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Absolute Configuration at the Tricarballylic Acid Moieties of Fumonisin B_2

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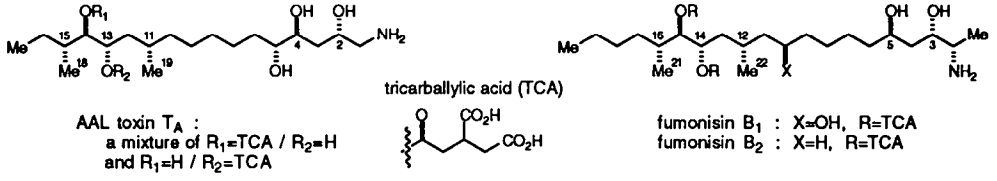
Abstract: The configuration at the chiral centers of the two tricarballylic acid moieties of fumonisin B_2 is shown to be *R*. This stereochemistry is *opposite* to that recently suggested by others for the tricarballylic acid portions of fumonisin B_1 and AAL toxin T_A.

Fumonisins are mycotoxins found in the corn pathogen *Fusarium moniliforme*,[1] and show a variety of biological properties. Most notably, fumonisins have been linked to human esophageal cancer in parts of China and southern Africa. Coupled with the detection of fumonisins in commercially based corn products worldwide, this biological activity has drawn considerable attention to the fumonisin family of mycotoxins.[2] AAL toxins, host-specific phytotoxins produced by the tomato fungus *Alternaria alternata* f. sp. *lycopersici*,[3] are structurally related to fumonisins. AAL toxins and fumonisins exhibit cross-bioactivity and have been shown to inhibit sphingolipid biosynthesis.[2,4]

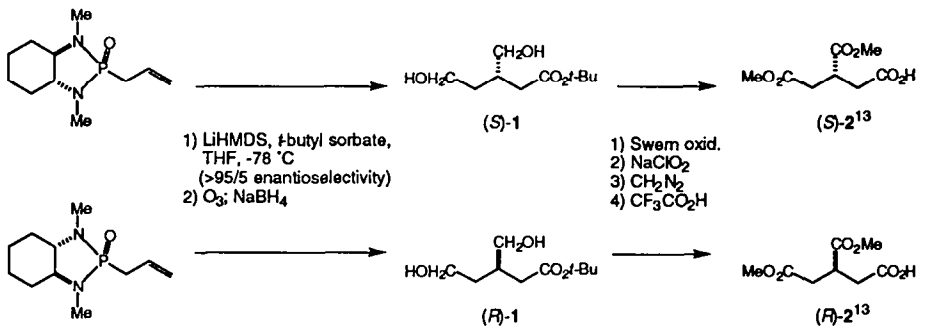


The relative and absolute stereochemistries of the backbones of AAL toxins and fumonisins have recently been established in these laboratories,[5] and subsequently by others.[6,7] However, the stereochemistry at the tricarballylic acid (TCA) moieties present in both AAL toxins and fumonisins has yet to be studied thoroughly. In this communication, we present experimental evidence demonstrating the absolute stereochemistry at the TCA moieties of fumonisin B_2 to be *R*, which is *opposite* to the stereochemistry recently suggested by Shier and co-workers for the TCA portions of fumonisin B_1 and AAL toxin T_A.[8]

In order to pursue our research plan, we required both enantiomers of TCA dimethyl ester monocarboxylic acid and employed the route shown in Scheme 1. The key step was the use of a modified[9] Hanessian procedure for the asymmetric Michael addition of a chiral allylphosphonamide to *t*-butyl sorbate.[10] Ozonolysis of the Michael adduct, followed by $NaBH_4$ reduction, provided (*S*)-**1** ($[\alpha]_D$ +2.2° (*c* 2.6, $CHCl_3$); +2.9° (*c* 2.5, $CHCl_3$); lit.[10]) and (*R*)-**1** ($[\alpha]_D$ -2.7° (*c* 2.5, $CHCl_3$)). The absolute stereochemistry of (*S*)-**1**, originally assigned by

