REARRANGEMENT - RING EXPANSION REACTION OF FUNCTIONALIZED CYCLIC ETHERS. STEREOSELECTIVE SYNTHESIS OF THE ST- AND XY-RING SYSTEMS OF MAITOTOXIN

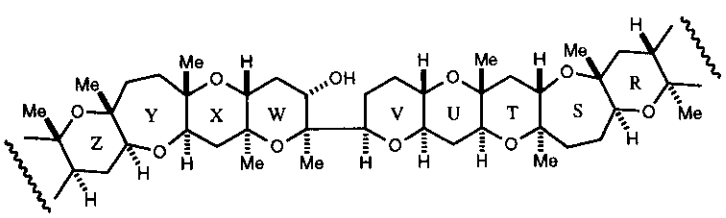
Kazuo Nagasawa,[a] Nobuyuki Hori,[b] Ryuichi Shiba,[b] and Tadashi Nakata[a]*

[a] The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama 351-01, Japan

[b] Tokyo Denki University, Kanda 2-2, Chiyoda-Ku, Tokyo 101, Japan

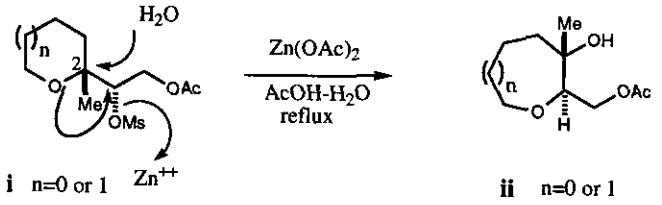
Abstract - The rearrangement of 6-membered ethers having olefinic functional groups on the C2-side chain with $Zn(OAc)_2$ proceeded smoothly with ring expansion to give the 7-membered ethers. The 5,7-membered ether, prepared from the 7-membered ether, was again subjected to the rearrangement-ring expansion reaction to give the 6,7-membered ether, corresponding to the ST- and XY-ring systems of maitotoxin.

Recently, marine polycyclic ethers as exemplified by brevetoxin B,[1] hemibrevetoxin B,[2] and maitotoxin (**1**)[3] have attracted the attention of synthetic organic chemists due to their unusual structural framework, novel functionalities, and potent biological activities. We have reported an efficient method for the synthesis of 6- and 7-membered ethers[4] and its application to the synthesis of the C- and CD-ring systems of hemibrevetoxin B[5] and the S- and Y-ring systems of maitotoxin.[6] The key reaction for this



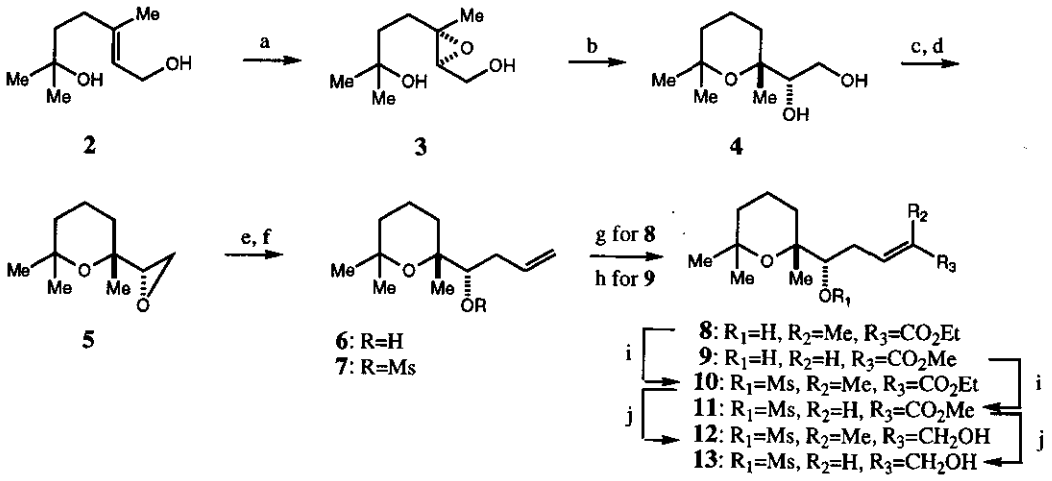
Partial Structure of Maitotoxin (**1**)

method involves the rearrangement-ring expansion of cyclic ethers (**i**) with $Zn(OAc)_2$ in aq. AcOH at reflux. Although cyclic ether (**i**) used in the previous paper has a (2-acetoxy-1-mesyloxy)ethyl group as the C2-side chain,[4] the substrate having olefinic functional groups such as an olefin, α,β-unsaturated ester, or allyl alcohol would be more effective for the ring elongation of the polycyclic ethers. We now report the rearrangement-ring expansion of the cyclic ethers having olefinic functional groups on the C2-side chain and its application to the synthesis of the ST- and XY-ring systems of maitotoxin (**1**).



