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 Ca^{2+} -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)

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.

The synthesis started with α,β -unsaturated ester **2**⁷⁾ prepared from geraniol. After protection of the alcohol as its silyl ether, the ester **2** was subjected to DIBALH reduction to give alcohol **3**. The Sharpless asymmetric epoxidation (AE)⁸⁾ of **3** with *t*-BuOOH, (-)-DIPT, and $\text{Ti}(\text{O}-i\text{Pr})_4$ in CH_2Cl_2 followed by treatment with PhCOOH and $\text{Ti}(\text{O}-i\text{Pr})_4$ ⁹⁾ produced diol **4**. Successive treatment of **4** with $\text{MsCl-Et}_3\text{N}$ and K_2CO_3 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-collidine ¹⁰⁾ produced the 6-

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Fig. 1

(a) TBPDPSCl, imidazole, DMF, rt (86%); (b) DIBAL, toluene, -78°C (94%); (c) $t\text{-BuOOH}$, (-)-DIPT, $\text{Ti}(\text{O-}i\text{Pr})_4$, CH_2Cl_2 , -25°C (88%); (d) PhCOOH , $\text{Ti}(\text{O-}i\text{Pr})_4$, CH_2Cl_2 , $0^\circ\text{C} \sim \text{rt}$ (83%); (e) MsCl , Et_3N , CH_2Cl_2 , $0^\circ\text{C} \sim \text{rt}$ (82%); (f) K_2CO_3 , MeOH , rt (71%); (g) allylMgCl , CuI , THF , rt (40%); (h) PhCOCl , DMAP, pyridine, rt (94%); (i) HF -pyridine, THF , rt (68%); (j) $t\text{-BuOOH}$, (-)-DIPT, $\text{Ti}(\text{O-}i\text{Pr})_4$, CH_2Cl_2 , -25°C ; (k) PPTS , CH_2Cl_2 , rt (78%; from 6); (l) AcCl , collidine, CH_2Cl_2 , -78°C (82%); (m) MsCl , Et_3N , CH_2Cl_2 , rt (100%); (n) $\text{Zn}(\text{OAc})_2$, $\text{AcOH-H}_2\text{O}$ (1:1), reflux; then Ac_2O , pyridine, rt (60%).

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 $\text{MsCl-Et}_3\text{N}$ to give the mesylate **9**, the substrate for the rearrangement-ring expansion. The NOE between C-1' H and C-5 β Me in **9** suggested that the configuration of the mesyloxy 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.¹¹⁾ Upon treatment with $\text{Zn}(\text{OAc})_2$ in $\text{AcOH-H}_2\text{O}$ 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 **12**⁶⁾ prepared from alcohol **11** in 8 steps. The Swern oxidation of **12** gave ketone **13**, which was treated with Me_3Al ¹³⁾ 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-5 β H in **15**

(a) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C , then Et_3N , rt (98%); (b) Me_3Al , CH_2Cl_2 , -20°C (47% for **14**, 10% for **15**); (c) aq AcOH , rt (83%); (d) MsCl , Et_3N , CH_2Cl_2 , 0°C (94%); (e) K_2CO_3 , MeOH , rt (95%); (f) vinylMgBr , CuI , THF , -23°C (54%); (g) MsCl , Et_3N , CH_2Cl_2 , rt (44%); (h) $\text{Zn}(\text{OAc})_2$, $\text{AcOH-H}_2\text{O}$ (1:1), reflux (46%).

and no corresponding NOE in **14**. The α -methyl compound **14** was converted into epoxide **16** in 3 steps: (1) deprotection of the acetonide, (2) selective mesylation of the primary alcohol, and (3) treatment with K_2CO_3 . 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-5 β 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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- 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**: $[\alpha]_D +2.94$ (c 0.068, $CHCl_3$); IR (neat) 3500 (br), 1740, 1719 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) 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**: $[\alpha]_D -19.2$ (c 0.51, $CHCl_3$); IR (neat) 3440 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) 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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