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SYNTHESIS OF 3a-(INDOL-3-YL)-1,2,3,3a,8,8a-HEXAHYDROPYRROLO-[2,3-*b*]INDOLE CORE OF LEPTOSINS D–F BASED ON NUCLEOPHILIC SUBSTITUTION REACTION ON INDOLE NUCLEUS[1]

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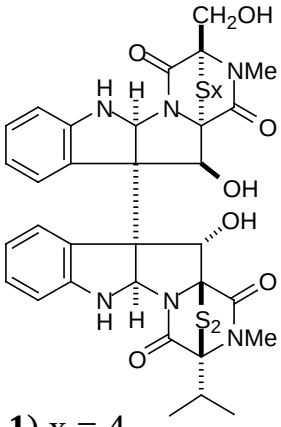
Abstract — A simple and convenient synthetic methodology for 3a-(indol-3-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole, the core structure of leptosins D–F is developed by applying nucleophilic substitution reaction of 1-hydroxy-tryptamines.

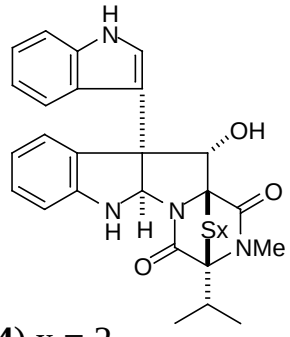
Leptosins A–C[2,3] (**1**–**3**, Figure 1) and D–F[3] (**4**–**6**) were isolated from the culture of a strain of *Leptosphaeria* sp. as cytotoxic substances against the P-388 lymphocytic leukemia cell line comparable to that of mytomycin C. Thusfar, only one group reported a synthetic study directed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

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[5] 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[6] (**B**) is generated and then it can be trapped with various nucleophiles to give imine[6] (**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[7] in indole chemistry, we have discovered various examples[5] based on 1-hydroxyindole chemistry. Quite recently we succeeded in demonstrating the evidence of indolyl cation (**B**) by trapping it with either *Nb*-acetyltryptamine[8] or THF[9] isolating **7** or **8**, respectively.