i n=0 or 1 **ii** n=0 or 1

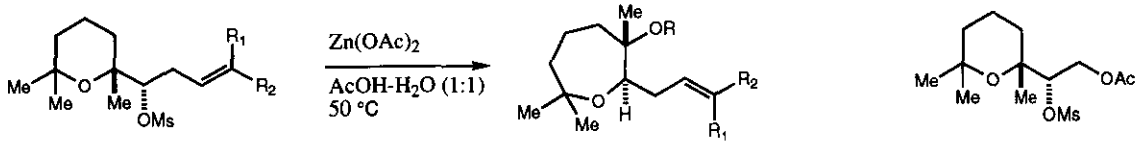
The substrates having olefinic functional groups on the C2-side chain were synthesized starting from diol (**2**)[7] prepared from geraniol. The Sharpless asymmetric epoxidation (AE)[8] of **2** with t-BuOOH, (+)-diethyl tartrate (DET), and $Ti(O\text{-}i\text{-}Pr)_4$ in CH_2Cl_2 at -23 °C produced the α-epoxide (**3**), which was treated with pyridinium p-toluenesulfonate (PPTS) in CH_2Cl_2 at room temperature to give the 6-membered ether (**4**) in 82% yield. Selective mesylation of the primary alcohol of **4** with MsCl-collidine[9] followed by K_2CO_3 treatment gave the epoxide (**5**) in 53% yield. Reaction of **5** with vinylmagnesium



Reagents and Conditions: (a) t-BuOOH, (+)-DET, $Ti(O\text{-}i\text{-}Pr)_4$, CH_2Cl_2, -23 °C; (b) PPTS, CH_2Cl_2, room temperature (82% from **2**); (c) MsCl, 2,4,6-collidine, CH_2Cl_2, -78 ~ 0 °C; (d) K_2CO_3, MeOH, room temperature (53% from **4**); (e) CH_2=CHMgBr, CuI, THF, -20 °C (60%); (f) MsCl, Et_3N, CH_2Cl_2, room temperature (71%); (g) O_3, MeOH, -78 °C; Ph_3P=C(Me)CO_2Et, toluene, 100 °C (68%); (h) O_3, MeOH, -78 °C; Ph_3P=CHCO_2Me, toluene, 100 °C (65%); (i) MsCl, Et_3N, CH_2Cl_2, 0 °C (93% for **10**, 81% for **11**); (j) DIBAH, toluene, -78 °C (90% for **12**, 97% for **13**).

bromide in the presence of CuI produced allyl alcohol (**6**) (60%), which was treated with MsCl-Et3N to give the mesylate (**7**) (71%). α,β-Unsaturated esters and allyl alcohols were then synthesized from **6** as follows: Ozonolysis of **6** followed by the Wittig reaction, using $Ph_3P{=}C(Me)CO_2Et$ and $Ph_3P{=}CHCO_2Me$, gave (*E*)-α,β–unsaturated esters (**8**) (68%) and (**9**) (65%) which led to the mesylates (**10**) (93%) and (**11**) (81%), respectively. Reduction of **10** and **11** with DIBAH afforded allyl alcohols (**12**) and (**13**), respectively, in 90% and 97% yields.

The rearrangement-ring expansion reactions of mesylates (**7**) and (**10** - **13**) were investigated. Upon treatment of the mesylates with $Zn(OAc)_2$ in aq. AcOH, the rearrangements took place very smoothly with ring expansion at 50 °C, giving 7-membered ethers (as alcohols (**14a-18a**) and acetates (**14b-18b**)) stereoselectively in excellent yields: **14a** (65%) and **14b** (17%) from **7**, **15a** (77%) and **15b** (16%) from **10**, **16a** (83%) and **16b** (13%) from **11**, **17a** (83%) and **17b** (11%) from **12**, and **18a** (62%) and **18b** (28%) from **13**. The rearrangements of these olefins were much faster under milder reaction conditions than that of the corresponding acetate (**19**) (reflux for 2 h or 80 °C for 8 h).[4] In the reaction of **19** with $Zn(OAc)_2$ at room temperature, the starting material (**19**) was recovered (75%) after 7 days along with the ring expanded 7-membered ether (19%), while the rearrangement of **7** with $Zn(OAc)_2$ proceeded smoothly even at room temperature for 21 h, giving the 7-membered ether (**14**) in 81% yield (**14a**: 77%, **14b**: 4%). In the case of the acetate (**19**), the acetoxyl group besides the mesyloxy group would also participate with $Zn(OAc)_2$ and might slightly prevent the smooth rearrangement-ring expansion. Thus, the substrates having the olefinic functional groups on the C2-side chain could be much more effectively used for the rearrangement-ring expansion and for ring elongation of the ether.



