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A FORMAL SYNTHESIS OF (+)-ASTELTOXIN

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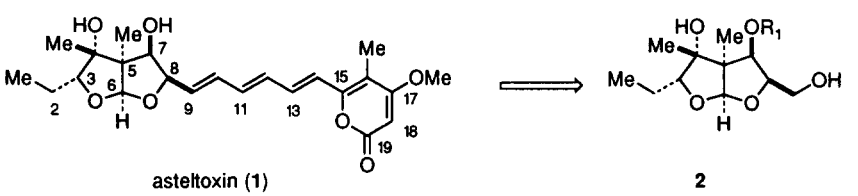
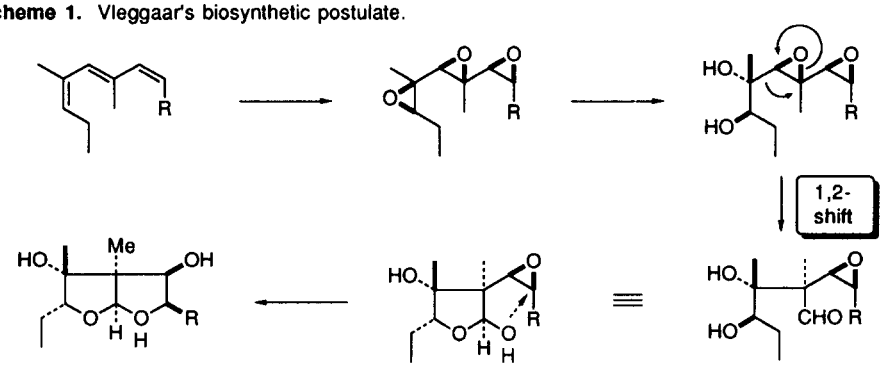
Abstract: An enantioselective synthesis of the highly functionalized bis(tetrahydrofuran) subunit of asteltoxin has been accomplished, in which a sterically congested quaternary center was constructed by the Lewis acid catalyzed rearrangement of epoxy silyl ethers.

Investigations of toxic maize cultures of *Aspergillus stellatus* led to the isolation and structural determination of asteltoxin (1).[2] It belongs to a group of polyene pyrone mycotoxins, most of which has been shown to function as inhibitors of oxidative phosphorylation. A key structural feature includes the unusual bis(tetrahydrofuran) moiety, a masked aldehyde, having six consecutive stereogenic centers. Based on extensive incorporation studies with ^{13}C-labelled precursors, one of us (R.V.) previously proposed a biosynthetic pathway for the formation of the 2,8-dioxabicyclo[3.3.0]octane moiety involving an epoxide-mediated rearrangement of the polyketide chain (Scheme 1).[3] Herein we report a new stereoselective synthesis of the bis(tetrahydrofuran) subunit **2**, which closely parallels its proposed biosynthesis.[4]

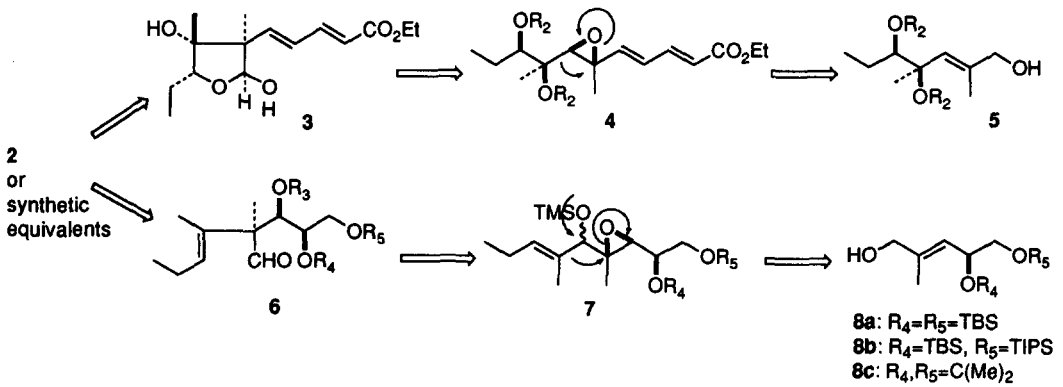


Scheme 1. Vleggaar's biosynthetic postulate.



