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Stereoselective Syntheses of the C′D′E′F′-Ring System of Maitotoxin and the FG-Ring System of Gambierol

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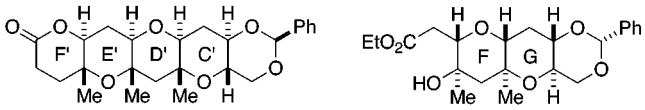
ABSTRACT



The stereoselective syntheses of the C′D′E′F′-ring system of maitotoxin and the FG-ring system of gambierol were accomplished. The key steps involve 6-*endo*-cyclization of methylepoxide, SmI_2-induced reductive cyclization, 6-*endo*-cyclization of vinylepoxide, and formation of the lactone ring.

Maitotoxin (MTX), isolated from the dinoflagellate *Gambierdiscus toxicus*, is the most toxic and largest natural product (MW 3422) known to date except for biopolymers such as proteins or polysaccharides.[1] MTX has been implicated in ciguatera food poisoning and is involved in Ca^{2+}-dependent mechanisms over a wide range of cell types.[2] The full structure and partial relative configuration of MTX were elucidated by Yasumoto et al.,[3]and then the relative configuration of the remaining parts and the absolute configuration were determined by the Tachibana[4] and Kishi[5] groups, independently. The unusual molecular structure of MTX contains 32 fused ether rings, 28 hydroxyl groups, 21 methyl groups, 2 sulfate esters, and 98 chiral centers (Figure 1). The skeletal novelty, complexity, and biological activity of MTX have attracted the attention of chemists and biologists alike.

We have already reported the stereoselective synthesis of the ST- and XY-ring systems,[6] which have 6,7-membered bicyclic ethers, based on our developed ring-expansion reaction.[7] We have also developed the SmI_2-induced reductive cyclization to synthesize the *trans*-fused ether ring systems stereoselectively[8] and have recently reported an efficient strategy for the stereoselective syntheses of 6,6- and 6,7-membered ether ring systems **1** having an angular methyl

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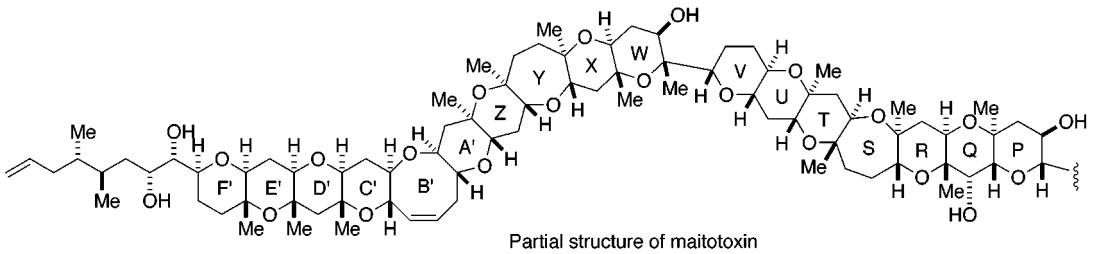
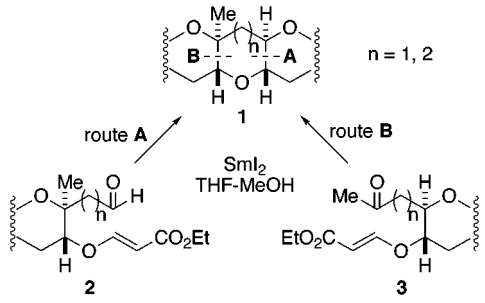


Figure 1.

group based on this SmI_2-induced cyclization of β-alkoxy acrylate with an aldehyde **2** (route A) and a ketone **3** (route B) (Scheme 1).[9] We now report the stereoselective syntheses

