HETEROCYCLES, Vol. 76, No. 2, 2008, pp. 1069 - 1074. © The Japan Institute of Heterocyclic Chemistry
Received, 8th May, 2008, Accepted, 12th June, 2008, Published online, 19th June, 2008. COM-08-S(N)113

STEREOSELECTIVE SYNTHESIS OF MAITOTOXIN GHI-RING SYSTEM HAVING A 1,2-DIOL SIDE CHAIN

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Abstract – The stereoselective synthesis of maitotoxin GHI-ring system having a 1,2-diol side chain was accomplished via successive SmI_2-induced reductive cyclizations of β-alkoxyacrylate–aldehyde and optically active (*E*)-β-alkoxyvinylsulfoxide–aldehyde, dihydroxylation of α,β-unsaturated δ-lactone, and Sharpless asymmetric dihydroxylation of the side chain.

Maitotoxin (MTX; **1**, Figure 1), one of the toxins implicated in ciguatera, was first discovered from the viscera of coral reef fish[1] and later isolated from the epiphytic dinoflagellate *Gambierdiscus toxicus*.[2] MTX is the most toxic and largest natural product (molecular weight 3422) known to date, except for biopolymers.[3] The full structure of MTX, including a partial stereochemical assignment, was established by the Murata-Yasumoto group.[4] The relative stereochemistry of the remaining acyclic parts and the absolute structure of MTX were determined independently by the Tachibana[5] and Kishi[6] groups.[7] The giant structure of MTX contains 32 fused ether rings, 28 hydroxy groups, 21 methyl groups, 2 sulfates, and 98 chiral centers. The unusual complex structure and potent toxicity have attracted the attention of both chemists and biologists. Partial syntheses of MTX have been reported by Tachibana[5], Kishi,[6] Nicolaou,[8] and our groups[9] so far. We have already reported the stereoselective synthesis of the BCDE-ring,[9g] GHI-ring,[9c] WXYZA'-ring,[9f] and C'D'E'F'-ring having a side chain.[9d,e] Our previous synthesis of the GHI-ring was accomplished starting from the G-ring.[9c] We now report an alternative and efficient synthesis of the GHI-ring system having a 1,2-diol side chain starting from the I-ring.

This paper is dedicated to Prof. Dr. Ryoji Noyori on the occasion of his 70th birthday.

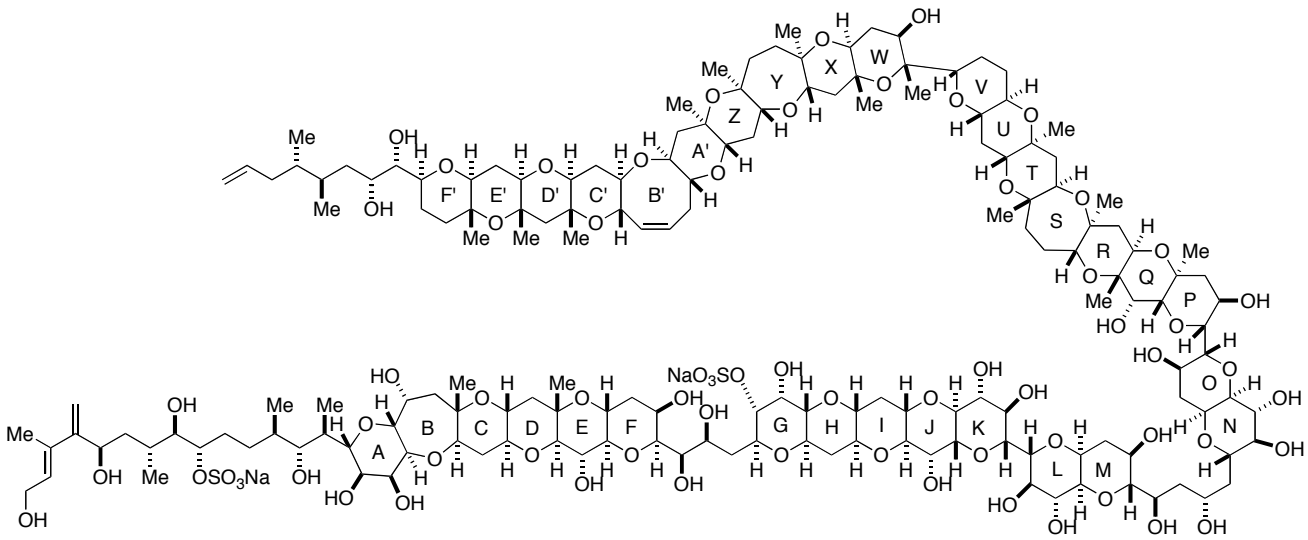
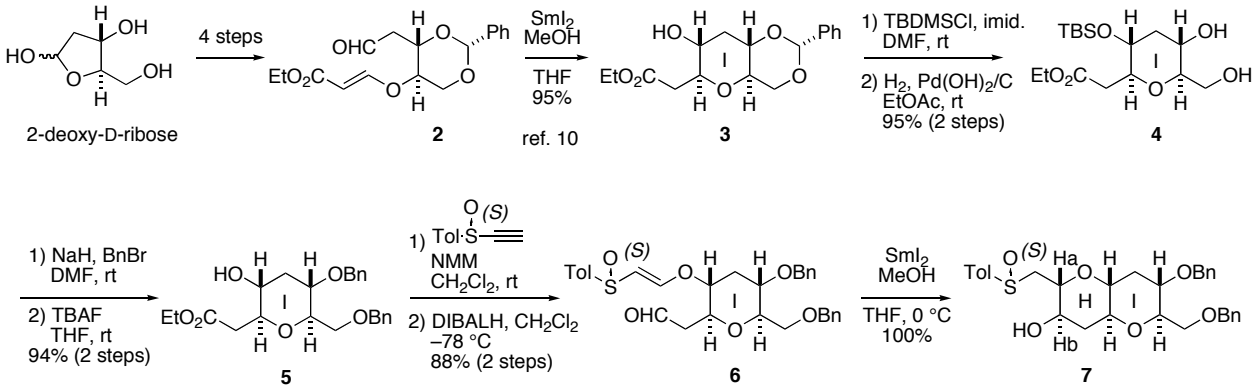


