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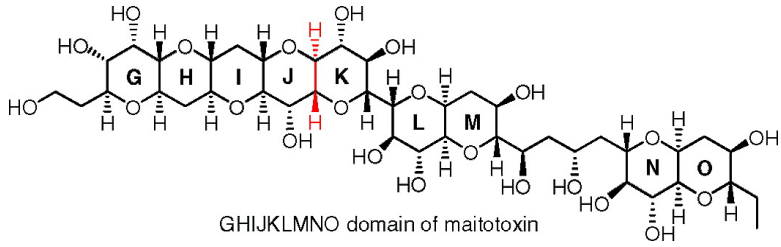

GHIJKLMNO domain of maitotoxin

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Chemical Synthesis of the GHIJKLMNO Ring System of Maitotoxin

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Abstract: As the largest secondary metabolite to be discovered as of yet, the polyether marine neurotoxin maitotoxin constitutes a major structural and synthetic challenge. After its originally proposed structure (**1**) had been questioned on the basis of biosynthetic considerations, we provided computational and experimental support for structure **1**. In an effort to provide stronger experimental evidence of the molecular architecture of maitotoxin, its GHIJKLMNO ring system **3** was synthesized. The ^{13}C NMR chemical shifts of synthetic **3** matched closely those corresponding to the same domain of the natural product providing strong evidence for the correctness of the originally proposed structure of maitotoxin (**1**).

Introduction

Maitotoxin is the largest secondary metabolite isolated[1] as yet from any living creature. Its legendary toxicity surpasses that of any known molecule, other than a few proteomic substances. As such, this impressive natural product elicited considerable attention from the scientific community.[1–5] Maitotoxin was first detected in the gut of the surgeonfish *Ctenochaetus striatus*,[1b,c] and later in the dinoflagellate *Gambierdiscus toxicus*.[1d] However, it would not be until 1988 that the substance was actually isolated from a broth of *G. toxicus* by Yasumoto and co-workers.[1e] The gross structure of maitotoxin was proposed by Yasumoto and co-workers in 1993.[2b] Its relative stereochemistry was defined by Kishi et al. in 1996,[3a] with its absolute stereochemistry assigned by Tachibana et al. in the same year (**1**, Figure 1).[4e] In 2006, the assigned structure of maitotoxin came under close scrutiny by Gallimore and Spencer on the basis of biosynthetic considerations, which suggested the opposite configuration at the two stereocenters of the JK junction (structure **1**, C-51, C-52, Figure 1).[6] Following this challenge, and in order to test the Gallimore−Spencer hypothesis, we resorted to computational chemistry, which provided support for the originally proposed (**1**), rather than a revised, structure.[7] In a subsequent study, we synthesized the GHIJK ring system **2** (Figure 1) of maitotoxin and compared its ^{13}C chemical shifts with the corresponding ^{13}C chemical shifts of the natural product (**1**), an exercise that provided experimental evidence in support of the originally proposed structure (**1**) of maitotoxin.[8] In this article, we describe the chemical synthesis of the entire GHIJKLMNO ring domain **3** (Figure 1) of structure **1**, and the comparison of the ^{13}C chemical shifts of this fragment to those reported for the same domain of the natural product, which provided further support for the originally proposed structure (**1**) of maitotoxin.

Results and Discussion

1. Retrosynthetic Analysis. Having defined our target as structure **3**, we proceeded to consider a strategy by which to

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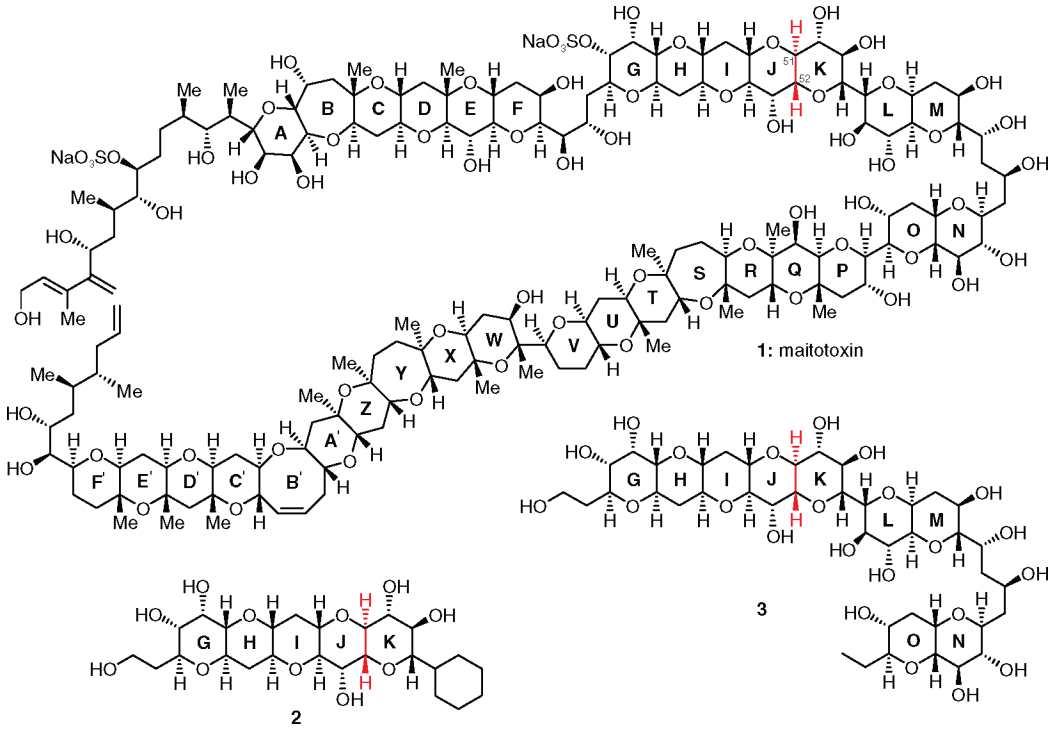

Figure 1. Structure of maitotoxin (**1**), previously synthesized GHIJK ring system **2**, and targeted GHIJKLMNO ring system **3**.

reach it. An appealing retrosynthetic analysis is shown in Figure 2 in which the molecule (**3**) is dissected approximately in the middle by rupturing the indicated C−C and C−O bonds. This dissection led to advanced intermediates aldehyde **4** and alkyne **5**, whose union/elaboration was expected to forge the missing ring (K). Aldehyde **4** was then dismantled at the indicated bonds (two C−C and two C−O bonds) furnishing ring systems **6** (G) and **7** (J) as potential key building blocks, whereas alkyne **5** was envisioned to arise from two molecules of a single key building block (**8**) by virtue of the pseudo symmetry of the molecule. Finally, all three key building blocks (**6**−**8**) were traced back to furan (**9**) and its derivatives. A strategy based on this analysis would have the advantage of high convergency and the aesthetic appeal of deriving a most complex polyether system from the simplest of oxygen heterocycles, furan itself.

2. Carbohydrate Approach to the LM, NO, and LMNO Fragments of Maitotoxin. As a prelude to devising a synthetic strategy to the targeted GHIJKLMNO maitotoxin domain, we needed to charter a viable route to its LMNO region (we already had enough intelligence regarding the GHIJK region gathered from our previous work).[8] Toward this end, we targeted the needed LM/NO common key building block **8** for which we developed the synthetic route depicted in Schemes 1 and 2. Thus, starting with diol **10** (conveniently derived from methyl-D-glucopyranoside),[9] the bis-benzyl ether **11** was prepared (NaH, BnBr, 97% yield) and converted to the new diol **12** by the action of CSA cat. in the presence of EtSH (91% yield). The primary alcohol **13** was then prepared from **12** by a two-step procedure involving bis-silylation (TBSOTf, 2,6-lut.) followed by selective monodesilylation (CSA cat., MeOH, 80% overall yield for the two steps). Swern oxidation of the latter compound [$(COCl)_2$, DMSO, −78 °C; Et_3N, 0 °C][10] followed by Baeyer−Villiger

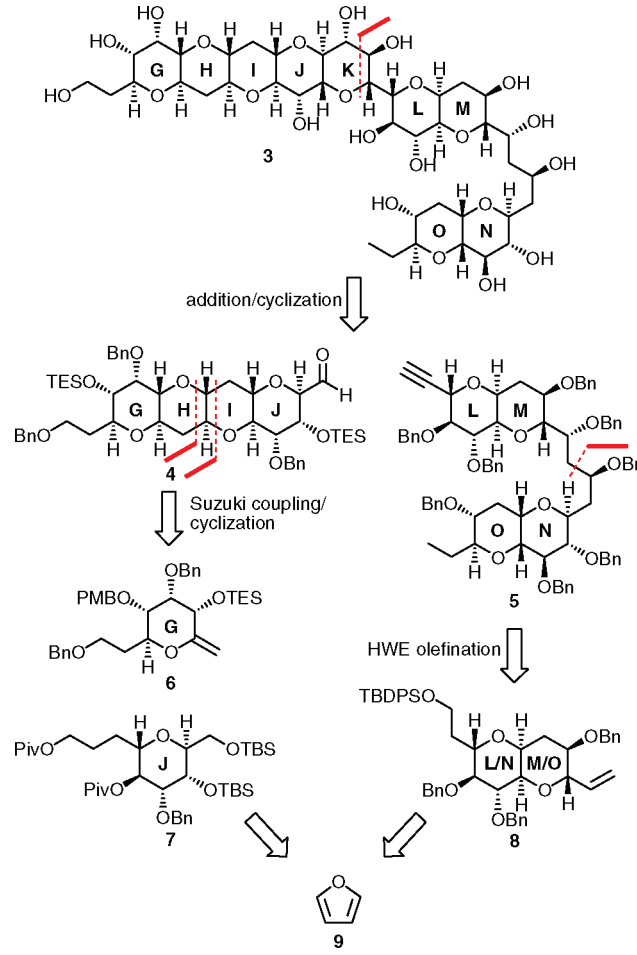

Figure 2. First retrosynthetic analysis of the GHIJKLMNO ring system **3** of maitotoxin.