Scheme 1

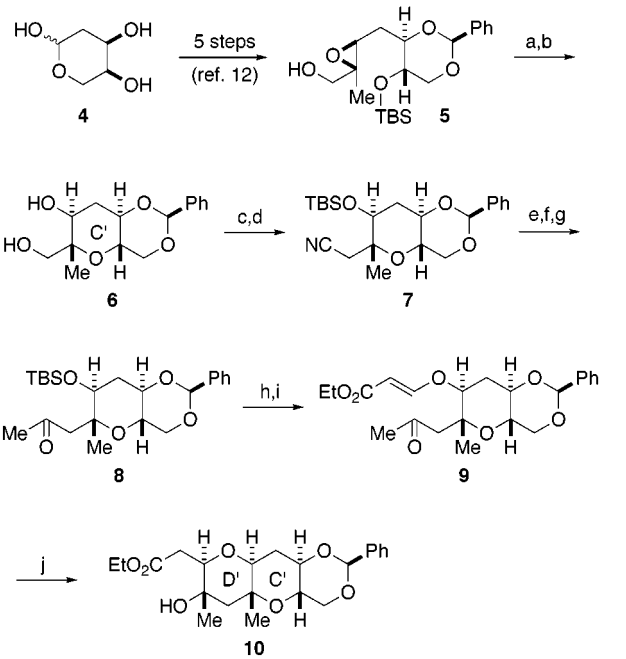


of the C′D′E′F′-ring system (6,6,6,6-membered tetracyclic ether having 1,3,5-triaxial angular methyl groups) of MTX and the FG-ring system (6,6-membered bicyclic ether having 1,3-diaxial angular methyl groups) of gambierol from the coupling of our SmI_2 cyclization with hydroxy epoxide cyclizations.

First, the C′-ring system of MTX was constructed by the 6-*endo*-cyclization of the methylepoxide[10] (Scheme 2). The required methylepoxide **5** was synthesized starting from 2-deoxy-L-ribose (**4**), which was synthesized from L-arabinose by the reported route,[11] following the same procedure for the synthesis of the enantiomer of **5**.[12] After deprotection of the TBS group with TBAF, the 6-*endo*-cyclization of the resulting alcohol proceeded predominantly by PPTS[13] treatment to give the *syn-trans*-tetrahydropyran **6** in quantitative yield, corresponding to the C′-ring.

The D′-ring system was then constructed by our developed SmI_2-induced reductive cyclization. Successive treatment of **6** with triflic anhydride and TBSOTf,[14] followed by substitution reaction with NaCN, afforded the nitrile **7** quantitatively, which was converted into the methyl ketone **8** in 72% yield by DIBAH reduction, Grignard reaction using MeMgBr, and TPAP−NMO oxidation.[15] Deprotection of the TBS group followed by the hetero-Michael reaction[16] using ethyl propiolate in the presence of *N*-methylmorpholine furnished the enol ether **9** in 99% yield. Treatment of **9** with 2.3 equiv of SmI_2[17] in the presence of 2.2 equiv of MeOH in THF effected radical-mediated reductive cyclization to give *syn-trans*-tetrahydropyran **10** in 99% yield,

Scheme 2[a]



[a] Reagents and conditions: (a) TBAF, THF, rt; (b) PPTS, CH_2Cl_2, rt (100% from **5**); (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; then TBSOTf; (d) NaCN, DMSO, 80 °C (100% from **6**); (e) DIBAH, CH_2Cl_2, −78 °C; (f) MeMgBr, THF, 0 °C; (g) TPAP, NMO, CH_2Cl_2, rt (72% from **7**); (h) TBAF, THF, rt; (i) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt (99% from **8**); (j) 2.3 equiv of SmI_2, 2.2 equiv of MeOH, THF, 0 °C (99%).

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(11) In two steps from L-arabinose: (1) Ac_2O, 30% HBr/AcOH, then Zn, $CuSO_4$, NaOAc, AcOH, H_2O; (2) $Ba(OH)_2$, H_2O, then 3 N H_2SO_4. (a) Shull, B. K.; Wu, Z.; Koreeda, M. *J. Carbohydr. Chem.* **1996**, *15*, 955. (b) Meisenheimer, J.; Jung, H. *Chem. Ber.* **1927**, *60*, 1462.

