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Fumonisin: A template for methodology development and drug discovery*

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Abstract: The chemistry and biology of the fumonisin family of natural products has inspired an integrated research program featuring methods development for stereoselective synthesis of homoallylic alcohols, accompanied by applications of these methods to the first synthesis of fumonisin B_1, and to preparing a family of stereoisomeric 2-amino-3,5-diol analogs of 1-deoxysphingolipids, as a possible approach to discovering new drugs for cancer chemotherapy.

Keywords: anticancer agents; drug discovery; natural products synthesis; stereoselective synthesis; stereospecific rearrangement.

INTRODUCTION

The fumonisins are a family of natural products produced by *Fusarium verticillioides*, a fungus that contaminates corn and food sources, including rice, sorghum, wheat bran, and soybean meal, and poultry feed [1]. The World Health Organization has established the tolerable daily intake of total fumonisins at 2 μg/kg body weight per day, and the tolerance value in dry corn products is set at 1 ppm of total fumonisins. More than three dozen fumonisins are known, with the most abundant and most toxic member as fumonisin B_1 (**1**, Fig. 1). The basic structure of fumonisin B_1 has been characterized by South African scientists [2], with stereochemistry subsequently determined by the laboratories of Hoye and Kishi [3]. A structurally related compound, AAL toxin (**7**), is produced by *Alternaria alternata*, a fungal parasite of tomatoes [4]. Diseases associated with fumonisin exposure include esophageal cancer and neural tube birth defects in humans [5], as well as equine leukoencephalomalacia (liquifaction of cerebrum white matter) and porcine pulmonary edema associated with left ventricle heart failure [6]. However, *N*-acyl derivatives (such as fumonisin A_1, **5**) are not cancer initiators, and saponification of the tricarballylic esters to aminopentol-1 (**8**) also reduces toxicity as well as cancer initiation activity [7]. The biological effects of fumonisins are attributed to disruptive effects on sphingolipid metabolism (Fig. 2). Specifically, ceramide synthase enzymes are inhibited, thus lowering the concentration of ceramide, which signals cell cycle arrest, apoptosis, senescence, and differentiation [8]. Notably, fumonisin B_1 is not a substrate for ceramide synthases (Fig. 3), in contrast to aminopentol-1 (**12**), which upon treatment with radiolabeled palmitoyl-CoA does give the *N*-palmitoyl derivative (**13**). In evaluating the in vitro cytotoxic activity of these compounds against HT-29 cells (human colon cancer), *N*-palmitoylaminopentol-1 (**13**) reduces cell number by >90 % at 50 μM concentration.

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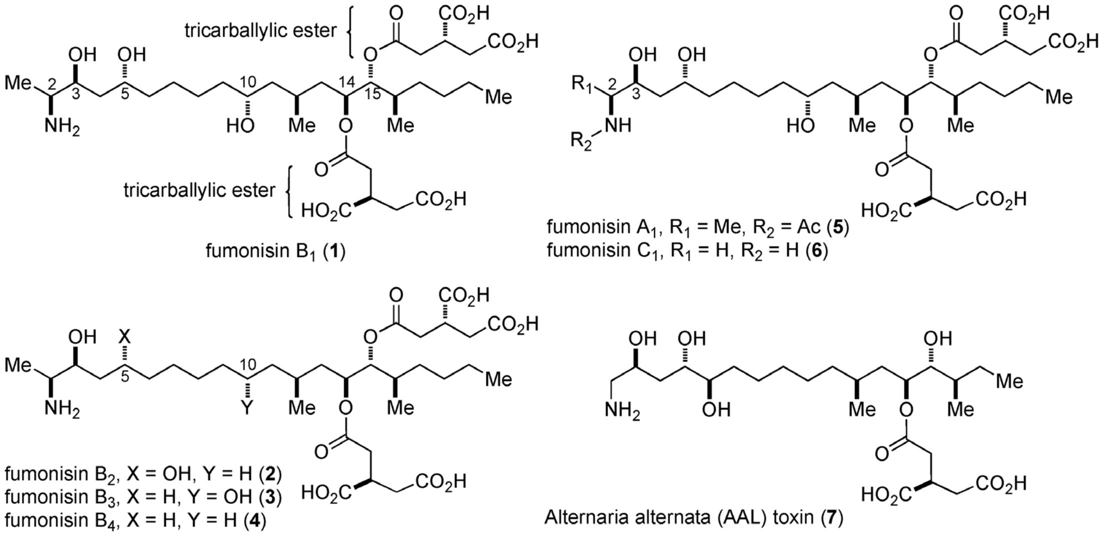


Fig. 1 Structures of fumonisin natural products.

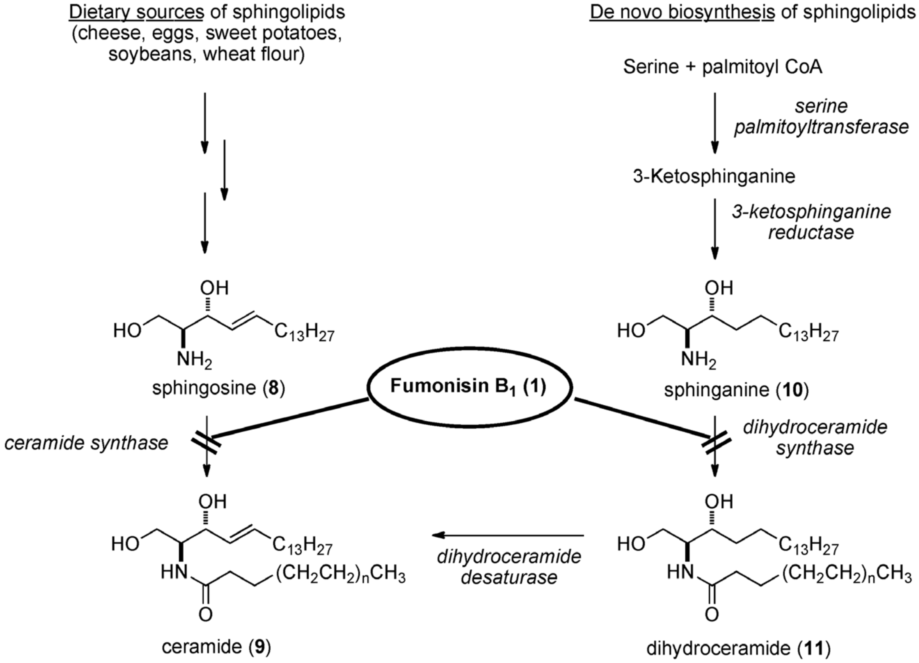


Fig. 2 Fumonisin B_1 disrupts sphingolipid biosynthesis as an inhibitor of ceramide synthases.

