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Published on Web 12/17/2010

Synthesis of the C′D′E′F′ Domain of Maitotoxin

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Abstract: A devised biomimetic strategy toward the C′D′E′F′ domain (**6**) of maitotoxin (**1**) led to hydroxy triepoxide **8** as a postulated polyepoxide precursor. However, all attempts to induce the desired cascade to form the targeted compound through a zip-type reaction under neutral or acidic conditions failed, prompting adoption of a linear stepwise approach to **6**. The successful synthetic strategy for the synthesis of the C′D′E′F′ domain of maitotoxin commenced from furfuryl alcohol (**11**), proceeded through F′ ring building block **15**, and involved two regio- and stereoselective intramolecular hydroxy epoxide openings and a stereoselective SmI_2-mediated ring closure to forge rings C′, E′, and D′, respectively. ^{13}C NMR spectroscopic analysis of the synthesized domain (**6**) and comparisons with previous results confirmed the original structural assignment of this region of maitotoxin. X-ray crystallographic analysis of **6** provided unambiguous proof of its structure.

Introduction

With the impressive molecular weight of 3422 Da, maitotoxin enjoys the status of the largest secondary metabolite to be isolated and characterized from nature as yet.[1] This remarkable natural product also stands as the most toxic molecule ever discovered, other than a few proteins, with an LD_{50} of 50 ng/kg.[2] First detected in 1971 by Yasumoto et al. in the gut of the surgeonfish *Ctenochaetus striatus*,[1b,c] it would be a quarter of a century before its full structural elucidation was completed. The originally assigned structure (**1**, Figure 1) of maitotoxin by the groups of Yasumoto,[3] Kishi,[4] and Tachibana[5] was subsequently challenged by Gallimore and Spencer,[6] who questioned the correctness of the two asymmetric centers comprising the JK ring junction of the molecule.[7] The cloud of uncertainty cast over the maitotoxin structure prompted us to undertake a reinvestigation of its structure that led, so far, to theoretical calculations[8] and the construction of several fragments of the molecule, including the GHIJK (**2**),[9] GHIJKLMNO (**4**),[10] ABCDEFG (**3**),[11] and QRSTU (**5**)[12] domains (Figure 1). These structures provided support for the originally assigned structure (**1**) of maitotoxin. Herein, we report the synthesis of the C′D′E′F′ domain (**6**, Figure 1) of maitotoxin and, in the following article, that of the remaining WXYZA′ segment (**7**, Figure 1).[13]

Results and Discussion

In addition to the nine stereogenic centers contained within the structure of the C′D′E′F′ ring system (**6**), the main challenge

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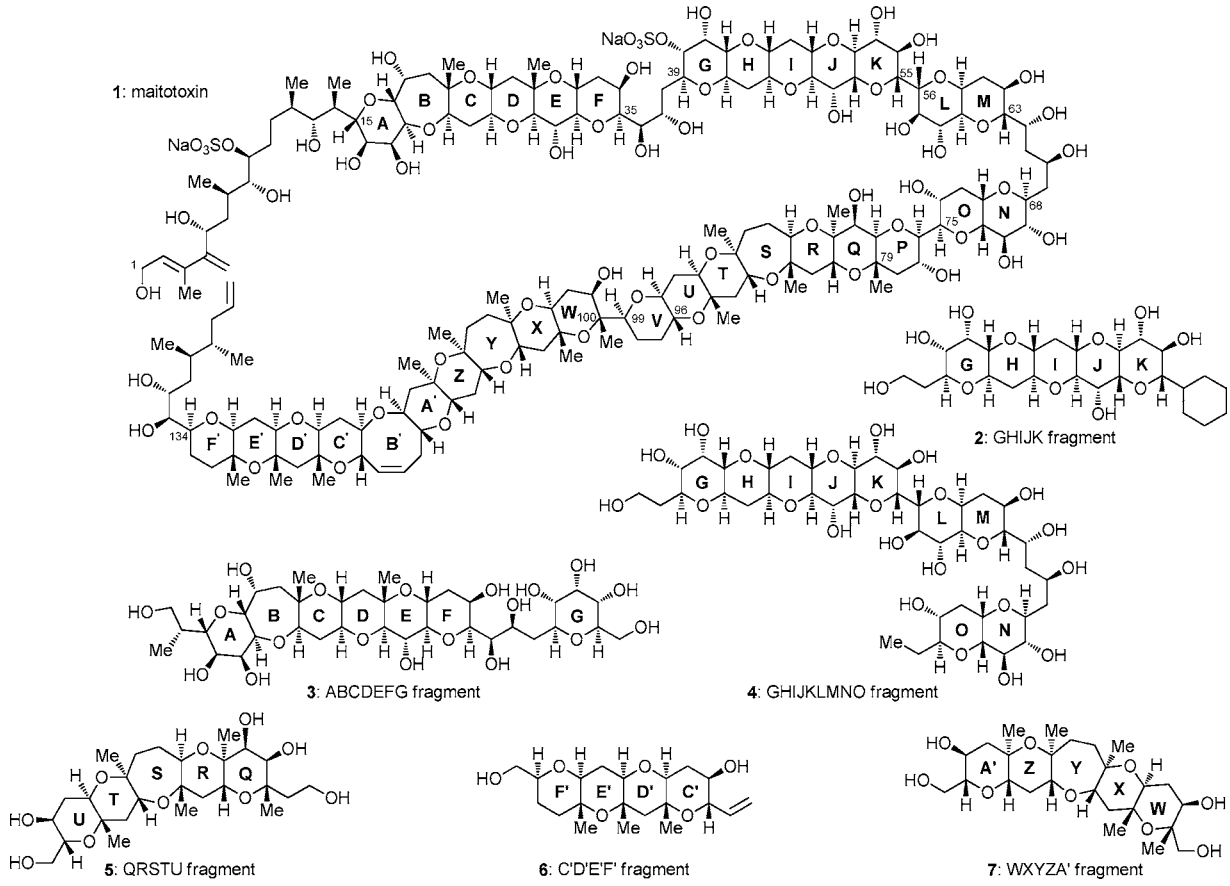

