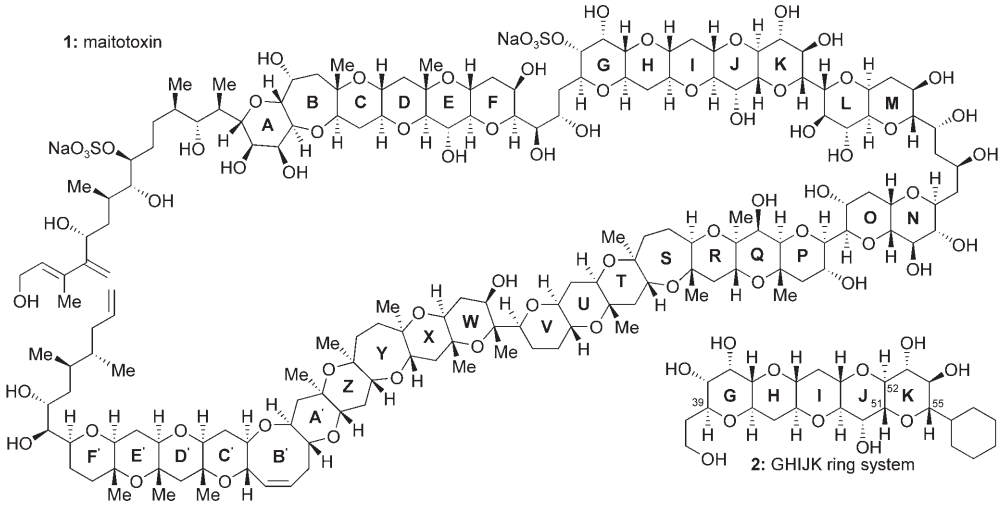
Natural Product Synthesis

DOI: 10.1002/anie.200703742

Chemical Synthesis of the GHIJK Ring System and Further Experimental Support for the Originally Assigned Structure of Maitotoxin**

K. C. Nicolaou, Kevin P. Cole, Michael O. Frederick, Robert J. Aversa, and Ross M. Denton*

Maitotoxin is a notorious marine neurotoxin that possesses unsurpassed molecular size and toxicity compared to any other known secondary metabolite.[1–4] In a recent essay[5] we provided computational support for the originally proposed structure[2–4] of maitotoxin (**1**, Scheme 1), whose stereochemistry at the JK ring junction was questioned on the basis of rational biosynthetic considerations.[6] Herein we provide further experimental support of the originally assigned structure of maitotoxin through chemical synthesis and NMR spectroscopic analysis of GHIJK ring system **2** (Scheme 1), a fragment that corresponds to the GHIJK domain of the naturally occurring molecule.



Scheme 1. Originally proposed structure of maitotoxin (**1**) and the targeted GHIJK ring system **2**.

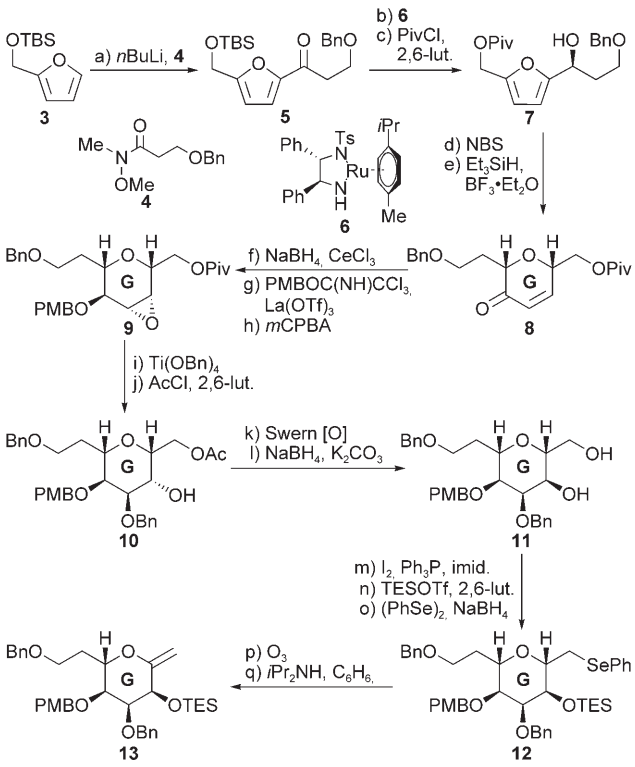
Representing the relevant region of maitotoxin, **2** was targeted for synthesis with the intention of comparing its ^{13}C NMR spectral data to those of the naturally occurring substance, an exercise of well-recognized diagnostic value in stereochemical assignments of complex molecules.[4,7] Concurrent with this objective, we had in mind the development of synthetic strategies suitable for an eventual total synthesis of larger fragments of maitotoxin for biological investigations. The devised synthetic plan for the construction of the GHIJK ring system **2** required the coupling and elaboration of fragments **13** (Scheme 2) and **33** (Scheme 5) to the targeted structure.

