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Total Synthesis of the Sphingolipid Biosynthesis Inhibitor Fumonisin B_1

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Fumonisin B_1 (**1**, Figure 1) is the primary mycotoxin produced by the fungus *Fusarium verticillioides*, a common contaminant of corn and corn products.[1,2] The fumonisin-induced "moldy corn poisoning" syndrome is fatal to horses and pigs[3] and in humans is associated with esophageal cancer and neural tube birth defects.[4] The similarity of some structural elements of fumonisins with sphingoid bases and the biological activity of fumonisins as sphingolipid biosynthesis inhibitors, specifically ceramide-synthase-mediated conversion of sphingoid bases to ceramides (*N*-acyl derivatives), suggests a biosynthetic relationship between the fumonisin and sphingolipid classes of natural products.[5] Although **1** exhibits nephrotoxicity and promotes liver cancer in rats,[6] hydrolysis of the tricarballylic esters attached to O14 and O15 provides a compound **2** that is less toxic in cell culture.[7] 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 B_1.[8] Simpler congeners of fumonisins have been synthesized, including the 10-deoxy compound fumonisin B_2[9] as well as the hydrolyzed form **2**,[10] but a synthesis of the most complex fumonisin, **1**, has not been previously described.[11] In this communication, we present the first total synthesis of fumonisin B_1 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**,[12] providing the homoallylic alcohol **6** with complete control of the chirality at the C5 alcohol as well as cis alkene selectivity (Scheme 1).[13] Vanadium-catalyzed hydroxyl-directed epoxidation[14] to **7** was followed by Mitsunobu inversion to form **8** with the correct C5 stereochemistry.[15] Introduction of the azide was achieved with modest selectivity at C2 using the chelating reagent $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$,[16] giving azidodiol **9** as the major regioisomer. The C1−C9 sector **10** was then completed by revealing the terminal alkyne 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[17] that combined the deconjugative aldol product **11** [18] with chiral nonracemic aldehyde **12** [19] in the presence of TMSOTf (Scheme 2). This transformation provided the core structure **13** having the stereochemistry of the C14 alcohol and trans alkene expected from 2-oxonia Cope

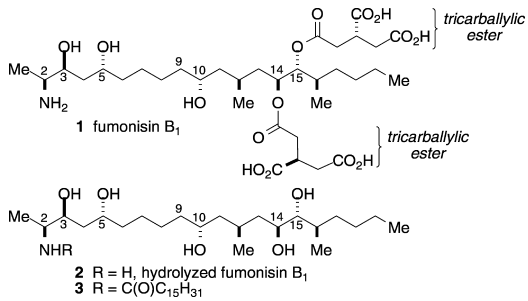
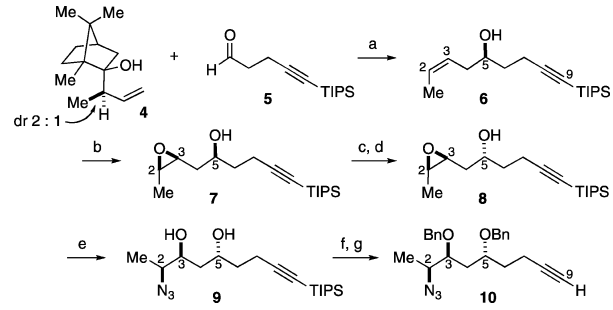


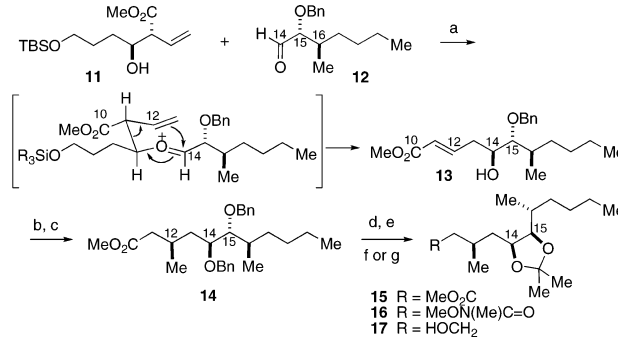
Figure 1. Fumonisin B_1 (**1**) and derivatives **2** and **3**.