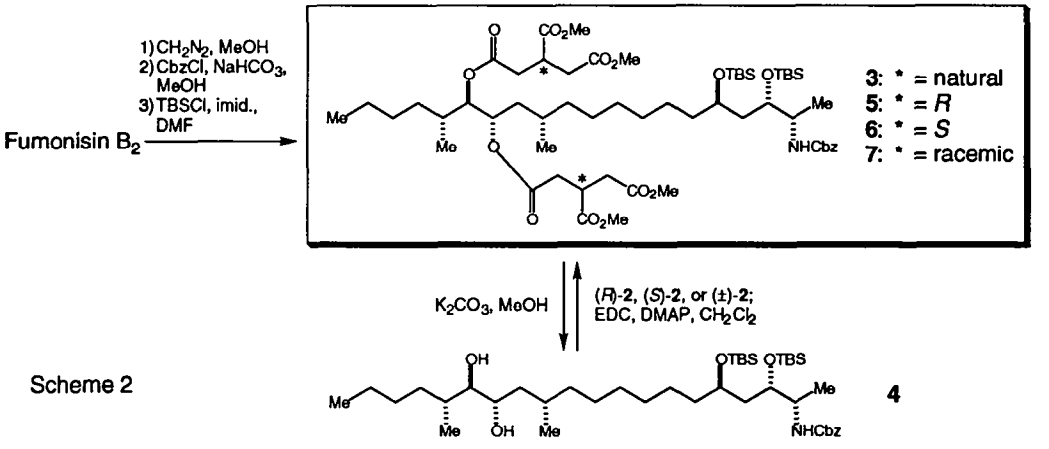
Hanessian,[11] was verified by its correlation with a compound of known absolute stereochemistry.[12] (*S*)-**1** and (*R*)-**1** were converted in four steps to TCA dimethyl ester monocarboxylic acids (*S*)-**2** and (*R*)-**2**, respectively.[13] Although the optical purity of (*S*)-**1** and (*R*)-**1** was greater than 95:5, that of (*S*)-**2** and (*R*)-**2** thus obtained was found to be ca. 5:1.[14]

Scheme 1



The second phase of our work was to prepare a fumonisin or AAL toxin derivative suitable for our studies. To this end, we submitted natural fumonisin B_2[15] to the derivatization reactions outlined in Scheme 2. Esterification of the TCA moieties with diazomethane, followed by Cbz protection of the amine[16] and TBS protection of the diol, gave the bis-TCA tetramethyl ester **3** with the stereochemistry at the TCA moieties intact. Selective cleavage of the TCA esters with K_2CO_3/MeOH yielded the diol **4**.

Scheme 2



The third phase was re-esterification of **4** with synthetic (*R*)-**2**, (*S*)-**2**, or racemic-**2**, furnishing the bis-TCA tetramethyl esters **5**, **6**, and **7**, respectively (Scheme 2). Comparison of the ^{1}H NMR spectra of **3**, **5**, **6**, and **7** (Figure 1) established unambiguously both the TCA asymmetric centers of fumonisin B_2 to be *R*. In principle, coupling of **4** with racemic-**2** would yield a mixture of four diastereomers. Indeed, the ^{1}H NMR spectrum of **7** showed 16 singlets in the methyl ester region, whereas **5** and **6** exhibited only four singlets, each

of which corresponded to a singlet observed in **7**. This demonstrated that all four possible diastereomers resulting from the TCA chiral centers were distinguishable by ^{1}H NMR. Finally, the ^{1}H NMR spectrum of **5** was found to be superimposable on that of **3**, derived from the natural product, concluding that both TCA asymmetric centers of fumonisin B_2 have the *R* configuration.

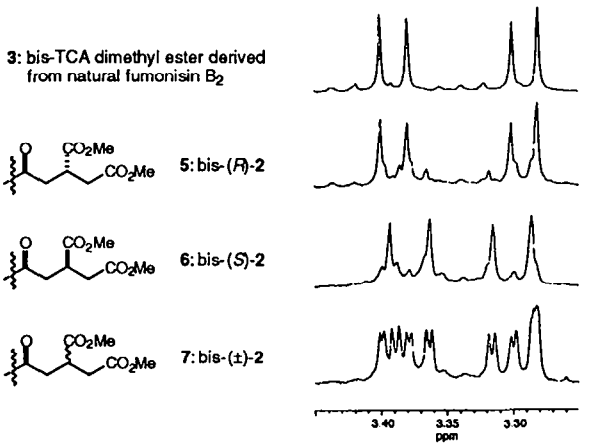


Figure 1. Methyl ester region of ^{1}H NMR (400 MHz, C_6D_6).

Curiously, Shier and co-workers have recently reported the stereochemistry of the TCA portions of fumonisin B_1 and AAL toxin T_A to be *S*,[8] which is *opposite* to that established in this work for fumonisin B_2. We are currently using the methodology described in this paper to prove, or disprove, Shier's stereochemical assignment of the TCA moieties of fumonisin B_1 and AAL toxin T_A.

Acknowledgment. Financial support from the National Institutes of Health (NS 12108) and the National Science Foundation (CHE 94-08247) is gratefully acknowledged. C. D. B. thanks Lederle Laboratories for a predoctoral fellowship.

References and Footnotes:

1. 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.

2. For 18 reviews regarding various aspects of biological activity of fumonisins and AAL toxins, see *Mycopathologia*, **1992**, *117*, 1-124.