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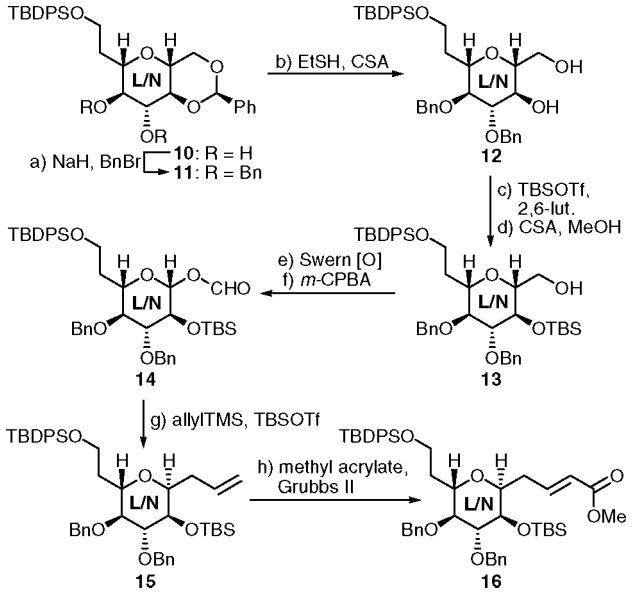
(10) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.

Scheme 1. Construction of the L/N Common Building Block **16**[a]

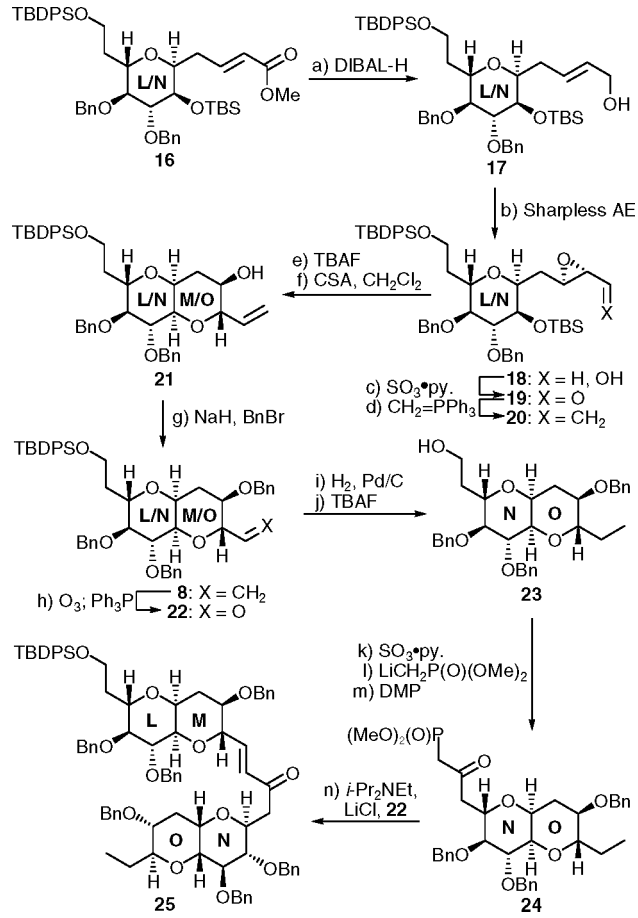


[a] Reagents and conditions: (a) BnBr (4.0 equiv), NaH (60% in mineral oil, 3.5 equiv), DMF, 0 → 25 °C, 3 h, 97%; (b) CSA (0.2 equiv), EtSH: CH_2Cl_2 (1:3), 25 °C, 16 h, 91%; (c) TBSOTf (3.0 equiv), 2,6-lut. (5.0 equiv), CH_2Cl_2, 0 °C, 2 h; (d) CSA (0.3 equiv), CH_2Cl_2:MeOH (1:1), 0 °C, 2 h, 80% over the two steps; (e) $(COCl)_2$ (3.0 equiv), DMSO (5.0 equiv), −78 °C, 1 h; Et_3N (10 equiv), 0 °C, 30 min; (f) *m*-CPBA (70%, 4.0 equiv), CH_2Cl_2, 25 °C, 3 h, 84% over the two steps; (g) allylTMS (6.0 equiv), TBSOTf (3.0 equiv), CH_3CN, −40 →0 °C, 1 h, 80%; (h) methyl acrylate (25 equiv), Grubbs II cat. (0.005 equiv), benzene, 85 °C, 2 h, 85%. Abbreviations: TBDPS = *tert*-butyldiphenylsilyl; DMF = *N,N*-dimethylformamide; CSA = (±)-camphor-10-sulfonic acid; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl; lut. = lutidine; DMSO = dimethyl sulfoxide; *m*-CPBA = meta-chloroperbenzoic acid; TMS = trimethylsilyl.

oxidation of the resulting aldehyde (*m*-CPBA)[11] afforded formate ester **14** in 84% overall yield for the two steps, setting the stage for the required chain extension. Indeed, treatment of **14** with allylTMS in the presence of TBSOTf gave *C*-glycoside **15** (β-anomer, 80% yield), which was subjected to cross-metathesis with methyl acrylate (Grubbs II cat.)[12] to afford the desired α,β-unsaturated ester **16** in 85% yield.

Ester **16** was then reduced (Scheme 2) with DIBAL-H (89% yield), and the resulting allylic alcohol (**17**) was subjected to Sharpless asymmetric epoxidation [(−)-diethyl tartrate, Ti(*i*-PrO)$_4$, *t*-BuOOH][13] to afford epoxide **18** in ca. 6:1 diastereomeric ratio and 86% combined yield. Subsequent oxidation of the latter with SO_3•py. and Et_3N furnished the corresponding aldehyde, which was subjected to methylenation (CH_3PPh_3Br, KHMDS) to give olefin **20** in 95% overall yield for the last two steps. The next ring was forged by selectively removing the TBS group from **20** (TBAF) and then inducing the expected regioselective cyclization of the resulting hydroxy epoxide by exposure to catalytic amounts of CSA to form bicycle **21** in

Scheme 2. Synthesis of the LMNO Enone **25**[a]



[a] Reagents and conditions: (a) DIBAL-H (1.0 M in CH_2Cl_2, 2.5 equiv), CH_2Cl_2, −78 °C, 1 h, 89%; (b) (−)-DET (1.2 equiv), Ti(*i*-PrO)$_4$ (1.0 equiv), *t*-BuOOH (5.0 M in decane, 4.0 equiv), 4 Å MS, CH_2Cl_2, −20 °C, 24 h, 86% (6:1 mixture of epoxides); (c) SO_3•py. (3.5 equiv), Et_3N (10 equiv), CH_2Cl_2:DMSO (5:1), 0 °C, 2 h; (d) CH_3PPh_3Br (2.0 equiv), KHMDS (0.5 M in PhMe, 1.9 equiv), THF, −78 → 0 °C, 1 h, 95% over the two steps; (e) TBAF (1.0 M in THF, 3.0 equiv), THF, 25 °C, 1 h; (f) CSA (0.2 equiv), CH_2Cl_2, 0 → 25 °C, 2 h, 65% over the two steps; (g) BnBr (3.0 equiv), TBAI (0.2 equiv), NaH (60% in mineral oil, 2.0 equiv), THF, 25 °C, 3 h, 72% yield; (h) O_3, CH_2Cl_2, −78 °C, 10 min; Ph_3P (1.5 equiv), −78 → 0 °C, 30 min, 100%; (i) 5% Pd/C (20% w/w), H_2, EtOAc, 25 °C, 1 h; (j) TBAF (1.0 M in THF, 3.0 equiv), THF, 25 °C, 16 h, 96% over the two steps; (k) SO_3•py. (3.5 equiv), Et_3N (10 equiv), CH_2Cl_2:DMSO (5:1), 0 °C, 2 h; (l) *n*-BuLi (1.6 M in hexanes, 5.0 equiv), $MeP(O)(OMe)_2$ (5.0 equiv), THF, −78 °C, 1 h; then aldehyde from **23**, THF, −78 °C, 1 h; (m) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 30 min, 75% over the three steps; (n) **22** (1.0 equiv), LiCl (2.0 equiv), *i*-Pr_2NEt (1.0 equiv), CH_3CN, 25 °C, 75%. Abbreviations: DIBAL-H = diisobutylaluminum hydride; DET = diethyl tartrate; MS = molecular sieves; KHMDS = potassium bis(trimethylsilyl)-amide; THF = tetrahydrofuran; TBAF = tetra-*n*-butylammonium fluoride; TBAI = tetra-*n*-butylammonium iodide; DMP = Dess−Martin periodinane.