The synthetic repertoire necessary to effect such an epoxide-induced rearrangement can be found in the related epoxide rearrangement protocols developed by either Yamamoto (i.e., **4** → **3**) or Tsuchihashi-Suzuki (i.e., **7** → **6**).[5-7] Retrosynthetic analysis based on these synthetic methods is summarized in Scheme 2. The ready availability of the epoxy alcohols such as **7** in enantiomerically pure form from a (*D*)-glyceraldehyde derivative prompted us to utilize the epoxy silyl ether rearrangement by the procedure of Tsuchihashi-Suzuki.[8]

Scheme 2



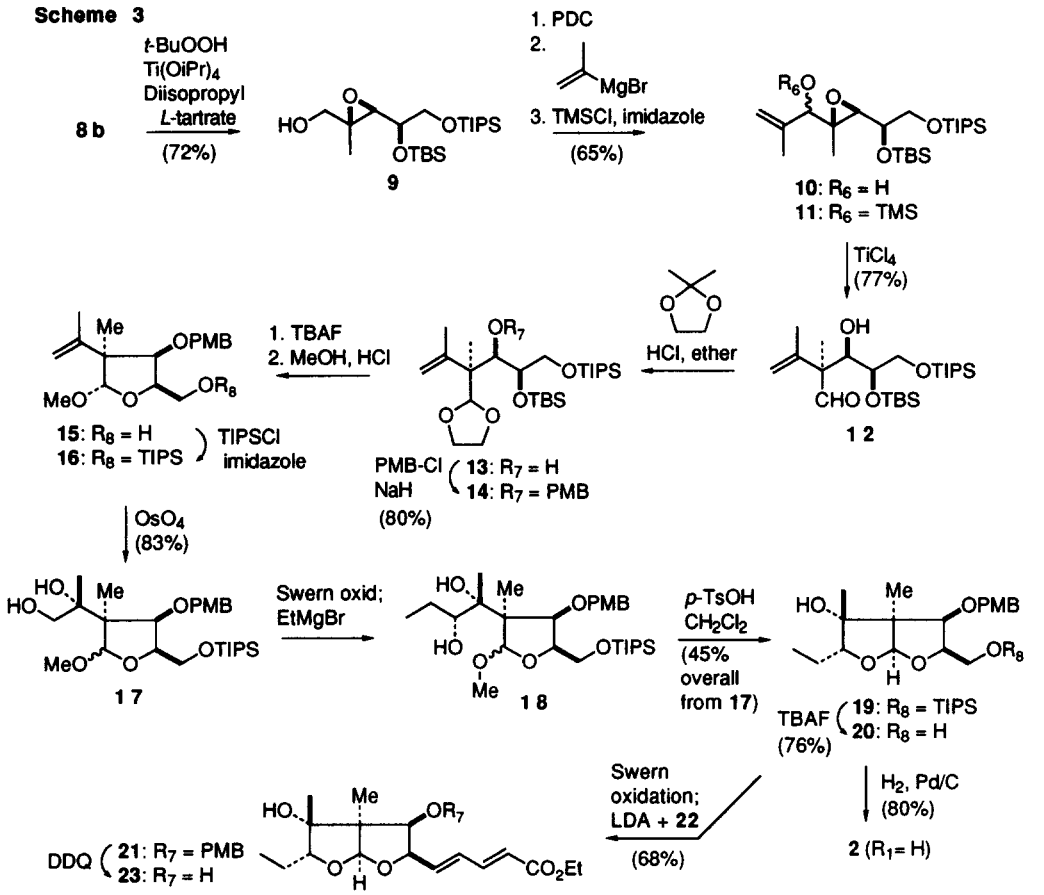
As shown in Scheme 3, our synthesis began with allylic alcohol **8b** (or **8a**) which was readily prepared by a slight modification of the literature procedure for preparing **8c**.[9] Sharpless asymmetric epoxidation of **8b** furnished epoxy alcohol **9** in 72% yield and 94% ds.[10] PDC oxidation, followed by treatment with 2-propenylmagnesium bromide and silylation with TMSCl provided the requisite rearrangement substrate **11** in 65% overall yield. As a preliminary study, we chose to employ readily available 2-propenylmagnesium bromide, although the use of 2-*E*-pentenyllithium would further streamline the remaining transformations (vide infra).[11]

The pivotal rearrangement of the epoxy silyl ether **11** was accomplished by the action of $TiCl_4$ to provide aldehyde **12** (77% yield), which was found to be surprisingly stable. Conversion to the corresponding acetal **13** by transacetalization with 2,2-dimethyl-1,3-dioxolane, followed by protection with *p*-methoxybenzyl chloride gave acetal **14** in 80% overall yield. Removal of the silyl protecting groups using *n*-Bu_4NF and subsequent treatment with methanolic hydrogen chloride gave the monocyclic acetal **15**. Upon silylation with TIPSCl, a fully protected acetal **16** was obtained (75% overall yield) as a single diastereomer.

Our attention was next directed to the stereocontrolled construction of the left-side tetrahydrofuran moiety. Osmylation of **16** took place with complete stereoselectivity to give diol **17** as a mixture of two anomers (83%). The stereochemical assignment was tentatively made based on inspection of molecular models,[12a] and was ultimately confirmed by its conversion to **2**. Swern oxidation and subsequent chelation-controlled addition of EtMgBr to the resulting aldehyde provided an efficient, stereoselective introduction of the ethyl side chain.[13] Bis(tetrahydrofuran) **19** was then obtained from acid-catalyzed cyclization of **18** in CH_2Cl_2.[12b]

Finally, deprotection (1. TBAF; 2. H_2, Pd/C) gave rise to bis(tetrahydrofuran) **2** (R_1 = H), the spectral data of which were in excellent agreement with literature values.[4a]

Scheme 3



In order to unequivocally determine the structure of bis(tetrahydrofuran) **20**, it was converted into the known diene **23**. Thus, Swern oxidation of alcohol **20** and subsequent Wittig olefination with trimethylphosphonocrotonate (**22**) furnished diene ester **21** (along with a small amount of its epimer). Deprotection of the PMB group with DDQ then furnished ester **23**, which exhibits spectral characteristics identical to literature values.[4a,b] Furthermore, since compound **23** has been successfully converted into asteltoxin (**1**) by Schreiber and Tadano,[4a,b] our work represents its formal total synthesis.

