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Synthesis of the ABCDEFG Ring System of Maitotoxin

K. C. Nicolaou, Robert J. Aversa, Jian Jin, and Fatima Rivas

Contribution from the Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

K. C. Nicolaou: kcn@scripps.edu

Abstract

Maitotoxin (**1**) continues to fascinate scientists not only because of its size and neurotoxicity but also due to its molecular architecture. In order to provide further support for its structure and facilitate fragment-based biological studies, we developed an efficient chemical synthesis of the ABCDEFG segment **3** of maitotoxin. ^{13}C NMR chemical shift comparisons of synthetic **3** with the corresponding values for the same carbons of maitotoxin revealed a close match, providing compelling evidence for the correctness of the originally assigned structure to this polycyclic system of the natural product. The synthetic strategy for the synthesis of **3** relied heavily on our previously developed furan-based technology involving sequential Noyori asymmetric reduction and Achmatowicz rearrangement for the construction of the required tetrahydropyran building blocks, and employed a *B*-alkyl Suzuki and a Horner–Wadsworth–Emmons olefination to accomplish their assembly and elaboration to the final target molecule.

Keywords

chemical synthesis; maitotoxin; natural products; neurotoxins; structure elucidation

Introduction

As the largest and most toxic of the secondary metabolites isolated¹ and characterized to date, maitotoxin (**1**; Figure 1) attracted considerable attention from the chemical community.² It was first detected in the gut of the surgeonfish *Ctenochaetus striatus* in 1976, 1b,c and subsequently isolated in small amounts from the dinoflagellate *Gambierdiscus toxicus* by Yasumoto et al. in 1988. 1d,e Maitotoxin is one of the causative agents of the ciguatera fish poisoning that infects consumers of contaminated seafood periodically around the Pacific Ocean, and, as such, constitutes a major environmental and health hazard.³ Its mode of action involves interference with cell membrane ion channels and Ca^{2+} ion influx that causes neurotoxicity.⁴ The structure of maitotoxin, including its absolute stereochemistry, has been assigned on the basis of NMR spectroscopic, mass spectrometric analysis, and the chemical synthesis of relatively small fragments.^{5–7} A recent challenge by Gallimore and Spencer to the 1996 Kishi–Tashibana–Yasumoto assigned structure of maitotoxin⁸ elicited a response from our laboratories that provided strong support for the originally assigned structure, first through computations⁹ and, subsequently, chemical synthesis of a GHIJK polycyclic system¹⁰ and a GHIJKLMNO

Correspondence to: K. C. Nicolaou, kcn@scripps.edu.

Supporting Information **Available**. Scheme for the synthesis of G ring aldehyde **4**, experimental procedures, and characterization data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

fragment (**2**; Figure 1), followed by NMR spectroscopic comparisons with the natural product.¹¹ In continuing our quest for further support of the structure of maitotoxin, and as a prelude to a possible synthesis of large domains of this molecule for biological investigations, we undertook the construction of a number of other fragments of the natural product. In this article we describe the synthesis and spectroscopic analysis of the ABCDEFG polycyclic system **3** (Figure 1).

Results and Discussion

The selection of fragment **3** and the design of its synthesis took into account the potential for further elaboration of key intermediates to larger fragments of maitotoxin, such as the decapentacyclic ABCDEFGHIJKLMNO domain. The immediate objective of this study, however, was to compare the NMR spectroscopic data of the synthetic material (**3**) with those of the corresponding region of the natural product as a means to confirm its originally assigned stereochemical configuration.¹²

