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Synthesis of the ABCDEFG Ring System of Maitotoxin

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Abstract: Maitotoxin (**1**) continues to fascinate scientists not only because of its size and potent neurotoxicity but also due to its molecular architecture. 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 coupling and a Horner−Wadsworth−Emmons olefination to accomplish their assembly and elaboration to the final target molecule.

1. Introduction

As the largest and most toxic of the secondary metabolites isolated[1] 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 1971[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 as well as 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 maitotoxin[8] elicited a response from our laboratories that provided strong support for the originally assigned structure, first through computations[9] and, subsequently, chemical synthesis of a GHIJK polycyclic system[10] and a GHIJKLMNO fragment (**2**, Figure 1), followed by NMR spectroscopic comparisons with the natural product.[11] In continuing our quest

(1) (a) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293. (b) Yasumoto, T.; Bagnins, R.; Randal, J. E.; Banner, A. H. *Nippon Suisan Gakkaishi* **1971**, *37*, 724. (c) Yasumoto, T.; Bagnins, R.; Vernoux, J. P. *Nippon Suisan Gakkaishi* **1976**, *42*, 359. (d) Yasumoto, T.; Nakajima, I.; Bagnis, R.; Adachi, R. *Nippon Suisan Gakkaishi* **1977**, *43*, 1021. (e) Yokoyama, A.; Murata, M.; Oshima, Y.; Iwashita, T.; Yasumoto, T. *J. Biochem.* **1988**, *104*, 184.

(2) (a) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335. (b) Nakata, T.; Nomura, S.; Matsukura, H. *Chem. Pharm. Bull.* **1996**, *44*, 627. (c) Nagasawa, K.; Hori, N.; Shiba, R.; Nakata, T. *Heterocycles* **1997**, *44*, 105. (d) Sakamoto, Y.; Matsuo, G.; Matsukura, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749. (e) Morita, M.; Ishiyama, S.; Koshino, H.; Nakata, T. *Org. Lett.* **2008**, *10*, 1675. (f) Morita, M.; Haketa, T.; Koshino, H.; Nakata, T. *Org. Lett.* **2008**, *10*, 1679. (g) Satoh, M.; Koshino, H.; Nakata, T. *Org. Lett.* **2008**, *10*, 1683.

(3) (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) *Phycotoxins: Chemistry and Biochemistry*; Botana, L. M., Ed.; Blackwell Publishing: Ames, IA, 2007; p 345.

(4) (a) Takahashi, M.; Ohizumi, Y.; Yasumoto, T. *J. Biol. Chem.* **1982**, *257*, 7287. (b) Gusovsky, F.; Daly, J. W. *Biochem. Pharmacol.* **1990**, *39*, 1633. (c) Ueda, H.; Tamura, S.; Fukushima, N.; Takagi, H. *Eur. J. Pharmacol.* **1986**, *122*, 379. (d) Konoki, K.; Hashimoto, M.; Nanomura, T.; Sasaki, M.; Murata, M.; Tachibana, K. *J. Neurochem.* **1998**, *70*, 409. (e) Murata, M.; Gusovsky, F.; Yasumoto, T.; Daly, J. W. *Eur. J. Pharmacol.* **1992**, *227*, 43.

(5) (a) Murata, M.; Iwashita, T.; Yokoyama, A.; Sasaki, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1992**, *114*, 6594. (b) Murata, M.; Naoki, H.; Iwashita, T.; Matsunaga, S.; Sasaki, M.; Yokoyama, A.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 2060. (c) Murata, M.; Naoki, H.; Matsunaga, S.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1994**, *116*, 7098. (d) Satake, M.; Ishida, S.; Yasumoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 7019.

(6) (a) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946. (b) Cook, L. R.; Oinuma, H.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 7928. (c) Kishi, Y. *Pure Appl. Chem.* **1998**, *70*, 339.

(7) (a) Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1995**, *36*, 9007. (b) Sasaki, M.; Nomomura, T.; Murata, M.; Tachibana, K.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 9011. (c) Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1994**, *35*, 5023. (d) Sasaki, M.; Matsumori, N.; Muruyama, T.; Nonomura, T.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1672. (e) Nonomura, T.; Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1675.

(8) Gallimore, A. R.; Spencer, J. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4406.

(9) Nicolaou, K. C.; Frederick, M. O. *Angew. Chem., Int. Ed.* **2007**, *46*, 5278.

