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Synthetic Studies on Maitotoxin. 1. Stereoselective Synthesis of the C′D′E′F′-Ring System Having a Side Chain

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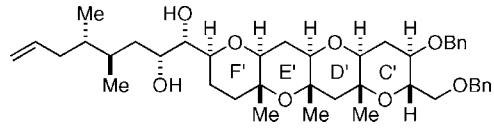
ABSTRACT



The stereoselective synthesis of the maitotoxin C′D′E′F′-ring system having a side chain has been accomplished through a convergent strategy. The key reactions include Horner-Wadsworth-Emmons coupling of the C′D′E′-ring and the side chain and subsequent construction of the F′-ring by silane reduction of dihydropyran.

Maitotoxin (MTX; **1**, Figure 1), isolated from the dinoflagellate *Gambierdiscus toxicus*, is one of the most structurally awe-inspiring and largest natural products (MW 3422) ever isolated.[1] It is implicated in ciguatera food poisoning, and influences Ca^{2+}-dependent mechanisms in a wide range of cell types.[2] The full structure of MTX, including a partial stereochemical assignment, was reported by the Murata-Yasumoto group between 1992−1995.[3] The relative stereochemistry of the remaining acyclic parts and the absolute structure of MTX were determined independently by Tachibana[4] and Kishi[5] and their colleagues in 1996.[6] The giant structure of MTX contains 32 fused ether rings, 28 hydroxyl groups, 21 methyl groups, 2 sulfates, and 98 chiral centers. The skeletal novelty, complexity, and biological activity of MTX have attracted the attention of both chemists and biologists. We now report the stereoselective synthesis of the MTX C′D′E′F′-ring having a side chain through a convergent strategy.[7]

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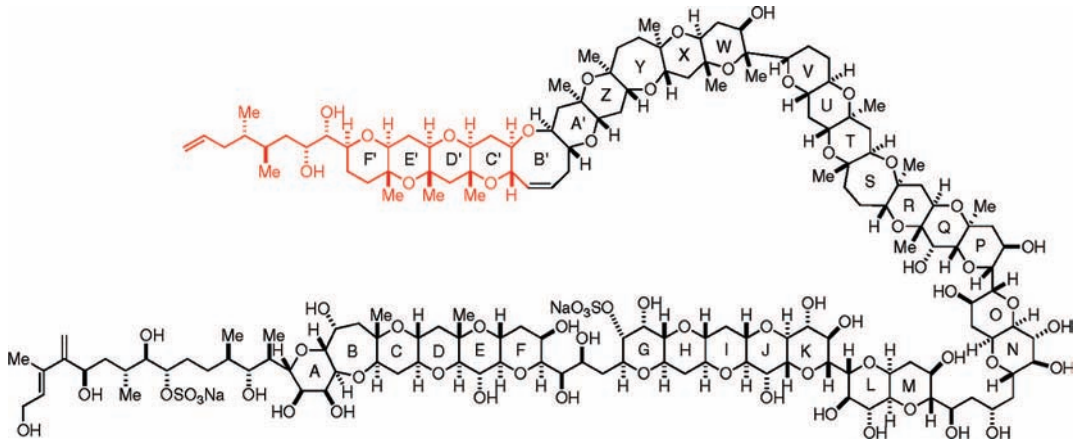
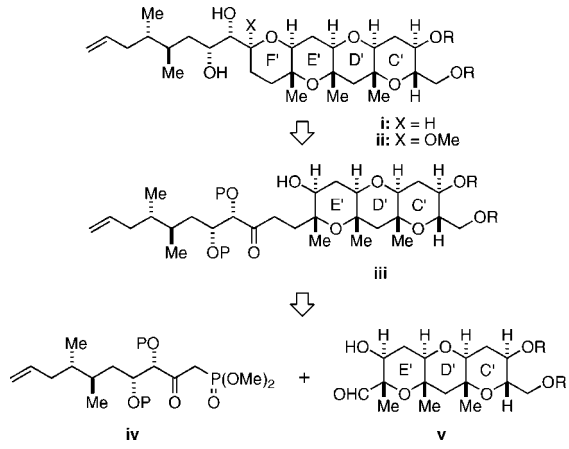
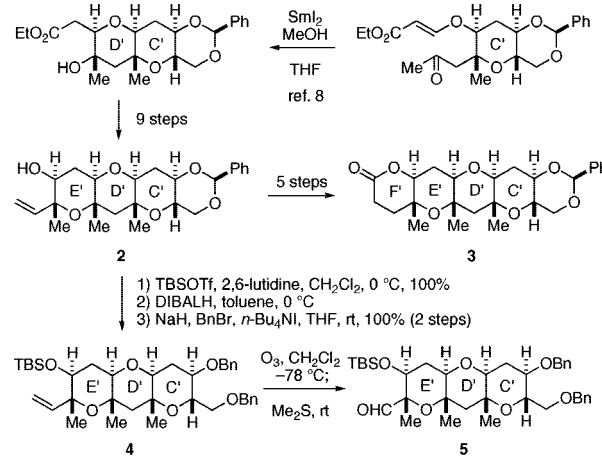


Figure 1. Structure of maitotoxin (**1**).