In conclusion, we have developed a biomimetic synthetic method for the highly functionalized bis(tetrahydrofuran) subunit of asteltoxin, whose sterically congested quaternary center was constructed by the Lewis acid catalyzed rearrangement of epoxy silyl ethers. Further applications of this rearrangement protocol in natural product synthesis will be forthcoming.[14]

References and Footnotes

1. (a) Recipient of an NIH Research Career Development Award, 1990-1995 (GM00575). (b) University of Alabama (c) University of Pretoria.

2. Kruger, G. J.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. *J. Chem. Soc., Chem. Commun.* **1979**, 441.

3. Vleggaar, R. *Pure Appl. Chem.* **1986**, *58*, 239.

4. To date two total syntheses of **1** have appeared: (a) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1984**, *106*, 4186. (b) Tadano, K.-i.; Yamada, H.; Idogaki, Y.; Ogawa, S.; Suami, T. *Tetrahedron* **1990**, *46*, 2353. See also (c) Mulzer, J.; Mohr, J.-T. *J. Org. Chem.* **1994**, *59*, 1160. (d) Nishiyama, S.; Kanai, H.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1322.

5. (a) Maruoka. K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431. (b) Maruoka. K.; Nagahara, S.; Ooi, T.; Yamamoto, H. *Tetrahedron Lett.* **1989**, *30*, 5607. (c) Maruoka. K.; Bureau, R.; Yamamoto, H. *Synlett* **1991**, 363. (d) Maruoka. K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983. (e) Maruoka. K.; Sato, J.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 5449. (f) Maruoka. K.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3303. (g) Maruoka. K.; Sato, J.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3749. (h) Sato, J.; Maruoka. K.; Yamamoto, H. *Org. Synth.* **1993**, *72*, 95.

6. (a) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G.-i. *J. Am. Chem. Soc.* **1986**, *108*, 3827. (b) Suzuki, K.; Shimazaki, M.; Tsuchihashi, G.-i. *Tetrahedron Lett.* **1986**, *27*, 6237. (c) Suzuki, K.; Matsumoto, T.; Tomooka, K.; Matsumoto, K.; Tsuchihashi, G.-i. *Chem. Lett.* **1987**, 113. (d) Suzuki, K.; Miyazawa, M.; Tsuchihashi, G.-i. *Tetrahedron Lett.* **1987**, *28*, 3515. (e) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G.-i. *Tetrahedron Lett.* **1987**, *28*, 5891. (f) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G.-i. *Tetrahedron* **1988**, *44*, 4061. (g) Shimazaki, M.; Hara, H.; Suzuki, K. *Tetrahedron Lett.* **1989**, *30*, 5443. (h) Shimazaki, M.; Morimoto, M.; Suzuki, K. *Tetrahedron Lett.* **1990**, *31*, 3335. See also (i) Cheer, C. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1968**, *90*, 178. (j) Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. J. *J. Org. Chem.* **1993**, *58*, 5944.

7. For a recent review on rearrangements of epoxy alcohols, see: Magnusson, G. *Org. Prep. Proced. Int.* **1990**, *22*, 547.

8. Synthetic studies on the Yamamoto rearrangement (i.e., **4** → **3**) will be presented in a full paper.

9. (a) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. (b) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis - Chiral Catalysis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1985; Vol. 5, Chapter 8.

10. On the other hand, the allylic alcohol **8c** has been shown to be one of the few poor substrates for Sharpless asymmetric epoxidation (70% ds using DIPT): ref 9b. More importantly, the rearrangement of the silyl epoxy ether derived from **8c** gave very little of the desired product, presumably due to incompatibility of the acetonide group with the Lewis acid used.

11. Such an approach utilizing 2-*E*-pentenyllithium is currently in progress, and will be reported in a full paper. Cf. Cooke, M. P., Jr. *J. Org. Chem.* **1982**, *47*, 4963.

12. (a) Rationalization for the origin of diastereoselectivity in osmylation of a related system has been advanced by Mulzer; see ref 4c. (b) As also noted by Mulzer, a remarkable difference in the rate of acid-catalyzed cyclization was found between two anomers of **18**.

13. Cf. (a) Stille, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035. (b) See also ref 4a.

14. We are grateful to the National Institutes of Health (GM 35956) for generous financial support and a Research Career Development Award (GM00575 to J.K.C.).

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