Scheme 2 depicts the enantioselective construction of the G-ring intermediate **13** from prochiral furan derivative **3** and features a Noyori reduction with catalyst **6**[8] as a means to introduce chirality into the emerging molecule. Thus, lithiation (*n*BuLi) of furan **3**[9] in THF at 0 °C followed by the addition of Weinreb amide **4**[10] at −78 °C afforded ketone **5** (91 % yield), which was then reduced asymmetrically with the (*S*,*S*)-Noyori catalyst **6** (5 mol %) in a 5:2 mixture of formic acid/triethylamine at 25 °C (94 % yield, > 95 % *ee*) to afford, after selective pivaloate protection of the primary hydroxy group (PivCl, 2,6-lut., 92 % yield), chiral furan **7**. An Achmatowicz rearrangement[11] was then initiated by the action of NBS in the presence of NaOAc and $NaHCO_3$ in aqueous THF to afford the corresponding hemiacetal, which proved quite unstable and was, therefore, reduced immediately with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ in MeCN to pyran **8**, obtained in 60 % overall yield as a single stereoisomer. The enone moiety within pyran **8** was then reduced selectively (β isomer) under Luche conditions[12] ($NaBH_4$, $CeCl_3{\cdot}7H_2O$, 94 % yield) to the corresponding allylic alcohol,

[*] Prof. Dr. K. C. Nicolaou, Dr. K. P. Cole, M. O. Frederick, R. J. Aversa, Dr. R. M. Denton
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92037 (USA)

[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. Financial support for this work was provided by the National Institutes of Health (USA) and the Skaggs Institute of Chemical Biology, as well as fellowships from the National Science Foundation (predoctoral to M.O.F.) and the National Institutes of Health (USA) (postdoctoral to K.P.C.)

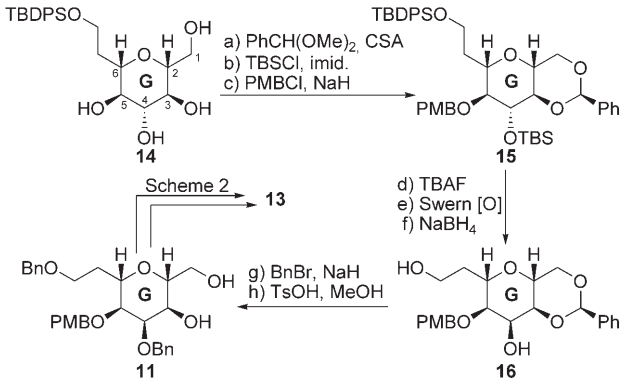
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Construction of G ring system **13**. Reagents and conditions: a) **3** (2.5 equiv), *n*BuLi (2.5 M in hexanes, 2.5 equiv), THF, 0 °C, 30 min; then −78 °C, **4** (1.0 equiv), 2 h, 91%; b) **6** (0.05 equiv), HCO_2H/Et_3N (5:2), 25 °C, 72 h, 94% (>95% *ee*); c) PivCl (1.4 equiv), 2,6-lut. (3.0 equiv), CH_2Cl_2, −78 °C, 1 h, 92%; d) NBS (1.0 equiv), NaOAc (1.0 equiv), $NaHCO_3$ (2.0 equiv), THF/H_2O (3:1), 0 °C, 1 h; e) Et_3SiH (5.0 equiv), $BF_3{\cdot}Et_2O$ (2.0 equiv), MeCN, 0 °C, 30 min, 60% over two steps; f) $CeCl_3{\cdot}7H_2O$ (0.5 equiv), $NaBH_4$ (1.0 equiv), $MeOH/CH_2Cl_2$ (1:1), −10 °C, 10 min, 94%; g) $PMBOC(NH)CCl_3$ (1.5 equiv), $La(OTf)_3$ (0.05 equiv), PhMe, 25 °C, 30 min, 92%; h) *m*CPBA (5.0 equiv), CH_2Cl_2, 25 °C, 48 h, 75%; i) $Ti(OBn)_4$ (3.0 equiv), PhMe, 100 °C, 28 h, 77%; j) AcCl (1.1 equiv), 2,6-lut. (3.0 equiv), CH_2Cl_2, −78 °C, 1 h, 95%; k) $(COCl)_2$ (3.0 equiv), DMSO (5.0 equiv), CH_2Cl_2, −78 °C, 2 h; then Et_3N (7.0 equiv), 0 °C, 1 h; l) $NaBH_4$ (4.0 equiv), MeOH, 0 °C, 15 min; then K_2CO_3 (5.0 equiv), 25 °C, 16 h, 95% over two steps; m) I_2 (2.0 equiv), Ph_3P (2.0 equiv), imid. (2.0 equiv), THF, 25 °C, 2 h, 89%; n) TESOTf (2.0 equiv), 2,6-lut. (3.0 equiv), CH_2Cl_2, 0 °C, 30 min, 93%; o) $(PhSe)_2$ (1.1 equiv), $NaBH_4$ (2.0 equiv), EtOH/THF (5:3), 0 to 25 °C, 3 h; p) O_3, CH_2Cl_2/MeOH (5:1), −78 °C, 10 min; q) $iPr_2NH{:}C_6H_6$ (1:10), 80 °C, 3 h, 86% over three steps. Bn = benzyl, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran, Piv = trimethylacetyl, lut. = lutidine, NBS = *N*-bromosuccinimide, PMB = *para*-methoxybenzyl, *m*CPBA = *meta*-chloroperbenzoic acid, DMSO = dimethyl sulfoxide, imid. = imidazole, TES = triethylsilyl, Tf = trifluoromethanesulfonyl.

