Pergamon

Tetrahedron Letters 39 (1998) 5963–5964

TETRAHEDRON LETTERS

# First Total Synthesis of Fungerin an Antifungal Alkaloid From *Fusarium* sp.

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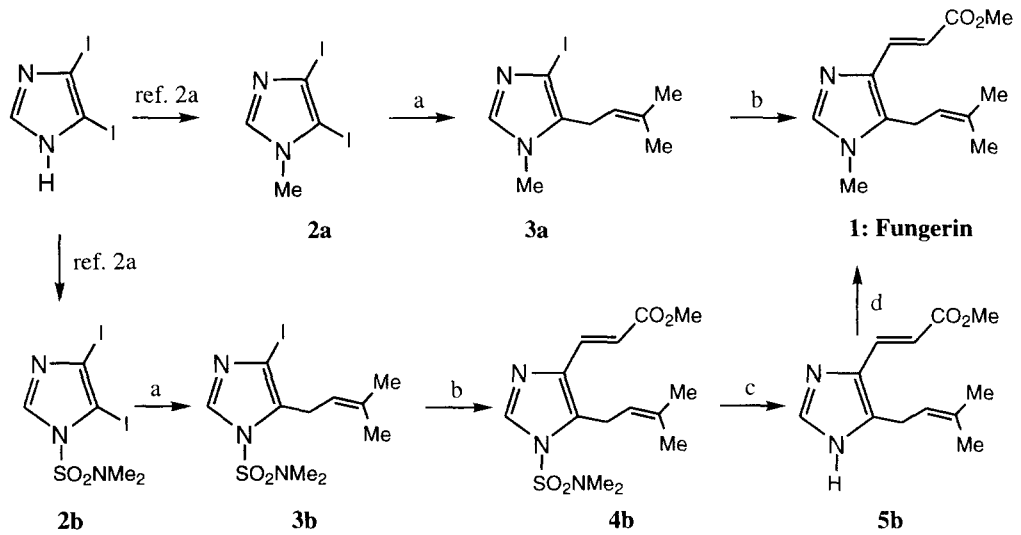
Received 13 May 1998; accepted 8 June 1998

*Abstract* : The first total synthesis of fungerin **1**, a new antifungal alkaloid, is described. Starting from a 4,5-diiodoimidazole derivative, the procedure involves regioselective prenylation and Heck type reaction steps to give **1** in high yield. 

Fungerin **1**, a metabolite of a *Fusarium* sp. fungus, has been recently isolated from a stalk of *Miscanthus sacchariflorus*. The new compound attracted a lot of attention because of its significant antifungal activity against *Penicillium chrysogenum*, *Colletorichum langenarium*, *Alternalia mali* and *Pyriccularia oryzae* (MIC values in the 12.5 to 50 µg/ml range)[1]. On the basis of its analytical and spectral data fungerin was given structure **1**[1] which makes the compound a prenylated derivative of urocanic methyl ester.




***Reagents and conditions***: a. i) EtMgBr, THF, -20°C, 30 min. ii) CuCN, 2LiCl (1eq.), 15 min at -20°C then prenylbromide: -20 to 0°C, 2h, (42% for **3a**, 87% for **3b**); b. $Pd(OAc)_2$ (0.05 eq), $Et_3N$, $PPh_3$ (0.1 eq), Methyl acrylate (4 eq), DMF, 80°C, 16h, (52% for **1**, 96% for **4b**); c. 80% aq. AcOH, 80°C, 1h, (96%); d. NaH, MeI, THF, rt, 15 min, (95%).

Herein, starting from an $N^1$-substituted imidazole[2] derivative, we report the first total synthesis of **1** by application of a synthetic scheme featuring the precise control of two important steps. Indeed, in the designed procedure a regioselective prenylation was followed by a Heck type reaction to introduce the prenyl and the trans-acrylic side chains in vicinal positions on the imidazole nucleus. For this purpose, the known 4,5-diiodoimidazole[2a], readily available from imidazole, was chosen as starting material. In a first attempt, its corresponding *N*-methyl derivative **2a**, obtained using standard methylation conditions, was prenylated by

0040-4039/98/$ - see front matter 
*PII:* S0040-4039(98)01203-9

application of a metallation[3]-transmetallation[4] process employing EtMgBr/CuCN, 2LiCN[4]. Unfortunately, this procedure gave **3a** in a moderate 42 % yield together with 4-iodo-$N^1$-methylimidazole (40%). However, treatment of iodoimidazole **3a** under classical Heck conditions[5] gave the desired fungerin **1**[6] in 75% yield (white needles: mp 92-93°C, lit.[1] 93-96°C) whose spectral data were found identical to those reported[1].