65% overall yield for the two steps.[14] Benzylation (NaH, BnBr) of the latter compound then gave the coveted common intermediate **8** (72% yield), whose divergence into key building blocks **22** (LM ring system) and **24** (NO ring system) was anticipated as part of the plan to reach the targeted LMNO ring system. Thus, the desired LM aldehyde fragment **22** was generated through ozonolysis (O_3; Ph_3P) of olefin **8** in quantitative yield, while the other required fragment NO ketophospho-

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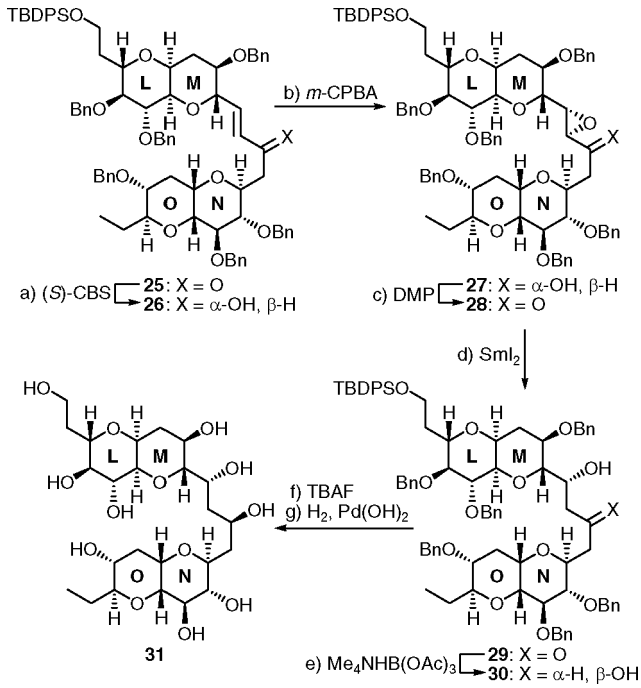
Scheme 3. Synthesis of LMNO Model Compound **31**[a]

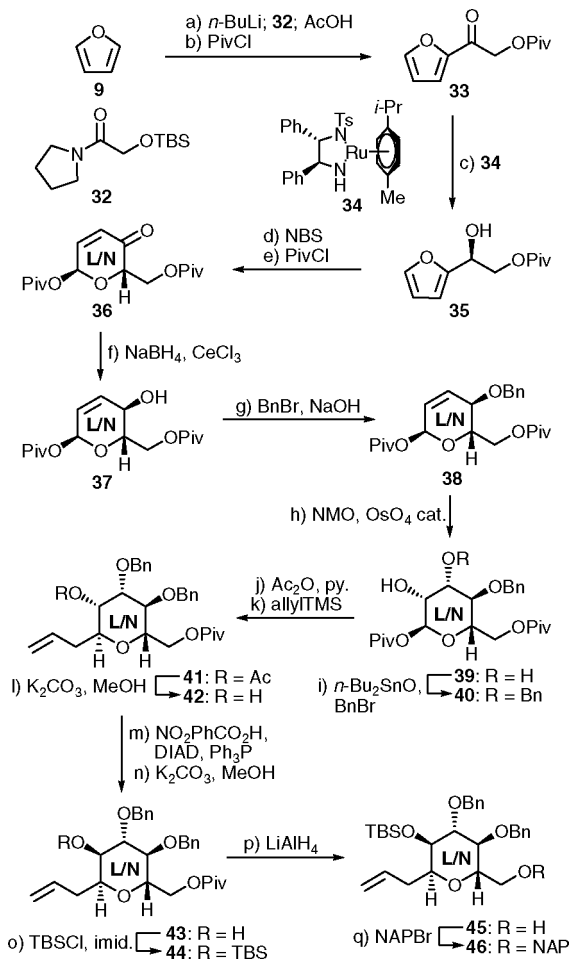


[a] Reagents and conditions: (a) (*S*)-CBS (1.0 M in PhMe, 1.2 equiv), BH_3•THF (1.0 M in THF, 1.2 equiv), THF, −20 °C, 1 h, 70%; (b) *m*-CPBA (3.0 equiv), CH_2Cl_2, 25 °C, 8 h, 60% + 21% of the other isomer; (c) DMP (1.5 equiv), CH_2Cl_2, 25 °C, 1 h, 100%; (d) SmI_2 (0.1 M in THF, 4.0 equiv), MeOH (10 equiv), THF, 0 °C, 10 min, 96%; (e) $Me_4NHB(OAc)_3$ (2.0 equiv), CH_3CN:AcOH (2:1), −20 °C, 5 h, 88%; (f) TBAF (1.0 M in THF, 2.0 equiv), THF, 25 °C, 12 h; (g) 20% $Pd(OH)_2$/C (30% w/w), H_2, MeOH:EtOAc (1:1), 25 °C, 12 h, 75% over the two steps. Abbreviations: CBS = 2-methyl-Corey−Bakshi−Shibata-oxazaborilidine.

nate (**24**), was reached through the five-step sequence depicted in Scheme 2. Thus, hydrogenation of the olefinic bond of **8** (H_2, 5% Pd/C) followed by cleavage of the TBDPS protecting group (TBAF) resulted in the formation of primary alcohol **23**, whose conversion to **24** required: (i) oxidation with SO_3•py. in the presence of Et_3N; (ii) reaction of the resulting aldehyde with the lithio derivative of dimethyl methylphosphonate [Me-P(O)$(OMe)_2$, *n*-BuLi]; and (iii) oxidation of the resulting 1:1 mixture of diastereomeric alcohols with Dess−Martin reagent,[15] a sequence that proceeded in 75% overall yield for the three steps. Coupling of fragments **22** and **24** was then accomplished through a Horner−Wadsworth−Emmons olefination (LiCl, *i*-Pr_2NEt),[16] providing enone **25** in 75% yield.

The overall plan of converting LMNO enone **25** to the targeted LMNO ring system **31** through epoxide formation and opening was implemented as shown in Scheme 3. Thus, having failed to realize a diastereomerically useful direct epoxidation of enone **25**, we adopted a sequence that involved first selective reduction of the enone moiety of **25** [BH_3•THF, (*S*)-CBS cat., 70% yield],[17] then epoxidation (*m*-CPBA, 60% yield, plus 21% yield of its diastereomeric epoxide) of the resulting allylic alcohol (**26**), and, finally, DMP oxidation (100% yield) of epoxy alcohol **27** to afford the desired epoxy ketone **28**. It should be noted that other epoxidation methods, such as Sharpless asymmetric epoxidation,[13] failed to provide any epoxide product,

Scheme 4. Synthesis of L/N Fragment **46**[a]



[a] Reagents and conditions: (a) *n*-BuLi (1.6 M in hexanes, 1.5 equiv), **9** (1.5 equiv), THF, 0 °C, 30 min; then **32** (1.0 equiv), −78 °C, 1 h; AcOH:H_2O (7:1), 50 °C, 12 h; (b) PivCl (1.4 equiv), Et_3N (2.5 equiv), CH_2Cl_2, 0 → 25 °C, 4 h, 69% yield over the three steps; (c) **34** (0.005 equiv), TBAB (0.3 equiv), HCO_2Na (10 equiv), CH_2Cl_2:H_2O (1:1), 25 °C, 36 h, 98%(≥ 95% ee); (d) NBS (1.0 equiv), NaOAc (1.0 equiv), $NaHCO_3$ (2.0 equiv), THF:H_2O (2.5:1), 0 °C, 1 h; (e) PivCl (1.0 equiv), Et_3N (1.25 equiv), 4-DMAP (0.05 equiv), CH_2Cl_2, −78 °C, 10 min, 65% yield over the two steps (+20% of the other anomer); (f) $NaBH_4$ (1.0 equiv), $CeCl_3$•$7H_2O$ (0.5 equiv), CH_2Cl_2:MeOH (1:1), −78 °C, 1 h, 98%; (g) BnBr (5.0 equiv), TBAI (0.5 equiv), 25% NaOH (aq.):PhMe (1:1), 25 °C, 18 h, 85%; (h) OsO_4 (1.0% in H_2O, 0.02 equiv), NMO (2.0 equiv), acetone:H_2O (5:1), 25 °C, 18 h, 80%; (i) *n*-Bu_2SnO (1.0 equiv), BnBr (1.4 equiv), TBAI (1.0 equiv), C_6H_6, reflux, 18 h, 89%; (j) Ac_2O (3.0 equiv), py. (6.0 equiv), 4-DMAP (0.05 equiv), CH_2Cl_2, 25 °C, 1 h, 99%; (k) allylTMS (3.0 equiv), BF_3•Et_2O (2.0 equiv), CH_3CN, 50 °C, 5 h, 94%; (l) K_2CO_3 (0.4 equiv), MeOH, 25 °C, 4 h, 79%; (m) 4-$NO_2C_6H_6CO_2H$ (2.0 equiv), DIAD (2.25 equiv), Ph_3P (2.25 equiv), PhMe, 70 °C, 5 h, 75%; (n) K_2CO_3 (0.4 equiv), MeOH, 25 °C, 0.5 h, 99%; (o) TBSCl (2.0 equiv), imid. (4.0 equiv), DMF, 70 °C, 18 h, 92%; (p) $LiAlH_4$ (1.0 M in THF, 2.0 equiv), Et_2O, −78 °C, 0.5 h, 91%; (q) NAPBr (1.2 equiv), TBAI (0.5 equiv), NaH (2.0 equiv), THF:DMF (1:1), 25 °C, 1 h, 92%. Abbreviations: Piv = trimethylacetyl; TBAB = tetra-*n*-butylammonium bromide; NBS = *N*-bromosuccinimide; DMAP = dimethylaminopyridine; NMO = 4-methylmorpholine *N*-oxide; py. = pyridine; DIAD = diisopropyl azodicarboxylate; imid. = imidazole; NAP = naphthyl.

presumably due to steric hindrance at the reaction site. The epoxide within the latter compound was then regioselectively opened with the aid of SmI_2 in the presence of MeOH to give *β*-hydroxy ketone **29** in 96% yield.[18] Finally, stereoselective

