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A contribution to the elucidation of the biosynthesis of 3-chloro-4-(3′-chloro-2′-nitrophenyl)-1*H*-pyrrole (pyrrolnitrin)

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ABSTRACT

Selective openings of the ring B of the derivative hexapyrroloindol in basic conditions confirm the rearrangement of the tryptophan to aminoarylpyrrol, analogously to the step catalyzed by the enzyme prnB in the biosynthesis of pyrrolnitrin.

The antibiotic pyrrolnitrin [3-chloro-4-(3′-chloro-2′-nitrophenyl)-1*H*-pyrrole] (PRN) **1** (Fig. 1), that is produced by many pseudomonas, is a secondary metabolite derived from tryptophan and has strong fungicidal activity.[1–4] Two biosynthetic pathways for PRN from tryptophan were proposed by Van Pée et al.[5] and by Chang et al.[6a] The first is based mainly on a ring rearrangement and the second was proposed based on the fate of several specific carbon and hydrogen isotopic labels during the transformation of tryptophan to PRN.

Ligon et al.[7] have also described four genes, *prnABCD*, from *Pseudomonas fluorescens,* which encode the biosynthesis of PRN **1** and described the function of each *prn* gene product, where the tryptophan was identified as the precursor for PRN.[4,6]

De Laurentis et al.[8] have realized the crystallographic characterization of *prnB*, and recently has showed[9] the reductive nature of the gene *prnB* and that the interaction of L-tryptophan with the gene is favored in basic conditions.

So far, the transformation catalyzed by *prnB* has no obvious chemical precedent. As a consequence, the exact nature of the compound undergoing the rearrangement to the aminophenylpyrrole (APP) skeleton as well as the type of reaction leading to its formation is still unclear.

On the other hand, Hino[10] described the first synthesis to obtain cyclic tautomers of tryptophan achieved through the reaction of N_b-methoxycarbonyl-DL-tryptophan methyl ester with phosphoric acid at room temperature. This reaction has been the key step to the preparation of the several natural products.[11]

In this Letter, we described a novel rearrangement carried out in (2*R*,3a*R*,8a*S*)-2-phenylselenyl-8-(toluene-4-sulfonyl)-3,3a,8,8a-hexahydro-2H-pyrrolo[2,3-*b*]indole-1-carboxylic acid methyl ester **5**[12] using a base as a promoter to provide an aminophenylpyrrole (APP) derivative **6**[15] as shown in Scheme 1.

The compound **5** was prepared from the commercially available L-tryptophan **2** through a series of transformations.[12–14] When the compound **5** is exposed to Brönsted and Lewis acids, the product isolated of this reaction is ring-opened racemic selenide.[12] However, when this compound was treated with a KOH solution in water/methanol at reflux temperature for 2 h, unexpectedly pyrrolnitrin derivative **6** was achieved in 68% yield as a white solid compound (mp 128 °C), as shown in Scheme 1.

The rearrangement was explored using different bases and different reaction conditions to furnish the aminophenylpyrrole derivative **6** (Scheme 2 and Table 1). The KOH was the best base to carry out this transformation (entry 5). In contrast, when LiOH was used as base the compound **6** was undetected (entries 3 and 4). Furthermore, the reflux temperature was necessary for the formation of **6**. The structure for the compound **6**[15] was confirmed by

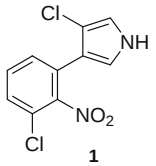

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Figure 1. Pyrrolnitrin (PRN) **1**.

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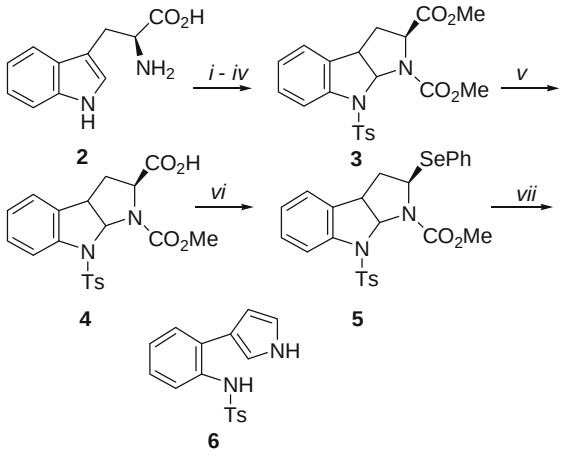
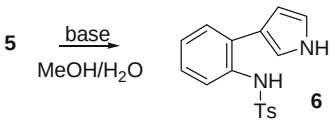


Scheme 1. Reagents and conditions: (i) $SOCl_2$, MeOH; (ii) MeOCOCl; (iii) H_3PO_3 85%; (iv) TsCl, Py; (v) KOH 1 N MeOH/H_2O; (vi) 1-oxa-2-oxo-3-thioindolizinium chloride, Et_3N, PhSeSePh; (vii) KOH, MeOH/H_2O.