which was protected as the PMB ether ($PMBOC(NH)CCl_3$, $La(OTf)_3$, 92% yield) and epoxidized with *m*CPBA to afford epoxide **9** as a single isomer in 75% yield. Treatment of the latter compound with $Ti(OBn)_4$ in toluene at 100 °C led to regioselective opening of its epoxide moiety and cleavage of its pivaloate ester to afford, after selective acetylation (AcCl, 2,6-lut.), hydroxy acetate **10** in 73% overall yield. The obligatory inversion of stereochemistry of the secondary hydroxy group was then carried out within compound **10** by an oxidation/reduction sequence [$(COCl)_2$, DMSO, Et_3N; $NaBH_4$] that afforded, after deacetylation with K_2CO_3 in MeOH, the desired diol **11** in 95% overall yield. With all four asymmetric centers set in the desired configuration for ring G, diol **11** was then selectively converted into the primary iodide in 89% yield through the action of iodine in the presence of Ph_3P and imidazole. The remaining secondary hydroxy group was then protected as a TES ether (TESOTf, 2,6-lut., 93% yield). At this point we were forced to call upon selenide **12** to serve as a precursor to the targeted ring G fragment **13** because of the failure of the corresponding iodide to furnish the desired elimination product in more than 40% yield under a variety of basic conditions. Thus, displacement of the iodide from the last intermediate of the sequence (PhSeSePh, $NaBH_4$) led to selenide **12** which was converted into **13** in 86% overall yield by exposure to O_3 at −78 °C followed by heating (80 °C) in benzene containing excess iPr_2NH.

The G-ring coupling partner **13** was also synthesized through an alternative route starting from known tetraol **14** (available in seven steps from methyl-D-glucopyranoside)[13] as shown in Scheme 3. Protection of the 1,3-diol system

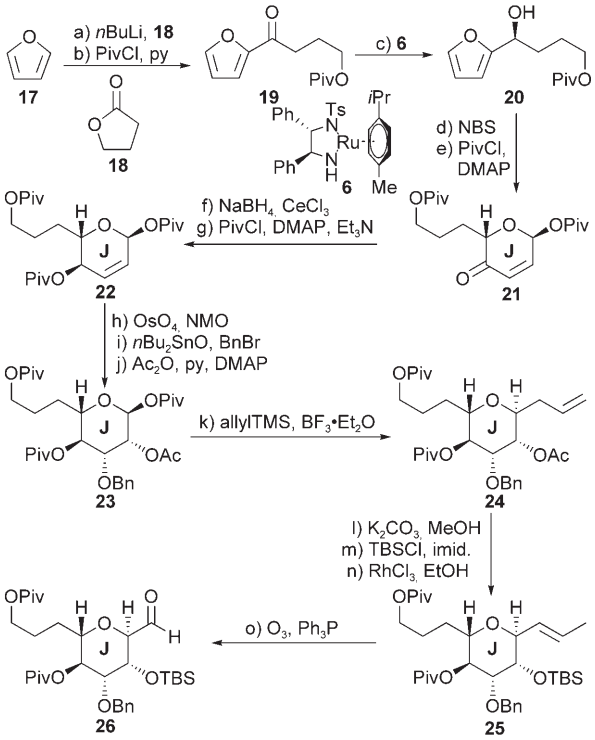


Scheme 3. Alternate construction of G ring system **13**. Reagents and conditions: a) $PhCH(OMe)_2$ (1.5 equiv), CSA (0.02 equiv), 4-Å MS, CH_2Cl_2, 25 °C, 2 h, 74%; b) TBSCl (2.0 equiv), imid. (3.0 equiv), DMF, 25 °C, 18 h, 88%; c) PMBCl (10 equiv), TBAI (0.5 equiv), NaH (6.0 equiv), DMF, 25 °C, 18 h, 80%; d) TBAF (5.0 equiv), THF, 25 °C, 18 h, 83%; e) $(COCl)_2$ (5.0 equiv), DMSO (10 equiv), CH_2Cl_2, −78 °C, 1 h; Et_3N (20 equiv), 0 °C, 30 min; f) $NaBH_4$ (2.2 equiv), MeOH, 0 °C, 86% over two steps; g) BnBr (7.0 equiv), TBAI (0.2 equiv), NaH (5.0 equiv), DMF, 25 °C, 18 h, 88%; h) TsOH (0.2 equiv), MeOH, 25 °C, 18 h, 85%. TBDPS = *tert*-butyldiphenylsilyl, CSA = (±)-camphor-10-sulfonic acid, MS = molecular sieves, DMF = *N*,*N*-dimethylformamide, TBAI = tetra-*n*-butylammonium iodide, TBAF = tetra-*n*-butylammonium fluoride.

