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Relative Stereochemistry of Fumonisin B_1 at C-2 and C-3

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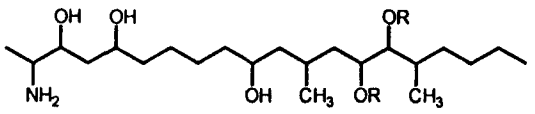
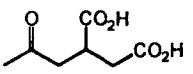
Abstract: Relative stereochemistry of the mycotoxin fumonisin B_1 at C-2 and C-3 has been established as *threo* by NMR studies of synthetic oxazoline derivatives.

Fumonisin B_1 (1) belongs to a class of mycotoxins first reported from cultures of *Fusarium moniliforme* isolated from corn (Zea mays).[1] Various diseases including leucoencephalomalacia in horses and pulmonary edema in swine have been attributed to ingestion of *Fusarium moniliforme* contaminated grains containing fumonisins.[2,3] Neoplastic activity in rat livers and esophogeal cancer in humans have been also reported.[4,5] Although the planar structure of fumonisin B_1 is well known,[1] the relative and absolute stereochemistry of the eight chiral centers of this compound, or of the hydrolysis product (2), have not been elucidated. Fumonisin



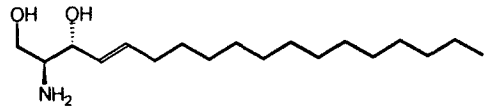


1. R =

2. R = H

B_1 has structural similarities to D-*erythro*-sphingosine (2S, 3R) (3) and the fumonisins have been shown to be inhibitors of sphingosine biosynthesis.[6,7] Thus, stereochemistry of the chiral centers of fumonisin B_1 is important in order to understand structure-activity relationships of fumonisin B_1 and related compounds with regard to inhibition of sphingosine biosynthesis.

To determine stereochemistry at C-2 and C-3, fumonisin B_1 was first subjected to basic hydrolysis conditions (2N KOH; 2.5 hr) in order to remove the two propane, 1,2,3 tricarboxylic acid side chains. The purpose of this hydrolysis was to increase solubility of the compound in more non-polar solvents, and to reduce complications due to side reactions. The hydrolyzed backbone of fumonisin B_1 (**2**) was then transformed into the corresponding oxazoline (**4**) by treating (**2**) in CH_2Cl_2 with a slight excess of methyl benzimidate·HCl at room temperature for 3 days, and **4** was purified by RP-HPLC. Literature indicates that preparation of oxazolines by this method occurs without inversion; i.e., methyl-*erythro*-2-amino-3-hydroxycaproate yields *cis*-2-phenyl-4-carbethoxy-5-propyl-2-oxazoline and ethyl *threo*-2-amino-3-hydroxycaproate yields *trans*-2-phenyl-4-carbethoxy-5-propyl-2-oxazoline.[8,9]



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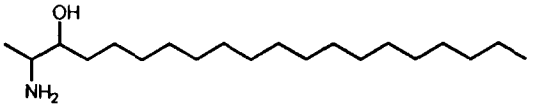


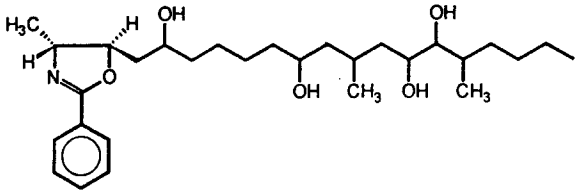
5

Synthetic analogs of fumonisin B_1, such as 2-amino-3-hydroxyeicosane (**5**), have also been prepared in our ongoing research. Preparation of 2-amino-3-hydroxyeicosane was accomplished by oxidation of octadecanol to octadecanal, followed by nitoethylation[10] using sodium methoxide in methanol. This procedure yielded a mixture of 3-hydroxy-2-nitroeicosane diastereomers which was reduced (5% Pd-C and ammonium formate) to provide a 1:1 diastereomeric mixture of 2-amino-3-hydroxyeicosanes (**5**). Separation of diastereomers was facilitated by conversion to the corresponding oxazolines (**6a** and **6b**) in a fashion similar to that described for the preparation of **4**, and resolution of the diastereomers (**6a** and **6b**) was accomplished by RP-HPLC.

Upon analysis of the ^1H NMR data for each isolated diastereomer, and by comparison with model compounds from the literature[11,12] the stereochemistry was deduced as *trans* for oxazoline **6a** and as *cis* for oxazoline **6b**: **6a** [^1H NMR (CD_3OD) H-1, 1.32 (d 6.7), H-2, 3.89 (dq 6.7, 6.7), H-3, 4.27 (ddd 7.2, 5.8); ^{13}C NMR (CD_3OD) 21.7 (C-1), 88.6 (C-2), 67.8 (C-3); and **6b** [^1H NMR (CD_3OD) H-1, 1.21 (d 7.0), H-2, 4.32 (dq 9.0, 7.0), H-3, 4.71 (ddd 9.4, 3.9); ^{13}C NMR (CD_3OD) 15.8 (C-1), 84.8 (C-2), 63.9 (C-3).

Accordingly, the oxazoline of the hydrolyzed backbone of fumonisin B_1 (**4**) was assigned as *trans* by comparison of NMR literature values (*trans* versus *cis*), and from NMR data of synthetic oxazolines **6a** (*trans*) versus **6b** (*cis*): **4** [^1H NMR (CD_3OD) H-1, 1.40 (d 6.7), H-2, 4.05 (dq 6.7, 6.7), H-3, 3.87 (ddd 7.2, 5.8); ^{13}C

NMR (CD_3OD) 20.6 (C-1), 87.5 (C-2), 66.5 (C-3). The upfield shift of H-3 observed in the NMR spectrum of **4** is apparently due to the additional chiral hydroxyl group at C-5.



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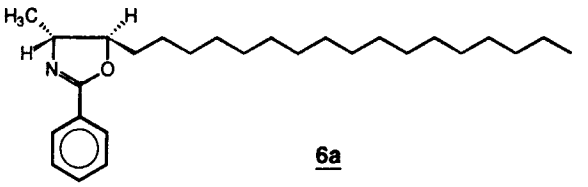
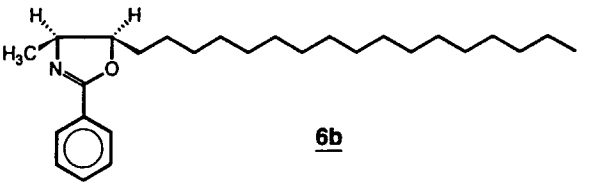


6a



6b

Thus, we conclude that compound **2** is the *threo*-2-amino-3-hydroxy derivative and that the relative stereochemistry at C-2 and C-3 of fumonisin B_1 (**1**) is opposite that of sphingosine (**3**). In a parallel study, ApSimon et al.[13] have deduced the same relative stereochemistry for **1** at C-2 and C-3. To our knowledge this is the first literature report of the use of oxazoline derivatives for the separation of diastereomers and determination of relative stereochemistry of the chiral centers of a natural product containing vicinal hydroxy and amino substituents.

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