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Synthetic Studies on Maitotoxin. 2. Stereoselective Synthesis of the WXYZA′-Ring System

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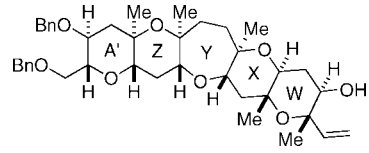
ABSTRACT



The stereoselective synthesis of the WXYZA′-ring system of maitotoxin has been accomplished via a linear synthetic approach, in which key reactions were SmI_2-induced cyclization of *β*-alkoxyacrylate for the construction of the A′-, Y-, and X-rings and 6-*endo* cyclization of hydroxy vinylepoxide for that of the Z- and W-rings.

The polyether marine natural product, maitotoxin (MTX, **1**, Figure 1), is currently one of the most toxic and complex natural products (MW 3422) known.[1] It possesses 32 fused ether rings, 28 hydroxyl groups, 21 methyl groups, 2 sulfates, and 98 chiral centers, and its structure was collectively deduced by three different groups.[2–5] The synthetically challenging complex structure and potent biological activity have attracted the attention of synthetic chemists and biochemists. In the preceding paper,[6] we reported a synthesis of the C′D′E′F′-ring system with an appropriate side chain. We now report the stereoselective synthesis of the WXYZA′-ring of MTX (**1**) through a linear strategy for the construction of polycyclic ether.

The WXYZA′-ring system of MTX consists of a trans-fused 6,6,7,6,6-pentacyclic ether core containing twelve chiral centers, one hydroxyl and five methyl groups. Our synthetic strategy to obtain the WXYZA′-ring **i** is shown in Scheme 1. Our synthesis features a linear synthetic route using efficient general methods for the construction of trans-fused polycyclic ethers, that is, SmI_2-induced reductive cyclization

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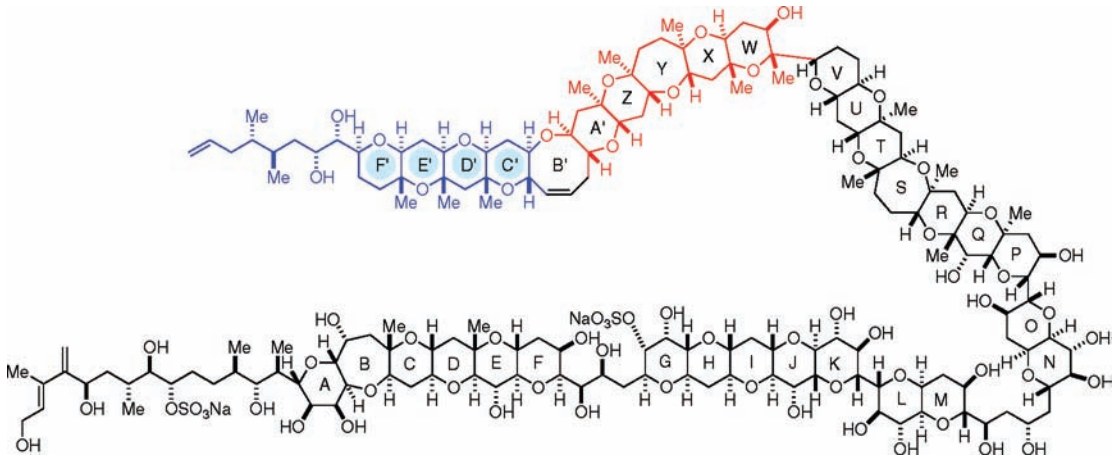
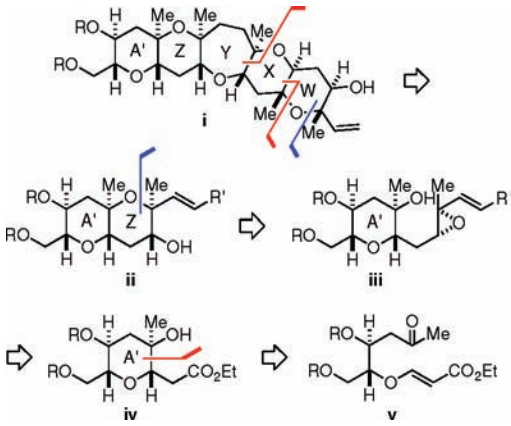


Figure 1. Structure of maitotoxin (**1**).