1. Retrosynthetic Analysis

From the outset, our retrosynthetic analysis was based on the desire to devise a strategy toward fragment **3** that would be highly convergent and applied our practical and successful furan-based technologies for the construction of tetrahydropyran systems,^{9,10} a strategy which has also been explored by others.¹³ In addition, we sought to accommodate the possibility of employing an advanced intermediate to synthesize the entire ABCDEFGHIJKLMNO domain of maitotoxin at a later time. Figure 2 outlines the retrosynthetic analysis of the ABCDEFG ring system **3**. Thus, sequential disconnection (Horner–Wadsworth–Emmons olefination; cyclization/reduction) of target **3** as shown led to G ring aldehyde **4** and ABCDE pentacyclic system **6** as possible precursors. While G building block **4** could be connected directly to furfuryl alcohol **5**,¹⁰ the ABCDE pentacyclic intermediate **6** had to be further disconnected to smaller fragments that could be traced back to simple furan derivatives. Thus, disassembly of ring C within **6** through a *B*-alkyl Suzuki coupling¹⁴ and an *S,O*-acetal formation/methylation as shown revealed AB endocyclic ketene acetal phosphate **7** and DE exocyclic vinyl ether **8** as the required building blocks. These fragments were then connected to furfural (**9**) and furfuryl alcohol (**5**), respectively, through envisioned routes based on the furan-based synthetic technology.

2. Furan-based Construction of the AB and DE Building Blocks **7** and **8**

With sufficient quantities of ring G building block **4** available to us through our previously developed route to a closely related fragment from furfuryl alcohol **5**,^{10,15} we focused on the synthesis of the AB and DE building blocks **7** and **8**.

Scheme 1 summarizes the construction of ring A intermediate **17** from furfural-derived ethylene ketal **10**. Thus, lithiation of **10** (*n*-BuLi) followed by addition of γ -lactone **11** (62% yield, 82% based on 20% recovered starting material) resulted, after pivaloate formation (PivCl, Et₃N, 94% yield), in the formation of ketone **12**. Ketone **12** was subjected to Noyori asymmetric transfer hydrogenation [HCO₂Na, *n*Bu₄Cl, **13** (cat.)]¹⁶ to afford the corresponding alcohol in 97% yield and 94% *ee* (Naproxen[®] ester NMR spectroscopic analysis). This alcohol was then protected as its benzyl ether (NaH, BnBr, quant.) and the aldehyde moiety was liberated through the action of aq. HCl (quant.) to afford furfural derivative **14**. Aldol reaction of aldehyde **14** with Evans chiral auxiliary **15** (*n*-Bu₂BOTf, Et₃N)¹⁷ furnished furfuryl alcohol **16** in 98% yield as a single diastereomer. Treatment of **16** with *m*-CPBA followed by addition of Et₃SiH and BF₃•OEt₂ resulted in the formation of enone **17** through Achmatowicz rearrangement¹⁸ and subsequent reduction of the resulting hemiketal product in 75% overall yield. This one-pot procedure was routinely carried out on 50 g scale and provided ample

quantities of key intermediate **17** for further elaboration. Thus, and as shown in Scheme 2, **17** was reduced under Luche conditions (NaBH_4 , CeCl_3)¹⁹ to afford the corresponding diol (80% yield), whose benzylation (NaOH , BnBr) led to bis-benzyl ether **18** in 91% yield. As suspected, direct dihydroxylation of **18** proceeded from the wrong side of the molecule (α face); therefore, the desired diol was obtained *via* an indirect method involving stereoselective epoxidation (*m*-CPBA, 71% yield, ca. 5:1 *dr*), epoxide opening with $\text{BnOH}\cdot\text{BF}_3\cdot\text{OEt}_2$ to afford tetra-benzyl ether **19** (91% yield), and oxidation–reduction (Swern [O]; NaBH_4) to afford hydroxy compound **20** (64% yield overall for the two steps) after chromatographic purification. Removal of the pivaloate group (Dibal-H, 83% yield) followed by oxidative lactonization [$\text{PhI}(\text{OAc})_2$, TEMPO] then led to AB ring system **21** in 92% yield. Finally, and in preparation for the planned Suzuki coupling, lactone **21** was converted to ketene acetal phosphate **7** in 97% yield through reaction with KHMDS and $(\text{PhO})_2\text{POCl}$.²⁰

