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SYNTHETIC STUDY OF THE C'D'E' RING SYSTEM OF MAITOTOXIN VIA FURAN BASED STRATEGY

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Abstract – Synthetic study of the C'D'E' ring system of maitotoxin was examined via Suzuki–Miyaura coupling of an *exo*-iodoolefin and a furanylborane derivative, followed by Sharpless asymmetric dihydroxylation, Achmatowicz reaction, borylation/oxidation, and reductive etherification.

Maitotoxin (MTX) is a ladder-shaped polyether isolated from the dinoflagellate *Gambierdiscus toxicus* (Figure 1).[1] Because of the potent biological activities and the complex molecular structure, MTX has attracted keen interest of the synthetic community.[2-4]

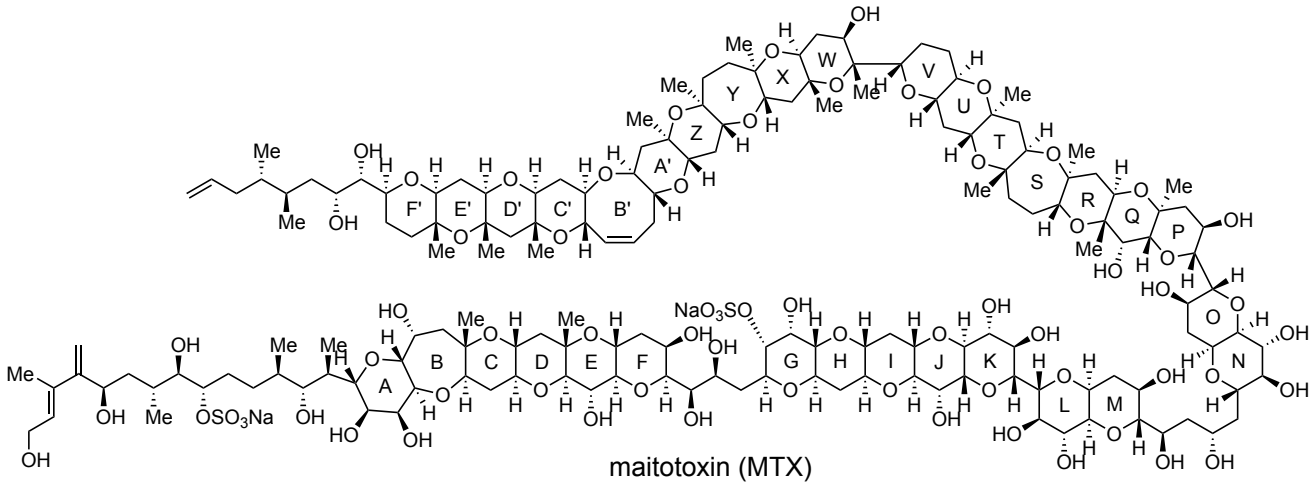


Figure 1. Structure of maitotoxin (MTX)

Among the synthesis of partial structures of MTX, construction of the C'D'E' ring system is a crucial issue due to the presence of the consecutive angular methyl groups in the 6/6/6-tricyclic ether system. Therefore, it was restricted to stepwise construction of the tetrahydropyran systems (linear strategy) by using acid-catalyzed 6-*endo* epoxide opening (Method A)[5] and SmI_2-induced reductive cyclization

(Method B)[6] as reported by Nicolaou,[2d] Nakata,[3a] and Oishi,[4c] respectively, with different combination of the methods and direction of the ring construction (Figure 2).

