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*J. Am. Chem. Soc.*, **2009**, 131 (17), 6066-6067 • DOI: 10.1021/ja9009265 • Publication Date (Web): 08 April 2009

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Total Synthesis of the Sphingolipid Biosynthesis Inhibitor Fumonisin B₁
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Fumonisin B₁ (1, Figure 1) is the primary mycotoxin produced by the fungus Fusarium verticillioides, a common contaminant of corn and corn products. The fumonisin-induced “moldy corn poisoning” syndrome is fatal to horses and pigs and in humans is associated with esophageal cancer and neural tube birth defects. The similarity of some structural elements of fumonisins with sphingoid bases and the biological activity of fumonisins as sphingolipid biosynthesis inhibitors, specifically ceramide-synthesemediated conversion of sphingoid bases to ceramides (N-acyl derivatives), suggests a biosynthetic relationship between the fumonisin and sphingolipid classes of natural products.

Although 1 exhibits nephrotoxicity and promotes liver cancer in rats, hydrolysis of the tricarballylic esters attached to O14 and O15 provides a compound 2 that is less toxic in cell culture. However, this hydrolyzed form is N-acylated by ceramide synthase in vivo and in vitro to provide the N-palmitoyl derivative 3, which is more cytotoxic to HT29 (human colon cancer) cells than fumonisin B₁. Simpler congeners of fumonisins have been synthesized, including the 10-deoxy compound fumonisin B₂, as well as the hydrolyzed form 2, but a synthesis of the most complex fumonisin, 1, has not been previously described. In this communication, we present the first total synthesis of fumonisin B₁ by a convergent approach that links the two functionality-rich sectors at the C9—C10 bond.

Our synthesis of the C1—C9 sector began with stereospecific allylic transfer from the camphor-derived reagent 4 to the alkynyl aldehyde 5, providing the homoallylic alcohol 6 with complete control of the chirality at the C5 alcohol as well as cis alkenic selectivity (Scheme 1). Vanadium-catalyzed hydroxyl-directed epoxidation of 7 to 8 was followed by Mitsunobu inversion to form 9 with the correct C5 stereochemistry. Introduction of the azide was achieved with modest selectivity at C2 using the chelating reagent Ti(O-i-Pr)₂(N₃)₂, giving azidodiol 10 as the major regiosomer. The C1—C9 sector 10 was then completed by revealing the terminal alkylamine and then protecting the two hydroxyls as benzyl ethers.

The key step in the construction of the C10—C20 sector was a stereospecific allylic transfer reaction of our own design that combined the deconjugative aldol product 11 with chiral nonracemic aldehyde 12 in the presence of TMSOTf (Scheme 2). This transformation provided the core structure 13 having the stereochromistry of the C14 alcohol and trans alkenic expected from 2-oxonia Cope rearrangement. After benzylization of the C14 alcohol under neutral conditions, catalytic asymmetric conjugate addition of methylmagnesium bromide afforded the ester 14. In order to selectively deblock the C14,C15-diol at a late stage of the synthesis, the benzyl ethers were replaced by the acetamide in 15. The ester of 15 was converted into the Weinreb amide 16 as well as the primary alcohol 17, which provided spectroscopic correlation with an intermediate in Kishi’s synthesis of fumonisin B₂ (10-deoxy-1).

The 20-carbon chain of fumonisin B₁ was then coupled from the lithium acetylide derived from 10 and the Weinreb amide 16 (Scheme 3). The C10 stereochemistry was set by enantioselective reduction of alkynyl ketone 18, which after benzyl ether formation and acid-catalyzed acetamide removal afforded the C14,C15-diol 19. Esterification of the two hydroxyl groups with tricarballylic acid dibenzyl ester (20) and global hydrogenation of the azide, the alkynyl, and the benzylc ethers and esters afforded 1, whose spectroscopic characteristics matched that of the natural product.

Scheme 1. Synthesis of the C1—C9 Sector

Scheme 2. Preparation of the C10—C20 Core via Allylic Transfer

Figure 1. Fumonisin B₁ (1) and derivatives 2 and 3.
those of a commercial fumonisin B\(_1\) sample. Furthermore, our synthetic material inhibited sphingolipid biosynthesis in a manner similar to that of commercial fumonisin B\(_1\).\(^{28}\)

The absence of tricarballylic esters in hydrolyzed fumonisin B\(_1\) (2) allowed an efficient protective group regime in which the dibenzyl ether 21 (obtained in one step from ester 14) was similarly coupled with terminal alkyne 10 after which enantioselective ketone reduction and global hydrogenation provided 2, which was further characterized as the known hexaaxetol derivative 22.\(^{10}\)

In conclusion, we have accomplished the first total synthesis of fumonisin B\(_1\) (1) by utilizing two variations on stereoselective allylic transfer methodology. Our synthesis of hydrolyzed fumonisin B\(_1\) (2) also provides the starting point for explorations into structure—activity relationships of fumonisin analogues as potential anticancer agents.\(^{29}\)

Acknowledgment. We thank Prof. Alfred H. Merrill, Jr. (Georgia Institute of Technology School of Biology) and Dr. Ronald T. Riley (USDA) for validating the biological activity of our synthetic fumonisin B\(_1\). We also acknowledge the use of shared instrumentation provided by the National Institutes of Health, the National Science Foundation, the Georgia Research Alliance, and the University Research Committee of Emory University.

Supporting Information Available: Experimental procedures and spectroscopic characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) 12 was synthesized in five steps from 2-hepten-1-ol: (a) Ti(O-t-Bu), D-LIPT, t-BuOH (87%); (b) Me,Al (75%); (c) PhCH(O)Me), CSA (74%); (d) Dibal (75%); (e) IBX (83%). See the Supporting Information for details.


(27) 20 was synthesized in three steps from 3-1,3-dioxolan-2-one (for which see: Naitomo, N. J. S.; Mangani, S.; Porrota, E.; Giannotti, D.; Bannicini, R.; Attalmi, M. Tetrahedron Lett. 2000, 41, 1261.). (a) LHMDS, benzyl bromoacetate (86%); (b) DIBAL (80%); (c) NaOCat. HClO(OH) (91%). See the Supporting Information for details.

(28) Our synthetic fumonisin B\(_1\) showed ~50% inhibition of \( ^{14} \text{C} \)-palmitate incorporation into the sphingoid base backbone of ceramide in RAW264.7 cells when added at 0.1 \( \mu \text{M} \), which is near the \( K \) for ceramide synthase: Merrill, A. H. (Georgia Institute of Technology); Riley, R. T. (USDA). Private communication.