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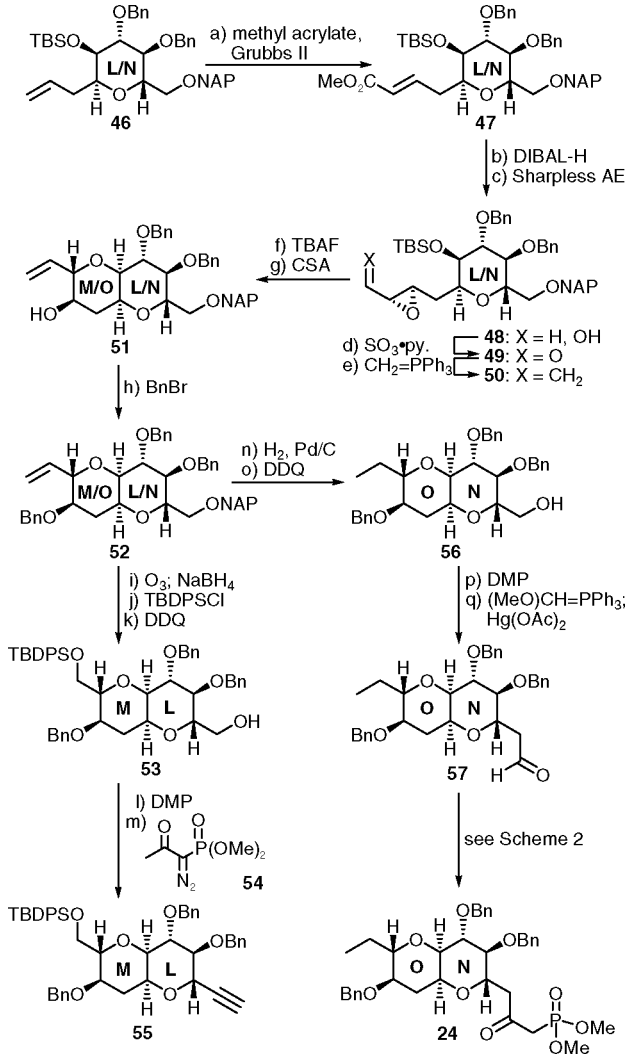
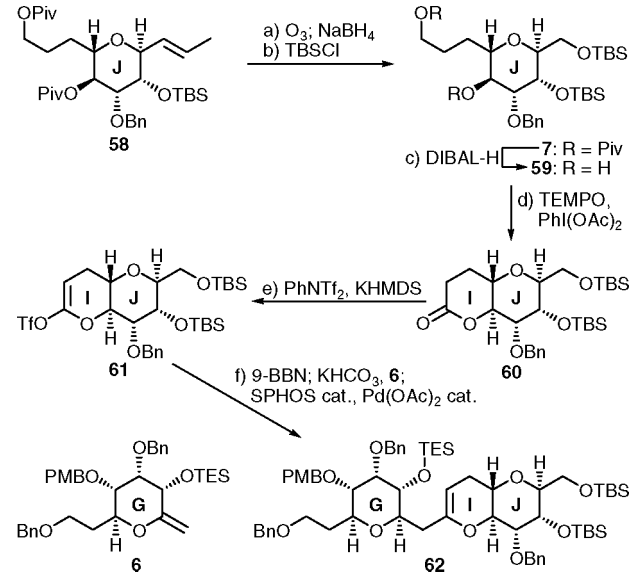
Scheme 5. Completion of the Furan-Based Synthesis of LM and NO Building Blocks **55** and **57**[a]



[a] Reagents and conditions: (a) methyl acrylate (20 equiv), Grubbs II cat. (0.005 equiv), benzene, 80 °C, 1 h, 91%; (b) DIBAL-H (1.0 M in CH_2Cl_2, 2.5 equiv), CH_2Cl_2, −78 °C, 1 h, 89%; (c) (−)-DET (1.2 equiv), Ti(*i*-PrO)$_4$ (1.0 equiv), *t*-BuOOH (5.0 M in decane, 4.0 equiv), 4 Å MS, CH_2Cl_2, −20 °C, 24 h, 84%; (d) SO_3•py. (3.5 equiv), Et_3N (10 equiv), CH_2Cl_2:DMSO (5:1), 0 °C, 2 h; (e) CH_3PPh_3Br (2.0 equiv), KHMDS (0.5 M in THF, 1.9 equiv), THF, −78 °C, 1 h; then **49** (1.0 equiv), THF, −78 → 0 °C, 1 h, 93% over the two steps; (f) TBAF (1.0 M in THF, 3.0 equiv), THF, 25 °C, 1 h; (g) CSA (0.2 equiv), CH_2Cl_2, 0 → 25 °C, 3 h, 65% yield over the two steps; (h) BnBr (3.0 equiv), TBAI (0.2 equiv), NaH (60% in mineral oil, 2.0 equiv), THF, 25 °C, 3 h, 91%; (i) O_3, CH_2Cl_2:MeOH (5:1), −78 °C, 15 min; $NaBH_4$ (1.0 equiv), −78 → 25 °C, 30 min, 75%; (j) TBDPSCl (1.5 equiv), imid. (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 89%; (k) DDQ (1.5 equiv), CH_2Cl_2:H_2O (5:1), 0 °C, 2 h, 80%; (l) DMP (1.5 equiv), CH_2Cl_2, 25 °C, 1 h; (m) **54** (4.0 equiv), K_2CO_3 (2.0 equiv), MeOH, 25 °C, 16 h, 86% over the two steps; (n) 5% Pd/C (20% w/w), H_2, EtOAc, 25 °C, 1 h; (o) DDQ (1.5 equiv), CH_2Cl_2:H_2O (5:1), 0 °C, 2 h, 82% yield over the two steps; (p) DMP (1.5 equiv), CH_2Cl_2, 25 °C, 1 h; (q) (MeO)CH_2PPh_3Cl (5.0 equiv), LHMDS (1.0 M in hexanes, 4.5 equiv), THF, 0 °C, 30 min; then aldehyde from **56** (1.0 equiv), THF, −78 °C, 2 h; $Hg(OAc)_2$ (5.0 equiv), THF:H_2O (2:1), 25 °C, 15 min; HI (8% aq.), 25 °C, 30 min, 76% yield over the two steps. Abbreviations: DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

reduction of the carbonyl group within β-hydroxy ketone **29** was achieved through the use of $Me_4NHB(OAc)_3$ to afford the anti diol **30** as a single diastereoisomer, and in 88% yield.[19] At this juncture we had the option of producing the initially targeted advanced LMNO alkyne fragment **5** as originally planned, or to seek a more practical route to prepare a more advanced, and therefore more relevant, maitotoxin fragment through our furan-based technology[8] that proved highly efficient in the synthesis of the GHIJK ring system of maitotoxin. We chose the latter option; but before abandoning this study, we decided to carry out two additional manipulations on our advanced intermediate **30** in order to reach LMNO nonaol **31**, an intermediate whose enantiomer was previously synthesized by Tachibana et al.[4b] To this end, diol **30** was sequentially treated with TBAF (to remove the TBDPS group) and H_2 in the presence of 20% $Pd(OH)_2$/C (to remove the benzyl groups) affording, in 75% overall yield for the last two steps, compound **31**. Indeed, the ^1H and ^{13}C NMR spectroscopic data of our synthetic intermediate **31** matched those reported for the enantiomer of **31**,[4b] thus confirming our stereochemical assignments along the described route.

Scheme 6. Construction of the GIJ Ring System **62**[a]



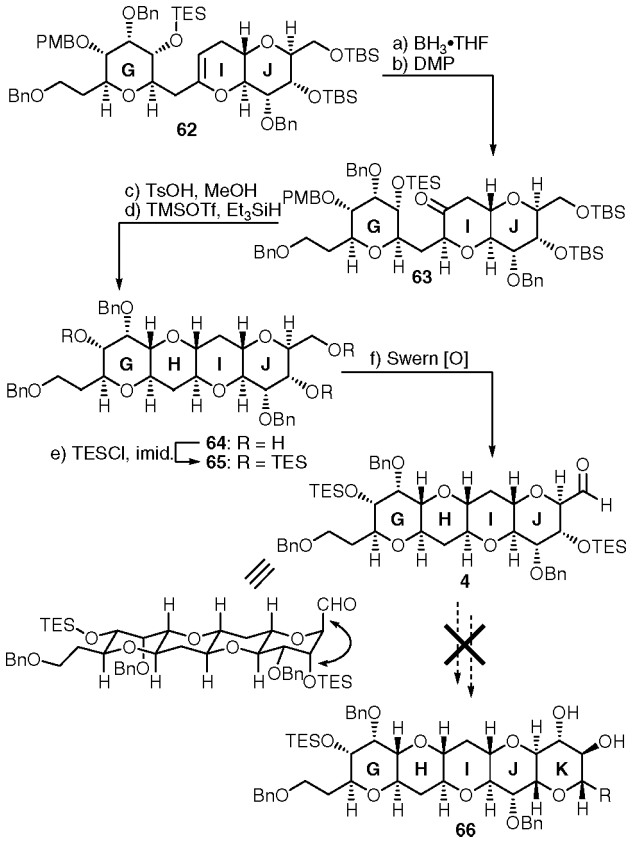
[a] Reagents and conditions: (a) O_3, CH_2Cl_2:MeOH (5:1), −78 °C, 10 min; then $NaBH_4$ (1.0 equiv), −78 → 25 °C, 30 min; (b) TBSCl (1.5 equiv), imid. (2.0 equiv), DMF, 25 °C, 2 h, 92% over the two steps; (c) DIBAL-H (1.0 M in CH_2Cl_2, 5.0 equiv), CH_2Cl_2, −78 °C, 30 min, 98%; (d) TEMPO (0.2 equiv), $PhI(OAc)_2$ (5.0 equiv), CH_2Cl_2, 25 °C, 18 h, 80%; (e) $PhNTf_2$ (5.0 equiv), KHMDS (0.5 M in PhMe, 5.0 equiv), THF, −78 °C, 30 min, 89%; (f) **6** (1.0 equiv), 9-BBN (0.5 M in THF, 4.0 equiv), THF, 60 °C, 3 h; then $KHCO_3$ (1.0 M in H_2O, 20 equiv), 25 °C, 30 min; then SPHOS (0.2 equiv), $Pd(OAc)_2$ (0.1 equiv), **56** (1.0 equiv), 25 °C, 48 h, 78%. Abbreviations: TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy; 9-BBN = 9-borabicyclo[3.3.1]nonane; SPHOS = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; TES = triethylsilyl; PMB = para-methoxybenzyl.