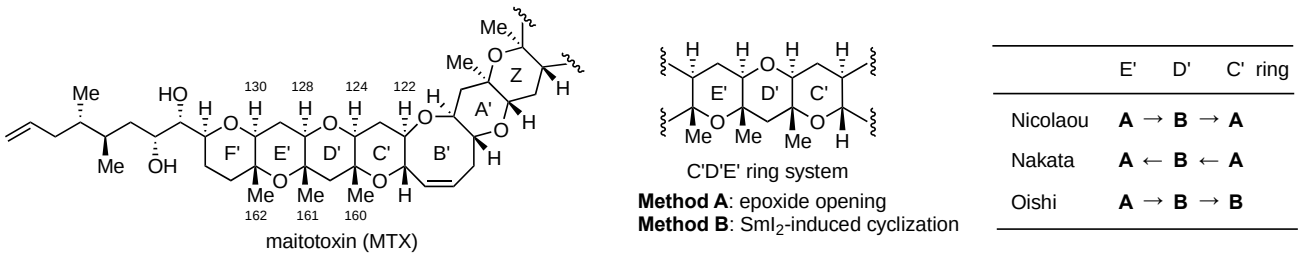
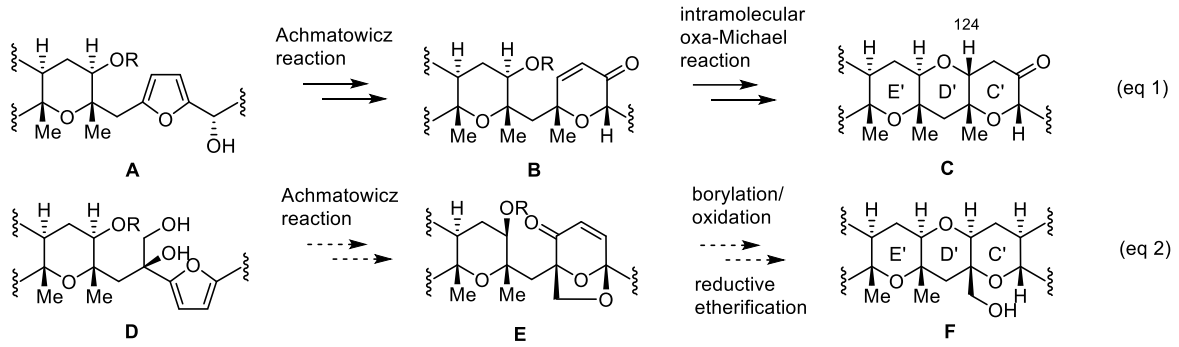


Figure 2. Partial structure of maitotoxin (MTX) and the linear synthetic strategy of the C'D'E' ring system

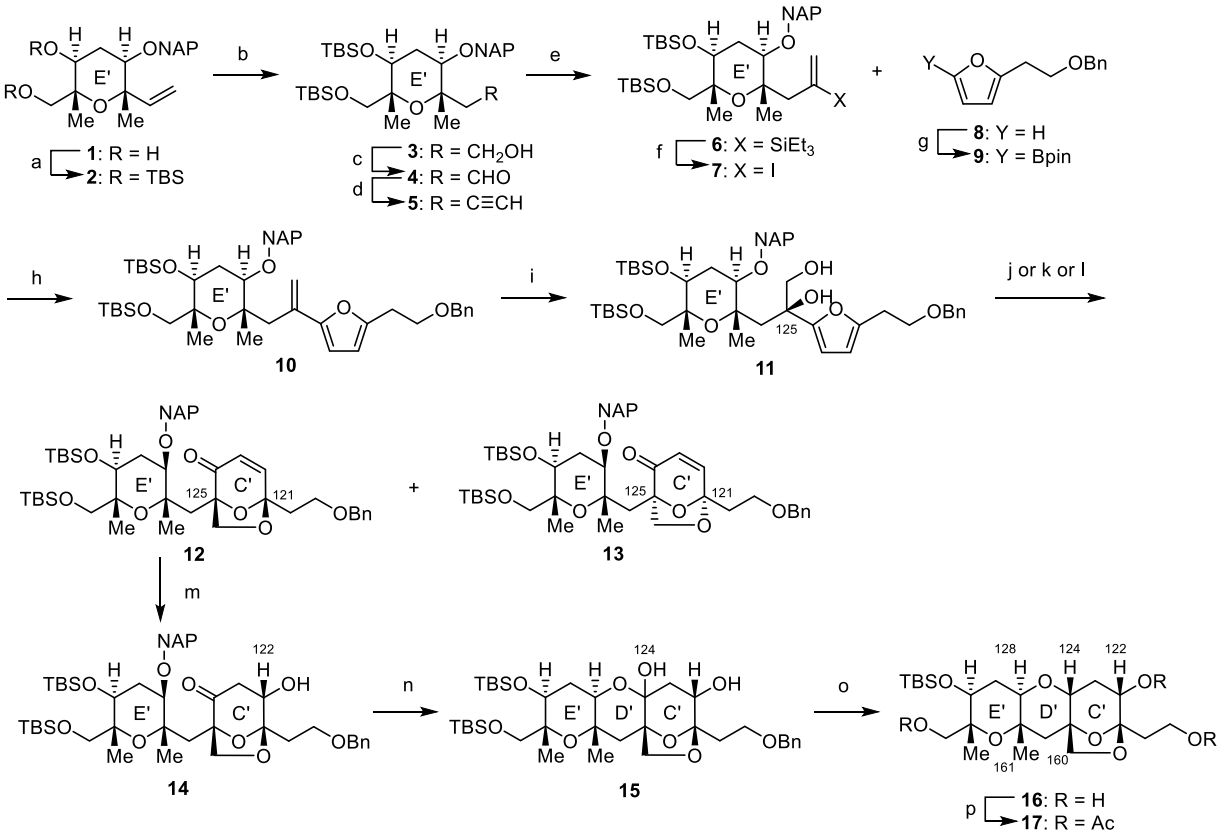
During the course of our synthetic studies of ladder-shaped polyethers, we developed furan based strategies to construct the 6/6/6-tricyclic ethers,[4g,7] and applied for the synthesis of the C'D'E' ring of MTX (Scheme 1, eq 1). Although furan derivative **A** was converted to enone **B** via Achmatowicz reaction,[8,9] the key reaction to construct the C' ring via intramolecular oxa-Michael reaction gave undesired C124-epimer.[4f] Herein, we report alternative approach to construct the C'D'E' ring system **F** via Achmatowicz reaction of **D** giving enone **E**, followed by borylation/oxidation and reductive etherification (Scheme 1, eq 2).