Figure 1. Structures of maitotoxin (**1**), previously synthesized fragments GHIJK (**2**), ABCDEFG (**3**), GHIJKLMNO (**4**), and QRSTU (**5**), and targeted fragments C′D′E′F′ (**6**) and WXYZA′ (**7**).

posed by this target is the array of its three methyl groups contiguously situated on the two central rings (D′ and E′), all of which are axially disposed.

1. Polyepoxide-Based Retrosynthetic Analysis. In our desire to attempt a biomimetic pathway to the C′D′E′F′ segment of maitotoxin, we adopted triepoxide **8** as a possible precursor as shown retrosynthetically in Figure 2. The polyepoxide hypothesis for the biosynthesis of brevetoxin B and related polyether neurotoxins was first proposed by Nakanishi[14] and one of us[15] and recently performed in a laboratory setting by Jamison and co-workers.[16] In an effort to introduce convergency into our synthetic strategy, precursor **8** was disconnected through a π-allyl Stille coupling[17] and two Shi epoxidations,[18] revealing allylic acetate **9** and vinyl stannane **10** as potential building blocks. The latter fragments were traced to furfuryl alcohol (**11**) and 1,2-dihydrofuran (**12**) as depicted in Figure 2.

2. Construction of Building Blocks 9 and 10. Key building block allylic acetate **9** was synthesized from furfuryl alcohol

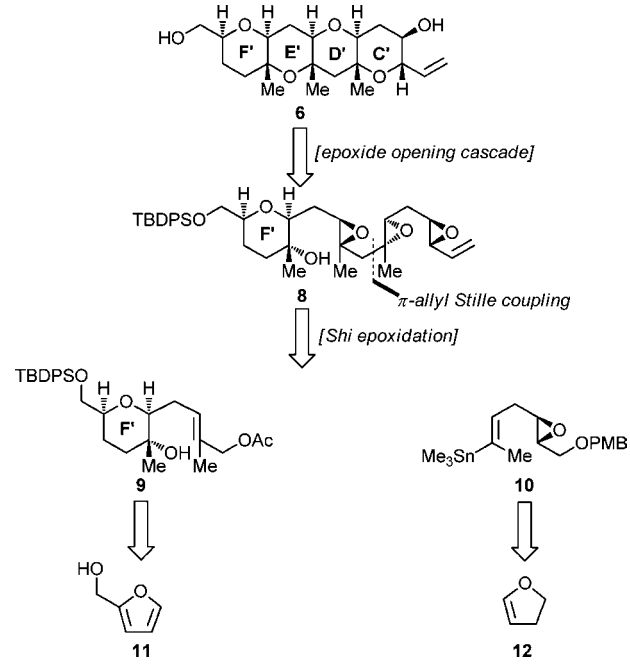

Figure 2. Cascade retrosynthetic analysis of C′D′E′F′ ring system **6**.

(**11**) as summarized in Scheme 1. Thus, following our previous synthetic strategy,[9−11,19] enone **13** was prepared from **11** (five steps, 77% overall yield)[11] and subjected to 1,2-addition of MeMgBr (Et_2O, −78 °C, 98% yield) and debenzylation [H_2, 20% $Pd(OH)_2$/C, 89% yield] to afford saturated diol **14**. The

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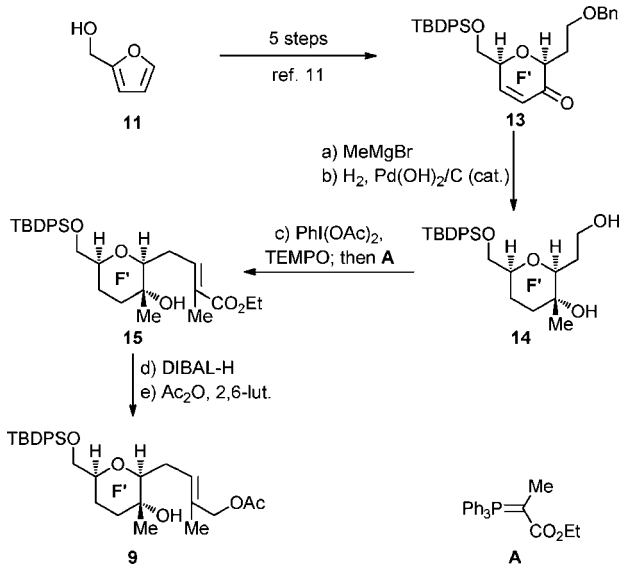
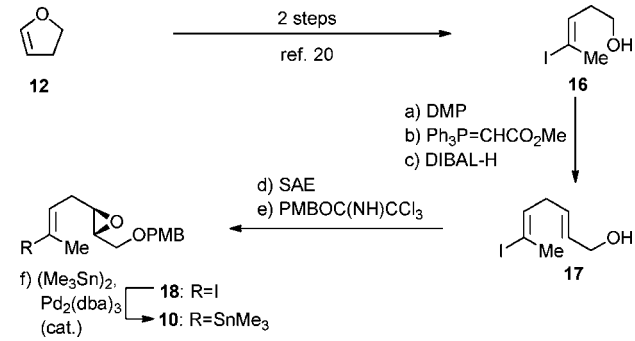
Scheme 1. Furan-Based Synthesis of F′ Ring Building Block **9**[a]