Figure 1. Structure of maitotoxin (**1**).

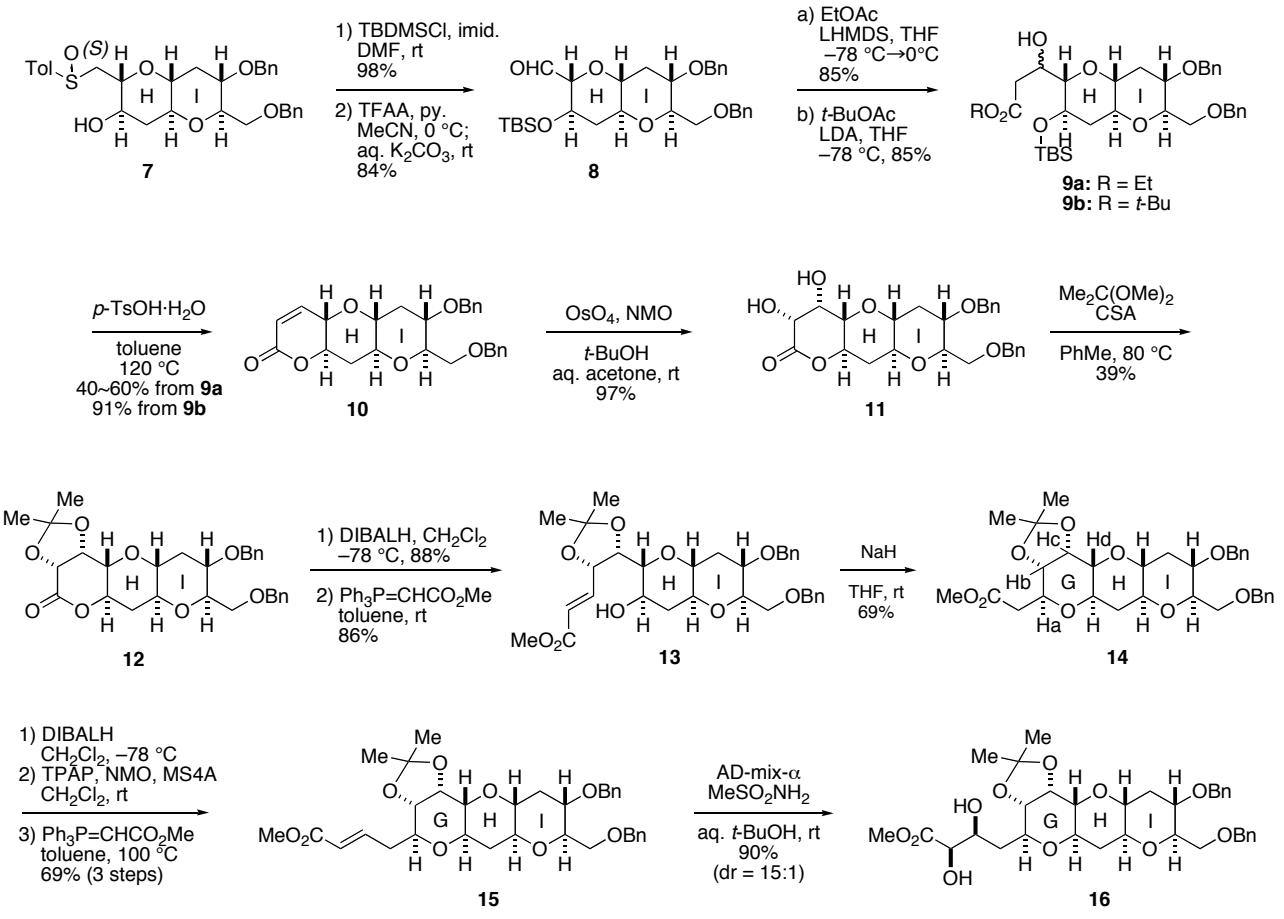
The synthesis of the GHI-ring started with the known compound **3**,[10] corresponding to the I-ring (Scheme 1). The tetrahydropyran I-ring **3** was stereoselectively synthesized by SmI_2-induced cyclization[11] of β-alkoxyacrylate–aldehyde **2**, prepared from 2-deoxy-D-ribose. Protection of alcohol **3** as the TBDMS ether followed by removal of the benzylidene group by hydrogenolysis afforded diol **4** in 95% yield (two steps), which was benzylated followed by desilylation to give dibenzyl ether **5** in 94% yield (two steps). The H-ring was then constructed based on our recently developed SmI_2-induced cyclization of β-alkoxyvinylsulfoxide–aldehyde.[12] Treatment of **5** with (*S*)-ethynyl-*p*-tolylsulfoxide in the presence of *N*-methylmorpholine (NMM) effected hetero-Michael reaction to give (*E*)-β-alkoxyvinylsulfoxide, which was reduced with DIBALH to give aldehyde **6** in 88% yield (two steps). Reductive cyclization of (*E*)-β-alkoxyvinylsulfoxide–aldehyde **6** with SmI_2 in the presence of MeOH in THF constructed *syn-trans*-tetrahydropyran to give the HI-ring **7** as a single product, quantitatively. The stereochemistry



Scheme 1. Synthesis of the HI-ring **7**.

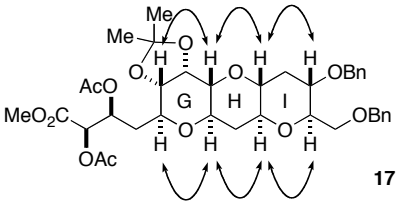
was confirmed by coupling constant ($J_{a,b}$ = 10.8 Hz) between Ha and Hb of **7**.