(10) Nicolaou, K. C.; Cole, K. P.; Frederick, M. O.; Aversa, R. J.; Denton, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8875.

(11) Nicolaou, K. C.; Frederick, M. O.; Burtoloso, A. C. B.; Denton, R. M.; Rivas, F.; Cole, K. P.; Aversa, R. J.; Gibe, R.; Umezawa, T.; Suzuki, T. *J. Am. Chem. Soc.* **2008**, *130*, 7466.

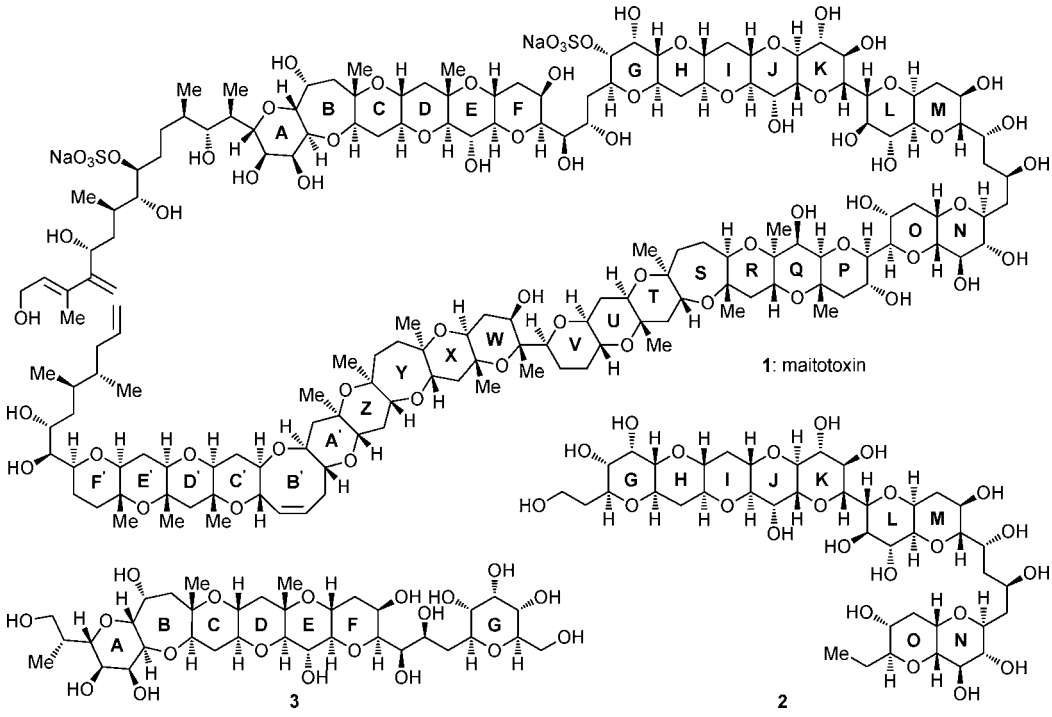


Figure 1. Structure of maitotoxin (**1**), previously synthesized GHIJKLMNO domain **2**, and targeted ABCDEFG fragment **3**.

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).

2. 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]