[a] Reagents and conditions: (a) MeMgBr (3.0 M in Et_2O, 2.5 equiv), Et_2O, −78 °C, 1 h, 98%; (b) 20% $Pd(OH)_2$/C (10% w/w), H_2, EtOAc/EtOH (1:2), 25 °C, 6 h, 89%; (c) $PhI(OAc)_2$ (2.5 equiv), TEMPO (0.1 equiv), CH_2Cl_2, 25 °C, 18 h; then **A** (3.0 equiv), 25 °C, 4 h, 92%; (d) DIBAL-H (1.0 M in CH_2Cl_2, 5.0 equiv), CH_2Cl_2, −78 → 25 °C, 1.5 h, 89% (e) AcCl (1.1 equiv), 2,6-lut. (3.0 equiv), CH_2Cl_2, −78 °C, 30 min, 95%. Abbreviations: TBDPS = *tert*-butyldiphenylsilyl; Bn = benzyl; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy; DIBAL-H = diisobutylaluminum hydride; Ac = acetyl; lut. = lutidine.

regio- and stereoselective Grignard addition to **13** was expected on reactivity and steric grounds. Oxidation of the primary alcohol of **14** was accomplished with $PhI(OAc)_2$ in the presence of TEMPO (cat.), and the resulting hydroxy aldehyde was reacted, in the same pot, with stabilized phosphorane **A** to generate α,β-unsaturated ester **15** in 92% overall yield. Reduction of the latter compound with DIBAL-H in CH_2Cl_2 at −78 °C gave the corresponding allylic alcohol (89% yield), whose selective acetylation (AcCl, 2,6-lut., −78 °C) led to the desired building block **9** in 95% yield.

Scheme 2. Synthesis of Vinyl Stannane **10**[a]



[a] Reagents and conditions: (a) DMP (1.5 equiv), CH_2Cl_2, 25 °C, 1.5 h; (b) $Ph_3P{=}CHCO_2Me$ (1.5 equiv), CH_2Cl_2, 25 °C, 2 h; (c) DIBAL-H (1.0 M in CH_2Cl_2, 5.0 equiv), CH_2Cl_2, −78 °C, 1.5 h, 79% over the three steps; (d) (−)-DET (1.2 equiv), Ti(O*i*-Pr)$_4$ (1.6 equiv), *t*-BuOOH (5.5 M in decane, 2.9 equiv), 4 Å MS, CH_2Cl_2, −20 °C, 1.5 h; (e) $PMBOC(NH)CCl_3$ (1.5 equiv), $La(OTf)_3$ (0.1 equiv), PhMe, 25 °C, 20 min, 80% over the two steps; (f) LiCl (3.0 equiv), $(2\text{-fur})_3P$ (0.5 equiv), $Me_3SnSnMe_3$ (3.0 equiv), $Pd_2(dba)_3$ (0.1 equiv), THF, 25 °C, 30 min, 65%. Abbreviations: DMP = Dess−Martin periodinane; DET = diethyltartrate; MS = molecular sieves; PMB = *para*-methoxybenzyl; Tf = trifluoromethanesulfonyl; fur = furyl; dba = dibenzylidineacetone.

The synthesis of vinyl stannane **10** commenced from 1,2-dihydrofuran (**12**) and proceeded through known intermediate **16** (two steps, 85% overall yield)[20] as shown in Scheme 2. Thus, a three-step sequence involving (a) oxidation (DMP), (b) Wittig olefination ($Ph_3P{=}CHCO_2Me$), and (c) reduction (DIBAL-H) led to skipped diene **17** in 79% overall yield. Sharpless asymmetric epoxidation[21] of the latter compound [Ti(O*i*-Pr)$_4$, (−)-DET, *t*-BuOOH, 4 Å MS] followed by PMB protection[22] [$PMBOC(NH)CCl_3$, $La(OTf)_3$ (cat.), 80% yield over the two steps] furnished epoxide PMB ether **18**. Subsequent palladium-catalyzed stannane installation [$Me_3SnSnMe_3$, $Pd_2(dba)_3$ (cat.), $(2\text{-fur})_3P$, 65% yield] completed the synthesis of the targeted vinyl stannane **10**, setting the stage for building block assembly.