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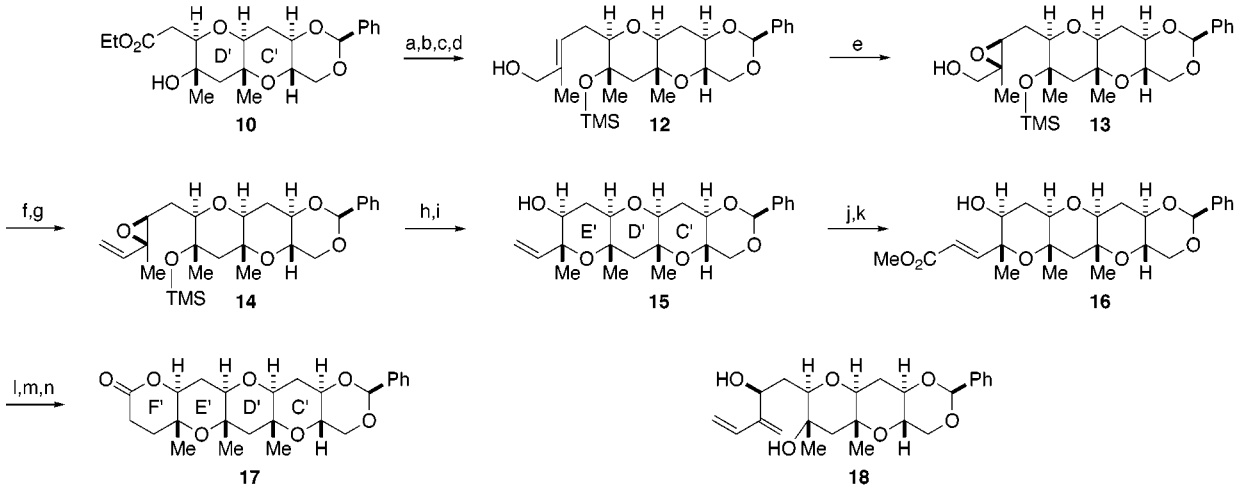
Scheme 3[a]



[a] Reagents and conditions: (a) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (b) DIBAH, toluene, −78 °C; (c) $Ph_3P{=}C(Me)CO_2Et$, toluene, 100 °C; (d) DIBAH, toluene, −78 °C (88% from **10**); (e) Sharpless AE (100%); (f) TPAP, NMO, CH_2Cl_2, rt; (g) $Ph_3P^+MeBr^-$, $NaN(TMS)_2$, THF, 0 °C (69% from **13**); (h) TBAF, THF, rt; (i) CSA, toluene, 0 °C (73% from **14**); (j) O_3, CH_2Cl_2, −78 °C; Me_2S; (k) $Ph_3P{=}CHCO_2Me$, toluene, 100 °C (72% from **15**); (l) H_2, Pd−C, EtOAc, rt; (m) LiOH, MeOH−H_2O, rt; (n) Ac_2O, pyridine, rt (65% from **16**).

corresponding to the D′-ring. Thus, the SmI_2-induced cyclization was completely stereoselective despite the steric hindrance present in both **9** and **10**. The stereoselectivity would be caused by the chelation transition state **i** (Figure 2). To our knowledge, this is the first report for the direct

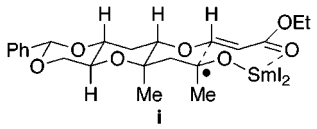


Figure 2.

construction of such a tetrahydropyran system, which has the 1,3-diaxial angular methyl groups adjacent to the methylene.[18]

We also synthesized the FG-ring **11** (the enantiomer of **10**) of gambierol,[19] a marine polycyclic ether (Figure 3),