The construction of the other defined coupling partner (*i.e.* **8**) for the proposed Suzuki coupling required D ring intermediate **29** involved the Noyori reduction/Achmatowicz rearrangement sequence, and proceeded through enone **26** as shown in Scheme 3. Thus, lithiation of the TBDPS derivative (**22**) of furfuryl alcohol (*n*-BuLi) followed by addition of amide **23** (available in two steps from glycolic acid)^{13e} provided the corresponding acyl furan derivative in 70% yield. Protecting group exchange (desilylation with CSA, 97% yield; pivaloylation with PivCl, 93% yield) then led to pivaloate **24**. Asymmetric reduction of **24**, employing the Noyori protocol [HCO_2Na , *n*-Bu₄Cl, *ent*-**13** (cat.)], delivered enantioenriched secondary alcohol **25** in 94% yield and $\geq 95\%$ *ee* (Naproxen[®] ester NMR spectroscopic analysis). Conversion of furanyl alcohol **25** to enone **26** was effectively carried out through the Achmatowicz rearrangement/reduction sequence (*m*-CPBA; then Et_3SiH , $\text{BF}_3\cdot\text{OEt}_2$) in 74% overall yield. In contrast to the one-pot conversion of **16** to **17** (Scheme 1) described above, this transformation required removal of the *m*-CPBA-derived byproducts by standard work-up prior to the reduction step for satisfactory yields. Introduction of the methyl group in the growing molecule was then achieved stereoselectively and exclusively in a 1,2-fashion by reaction of enone **26** with MeMgBr to afford, after silylation of the resulting tertiary alcohol (TMSOTf , 98% yield), TMS ether **27**. The axially disposed methyl group within **27** compound played a crucial role in the exclusive regio- and stereoselective addition of diisoamylborane across the double bond to afford, upon oxidative work-up (corresponding alcohol, 75% yield) and PMB ether formation [$\text{PMBOC}(\text{NH})\text{CCl}_3$, $\text{La}(\text{OTf})_3$, 97% yield], fully protected D ring system **28**.²¹ The pivaloate group was then removed (Dibal-H, 81% yield) to afford the desired primary alcohol **29**.

Scheme 4 summarizes the completion of the synthesis of the targeted DE fragment **8** that involved a silver-promoted cyclization of a hydroxy ynone (**32**→**33**) followed by stereoselective elaboration of the resulting bicycle to the desired system. Thus, lithiation of acetylenic compound **31** (obtained from (*S*)-glycidol through a standard, 5-step sequence)¹⁵ followed by addition of aldehyde **30** (obtained by DMP oxidation of alcohol **29**) led to a diastereomeric mixture of secondary alcohols (86% yield, ca. 7:1 *dr*), which was subjected to sequential selective desilylation (K_2CO_3 , MeOH, 99% yield) and DMP oxidation to afford hydroxy ynone **32** in 91% overall yield. Exposure of the latter to AgOTf ^{22,10} caused ring closure, furnishing DE ring enone **33** in 76% yield. (*R*)-CBS reduction²³ of enone **33** resulted in the selective formation of the corresponding α -hydroxy compound (93% yield), whose reaction with TBSCl and imidazole furnished, after hydroboration ($\text{BH}_3\cdot\text{THF}$) and oxidative workup, hydroxy TBS ether **34** (53% overall yield for the two steps). The installment of the bulky TBS group prior to the hydroboration step ensured the diastereoselectivity of the reaction, thus securing the desired stereochemical configuration around ring E. Desilylation of **34** with excess TBAF led to the corresponding triol (quant.), whose selective benzylation was achieved with BnBr and *n*-Bu₄NI under the facilitating influence of *n*-Bu₂SnO to afford diol **35** in 85% yield.²⁴ DE bicyclic enol ether **8** was then derived from diol **35** through a three-step sequence

involving selective tosylation of the primary hydroxyl group (TsCl, Et₃N), iodide formation (NaI, 89% yield for the two steps), base-induced elimination (KO^t-Bu), and PMB ether formation (NaH, PMBCl). The last two operations were carried out in the same pot and proceeded in 88% overall yield.