2.1. 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; cy-

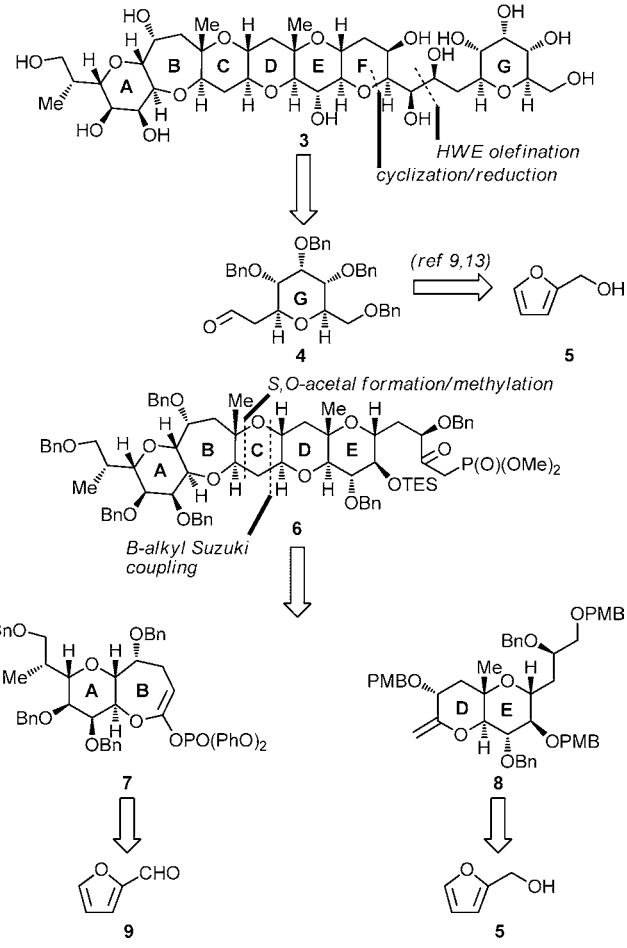
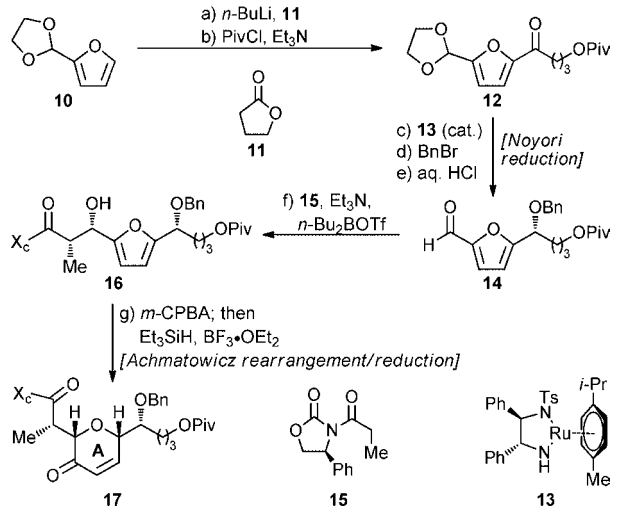


Figure 2. Retrosynthetic analysis of ABCDEFG heptacyclic system **3**.

(12) For a review on wrongly assigned structures to natural products, see: Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012.

(13) (a) Guo, H.; O'Doherty, G. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5206. (b) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485. (c) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609. (d) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17. (e) Li, M.; Scott, J.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005. (g) Henderson, J. A.; Jackson, K. L.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 5299. (h) Jackson, K. L.; Henderson, J. A.; Motoyoshi, H.; Phillips, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2346. (i) Krishna, U. M.; Srikanth, G. S. C.; Trivedi, G. K. *Tetrahedron Lett.* **2003**, *44*, 8277.

Scheme 1. Furan-Based Synthesis of A Ring Building Block **17**[a]



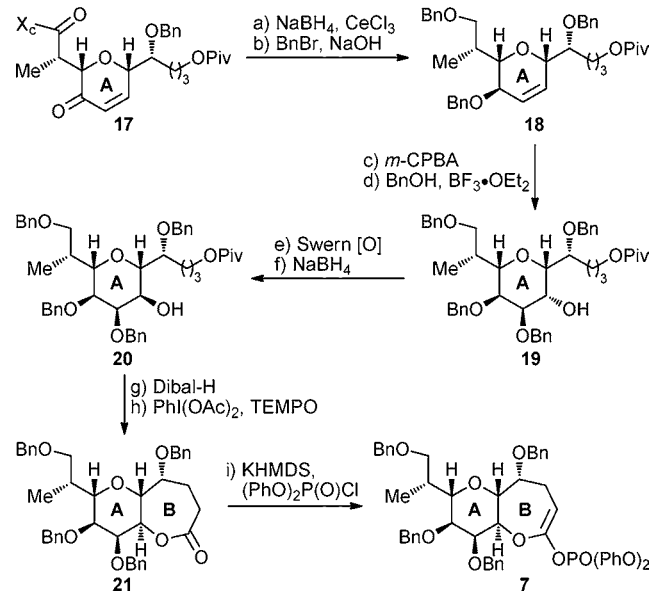
[a] Reagents and conditions: (a) *n*-BuLi (2.5 M in hexanes, 1.0 equiv), THF, −78 °C, 15 min; then **11** (1.0 equiv), −78 °C, 2.5 h, 62% plus 20% recovered starting material (**10**); (b) PivCl (1.2 equiv), Et_3N (3.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, 25 °C, 20 min, 94%; (c) catalyst **13** (0.01 equiv), *n*-Bu_4NCl (0.3 equiv), HCO_2Na (10.0 equiv), CH_2Cl_2/H_2O (1:1), 25 °C, 48 h, 97% (94% ee by Naproxen ester NMR spectroscopic analysis); (d) BnBr (2.5 equiv), *n*-Bu_4NI (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*-Bu_2BOTf (1.0 M in CH_2Cl_2, 1.2 equiv), Et_3N (1.3 equiv), −78 → 0 °C, CH_2Cl_2, 45 min; then **14**, −78 → 0 °C, 4.5 h, 98%; (g) *m*-CPBA (1.2 equiv), CH_2Cl_2, 0 → 25 °C 2.5 h; then Et_3SiH (2.0 equiv), BF_3•OEt_2 (2.0 equiv), −50 → −10 °C, 20 min, 75%.

clization/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 coupling[14] 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.