3. Building Block Coupling and Polyepoxide Opening Cascade Attempt. The π-allyl Stille coupling of building blocks allylic acetate **9** and vinyl stannane **10** proceeded smoothly under standard conditions [$Pd_2(dba)_3$ (cat.), LiCl, *i*-Pr_2NEt] to provide skipped diene **19** in 84% yield (Scheme 3). Shi epoxidation of this epoxy diene (**B**,[18b,23] Oxone) led to triepoxide **20** in 91% yield as a mixture (ca. 7:1), presumably diastereomeric at the epoxide site nearest to the F′ ring. This assumption was made based on the expected influence of the F′ ring on the diastereoselectivity of the epoxidation at its nearest site of unsaturation.[24] Hoping to influence favorably the regioselectivity of the terminating epoxide opening event, we installed a vinyl group at the end of the chain as shown in intermediate **21**.[25] This modification was accomplished from triepoxide PMB ether **20** through a three-step sequence involving (a) DDQ cleavage of the PMB ether, (b) DMP oxidation of the resulting alcohol, and

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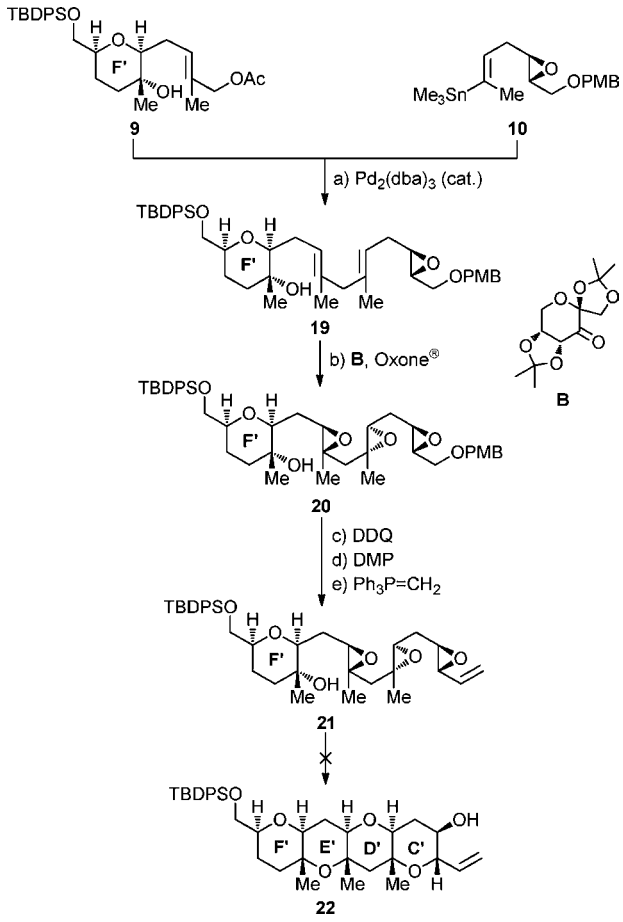
Scheme 3. Construction of Hydroxy Triepoxide **21**[a]



[a] Reagents and conditions: (a) **9** (1.0 equiv), **10** (2.0 equiv), LiCl (3.0 equiv), *i*-Pr_2NEt (4.0 equiv), $Pd_2(dba)_3$ (0.2 equiv), NMP, 40 °C, 3 h, 84%; (b) **B** (2.0 equiv), Oxone (4.0 equiv), *n*-Bu_4NHSO_4 (0.2 equiv), $Na_2B_4O_2 \cdot 7H_2O$ (1.0 equiv), DMM/CH_3CN/0.4 mM aq. Na_2EDTA/0.89 M aq. K_2CO_3 (2:1:4:2), 0 °C, 3 h, 91% (7:1 *dr*); (d) DDQ (6.0 equiv), CH_2Cl_2/H_2O (10:1), 0 → 25 °C, 1.5 h, 80%; (e) DMP (3.0 equiv), $NaHCO_3$ (10.0 equiv), CH_2Cl_2, 25 °C, 1 h; (f) Ph_3PCH_2Br (2.2 equiv), NaHMDS (0.6 M in PhMe, 2.0 equiv), THF, 0 → 25 °C, 1 h, 63% over the two steps. Abbreviations: NMP = *N*-methylpyrrolidone; DMM = dimethoxymethane; EDTA = ethylenediaminetetraacetate; DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; NaHMDS = sodium bis(trimethylsilyl)amide; THF = tetrahydrofuran.