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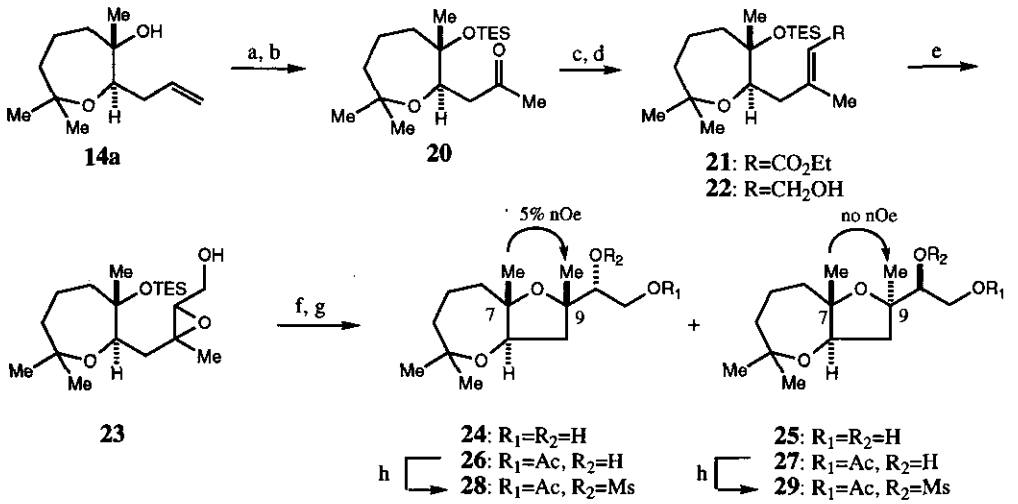
7: R_1=R_2=H	3.0 h	**14**: R_1=R_2=H	**a**: R=H (65%), **b**: R=Ac (17%)
10: R_1=Me, R_2=CO_2Et	3.0 h	**15**: R_1=Me, R_2=CO_2Et	**a**: R=H (77%), **b**: R=Ac (16%)
11: R_1=H, R_2=CO_2Me	2.5 h	**16**: R_1=H, R_2=CO_2Me	**a**: R=H (83%), **b**: R=Ac (13%)
12: R_1=Me, R_2=CH_2OH	3.0 h	**17**: R_1=Me, R_2=CH_2OH	**a**: R=H (83%), **b**: R=Ac (11%)
13: R_1=H, R_2=CH_2OH	1.5 h	**18**: R_1=H, R_2=CH_2OH	**a**: R=H (62%), **b**: R=Ac (28%)

Ring elongation using the present rearrangement-ring expansion was then investigated. The construction of the ST-ring (and XY-ring) model system of maitotoxin (**1**), one of the crucial steps for the synthesis of **1**, was undertaken starting from the 7-membered ether (**14a**). Rearrangement-ring

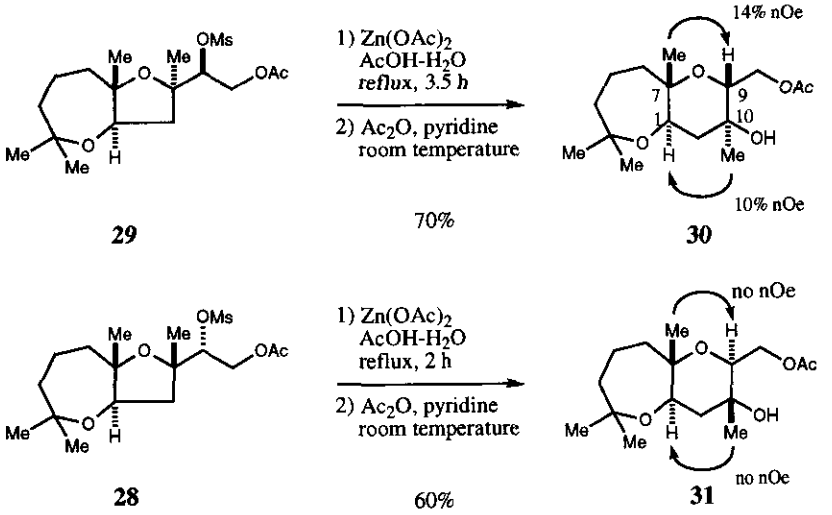
expansion of **7** with $Zn(OAc)_2$ followed by hydrolysis with K_2CO_3 in MeOH produced the 7-membered ether (**14a**) in 88% yield. After protection as the triethylsilyl (TES) ether, the alcohol (**14a**) was subjected to the Wacker oxidation to give the methyl ketone (**20**) in 91% yield. The Horner-Wadsworth-Emmons reaction of **20** with $(EtO)_2P(O)CH_2CO_2Et$ did not afford ester (**21**). This problem was overcome using high pressure. Treatment of **20** with $(EtO)_2P(O)CH_2CO_2Et$ and NaH in toluene at 1.5 GPa for 96 h produced the desired (*E*)-α,β-unsaturated ester (**21**) in 73% yield.[9] DIBAH reduction of the ester (**21**) gave allyl alcohol (**22**) (92%), which was subjected to the Sharpless AE using (+)-diisopropyl tartrate (DIPT) to give a mixture of the α- and β-epoxides (**23**). Upon treatment of **23** with n-Bu_4NF, deprotection and 5-*exo*-cyclization simultaneously took place giving the 5,7-membered bicyclic ethers (**24**) and (**25**) (67% yield from **22**). The mixture of alcohols (**24**) and (**25**) was