Next, construction of the G-ring and the side chain having β-diol was investigated (Scheme 2). After protection of **7** with TBDMSCl (98%), Pummerer rearrangement by treatment with TFAA in pyridine followed by aqueous K_2CO_3 afforded aldehyde **8** in 84% yield. After aldol reaction of **8** with EtOAc and LHMDS (85%), treatment of the resulting hydroxy ester **9a** with *p*-TsOH·H_2O in toluene at reflux effected desilylation, lactonization and dehydration in one pot to give α,β-unsaturated δ-lactone **10** in 40~60% yield. The yield of **10** was improved to 91% by using *t*-butyl ester **9b**, which was obtained by aldol reaction of **8** with *t*-BuOAc and LDA (85%). Treatment of the α,β-unsaturated δ-lactone **10** with OsO_4 in the presence of *N*-methylmorpholine *N*-oxide (NMO) exclusively afforded the desired α-diol **11** in 97% yield. After protection of the diol **11** as the acetonide **12** (39%),[13] DIBALH reduction followed by Wittig reaction using $Ph_3P{=}CHCO_2Me$ afforded α,β-unsaturated ester **13** in 86% yield. Upon treatment of **13** with NaH in THF, an intramolecular hetero-Michael addition[14] took place stereoselectively to give the GHI-ring **14** in 69% yield. The stereochemistry of the G-ring was confirmed by coupling constants ($J_{a,b}$ = 9.2 Hz, $J_{b,c}$ = $J_{c,d}$ = 3.6 Hz). Reduction of **14** with DIBALH followed by tetra-*n*-propylammonium perruthenate (TPAP)-NMO oxidation[15] gave an aldehyde, which was treated with $Ph_3P{=}CHCO_2Me$ to



