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# (+)-Mycotrienins I and II: Relative and Absolute Stereochemistry

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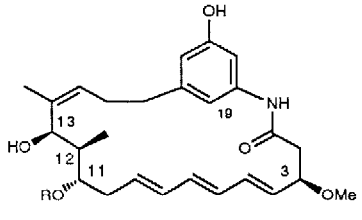
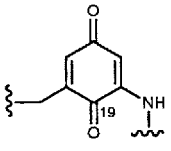
**Summary:** The complete relative and absolute stereochemistry of the potent antifungal antibiotics (+)-mycotrienin I and (+)-mycotrienin II have been established by chemical correlation with the antitumor agent (+)-trienomycin A

Recently, Umezawa and coworkers reported the isolation of several ansamycin antibiotics from the culture broth of *Streptomyces* sp. No. 83-16.[1] Termed the trienomycins, these compounds exhibited strong *in vitro* cytotoxicity against HeLa $S_3$ cells [2] The most active and most abundant congener, (+)-trienomycin A (**1**), had been found earlier as a minor constituent of the *S rishiriensis* T-23 fermentation broth,[3] which furnished as the major components (+)-mycotrienins I and II (**2** and **3**). Independent NMR studies indicated that the mycotrienins and trienomycins were very similarly constituted, differing only in the C(19) oxidation states.[1a] However, the elucidation of these structures had not heretofore been extended to the stereochemical level.[1,2] As a prelude to total synthesis, we recently reported the complete relative and absolute configurations of (+)-trienomycins A, B, and C, as well as (+)-trienomycinol (**4**).[4] Herein we disclose studies which allow extension of the trienomycin stereochemical assignments to (+)-mycotrienins I and II, and hence to (+)-mycotrienols I and II (**5** and **6**).[5] Importantly, this correlation indicates that the dramatic differences in biological activity of the trienomycins (antitumor) and mycotrienins (antifungal) derive from modification of the aromatic nucleus and not changes in relative stereochemistry.

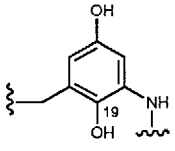
The chemical correlation entailed selective oxidation at C(19) of (+)-trienomycin A. Specifically, (+)-**1** (36 mg, 0.058 mmol) was added in one portion to a solution of Fremy's salt[6] (0.250 g, 0 932 mmol) in 5 mL of acetone and 10 mL of 0 33 M $KH_2PO_4$ at 40 °C After 40 min, TLC analysis revealed the formation of a less polar component which coeluted



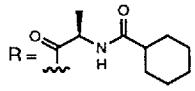

(+)-Trienomycin A (**1**)




(+)-Mycotrienin I (**2**)




(+)-Mycotrienin II (**3**)




**1-3**

R = H
**4-6**

(+)-Trienomycinol (**4**)

(+)-Mycotrienol I (**5**)

(+)-Mycotrienol II (**6**)

with natural (+)-mycotrienin I.[7] Significant amounts of unreacted (+)-**1** and baseline material were also observed The reaction mixture was then diluted with $Et_2O$ (10 mL) and the phases separated. Ether extraction of the aqueous phase (3 X 15 mL) and drying ($Na_2SO_4$), followed by solvent removal *in vacuo* and flash chromatography (2 5% MeOH/$CH_2Cl_2$), provided 2 mg (ca. 3% yield) of (+)-**2** as a yellow powder The product suffered partial decomposition upon exposure to silica (mp 74 °C, lit.[3a] 117 °C). Nonetheless, the identity of synthetic mycotrienin I was unambiguously established by comparison [500-MHz $^1H$ and 125-MHz $^{13}C$ (INEPT) NMR, IR, UV, MS, and optical rotation] with an authentic sample [7] The scarcity of natural (+)-trienomycin A has to date precluded optimization of this oxidation protocol

Following similar oxidation of a second portion of (+)-trienomycin A (21 5 mg), a solution of the crude product in 15 mL of EtOAc was washed with 6 mL of sodium dithionite solution (5% aq), resulting in reduction of the quinone to the corresponding hydroquinone.[3a] Flash chromatography then provided 5 5 mg of (+)-trienomycin A and 2 2 mg [13% yield based on recovered (+)-**1**] of a slightly yellow powder (mp 148-150 °C; lit [3a] 151 °C), identified as mycotrienin II via comparison [500-MHz $^1H$ and 125-MHz $^{13}C$ (INEPT) NMR, IR, UV, MS, and optical rotation] with an authentic sample. These results indicate that the (+)-mycotrienins share the 3*R*, 11*S*, 12*R*, 13*R* stereochemistry of the (+)-trienomycins

In summary, the complete relative and absolute stereochemistry of (+)-mycotrienins I and II and (+)-mycotrienols I and II have been established by chemical correlation with (+)-trienomycin A Studies directed toward the total syntheses of the trienomycins and mycotrienins are currently underway in our laboratories

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5 Mycotrienin II has been converted to mycotrienols I and II a) ref 3c, b) Sugita, M , Hiramoto, S , Ando, C ; Sasaki, T , Furihata, K., Seto, H ; Ōtake, N *J. Antibiotics* **1985**, *38*, 799

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