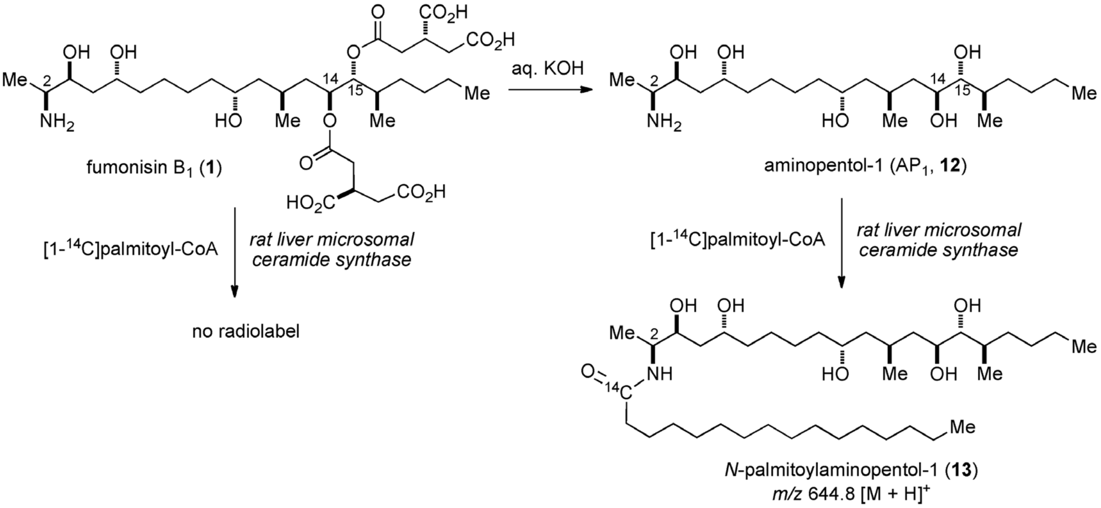


Fig. 3 Aminopentol-1 is a substrate for ceramide synthase, but not fumonisin B_1.

FUMONISIN AS A TEMPLATE FOR METHODOLOGY DEVELOPMENT

With this background in mind, we embarked on a research program directed toward the laboratory syntheses of aminopentol-1 (**12**) and fumonisin B_1 (**1**), as well as simple analogs of aminopentol-1 as 1-deoxysphingolipid analogs [9]. In considering the synthesis of two fragments **14** and **15** to be connected at C9–C10 (Fig. 4), we encountered a common theme of homoallylic alcohols **16** and **17**, requir-

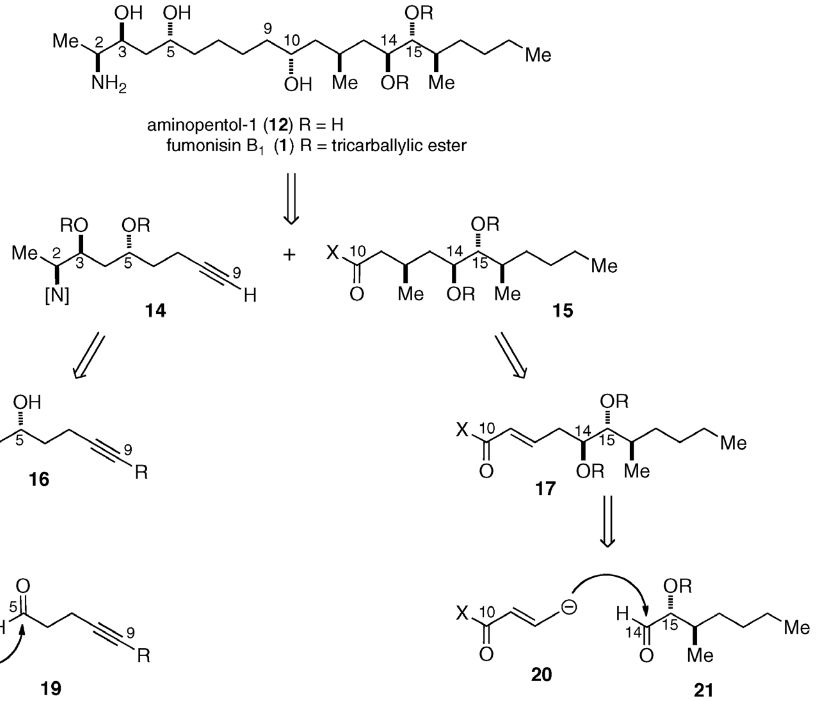


Fig. 4 Retrosynthetic analysis for aminopentol-1 and fumonisin B_1.

ing stereocontrol of the chiral secondary alcohols as well as the 1,2-disubstituted alkenes. We proposed that an efficient synthesis would control both stereochemical elements in a single transformation. To this end, several laboratories previously explored the synthesis of homoallylic alcohols utilizing stereospecific pericyclic rearrangements [10]. Specifically, the oxonia-Cope rearrangement (Fig. 5) offered promising grounds for an allylic transfer process, although the Prins cyclization could be a competing process in the presence of a nucleophile (:Nu). The first precedents for this allylic transfer process were reported by Nokami over a decade ago, in which the kinetic α-aldol product **29** generated by deconjugative aldol reaction underwent Lewis acid-catalyzed rearrangement to the thermodynamically favored γ-aldol regioisomer [11]. Moreover, a transfer process into a saturated aldehyde **30** provided allylic *transfer* to produce benzaldehyde (**35**) as a byproduct along with products **31** and **32** (Scheme 1). This work also established that diastereomerically pure samples of the aldol compounds **29** underwent stereospecific reaction to give either the *cis*-alkene of lactone **31** or the *trans*-alkene of alcohol **32**. However, the product yields for compounds **31** and **32** were diminished by internal rearrangement processes.