3. Fragment Coupling and Completion of the Synthesis of the Maitotoxin ABCDEFG Ring System

With ample quantities of both fragments (**7** and **8**) in hand, we proceeded to explore their union through the planned *B*-alkyl Suzuki coupling. It was upon considerable experimentation that we discovered the critical factors necessary for success in this reaction. Thus, an excess of cyclic vinyl ether partner **8** and relatively larger amounts of Buchwald's SPhos ligand²⁵ were needed for this process, which proceeded smoothly under the developed conditions [**8** (1.5 equiv.), 9-BBN; then aq. KHCO₃; then **7** (1.0 equiv), SPhos (0.3 equiv), Pd(OAc)₂ (0.15 equiv), 25 °C, 72 h] to afford coupling product **36** in 90% yield (based on phosphate **7**; the excess of vinyl ether **8** was converted to the corresponding alcohol via its borane by oxidative work-up and recovered as the corresponding primary alcohol which could be recycled). In preparation for the fusion of ring C, vinyl ether **36** was regio- and stereoselectively hydroborated and converted to the corresponding α and β alcohols upon oxidative work-up (85% combined yield, α : β ca. 4.5:1 *dr*). The two isomers were chromatographically separated and oxidized separately with DMP to afford the respective ketones (epimeric at C₂₃, maitotoxin numbering) [**37** (97% yield) and C₂₃-*epi*-**37** (84% yield)]. Equilibration of the wrong diastereomer (i.e. C₂₃-*epi*-**37**) with imidazole at 105 °C delivered a chromatographically separable mixture of **37** and C₂₃-*epi*-**37** (ca. 2.5:1 ratio, 91% combined yield), from which further amounts of the desired ketone isomer **37** could be obtained.²⁶ Treatment of **37** with EtSH in the presence of Zn(OTf)₂ caused sequential cleavage of the PMB groups within the substrate and thioacetalization to provide the corresponding hydroxy cyclic *S,O*-acetal, from which the TES protected *S,O*-acetal **38** was generated (TESCl, imid., 91% overall yield for the two steps). Finally, fully protected ABCDE ring system **39** was generated from **38** through sequential *m*-CPBA oxidation (to afford the corresponding sulfone) and axial methyl group installment (AlMe₃, same pot) in 94% overall yield.

As a prelude to growing the synthesized pentacyclic fragment of maitotoxin to include rings G and F, ABCDE ring system **39** was transformed to ketophosphonate **6**. Scheme 6 depicts the developed sequence to the latter intermediate, its coupling with G ring aldehyde **5**, and the elaboration of the resulting product to the targeted maitotoxin ABCDEFG ring system **3**. Thus, selective primary TES removal from **39** (PPTS, CH₂Cl₂-MeOH, 88% yield) followed by NMO-TPAP (cat.) oxidation of the resulting primary alcohol yielded aldehyde **40** (78% yield). Addition of the lithio derivative of dimethyl methylphosphonate [(MeO)₂POMe, *n*-BuLi] to aldehyde **40** followed by DMP oxidation of the so obtained secondary alcohol furnished ketophosphonate **6** in 66% overall yield (plus 17% recovered starting material **40**). The Horner-Wadsworth-Emmons coupling of ketophosphonate **6** with G ring aldehyde **4**^{10,15} proceeded smoothly under the Masamune-Roush conditions (*i*-Pr₂NEt, LiCl)²⁷ to afford enone **41** in 91% yield (plus 4% recovered starting material **6**). From the latter intermediate to the final targeted product of ABCDEFG ring system **3**, all that remained to be accomplished was forging of ring F and functionalization of the linker between the resulting fused hexacyclic system and ring G. To this end, enone **41** was treated with TsOH in MeOH:CH₂Cl₂ (3:1), conditions that facilitated formation of the F ring-containing heptacycle as its mixed methoxy acetal **42**, of which reduction with Et₃SiH in the presence of TMSOTf led to advanced intermediate **43** in 69% overall yield for the two steps. Initial attempts to install stereoselectively the missing 1,2-diol on substrate **43** through a Sharpless asymmetric dihydroxylation²⁸ were met with difficulties, presumably due to steric congestion around the olefinic bond, forcing us to resort to the simpler NMO-OsO₄ (cat.) protocol. Under the latter conditions, diol **44** was obtained