Scheme 2. Synthesis of the GHI-ring **16** having a 1,2-diol side chain.

give α,β-unsaturated ester **15** in 69% yield (three steps). The Sharpless asymmetric dihydroxylation[16] of **15** furnished β-diol **16** (dr = 15:1) in 90% yield.[17] The stereostrucure of **16** was confirmed by NOE measurement of the corresponding diacetate **17** (Figure 2),[18] which was prepared by acetylation of **16**.



17

Figure 2. Observed NOE of the acetate **17**.

In summary, MTX GHI-ring system **16** having a 1,2-diol side chain was stereoselectively synthesized starting from 2-deoxy-D-ribose via successive SmI_2-induced cyclizations, dihydroxylation of α,β-unsaturated δ-lactone, intramolecular hetero-Michael addition, and Sharpless asymmetric dihydroxylation.[19]

ACKNOWLEDGEMENTS

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

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17. The stereochemistry of the β-diol in **16** was assigned according to the empirical rule for Sharpless asymmetric dihydroxylation.[16a]
18. Data for **17**: IR (neat) 2926, 2855, 1749, 1455, 1373, 1218, 1097, 1057, 867, 742, 700, 602, 508 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.53-7.28 (m, 8H), 7.21-7.19 (m, 2H), 5.56 (ddd, *J* = 7.9, 4.9, 2.6 Hz, 1H), 5.16 (d, *J* = 2.6 Hz, 1H), 4.62 (d, *J* = 12.5 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 2H), 4.49 (br dd, *J* = 4.2, 3.8 Hz, 1H), 4.40 (d, *J* = 11.3 Hz, 1H), 3.82 (dd, *J* = 9.3, 4.2 Hz, 1H), 3.75 (dd, *J* = 13.2, 11.0 Hz, 1H), 3.73 (s, 3H), 3.66 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.56 (ddd, *J* = 11.3, 10.2, 4.4 Hz, 1H), 3.51 (ddd, *J* = 11.0, 10.3, 4.3 Hz, 1H), 3.41 (m, 1H), 3.32 (ddd, *J* = 9.6, 9.3, 2.5 Hz, 1H), 3.28 (dd, *J* = 9.1, 4.2 Hz, 1H), 3.16 (ddd, *J* = 11.0, 9.1, 4.2 Hz, 1H), 3.12 (ddd, *J* = 11.3, 9.1, 4.0 Hz, 1H), 2.57 (ddd, *J* = 11.3, 4.4, 4.0 Hz, 1H), 2.46 (ddd, *J* = 11.0, 4.3, 4.0 Hz, 1H), 2.19 (s, 3H), 2.06 (ddd, *J* = 14.3, 7.9, 2.5 Hz, 1H), 2.04 (s, 3H), 1.70 (ddd, *J* = 14.3, 9.6, 4.9 Hz, 1H), 1.64 (ddd, *J* = 11.3, 11.3, 11.3 Hz, 1H), 1.53 (s, 3H), 1.44 (ddd, *J* = 11.0, 11.0, 11.0 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.8, 167.9, 138.2, 138.0, 128.4 (2C), 128.3 (2C), 127.9 (2C), 127.7 (2C), 127.6 (2C), 111.4, 80.4, 77.6, 77.1, 75.9, 74.7, 73.5, 73.3, 73.1, 72.3, 71.0, 69.9, 69.1, 69.0, 52.6, 35.1, 35.0, 33.6, 29.7, 28.3, 26.4, 20.7, 20.5; HRMS (ESI) calcd for $C_{38}H_{48}O_{13}Na$ ($M+Na^+$) 735.2987, found 735.2958.
19. The previous synthesis of the GHI-ring was accomplished in 31 steps from methyl α-D-glucopyranoside.[9c] The present synthesis of the GHI-ring, including the construction of 1,2-diol side chain, was efficiently accomplished in 25 steps from 2-deoxy-D-ribose.