Enantioselective Total Synthesis of Fumonisin B_2

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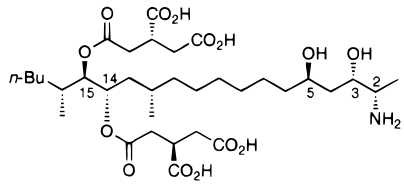
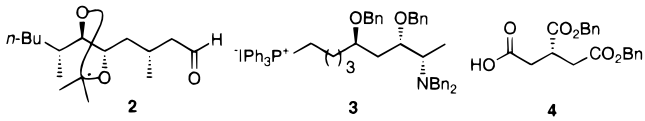
The work on the assignment of the stereochemistry of AAL toxins/fumonisins[1] and maitotoxin[2] from this laboratory has yielded a vast volume of experimental data on the structural properties of fatty acids and related classes of compounds. These data show that the structural properties of a compound in question are inherent to the specific stereochemical arrangements of (small) substituents on its carbon backbone and are independent from the rest of the molecule. We then recognized the possibility that fatty acids and related compounds bearing (small) substituents on their backbones have the capacity of creating unique structural motifs, carrying specific information, and serving as functional materials.[2a]

In this context, we are intrigued with the fumonisin class of natural products. Fumonisin B_2 (FB_2, **1**),[3] a representative member of this class of mycotoxins, is known to exhibit a wide range of biological activities.[4] Structurally, FB_2 possesses two distinct halves, each containing clustered chiral centers on its backbone, which are separated by six methylene units. Thus, according to our hypothesis, FB_2 contains two structural motifs, and each of them could be linked to a specific biological event(s) independent from the other. This class of natural products might therefore present an interesting opportunity to test our hypothesis experimentally. In this communication, we report an enantioselective total synthesis of FB_2 that is flexible and effective for the preparation of the remote diastereomers of FB_2 and other analogs required for the proposed experimental work.

A convergent approach to FB_2 was adopted, with the molecule being divided into three fragments—the left segment **2**, the right segment **3**, and the tricarballylic acid (TCA) segment **4**.[5] A Wittig reaction between **2** and **3** was used to form the backbone, and the TCA segment **4**



1: Fumonisin B_2



2 **3** **4**

was subsequently installed on to the backbone. The benzyl group was chosen to protect the C2 amino, the C3 and C5 hydroxyl,[6] and the TCA carboxylic groups so that all the protecting groups could be removed in a single step at the end of synthesis.

The synthesis of the left segment **2** began with coupling of the chiral alkyne **5**[7] with the triflate **6**[8] to give the alkyne **7** (Scheme 1). The alkyne **7** was converted to the *trans*-alkene acid **8** via (1) site-selective osmylation, (2) $Pb(OAc)_4$ cleavage of the resultant diol, followed by $NaBH_4$ reduction, (3) Na/NH_3 reduction of the alkyne to a *trans*-alkene, and (4) Swern[9] and then $NaClO_2$[10] oxidations of the primary alcohol to the acid. The vicinal hydroxyl groups at C14 and C15 were stereoselectively introduced on the backbone of **8** in three steps: (1) iodolactonization of **8** under equilibrium conditions in CH_3CN at −30 °C to give the iodo lactone **9** in 84% yield, with a diastereomeric ratio greater than 20:1,[11] (2) ring opening of the lactone with $PhCH_2ONa$ to yield the C14−C15 epoxide benzyl ester, and (3) deprotection of the resultant benzyl ester, with concomitant epoxide ring opening, to furnish the lactone alcohol with the desired stereochemistry at both C14 and C15. The lactone alcohol was reduced to a triol, the two vicinal hydroxyl groups were protected as an acetonide, and Swern oxidation of the resultant primary alcohol furnished the left segment **2**.[12]

The synthesis of the right segment **3** is outlined in Scheme 2. Allylation of α-amino aldehyde **10**[13,14] with

(1) (a) For the stereochemistry assignment of the AAL toxins and fumonisins from this and other groups up to the beginning of 1995, see: Boyle, C. D.; Kishi, Y. *Tetrahedron Lett.* **1995**, *36*, 5695 and references cited therein. (b) For more recent work on this subject, see: Blackwell, B. A.; Edwards, O. E.; Fruchier, A.; ApSimon, J. W.; Miller, J. D. *Fumonisins in Food*; Jackson, L., *et al.*, Eds.; Plenum Press: New York, 1996; pp 75−91 and references cited therein.

(2) For the stereochemistry assignment of maitotoxin, see: (a) Zheng, W.; Demattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946. (b) Nonomura, T.; Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1675 and references cited therein.

(3) Bezuidenhout, S. C.; Gelderblom, W. C. A.; Gorst-Allman, C. P.; Horak, R. M.; Marasas, W. F. O.; Spiteller, G.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1988**, 743.

(4) For examples, see: (a) *Mycopathologia* **1992**, *117*, pp 1−124 for 18 reviews regarding various aspects of biological activity of fumonisins and AAL toxins. (b) Merrill, A. H., Jr.; Wang, E.; Gilchrist, D. G.; Riley, R. T. *Adv. Lipid Res.* **1993**, *26*, 215.

