ORGANIC LETTERS

2008
Vol. 10, No. 9
1683−1685

Synthetic Studies on Maitotoxin. 3. Stereoselective Synthesis of the BCDE-Ring System

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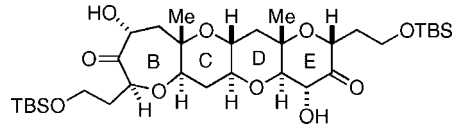
Received February 6, 2008

ABSTRACT



The stereoselective synthesis of the BCDE-ring system of maitotoxin has been accomplished through a two-directional strategy for the construction of polycyclic ether. The key reactions involve SmI_2-induced double cyclization of a β-alkoxyacrylate and a double dihydroxylation for construction of the B- and E-rings.

Maitotoxin (MTX, **1**, Figure 1), isolated from the dinoflagellate *Gambierdiscus toxicus*, is the most toxic and largest natural product (MW 3422) known thus far, except for biopolymers, such as proteins or polysaccharides.[1] The complete relative and absolute structure of MTX was determined by the Murata−Yasumoto,[2] Tachibana[3] and Kishi[4] groups.[5] MTX has 32 fused ether rings, 28 hydroxyl groups, 21 methyl groups, 2 sulfates, and 98 chiral centers; the complex structure presents a formidable challenge to synthetic chemists. In the previous papers,[6] we reported the syntheses of the C′D′E′F′-ring system having a side chain and the WXYZA′-ring system. We now report an efficient synthesis of the BCDE-ring system of MTX (**1**) through a two-directional strategy for the construction of polycyclic ether.

The ABCDEF-ring system of MTX consists of a trans-fused 6,7,6,6,6,6-membered hexacyclic ether core containing 17 chiral centers, two angular methyl groups, and five hydroxyl groups. Our first issue was the construction of the BCDE-ring system, because the A- and F-rings could be constructed at the late stage, following coupling with appropriate side chains. Our synthetic strategy for the BCDE-

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10.1021/ol8002699 CCC: $40.75
Published on Web 04/08/2008

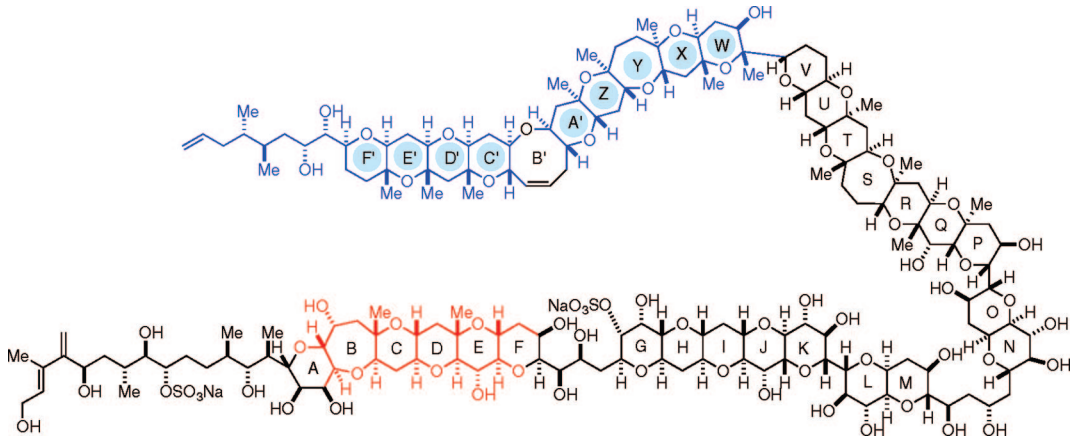
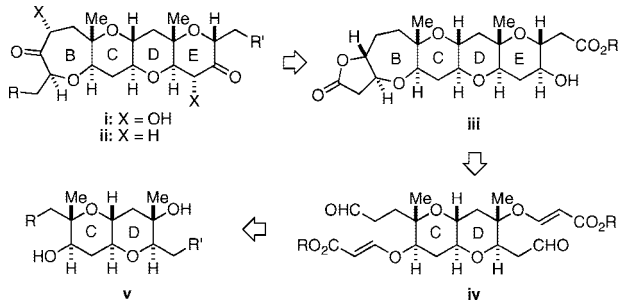
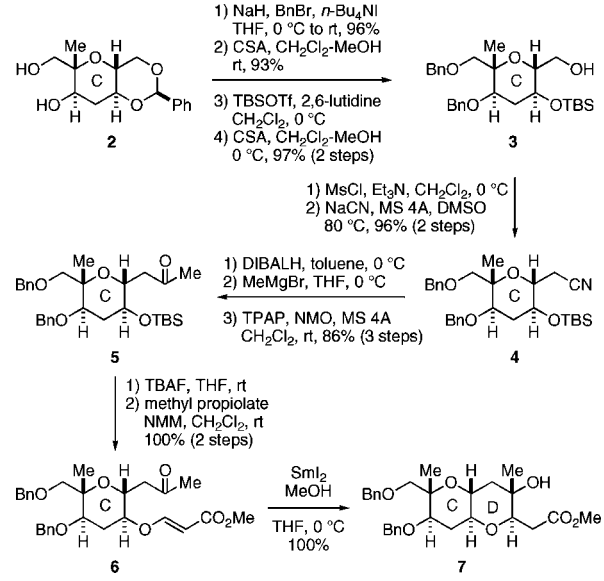