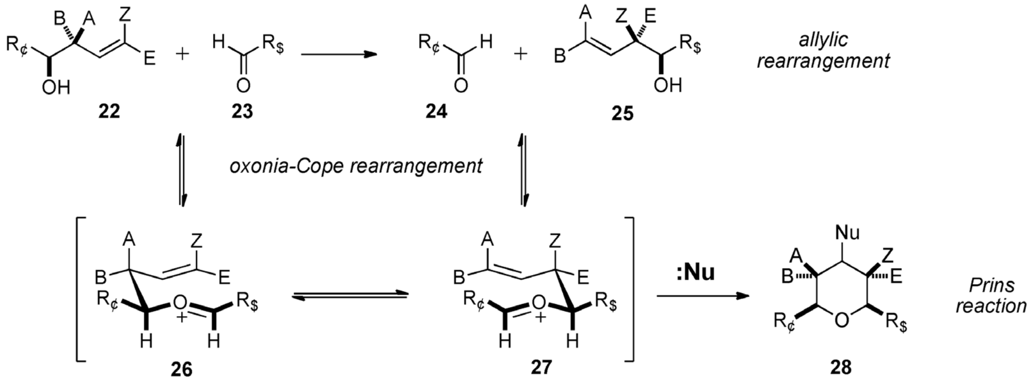
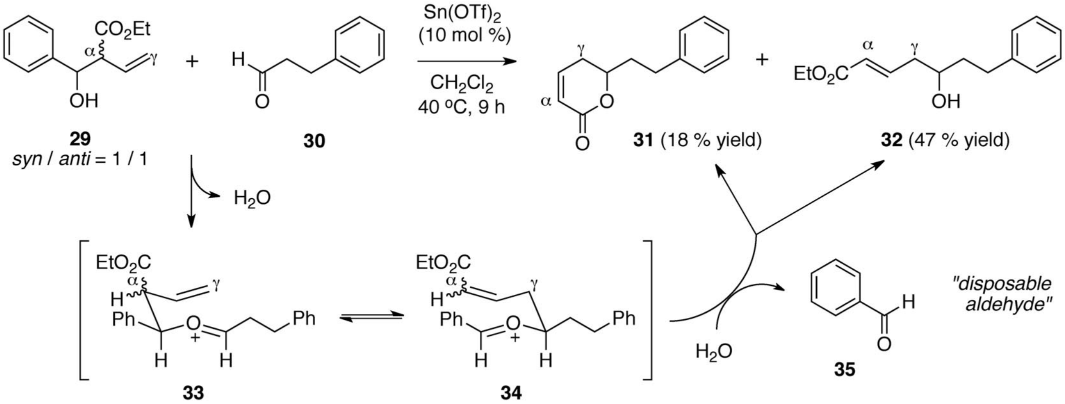
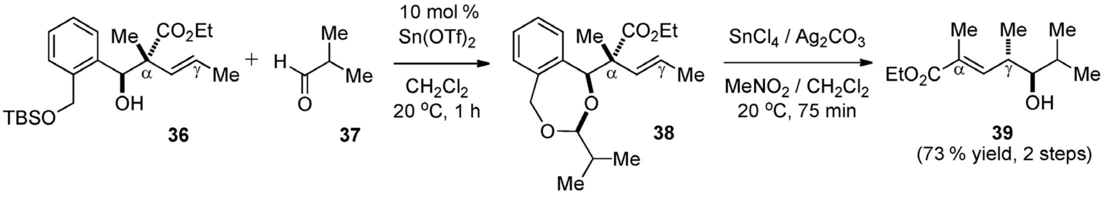


Fig. 5 Oxonia-Cope rearrangement pathways to allylic rearrangements.



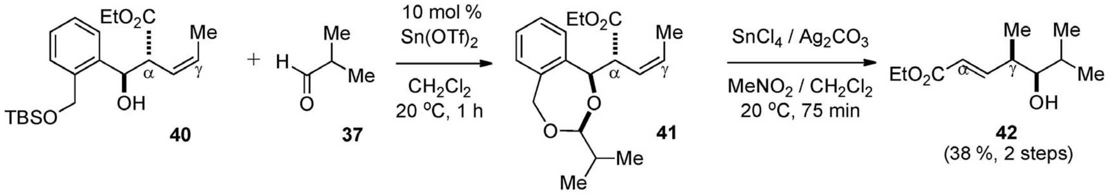
Scheme 1 An early reagent for allylic transfer via oxonia-Cope rearrangement.

We proposed that a tethered oxygen nucleophile might intercept the product side of the oxonia-Cope rearrangement equilibrium, thus driving the reaction exclusively with a new acceptor aldehyde. The idea was successfully realized in the context of synthesizing bispropionate structures, albeit with the surprising formation of a seven-membered ring acetal intermediate **38** upon tin(II) triflate-catalyzed reaction of **36** with 1 equiv of isobutyraldehyde (**37**, Scheme 2) [12]. This acetal was stable to tin(II) triflate, but upon reaction with stronger Lewis acidic conditions, the expected product was generated in good yield and with virtually perfect stereospecific translation of all stereochemical elements. For instance, the *anti*-stereochemistry of compound **36** resulted in the *E*-alkene of product **39**, whereas the *syn*-diastereomer of **36** resulted in clean formation of the *Z*-alkene, isolated as the unsaturated lactone (not shown). Likewise, the *trans*-alkene of compound **36** was expressed as the *anti*-diastereomer of product **39**.



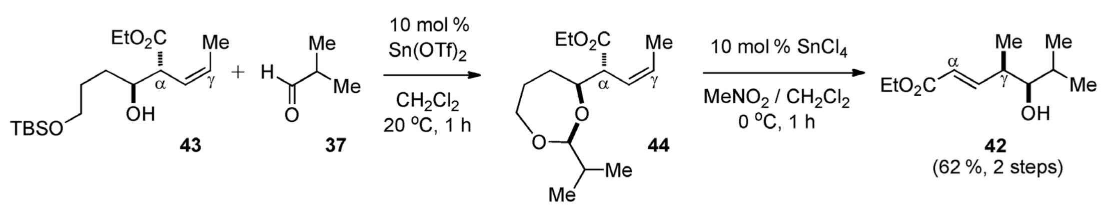
Scheme 2 Our first reagent for allylic transfer via oxonia-Cope rearrangement.