Scheme 1. Synthetic Strategy for the C′D′E′F′-Ring System



Scheme 2



The C′D′E′F′-ring system of MTX consists of a trans-fused 6,6,6,6-membered tetracyclic ether core containing nine chiral centers, three angular methyl groups, and a 1,2-*syn*-dihydroxy-4,5-*anti*-dimethyl-oct-7-ene side chain. Our synthetic strategy to obtain the C′D′E′F′-ring **i** having a side chain is shown in Scheme 1. The synthesis of the target compound **i** would be accomplished via coupling of the side chain β-ketophosphonate **iv** and the C′D′E′-ring aldehyde **v** using a Horner−Wadsworth−Emmons (HWE) reaction. The F′-ring would be synthesized by Lewis acid-mediated silane reduction of methyl acetal **ii**, which would be prepared from hydroxy ketone **iii**.

We have already reported the stereoselective synthesis of the C′D′E′F′-ring lactone **3** via **2**,[8] in which construction of 1,3-diaxial angular methyl groups of the D′-ring was efficiently accomplished by SmI_2-induced cyclization.[9] The intermediate **2** was converted into the key aldehyde **5** required as a coupling partner (Scheme 2). After protection of the alcohol **2** with TBSOTf, successive DIBALH reduction and benzylation afforded dibenzyl ether **4**, quantitatively. Cleavage of the olefin **4** by ozonolysis thereafter provided the desired aldehyde **5**.

The synthesis of the side chain **14** having four chiral centers began with the known alcohol **6**[10,11] (Scheme 3). Oxidation of **6** with SO_3•py-DMSO gave aldehyde,[11a] which was subjected to HWE reaction with a chiral imide **15**[12] to

(7) Kishi et al.[5a] reported the synthesis of an E′F′-ring model compound with no angular methyl groups, having a side chain, for structure determination.

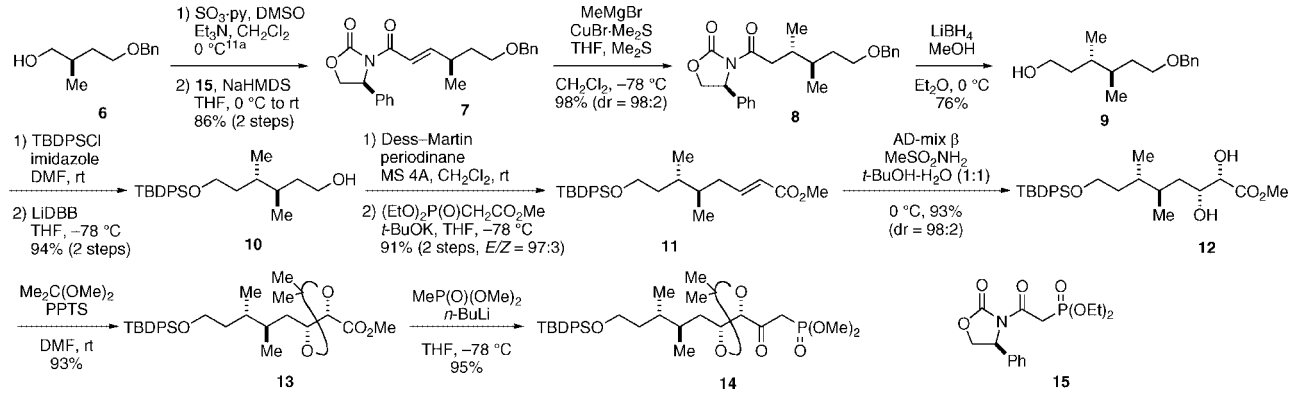
(8) Sakamoto, Y.; Matsuo, G.; Matsukura, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749.

(9) (a) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811. (b) Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett.* **1999**, *1*, 1099. (c) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8859. (d) Suzuki, K.; Matsukura, H.; Matsuo, G.; Koshino, H; Nakata, T. *Tetrahedron Lett.* **2002**, *43*, 8653. (e) Hori, N.; Matsuo, G.; Matsukura, H.; Nakata, T. *Tetrahedron* **2002**, *58*, 1853.