(5) The TCA segment **4** was synthesized by using the asymmetric Michael reaction reported by Hanessian [Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032]; the antipode of compound **8** in the Hanessian paper was subjected to (1) O_3, then Jones oxidation, (2) BnOH, EDCI, DMAP, and (3) TFA to give (−)-**4** in approximately 29% overall yield. Its optical purity was estimated to be greater than 90% ee from the ^{1}H NMR spectrum of its (−)-menthol ester, and its absolute configuration was established by a chemical correlation with a known compound [Boyle, C. D.; Kishi, Y. *Tetrahedron Lett.* **1995**, *36*, 4579].

(6) The numbering system adopted in this paper corresponds to that of FB_2, cf. the structure **1**.

(7) The alkyne **5** was synthesized in 65% overall yield from (*R*)-2-methyl-1-hexanol [Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361] via a Swern oxidation,[9] followed by a Corey−Fuchs protocol [Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769]. The optical purity of the alcohol was estimated to be greater than 95% ee from the ^{1}H NMR spectrum of its Mosher ester.

(8) The triflate **6** was synthesized from (*S*)-2,5-dimethyl-4-hexen-1-ol, obtained by using the pseudoephedrine-based asymmetric alkylation developed by Myers.[7] The optical purity of the alcohol was estimated to be greater than 95% ee from the ^{1}H NMR spectrum of its Mosher ester.

(9) Mancuso, A.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(10) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.

(11) For reviews on this subject, see: (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (b) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317.

(12) Previous work in this laboratory showed that the installation of the C14 and C15 hydroxyl groups via dihydroxylation of a cis-olefin without the use of a chiral ligand resulted in a 1:3 ratio of desired to undesired diols, with the best result being a 1:1 ratio of desired to undesired diols using the Sharpless DHQ-IND ligand. See: (a) the supporting information of Boyle, C. D.; Harmange, J.-C.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4995. (b) Boyle, C. D. Ph.D. Thesis, Harvard University, 1995.

(13) Fehrentz, J-A.; Castro, B. *Synthesis* **1983**, 676.

(14) The optical purity of **10** was estimated to be greater than 96% ee from the ^{1}H NMR spectrum of the Mosher ester prepared from **10** via $NaBH_4$ reduction followed by esterification.

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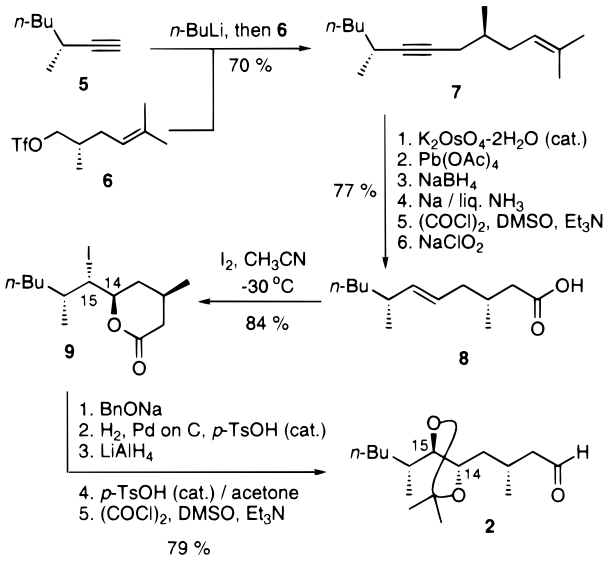
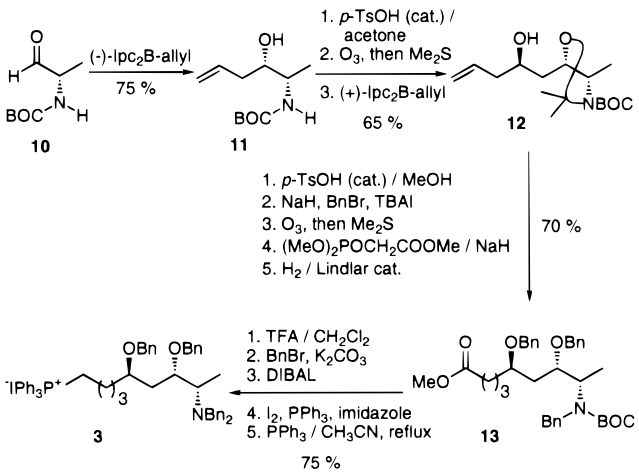
Scheme 1



