyrrolo[2,3-*b*]indole skeleton (**D**). Although such nucleophilic substitution reaction is quite rare<sup>7</sup> in indole chemistry, we have discovered various examples<sup>5</sup> based on 1-hydroxyindole chemistry. Quite recently we succeeded in demonstrating the evidence of indolyl cation (**B**) by trapping it with either *Nb*-acetyltryptamine<sup>8</sup> or THF<sup>9</sup> isolating **7** or **8**, respectively.

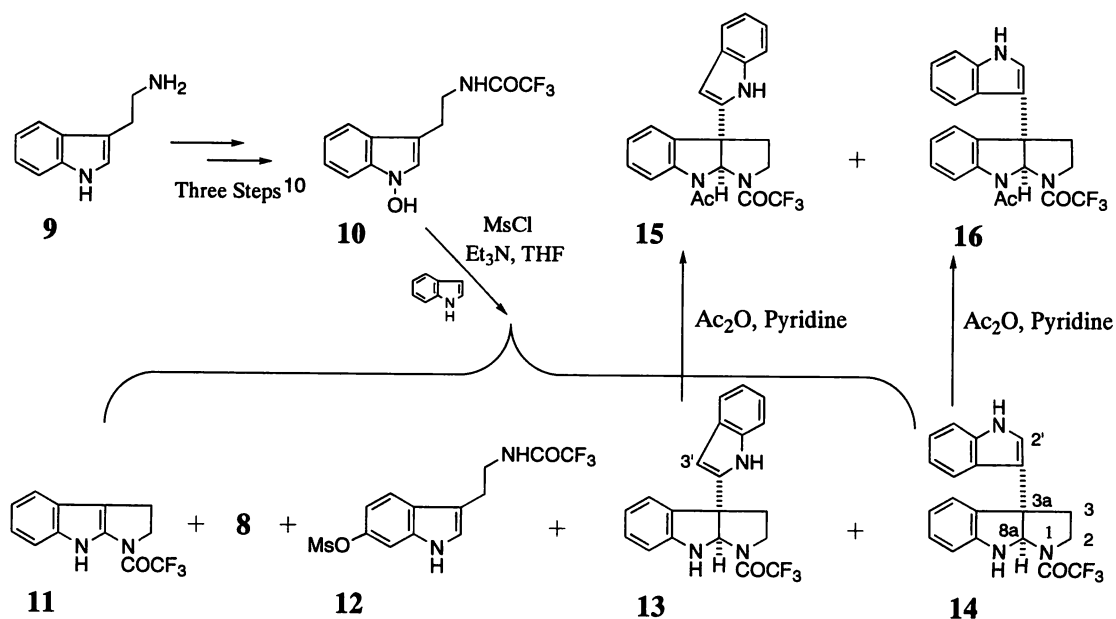
Figure 1



## Scheme 1



## Scheme 2



Based on the above background, we planned to employ indole itself as a nucleophile to trap **B**, expecting to establish a simple methodology for the synthesis of leptosins and their analogs. Thus, 1-hydroxy-*Nb*-trifluoroacetyltryptamine (**10**, Scheme 2), readily available in three steps<sup>10</sup> from tryptamine (**9**), was treated with mesyl chloride in THF in the presence of indole (3 mol eq) and triethylamine at 0 °C, thereby as expected, smooth reaction occurred to provide 1-trifluoroacetyl-1,2,3,8-tetrahydropyrrolo[2,3-*b*]indole<sup>9,10</sup> (**11**), 1-trifluoroacetyl-3a-(4-chlorobutoxy)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole<sup>9</sup> (**8**), *Nb*-trifluoroacetyl-6-mesyloxytryptamine<sup>9,11</sup> (**12**), 3a-(indol-2-yl)- (**13**), and 3a-(indol-3-yl)-1-trifluoroacetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**14**) in 25, 6, 8, 5, and 12% yields, respectively. When the reaction was carried out in CHCl<sub>3</sub>, the yield of **14** was improved to 21% together with the formations of **11**, **12**, and **13** in the respective yields of 14, 4, and 5%. Under similar reaction conditions, the use of excess indole (10 mol eq) further raised the yield of **14** up to 30% in addition to the concomitant formations of **11**, **12**, and **13** in 4, 1, and 7% yields, respectively.

The high resolution MS and other spectral data of **13** and **14** show the presence of an extra indole moiety in both molecules. In the  $^1\text{H-NMR}$  spectra, **13** and **14** have characteristic C-(8a) proton signal at  $\delta$  5.63 and 5.91, respectively, proving the presence of hexahydropyrrolo[2,3-*b*]indole skeleton. Additionally, in the case of **14**, a long-range coupled doublet proton ( $J = 2.5$  Hz) at  $\delta$  6.92 is observed and assigned to be C(2')-proton, which is unusually shielded compared to the usual indole C(2)-proton.<sup>2,4</sup> Similarly, a double doublets proton ( $J = 2.2$  and 0.7 Hz) resonated at  $\delta$  6.48 in the spectrum of **13** is attributed to the C(3')-proton. The structures of **13** and **14** were further confirmed by treating them with  $\text{Ac}_2\text{O}$  and pyridine to afford the acetyl derivatives (**15** and **16**) in the respective yields of 65 and 56%.

From these data, **13** and **14** were deduced to be indol-2-yl and indol-3-yl compounds, respectively.

Luckily, **13** became suitable prisms for X-Ray single crystallographic analysis and the structure was determined unequivocally as shown in Figure 2. As the indol-2-yl structure of **13** is established, then it follows that the other isomer (**14**) is the indol-3-yl compound.

The preferred formation of **14** to **13** is in accord with the well-known

positional order 3>2 for reactivity of unsubstituted indole. Although yields of **13** and **14** are not high, we expect that examinations of optimum reaction conditions would improve their yields. Application of the present methodology to the 1-hydroxy-L-tryptophan<sup>12</sup> derivatives would provide an asymmetric synthetic route to leptosins. Extensions of the present reaction to other various nucleophiles would also be promising for new pyrrolo[2,3-*b*]indole compounds (**D**).

## ACKNOWLEDGMENT

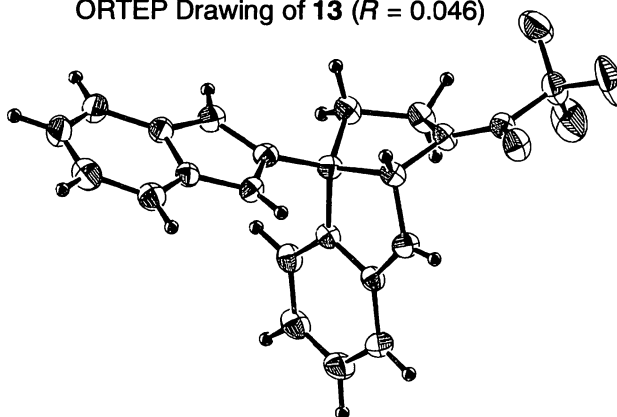
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**Figure 2**

ORTEP Drawing of **13** ( $R = 0.046$ )



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