(c) Witting methylenation, in 50% overall yield. Disappointingly, all attempts to effect the much anticipated cascade polyepoxide opening to afford the targeted tetracyclic system from **21** under the reported (i.e., H_2O, 90 °C, 7 days)[16d] or modified conditions proved fruitless. Similarly, PMB ether **20** did not engage in any productive reaction toward the desired tetracycle. Attempts to employ different conditions (e.g., microwave irradiation, organic solvent additives, phase transfer catalysts, salt additives) frustratingly failed to improve the situation, with starting material being recovered and/or intractable mixtures of highly polar compounds being formed. The latter species are presumably generated through preferential H_2O attack of the epoxide moieties[26] over the desired pathway, which is most likely prohibited by the unfavorable 1,3-diaxial interactions between the methyl groups on the D′ and E′ rings of the anticipated product (**22**) and transition states leading to it. We should note that the use of protic or Lewis acids[25] also failed to produce

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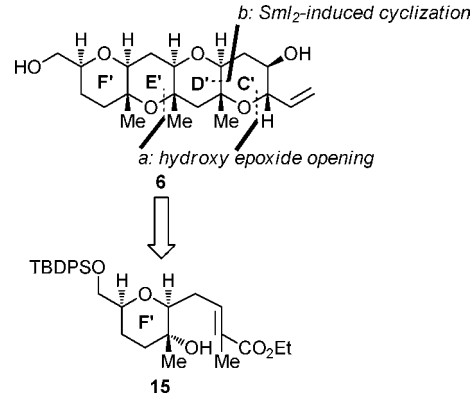


Figure 3. Linear retrosynthetic analysis of C′D′E′F′ ring system **6**.

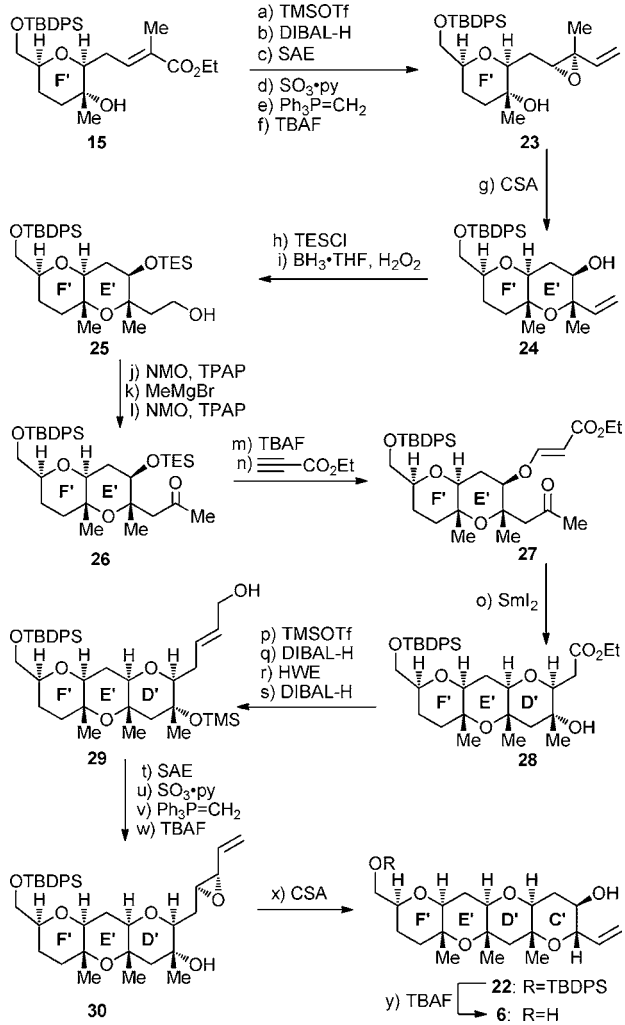
the desired polycyclic product, leading instead and as expected to mixtures of compounds derived from undesired epoxide openings. These failures led us to devise an alternative strategy toward the C′D′E′F′ domain of maitotoxin as described below.

4. Linear Strategy toward the C′D′E′F′ Maitotoxin Domain. Having tested and failed to implement the rather daring polyepoxide opening cascade to the C′D′E′F′ domain (**6**) of maitotoxin, we adopted a more conventional and linear approach to this tetracyclic system. Figure 3 depicts, in retrosynthetic format, the main disconnections (two hydroxy epoxide cyclizations and a SmI_2-induced ring closure) that led to intermediate **15** (see Scheme 1) as a starting material.

Through this strategy, which relied on previously developed synthetic technologies by us[25] and others,[27] we were able to prepare multigram quantities of fragment **6** in enantiomerically pure form. The practical and highly efficient synthesis of F′ ring intermediate **15** (Scheme 1) based on the furan methodology[9−11,19] served as the first leg of the developed route, which is shown in Scheme 4. Thus, **15** was rapidly converted to hydroxy allylic epoxide **23** through a sequence involving TMS protection of the tertiary alcohol (TMSOTf, 2,6-lut., 98% yield), reduction of the ester moiety to the corresponding allylic alcohol (DIBAL-H, 94% yield), Sharpless asymmetric epoxidation [Ti(O*i*-Pr)$_4$, (−)-DET, *t*-BuOOH, 4 Å MS, 97% yield], oxidation to the corresponding epoxy aldehyde ($SO_3 \cdot$py), Wittig olefination ($Ph_3P{=}CH_2$, 93% yield for the two steps), and TMS removal (TBAF, quant. yield). Casting of the E′ ring proceeded smoothly from **23** through a hydroxy epoxide cyclication (CSA)[25] to afford bicycle **24** in 75% yield. Protection of the hydroxyl group (TESCl, imid., quant. yield) of the latter compound, followed by hydroboration of the olefin with $BH_3 \cdot$THF, furnished, upon oxidative workup (aq. NaOH, H_2O_2, 83% yield), primary alcohol **25**. A three-step sequence [NMO, TPAP (cat.); MeMgBr; NMO, TPAP (cat.)] was employed to convert alcohol **25** to methyl ketone **26** in 91% overall yield. From the several attempts to forge ring D′, Nakata's samarium diiodide-promoted tetrahydropyran formation[27] proved the most expedient. Thus, selective desilylation of **26** [TBAF, 97% yield], followed by conjugate addition of the resulting hydroxyl compound to ethyl propiolate in the presence of *N*-methylmorpholine, resulted in the formation of vinyl ether **27** (exclusively *E*) in 99% yield. Treatment of the latter compound with SmI_2