X-ray analysis (Fig. 2).[16] Interestingly, the conformation stabilized for **6** in the solid state compares well with that of PRN. A rather low resolution X-ray study was published for PRN,[17] which shows that the dihedral angle between the pyrrole and the benzene ring is 52°, very close to that observed in **6**: 47.7°. Also, in both cases, molecules are associated in the crystal structure as dimers through weak intermolecular hydrogen bonds. In the case of **6**, centrosymmetric dimers are formed by N–H···O bonds involving the pyrrole NH functionality and one O atom of the SO_2 group.

The obtaining of **6** can be explained by the instability of the carbamate ion I generated by the hydrolysis which stabilizes producing CO_2, forming a double bond N–C (pyrrole) and breaking the bond N–C (indole), which lead to the B ring opening. A proton is removed from the **II** to form the compound **III**. Finally, an elimination reaction is carried out to yield **6**, as shown in Scheme 3.

In conclusion, we have found a new rearrangement that was carried out in (2*R*,3a*R*,8a*S*)-2-phenylselenyl-8-(toluene-4-sulfonyl)-3,3a,8,8a-hexahydro-2H-pyrrolo[2,3-*b*]indole-1-carboxylic acid methyl ester **5** promoted by a base to provide the aminophenylpyrrole (APP) derivative **6**, that is, an intermediate of the biosynthesis of pyrrolnitrin (PRN) **1**. Current efforts are being directed toward the total synthesis of pyrrolnitrin (PRN).



Scheme 2. Rearrangement of **5** to formation aminophenylpyrrole (APP) derivative.

Table 1
Synthesis of the (APP) derivative **6** using different bases

Entry	*T* (°C)	Base MeOH/H_2O	*t* (h)	Yield[b] (%)	Compound
1	Reflux	NaOH	2	25	**6**
2	Room	NaOH	48	—	—
3	Reflux	LiOH	48	—	—
4	Room	LiOH	48	—	—
5	Reflux	KOH	1.5	68	**6**
6	Room	KOH	48	—	—
7	Room/U.S.[a]	KOH	1	37	**6**

[a] U.S. ultrasonic.
[b] Purified yield.

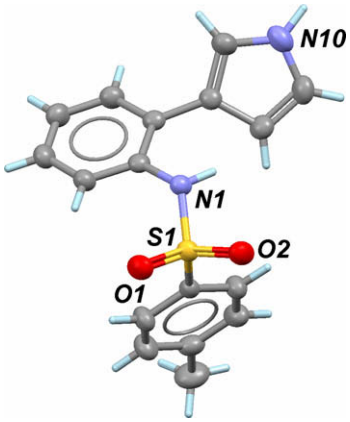
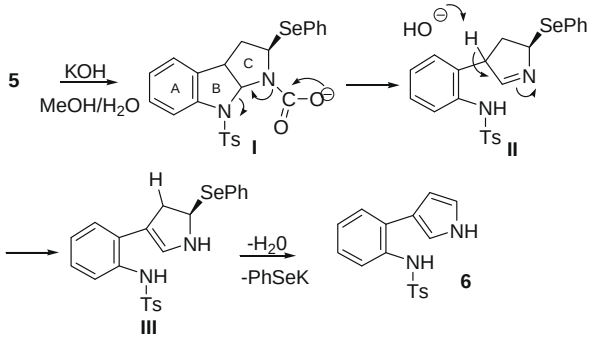


Figure 2. Molecular structure of **6** confirmed by X-ray analysis.



Scheme 3. Possible course of the reaction from **5** to **6**.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.034.

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15. Preparation of **6**. Compound **5** (0.1 g 0.1894 mmol) was dissolved in a 2 N KOH solution in H_2O/MeOH, 7:3, and refluxed for about 120 min. The reaction was followed by TLC until the starting material disappeared. The workup was done with 20 mL of 10% HCl solution, extraction with 20 mL of DCM (three times), drying with Na_2SO_4, concentration was done under reduced pressure, and purification was done by chromatography with a mixture of DCM:hexane, 2:1, to achieve **6** with a yield of 68% (32 mg, 0.1290 mmol) like a white solid with a mp of 128 °C. ^{1}H NMR δ: 2.37 (3H, s), 5.99 (1H, d J = 1.5 Hz), 6.58 (1H, d, J = 1.8 Hz), 6.48 (1H, d, J = 2.1 Hz), 7.03–7.28 (5H, m), 7.61 (3H, d, J = 7.2 Hz) 8.46. ^{13}C NMR δ: 21.5, 109.3, 113.4, 119.8, 120.1, 122.2, 123.5, 123.7, 124.5, 125.1, 127, 128.2, 142.3; FAB+MS 313, 154 (base peak) HRMS calcd for $C_{17}H_{16}N_2O_2S$ [M^+] 313.0999, found 313.1011.
16. Colorless crystals, $P2_1/c$, a = 8.8157(12), b = 12.172(3), c = 14.7456(16) Å, β = 101.886(7)°. Data (4858 reflections) collected with the Mo-$K\alpha$ radiation at 298 K (Bruker P4 diffractometer) and corrected for absorption effects. The structure was refined without restraints; data to parameters ratio: 2740/206; Final R_1 residual for 2111 $F_o > 4\sigma(F_o)$: 0.040. Further details may be found in the archived CIF, deposition number: CCDC 707014.
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