as a mixture with its opposite diastereomer (ca. 3:1 *dr*), from which the desired isomer was isolated in 61% yield.^{6a,7a} Finally, global debenzoylation [H₂, Pd(OH)₂ (cat.)] revealed the targeted ABCDEFG maitotoxin fragment **3** in 97% yield.

4. Comparison of ¹³C NMR Chemical Shifts of the ABCDEFG Ring System **3** with Those Corresponding to the Same Region of Maitotoxin

NMR spectroscopic analysis of synthetic ABCDEFG fragment **3** confirmed its expected stereochemical configurations and allowed assignment of all its ¹³C NMR chemical shifts.²⁹ These are listed in Table 1, together with the values reported^{4d} for the same carbons (C₁₃ to C₄₄ and C₁₄₇ to C₁₄₉) within the corresponding region of maitotoxin. As seen from the small differences between these values ($\Delta\delta$, ppm, see Table 1), which are also graphically depicted in Figure 3, there is compelling agreement between the two sets of chemical shifts (δ , ppm) for the two structures, except for those carbons residing at the edges of these structural motifs due to the drastically different structural motifs at these locations. Thus, the average chemical shift difference ($\Delta\delta$) between the two sets of values for the C₁₅ to C₃₈ and C₁₄₇ to C₁₄₉ is 0.22 ppm, and the maximum difference for a given carbon is 2.0 ppm (C₃₂). These compelling experimental values provide strong support for the originally assigned structure^{5–7} to the ABCDEFG region of maitotoxin (**1**).

Conclusion

The described chemistry provides access to the ABCDEFG fragment of maitotoxin for biological investigations and opens a possible pathway to the construction of larger domains of this biotoxin. It also secures further support for the originally assigned structure to this region of maitotoxin through ¹³C spectroscopic analysis and comparisons with the reported data for the same region of the natural product.^{5d} The success of the developed synthetic route demonstrates the power of the furan-based, Noyori reduction/Achmatowicz rearrangement approach to tetrahydropyran building blocks suitable for incorporation into polyether assemblies of the type found in maitotoxin and other marine neurotoxins.³⁰

Supplementary Material

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Acknowledgments

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Figure 1.
Structure of maitotoxin (1), previously synthesized GHIIJKLMNO domain 2, and targeted ABCDEFG fragment 3.

Figure 2.
Retrosynthetic analysis of ABCDEFG heptacyclic system **3**.

Figure 3. Graphically depicted ^{13}C chemical shift differences ($\Delta\delta$, ppm) for each carbon between C_{13} to C_{44} and C_{147} to C_{149} for maitotoxin (**1**) and ABCDEFG ring system **3**.