In order to improve the prenylation step, an imidazole having an ortho-directing group at the $N^1$-position was chosen instead of **2a**[7]. Thus, when using the $N^1$-dimethylsulfamoyl derivative **2b** we were pleased to observe that prenylation occurred in high yield to provide **3b**. Cross-coupling to give **4b**, followed by cleavage of the protecting group with 80% aqueous AcOH gave precursor **5b**. Regioselective methylation of **5b** afforded fungerin **1** in quantitative yield[8]. Interestingly, the last three steps can be achieved in one pot without purification of the intermediates[9].

In summary, we have accomplished the first total synthesis of the antifungal alkaloid fungerin **1** in high yield. The proposed synthesis can be easily scaled up to allow a convenient access to a variety of substituted analogues of fungerin **1** for structure-activity relationship studies. In this regard, of particular interest would be to examine the role of the substituent at the $N^1$-position. It is also noteworthy that *N*-methylurocanic acid units are found in a number of recently isolated naturally occurring biologically promising compounds[10].

## References and Notes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6 **1** Fungerin: mp (ether) 92-93°C (lit.[1] 93-95°C). $^1$H NMR ($CDCl_3$) 1.73 and 1.76 (2s, 6H, 2Me), 3.41 (d, 2H, *J*= 7.5Hz, $CH_2$), 3.54 (s, 3H, NMe), 3.77 (s, 3H, OMe), 5.03 (m, 1H, prenyl), 6.54 (d, 1H, *J*= 15 Hz), 7.39 (s, 1H, H-2), 7.62 (d, *J*= 15 Hz). $^{13}$C NMR 17.96, 22.37, 25.54, 31.61, 51.33, 114.14, 119.32, 134.30, 135.33, 138.48, 168.48. MS (IC) *m/z* 277 ($MH^+$). Calc. for $C_{13}H_{18}N_2O_2$ C 39.17, H 4.73, N 9.76; found: C 39.05, H 4.86, N 9.93.

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9 **3a**: mp (ether) 59-61°C. $^1$H NMR ($CDCl_3$) 1.71 and 1.75 (2s, 6H, 2Me), 3.39 ( d, 2H, *J* = 7.5Hz, $CH_2$), 3.56 (s, 3H, NMe), 5.04 (m, 1H, prenyl), 7.34 (s, 1H, H-2). $^{13}$C NMR 18.02, 24.00, 25.49, 32.30, 82.78, 119.25, 133.36, 133.69, 138.81. MS (IE) *m/z* 276 ($M^+$). Calc. for $C_9H_{14}IN_2$: C 39.17, H 4.73, N 9.76; found: C 39.15, H 4.75, N 10.15. **3b**: mp (ether) 66-68°C. $^1$H NMR ($CDCl_3$) 1.72 and 1.78 (2s, 6H, 2Me), 2.89 and 2.90 (2s, 6H, $SO_2N(Me)_2$), 3.51 (d, 2H, *J*= 7.5Hz, $CH_2$), 5.05 (m, 1H, prenyl), 7.85 (s, 1H, H-2). $^{13}$C NMR 18.39, 24.67, 25.55, 37.99, 60.31, 119.59, 133.03, 133.81, 138.00. MS (IE) *m/z* 369 ($M^+$). Calc. for $C_{10}H_{16}IN_3O_2S$ : C 31.92, H 4.36, N 11.49; found: C 32.13, H 4.37, N 11.38. **4b**: mp (ether) 125-127°C. $^1$H NMR ($CDCl_3$,) 1.71 and 1.76 (2s, 6H, 2Me), 2.90 (s, 6H, $SO_2N(Me)_2$), 3.62 (d, 2H, *J*= 6.3 Hz, $CH_2$), 3.78 (s, 3H, OMe), 5.05 (m, 1H, prenyl), 6.63 (1H, d, *J*= 15.4 Hz), 7.55 (d, 1H, *J*= 15.4Hz), 7.87 (s, 1H, H-2). $^{13}$C NMR 18.04, 22.78, 25.50, 37.97, 51.57, 117.82, 120.08, 132.71, 133.88, 134.16, 138.27, 167.67. MS (IC): *m/z* 328 ($MH^+$). Calc. for $C_{14}H_{21}N_3O_4S$: C 51.31, H 6.64, N 13.05; found: C 51.36, H 6.47, N 12.83. **5b**: mp (ether) 91-92°C. $^1$H NMR ($CDCl_3$) 1.67 (s, 6H, 2Me), 3.42 (d, 2H, *J*= 7.1Hz, $CH_2$), 3.76 (s, 3H, OMe), 5.22 (m, 1H, prenyl), 6.37(d, 1H, *J*=15.9 Hz), 7.58 (d, 1H, *J*=15.9 Hz), 7.67 (s, 1H, H-2). $^{13}$C NMR 17.74, 24.29, 25.5, 51.5, 113.8, 119.8, 132.8, 133.7, 134.4, 136.3, 137.9, 168.3. MS (IC) *m/z* 221 ($MH^+$). Calc. for $C_{12}H_{16}N_2O_2$, $0.5H_2O$: C 62.86, H 7.47, N 12.22; found: C 63.02, H 7.74, N 12.09.

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