Reagents and Conditions: (a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (b) O_2, $PdCl_2$, CuCl, H_2O, DMF (91% from **14a**); (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, toluene, 1.5 GPa, 96 h (73%); (d) DIBAH, toluene, -78 °C (92%); (e) t-BuOOH, (+)-DIPT, $Ti(O\text{-}i\text{-}Pr)_4$, MS-4A, CH_2Cl_2, -23 °C; (f) n-Bu_4NF, CH_2Cl_2, room temperature (67% from **22**); (g) AcCl, 2,4,6-collidine, CH_2Cl_2, -78 °C (91%), then hplc separation; (h) MsCl, Et_3N, CH_2Cl_2, 0 °C (92% for **29**, 90% for **28**).

regioselectively acetylated with AcCl-collidine[10] to give a 1 : 2.8 mixture of two isomeric acetates (**26**) and (**27**) (91%), which were separated by hplc. Treatment of both isomers (**26**) and (**27**) with MsCl-Et3N afforded the mesylate (**28**) (92%) and (**29**)[11] (90%), respectively. The stereostructures of **28** and **29** were determined by the nOe measurement; the nOe between C7-Me and C9-Me was observed in **28** but not in **29**. The reaction of the desired **29** with $Zn(OAc)_2$ in aq. AcOH at reflux for 3.5 h produced the ring expanded ether which was acetylated to give **30**[12] in 70% yield. The nOe observation between C7-Me and C9-H, C10-Me and C1-H confirmed the stereostrucure of the product (**30**). Thus, the second rearrangement-ring expansion successfully took place for ring elongation giving the desired **30**,

corresponding to the ST- and XY-ring systems of maitotoxin (**1**). On the other hand, the rearrangement of the other isomer (**28**) with $Zn(OAc)_2$ followed by acetylation also stereoselectively produced the isomeric 6,7-membered bicyclic ether (**31**) in 60% yield.



In summary, the rearrangement of 6-membered ethers (**7**) and (**10** - **13**) having olefinic functional groups on the C2-side chain proceeded effectively with ring expansion, giving the 7-membered ethers (**14** - **18**). The 7-membered ether (**14a**) was converted into the mesylate (**29**) *via* the Sharpless AE followed by *exo*-cyclization. A second rearrangement-ring expansion of **29** with $Zn(OAc)_2$ proceeded effectively to give the desired 6,7-membered bicyclic ether (**30**), corresponding to the ST- and XY-ring systems of maitotoxin.

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10. High pressure reaction was carried out using the apparatus made by Instrumentation Center of this institute (RIKEN).

11. Data for **29**: $[\alpha]_D^{21}$ -0.43 ° (c 0.93, $CHCl_3$); ir (neat) 1747 cm^{-1}; ^1H nmr (500 MHz, $CDCl_3$) δ 4.77 (d, J=8.6 Hz, 1H), 4.54 (d, J=12.5 Hz, 1H), 4.17 (dd, J=12.5, 8.6 Hz, 1H), 4.00 (dd, J=11.6, 7.3 Hz, 1H), 3.07 (s, 3H), 2.24 (t, J=11.9 Hz, 1H), 2.10 (s, 3H), 1.90 (dd, J=11.9, 7.0 Hz, 1H), 1.24 (s, 3H), 1.18 (s, 3H), 1.16 (s, 6H).

12. Data for **30**: $[\alpha]_D^{21}$ +44.4 ° (c 0.61, $CHCl_3$); ir (neat) 3448, 1739 cm^{-1}; ^1H nmr (500 MHz, $CDCl_3$) δ 4.38 (dd, J=11.5, 3.0 Hz, 1H), 3.93 (dd, J=11.5, 7.7 Hz, 1H), 3.58 (dd, J=7.7, 3.0 Hz, 1H), 3.39 (dd, J=11.1, 6.0 Hz, 1H), 2.07 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H).

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