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Synthesis of the QRSTU Domain of Maitotoxin and Its 85-*epi*- and 86-*epi*-Diastereoisomers

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Abstract: A devised synthetic strategy toward the QRSTU ring system **4** of the marine-derived biotoxin maitotoxin (**1**) delivered, in addition to **4**, its diastereoisomers 85-*epi*-QRSTU and 86-*epi*-QRSTU ring systems **5** and **6**. The convergent route to these maitotoxin fragments involved coupling of UT and Q building blocks **9** (obtained from 2-deoxy-D-ribose) and **10** (obtained from D-ribose) followed by ring-closing metathesis to afford enol ether **8**, whose elaboration to the targeted QRSTU ring system **4** required its conversion to hydroxy ketone **7**. The latter compound (**7**) was transformed to the final product through a hydroxy dithioketal cyclization, followed by oxidation/methylation of the resulting *O*,*S*-mixed ketal to install the last of the five methyl groups contained within the target molecule (**4**). ^{13}C NMR spectroscopic analysis of synthesized fragments **4**, **5**, and **6** and comparisons with maitotoxin provided strong support for the originally assigned structure of the QRSTU domain of the natural product.

Introduction

Maitotoxin (**1**, Figure 1) is the largest (MW 3422 Da) and most toxic secondary metabolite discovered to date.[1] The Yasumoto group reported its isolation from the dinoflagellate *Gambierdiscus toxicus* in 1988,[1d,e] and its gross structure in 1993.[2] By 1996, the work of Yasumoto et al.,[3] Kishi et al.[4] and Tachibana et al.[5] culminated in the assignment of the complete relative stereochemistry of this structure and its absolute configuration. Hailed as the most powerful nonproteinoic biotoxin, maitotoxin exerts its neurotoxicity through binding to cell membrane ion channels, an interference that results in harmful Ca^{2+} ion influx.[6] We recently reported the synthesis of the GHIJKLMNO and ABCDEFG fragments, **2** and **3**, of this natural product (Figure 1).[7,8] In this article, we report the chemical synthesis of the QRSTU ring system (**4**, Figure 1) of maitotoxin, the only extended ring system of the molecule that remained elusive until now, and its two diastereoisomers, epimeric at C_{85} (**5**, Figure 1) and C_{86} (**6**, Figure 1). We also report the spectroscopic analysis and comparison of these synthetic QRSTU polycyclic systems with maitotoxin, providing further support for the originally assigned structure of the QRSTU domain of this highly complex marine natural product.

Results and Discussion

The pentacyclic QRSTU ring framework of maitotoxin is distinct from any other within this and other polyether marine biotoxins in that it includes a high density of angular methyl groups, namely five.[9] This high degree of methyl substitution imparts severe steric congestion to the structure, amounting to a special challenge to its construction, particularly with regard to the fusion of certain rings

(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) Murata, M.; Naoki, H.; Iwashita, T.; Matsunaga, S.; Sasaki, M.; Yokoyama, A.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 2060.

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

(4) Zheng, W.; DeMattei, J. A.; Wu, J. P.; Duan, J. J.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946.

(5) (a) Sasaki, M.; Matsumori, N.; Muruyama, T.; Nonomura, T.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1672. (b) Nonomura, T.; Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1675.

(6) (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. (e) Konoki, K.; Hashimoto, M.; Murata, M.; Tachibana, K. *Chem. Res. Toxicol.* **1999**, *12*, 993. (f) Murata, M.; Matsumori, N.; Konoki, K.; Oishi, T. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 307.

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

(8) Nicolaou, K. C.; Aversa, R. J.; Jin, J.; Rivas, F. *J. Am. Chem. Soc.* **2010**, *132*, 6855.

(9) 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) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (c) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379.