3. Furan Approach to the LM, NO, and LMNO Fragments. The furan approach to the LM, NO, and LMNO fragments of maitotoxin proceeded through enone **36**, an intermediate prepared from furan in a manner similar to those described by us[8] and others.[20] Thus, lithiation of furan (**9**, *n*-BuLi, Scheme 4) followed by addition of amide **32** led to, after removal of

(19) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(20) (a) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165. (b) Guo, H.; O'Doherty, G. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5206. (c) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485. (d) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609. (e) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17. (f) Li, M.; Scott, J.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005. (g) Henderson, J. A.; Jackson, K. A.; Phillips, A. L. *Org. Lett.* **2007**, *9*, 5299.

Scheme 7. Failed Attempt to Construct the GHIJK Ring System **66**[a]



[a] Reagents and conditions: (a) 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, 5 h, 78%; (b) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 92%; (c) TsOH (2.0 equiv), MeOH, 50 °C, 18 h; (d) TMSOTf (3.0 equiv), Et_3SiH (5.0 equiv), CH_3CN, 0 °C, 30 min, 90% over the two steps; (e) TESCl (30 equiv), imid. (50 equiv), CH_2Cl_2, 25 °C, 10 h, 91%; (f) $(COCl)_2$ (50 equiv), DMSO (75 equiv), CH_2Cl_2, −78 °C, 1 h; then Et_3N (125 equiv), 0 °C, 20 min, 90%. Abbreviations: Ts = para-toluenesulfonyl.

the TBS group (AcOH, 50 °C) and protecting the resulting primary alcohol as a pivaloate ester (PivCl, Et_3N), ketone **33** (69% yield over the three steps). Ketone **33** was subjected to a Noyori reduction (HCO_2Na, *n*-Bu_4NBr, **34** cat.)[21] to afford alcohol **35** in 98% yield and ≥95% ee. The latter compound was converted to **36** through an Achmatowicz rearrangement[20a] (NBS, NaOAc, $NaHCO_3$) followed by pivaloate formation (PivCl, Et_3N, 4-DMAP) at the anomeric position, in 65% overall yield for the two steps. This highly efficient process also yielded the β-anomer of **36**, isolated in 20% overall yield from **35**. Luche reduction ($NaBH_4$, $CeCl_3$•$7H_2O$)[22] of enone **36** proceeded stereoselectively (as expected based on steric grounds) and provided allylic alcohol **37**, in 98% yield, which was benzylated under biphasic conditions (25% aq. NaOH:PhMe 1:1, BnBr, TBAI cat.) to afford benzyl ether **38** in 85% yield. Dihydroxylation of the latter compound (NMO, OsO_4 cat.) then furnished diol **39** in 80% yield and with complete stereocontrol. The conversion of this diol to the next key intermediate required allylation at the anomeric position and inversion of stereochemistry at C-2. To this end, the C-2 and C-3 hydroxyl groups within

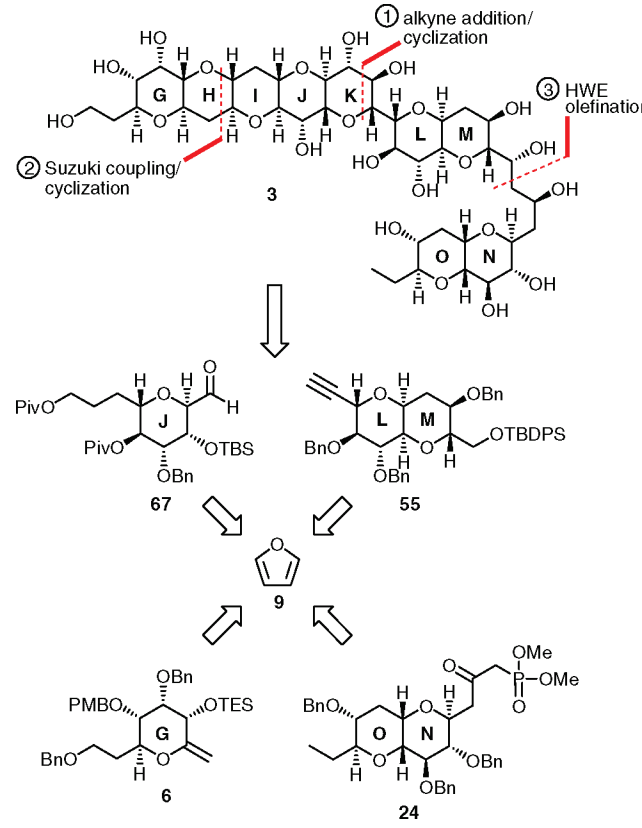


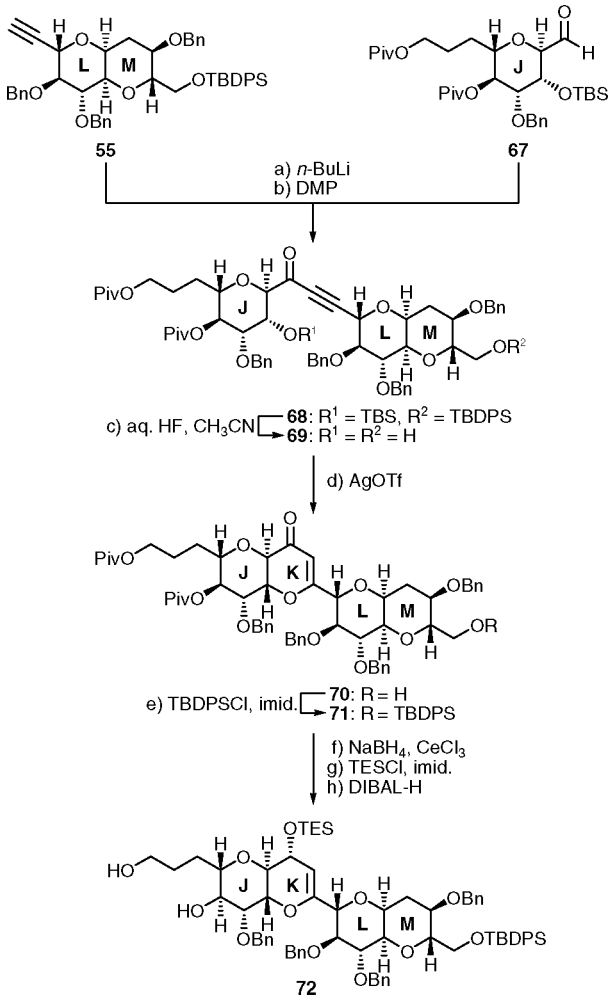
Figure 3. Second generation retrosynthetic analysis of the GHIJKLMNO ring system **3**. The order ①, ②, and ③ refers to the synthetic direction.

39 were differentiated by selective protections [(i) *n*-Bu_2SnO, BnBr, TBAI cat., **40**, 89% yield;[23] (ii) Ac_2O, py., 4-DMAP, 99% yield] to afford the corresponding 2-acetoxy-1-pivaloate. Designed for its potential to undergo a stereoselective *C*-allylation (by virtue of the directing effect of the 2-acetoxy group), the latter intermediate was reacted with allylTMS in the presence of BF_3•Et_2O to afford, indeed, the desired *C*-allylation product **41** in 94% yield as a single diastereoisomer. Having accomplished its mission, the acetate group was then removed from **41**, generating alcohol **42** and setting the stage for the required inversion, which was carried out through a Mitsunobu reaction (*p*-$NO_2C_6H_4COOH$, DIAD, Ph_3P)[24] followed by ester hydrolysis (K_2CO_3, MeOH), affording the desired alcohol **43** in 59% overall yield for the three steps. Anticipated operations going forward dictated protection of the free hydroxyl group of **43** as a TBS ether (TBSCl, imid., **44**, 92% yield) and exchange of the pivaloate ester for a naphthyl ether [(i) $LiAlH_4$; (ii) NAPBr, TBAI cat., NaH, 84% overall yield], leading to the L/N ring system **46** through intermediate **45**.

With all stereocenters on the L/N rings of **46** set, the next task was to append the M/O rings. To this end, alkene **46** was subjected to olefin cross metathesis with methyl acrylate in the presence of Grubbs II catalyst[12] to afford α,β-unsaturated ester **47** in 91% yield as a single geometrical isomer (Scheme 5). DIBAL-H reduction of **47** provided the corresponding allylic alcohol (89% yield), whose Sharpless asymmetric epoxidation [(−)-DET, Ti(*i*-PrO)$_4$, *t*-BuOOH][13] resulted in the formation of epoxide **48** (84% yield) as a

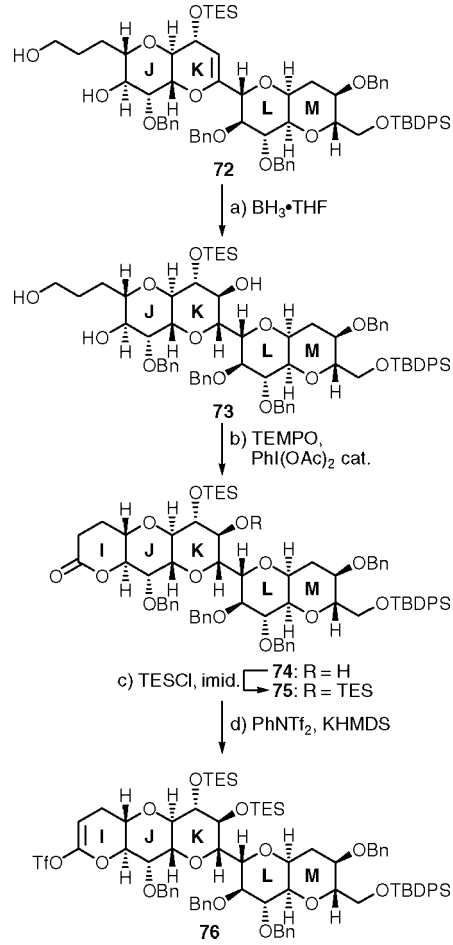
(21) (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (b) Ferrie, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2007**, *9*, 2461.
(22) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(23) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
(24) For reviews on the Mitsunobu inversion, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. Prep.* **1996**, *28*, 127.