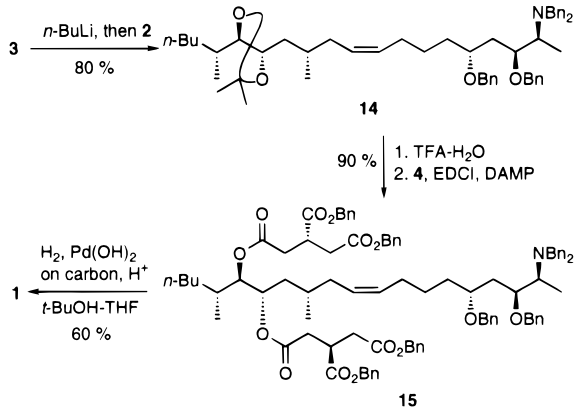
Scheme 2



Brown's chiral (−)-*B*-allyldiisopinocampheylborane[15] gave *syn*-amino alcohol **11** in 75% yield with a diastereoselectivity of 94%.[16] Protection of **11** as an acetonide and ozonolysis of the alkene with a dimethyl sulfide workup provided an aldehyde, which was then reacted with (+)-*B*-allyldiisopinocampheylborane[15] to give the *anti*-alcohol **12** with a diastereomeric ratio of about 10:1 in 65% overall yield.[17] Acetonide deprotection of **12** followed by benzyl group protection provided an alkene, which was transformed into an aldehyde by ozonolysis with a dimethyl sulfide workup. A two-carbon chain elongation in two steps, i.e., (1) Horner−Wadsworth−Emmons olefination and (2) hydrogenation (Lindlar catalyst), furnished the ester **13** in 70% overall yield from **12**. Removal of the BOC group, protection of the resultant amine, and DIBAL reduction of the methyl ester resulted in an alcohol, which was transformed into an alkyl iodide and then treated with PPh_3 in acetonitrile to give the right-half segment **3** in 75% overall yield from **13**.

The completion of FB_2 synthesis is depicted in Scheme 3. As planned, the backbone **14** was installed through a

Scheme 3



Wittig reaction of the ylide generated from the phosphonium salt **3** with the aldehyde **2** in 80% yield. Trifluoroacetic acid treatment to remove the acetonide and acylation of the resultant diol with the (−)-TCA segment **4**[5] gave the fully protected FB_2 **15** in 90% yield. Hydrogenation of the alkene and hydrogenolysis of all the benzyl protecting groups were accomplished under the conditions of H_2 (1 atm)/Pearlman's catalyst/HCl (3 equiv)/*t*-BuOH[18]−THF/rt, to furnish the synthetic FB_2 in 60% yield. On comparison of spectroscopic and chromatographic data, the synthetic FB_2 was found to be identical with naturally occurring FB_2.[19,20]

In conclusion, the first total synthesis of FB_2 was accomplished in a convergent manner from the three building blocks **2**, **3**, and **4**. This synthesis was designed in such a way that the remote diastereomers of FB_2 and their analogs, with different tether lengths or different tethers between the two structural motifs, can also be synthesized for the purpose of probing our hypothesis experimentally.[21]

Acknowledgment. Financial support from the National Institutes of Health (NS 12108) and the National Science Foundation (CHE 89-09762) is gratefully acknowledged. We thank the National Institutes of Health for a Postdoctoral Fellowship to Y.S. (GM 17540).

Supporting Information Available: Experimental details for the syntheses reported and ^1H NMR spectra of FB_2 (synthetic and natural) and its diastereomer at the TCA moiety (17 pages).

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(15) Brown, H. C.; Bhat, K. S.; Randad, R. S. J. *J. Org. Chem.* **1989**, *54*, 1570.

(16) When (+)-*B*-allyldiisopinocampheylborane was employed, the *anti*-amino alcohol corresponding to **12** was obtained in 94% de.

(17) When (−)-*B*-allyldiisopinocampheylborane was used, the *syn*-alcohol corresponding to **13** was obtained in greater than 18:1 ratio.

(18) The choice of solvents for hydrogenation/hydrogenolysis is important. For example, conducting the reduction in methanol led to the formation of methyl esters.

(19) Fumonisin B_2 was purchased from the South African Research Council, Tygerberg, South Africa, and was isolated from the *Fusarium moniliforme* strain MRC 826.

(20) There is a disagreement on the absolute configuration of the TCA moieties of fumonisins; see (a) Shier, W. T.; Abbas, H. K.; Badria, F. A. *Tetrahedron Lett.* **1995**, *36*, 1571 and (b) Boyle, C. D.; Kishi, Y. *Tetrahedron Lett.* **1995**, *36*, 5695. Therefore, the diastereomer of FB_2 bearing (*S*)-TCA was also synthesized from **14** and the antipode of **4**. It exhibited a ^1H NMR spectrum distinctly different from that of the natural and synthetic FB_2 (see the spectra attached in Supporting Information), thereby confirming our previous conclusion.

(21) By combination of the left segment **2** or its antipode with the right segment **3** or its antipode, we have recently completed the synthesis of all four remote diastereomers of the FB_2 aminopolyol backbone and also all the possible (+)- and (−)-**4** attached FB_2 remote diastereomers. In addition, the olefin **12** provides easy access to analogs with different tether lengths or different tethers between the two structural motifs. We will study the biological behaviors of these analogs, in reference to the eicosane derivatives bearing only the left-half or right-half functional groups.