involving the primary alcohol within **14** (C-1, C-3) was accomplished with $PhCH(OMe)_2$ and CSA (cat.) in 74% yield. The less hindered secondary hydroxy group of the molecule (C-4) was then protected as the TBS ether (TBSCl, imid.), and the remaining free hydroxy group was converted into its PMB ether (PMBCl, TBAI, NaH) to give to the fully protected pyran system **15** (70% yield for the two steps). Treatment of the latter intermediate with TBAF then effected removal of both its silyl groups, thereby furnishing the corresponding diol in 83% yield. The secondary hydroxy moiety was then inverted through an oxidation/reduction sequence [$(COCl)_2$, DMSO, Et_3N; $NaBH_4$, 86% yield over

two steps] to provide the desired diol **16**. Benzylation of **16** (BnBr, TBAI, NaH, 88% yield) followed by removal of the benzylidene group (TsOH, MeOH) then provided 1,3-diol **11** (85% yield), which was converted into coupling partner **13** as described in Scheme 2.

The synthesis of the J-ring fragment **26** also started from a prochiral furan and proceeded through a route that introduced chirality in high enantioselectivity through a Noyori reduction as shown in Scheme 4. Lithiation of furan (**17**) with *n*BuLi in THF at 0 °C, followed by addition of γ-butyrolactone (**18**) at −78 °C afforded the corresponding keto alcohol (58% yield), which was then converted into its pivaloate ester **19** (PivCl, py, 86% yield). Asymmetric reduction of the carbonyl group in the latter compound with 2.5 mol% (*S*,*S*)-Noyori catalyst **6** in formic acid and triethylamine (5:2) provided

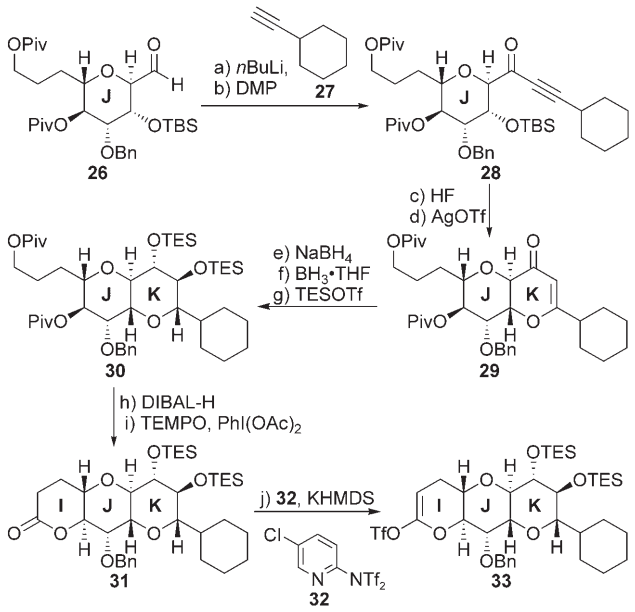


Scheme 4. Construction of J ring aldehyde **26**. Reagents and conditions: a) *n*BuLi (1.05 equiv), THF, 0 °C, 1 h; then **18** (2.0 equiv), −78 °C, 1 h, 58%; b) PivCl (1.25 equiv), py (3.0 equiv), CH_2Cl_2, 0 °C, 4 h, 86%, c) **6** (2.5 mol%), HCO_2H/Et_3N (5:2), 30 °C, 48 h, 89% (>95% *ee*); d) NBS (1.0 equiv), NaOAc (1.0 equiv), $NaHCO_3$ (2.0 equiv), THF/H_2O (3:1), 0 °C, 1 h, 96%; e) PivCl (1.5 equiv), Et_3N (2.5 equiv), DMAP (0.05 equiv), CH_2Cl_2, −78 °C, 2 h, 64% (+20% other anomer); f) $CeCl_3 \cdot 7H_2O$ (0.5 equiv), $NaBH_4$ (1.0 equiv), $MeOH/CH_2Cl_2$ (1:1), −78 °C, 30 min, 100%; g) PivCl (1.5 equiv), Et_3N (3.0 equiv), DMAP (0.05 equiv), CH_2Cl_2, 0 °C, 6 h, 89%; h) OsO_4 (0.02 equiv), NMO (2.0 equiv), acetone/H_2O (10:1), 25 °C, 48 h, 93%; i) nBu_2SnO (1.0 equiv), C_6H_6, reflux, 18 h; then BnBr (1.4 equiv), TBAI (1.0 equiv), 3 h, 98%; j) Ac_2O (4.0 equiv), DMAP (0.05 equiv), py (8.0 equiv), CH_2Cl_2, 25 °C, 12 h, 97%; k) allylTMS (5.0 equiv), $BF_3 \cdot Et_2O$ (2.5 equiv), MeCN, 60 °C, 4 h, 87%; l) K_2CO_3 (0.1 equiv), MeOH, 25 °C, 6 h, 84%; m) TBSCl (2.0 equiv), imid. (4.0 equiv), DMF, 40 °C, 24 h, 85%; n) $RhCl_3 \cdot H_2O$ (0.05 equiv), EtOH, 80 °C, 3 h; o) O_3, $CH_2Cl_2/MeOH$ (5:1), −78 °C, 5 min; then Ph_3P (1.5 equiv), 96% over two steps. py = pyridine, DMAP = 4-dimethylaminopyridine, NMO = 4-methylmorpholine *N*-oxide, TMS = trimethylsilyl.