2.2. 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 installation (PivCl, Et_3N, 94% yield), in the formation of ketone **12**. Ketone **12** was subjected to Noyori asymmetric

Scheme 2. Completion of the Synthesis of AB Ring System **7**[a]



[a] Reagents and conditions: (a) $NaBH_4$ (4.0 equiv), $CeCl_3$ (2.0 equiv), CH_2Cl_2/MeOH (1:1), −30 → −10 °C, 15 min, 80%; (b) BnBr (25 equiv), *n*-Bu_4NI (0.75 equiv), NaOH (25% aq.)/PhMe (1:1), 25 °C, 48 h, 91%; (c) *m*-CPBA (3.0 equiv), CH_2Cl_2, 25 °C, 48 h, 71% (5:1 *dr*); (d) BnOH (2.5 equiv), BF_3•OEt_2, CH_2Cl_2, 25 °C, 18 h, 91%; (e) $(COCl)_2$ (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) $PhI(OAc)_2$ (5.0 equiv), TEMPO (0.2 equiv), CH_2Cl_2, 25 °C, 48 h, 92%; (i) $(PhO)_2P(O)Cl$ (10.0 equiv), KHMDS (0.5 M in PhMe, 3.0 equiv), THF/HMPA (10:1), −78 °C, 30 min, 97%.

transfer hydrogenation [HCO_2Na, *n*-Bu_4Cl, **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*-Bu_2BOTf, Et_3N)[17] furnished furfuryl alcohol **16** in 98% yield as a single diastereomer. Treatment of **16** with *m*-CPBA followed by addition of Et_3SiH and BF_3•OEt_2 resulted in the formation of enone **17** through Achmatowicz rearrangement[18] 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 BnOH−BF_3•OEt_2 to afford tetrabenzyl ether **19** (91% yield),

(14) (a) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027. (b) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075. (c) Sasaki, M.; Ishikawa, M.; Fuwa, H.; Tachibana, K. *Tetrahedron* **2002**, *58*, 1889. For a comprehensive review of applications of *B*-alkyl Suzuki couplings in total synthesis, see: (d) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(15) For full details, see Supporting Information.

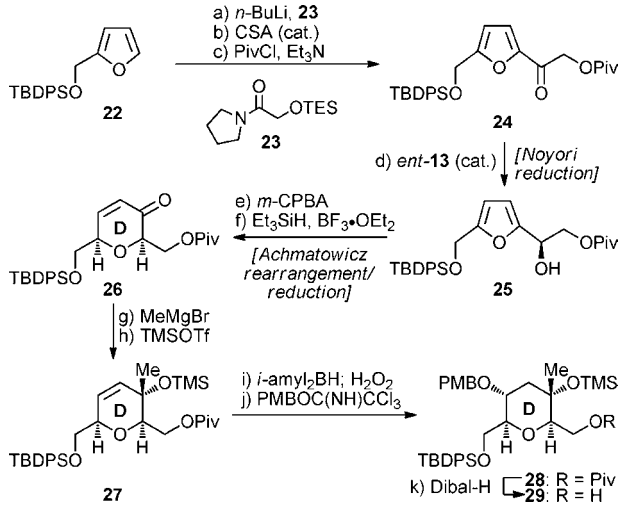
(16) (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (b) Ferrie, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2007**, *9*, 2461.

(17) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2126. (b) Ager, D. J.; Allen, D. R.; Shaad, D. R. *Synthesis* **1996**, 1283. (c) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14095.

(18) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165.