10.1021/ja103708j

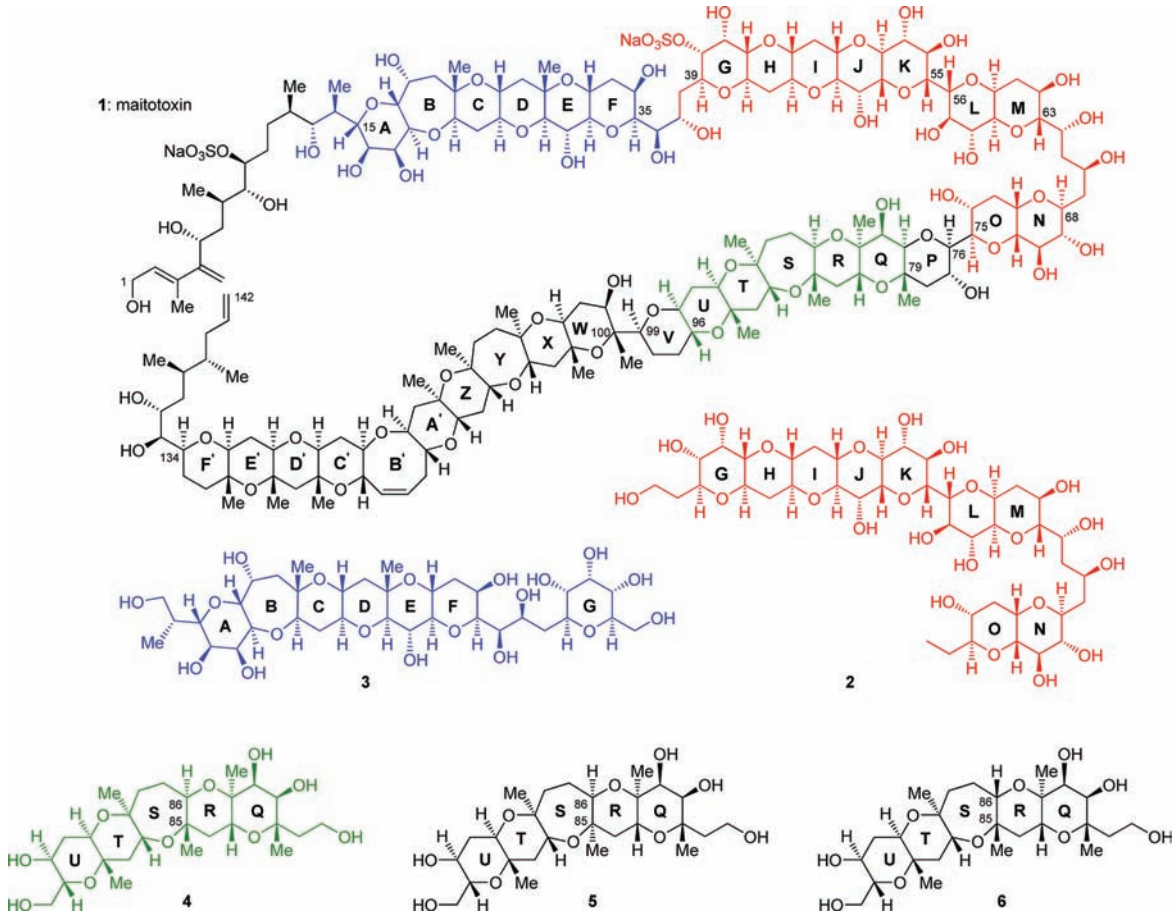


Figure 1. Structures of maitotoxin (**1**), previously synthesized maitotoxin domains GHIJKLMNO (**2**) and ABCDEFG (**3**), targeted QRSTU domain (**4**), and its diastereomeric 85-*epi*-QRSTU domain (**5**) and 86-*epi*-QRSTU domain (**6**).

and the proper spacial placement of these methyl groups around the periphery of the target molecule.

Retrosynthetic Analysis. Aiming for optimum convergency and flexibility for the synthetic strategy toward our defined structure (i.e., **4**), we focused on the retrosynthetic blueprint depicted in Figure 2. It was envisioned that the oxepane ring in **4** may be forged through a hydroxy dithioketal cyclization of **7**,[10] followed by installation of the final angular methyl group at C_{85}. It was reasoned that ketone **7** might arise from enol ether **8**. Disassembly of the R ring of the latter intermediate at the indicated bonds suggested its construction from building blocks **9** and **10** through ester coupling followed by a Takai olefination/ring-closing metathesis cascade sequence.[11] Finally, the two tetrahydropyran systems **9** and **10** could be traced back to the enantiomerically pure, and readily available, starting materials, 2-deoxy-D-ribose (**11**) and D-ribose (**12**), respectively.