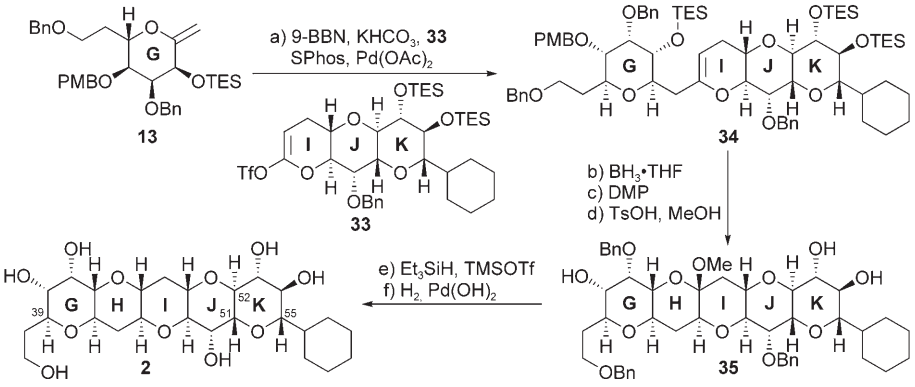
chiral alcohol **20** in 89% yield and greater than 95% *ee*. An Achmatowicz rearrangement was then induced on **20** by treatment with NBS, NaOAc, and $NaHCO_3$ in aqueous THF (96% yield), and the resulting hemiacetal was protected as the pivaloate **21** (PivCl, DMAP, Et_3N) in 64% yield. The undesired anomer of **21** was also produced in this reaction (20% yield). Enone **21** was then reduced selectively under Luche conditions ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, −78 °C, 100% yield) to give the corresponding allylic alcohol, which was converted into its pivaloate ester **22** (PivCl, DMAP, Et_3N, 89% yield). The ensuing dihydroxylation of the olefinic bond within **22** (NMO, cat. OsO_4) proceeded selectively from the face opposite the pivaloate groups, thus furnishing the expected 1,2-diol, whose selective monobenzylation (nBu_2SnO, BnBr, TBAI, benzene, Δ, 98% yield) proceeded smoothly at the equatorial hydroxy group (C-3). This was followed by acetylation at the remaining axial hydroxy moiety (C-2) to afford the fully protected intermediate **23** (97% yield). Addition of allylTMS to **23** in the presence of $BF_3 \cdot Et_2O$ (MeCN, 60 °C) then afforded stereoselectively the allyl derivative **24** (87% yield). The acetate in **24** was then exchanged for a TBS group (K_2CO_3, MeOH; TBSCl, imid., 72% overall yield) and the terminal double bond was migrated inside the carbon chain by using $RhCl_3 \cdot H_2O$[14] (EtOH, 80 °C) to afford *E*-olefin **25**. Ozonolysis of the latter compound (O_3, CH_2Cl_2/MeOH, −78 °C; Ph_3P) then led to the targeted aldehyde **26** in 96% yield for the last two steps.

Scheme 5 summarizes the construction of the IJK building block **33** from the J-ring aldehyde **26**. Thus, aldehyde **26** was added to the lithium anion derived from cyclohexylacetylene (**27**) and *n*BuLi in THF at −78 °C to afford, after oxidation of the resulting propargylic alcohol with DMP,[15] ynone **28** in 89% overall yield. Exposure of the latter compound to aqueous HF in MeCN resulted in the cleavage of the TBS group to afford the corresponding hydroxy ynone intermediate, whose ring closure required considerable experimentation. It was finally discovered that treatment of this substrate with AgOTf in CH_2Cl_2 at 40 °C cleanly promoted the desired cyclization to afford pyranone **29** in 84% overall yield from **28**. Subsequent reduction of **29** under Luche conditions ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) led stereoselectively to the corresponding hydroxy compound (α isomer) whose hydroboration/oxidation ($BH_3 \cdot THF$; NaOH, H_2O_2) proceeded regio- and stereoselectively to afford, after protection of the resulting diol with TESOTf in the presence of 2,6-lutidine, the bis-TES silyl ether **30** in 65% overall yield for the three steps. Lactone **31** was then derived from bis-pivaloate **30** by reduction with DIBAL-H, followed by oxidation of the resulting diol mediated by a $PhI(OAc)_2$/TEMPO catalyst[16] (82% overall yield). Lactone **31** was finally converted into the requisite coupling partner, vinyl triflate **33**, in 93% yield by treatment with KHMDS and Comin's reagent (**32**) in THF at −78 °C, thus setting the stage for the casting of the final two rings.