In extending the scope of this transformation, we prepared the *cis*-alkene reagent **40** (Scheme 3) [13]. Although the reaction with isobutyraldehyde proceeded with the expected *syn*-diastereoselectivity in compound **42**, the product yield was relatively low.



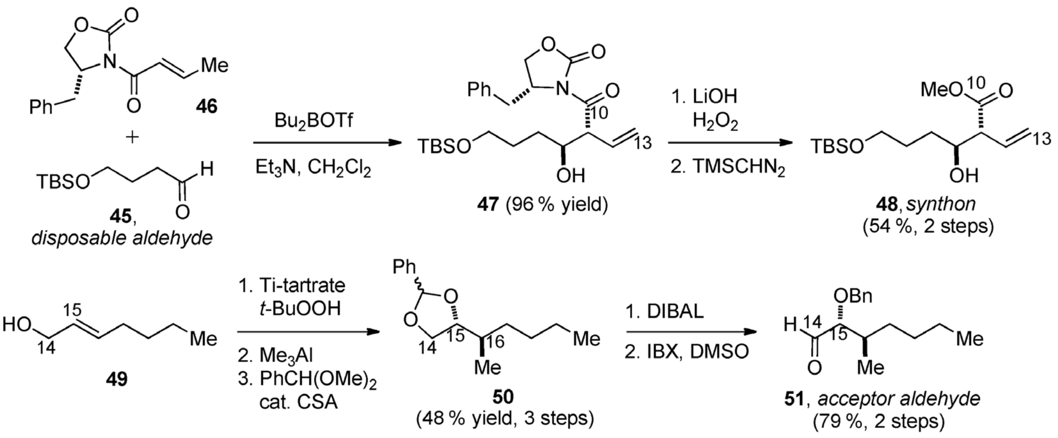
Scheme 3 Allylic transfer from *cis*-alkene **40** provided the *syn*-diastereomer **42**.

We then wondered if a saturated tether to the nucleophilic oxygen would be sufficient for the reaction, as in synthon **43** (Scheme 4). Indeed, the expected transformation occurred, and compound **42** was produced in substantially better yield. From this stage forward, the aldehyde precursor to this tether, 4-silyloxybutanal (**45**), became our preferred "disposable aldehyde".



Scheme 4 Allylic transfer from synthon **43** bearing a saturated tether.

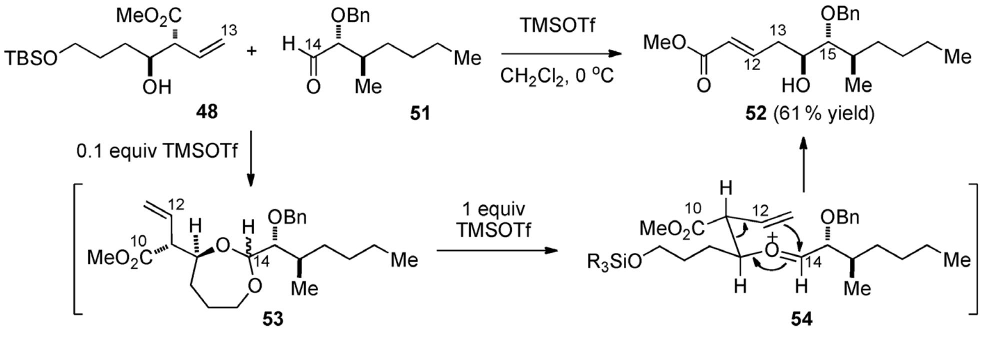
For the C10–C20 sector of fumonisin B_1 corresponding to structure **17** in our retrosynthetic analysis (Fig. 4), we prepared the synthon **48** (Scheme 5) as a single stereoisomer, utilizing deconjugative aldol reaction of the *N*-crotonyloxazolidone **46** [14] with disposable aldehyde **45**, followed by



Scheme 5 Preparation of synthon **48** and acceptor aldehyde **51**.

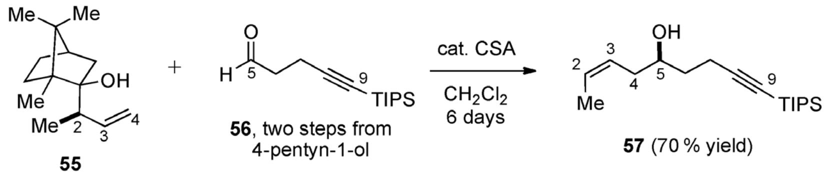
removal of the chiral auxiliary from **47** leading to the methyl ester **48**. The acceptor aldehyde **51** was prepared in straightforward fashion from 2-hepten-1-ol (**49**), with Sharpless–Katsuki titanium-tartrate epoxidation [15] followed by regioselective addition with trimethylaluminum [16], setting the chiral centers at C15 and C16. Regioselective reductive cleavage of the benzylidene acetal **50** revealed the primary alcohol precursor to aldehyde **51**.

The allylic transfer reaction proceeded with equimolar amounts of **48** and **51** under optimized conditions using trimethylsilyl trifluoromethanesulfonate (TMSOTf), providing product **52** with *trans*-alkene selectivity and only one diastereomer (Scheme 6). The seven-membered ring acetal **53** was formed as the initial product with catalytic TMSOTf, but upon reaction with a full equivalent of TMSOTf, the transformation directly provided **52**, consistent with rearrangement of oxonium ion intermediate **54**.



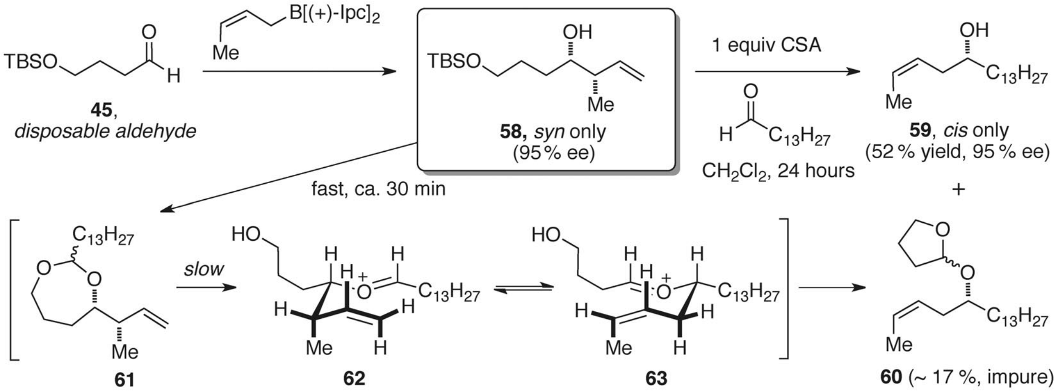
Scheme 6 Application of the γ-vinylogous aldol synthon to prepare compound **52**.