Scheme 8. Synthesis of JKLM Ring System **72**[a]



[a] Reagents and conditions: (a) *n*-BuLi (1.6 M in hexanes, 2.0 equiv), **55** (2.0 equiv), THF, −78 °C, 1 h; then **67** (1.0 equiv), −78 °C, 30 min, 78%; (b) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 2 h, 96%; (c) HF (48% aq.):CH_3CN (1:3), 25 °C, 16 h, 89%; (d) AgOTf (0.5 equiv), CH_2Cl_2, 35 °C, 48 h, 95%; (e) TBDPSCl (2.0 equiv), imid. (3.0 equiv), CH_2Cl_2, 25 °C, 3 h, 89%; (f) $NaBH_4$ (1.1 equiv), $CeCl_3 \cdot 7H_2O$ (0.3 equiv), CH_2Cl_2:MeOH (1:1), 0 °C, 30 min; (g) TESCl (2.0 equiv), imid. (3.0 equiv), CH_2Cl_2, 25 °C, 2 h; (h) DIBAL-H (1.0 M in CH_2Cl_2, 10 equiv), CH_2Cl_2, −78 °C, 30 min, 98% over the three steps.

Scheme 9. Synthesis of IJKLM Vinyl Triflate Coupling Partner **76**[a]



[a] Reagents and conditions: (a) $BH_3 \cdot THF$ (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, 5 h, 79%; (b) TEMPO (0.2 equiv), $PhI(OAc)_2$ (5.0 equiv), CH_2Cl_2, 25 °C, 18 h, 80%; (c) TESCl (20 equiv), imid. (30 equiv), CH_2Cl_2, 25 °C, 4 h, 92%; (d) $PhNTf_2$ (5.0 equiv), KHMDS (0.5 M in PhMe, 5.0 equiv), THF, −78 °C, 15 min, 89%.

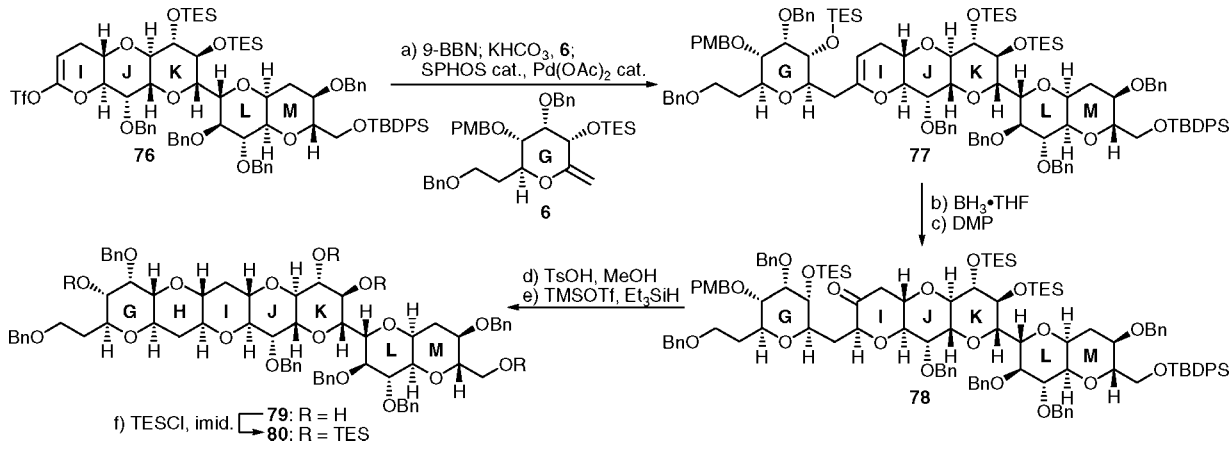
single isomer. Oxidation of the latter compound with $SO_3 \cdot$py. led to aldehyde **49**, which was subjected to methylenation (CH_3PPh_3Br, KHMDS, 93% yield over the two steps) to afford olefinic epoxide **50**. Removal of the TBS group (TBAF) from the latter intermediate, followed by exposure of the resulting hydroxy epoxide to CSA, led to bicyclic system **51** in 65% yield over the two steps (plus 12% of the chromatographically separable 5-membered ring).[14] Benzylation of the remaining hydroxyl group within the latter compound (NaH, BnBr, TBAI cat. 91% yield) then furnished fully protected common intermediate **52**.

From intermediate **52**, the synthetic route diverged toward LM alkyne **55** and NO ring system ketophosphonate **24** as shown in Scheme 5. For the synthesis of alkyne **55**, intermediate **52** was first converted to primary alcohol **53** by a three-step sequence involving: (i) ozonolysis/$NaBH_4$ reduction (75% yield); (ii) silylation with TBDPSCl-imid. of the resulting primary alcohol (89% yield); and (iii) removal of the NAP group with DDQ (80% yield). The latter compound was then oxidized (DMP) and the resulting aldehyde was reacted with Ohira−Bestmann reagent (**54**)[25] to afford the targeted key building block (**55**, 86% yield for the two steps). The NO ring system ketophosphonate **24** was obtained from the same intermediate **52** via primary alcohol **56** [(i) H_2, 5% Pd/C; (ii) DDQ, 82% yield overall for the two steps] and aldehyde **57** [(i) DMP; (ii) $(MeO)CH_2PPh_3Cl$-LHMDS; $Hg(OAc)_2$,[26] 76% overall yield for the two steps]. The elaboration of the latter compound to ketophosphonate **24** has already been described above (Scheme 2).

4. Initial Attempt to Construct the GHIJKLMNO Ring System. With ample supplies of the LM and NO coupling partners **55** and **57**, we then turned our attention to the next phase of the drive toward the target molecule, namely the construction of the GHIJ advanced intermediate **4**, as required by the strategy outlined in Figure 2. As shown in Scheme 6, this synthesis began with our furan-derived J ring system **58**[8] and proceeded through coupling of vinyl triflate **61** and the borane obtained from vinyl ether G ring system **6**.[8] Thus, ozonolysis of **58** followed by $NaBH_4$ reduction of the resulting

(25) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Muller, S.; Liepold, B.; Roth, G.; Bestmann, H. J. *Synlett* **1996**, 521. (c) Roth, G.; Liepold, B.; Muller, S.; Bestmann, H. J. *Synthesis* **2004**, 59.
(26) Su, Q.; Dakin, L. A.; Panek, J. S. *J. Org. Chem.* **2007**, *72*, 2.

Scheme 10. Construction of the GHIJKLM ring system **80**[a]



[a] Reagents and conditions: (a) **6** (3.0 equiv), 9-BBN (0.5 M in THF, 8.0 equiv), THF, 60 °C, 3 h; then $KHCO_3$ (1.0 M in H_2O, 20 equiv), 25 °C, 30 min; then SPHOS (0.2 equiv), $Pd(OAc)_2$ (0.1 equiv), **76** (1.0 equiv), 25 °C, 48 h, 72%; (b) 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, 5 h, 85%; (c) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 2 h, 93%; (d) TsOH (2.0 equiv), MeOH, 50 °C, 18 h; (e) TMSOTf (5.0 equiv), Et_3SiH (10 equiv), CH_3CN, 0 °C, 30 min, 95% over the two steps; (f) TESCl (20 equiv), imid. (25 equiv), CH_2Cl_2, 25 °C, 3 h, 96%.

ozonide led to the corresponding primary alcohol, which was silylated (TBSCl, imid.) to yield intermediate **7** in 92% overall yield for the two steps. Removal of both pivaloate groups from **7** (DIBAL-H, 98% yield) followed by selective oxidation of the primary alcohol of the resulting diol [**59**, TEMPO, PhI(OAc)$_2$][27] then furnished lactone **60**, through the intermediate lactol, in 80% yield. Lactone **60** was converted to vinyl triflate **61** by the action of $PhNTf_2$ and KHMDS (89% yield). The latter intermediate was then subjected to a Suzuki coupling with the borane derived from vinyl ether **6** and 9-BBN,[28] carried out in the presence of $KHCO_3$ and catalytic amounts of SPHOS[29] and $Pd(OAc)_2$, to afford the desired coupling product **62** in 78% yield.