Scheme 1. Synthesis of the C1−C9 Sector[a]



[a] Conditions: (a) cat. CSA, CH_2Cl_2 (70% yield, >95:5 er, cis alkene only); (b) cat. $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 0 °C (73% yield, 10:1 dr); (c) Ph_3P, DIAD, HOAc (87% yield); (d) K_2CO_3, MeOH (85% yield); (e) $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$, benzene, 80 °C (47% yield of **9** + 17% yield of the C3−azide regioisomer); (f) Bu_4NF, THF (84% yield); (g) NaH, BnBr, THF/DMF (85% yield).

Scheme 2. Preparation of the C10−C20 Core via Allylic Transfer[a]



[a] Conditions: (a) TMSOTf, CH_2Cl_2 (61% yield, >95:5 dr, trans alkene only); (b) 2-benzyloxy-*N*-methylpyridinium triflate, MgO, $PhCF_3$ (66% yield); (c) MeMgBr, cat. CuI, cat. (*R*)-tol-BINAP, MTBE, −20 °C (69% yield); (d) BCl_3, CH_2Cl_2 (88% yield); (e) $Me_2C(OMe)_2$, cat. TsOH (80% yield); (f) Me(MeO)NH-HCl, *i*-PrMgCl, THF (83% yield); (g) $LiAlH_4$, THF (71% yield).

rearrangement.[20] After benzylation of the C14 alcohol under neutral conditions,[21] catalytic asymmetric conjugate addition of methylmagnesium bromide afforded the ester **14**.[22] In order to selectively deblock the C14,C15-diol at a late stage of the synthesis, the benzyl ethers were replaced by the acetonide in **15**.[23] 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 B_2 (10-deoxy-**1**).[9]

The 20-carbon chain of fumonisin B_1 was then coupled from the lithium acetylide derived from **10** and the Weinreb amide **16** (Scheme 3).[24] The C10 stereochemistry was set by enantioselective reduction[25] of alkynyl ketone **18**, which after benzyl ether formation and acid-catalyzed acetonide removal afforded the C14,C15-diol **19**.[26] Esterification of the two hydroxyl groups with tricarballylic acid dibenzyl ester (**20**)[27] and global hydrogenation of the azide, the alkyne, and the benzylic ethers and esters afforded **1**, whose spectroscopic characteristics matched

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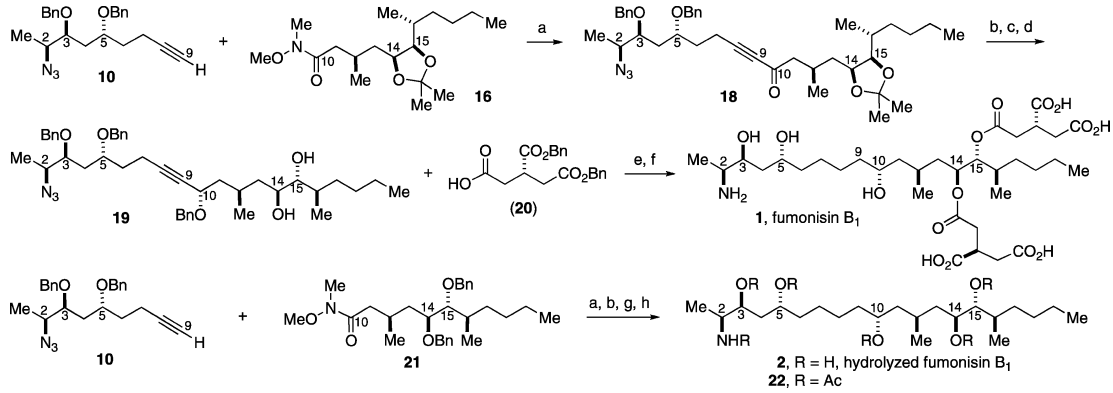
Scheme 3. Syntheses of Fumonisin B_1 (**1**) and Hydrolyzed Fumonisin B_1 (**2**)[a]



[a] Conditions: (a) **10**, *n*-BuLi, THF, then **16** or **21** (65% yield from **16**, 76% yield from **21**); (b) (*R*)-CBS, catecholborane (71−75% yield, 9:1 dr); (c) NaH, BnBr, THF/DMF (86% yield); (d) Amberlite-120 H^+, MeOH (80% yield); (e) **20**, EDCI, DMAP, CH_2Cl_2 (71% yield); (f) H_2, $Pd(OH)_2$/C, *t*-BuOH/THF/HCl (45% yield); (g) H_2, $Pd(OH)_2$/C, MeOH (94% yield); (h) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (56% yield).

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 hexaacetyl 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]

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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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