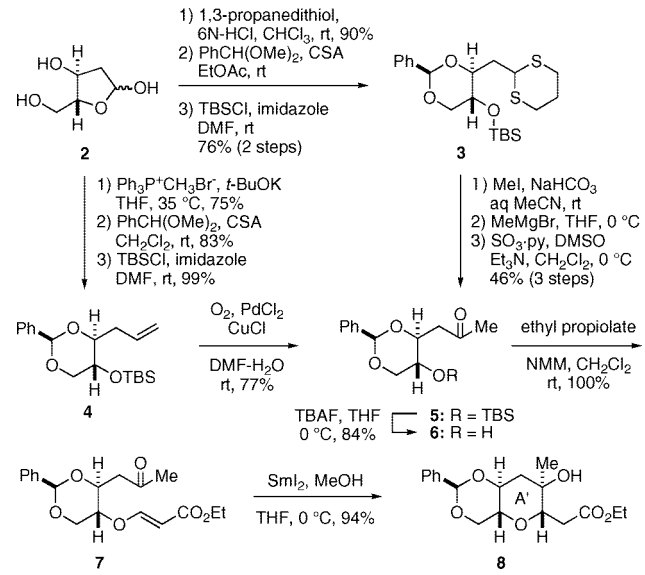
Scheme 1. Synthetic Strategy for the WXYZA′-Ring System



of a β-alkoxyacrylate (e.g., **v**→**iv**),[7] and 6-*endo* cyclization of a hydroxy vinylepoxide (e.g., **iii**→**ii**).[8] The tetrahydropyran A′- and X-rings, and oxepane Y-ring, having 2,3-*trans*-3-hydroxy-3-methyl groups, would be constructed by SmI_2-induced cyclization,[7] and the tetrahydropyran W- and Z-rings, having 2,3-*trans*-3-hydroxy-2,6-dimethyl groups, would be synthesized by 6-*endo* cyclization.[8]

First, the A′-ring was synthesized as shown in Scheme 2. After thioacetalization of 2-deoxy-D-ribose (**2**) and protection as the benzylidene acetal,[9] TBS protection gave thioacetal

Scheme 2



3. Successive deprotection of the thioacetal, Grignard reaction using MeMgBr, and oxidation with SO_3•py-DMSO afforded methyl ketone **5** in 46% yield (three steps). The methyl ketone **5** was alternatively synthesized via olefin **4**. After the Wittig reaction of **2** with $Ph_3P{=}CH_2$ (75%),[10] protection as the benzylidene acetal (83%) followed by TBS protection afforded olefin **4** in 99% yield. Wacker oxidation of **4** provided methyl ketone **5** in 77% yield. After removal of the TBS group, hetero-Michael addition of **6** with ethyl propiolate in the presence of *N*-methylmorpholine (NMM) afforded β-alkoxyacrylate **7**, quantitatively. Treatment of **7** with SmI_2[11] in the presence of MeOH in THF at 0 °C