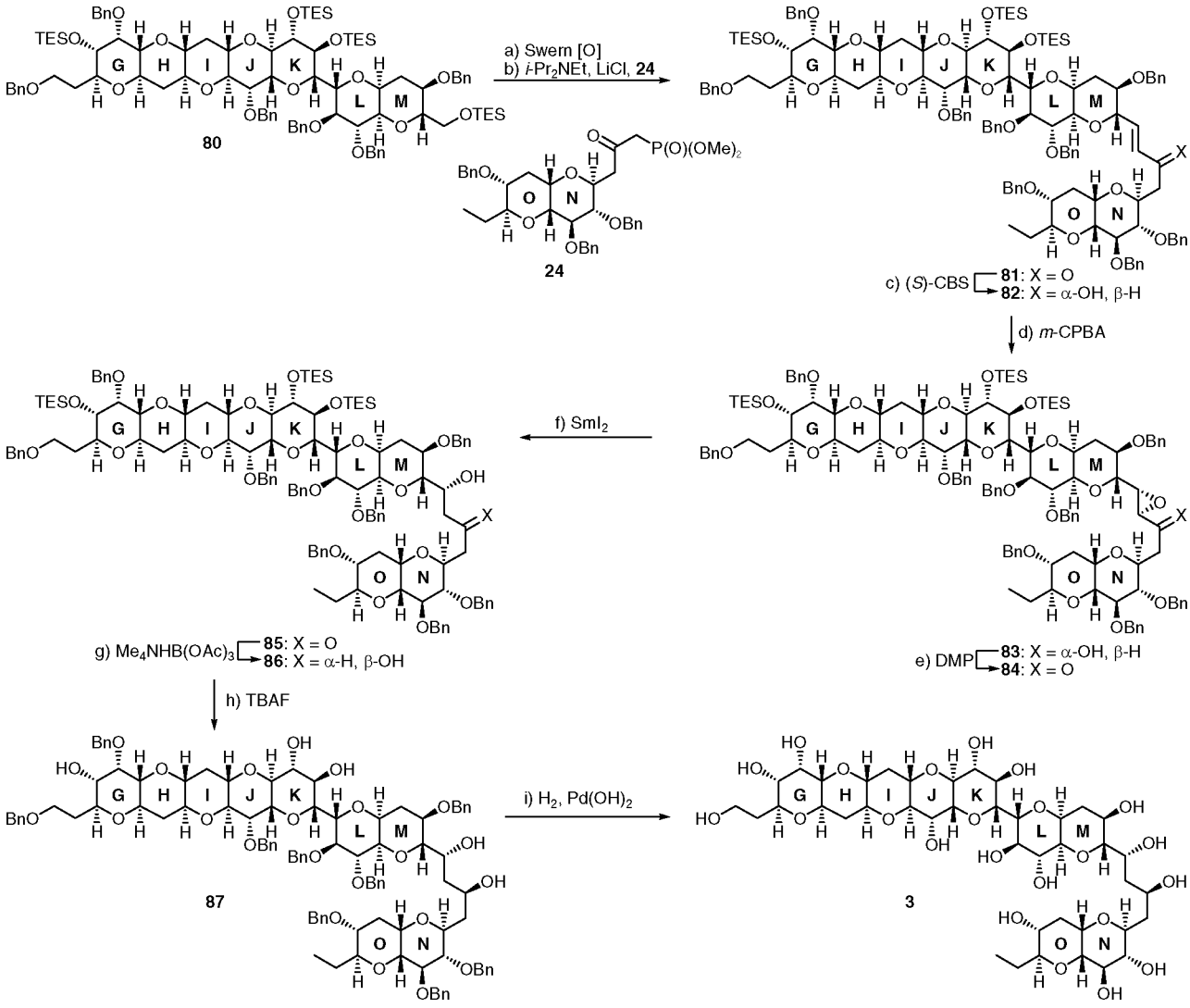
The elaboration of the GIJ intermediate **62** to the tetracyclic GHIJ ring system **4** required the casting of the missing ring (H), an objective that was achieved through the sequence depicted in Scheme 7. Thus, regioselective hydroboration/oxidation of **62** (BH_3•THF; H_2O_2, NaOH) followed by DMP oxidation of the resulting secondary alcohol furnished ketone **63** (72% overall yield). Exposure of **63** to TsOH in MeOH at 50 °C for 18 h then caused cleavage of the TES, TBS, and PMB groups, forming the corresponding H ring methyl acetal (β anomer), which was reduced stereoselectively with Et_3SiH in the presence of TMSOTf to afford tetracyclic triol **64** (90% overall yield for the two steps).[30] The latter compound was then loaded with three TES groups by exhaustive silylation (TESCl, imid., 91% yield), and the resulting tri-TES ether (**65**) was subjected to Swern oxidation conditions [$(COCl)_2$, DMSO; Et_3N][31] to afford, selectively and as expected, aldehyde **4** with the two secondary TES groups remaining intact. Unfortunately, all attempts to forge the remaining ring (K) on this intermediate proved unsuccessful, bringing this route to the targeted pentacyclic intermediate **66** to a hold. The inability to generate the fifth ring of the desired system in this instance was attributed to the diaxial arrangement of the tail-end substituent on ring J (determined by ^{1}H NMR spectroscopic analysis) and the rigidity of the J ring caused by the GH and I rings, facts that keep the two functionalities too far apart for productive engagement. A new plan clearly had to be devised in order to overcome this hurdle.

5. Second Generation Retrosynthetic Analysis of the GHIJKLMNO Ring System of Maitotoxin. Having failed to reach the target molecule (**3**) through the originally planned strategy, we then devised a new plan based on the modified retrosynthetic analysis shown in Figure 3. Although the same disconnections were adopted in the second generation retrosynthetic analysis of the GHIJKLMNO ring system **3**, the order of the main coupling reactions was projected differently. Thus, it was envisioned that the four key building blocks (**6**, **24**, **55**, and **67**) defined by this new analysis, would be processed in the synthetic direction as follows: ① alkyne addition, followed, after appropriate elaboration, by cyclization to form the JKLM ring system; ② Suzuki coupling of a borane derived from G ring system **6** and the appropriate IJKLM vinyl triflate followed by cyclization to cast the GHIJKLM ring system; and ③ a Horner−Wadsworth−Emmons olefination between ketophosphonate **24** and the appropriate GHIJKLM aldehyde followed by final elaborations. The formation of the K ring that proved problematic in our first approach (vide supra) was hoped to be more facile by the new approach now involving the more flexible ring J alone, and without the restraints associated with the polycyclic system employed previously.

6. Construction of the Maitotoxin GHIJKLMNO Ring System. The construction of the targeted maitotoxin GHIJKLMNO ring system **3** began with the coupling of the LM acetylenic fragment **55** with J ring aldehyde **67**[8] and the elaboration of the product to JKLM ring system **72** as shown in Scheme 8. Thus, addition of the lithium acetylide generated from acetylene **55** and *n*-BuLi (−78 °C) to aldehyde **67** at −78 °C followed by DMP oxidation of the resulting alcohol furnished ynone **68** in 75% overall yield. In preparation for the pending ring closure to form ring K, the TBS group was

(27) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57.
(28) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.
(29) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.
(30) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136.
(31) Tolstikov, G. A.; Miftakhov, M. S.; Adler, M. E.; Komissarova, N. G.; Kuznetsov, O. M.; Vostrikov, N. S. *Synthesis* **1989**, 940.

Scheme 11. Completion of the Synthesis of the Maitotoxin GHIJKLMNO Ring System **3**[a]



[a] Reagents and conditions: (a) $(COCl)_2$ (50 equiv), DMSO (75 equiv), CH_2Cl_2, −78 °C, 2 h; then Et_3N (125 equiv), 0 °C, 20 min; (b) **24** (1.5 equiv), *i*-Pr_2NEt (3.0 equiv), LiCl (3.0 equiv), CH_3CN, 25 °C, 5 h, 74% over the two steps; (c) (*S*)-CBS (1.0 M in PhMe, 2.0 equiv), BH_3•THF (1.0 M in THF, 2.0 equiv), THF, −20 °C, 2 h, 79%; (d) *m*-CPBA (4.0 equiv), CH_2Cl_2, 18 h, 55% + 20% of the other diastereoisomer; (e) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 2 h, 99%; (f) SmI_2 (0.1 M in THF, 4.0 equiv), MeOH (10 equiv), THF, 0 °C, 30 min, 100%; (g) $Me_4NHB(OAc)_3$ (2.0 equiv), CH_3CN:AcOH (2:1), −20 °C, 6 h, 86%; (h) TBAF (1.0 M in THF, 10 equiv), THF, 25 °C, 5 h, 76%; (i) 20% $Pd(OH)_2$/C (50% w/w), H_2, EtOH, 100 h, 71%.

removed from **68** by the action of aq. HF in acetonitrile in a process that also cleaved the TBDPS group from the primary hydroxyl moiety, leading to diol **69** in 89% yield. Upon considerable experimentation, it was found that gentle heating of dihydroxy ynone **69** in the presence of AgOTf induced the desired cyclization to form the JKLM enone **70** in 95% yield.[32] Protection of the remaining hydroxyl group within **70** as a TBDPS ether (TBDPSCl, imid., 89% yield) then led to **71**, which underwent smooth and stereoselective Luche reduction ($NaBH_4$, $CeCl_3$•$7H_2O$) to afford, after TES protection (TESCl, imid.) and removal of the pivaloate groups (DIBAL-H), diol **72** in 98% overall yield for the three steps.

Tetracycle **72** was then elaborated to the desired pentacyclic vinyl triflate **76** by the short sequence depicted in Scheme 9. Thus, hydroboration/oxidation (BH_3•THF; aq. H_2O_2, NaOH)[5a] of the enol ether in **72** afforded triol **73** as a single stereoisomer in 79% yield. Subsequent oxidation of the latter compound with $PhI(OAc)_2$ in the presence of catalytic amounts of TEMPO[27] proceeded smoothly and selectively to afford hydroxy lactone **74** (80% yield), whose silylation (TESCl, imid.) furnished the fully protected pentacyclic lactone **75** in 92% yield. Finally, the IJKLM vinyl triflate **76** was generated from lactone **75** through the sequential action of $PhNTf_2$ and KHMDS in 89% yield.