Scheme 6 depicts the completion of the synthesis of the GHIJK ring system **2**. Hydroboration of the G-ring alkene **13** with 9-BBN in THF at 50 °C furnished the expected alkylborane which underwent smooth *B*-alkyl Suzuki coupling[17] with vinyl triflate **33** in the presence of a $Pd(OAc)_2$ catalyst, SPhos



Scheme 5. Construction of IJK ring system **33**. Reagents and conditions: a) *n*BuLi (2.0 equiv), **27** (2.0 equiv), THF, −78 °C, 1 h; then **26** (1.0 equiv), 15 min, 93 %; b) DMP (1.5 equiv), CH_2Cl_2, 25 °C, 1 h, 96 %; c) 48 % aq HF/MeCN (1:3), 25 °C, 18 h, 94 %; d) AgOTf (0.1 equiv), CH_2Cl_2, 40 °C, 18 h, 89 %; e) $CeCl_3 \cdot 7H_2O$ (0.2 equiv), $NaBH_4$ (1.1 equiv), MeOH/CH_2Cl_2 (1:1), 0 °C, 15 min; f) BH_3·THF (1.0 M in THF, 10 equiv), THF, 0 °C, 3 h; then NaOH (1.0 M aq), H_2O_2 (35 % aq), 1 h, 71 % over two steps; g) TESOTf (15 equiv), 2,6-lut. (20 equiv), CH_2Cl_2, 0 °C, 2 h, 92 %; h) DIBAL-H (1.0 M in CH_2Cl_2, 10 equiv), CH_2Cl_2, −78 °C, 10 min; i) TEMPO (0.1 equiv), $PhI(OAc)_2$ (3.0 equiv), CH_2Cl_2, 25 °C, 18 h, 82 % over two steps; j) **32** (2.0 equiv), KHMDS (0.5 M in THF, 2.0 equiv), THF, −78 °C, 10 min, 93 %. DMP = Dess–Martin periodinane, DIBAL-H = diisobutylaluminum hydride, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, KHMDS = potassium bis(trimethylsilyl)amide.



Scheme 6. Completion of the synthesis of GHIJK ring system **2**. Reagents and conditions: a) **13** (2.0 equiv), 9-BBN (4.0 equiv), THF, 50 °C, 3 h; then $KHCO_3$ (1.0 M aq, 20 equiv), **33** (1.0 equiv), SPhos (0.2 equiv), $Pd(OAc)_2$ (0.1 equiv), 25 °C, 48 h, 78 %; b) BH_3·THF (1.0 M in THF, 10 equiv), THF, 0 °C, 18 h; then NaOH (1.0 M aq), H_2O_2 (35 % aq), 1 h, 71 %; c) DMP (1.5 equiv), CH_2Cl_2, 25 °C, 2 h, 95 %; d) TsOH (1.0 equiv), MeOH, 50 °C, 48 h, 85 %; e) Et_3SiH (5.0 equiv), TMSOTf (2.0 equiv), MeCN, 0 °C, 15 min, 98 %; f) H_2, 20 % $Pd(OH)_2$/C (25 % w/w), EtOH, 25 °C, 18 h, 70 %. 9-BBN = 9-borabicyclo[3.3.1]nonane, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, Ts = *p*-toluenesulfonyl.

ligand (cat.),[18] and $KHCO_3$ (1.0 M aq, 20 equiv) to afford tetracycle **34** in 78 % yield. The hydroboration of **34** with BH_3·THF in THF at 0 °C proceeded regio- and stereoselectively to afford the expected hydroxy compound (α isomer, 71 % yield) which was oxidized to the corresponding ketone in 95 % yield through the action of DMP. Heating this compound with TsOH in MeOH at 50 °C for 48 h resulted in the formation of pentacyclic trihydroxy methyl acetal **35**, through removal of the PMB and TES groups and ring closure, in 85 % yield. The methoxy group was then reductively removed from **35** by the action of Et_3SiH in the presence of TMSOTf in MeCN at 0 °C to afford, after hydrogenolysis of the three benzyl groups (H_2, 20 % $Pd(OH)_2$/C (cat.), EtOH, 69 % overall yield), the targeted GHIJK ring system **2** (see the Experimental Section).[19]

