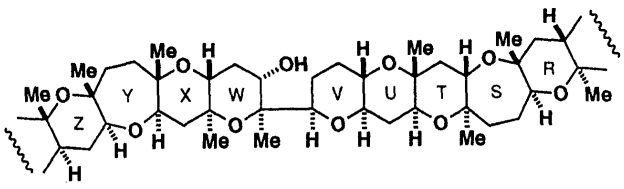
STEREOSELECTIVE SYNTHESIS OF THE S- AND Y-RING SYSTEMS OF MAITOTOXIN

Tadashi NAKATA,* Sumihiro NOMURA,[1] and Hiroko MATSUKURA
The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama 351-01, Japan

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.

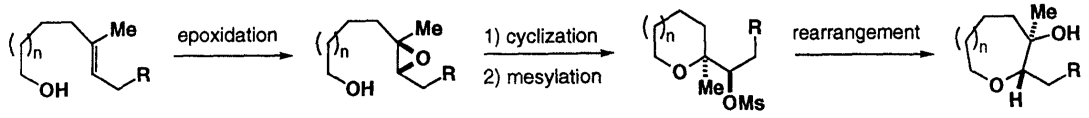
KEY WORDS maitotoxin; S-ring; Y-ring; rearrangement; ring expansion; seven-membered ether

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-H_2O 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 DIBAH reduction to give alcohol **3**. The Sharpless asymmetric epoxidation (AE)[8] of **3** with t-BuOOH, (-)-DIPT, and $Ti(O\text{-}iPr)_4$ in CH_2Cl_2 followed by treatment with PhCOOH and $Ti(O\text{-}iPr)_4$[9] produced diol **4**. Successive treatment of **4** with MsCl-Et_3N 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-

* To whom correspondence should be addressed.

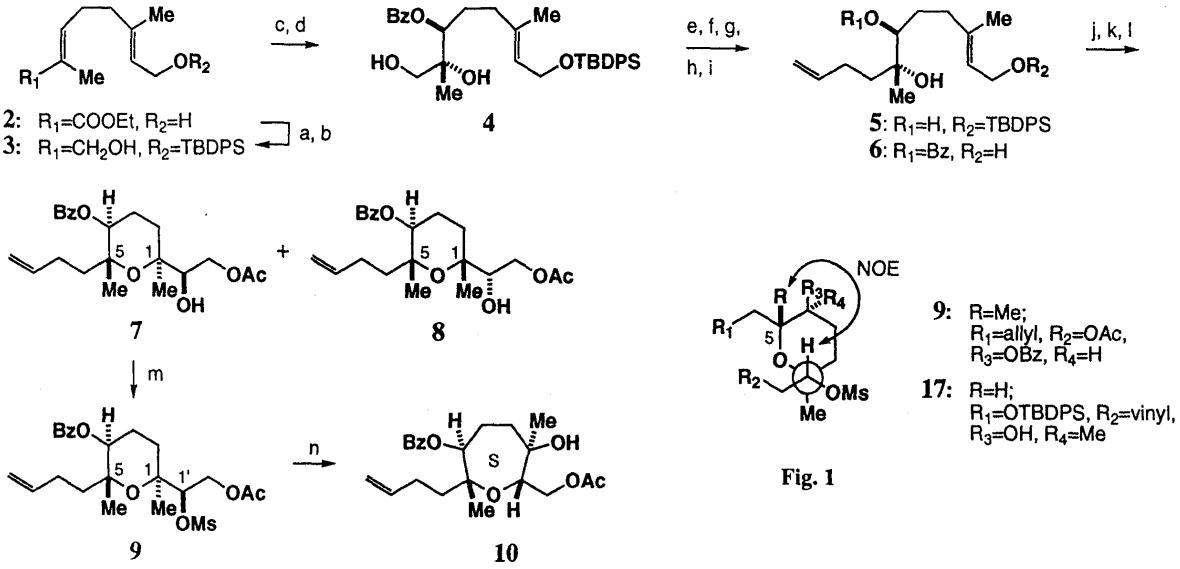
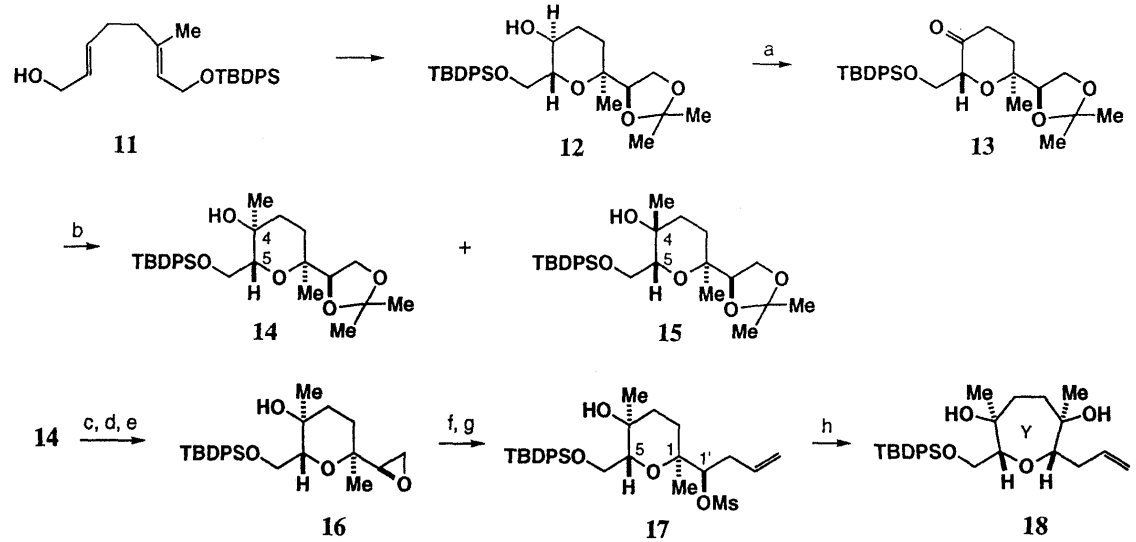