(19) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

Scheme 3. Furan-Based Synthesis of D Ring Intermediate **29**[a]

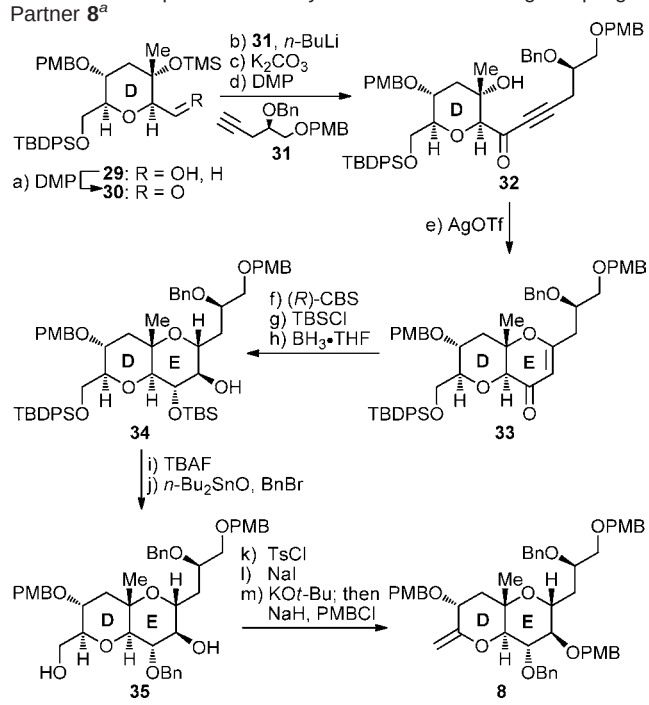


[a] Reagents and conditions: (a) **22** (1.2 equiv), *n*-BuLi (2.5 M in hexanes, 1.2 equiv), THF, −78 → 0 °C, 1 h; then **23** (1.0 equiv), −78 → 0 °C, 1 h, 84%; (b) CSA (0.1 equiv), CH_2Cl_2/MeOH (5:1), 25 °C, 1 h, 97%; (c) PivCl (1.2 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 25 °C, 12 h, 93%; (d) *ent*-**13** (0.02 equiv), *n*-Bu_4NCl (0.3 equiv), HCO_2Na (10.0 equiv), CH_2Cl_2/H_2O (1:1), 25 °C, 24 h, 94% (≥95% ee by Naproxen ester NMR spectroscopic analysis); (e) *m*-CPBA (1.2 equiv), CH_2Cl_2, 0 → 25 °C, 2 h; (f) Et_3SiH (3.0 equiv), BF_3•OEt_2 (2.0 equiv), CH_2Cl_2, −78 → −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), Et_3N (2.5 equiv), CH_2Cl_2, −78 °C, 1 h, 98%; (i) diisoamylborane (4.0 equiv), THF, −78 → 0 °C, 72 h; then H_2O_2 (35% aq., 40 equiv), NaOH (1.0 M aq., 80 equiv), 25 °C, 5 h, 75%; (j) $PMBOC(NH)CCl_3$ (2.0 equiv), $La(OTf)_3$ (0.05 equiv), PhMe, 25 °C, 3 h, 96%; (k) Dibal-H (2.2 equiv), CH_2Cl_2, −78 °C, 84%.

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 [$PhI(OAc)_2$, 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 $(PhO)_2POCl$.[20]

The construction of the other defined coupling partner (i.e., **8**) for the proposed Suzuki coupling required D ring intermediate **29** and involved the Noyori reduction/Achmatowicz rearrangement sequence which 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 84% 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*-Bu_4Cl, *ent*-**13** (cat.)], delivered enantioenriched secondary alcohol **25** in 94% yield and ≥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, BF_3•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 workup prior to the reduction step for

Scheme 4. Completion of the Synthesis of the DE Ring Coupling Partner **8**[a]



[a] Reagents and conditions: (a) DMP (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 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) K_2CO_3 (5.0 equiv), MeOH, 25 °C, 30 min, 99%; (d) DMP (1.5 equiv), CH_2Cl_2, 25 °C, 1 h, 91%; (e) AgOTf (0.9 equiv), CH_2Cl_2, −40 °C, 20 h, 76%; (f) (*R*)-CBS (1.0 M in PhMe, 1.5 equiv), BH_3•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), CH_2Cl_2, 25 °C, 1 h, 98%; (h) BH_3•THF (1.0 M in THF, 10 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, 54%; (i) TBAF (1.0 M in THF, 5.0 equiv), THF, 25 °C, 16 h, quant.; (j) *n*-Bu_2SnO (1.0 equiv), PhMe, 110 °C, 12 h; then BnBr (1.5 equiv), *n*-Bu_4NI (1.0 equiv), 100 °C, 4.5 h, 85%; (k) TsCl (3.0 equiv), Et_3N (6.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, 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*-Bu_4NI (0.5 equiv), 25 °C, 36 h, 88%.