The much-anticipated comparison of the ^{13}C chemical shifts of the GHIJK ring system **2** with those of the corresponding region of maitotoxin (**1**)[2d] was then made (Figure 1). As shown, the ^{13}C NMR chemical shifts (ppm) for the two compounds are in excellent agreement, with an average difference ($\Delta\delta$/ppm) of less than 0.1 ppm and a maximum deviation of 0.6 ppm for carbon atoms C-42 to C-53. The larger differences between the values of the two compounds for carbon atoms C-39 to C-41 and C-54 to C-55 are apparently due to the special functional groups present on rings G (a sulfate moiety) and K (a dihydroxypyran) of maitotoxin (**1**) as compared to the simpler model system **2** which contains only free hydroxy groups on ring G and a cyclohexyl moiety on ring K (Figure 1). These observations lend strong support for our computationally derived conclusion[5] that the originally proposed structure[2–4] for maitotoxin (**1**) is, indeed, most likely correct, at least in this region of the molecule, despite the noted biosynthetic anomaly.[6]

The described chemistry provides further experimental support for the originally proposed stereochemical assignment for the JK junction of maitotoxin, and should facilitate the construction of larger fragments of this notable marine neurotoxin.

Experimental Section

2: $R_f = 0.27$ (silica gel, EtOAc/MeOH 4:1); $[\alpha]_D^{25} = -5.7\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.11\ g\,cm^{-3}$, MeOH); IR (film): $\tilde{\nu}_{max} =$ 3453, 3414, 2925, 2850, 1648, 1446, 1350, 1069 cm^{-1}; ^1H NMR (600 MHz, [D$_4$]MeOD/[D$_5$]pyridine): $\delta = 4.30$ (t, $J = 2.4$ Hz, 1H), 4.22 (t, $J = 4.8$ Hz, 1H), 3.92 (dt, $J = 9.0$, 3.0 Hz, 1H), 3.88 (dd, $J = 10.8$, 8.4 Hz, 1H), 3.88–3.82 (m, 2H), 3.81–3.77 (m, 2H), 3.74 (t, $J =$ 8.4 Hz, 1H), 3.74–3.70 (m, 1H), 3.61 (dd, $J = 10.8$, 4.8 Hz, 1H), 3.55 (t, $J =$ 9.6 Hz, 1H), 3.43 (dd, $J = 9.6$, 3.0 Hz, 1H), 3.25 (dd, $J = 9.6$, 1.8 Hz, 1H), 3.16–3.08 (m, 3H), 2.40 (dt, $J = 10.8$, 3.6 Hz, 1H), 2.35 (dt, $J = 10.8$, 4.2 Hz, 1H), 2.33–2.27 (m, 1H), 1.93–1.87 (m, 1H), 1.75 (ddt, $J = 14.4$, 8.4, 6.0 Hz, 1H), 1.68–1.63 (m, 1H), 1.63–1.53 (m, 3H), 1.52–1.44 (m, 3H), 1.31 (dq, $J = 12.6$, 3.0 Hz, 1H), 1.21–1.11 (m, 2H), 1.09–1.01 (m, 1H), 0.98–0.90 ppm (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 85.8$, 85.0, 81.2, 79.3, 77.8, 77.5, 74.9, 74.5, 73.2, 72.1, 71.3, 70.3, 70.1, 69.8, 67.7, 59.6, 38.7, 37.7, 36.6, 36.3, 31.4, 27.7, 27.31, 27.26,

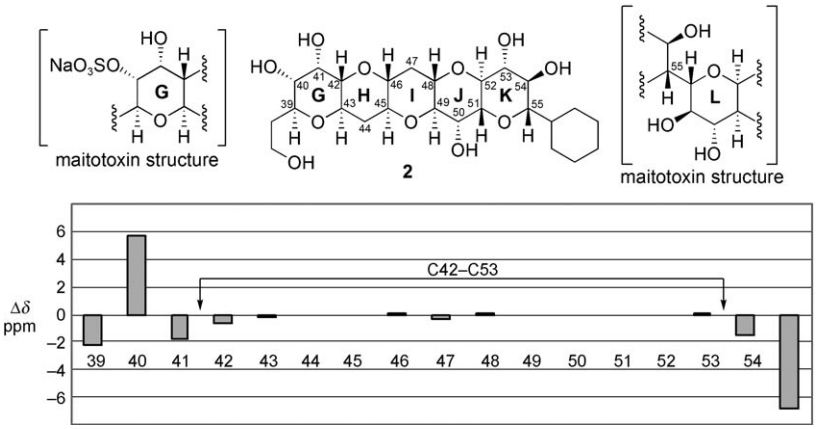


Figure 1. Differences in the ^{13}C chemical shift ($\Delta\delta$/ppm) between GHIJK fragment **2** and the values reported for maitotoxin (**1**) in the same solvent system. ^{13}C chemical shifts of **2** [150 MHz, 1:1 [D_4]methanol/[D_5]pyridine (reported values for maitotoxin in parentheses)][19]: C-39: 74.5 (72.3), C-40: 73.2 (78.9), C-41: 70.3 (68.5), C-42: 81.2 (80.6), C-43: 69.8 (69.6), C-44: 36.3 (36.3), C-45: 77.8 (77.7), C-46: 77.4 (77.5), C-47: 37.7 (37.4), C-48: 67.7 (67.8), C-49: 85.8 (85.8), C-50: 70.1 (70.1), C-51: 74.9 (74.9), C-52: 72.1 (72.1), C-53: 79.3 (79.4), C-54: 71.3 (69.8), C-55: 85.0 (78.2).