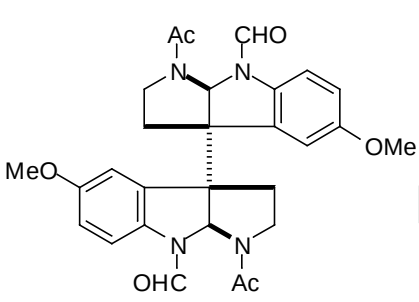
Figure 1



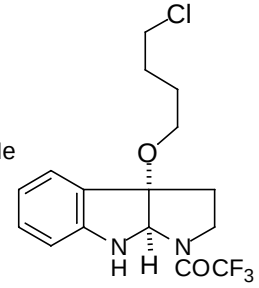
1) x = 4
2) x = 3
3) x = 2



4) x = 2
5) x = 3
6) x = 4

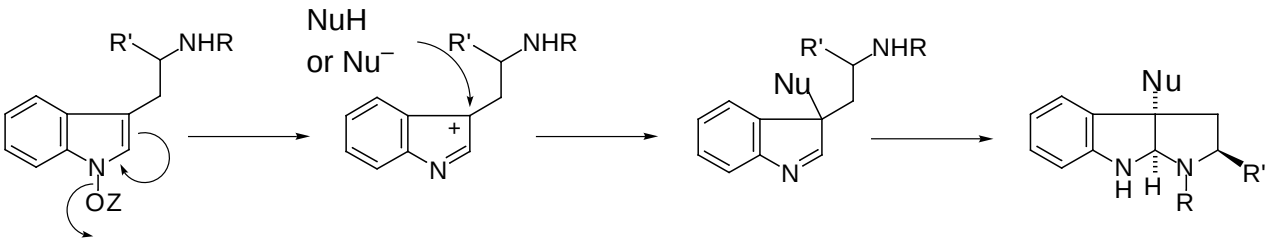


7

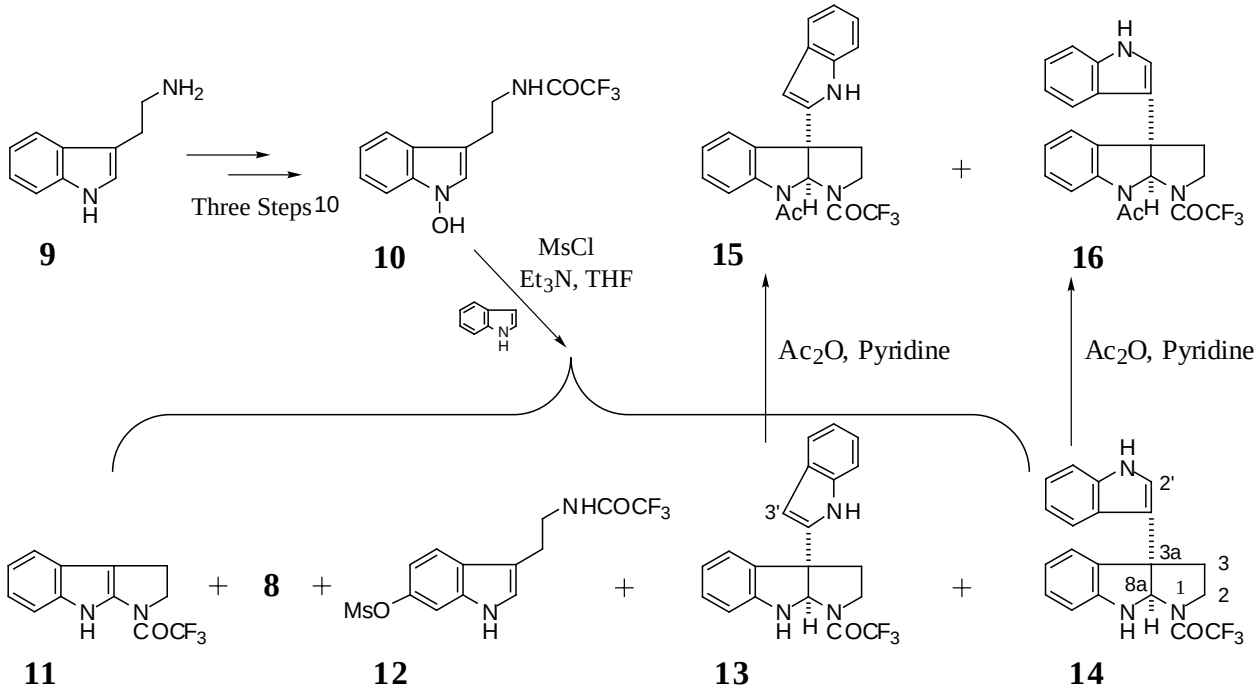


8

Scheme 1



Scheme 2



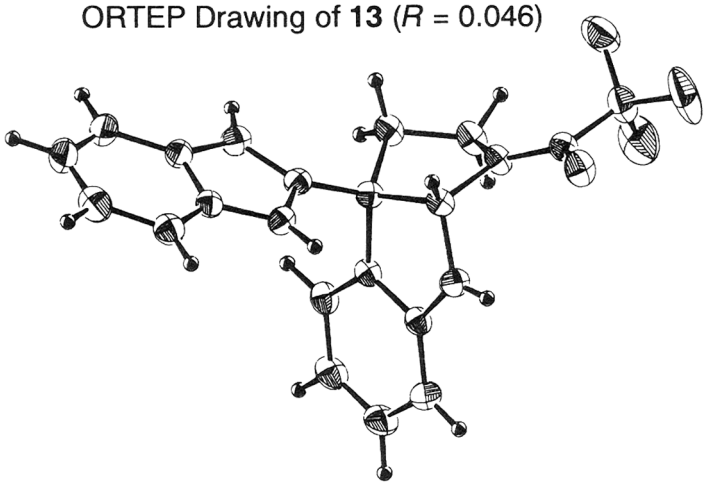
Based on the above background, we planned to employ indole itself as a nucleophile to trap **B**, expecting to establish a simple methodology for the synthesis of leptosins and their analogs. Thus, 1-hydroxy-*Nb*-trifluoroacetyltryptamine (**10**, Scheme 2), readily available in three steps[10] from 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[9,10] (**11**), 1-trifluoroacetyl-3a-(4-chlorobutoxy)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole[9] (**8**), *Nb*-trifluoroacetyl-6-mesyloxytryptamine[9,11] (**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 $CHCl_3$, 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}H-NMR specta, **13** and **14** have characteristic C-(8a) proton signal at δ 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 δ 6.92 is observed and assigned to be C(2')-proton, which is unusually shielded compared to the usual indole C(2)-proton.[2,4] Similarly, a double doublets proton (J = 2.2 and 0.7 Hz) resonated at δ 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 Ac_2O 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.

Figure 2

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



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[12] derivatives would provide an asymmetric synthetic route to leptosins. Extentions of the present reaction to other various nucleophiles would also be promising for new pyrrolo[2,3-*b*]indole compounds (**D**).

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REFERENCES AND NOTES

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