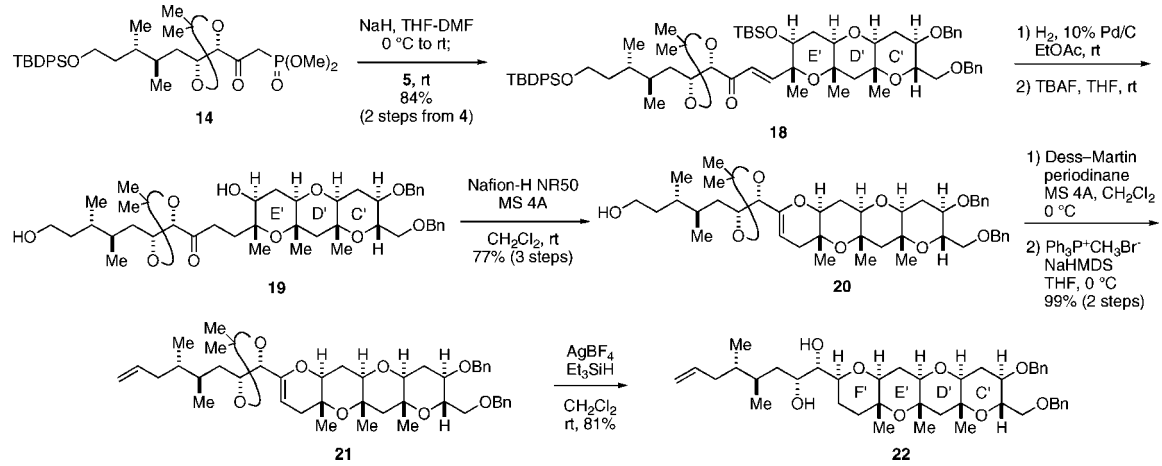
(10) The alcohol **6** was synthesized starting from (*R*)-3-*tert*-butyloxycarbonyl-2-methylpropanoic acid (>99.6% ee) in five steps: (1) BH_3, (2) MOMCl, (3) $LiAlH_4$, (4) NaH, BnBr, (5) conc. HCl, MeOH. We thank Mitsubishi Rayon Co., Ltd. for providing the starting carboxylic acid.

(11) (a) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179. (b) White, J. D.; Xu, Q.; Lee, C.-S.; Valeriote, F. A. *Org. Biomol. Chem.* **2004**, *2*, 2092.

Scheme 3



Scheme 4



give **7** in 86% yield (two steps). 1,4-Conjugate addition of **7** with MeMgBr and CuBr•Me_2S[13] afforded α-methyl adduct **8** in 98% yield (dr = 98:2).[14] Reduction of **8** with $LiBH_4$, protection with *tert*-butyldiphenylsilylchloride (TBDPSCl), and removal of the benzyl group with lithium di-*tert*-butylbiphenylide (LiDBB)[15] afforded alcohol **10** in 71% yield (three steps). Oxidation of **10** with Dess−Martin periodinane followed by HWE reaction using $(EtO)_2P(O)CH_2CO_2Me$ and *t*-BuOK afforded α,*β*-unsaturated ester **11** in 91% yield (two steps). The Sharpless asymmetric dihydroxylation[16] using AD-mix-*β* provided α-diol **12** (dr = 98:2) in 93% yield.[17] After protection of the diol as its acetonide (93%), the resulting ester **13** was treated with $(MeO)_2P(O)Me$ and *n*-BuLi to give *β*-ketophosphonate **14** in 95% yield.

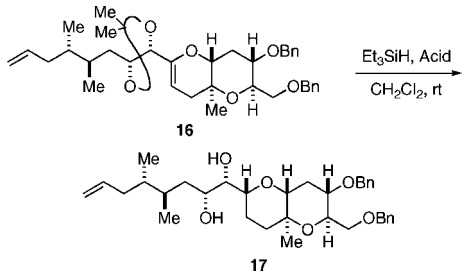
With the requisite coupling partners **5** and **14** in hand, we focused our attention on the synthesis of the C′D′E′F′-ring system **22** (Scheme 4). The HWE reaction of the C′D′E′-ring aldehyde **5** with **14** was too slow to give the coupling product. However, the present reaction using 10 equiv of **14** proceeded slowly, and enone **18** was obtained in 84% yield (two steps from the olefin **4**) after three days. Hydrogenation of **18** followed by TBAF treatment afforded diol-ketone **19**. Attempts to achieve methyl acetalization of **19** under various conditions failed, giving a complex mixture, for example, camphorsulfonic acid (CSA) and $CH(OMe)_3$ in CH_2Cl_2-MeOH. During these reactions, dihydropyran was first formed and gradually decomposed. Thus, we turned our efforts to the formation of dihydropyran, which might be converted to the desired tetrahydropyran. Several attempts to generate the dihydropyran ring gave unsatisfactory results, for example, treatment with CSA, TsOH, PPTS, etc. After many trials, we found that treatment of **19** with Nafion-H NR50[18] in the presence of molecular sieve (MS) 4A in CH_2Cl_2 at rt effectively induced dehydration to give the desired dihydropyran **20** in 77% yield (three steps from **18**). Dess−Martin oxidation of **20** followed by Wittig reaction using $Ph_3P{=}CH_2$ afforded olefin **21**, quantitatively.