For the C1–C9 sector, we envisioned mechanistically similar methodology for preparing the *cis*-alkenyl alcohol corresponding to compound **16** in our retrosynthetic analysis (Fig. 4). Indeed, a camphor-derived crotyl-transfer reagent **55** developed by Loh [17] provided the desired product **57**, although this transformation required 5–6 days for complete conversion of the aldehyde **56** (Scheme 7).



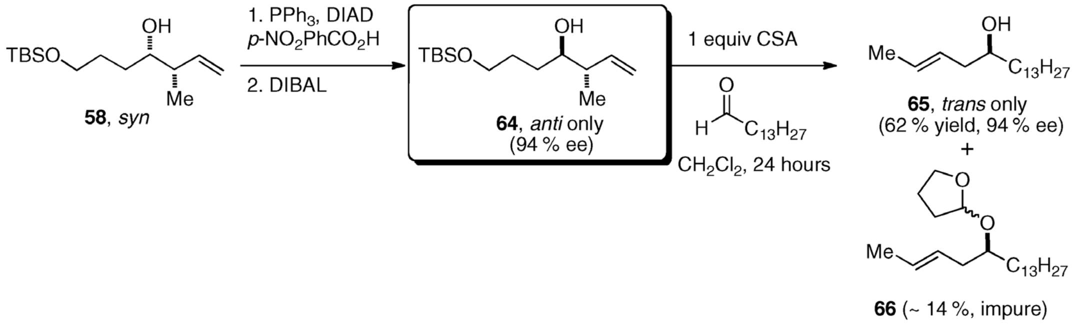
Scheme 7 Synthesis of en-yne-ol **57** via allylic transfer from camphor-derived reagent **55**.

As other allylic transfer methods had proceeded with much faster rates, we sought to determine if a simplified synthon **58** (Scheme 8) would give better results. Thus, enantio- and diastereoselective crotylboration [18] of our disposable aldehyde **45** provided the branched homoallylic alcohol **58** with high stereoselectivity. Upon reaction with camphorsulfonic acid (CSA), once again the seven-membered ring acetal **61** was formed, but with a full equivalent of CSA and stirring for a full day, crotyl transfer occurred to provide product **59** as only the *cis*-alkene, and with enantioselectivity equivalent to the stereochemical purity of synthon **58** [19]. For the first time, we also observed the cyclic tetrahydrofuranyl acetal **60**, albeit as a minor byproduct, but consistent with nucleophilic trapping of the product oxonium ion **63** by the pendant hydroxyl group. Although the best yields of **59** resulted from CSA, the reactions were considerably quicker when conducted with 0.4 equiv of $Sn(OTf)_2$ (1 h at 20 °C, 42 % yield of **59**) or with 1 equiv of TMSOTf (less than 30 min at 0 °C, 40 % yield of **59**).



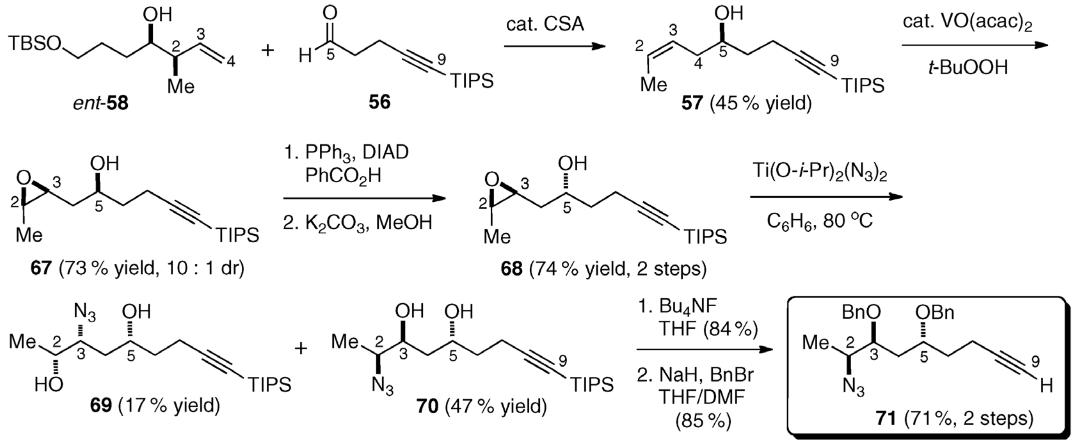
Scheme 8 Tethering an oxygen nucleophile to drive the oxonia-Cope rearrangement to product.

In order to prepare the diastereomeric synthon with the highest stereoselectivity, Mitsunobu reaction [20] of **58** followed by reductive cleavage of the ester afforded synthon **64** exclusively as the *anti*-diastereomer (Scheme 9). The reaction of **64** with tetradecanal proceeded with complete stereoselectivity for the *trans*-homoallylic alcohol **65**, accompanied by the tetrahydrofuranyl acetal byproduct **66**.