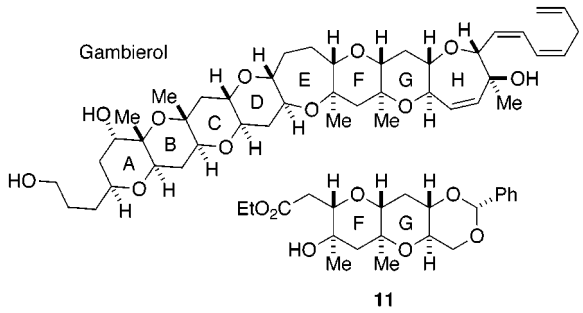


Figure 3.

following the same procedure starting from commercially available 2-deoxy-D-ribose.[20]

Then, the construction of the E′-ring system was investigated by the 6-*endo*-cyclization of the tertiary hydroxyl group to methylepoxide activated by a vinyl group[21] (Scheme 3). Protection of the tertiary alcohol in **10** with TMSOTf and reduction of the ester to aldehyde with DIBAH followed

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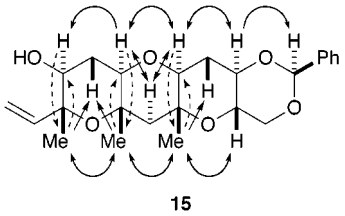
(21) In our synthesis of the F-ring (2,6-dimethyltetrahydropyran) of brevetoxin B,[22] the Nicolaou procedure[23] using vinylepoxide gave better results than our procedure[24] using styrylepoxide. Thus, the Nicolaou procedure was applied to the construction of the E′-ring system.



15

Figure 4. Selected NOEs (arrows) and $^3J_{C,H}$ correlations in HMBC (dotted arrows).

by Wittig reaction and DIBAH reduction afforded the allyl alcohol **12** in 88% yield. The Sharpless asymmetric epoxidation[25] stereoselectively gave the β-epoxide **13** in almost quantitative yield. Epoxidation with *m*CPBA in CH_2Cl_2 also gave the same single compound **13**. Oxidation of the alcohol **13** with TPAP−NMO followed by the Wittig reaction with $Ph_3P{=}CH_2$ furnished the vinylepoxide **14** in 69% yield. Deprotection of the TMS group in **14** followed by treatment with CSA in *toluene* at 0 °C effected 6-*endo*-cyclization to give the E′-ring of **15** stereoselectively in 73% yield. The standard conditions for this cyclization with PPTS or CSA in CH_2Cl_2 resulted in production of a mixture of cyclized product **15** and a conjugated diene **18** as a serious side product. The structure of **15** was confirmed by NMR studies including NOE, HMQC, and HMBC (Figure 4). Interestingly, the coupling constants (9.8 and 5.9 Hz) of the methine proton adjacent to the hydroxyl group is slightly different from the typical values (11.0−12.0 and 4.0−5.0 Hz) of the related tetrahydropyrans in a chair form.[26] This would indicate that the compound **15** partially has a boat-form conformation on the E′-ring. It could arise from the steric repulsion among the 1,3,5-trimethyl groups, which would also cause the difficulty in cyclization of the E′-ring under the standard conditions.

Then, the F′-ring system was constructed as the δ-lactone. Ozonolysis of the double bond in **15** followed by the Wittig reaction using $Ph_3P{=}CHCO_2Me$ gave the α,β-unsaturated ester **16** in 72% yield. Hydrogenation on Pd−C, hydrolysis with LiOH, and treatment with Ac_2O−pyridine afforded the δ-lactone **17** in 65% yield. The introduction of the side chain was already reported from the model lactone, corresponding to the C′D′-ring, which has no angular methyl group, by Kishi.[5a]

In summary, we have accomplished the syntheses of the C′D′E′F′-ring system of maitotoxin and the FG-ring system of gambierol. To our knowledge, this is the first report for the synthesis of the polytetrahydropyran system having 1,3,5-triaxial angular methyl groups.

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Supporting Information Available: Experimental procedures (from **6** to **17**) and characterization data for compounds **7**−**10** and **12**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) The acetate derivative of **15** showed coupling constants (7.3 and 6.8 Hz) significantly different from the typical values.