(27) (a) Hori, N.; Matsukura, K.; Matsui, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811. (b) Hori, N.; Matsukura, K.; Nakata, T. *Org. Lett.* **1999**, *1*, 1099. (c) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8859. (d) Hori, N.; Matsukura, H.; Matsui, G.; Nakata, T. *Tetrahedron* **2002**, *58*, 1853.

Scheme 4. Synthesis of C′D′E′F′ Ring System **6** through a Linear Strategy[a]



[a] Reagents and conditions: (a) TMSOTf (1.3 equiv), 2,6-lut. (2.0 equiv), CH_2Cl_2, 0 °C, 2 h, 98%; (b) DIBAL-H (1.0 M in hexanes, 2.5 equiv), CH_2Cl_2, −78 °C, 1 h; then 0 °C, 30 min, 94%; (c) (−)-DET (1.2 equiv), Ti(O*i*-Pr)$_4$ (1.0 equiv), *t*-BuOOH (5.0 M in decane, 3.0 equiv), 4 Å MS, CH_2Cl_2, −20 °C, 1 h, 97%; (d) SO_3•py (4.0 equiv), Et_3N (8.0 equiv), CH_2Cl_2/DMSO (5:1), 0 → 25 °C, 9 h; (e) CH_3PPh_3Br (2.0 equiv), NaHMDS (0.6 M in toluene, 1.9 equiv), THF, 0 °C, 30 min; then −78 °C, aldehyde (1.0 equiv), THF, −78 → 0 °C, 93% over the two steps; (f) TBAF (1.0 M in THF, 1.2 equiv), THF, 0 °C, 30 min, 100%; (g) CSA (0.2 equiv), CH_2Cl_2, 0 °C, 30 min, 75%; (h) TESCl (2.0 equiv), imidazole (3.0 equiv), CH_2Cl_2, 0 → 25 °C, 1 h, 100%; (i) BH_3•THF (1.0 M in THF, 1.2 equiv), THF, 0 °C, 2 h; then H_2O_2 (35% aq, 3.0 equiv), NaOH (2.0 M aq, 2.0 equiv), 25 °C, 1 h, 83%; (j) TPAP (0.1 equiv), NMO (3.0 equiv), 4 Å MS, 0 → 25 °C, 1 h, 95%; (k) MeMgBr (3.0 M in ether, 5.0 equiv), THF, 0 °C, 1 h; (l) TPAP (0.1 equiv), NMO (3.0 equiv), 4 Å MS, 0 → 25 °C, 12 h, 96% over the two steps; (m) TBAF (1.0 M in THF, 1.1 equiv), THF, 0 °C, 30 min, 97%; (n) ethyl propiolate (4.0 equiv), *N*-methylmorpholine (8.0 equiv), CH_2Cl_2, 25 °C, 23 h, 99%; (o) SmI_2 (0.1 M in THF, 2.5 equiv), MeOH (2.5 equiv), THF, 0 °C, 20 min, 97%; (p) TMSOTf (1.5 equiv), 2,6-lut. (2.5 equiv), CH_2Cl_2, 0 °C, 1 h, 95%; (q) DIBAL-H (1.0 M in CH_2Cl_2, 1.1 equiv), CH_2Cl_2, −78 °C, 1 h, 90%; (r) $MeO_2CCH_2P(O)(OEt)_2$ (2.0 equiv), NaHMDS (0.6 M in PhMe, 1.9 equiv), THF, 0 °C, 1 h, 96%; (s) DIBAL-H (1.0 M in CH_2Cl_2, 2.5 equiv), CH_2Cl_2, −78 °C, 40 min, 93%; (t) (−)-DET (1.2 equiv), Ti(O*i*-Pr)$_4$ (1.0 equiv), *t*-BuOOH (5.0 M in decane, 3.0 equiv), 4 Å MS, CH_2Cl_2, −20 °C, 1 h, 96%; (u) SO_3•py (5.0 equiv), DMSO (14 equiv), Et_3N (5.5 equiv), CH_2Cl_2, 0 → 25 °C, 1 h, 84%; (v) Ph_3PCH_3Br (2.0 equiv), NaHMDS (0.6 M in PhMe, 1.9 equiv), THF, −78 °C → 0 °C, 90%; (w) TBAF (1.05 equiv), THF, 0 °C, 1 h, 78%; (x) CSA (0.1 equiv), CH_2Cl_2, 0 °C, 3 h, 90%; (y) TBAF (1.0 M in THF, 5.0 equiv), THF, 25 °C, 2 h, 79%. Abbreviations: TMSOTf = trimethylsilyl trifluoromethanesulfonate; py = pyridine; DMSO = dimethylsulfoxide; TBAF = tetra-*n*-butylammonium fluoride; CSA = camphorsulfonic acid; TES = triethylsilyl; TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine oxide.