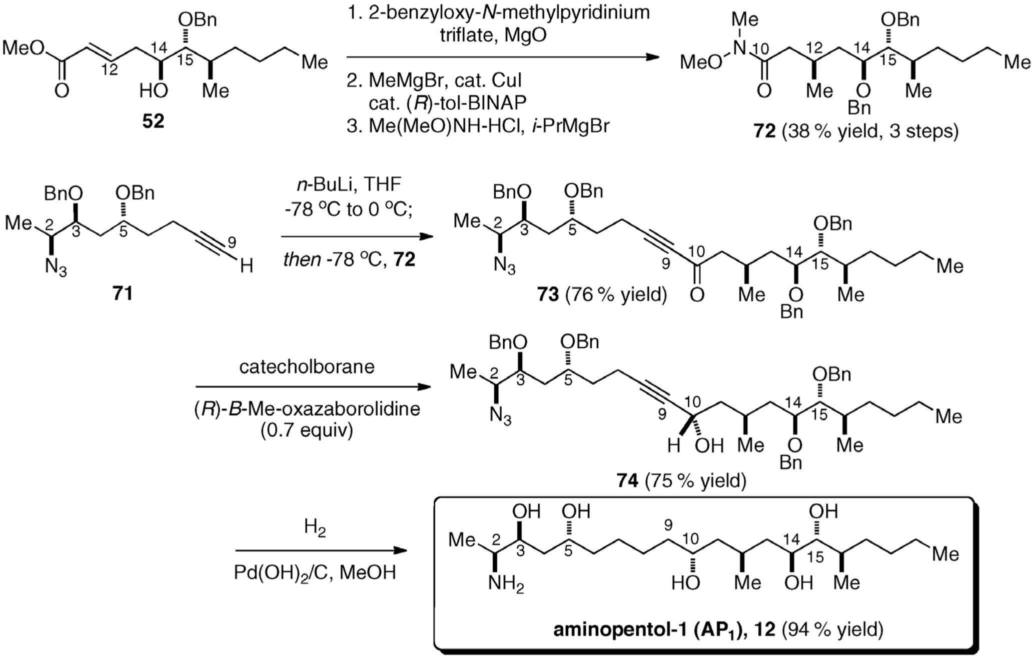
Scheme 9 Preparation and reaction of the synthon **64** for *trans*-homoallylic alcohol.

In our application of synthon *ent*-**58** to the synthesis of the C1–C9 sector of fumonisin, we observed that the silylalkyne somehow inhibited the reaction, so as of this writing, the procedure described in Scheme 7 utilizing the camphor-based reagent has provided better throughput of the enynol **57** (Scheme 10). We deliberately prepared the C5-alcohol with (*S*)-configuration, opposite to that observed in fumonisin aminopentol, as the best method for highly stereoselective epoxidation of the *cis*-alkene of **57** utilized hydroxyl-directed vanadium-catalyzed epoxidation [21], to afford epoxy-alcohol **67**, which was converted into the desired diastereomer **68** by Mitsunobu reaction at C5. Although Sharpless had reported titanium-promoted regioselective additions of azide to glycidols [22], this method had never been reported for epoxides of homoallylic alcohols. In our case with epoxy-alcohol **68**, regioselectivity was modest, favoring **70** in a 2.5:1 mixture of regioisomers. (The paper will later return to this step.) Benzyl ether protection of C3 and C5 diol and desilylation revealed the terminal alkyne of **71**, which would be utilized to cross-couple this C1–C9 section with C10–C20.



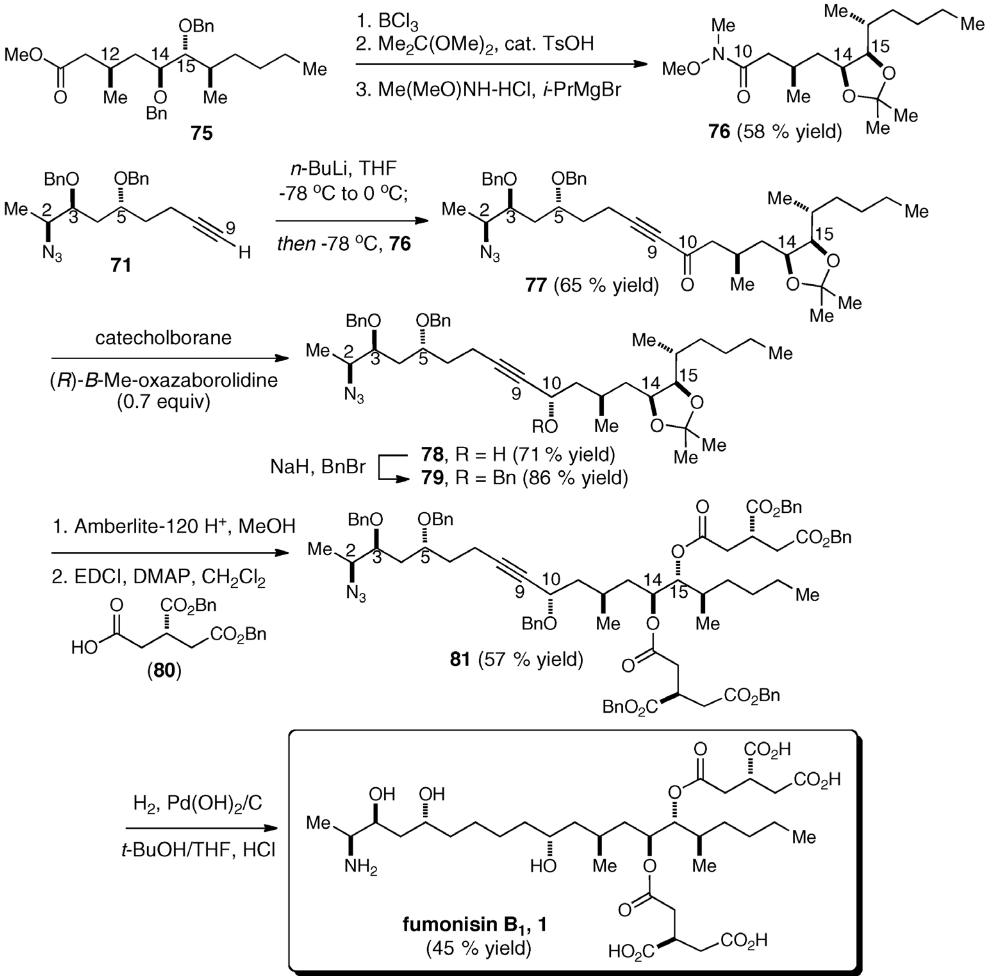
Scheme 10 Synthesis of the C1–C9 sector of fumonisin.