Scheme 1. Furan based strategies for synthesizing the C'D'E' ring system of MTX

Synthetic study of the C'D'E' ring system is shown in Scheme 2. Protection of diol **1**[4g] as TBS ether and hydroboration of the terminal olefin **2** with 9-BBN furnished primary alcohol **3** (quant). TEMPO oxidation of **3** followed by treatment of the resulting aldehyde **4** with $TMSCHN_2$/*n*-BuLi afforded terminal alkyne **5** (82%, 2 steps). Ru-Catalyzed hydrosilylation[10] of **5** giving alkenylsilane **6** followed by treatment with iodine resulted in the formation of iodoolefin **7** (76%, 2 steps). On the other hand, pinacolborane derivative **9** was prepared from furan derivative **8**[11] by Ir-catalyzed coupling reaction with

B_2pin_2 (70%).[12] Suzuki–Miyaura coupling of **7** and **9** using $PdCl_2(PPh_3)_2$ as a catalyst in the presence of aqueous Na_2CO_3 resulted in the formation of **10** (76%). Sharpless asymmetric dihydroxylation of the *exo*-olefin **10** with $(DHQD)_2PHAL$ as a ligand afforded diol **11** (90%) as a single diastereomer. The next task is the formation of bicyclic acetal via Achmatowicz reaction of **11**.[13] When MCPBA was used as an oxidant,[14,15] the desired product **12** was obtained with concomitant formation of the diastereomer at C121 and C125 **13** as an inseparable mixture (43%) in a 1 : 0.8 ratio. Since diasteromerically pure **11** was used for the reaction, epimerization of **11** at C125 might occur under the reaction conditions presumably via carbocation generated at C125. When **11** was reacted with $MeReO_3$/urea hydroperoxide[16] followed by treating with PPTS, a mixture of **12** and **13** was also obtained (36%, **12** : **13** = 1 : 0.2).



Scheme 2. Reagents and conditions: (a) TBSCl, imidazole, DMF, rt to 90 °C, 21 h, quant; (b) 9-BBN, THF, rt, 2 h; aq H_2O_2, aq $NaHCO_3$, rt, 50 min, quant; (c) TEMPO, $NaOCl{\cdot}5H_2O$, CH_2Cl_2, aq KBr, aq $NaHCO_3$, 0 °C, 40 min; (d) $TMSCHN_2$, *n*-BuLi, THF, –78 to 0 °C, 50 min, 82% (2 steps); (e) $[Cp^*Ru(MeCN)_3]PF_6$, Et_3SiH, CH_2Cl_2, rt, 5 h; (f) I_2, 2,6-lutidine, CH_2Cl_2, rt, 3 h, 76% (2 steps); (g) $[IrCl(COD)]_2$-dtbpy, B_2pin_2, octane, 80 °C, 18 h, 70%; (h) $PdCl_2(PPh_3)_2$, Na_2CO_3, DMF, H_2O, 95 °C, 3.5 h, 76%; (i) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOMe, *t*-BuOH, H_2O, rt, 2 h, 90%; (j) MCPBA, 43%, **12** : **13** = 1 : 0.8; (k) $MeReO_3$, $H_2NCONH_2{\bullet}H_2O_2$, 36%, **12** : **13** = 1 : 0.2; (l) Oxone, acetone, aq $NaHCO_3$, rt, 4 h; PPTS, CH_2Cl_2, 0 °C, 1 h, 74% (2 steps), **12** (single isomer); (m) B_2pin_2, $CuCO_3{\cdot}Cu(OH)_2$, PPh_3, THF, H_2O, rt, 2.5 h; aq H_2O_2, aq $NaHCO_3$, rt, 20 min, 95%; (n) DDQ, CH_2Cl_2, pH7 buffer, rt, 35 min, 83%; (o) $TiCl_4$, Et_3SiH, CH_2Cl_2, –40 °C to rt, 2.5 h; (p) Ac_2O, DMAP, pyridine, rt, 3 h, 42% (2 steps).