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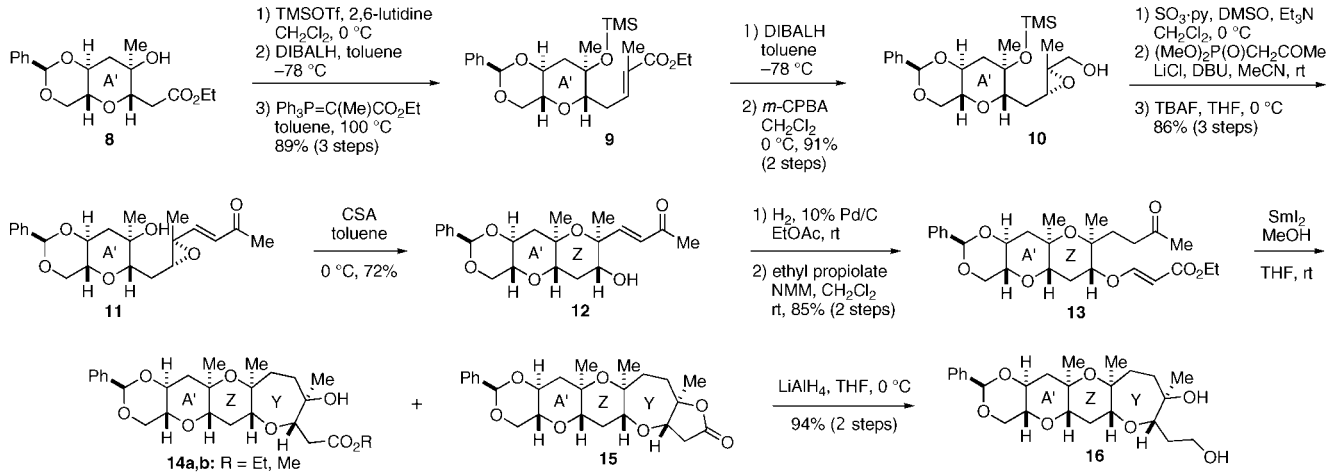
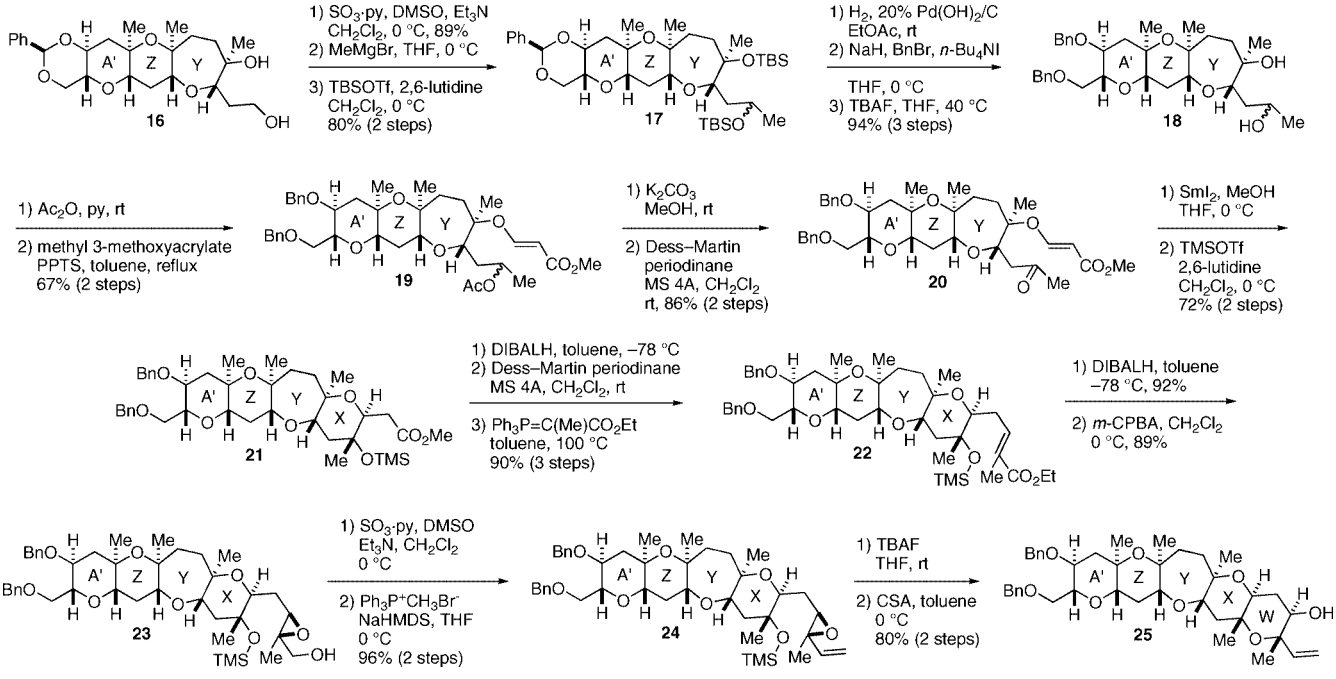
Scheme 3



Scheme 4



effected reductive cyclization to give the *syn-trans*-A′-ring **8** in 94% yield with complete stereoselection.

The Z and Y rings were synthesized by 6-*endo* cyclization of hydroxy vinylepoxide[8] and SmI_2-induced cyclization,[7] respectively (Scheme 3). The alcohol **8** was converted into α,*β*-unsaturated ester **9** in 89% yield by TMS-protection, DIBALH reduction, and Wittig reaction. After reduction of **9** with DIBALH, treatment of the resulting allylic alcohol with *m*-CPBA predominantly afforded α-epoxide **10** in 91% yield (two steps).[12,13] Oxidation of the alcohol **10** with SO_3·py-DMSO followed by HWE reaction using $(MeO)_2$-$P(O)CH_2COMe$ in the presence of LiCl and DBU gave α,*β*-unsaturated methyl ketone, which was treated with TBAF to give alcohol **11** in 86% yield (three steps). Upon treatment of **11** with camphorsulfonic acid (CSA) in toluene at 0 °C, 6-*endo* cyclization regioselectively took place to give the *syn-trans*-tetrahydropyran Z-ring **12** in 72% yield. Hydrogenation of the α,*β*-unsaturated ketone **12** on Pd/C gave saturated methyl ketone, which was subjected to hetero-Michael addition with ethyl propiolate to give *β*-alkoxyacrylate **13** in 85% yield (two steps). Treatment of **13** with SmI_2 in the presence of MeOH at rt constructed the *syn-*

(12) The epoxidation would proceed stereoselectively from the opposite side of the silyloxy group through a fixed conformation (see the Supporting Information).

(13) (a) Sakamoto, Y.; Matsuo, G.; Matsukura, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749. (b) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517.

trans-oxepane ring with complete stereoselection to give a mixture of esters **14a**,**b** and lactone **15**. The mixture was reduced with $LiAlH_4$ to give diol **16** as a single product in 94% yield (two steps). The stereostructure of **16** was confirmed by extensive NMR analyses (^{1}H and ^{13}C NMR, NOE, and HMBC).