3. (a) Bottini, A. T.; Gilchrist, D. G. *Tetrahedron Lett.* **1981**, *22*, 2719. (b) Bottini, A. T.; Bowen, J. R.; Gilchrist, D. G. *Tetrahedron Lett.* **1981**, *22*, 2723.

4. Merrill, A. H., Jr.; Wang, E.; Gilchrist, D. G.; Riley, R. T. *Adv. Lipid Res.* **1993**, *26*, 215.

5. (a) Relative and absolute stereochemistry of the AAL toxin T_A backbone: Boyle, C. D.; Harmange, J.-C.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4995. (b) Relative and absolute stereochemistry of the fumonisin B_2 backbone: Harmange, J.-C.; Boyle, C. D.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 6819.

6. (a) Relative and absolute stereochemistry of the AAL toxin T_A backbone: Oikawa, H.; Matsuda, I.; Kagawa, T.; Ichihara, A.; Kohmoto, K. *Tetrahedron* **1994**, *50*, 13347. (b) For work on the right half of the AAL toxin T_A backbone from the same laboratories, see: Oikawa, H.; Matsuda, I.; Ichihara, A.; Kohmoto, K. *Tetrahedron Lett.* **1994**, *35*, 1223.

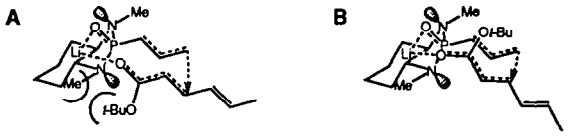
7. (a) Relative and absolute stereochemistry of the fumonisin B_1 backbone: Hoye, T. R.; Jiménez, J. I.; Shier, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 9409. (b) For work on the right half of the fumonisin B_1 backbone, see: ApSimon, J. W.; Blackwell, B. A.; Edwards, O. E.; Fruchier, A. *Tetrahedron Lett.* **1994**, *35*, 7703; Poch, G. K.; Powell, R. G.; Plattner, R. D.; Weisleder, D. *Tetrahedron Lett.* **1994**, *35*, 7707. (c) For work on the left half of the fumonisin B_1 backbone, see: Blackwell, B. A.; Edwards, O. E.; ApSimon, J. W.; Fruchier, A. *Tetrahedron Lett.* **1995**, *36*, 1973.

8. Shier, W. T.; Abbas, H. K.; Badria, F. A. *Tetrahedron Lett.* **1995**, *36*, 1571.

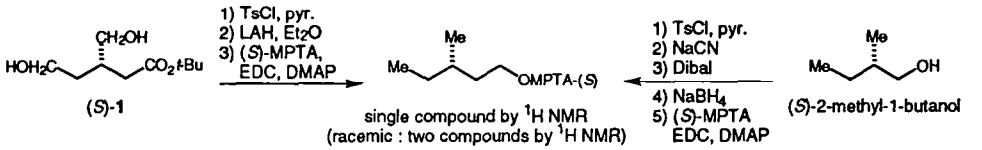
9. In the original procedure,[10] the allylphosphonamide was deprotonated by *n*-BuLi at -78 °C, followed by the immediate addition of *t*-butyl sorbate. We obtained cleaner reactions and higher yields by adding LiHMDS to a mixture of allylphosphonamide and *t*-butyl sorbate at -78 °C.

10. Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032.

11. The authors have proposed transition state **A** to explain the selectivity of the conjugate addition of chiral allylphosphonamides to unsaturated carbonyl compounds.[10] This transition state explains the stereochemical outcome for cyclic systems. For trans unsaturated *t*-butyl esters, however, transition state **A** predicts absolute stereochemistry opposite to that observed in the product. We suggest transition state **B** to explain this anomaly. Note that because of steric repulsion between the bulky *t*-butyl ester and the N-methyl group, transition state **A** is sterically destabilized compared with transition state **B**.



12. (*S*)-**1** was converted to its 3-methyl-1-pentanol derivative. The (*S*)-MPTA ester of this substance was compared with the (*S*)-MPTA esters of (*S*)-3-methyl-1-pentanol (derived from (*S*)-2-methyl-1-butanol purchased from Aldrich) and (±)-3-methyl-1-pentanol, verifying the stereochemical assignment depicted in Scheme 1.



13. For compounds (*S*)-**2** and (*R*)-**2**, we adopted the unconventional (*S*)/(*R*) nomenclature for convenience.

14. (*S*)-**2** and (*R*)-**2** were each submitted to EDC/DMAP in the presence of (-)-menthol. The resulting (-)-menthyl esters of (*S*)-**2** and (*R*)-**2** were diastereomers of each other, each having ca. 5:1 diastereomeric purity.

15. Fumonisin B_2 used for these studies was purchased from the South African Research Council, Tygerberg, South Africa.

16. These reactions are precedented for AAL toxin T_A; see ref. 6a.

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