The next task was fusion of the GH ring system onto the growing molecule (i.e., **76**) by attaching ring G fragment **6** and appropriately elaborating the product. This operation required another short sequence as shown in Scheme 10. Thus, the Suzuki coupling[28] of the IJKLM vinyl triflate **76** with the alkyl borane generated in situ from alkene **6** and 9-BBN, as facilitated by the catalytic action of $Pd(OAc)_2$ cat. and SPHOS cat.[29] in the presence of $KHCO_3$, afforded coupling product **77** in 72% yield. Regio- and stereoselective hydroboration/oxidation of **77** (BH_3•THF; aq. H_2O_2, NaOH, 85% yield)[5a] followed by DMP oxidation (93% yield) of the resulting alcohol then led to ketone **78**. Exposure of this hexacyclic compound (**78**) to TsOH in

(32) Wang, C.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 2997.

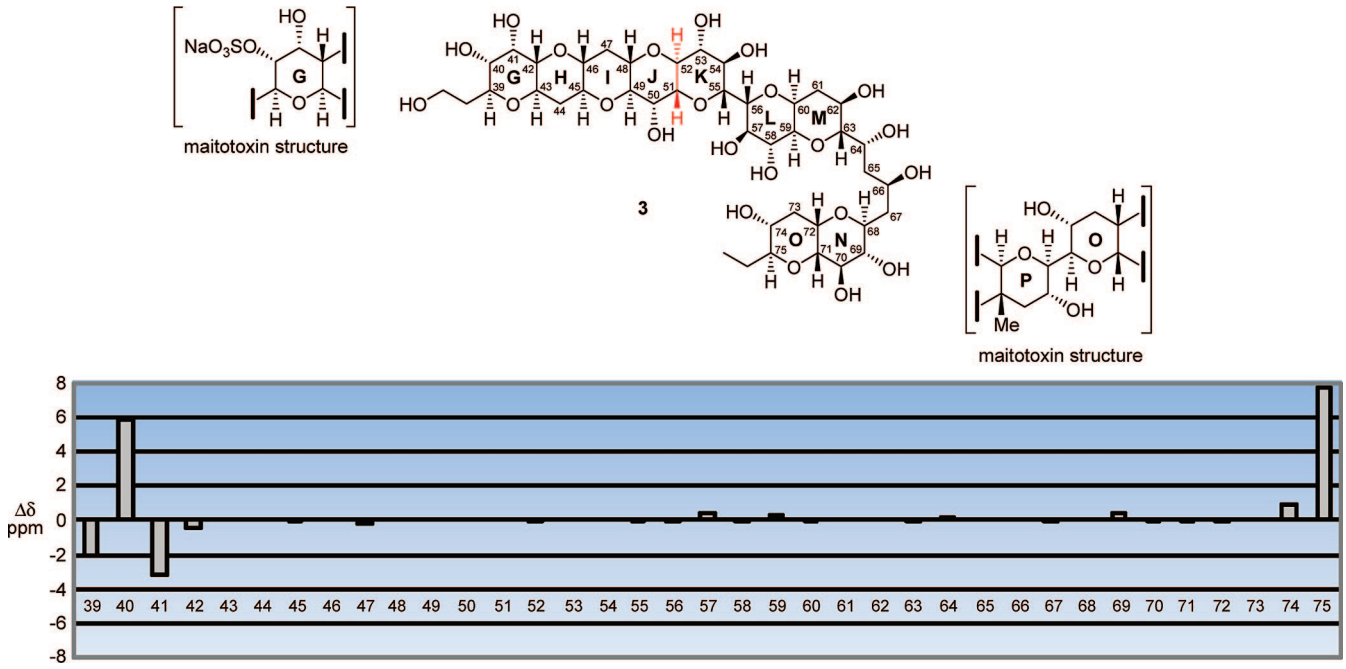


Figure 4. Graphically depicted ^{13}C chemical shift differences ($\Delta\delta$, ppm) for each carbon between C-39 to C-75 for maitotoxin (**1**) and GHIJKLMNO ring system **3**. See Table 1.

MeOH at 50 °C resulted in the removal of the TES, PMB, and TBDPS groups and caused concomitant ring closure to form the corresponding heptacyclic methyl acetal (as a single β-isomer), which was reduced stereoselectively with Et_3SiH in the presence of TMSOTf[30] to afford the heptacyclic tetraol **79** in 95% yield over the two steps. The four hydroxyl groups of **79** were then silylated (TESCl, imid.) to provide the desired GHIJKLM ring system **80** in 96% yield.

The final drive toward the desired GHIJKLMNO ring system **3** required the attachment of the NO ring system to the growing molecular assembly (i.e., **80**) and further elaboration of the product. This task was accomplished as summarized in Scheme 11. Thus, upon exposure to Swern oxidation conditions [$(COCl)_2$, DMSO, −78 °C; Et_3N, 0 °C][31] the tetra-TES protected heptacycle **80** underwent selective deprotection/oxidation at the primary TES ether site, furnishing the corresponding aldehyde, which entered smoothly into a Horner−Wadsworth−Emmons olefination reaction with ketophosphonate **24** (*i*-Pr_2NEt, LiCl)[16] to afford enone **81** in 74% overall yield for the two steps. This enone was then subjected to a CBS reduction (BH_3•THF, (*S*)-CBS cat. 79% yield)[17] to afford, stereoselectively, a major allylic alcohol (**82**, ca. ≥ 10:1 ratio), which was presumed to possess the desired α-stereochemistry on the basis of the chirality of the catalyst used and by analogy to our previous results with the LMNO system **25** (vide supra, Scheme 3). Allylic alcohol **82** was then epoxidized with *m*-CPBA, furnishing the desired α-epoxide (**83**) as the major product (55% yield) together with the undesired β-epoxide (20% yield), the two isomers being chromatographically separated. Again, the stereochemistry of the major isomer (**83**) was presumed to be the desired one on the basis of the expected directing effect of the nearby hydroxyl group and by analogy to our previous studies with the LMNO model system **26** (vide supra, Scheme 3). Oxidation of alcohol **83** then gave epoxy ketone **84**, which underwent regioselective opening with SmI_2 to afford hydroxy ketone **85** in 99% overall yield for the two steps.

Table 1. C-39 to C-75 Chemical Shifts (δ) for Maitotoxin (MTX, **1**) and GHIJKLMNO Ring System **3** and Their Differences ($\Delta\delta$, ppm)[a]

carbon	δ for MTX (**1**) (ppm)	δ for **3** (ppm)	difference (ppm)
39	72.3	74.4	−2.1
40	78.9	73.0	5.9
41	68.5	71.7	−3.2
42	80.6	81.0	−0.4
43	69.6	69.6	0.0
44	36.3	36.3	0.0
45	77.7	77.8	−0.1
46	77.4	77.4	0.0
47	37.4	37.6	−0.2
48	67.8	67.8	0.0
49	85.8	85.8	0.0
50	70.1	70.1	0.0
51	74.9	74.9	0.0
52	72.1	72.0	0.1
53	79.4	79.4	0.0
54	69.8	69.8	0.0
55	78.2	78.1	0.1
56	71.4	71.5	−0.1
57	70.6	70.2	0.4
58	69.6	69.7	−0.1
59	76.5	76.2	0.3
60	71.7	71.8	−0.1
61	33.9	33.9	0.0
62	66.1	66.1	0.0
63	77.2	77.3	−0.1
64	67.7	67.5	0.2
65	43.2	43.2	0.0
66	66.0	66.0	0.0
67	42.5	42.4	0.1
68	71.4	71.4	0.0
69	76.7	76.3	0.4
70	69.2	69.3	−0.1
71	76.8	76.7	0.1
72	71.2	71.1	0.1
73	34.2	34.2	0.0
74	65.1	64.2	0.9
75	72.4	64.6	7.8

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

Stereoselective reduction of the β-hydroxy ketone moiety within **85** with $Me_4NHB(OAc)_3$[19] provided 1,3-anti-diol **86** as a single stereoisomer, and in 86% yield. Finally, desilylation of **86** with TBAF afforded pentaol **87** (76% yield), and subsequent debenzylation of **87** with 20% $Pd(OH)_2$/C and H_2 led to the coveted maitotoxin GHIJKLMNO ring system **3** in 71% yield.[34]

7. Comparison of the ^{13}C NMR Chemical Shifts of GHIJKLMNO Ring System 3 with Those Corresponding to the Same Region of Maitotoxin. The C-39 to C-75 ^{13}C NMR chemical shifts (δ) exhibited by the GHIJKLMNO ring system **3** and those reported for the corresponding carbons of maitotoxin,[2d] together with their differences, are listed in Table 1. The observed chemical shift ($\Delta\delta$) differences for these carbons are graphically displayed in Figure 4. As seen in both depictions, there is compelling agreement between the two sets of ^{13}C chemical shifts, although the two compounds exhibit significant differences at the tail-ends of the GHIJKLMNO domain. This is to be expected, of course, due to the rather drastic changes of substituents at those ends. Thus, the average difference ($\Delta\delta$) between the two sets of δ values for carbons C-42 to C-73 is 0.09 ppm, and the maximum difference ($\Delta\delta$) between these values is 0.4 ppm. These striking experimental results render compelling support for the correctness of the Yasumoto−Kishi−Tachibana structure **1** originally proposed for maitotoxin.

Conclusion

The described chemistry rendered a substantial portion (**3**) of the maitotoxin molecule (**1**) readily available for further chemical and biological studies. The synthesized GHIJKLMNO ring system **3** demonstrated strong correlation with the corresponding region of maitotoxin in terms of its ^{13}C NMR chemical shifts, thus lending compelling support for the originally proposed structure of this natural product. Relying on furan as starting material and a Noyori asymmetric reduction as a source of chirality, the developed synthetic strategy for the maitotoxin-like structures differs significantly from the previously used methods[33] toward polyether marine toxins, which relied heavily on carbohydrate-based starting materials. The efficiency and flexibility of the furan approach to polyether marine natural products through asymmetric catalysis bodes well for its scope and future applications beyond the content described within this article.

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Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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