Figure 1. Structure of maitotoxin (**1**).

Scheme 1. Synthetic Strategy for the BCDE-Ring System



Scheme 2



ring system **i** is shown in Scheme 1. We planned to apply a two-directional strategy for efficient construction of the B- and E-rings, because they have similar functional groups on the rings, although the ring sizes are different. Thus, double hydroxylation of diketone **ii** would provide the BCDE-ring **i**. The precursor **iii** would be synthesized from bis(aldehyde) **iv** in one step by our recently developed SmI_2-induced cyclization.[7] The bis(aldehyde) **iv** would be efficiently synthesized from the CD-ring **v** by means of several double reactions at the left and right sides.

The synthesis of the CD-ring began with the known tetrahydropyran **2**[8] as the C-ring, prepared from commercially available 2-deoxy-D-ribose (Scheme 2). The diol **2** was converted into dibenzyl ether **3** by protective group manipulation, that is, (1) benzylation, (2) removal of benzylidene, (3) di-TBS protection, and (4) selective removal of the TBS group. Mesylation of the alcohol **3** followed by treatment with NaCN in DMSO afforded nitrile **4** in 96% yield (two steps). Reduction of **4** with DIBALH, Grignard reaction using MeMgBr, and TPAP—NMO oxidation[9] gave methyl ketone **5** in 86% yield (three steps). After removal of the TBS group in **5**, hetero-Michael addition with methyl propiolate in the presence of *N*-methylmorpholine (NMM) afforded β-alkoxyacrylate **6**, quantitatively. Upon treatment of **6** with SmI_2[10] in the presence of MeOH in THF, reductive cyclization effectively took place to give the desired trans-fused CD-ring **7** as a single product, quantitatively.[7]

The dibenzyl ether **7** was converted into bis(β-alkoxyacrylate) **13**, a key intermediate for double construction of the B- and E-rings (Scheme 3). Removal of the dibenzyl