Construction of UT and Q Fragments 9 and 10. Having defined building blocks **9** and **10** as potential precursors to the targeted maitotoxin fragment, their synthesis was commenced in earnest. Scheme 1 summarizes the construction of fragment **9** starting from 2-deoxy-D-ribose (**11**). Thus, following a previously developed route,[12] intermediate **13** was synthesized from **11** (11 steps, 43% overall yield). Swern oxidation of primary alcohol **13** gave aldehyde **14**, which reacted with stabilized phosphorane $Ph_3PC(Me)CO_2Et$ to afford α,β-unsaturated ester **15** in 91% overall yield. DIBAL-H reduction of the latter compound (95% yield) and Sharpless asymmetric epoxidation[13] of the resulting allylic alcohol (**16**) led to epoxide **17** in 95% yield. Transformation of epoxide **17** to α,β-unsaturated ester epoxide **19** was achieved through $SO_3\cdot$py oxidation to afford aldehyde **18** and reaction of the latter intermediate with Ph_3PCHCO_2Me (98% overall yield for the two steps). In anticipation of the pending ring T closure, the TBS group was removed from **19** (TBAF, 100% yield) to furnish hydroxy epoxide **20**. Exposure of the latter intermediate to PPTS

(10) (a) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321. (b) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1986**, *108*, 2468. (c) Nicolaou, K. C.; Yang, Z.; Shi, G.-Q.; Gunzner, J. L.; Agrios, K. A.; Gärtner, P. *Nature* **1998**, *392*, 264.

(11) Takai−Utimoto reagent: (a) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668. For a review summarizing the applications of olefin metathesis in the synthesis of fused polyethers see: (b) Clark, J. S. *Chem. Commun.* **2006**, 3571. For earlier methods using ring-closing metathesis to form enol ethers, see: (c) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426. (d) Fu, G. C.; Nguyn, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (e) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029. (f) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (g) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335. (h) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123. (i) Clark, J. S.; Kettle, J. G. *Tetrahedron* **1999**, *55*, 8231. For recent work using the Takai−Utimoto reagent for the synthesis of polyethers, see: (j) Majumder, U.; Rainier, J. D. *Tetrahedron Lett.* **2005**, *46*, 7209. (k) Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2007**, *129*, 12604.

(12) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron.* **1990**, *46*, 4517.

