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Synthesis of visoltricin and fungerin: imidazole derivatives of *Fusarium* sp.

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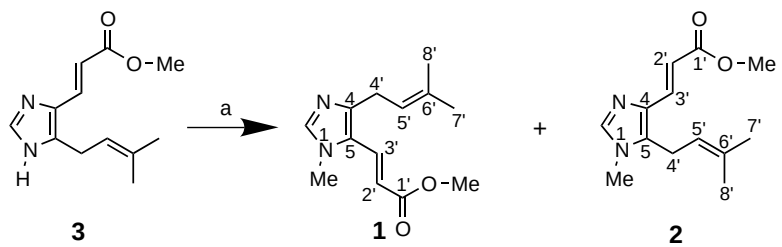
Abstract—The synthesis of two imidazole derivatives of *Fusarium* sp. is described. 3-[1-Methyl-4-(3-methyl-2-butenyl)-1*H*-imidazol-5-yl]-2(*E*)-propenoic acid methylester was synthesized for the first time and spectroscopic data showed differences to the reported data. Naturally occurring visoltricin proved to be identical to fungerin and the structure of visoltricin is revised. © 2002 Elsevier Science Ltd. All rights reserved.

Visoltricin is reported to be an active metabolite produced by *Fusarium tricinctum*.[1] It is toxic in *Artemia salina* test, cytotoxic against human tumor cell lines and shows a miotic effect on rabbit eyes caused in parts by the anticholinesterase activity of visoltricin.[2] Its structure was elucidated by spectroscopic means and was suggested to be 3-[1-methyl-4-(3-methyl-2-butenyl)-1*H*-imidazol-5-yl]-2(*E*)-propenoic acid methylester,[3] according to structure **1**.

Independently fungerin **2** was isolated from a strain of *Fusarium* sp. with good antifungal activity against *Penicillium chrysogenum*, *Colletotrichum langenarium*, *Alternaria mali* and *Pyricularia oryzae*. Fungerin was established as 3-[1-methyl-5-(3-methyl-2-butenyl)-1*H*-imidazol-4-yl]-2(*E*)-propenoic acid methylester.[4]

Synthesis of **1** and **2** was performed using a modified procedure by Benhida et al. who recently presented the first synthesis of fungerin.[5] In the protocol of Benhida et al. the final *N*-methylating step with NaH/MeJ in THF yielded **2** in 96%, without producing the isomer **1**. This result needed further investigation. A first attempt in THF produced the expected mixture of **2** and **1** in a mass ratio of 10:1, after separation on reversed phase HPLC.[6] Using acetonitrile as solvent the mass ratio could be shifted in favour of **1** to 4:1 (Scheme 1),[7] albeit the yield was only moderate.

To confirm the correct position of the two side chains in **1**, ^{1}H–^{15}N HMBC technique[8] was used (Fig. 1). The *N*-methyl (N-1) δ_N 159.1 was correlated with the H-2 of the imidazole ring at δ_H 7.40, the *N*-methyl protons at δ_H 3.66 and showed long-range correlation with H-3′ at δ_H 7.58. The second N of the imidazole ring (N-3) at δ_N 260.3 correlated with H-2 and H-4′ at δ_H 3.38. The chemical shifts in fungerin for N-1 and N-3 are reported to be δ_N 142.3 and 228.8 referred to $^{15}NH_4NO_3$ in DMSO-d_6.



3 **1** **2**

Scheme 1. *Reagents and conditions*: (a) NaH, MeI, MeCN, rt, 15 min (46% **2**, 12% **1**).

Keywords: antifungals; natural products; imidazole; visoltricin; fungerin.

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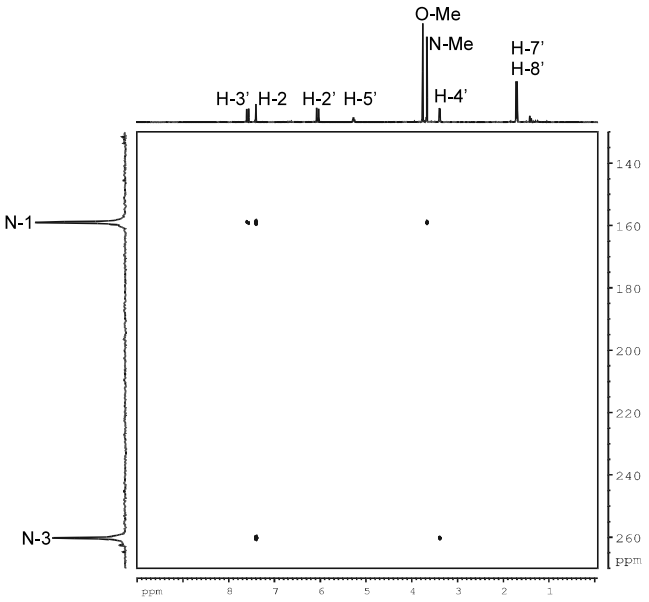

Figure 1. ^{1}H–^{15}N HMBC spectrum of **1**.