For the synthesis of the aminopentol-1 (Scheme 11), the homoallylic alcohol **52** (from Scheme 6) was protected as the benzyl ether under mild conditions [23], as compound **52** was susceptible to retro-aldol reaction under basic conditions. Enantioselective conjugate addition [24] introduced the methyl at C12, and the ester was converted into the Weinreb amide **72** for C9–C10 bond construction [25]. Deprotonation of the terminal alkyne of C1–C9 sector **71** and addition of the resulting alkynyllithium to compound **72** afforded the yne-one **73**, bearing all of the carbon, nitrogen, and oxygen atoms of



Scheme 11 Synthesis of aminopentol-1.

aminopentol-1. Enantioselective ketone reduction [26] provided the propargylic alcohol **74** as the major component of a 9:1 mixture, and global hydrogenolysis/hydrogenation of the azide, alkyne, and four benzyl ethers provided the aminopentol-1 (**12**), which matched the physical and spectroscopic properties of a sample obtained from the saponification of fumonisin B_1. For the synthesis of fumonisin B_1 (Scheme 12), the protective group pattern at C14 and C15 needed to be orthogonal from the other oxygen protective groups, for late-stage introduction of the tricarballylic esters. Thus, the benzyl ethers of **75** were removed and the diol was reprotected as the acetonide, prior to formation of the Weinreb amide **76**. As described before, addition of the alkynyllithium derived from **71** and enantioselective reduction of the ketone of **77** afforded the propargylic alcohol **78**. Benzyl ether formation at C10 was followed by acetonide hydrolysis to reveal the C14,C15-diol, for acylation with the dibenzyl diester tricarballylic ester synthon **80** [27], to give compound **81**. Global hydrogenation/hydrogenolysis of azide, alkyne, three benzyl ethers, and four benzyl esters completed the first laboratory synthesis of fumonisin B_1 (**1**) [28].



Scheme 12 Total synthesis of fumonisin B_1.

FUMONISIN AS A TEMPLATE FOR DRUG DISCOVERY

Sphingosine (**8**) is a highly bioactive compound with important roles in signal transduction, especially through its co-metabolite sphingosine-1-phosphate (**82**, Fig. 6). Sphingosine exhibits cytotoxic activity against several cancer cell lines, by cell cycle arrest and apoptosis as well as autophagy [29]. However, in vivo phosphorylation of the primary alcohol generates sphingosine-1-phosphate (**82**), which is mitogenic, angiogenic, and inhibitory for apoptosis, thus reversing the antitumor effects of sphingosine [30].

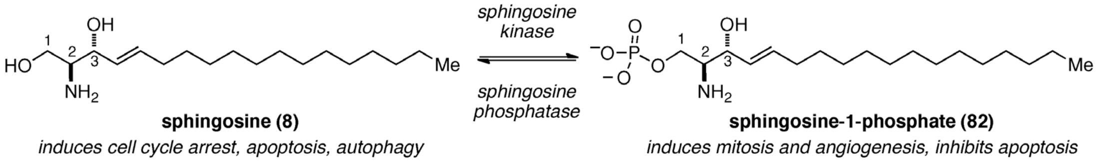
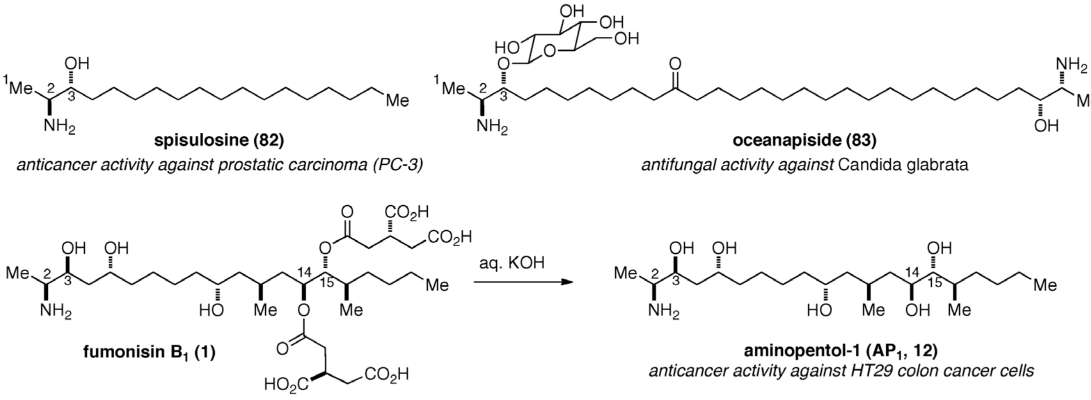


Fig. 6 Phosphorylation of sphingosine.

Given the anticancer and antimicrobial actions of several 1-deoxysphingolipid natural products (**82**, **83**, Fig. 7) [31,32], fumonisins and aminopentol-1 (**12**) were considered as structurally complex 1-deoxysphingolipid analogs. Based on their observations of the anticancer activity of *N*-palmitoyl-aminopentol from the ceramide synthase-catalyzed *N*-acylation of aminopentol-1 (**12**), the Merrill and Liotta laboratories proposed 2-aminooctadecane-3,5-diol (**84**, Fig. 8), projected to have lipophilicity similar to that of sphingosine, as a simplified analog of fumonisins and aminopentol-1 [33].



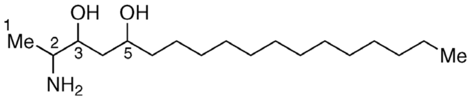
spisulosine (82)
anticancer activity against prostatic carcinoma (PC-3)

oceanapiside (83)
antifungal activity against Candida glabrata

fumonisin B$_1$ (1)