Oxidation of **16** with SO_3•py—DMSO afforded aldehyde (89%), which was treated with MeMgBr and then TBSOTf to give di-TBS ether **17** in 80% yield (two steps) (Scheme 4). The benzylidene acetal **17** was converted to dibenzyl ether **18** in 94% yield by protective group manipulation, that is, (1) hydrogenolysis, (2) dibenzylation, and (3) desilylation. After acetylation of the secondary alcohol, hetero-Michael addition to the tertiary alcohol of **18** using ethyl propiolate in the presence of NMM was unsuccessful. However, this problem was overcome by treatment with methyl 3-methoxyacrylate and PPTS in toluene at reflux to give **19** in 67% yield (two steps).[7d] Alkaline methanolysis of the acetate **19** followed by Dess—Martin oxidation afforded methyl ketone **20** in 86% yield (two steps). Treatment of **20** with SmI_2 produced a *syn-trans*-tetrahydropyran and gave the XYZA′-ring as a single product; this was treated with TMSOTf to give TMS ether **21** in 72% yield (two steps). Reduction of **21** with DIBALH followed by Dess—Martin oxidation afforded aldehyde, which was subjected to Wittig reaction to give α,β-unsaturated ester **22** in 90% yield (three steps). After DIBALH reduction (92%), epoxidation of **22** with *m*-CPBA predominantly afforded β-epoxide **23** in 89% yield.[12,13] The epoxy alcohol **23** was converted into vinylepoxide **24** (96%, two steps) by oxidation and Wittig reaction. After removal of the TMS group, treatment of **24** with CSA effected 6-*endo* cyclization to give the *syn-trans*-tetrahydropyran W-ring **25** in 80% yield (two steps), corresponding to the WXYZA′-ring of MTX (**1**). The stereostructure of **25** was unequivocally confirmed by extensive NMR analyses (^{1}H and ^{13}C NMR, NOE, and HMBC).

Figure 2 shows the difference in the ^{1}H (600 MHz) and ^{13}C (150 MHz) chemical shifts between synthetic WXYZA′-ring **25** and MTX (**1**).[14] The ^{1}H and ^{13}C NMR chemical shifts for both compounds are in excellent accordance, although several values are different from those of MTX, because of the absence of the tetrahydropyran V-ring and oxepene B′-ring, etc. This synthesis provides reconfirmation of the stereostructure of the corresponding portion in MTX.

(14) The numbering of **25** follows that the corresponding carbon atoms in MTX.

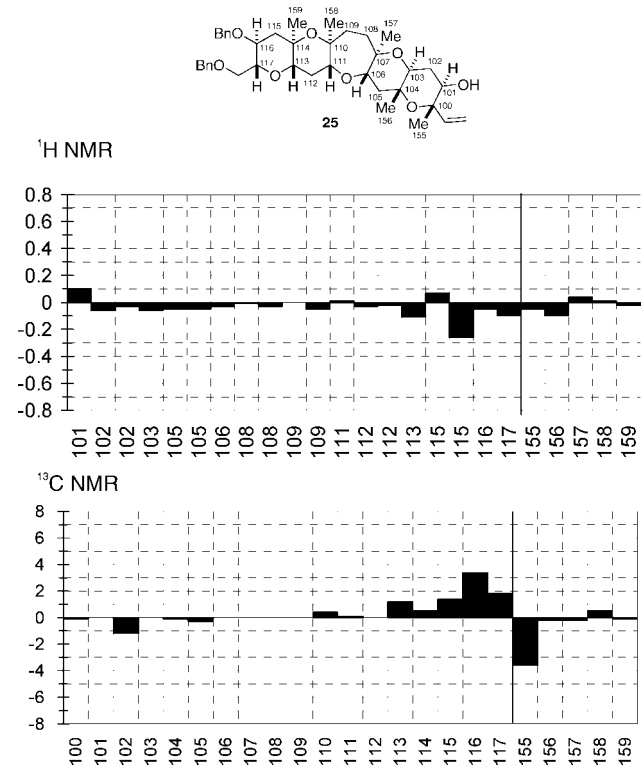


Figure 2. Differences in the ^{1}H (600 MHz) and ^{13}C (150 MHz) chemical shifts (Δδ/ppm) between synthetic **25** and the values reported for MTX (1:1 C_5D_5N—CD_3OD). The *x*- and *y*-axes represent carbon number and Δδ (Δδ = δMTX − δ**25** in ppm), respectively.

In summary, stereoselective synthesis of the WXYZA′-ring system of MTX (**1**) has been accomplished via a linear synthetic route based on SmI_2-induced cyclization of β-alkoxyacrylate and methyl ketone, and 6-*endo* cyclization of hydroxy vinylepoxide.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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