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 (80% yield) to afford, after silylation of the resulting tertiary alcohol (TMSOTf, 98% yield), TMS ether **27**. The axially disposed methyl group within compound **27** played a crucial role in the exclusive regio- and stereoselective addition of diisoamylborane across the double bond to afford, upon oxidative workup (corresponding alcohol, 75% yield) and PMB ether formation [$PMBOC(NH)CCl_3$, $La(OTf)_3$, 98% yield], fully protected D ring system **28**.[21] The pivaloate group was then removed (Dibal-H, 84% 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, five-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%

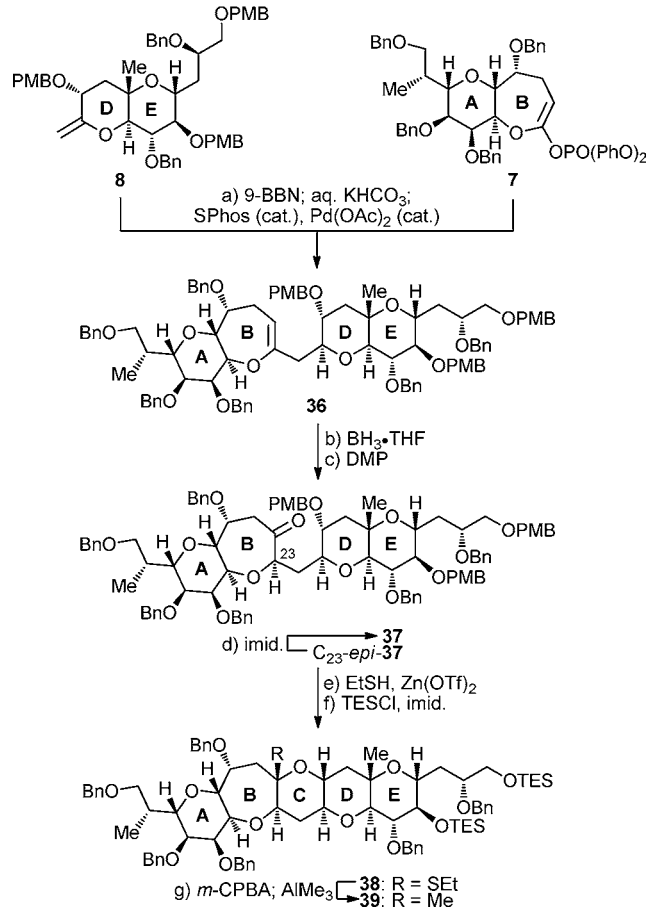
(20) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467.

(21) Rai, A. N.; Basu, A. *Tetrahedron Lett.* **2003**, *44*, 2267.

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% yield. Exposure of the latter to AgOTf[22,10] caused ring closure, furnishing DE ring enone **33** in 76% yield. (*R*)-CBS reduction[23] 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 (BH_3•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*-Bu_4NI under the facilitating influence of *n*-Bu_2SnO to afford diol **35** in 85% overall 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, Et_3N), 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.

2.3. 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 ligand[25] were needed for this process, which proceeded smoothly under the developed conditions [**8** (1.5 equiv), 9-BBN; then aq. $KHCO_3$; 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 workup and 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 workup (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 C_{23}, maitotoxin numbering) [**37** (97% yield) and C_{23}-*epi*-**37** (84% yield)]. Equilibration of the wrong diastereomer (i.e., C_{23}-*epi*-**37**) with imidazole at 105 °C delivered a chromatographically separable mixture of **37** and C_{23}-*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** (Scheme 5) was generated from **38** through

Scheme 5. Synthesis of ABCDE Ring System **39**[a]