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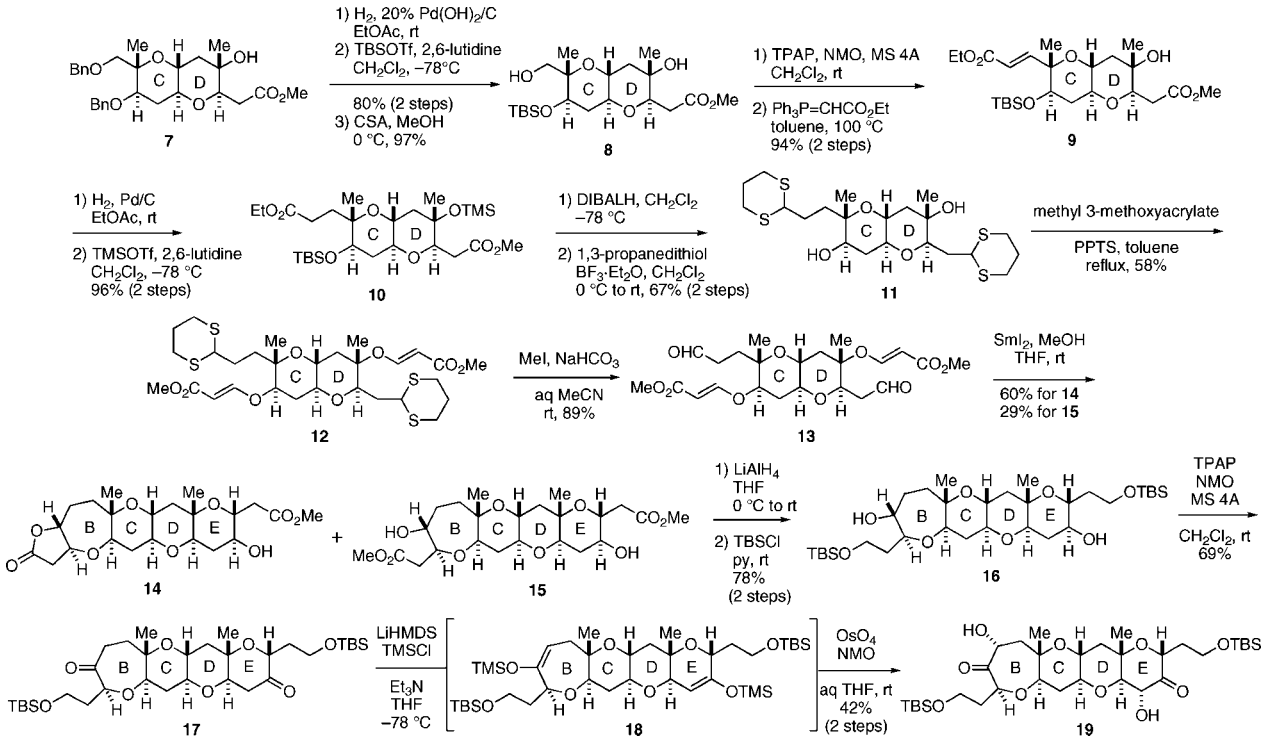
Scheme 3



group in **7**, di-TBS protection, and selective removal of the TBS group with CSA afforded diol **8** in 78% yield (three steps). Oxidation of **8** with TPAP—NMO followed by Wittig reaction using $Ph_3P{=}CHCO_2Et$ afforded α,β-unsaturated ester **9** in 94% yield (two steps), and this was subjected to successive hydrogenation and TMS protection to give diester **10** in 96% yield (two steps). The diester **10** was efficiently converted into the desired bis(aldehyde) **13** via several double reactions at the left and right sides. Reduction of **10** with DIBALH afforded bis(aldehyde), which was treated with 1,3-propanedithiol and $BF_3{\cdot}Et_2O$ to give bis(thioacetal) **11** in 67% yield (two steps). Treatment of **11** with methyl 3-methoxyacrylate and PPTS in toluene at reflux[7d] effected double hetero-Michael addition to give bis(β-alkoxyacrylate) **12** in 58% yield. Removal of two thioacetals in **12** by treatment with MeI afforded bis(aldehyde) **13** in 89% yield. Upon treatment with SmI_2 in the presence of MeOH in THF, the desired double cyclization took place, constructing the *syn-trans*-oxepane B-ring and *syn-trans*-tetrahydropyran E-ring with complete stereoselection, to give ester—lactone **14** (60%) and diester **15** (29%). Each product, **14** and **15**, was treated with $LiAlH_4$ to give the same tetraol as a single product, which was treated with TBSCl to give di-TBS ether **16** in 78% yield (two steps). Oxidation of the diol **16** with TPAP—NMO afforded diketone **17** in 69% yield. Treatment of **17** with LiHMDS and TMSCl gave bis(silylenol ether) **18**, which, upon treatment with OsO_4—NMO, stereoselectively underwent double hydroxylation to provide di-TBS **19** in 42% yield (two steps), corresponding to the BCDE-ring system of MTX (**1**). The stereoselective hydroxylation of **18** would proceed from the less hindered α-side to give **19**, bacause of the steric hindrance of angular Me groups with β-axial configuration. The structure of **19** was unequivocally confirmed by extensive NMR analyses (^1H and ^{13}C NMR, NOE, and HMBC).

In summary, stereoselective synthesis of the BCDE-ring system **19** has been accomplished through a two-directional strategy based on several double reactions at the left and right sides, including SmI_2-induced reductive cyclization.

Acknowledgment. This work was financially supported in part by the Uehara Memorial Foundation and a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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

OL8002699