(13) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

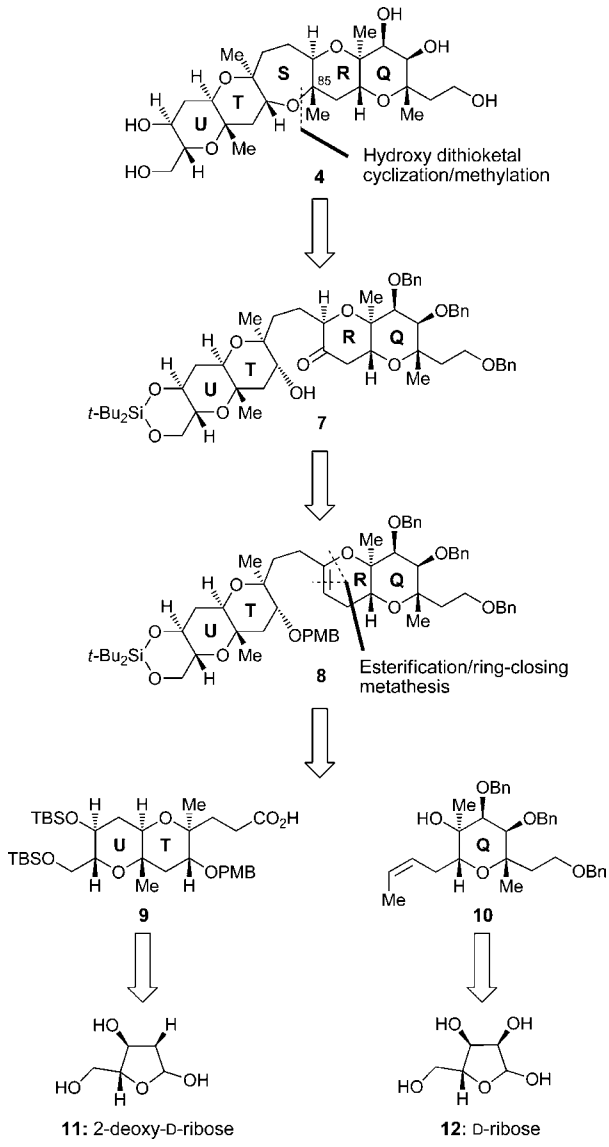
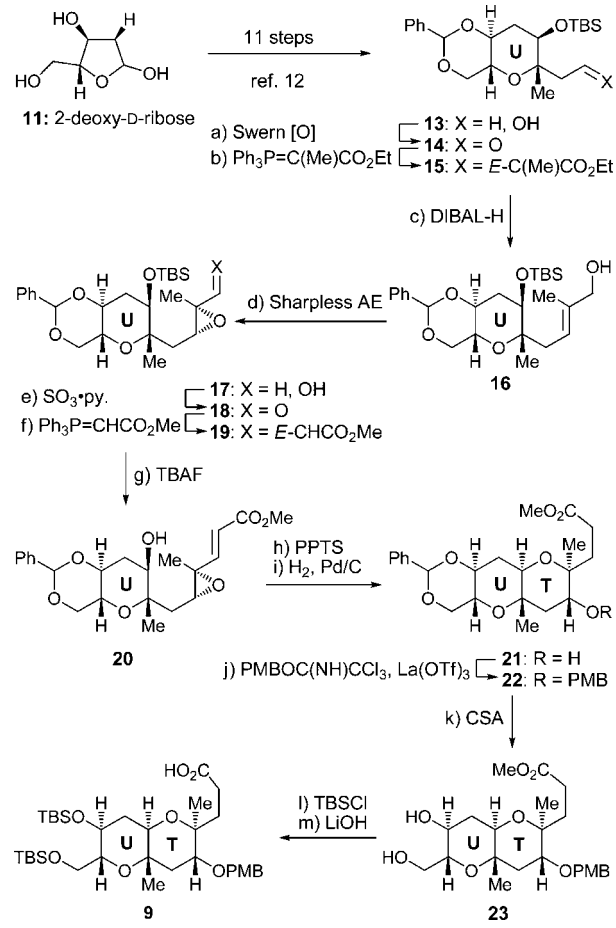


Figure 2. Retrosynthetic analysis of QRSTU pentacyclic system **4**.

facilitated the intended cyclization (97% yield),[14] which was followed by hydrogenation (H_2, 10% Pd/C, 94% yield) of the resulting product to afford the desired UT ring system hydroxy methyl ester **21**. The inversion of configuration of the Me-bearing center during the hydroxyl epoxide cyclization secured the desired stereochemical arrangement in the growing molecule (i.e., **21**). Protection of the hydroxyl group within the latter compound [(PMBOC(NH)CCl_3, La$(OTf)_3$ cat., 96% yield], followed by removal of the benzylidene group (CSA, 90% yield) gave diol **23**. bis-Silylation of diol **23** (TBSCl, imid.) followed by saponification of the resulting methyl ester bis-TBS ether derivative yielded UT carboxylic acid fragment **9** (100% overall yield).