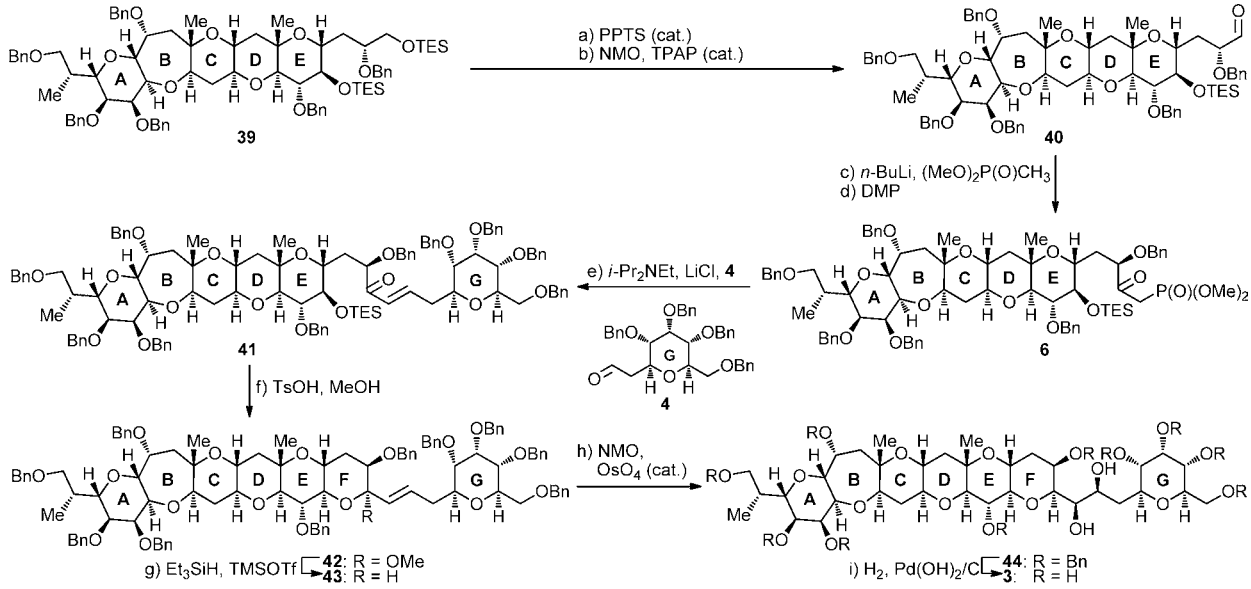
[a] Reagents and conditions: (a) **8** (1.5 equiv), 9-BBN (0.5 M in THF, 4.5 equiv), THF, 25 °C, 4 h; then $KHCO_3$ (0.5 M aq., 13.5 equiv), 25 °C, 20 min; then **7**, SPhos (0.3 equiv), $Pd(OAc)_2$ (0.15 equiv), 25 °C, 72 h, 90%; (b) BH_3•THF (1.0 M in THF, 10.0 equiv), THF, 0 °C, 18 h; then H_2O_2 (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 → 25 °C, 2 h, 97% for **37**, 84% for C_{23}-*epi*-**37**; (d) imid. (200 equiv), PhMe, 105 °C, 120 h, 65% plus 26% recovered starting material (C_{23}-*epi*-**37**); (e) **37** (1.0 equiv), $Zn(OTf)_2$ (5.0 equiv), EtSH:CH_2Cl_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), CH_2Cl_2, 0 °C, 30 min; then $AlMe_3$ (2.0 M in hexanes, 5.0 equiv), 0 °C, 30 min, 94%.

sequential *m*-CPBA oxidation (to afford the corresponding sulfone) and axial methyl group installment ($AlMe_3$, 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 **4**, and the elaboration of the resulting product to the targeted maitotoxin ABCDEFG ring system **3**. Thus, selective primary TES removal from **39** (PPTS, CH_2Cl_2−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 [$(MeO)_2P(O)CH_3$, *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 condi-

(22) Wang, C.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 2997.
(23) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987.
(24) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
(25) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.
(26) Johnson, H. W. B.; Majumder, U.; Rainer, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848.

Scheme 6. Completion of the Synthesis of the Maitotoxin ABCDEFG Ring System **3**[a]



[a] Reagents and conditions: (a) PPTS (0.5 equiv), CH_2Cl_2/MeOH (10:1), 0 °C, 1 h, 88%; (b) NMO (3.0 equiv), TPAP (0.1 equiv), 4 Å MS, CH_2Cl_2/MeCN (9:1), 25 °C, 30 min, 78%; (c) $(MeO)_2P(O)CH_3$ (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), CH_2Cl_2, 25 °C, 30 min, 66% over the two steps plus 17% recovered starting material (**40**); (e) *i*-Pr_2NEt (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/CH_2Cl_2 (3:1), 25 °C, 2 h; (g) Et_3SiH (10.0 equiv), TMSOTf (5.0 equiv), MeCN, −40 → −25 °C, 30 min, 69% over the two steps; (h) NMO (3.0 equiv), OsO_4 (2.5 wt % in *t*-BuOH, 0.05 equiv), acetone/H_2O (4:1), 72 h, 61%, plus 26% of the opposite diastereomer; (i) 20% $Pd(OH)_2$/C (50% w/w), H_2, EtOH, 6 d, 97%.