Table 1. C_{119} to C_{135} and C_{160} to C_{162} Chemical Shifts (δ) for Maitotoxin (MTX, **1**) and C′D′E′F′ Ring System **6** and Their Differences ($\Delta\delta$, ppm)[a]

carbon	δ for MTX (**1**) (ppm)	δ for **6** (ppm)	difference ($\Delta\delta$, ppm)
135	77.7	65.7	12.0
134	81.6	81.1	0.5
133	26.5	26.7	−0.2
132	39.4	39.1	0.3
131	74.8	74.8	0.0
162	22.0	21.9	0.1
130	84.2	83.9	0.3
129	28.9	28.7	0.2
128	86.9	86.7	0.2
127	75.6	75.4	0.2
161	22.2	22.2	0.0
126	54.0	54.0	0.0
125	73.5	73.7	−0.2
160	18.3	18.6	−0.3
124	84.1	84.3	−0.2
123	33.4	34.6	−1.2
122	80.3	71.5	8.8
121	72.1	76.1	−4.0
120	135.9	138.4	−2.5
119	126.8	116.7	10.1

[a] 150 MHz, 1:1 methanol-d_4/pyridine-d_5.

gave, stereoselectively, the expected hydroxy ester tricyclic system **28**, in 97% yield, through ketyl generation and intramolecular 1,4-addition of the incipient carbon radical into the α,β-unsaturated ester moiety.[27] Installation of a TMS group on the tertiary alcohol of **28** (TMSOTf, 2,6-lut., 95% yield), followed by DIBAL-H reduction of the ester group under carefully controlled conditions, led to the corresponding aldehyde in 90% yield. Horner−Wadsworth−Emmons olefination of this aldehyde [$MeO_2CCH_2P(O)(OEt)_2$, NaHMDS, 96% yield] and DIBAL-H reduction of the resulting α,β-unsaturated ester afforded allylic alcohol **29** (93% yield). Allylic alcohol **29** was transformed to hydroxy epoxide **30** through a standard four-step sequence involving Sharpless epoxidation [Ti(O*i*-Pr)$_4$, (−)-DET, *t*-BuOOH, 4 Å MS, 96% yield], oxidation (SO_3•py, Et_3N, DMSO, 84% yield), Wittig methylenation ($Ph_3P{=}CH_2$, 90% yield), and selective desilylation (TBAF, 78% yield). Intramolecular CSA-induced hydroxy epoxide opening of substrate **30** forged the remaining (C′) ring, furnishing C′D′E′F′ ring system **22** in 90% yield. Finally, exposure of tetracyclic compound **22** to TBAF liberated the primary hydroxyl group, thus completing the synthesis of the C′D′E′F′ domain (**6**) of maitotoxin. Despite its linear and stepwise nature, this sequence is notable for its practicality and efficiency (average 93% yield per step).

5. Comparison of ^{13}C NMR Chemical Shifts of the C′D′E′F′ Ring System 6 with Those Corresponding to the Same Region of Maitotoxin. NMR spectroscopic analysis of our synthetic C′D′E′F′ domain **6** confirmed its stereochemical configurations and led to assignment of the ^{13}C chemical shifts for all its carbons.[28] Assignment of these chemical shifts allowed us to compare them to those corresponding to the same region of maitotoxin,[3d] an exercise that has previously served as a means for supporting the assigned structure of the natural product.[3−5,8−12,13d,e,g] The chemical shifts (δ, ppm) for synthetic fragment **6**, those for the same carbons (C_{119} to C_{135} and C_{160} to C_{162}) of maitotoxin (**1**),[3d] and their differences ($\Delta\delta$, ppm) are given in Table 1. Figure 4 provides a graphical representation

(28) The stereochemistry and ^{13}C chemical shift assignments of **6** were based on ^{1}H coupling constants and COSY, ROESY, HSQC, and HMBC NMR spectroscopic experiments.

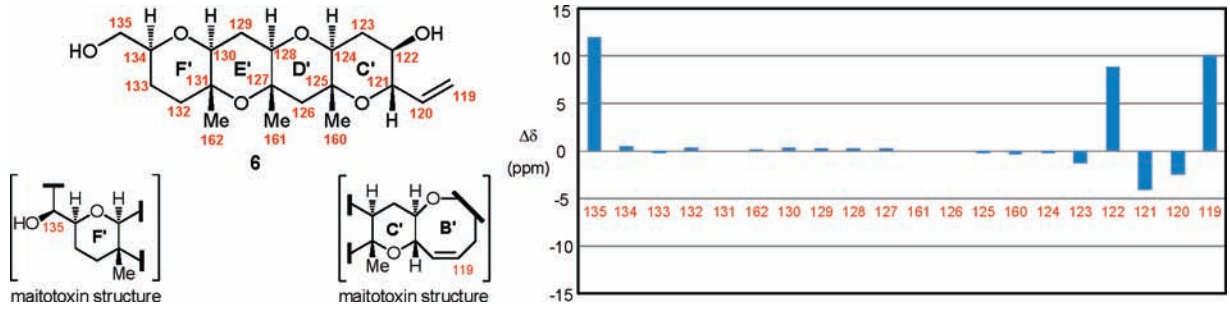


Figure 4. Graphically depicted ^{13}C chemical shift differences ($\Delta\delta$, ppm) for each carbon between C_{119} to C_{135} and C_{160} to C_{162} for maitotoxin (**1**) and C′D′E′F′ ring system **6**.