The construction of fragment Q (**10**) commenced from D-ribose (**12**) and proceeded as shown in Scheme 2. Thus, following a previously reported sequence,[15] **12** was converted to hydroxy α,β-unsaturated ester **24** (three steps, 65% overall yield). Silylation of **24** (TESOTf, 2,6-lut., 88% yield), followed by DIBAL-H reduction (96% yield) and Sharpless asymmetric epoxidation[16] gave hydroxy epoxide **25** in 80% yield. Parikh–Doering oxidation[17] of **25** led to aldehyde **26**, whose methylenation ($PPh_3{=}CH_2$) and desilylation (TBAF) afforded diol epoxide **28** with an 86% overall yield for the three steps. Initially, exposure of epoxide **28** to different protic acids (i.e., PPTS, CSA) in either catalytic or stochiometric amounts under various conditions did not promote the desired ring closure in acceptable yields. Finally, it was found that, when epoxide **28** was subjected to the conditions recently reported by the Jamison group (H_2O, 70 °C, 24 h),[18] the desired tetrahydropyran compound **29** was obtained in excellent yield (83%), and with

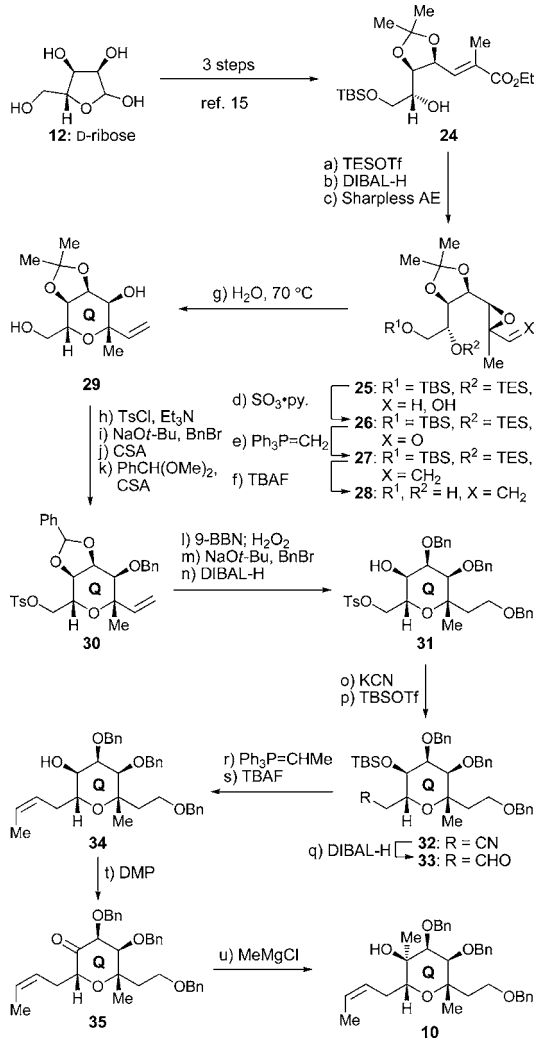
Scheme 1. Synthesis of UT Ring System **9**[a]



[a] Reagents and conditions: a) $(COCl)_2$ (1.5 equiv), DMSO (2.0 equiv), CH_2Cl_2, −78 °C, 20 min; then Et_3N (4.0 equiv), 0 °C, 30 min; b) $Ph_3PCMe(CO_2Et)$ (1.3 equiv), PhMe, 70 °C, 3 h, 91% over the two steps; c) DIBAL-H (1.0 M in CH_2Cl_2, 2.5 equiv), CH_2Cl_2, −78 °C, 1 h, 95%; d) (−)-DET (0.26 equiv), Ti(*i*-PrO)$_4$ (0.22 equiv), *t*-BuOOH (5.0 M in decane, 1.5 equiv), 4 Å MS, CH_2Cl_2, −20 °C, 10 h, 95%; e) SO_3•py (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2:DMSO (4:1), 25 °C, 1 h; f) $Ph_3PCH(CO_2Me)$ (1.3 equiv), CH_2Cl_2, 25 °C, 12 h, 98% over the two steps; g) TBAF (1.5 equiv), THF, 25 °C, 1 h, 100%; h) PPTS (1.0 equiv), CH_2Cl_2, 50 °C, 3 h, 97%; i) H_2, 10% Pd/C (20% w/w), EtOAc, 25 °C, 17 h, 94%; j) PMBOC(NH)CCl_3 (1.4 equiv), La$(OTf)_3$ (0.05 equiv), PhMe, 25 °C, 30 min, 96%; k) CSA (0.2 equiv), CH_2Cl_2:MeOH (2:3), 25 °C, 12 h, 90%; l) TBSCl (3.0 equiv), imid. (5.0 equiv), DMF, 25 °C, 6 h, 99%; m) LiOH (4.0 equiv), THF:H_2O (2:1), 25 °C, 20 h, 100%. DMF = dimethyl formamide, imid. = imidazole, PMB = *p*-methoxybenzyl, PPTS = pyridinium *p*-toluenesulfonate.