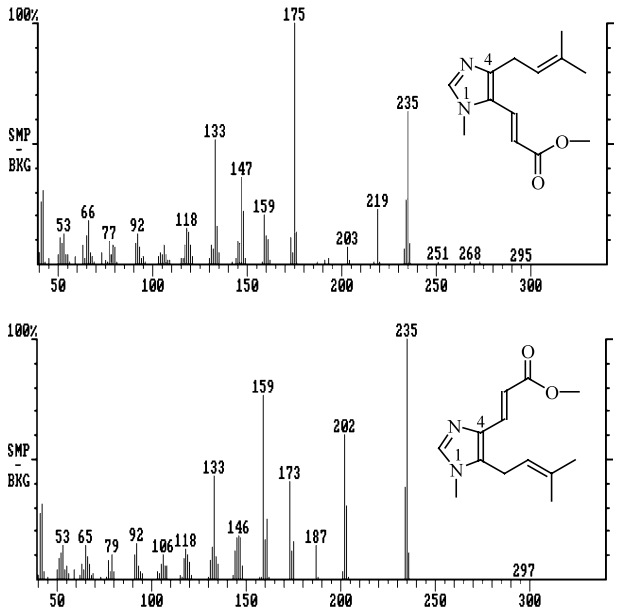

Figure 2. MS (EI, 70 eV) of **1** (top) and **2** (bottom).

Large differences in the chemical shifts were also observed in the ^{13}C NMR for the annular tautomeric C-atoms of the imidazole ring, which were reported to be δ_C 134.14 (C-4), δ_C 134.18 (C-5) for fungerin[4] and δ_C 134.3 (C-4), δ_C 134.2 (C-5) for visoltricin.[3] The shifts of C-4 and C-5 in **1** appeared at δ_C 147.43 and δ_C 120.63 and were remarkably different from the values in fungerin, which resonance accidentally at nearly the same frequency.

1 and **2** could also be distinguished by GC[9] and by the fragmentation pattern of their MS. **1** showed a base peak at m/z 175 $[M+H-MeOH-CO]^+$ and the $[M+H]^+$ peak had a relative intensity of 65%. Minor characteristic peaks appeared at m/z (rel. intensity) 219 (25) $[M-Me]^+$ and m/z 203(5) $[M+H-MeOH]^+$. In contrast, the base peak in **2** was the molecular peak at m/z 235 $[M+H]^+$ and prominent peaks were m/z 202 (60) $[M-MeOH]^+$, m/z 187 (15) $[M-MeOH-Me]^+$, m/z 173 (40) $[M-MeOH-Me-CH_2]^+$ and m/z 159 (80) $[M-MeOH-Me-CO]^+$ (Fig. 2).

An antifungal metabolite that we have isolated from a strain of *Fusarium* sp. from surface sterilized grain and authentic samples of naturally visoltricin (from Dr. Visconti) and fungerin (from Dr. Koshino) showed the same retention time in GC and identical MS spectra as **2**. This result shows that the naturally produced isomer was in all three cases fungerin and that the structure of visoltricin has to be revised. This means that the reported biological activities of visoltricin are due to fungerin.

Acknowledgements

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5. Benhida, R.; Lezama, R.; Fourrey, J.-L. *Tetrahedron Lett*. **1998**, *39*, 5963–5964.
6. Kromasil C18, 5μ, 250×20 mm, precolumn Kromasil C18, 10μ, 50×20 mm, 60% aq. MeOH, 20 ml/min, retention times: **1** 17.0 min, **2** 12.6 min.
7. **1**: white to pale yellow solid, withstanding crystallization from diethyl ether, mp (residue from *tert*-butylmethylether, stream of N_2) 62–64°C. UV λ_{max}^{MeOH} nm (ε) 309 (19700). ^1H NMR (400 MHz, $CDCl_3$) 1.69 (s, 3H, Me), 1.71 (s, 3H, Me), 3.38 (d, 2H, $J=6.8$ Hz, CH_2), 3.66 (s, 3H, NMe), 3.75 (s, 3H, OMe), 5.26 (t, 1H, $J=6.8$ Hz, CH), 6.05 (d, 1H, $J=16.2$ Hz, CH), 7.40 (s, 1H, CH), 7.58 (d, 1H, $J=16.2$ Hz, CH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.90, 25.59, 27.84, 33.05, 51.55, 114.18, 120.63, 123.66, 130.26, 133.04, 139.84, 147.43, 167.65. HRMS: 234.1364, calcd 234.1368.
8. δ_H, δ_N calculated with 'gross-theta' = 0.101329118 referred to liquid NH_3/25°C = 0 ppm, Wishart, D. S., et al. *J. Biomol. NMR* **1995**, *6*, 135–140.
9. DB-5MS (J&W), 30 m×0.25 mm i.d., 0.25 μm film, He 20 cm/s, 0.6 bar, 60°C for 1 min, then 10°C/min to 310°C (10 min), total injection, split open after 1 min, detection: MS ITD 800 (Finnigan Mat) directly coupled to the GC (Dani), retention times: **1** 1224 s, **2** 1312 s.