(12) We thank Chemicrea Inc. for providing (*S*)-4-phenyl-2-oxazolidinone as the starting material for preparing **15**.

(13) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766.

(14) The anti configuration of the dimethyl group in **8** was confirmed by comparison of NMR data of the diol, prepared from **10** by TBAF treatment, and those of authentic *anti*-3,4-dimethylhexane-1,6-diol reported by Kishi et al.[5]

Here, reduction of dihydropyran to tetrahydropyran, a crucial step, was examined using model compound **16**. Reduction of **16** with Et_3SiH in the presence of TFA or TMSOTf in CH_2Cl_2 at rt afforded tetrahydropyran **17** in 55% or 50% yield, respectively. The best result (74%) was obtained by treatment with Et_3SiH in the presence of $AgBF_4$.



Thus, that condition was applied to the reduction of **21**. Upon treatment of **21** with Et_3SiH and $AgBF_4$ in CH_2Cl_2 at rt, reduction of dihydropyran took place, accompanied with deprotection of the acetonide, to give the desired tetrahydropyran **22** in 81% yield, corresponding to the MTX C′D′E′F′-ring having a side chain. The stereostructure of **22** was unequivocally confirmed by NMR analyses (^1H and ^{13}C NMR, NOE, and HMBC).

Figure 2 shows the difference in the ^1H (600 MHz) and ^{13}C (150 MHz) chemical shifts between synthetic C′D′E′F′-ring **22** and MTX (**1**).[19] The ^1H and ^{13}C NMR chemical shifts for both compounds are in excellent accordance, although several values differ from those of MTX, because of the absence of the oxepene B′-ring, etc. This synthesis provides reconfirmation of the stereostructure of the corresponding portion in MTX.

In summary, stereoselective synthesis of the MTX C′D′E′F′-ring system having a side chain has been accomplished via HWE coupling of the C′D′E′-ring and the side chain, followed by construction of the F′-ring.

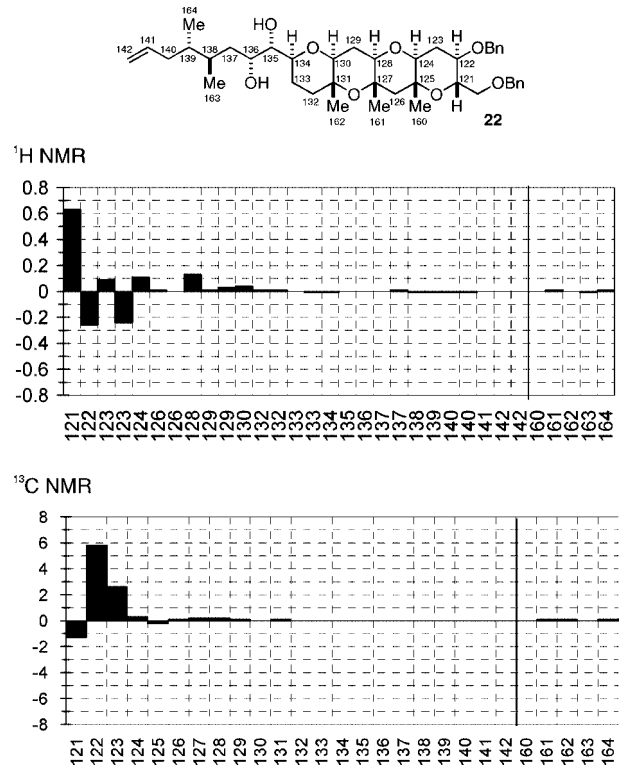


Figure 2. Differences in the ^1H (600 MHz) and ^{13}C (150 MHz) chemical shifts ($\Delta\delta$/ppm) between synthetic **22** and the values reported for MTX (1:1 C_5D_5N-CD_3OD). The *x*- and *y*-axes represent carbon number and $\Delta\delta$ ($\Delta\delta = \delta$MTX $- \delta$**22** in ppm), respectively.

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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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(17) Stereochemistry of the α-diol in **12** was assigned according to the empirical rule for Sharpless asymmetric dihydroxylation.[16]
(18) Olah, G. A.; Iyer, P. S.; Prakash, G. K. S. *Synthesis* **1986**, 513.
(19) The numbering of **22** follows that of the corresponding carbon atom in MTX.