Scheme 1. Furan-based Synthesis of A Ring Building Block 17^a

^aReagents and conditions: (a) *n*-BuLi (2.5 M in hexanes, 1.0 equiv), THF, −78 °C, 15 min; then **11** (1.0 equiv), −78 °C, 2.5 h, 62% plus 20% recovered starting material (**10**); (b) PivCl (1.2 equiv), Et₃N (3.0 equiv), DMAP (0.1 equiv), CH₂Cl₂, 25 °C, 20 min, 94%; (c) catalyst **13** (0.01 equiv), *n*-Bu₄NCl (0.3 equiv), HCO₂Na (10.0 equiv), CH₂Cl₂:H₂O (1:1), 25 °C, 48 h, 97% (94% ee by Naproxen[®] ester NMR spectroscopic analysis); (d) BnBr (2.5 equiv), *n*-Bu₄NI (0.5 equiv), NaH (60% in mineral oil, 4.0 equiv), THF, 0 → 25 °C, 16 h, quant.; (e) 2.0 M aq. HCl:THF (1:2), 25 °C, quant.; (f) **15** (1.0 equiv), *n*-Bu₂BOTf (1.0 M in CH₂Cl₂, 1.2 equiv), Et₃N (1.3 equiv), −78 → 0 °C, CH₂Cl₂, 45 min; then **14**, −78 → 0 °C, 4.5 h, 98%; (g) *m*-CPBA (1.2 equiv), CH₂Cl₂, 0 → 25 °C 2.5 h; then Et₃SiH (2.0 equiv), BF₃·OEt₂ (2.0 equiv), −50 → −10 °C, 20 min, 75%.

Scheme 2. Completion of the Synthesis of AB Ring System 7^a

^aReagents and conditions: (a) NaBH_4 (4.0 equiv), CeCl_3 (2.0 equiv), CH_2Cl_2 : MeOH (1:1), $-30 \rightarrow -10^\circ\text{C}$, 15 min, 80%; (b) BnBr (25 equiv), $n\text{-Bu}_4\text{NI}$ (0.75 equiv), NaOH (25% aq.): PhMe (1:1), 25°C , 48 h, 91%; (c) $m\text{-CPBA}$ (3.0 equiv), CH_2Cl_2 , 25°C , 48 h, 71% (5:1 *dr*); (d) BnOH (2.5 equiv), $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 25°C , 18 h, 91%; (e) $(\text{COCl})_2$ (2.0 equiv), DMSO (4.0 equiv), CH_2Cl_2 , -78°C , 2 h; then Et_3N (6.0 equiv), 0°C , 1 h; (f) NaBH_4 (2.0 equiv), MeOH , -78°C , 45 min, 64% over the two steps; (g) Dibal-H (1.0 M in CH_2Cl_2 , 2.5 equiv), CH_2Cl_2 , -78°C , 1 h, 83%; (h) $\text{PhI}(\text{OAc})_2$ (5.0 equiv), TEMPO (0.2 equiv), CH_2Cl_2 , 25°C , 48 h, 92%; (i) $(\text{PhO})_2\text{P}(\text{O})\text{Cl}$ (10.0 equiv), KHMDs (0.5 M in PhMe , 3.0 equiv), THF : HMPA (10:1), -78°C , 30 min, 97%.

Scheme 3. Furan-Based Synthesis of D Ring Intermediate 29^a

^aReagents and conditions: (a) **22** (1.2 equiv), *n*-BuLi (2.5 M in hexanes, 1.2 equiv), THF, $-78 \rightarrow 0$ °C, 1 h; then **23** (1.0 equiv), $-78 \rightarrow 0$ °C, 1 h, 84%; (b) CSA (0.1 equiv), CH₂Cl₂:MeOH (5:1), 25 °C, 1 h, 97%; (c) PivCl (1.2 equiv), Et₃N (2.0 equiv), CH₂Cl₂, 25 °C, 12 h, 93%; (d) *ent*-**13** (0.02 equiv), *n*-Bu₄NCl (0.3 equiv), HCO₂Na (10.0 equiv), CH₂Cl₂:H₂O (1:1), 25 °C, 24 h, 94% ($\geq 95\%$ ee by Naproxen[®] ester NMR spectroscopic analysis); (e) *m*-CPBA (1.2 equiv), CH₂Cl₂, 0 $\rightarrow$ 25 °C, 2 h; (f) Et₃SiH (3.0 equiv), BF₃•OEt₂ (2.0 equiv), CH₂Cl₂, $-78 \rightarrow -20$ °C, 3 h, 74% over the two steps; (g) MeMgBr (2.0 equiv), THF, -78 °C, 2 h, 80%; (h) TMSOTf (1.5 equiv), Et₃N (2.5 equiv), CH₂Cl₂, -78 °C, 1 h, 98%; (i) diisooamylborane (4.0 equiv), THF, $-78 \rightarrow 0$ °C, 72 h; then H₂O₂ (35% aq., 40 equiv), NaOH (1.0 M aq., 80 equiv), 25 °C, 5 h, 75%; (j) PMBOC(NH)CCl₃ (2.0 equiv), La(OTf)₃ (0.05 equiv), PhMe, 25 °C, 3 h, 96%; (k) Dibal-H (2.2 equiv), CH₂Cl₂, -78 °C, 84%.