aminopentol-1 (AP$_1$, 12)
anticancer activity against HT29 colon cancer cells

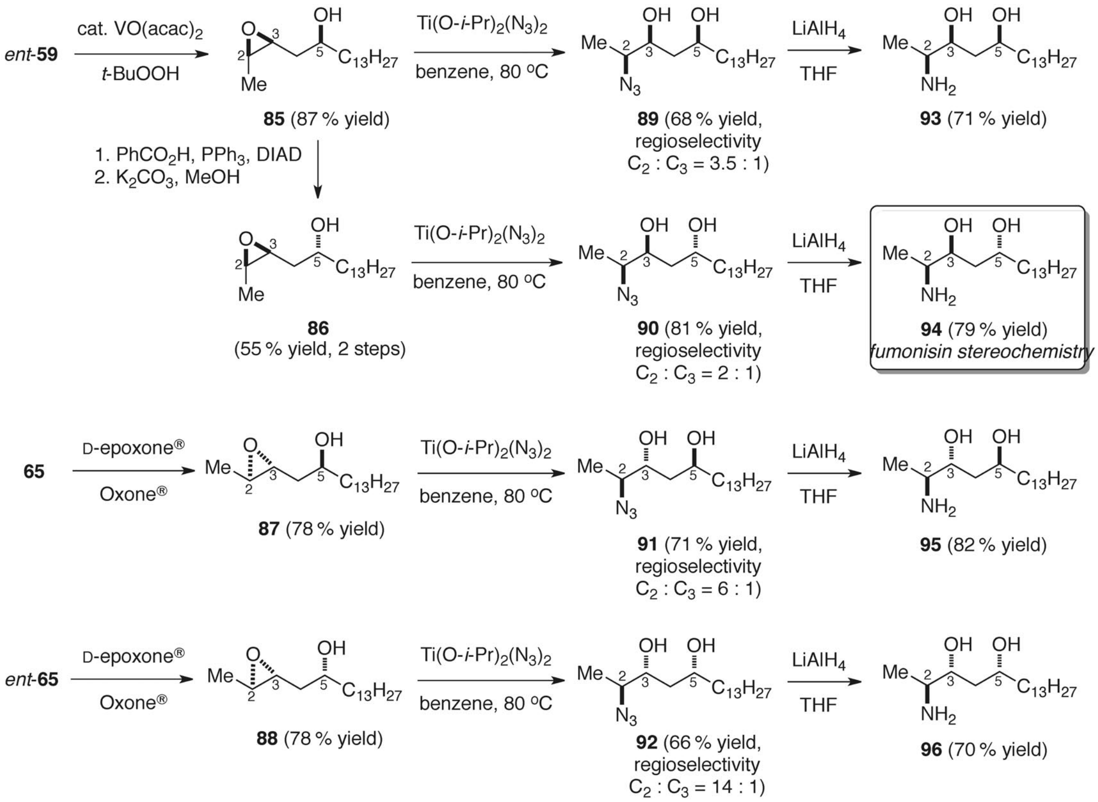
Fig. 7 Representative 1-deoxysphingolipid-like natural products.



"enigmol" series, 84

Fig. 8 Structure of enigmol (**84**) as synthetic 1-deoxy sphingolipid analogs.

Although several syntheses were known for the aminodiol **84** [33,34], which Merrill dubbed "enigmols", we sought to utilize the products arising from our allylic transfer methodology developed in our fumonisin and aminopentol-1 syntheses to prepare a family of diastereomers, to explore the anticancer activity of these compounds. To this end, compound *ent*-**59** underwent hydroxyl-directed epoxidation to epoxyalcohol **85** and Mitsunobu inversion to **86** (Scheme 13), whereas the *trans*-alkene **65** and its enantiomer underwent Shi enantioselective epoxidation [35] to afford **87** and **88**. For the *cis*-epoxides **85** and **86**, titanium-promoted azide additions provided only modest selectivities for the C2-azide regioisomers **89** and **90**. However, azide additions to *trans*-epoxides **87** and **88** were much more highly regioselective, perhaps due to diminished steric interactions at C2 of the *trans*-epoxides. Lithium aluminum hydride reduction of each azide afforded pure samples of each diastereomeric 2-amino-3,5-diol **93–96**.



Scheme 13 Regioselectivity of azide additions, and generation of 2-amino-3,5-diols.

Cytotoxicity of each aminodiol diastereomer was evaluated against DU145 (prostate cancer) and HT29 (colon cancer) cell lines vs. sphingosine **8** as the control (Fig. 9). For both cell lines, the *S,S,S*-isomer **93** showed inhibition at levels superior to sphingosine as well as the other diastereomers, includ-

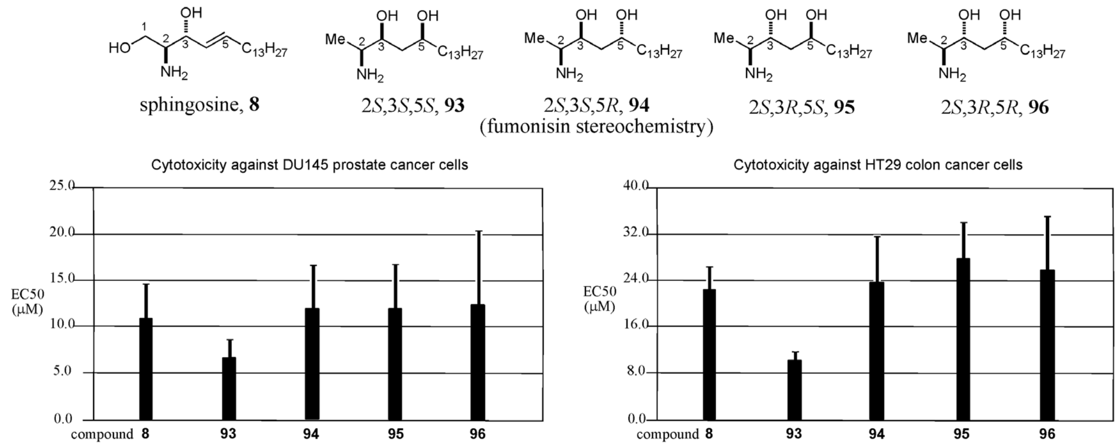


Fig. 9 Cytotoxicity studies against cancer cell lines.

ing the diastereomer **94** corresponding to the stereochemistry of fumonisin. Enigmol **93** was subsequently studied more extensively by our collaborators, including in vivo studies on nude mice with prostate cancer xenografts, which revealed that **93** was orally deliverable, showing significant inhibition of tumor growth, without any signs of toxicity [36].

CONCLUSIONS

This paper has described an integrated program in synthetic methodology, natural products synthesis, and medicinal chemistry. In this work, a new family of synthons has been described for the simultaneous generation of di- and trisubstituted alkenes along with chiral secondary homoallylic alcohols, and applied to the first laboratory synthesis of the most complex and most abundant of the fumonisin natural products. Further studies are directed toward improving the potency and selectivity of these aminodiol analogs, in our efforts to discover new and effective drugs for cancer chemotherapies.

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