Although reactions with $VO(acac)_2$/TBHP,[17] NBS/NaOAc/$NaHCO_3$,[18] and Oxone/KBr/$NaHCO_3$[19] gave complex mixture, treatment of **11** with dimethyldioxirane[20] prepared in situ from Oxone and acetone[21] in the presence of $NaHCO_3$ followed by treatment with PPTS resulted in the formation of bicyclic enone **12** (74%) as a single isomer. Then, borylation of **12** with Cu catalyst and B_2pin_2 proceeded regio- and stereoselectively to afford alcohol **14** as a single isomer after the oxidative work up with H_2O_2.[22] Presumably, borylation of **12** proceeded from α-face (convex face) giving the undesired isomer, in an analogous manner as the previous example of epoxidation reported by Ogasawara,[15] but it would be possible to invert the stereochemistry at the later stage. Removal of the NAP group of **14** with DDQ gave hemiacetal **15** (83%) as a single isomer (the stereochemistry at C124 was not determined). Although reductive etherification of **15** with $TiCl_4$/Et_3SiH proceeded at the hemiacetal moiety (C124), the bicyclic acetal (C121) remained intact contrary to the previous example of the simple bicyclic acetal reported by Kotsuki.[23] In addition, concomitant removal of the TBS and Bn groups at the primary alcohols occurred to afford **16** as a single isomer. The polar triol **16** was isolated as triacetate **17** (42%, 2 steps). Structure analysis of **17** was carried out by NOSEY experiments as shown in Figure 3A, and NOEs were observed between H124 and CH_2 of C160, and CH_3 of C161, respectively, but not between H124 and H128. Therefore, in the reductive etherification of **15**, hydride attack to the oxocarbenium ion occurred from the β-face, convex face of the C'D'-fused ring system in which the D' ring takes boat conformation to avoid 1,3-diaxial interaction between the CH_2 of C160 and CH_3 of C161 (Figure 3B).

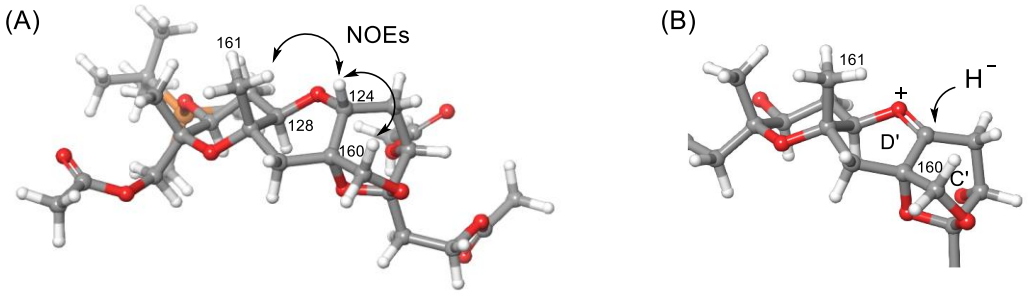


Figure 3. (A) NOE experiments of **17** and (B) plausible transition state of the reductive etherification of **15**

In conclusion, synthesis of the C'D'E' ring system of MTX was examined via Suzuki–Miyaura coupling, followed by Sharpless asymmetric dihydroxylation, Achmatowicz reaction, borylation/oxidation, and reductive etherification. Although the resulting product was the diastereomer at C122 and C24, these findings obtained through the synthetic study including reactivity of the bicyclic acetal might be useful guidance to design synthetic strategy of polycyclic ether system. Further synthetic study on the C'D'E' ring system of MTX is currently underway in our laboratory.

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

Supplementary data (Experimental procedures and details, Characterization data for products, NMR spectra for all compounds) associated with this article can be found, in the onlineversion, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27429/102/12.

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