Scheme 4. Completion of the Synthesis of the DE Ring Coupling Partner 8^a

^aReagents and conditions: (a) DMP (1.5 equiv), NaHCO₃ (5.0 equiv), CH₂Cl₂, 25 °C, 1 h; (b) **31** (2.5 equiv), *n*-BuLi (2.5 M in hexanes, 2.5 equiv), THF, -78 → -40 °C, 10 min; then **30** (1.0 equiv), -78 → -50 °C, 1.5 h, 86% over the two steps; (c) K₂CO₃ (5.0 equiv), MeOH, 25 °C, 30 min, 99%; (d) DMP (1.5 equiv), CH₂Cl₂, 25 °C, 1 h, 91%; (e) AgOTf (0.9 equiv), CH₂Cl₂, -40 °C, 20 h, 76%; (f) (*R*)-CBS (1.0 M in PhMe, 1.5 equiv), BH₃·THF (1.0 M in THF, 1.5 equiv), PhMe, -50 → -20 °C, 1 h, 93%; (g) TBSCl (6.0 equiv), imid. (10.0 equiv), CH₂Cl₂, 25 °C, 1 h, 98%; (h) BH₃·THF (1.0 M in THF, 10 equiv), THF, 0 °C, 18 h; then H₂O₂ (35% aq., 100 equiv), NaOH (1.0 M aq., 200 equiv), 25 °C, 6 h, 54%; (i) TBAF (1.0 M in THF, 5.0 equiv), THF, 25 °C, 16 h, quant.; (j) *n*-Bu₂SnO (1.0 equiv), PhMe, 110 °C, 12 h;

then BnBr (1.5 equiv), *n*-Bu₄NI (1.0 equiv), 100 °C, 4.5 h, 85%; (k) TsCl (3.0 equiv), Et₃N (6.0 equiv), DMAP (0.1 equiv), CH₂Cl₂, 25 → 45 °C, 20 h; (l) NaI (10.0 equiv), DME, 85 °C, 7 h, 89% over the two steps; (m) KO*t*-Bu (12 equiv), THF, 0 °C, 16 h; then PMBCl (5.0 equiv), NaH (60% suspension in mineral oil, 10.0 equiv), *n*-Bu₄NI (0.5 equiv), 25 °C, 36 h, 88%.

Scheme 5. Synthesis of ABCDE Ring System 39^a

^aReagents and conditions: (a) **8** (1.5 equiv), 9-BBN (0.5 M in THF, 4.5 equiv), THF, 25 °C, 4 h; then KHCO_3 (0.5 M aq., 13.5 equiv), 25 °C, 20 min; then **7**, SPhos (0.3 equiv), $\text{Pd}(\text{OAc})_2$ (0.15 equiv), 25 °C, 72 h, 90%; (b) $\text{BH}_3 \cdot \text{THF}$ (1.0 M in THF, 10.0 equiv), THF, 0 °C, 18 h; then H_2O_2 (35% aq., 100 equiv), NaOH (1.0 M aq., 200 equiv), 25 °C, 6 h, 70% (α -diastereomer) plus 15% (β -diastereomer); (c) DMP (4.0 equiv), CH_2Cl_2 , 0 $\rightarrow$ 25 °C, 2 h, 97% for **37**, 84% for $\text{C}_{23}\text{-epi-37}$; (d) imid. (200 equiv), PhMe, 105 °C, 120 h, 65% plus 26% recovered starting material ($\text{C}_{23}\text{-epi-37}$); (e) **37** (1.0 equiv), $\text{Zn}(\text{OTf})_2$ (5.0 equiv), $\text{EtSH}:\text{CH}_2\text{Cl}_2$ (1:5), 25 °C, 20 h; (f) TESCl (10.0 equiv), imid. (20 equiv), CH_2Cl_2 , 25 °C, 1