tions (*i*-Pr_2NEt, 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/CH_2Cl_2 (3:1), conditions that facilitated formation of the F ring-containing heptacycle as its mixed methoxy acetal **42**, of which reduction with Et_3SiH 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 dihydroxylation[28] were met with difficulties, presumably due to steric congestion around the olefinic bond, forcing us to resort to the simpler NMO-OsO_4 (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 debenzylation [H_2, $Pd(OH)_2$ (cat.)] revealed the targeted ABCDEFG maitotoxin fragment **3** in 97% yield.

2.4. Comparison of ^{13}C 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 ^{13}C

Table 1. C_{13} to C_{44} and C_{147} to C_{149} 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-d_4/pyridine-d_5.

(27) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(28) (a) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263. (b) Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 2999. (c) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (d) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(29) The stereochemistry and ^{13}C chemical shift assignments of **3** were based on ^1H coupling constants and COSY, ROESY, HSQC, and HMBC NMR spectroscopic experiments.

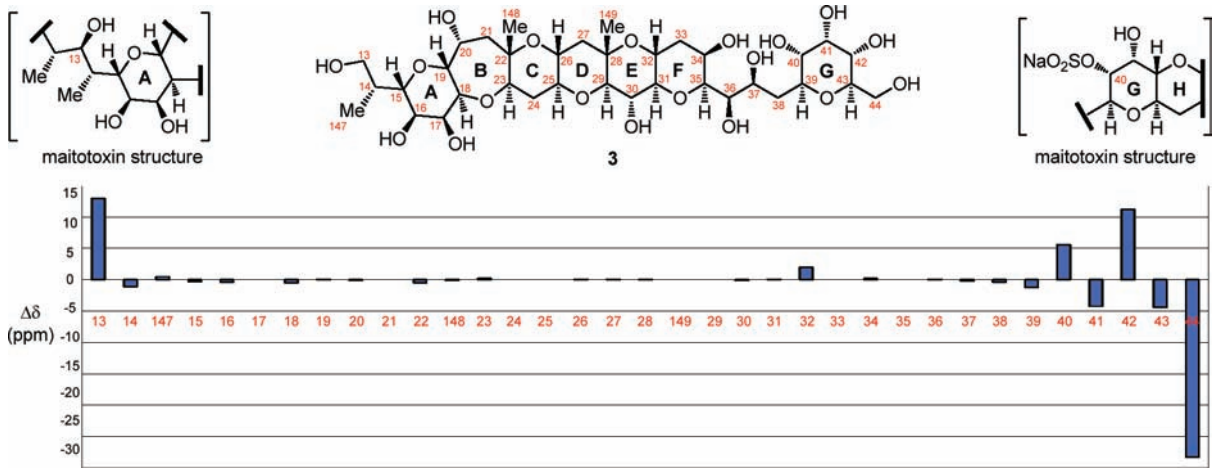


Figure 3. Graphically depicted ^{13}C chemical shift differences ($\Delta\delta$, ppm) for each carbon between C_{13} to C_{44} and C_{147} to C_{149} for maitotoxin (**1**) and ABCDEFG ring system **3**.

NMR chemical shifts.[29] These are listed in Table 1, together with the values reported[5d] for the same carbons (C_{13} to C_{44} and C_{147} to C_{149}) 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 features at these locations. Thus, the average chemical shift difference ($\Delta\delta$) between the two sets of values for the C_{15} to C_{38} and C_{147} to C_{149} is 0.22 ppm, and the maximum difference for a given carbon is 2.0 ppm (C_{32}). These compelling experimental values provide strong support for the originally assigned structure[5–7] to the ABCDEFG region of maitotoxin (**1**).

3. 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 ^{13}C NMR 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]

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Note Added after ASAP Publication. In the version published April 23, 2010, there was an error in the Supporting Information on page S117. This has been corrected, and the revised Supporting Information has been published with the article on May 12, 2010.

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.

JA102260Q

(30) For selected reviews on the synthesis of fused polyether natural products, see: (a) Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7182. (b) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 588. (c) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (d) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379. (e) Sasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 856.