Fig. 1

(a) TBDPSCl, imidazole, DMF, rt (86%); (b) DIBAH, toluene, -78°C (94%); (c) t-BuOOH, (-)-DIPT, $Ti(O\text{-}iPr)_4$, CH_2Cl_2, -25°C (88%); (d) PhCOOH, $Ti(O\text{-}iPr)_4$, CH_2Cl_2, 0°C ~ rt (83%); (e) MsCl, Et_3N, CH_2Cl_2, 0°C ~ 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-BuOOH, (-)-DIPT, $Ti(O\text{-}iPr)_4$, 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) $Zn(OAc)_2$, AcOH-H_2O (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 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 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 $Zn(OAc)_2$ in AcOH-H_2O 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-5β H in **15**



(a) $(COCl)_2$, 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) $Zn(OAc)_2$, AcOH-H_2O (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-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-H_2O 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.

ACKNOWLEDGMENTS This work was supported in part by Grant-in-Aid for Scientific Research on Priority Areas (Asymmetric Synthesis of Chiral Molecules) from the Ministry of Education, Science, and Culture, Japan. The authors thank Dr. H. Koshino (RIKEN) for the NMR measurement and Dr. A. Kinumaki (Marugo Laboratory Service Center) for the NMR and mass spectral measurements.

REFERENCES AND NOTES

1) Visiting scientist from Tanabe Seiyaku Co., Ltd.
2) Yokoyama A., Murata M., Oshima Y., Iwashita T., Yasumoto T., *J. Biochem.*, **104**, 184 (1988).
3) Takahashi M., Ohizumi Y., Yasumoto T., *J. Biol. Chem.*, **257**, 7287 (1982).
4) a) Murata M., Iwashita T., Yokoyama A., Sasaki M., Yasumoto T., *J. Am. Chem. Soc.*, **114**, 6594 (1992); b) Murata M., Naoki H., Iwashita T., Matsunaga S., Sasaki M., Yokoyama A., Yasumoto T., *J. Am. Chem. Soc.*, **115**, 2060 (1993); c) Murata M., Naoki H., Matsunaga S., Satake M., Yasumoto T., *J. Am. Chem. Soc.*, **116**, 7089 (1994); d) Satake M., Ishida S., Yasumoto T., Murata M., Utsumi H., Hinomoto T., *J. Am. Chem. Soc.*, **117**, 7019 (1995); e) Sasaki M., Nonomura T., Murata M., Tachibana K., *Tetrahedron Lett.*, **35**, 5023 (1994).
5) Nakata T., Nomura S., Matsukura H., *Tetrahedron Lett.*, **37**, 213 (1996).
6) Nakata T., Nomura S., Matsukura H., Morimoto M., *Tetrahedron Lett.*, **37**, 217 (1996).
7) Corey E. J., Achiwa K., Katzenellenborgen J. A., *J. Am. Chem. Soc.*, **91**, 4318 (1969).
8) Katsuki T., Sharpless K. B., *J. Am. Chem. Soc.*, **102**, 5976 (1980).
9) Caron M., Sharpless K. B., *J. Org. Chem.*, **50**, 1557 (1985).
10) Ishihara K., Kurihara H., Yamamoto H., *J. Org. Chem.*, **58**, 3791 (1993).
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).
13) a) Nicolaou K. C., Duggan M. E., Hwang C.-K., *J. Am. Chem. Soc.*, **111**, 6666 (1989); b) Ashby E. C., Laemmie J. T., *Chem. Rev.*, **75**, 521 (1975).

(Received January 16, 1996; accepted January 31, 1996)