STEREOSELECTIVE SYNTHESIS OF THE S- AND Y-RING SYSTEMS OF MAITOTOXIN

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The seven-membered S- and Y-ring systems of maitotoxin (1) were stereoselectively synthesized based on the rearrangement-ring expansion of the six-membered ethers having the mesylate group on the α-side chain.  

KEY WORDS maitotoxin; S-ring; Y-ring; rearrangement; ring expansion; seven-membered ether

Maitotoxin (1) (MTX), isolated from the dinoflagellate Gambierdiscus toxicus, is the most toxic and largest natural product (MW 3422) known to date except for biopolymers like proteins or polysaccharides.2) MTX (1) is implicated in ciguatera food poisoning and involved in Ca2+-dependent mechanisms over a wide range of cell types.3) Recently, the full structure and partial relative configuration of 1 were elucidated,4) although the complete absolute configuration has not yet been determined. Its unusual molecular structure contains 32 fused ether rings, 28 hydroxyl groups, 2 sulfate esters, and 98 chiral centers. The skeletal novelty, complexity, and biological activity of 1 have attracted serious attention from chemists and biologists alike.

![Partial Structure of Maitotoxin (1)](image)

The construction of the 7-membered ether ring systems of MTX (1) would be one of the crucial steps for the synthesis of 1. Recently, an efficient method for the synthesis of 6- and 7-membered ether rings was developed in this laboratory.5) The method consists of the epoxidation of olefin i, exo-cyclization of ii followed by mesylation, and rearrangement of iii with ring expansion. Namely, upon treatment of the mesylate iii with zinc acetate in AcOH-H2O at reflux, the rearrangement took place, giving the ring expanded ether iv. The method was successfully applied to the synthesis of the C- and CD-ring systems of hemibrevetoxin B.6) We now report the stereoselective synthesis of the S- and Y-ring systems of MTX (1) based on the above method.

![Chemical Structures](image)

The synthesis started with α,β-unsaturated ester 7 prepared from geraniol. After protection of the alcohol as its silyl ether, the ester 2 was subjected to DIBAH reduction to give alcohol 3. The Sharpless asymmetric epoxidation (AE)8) of 3 with t-BuOCH, (-)-DIPT, and Ti(O-iPr)4 in CH2Cl2 followed by treatment with PhCOOH and Ti(O-iPr)49) produced diol 4. Successive treatment of 4 with MsCl-Et3N and K2CO3 gave an epoxide which was treated with allylmagnesium chloride in the presence of CuI in THF to afford diol 5. Protection of the secondary hydroxyl group of 5 with benzoylchloride and successive desilylation with HF-pyridine gave allyl alcohol 6. The Sharpless AE of 6 using (-)-DIPT, exo-cyclization with PPTS, and regioselective acetylation with AcCl-collidine10) produced the 6-
membered ether 7 and its stereoisomer 8 in a ratio of ca. 6:1. Their stereostructures were determined based on the NMR analyses, in which an NOE between C-1 Me and C-5 Me was observed in 8 but not in 7. The desired alcohol 7 was treated with MsCl-Et3N to give the mesylate 9, the substrate for the rearrangement-ring expansion. The NOE between C-1’-H and C-5β Me in 9 suggested that the configuration of the mesoxylo group and C-O bond of the ether ring should be antiperiplanar, as shown in Fig. 1. Thus, the mesylate 9 would have the favored conformation for the rearrangement-ring expansion. Upon treatment with Zn(OAc)2 in AcOH-H2O at reflux, the rearrangement of 9 took place smoothly, giving the ring expanded ether which was acetylated to give 10,12 corresponding to the S-ring, in 60% yield.

The synthesis of the Y-ring was then carried out starting from acetonide 126 prepared from alcohol 11 in 8 steps. The Swern oxidation of 12 gave ketone 13, which was treated with Me3Al13 to give the α- and β-methyl compounds, 14 (47%) and 15 (10%). The stereostructures were confirmed by NOE between C-4 Me and C-5β H in 15.
and no corresponding NOE in 14. The α-methyl compound 14 was converted into epoxide 16 in 3 steps: (1) deprotection of the acetone, (2) selective mesylation of the primary alcohol, and (3) treatment with K₂CO₃. The reaction of 16 with vinylmagnesium bromide in the presence of CuI in THF afforded the alcohol which was treated with MsCl to give the mesylate 17. The NOE between C-1′ H and C-5β H in 17 was also observed, suggesting the favored conformation for the rearrangement-ring expansion (Fig. 1). ¹¹ The reaction of 17 with Zn(OAc)₂ in AcOH-H₂O at reflux gave the 7-membered ether 18, ¹² corresponding to the Y-ring, in 46% yield.

In summary, the unique rearrangement with ring expansion was successfully applied to the stereoselective synthesis of the S- and Y-ring systems of MTX (1). Ring elongation is now in progress.

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REFERENCES AND NOTES
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11) The antiperiplanar configuration of the C-O bond in the ether ring and the mesyloxy group as the leaving group should be very important in this rearrangement-ring expansion. The results will be reported in due course.
12) The structure was confirmed based on the NMR analysis (NOE and HMBC). Data for 10: [α]D +2.94 (c 0.068, CHCl₃); IR (neat) 3500 (br), 1740, 1719 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.23 (s, 3H), 1.27 (s, 3H), 2.08 (s, 3H), 3.96 (dd, J=8.9, 2.7 Hz, 1H), 4.09 (dd, J=11.3, 8.9 Hz, 1H), 4.39 (dd, J=11.3, 2.7 Hz, 1H), 4.95 (dd, J=10.4, 1.8 Hz, 1H), 5.03 (dd, J=17.1, 1.8 Hz, 1H), 5.19 (dd, J=7.3, 0.9 Hz, 1H), 5.82 (ddt, J=17.1, 10.4, 6.4 Hz, 1H). Data for 18: [α]D -19.2 (c 0.51, CHCl₃); IR (neat) 3440 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.06 (s, 9H), 1.10 (s, 3H), 1.26 (s, 3H), 3.27 (dd, J=10.1, 2.6 Hz, 1H), 3.31 (s, 1H), 3.52 (dd, J=9.1, 5.8 Hz, 1H), 3.69 (dd, J=10.1, 9.1 Hz, 1H), 3.76 (dd, J=10.1, 5.8 Hz, 1H), 4.85 (d, J=10.2 Hz, 1H), 4.95 (d, J=17.1 Hz, 1H), 5.69 (ddt, J=17.1, 10.2, 6.9 Hz, 1H).

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