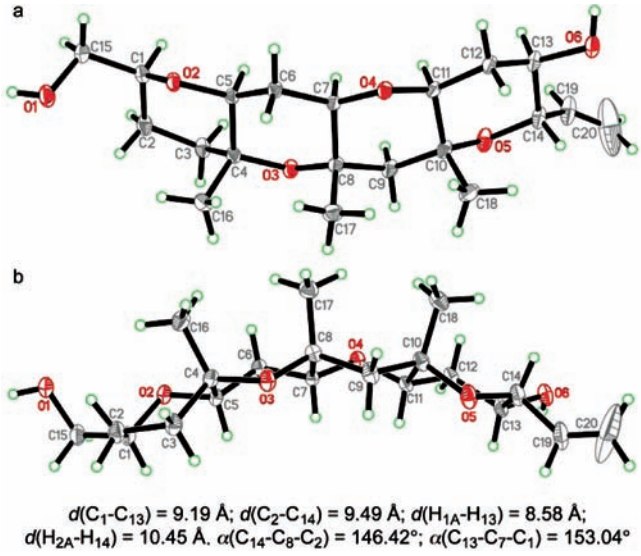


Figure 5. ORTEP representation of maitotoxin domain **6** (a: top view; b: side view) and key distances (*d*) and angles (α).

of the chemical shift differences between **6** and **1**. As seen from both the table and the figure, there is excellent agreement between the two sets of chemical shifts (except for the carbons at the edges of **6** due to the drastically different structural motifs between the synthetic fragment and maitotoxin; see Figure 4). Thus, the average chemical shift deviation ($\Delta\delta$, ppm) for C-123 to C-134 and C-160 to C-162 is 0.26 ppm with the largest difference being 1.2 ppm (C_{123}). These values lend additional support for the assigned structure of maitotoxin (**1**).[13d]

6. X-ray Crystallographic Analysis of C′D′E′F′ Maitotoxin Domain 6. On standing in EtOAc, compound **6** crystallized in colorless needles, mp 226−228 °C. One of these crystals yielded to X-ray crystallographic analysis (see ORTEP representations, Figure 5). In addition to providing unambiguous proof of the structure of the synthesized domain, this analysis provided a more precise picture of its conformation. Thus, structure **6** appears to assume a distorted conformation in the solid state that leads to a significant bending of its tetracyclic ladder-like structure in order to relieve the strain imposed by its three axial methyl groups. The concavity of the molecule is defined by a number of key distances (*d*) and angles (α) revealed by this X-ray structure as shown in Figure 5 [$d(C_1-C_{13}) = 9.19$ Å; $d(C_2-C_{14}) = 9.49$ Å; $d(H_{1A}-H_{13}) = 8.58$ Å; $d(H_{2A}-H_{14}) = 10.45$ Å. $\alpha(C_{14}-C_8-C_2) = 146.42°$; $\alpha(C_{13}-C_7-C_1) = 153.04°$]. This deviation from linearity of the C′D′E′F′ maitotoxin domain **6** may be significant for its contributions to the physical and biological properties of the natural product.

Conclusion

Described herein are two approaches to the C′D′E′F′ domain (**6**) of maitotoxin (**1**). The first, based on biosynthetic considerations, started with furfuryl alcohol (**11**) and called upon a zip-type cascade hydroxy triepoxide (i.e., **21**) opening sequence to forge the targeted molecule. Despite our expectation, however, this biomimetic hypothesis could not be implemented under a variety of conditions, underscoring the current limitations of such schemes, elegant as they are. A second approach to the C′D′E′F′ target molecule, also commencing from furfuryl alcohol (**11**), proceeded smoothly in a linear fashion, delivering each ring system in a stepwise fashion in excellent overall yield. The successful sequence relied upon the Achmatowicz/Noyori technology,[9−11,19] the hydroxy epoxide opening,[25] and the SmI_2-induced[27] tetrahydropyran processes to cast the desired tetracyclic system. This synthesis delivered multigram quantities of the C′D′E′F′ domain, demonstrating the power of the employed synthetic technologies. It also allowed ^{13}C NMR comparisons that supported the previously assigned structure of this region of the natural product and an X-ray crystallographic analysis that proved its structure unambiguously, revealing at the same time an interesting twist in its conformation, apparently due to the three axial methyl groups. The reported chemistry may facilitate further synthetic and biological studies in the marine polyether neurotoxin area.[29]

Acknowledgment. We thank Drs. D.-H. Huang, G. Siuzdak, and R. Chadha for spectroscopic, mass spectrometric, and X-ray crystallographic assistance, respectively. Financial support for this work was provided by the National Institutes of Health (U.S.A.), The Skaggs Institute of Chemical Biology, and Daiichi-Sankyo Co., Ltd. (T.N.).

Supporting Information Available: Experimental procedures, characterization data for all compounds, and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

JA109531D

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