26.2 ppm; HRMS [electrospray ionization (ESI)]: calcd for $C_{25}H_{40}O_{11}Na^+$ [M+Na^+]: 539.2463, found: 539.2451.

Received: August 14, 2007
Published online: October 17, 2007

Keywords: maitotoxin · natural products · neurotoxins · NMR spectroscopy · structure elucidation

[1] a) M. Murata, T. Yasumoto, *Nat. Prod. Rep.* **2000**, *17*, 293; b) T. Yasumoto, R. Bagnins, J. E. Randal, A. H. Banner, *Bull. Jpn. Soc. Sci. Fish* **1976**, *37*, 724; c) T. Yasumoto, R. Bagnins, J. P. Vernoux, *Bull. Jpn. Soc. Sci. Fish.* **1976**, *42*, 359.

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

[3] a) M. Sasaki, T. Nonomura, M. Murata, K. Tachibana, *Tetrahedron Lett.* **1995**, *36*, 9007; b) M. Sasaki, T. Nomomura, M. Murata, K. Tachibana, T. Yasumoto, *Tetrahedron Lett.* **1995**, *36*, 9011; c) M. Sasaki, T. Nonomura, M. Murata, K. Tachibana, *Tetrahedron Lett.* **1994**, *35*, 5023; d) M. Sasaki, N. Matsumori, T. Muruyama, T. Nonomura, M. Murata, K. Tachibana, T. Yasumoto, *Angew. Chem.* **1996**, *108*, 1782; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1672; e) T. Nonomura, M. Sasaki, N. Matsumori, M. Murata, K. Tachibana, T. Yasumoto, *Angew. Chem.* **1996**, *108*, 1786; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1675.

[4] a) W. Zheng, J. A. DeMattei, J.-P. Wu, J. J.-W. Duan, L. R. Cook, H. Oinuma, Y. Kishi, *J. Am. Chem. Soc.* **1996**, *118*, 7946; b) L. R. Cook, H. Oinuma, M. A. Semones, Y. Kishi, *J. Am. Chem. Soc.* **1997**, *119*, 7928.

[5] K. C. Nicolaou, M. O. Frederick, *Angew. Chem.* **2007**, *119*, 5372; *Angew. Chem. Int. Ed.* **2007**, *46*, 5278.

[6] A. R. Gallimore, J. B. Spencer, *Angew. Chem.* **2006**, *118*, 4514; *Angew. Chem. Int. Ed.* **2006**, *45*, 4406.

[7] a) S. Higashibayashi, W. Czechtizky, Y. Kobayashi, Y. Kishi, *J. Am. Chem. Soc.* **2003**, *125*, 14379; b) B. A. Blackwell, O. E. Edwards, J. W. ApSimon, A. Fruchier, *Tetrahedron Lett.* **1995**, *36*, 1973.

[8] A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 2521.

[9] S. Celanire, F. Marlin, J. E. Baldwin, R. M. Adlington, *Tetrahedron Lett.* **2005**, *61*, 3025.

[10] Prepared from the corresponding carboxylic acid (L. V. Heumann, G. E. Keck, *Org. Lett.* **2007**, *9*, 1951) by reaction with *N*,*O*-dimethylhydroxylamine in the presence of carbonyl diimidazole.

[11] For recent examples of the application of the Achmatowicz reaction to the conversion of prochiral keto furans into enantioenriched pyrans, see a) H. Guo, G. A. O'Doherty, *Angew. Chem.* **2007**, *119*, 5298; *Angew. Chem. Int. Ed.* **2007**, *46*, 5206; b) M. Zhou, G. A. O'Doherty, *J. Org. Chem.* **2007**, *72*, 2485; c) H. Guo, G. A. O'Doherty, *Org. Lett.* **2006**, *8*, 1609; d) J. M. Harris, M. D. Keranen, H. Nguyen, V. G. Young, G. A. O'Doherty, *Carbohydr. Res.* **2000**, *328*, 17.

[12] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226.

[13] M. Sasaki, M. Ishikawa, H. Fuwa, K. Tachibana, *Tetrahedron* **2002**, *58*, 1889.

[14] D. L. J. Clive, M. Sannigrahi, S. Hisaindee, *J. Org. Chem.* **2001**, *66*, 954.

[15] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.

[16] T. M. Hansen, G. J. Florence, P. Lugo-Mas, J. Chen, J. N. Abrams, C. J. Forsyth, *Tetrahedron Lett.* **2003**, *44*, 57.

[17] S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676; *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.

[18] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685.

[19] The ^{13}C NMR signals and NOE interactions ascribed for **2** were based on COSY, ROESY, and HMQC experiments, and they closely conform with those reported for maitotoxin.[2c,d]