h, 91% over the two steps; (g) *m*-CPBA (2.5 equiv), CH₂Cl₂, 0 °C, 30 min; then AlMe₃ (2.0 M in hexanes, 5.0 equiv), 0 °C, 30 min, 94%.

Scheme 6. Completion of the Synthesis of the Maitotoxin ABCDEFG Ring System 3^a

^aReagents and conditions: (a) PPTS (0.5 equiv), CH₂Cl₂:MeOH (10:1), 0 °C, 1 h, 88%; (b) NMO (3.0 equiv), TPAP (0.1 equiv), 4 Å MS, CH₂Cl₂:MeCN (9:1), 25 °C, 30 min, 78%; (c) (MeO)₂P(O)CH₃ (5.0 equiv), *n*-BuLi (2.5 M in hexanes, 5.0 equiv), THF, −78 °C, 1 h; then **40** (1.0 equiv), −78 °C, 2.5 h; (d) DMP (3.0 equiv), CH₂Cl₂, 25 °C, 30 min, 66% over the two steps plus 17% recovered starting material (**40**); (e) *i*-Pr₂NEt (3.0 equiv), LiCl (3.0 equiv), **4** (1.4 equiv), MeCN, 25 °C, 72 h, 91% (95% brsm); (f) TsOH (3.0 equiv), MeOH:CH₂Cl₂ (3:1), 25 °C, 2 h; (g) Et₃SiH (10.0 equiv), TMSOTf (5.0 equiv), MeCN, −40 → −25 °C, 30 min, 69% over the two steps; (h) NMO (3.0 equiv), OsO₄ (2.5 wt % in *t*-BuOH, 0.05 equiv), acetone:H₂O (4:1), 72 h, 61%, plus 26% of the opposite diastereomer; (i) 20% Pd(OH)₂/C (50% w/w), H₂, EtOH, 6 d, 97%.

Table 1

C₁₃ to C₄₄ and C₁₄₇ to C₁₄₉ Chemical Shifts (δ) for Maitotoxin (MTX, **1**) and ABCDEFG Ring System **3** and Their Differences ($\Delta\delta$, ppm)^a

carbon	δ for MTX (1) (ppm)	δ for 3 (ppm)	difference ($\Delta\delta$, ppm)
13	78.8	65.8	13.0
14	35.8	36.9	-1.1
147	11.0	10.5	0.5
15	74.8	75.1	-0.3
16	69.0	69.4	-0.4
17	72.4	72.4	0.0
18	76.0	76.5	-0.5
19	76.8	76.7	0.1
20	71.4	71.5	-0.1
21	48.3	48.3	0.0
22	79.1	79.6	-0.5
148	21.5	21.6	-0.1
23	76.7	76.5	0.2
24	34.4	34.4	0.0
25	80.7	80.7	0.0
26	69.8	69.7	0.1
27	45.0	44.9	0.1
28	75.4	75.3	0.1
149	17.9	17.9	0.0
29	86.0	86.0	0.0
30	69.6	69.7	-0.1
31	85.4	85.3	0.1
32	68.2	66.2	2.0
33	38.8	38.8	0.0
34	66.5	66.3	0.2
35	81.0	81.0	0.0
36	73.1	73.0	0.1
37	67.3	67.5	-0.2
38	37.4	37.8	-0.4
39	72.3	73.5	-1.2
40	78.9	73.3	5.6
41	68.5	72.7	-4.2
42	80.6	69.4	11.2
43	69.6	74.0	-4.4
44	36.3	64.6	-28.3

^a 150 MHz, 1:1 methanol-d₄:pyridine-d₅