(14) Nicolaou, K. C.; Veale, C. A.; Hwang, C.-K.; Hutchinson, J.; Prasad, C. V. C.; Ogilvie, W. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 299.
(15) (a) Kane, P. D.; Mann, J. *J. Chem. Soc., Chem. Commun.* **1983**, 224. (b) Kane, P. D.; Mann, J. *J. Chem. Soc., Perkin Trans. I* **1984**, 657.
(16) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Redd, L. A.; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245.
(17) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

Scheme 2. Synthesis of Q Ring Building Block **10**[a]



[a] Reagents and conditions: a) TESOTf (1.2 equiv), 2,6-lut. (1.5 equiv), CH_2Cl_2, 0 °C, 14 h, 88%; b) DIBAL-H (1.0 M in CH_2Cl_2, 2.2 equiv), CH_2Cl_2, −78 °C, 30 min, 96%; c) (−)-DET (0.39 equiv), Ti(*i*-PrO)$_4$ (0.30 equiv), *t*-BuOOH (5.0 M in decane, 2.2 equiv), 4 Å MS, CH_2Cl_2, −20 °C, 48 h, 80%; d) SO_3•py (3.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2/DMSO (5:1), 25 °C, 3 h; e) CH_3PPh_3Br (1.5 equiv), NaHMDS (1.0 M in THF, 1.4 equiv), THF, 0 °C, 40 min; then **26** (1.0 equiv), THF, 0 → 25 °C, 3 h, 86% over the two steps; f) TBAF (2.5 equiv), THF, 25 °C, 1 h, 100%; g) 0.1 M in H_2O, 70 °C, 16 h, 83%; h) TsCl (1.5 equiv), Et_3N (1.9 equiv), CH_2Cl_2, 50 °C, 12 h, 97%; i) BnBr (2.0 equiv), NaO*t*-Bu (2.5 equiv), THF, 25 °C, 4 h, 100%; j) CSA (0.05 equiv), MeOH/CH_2Cl_2 (4:1), 25 °C, 48 h, 85%; k) $PhCH(OMe)_2$ (3.0 equiv), CSA (0.05 equiv), CH_2Cl_2, 25 °C, 24 h, 75%; l) 9-BBN (3.0 equiv), THF, 80 °C, 2 h; then H_2O_2 (35% aq, 15 equiv), NaOH (3.0 M aq, 15 equiv), 25 °C, 3 h, 95%; m) BnBr (2.5 equiv), NaO*t*-Bu (3.0 equiv), THF, 25 °C, 2 h, 86%; n) DIBAL-H (1.0 M in CH_2Cl_2, 3.0 equiv), CH_2Cl_2, 0 °C, 30 min; o) KCN (2.0 equiv), DMSO, 80 °C, 14 h; p) TBSOTf (1.5 equiv), 2,6-lut. (2.0 equiv), CH_2Cl_2, 0 °C, 45 min, 81% over the three steps; q) DIBAL-H (1.0 M in CH_2Cl_2, 3.0 equiv), Et_2O, 0 °C, 30 min; r) $CH_3CH_2PPh_3Br$ (3.2 equiv), NaHMDS (1.0 M in THF, 3.0 equiv), THF, 0 °C, 5 min; then **33** (1.0 equiv), THF, 0 °C, 15 min, 81% over the two steps; s) TBAF (2.0 equiv), THF, 25 °C, 1 h; t) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 30 min, 95% over the two steps; u) MeMgCl (4.0 equiv), Et_2O, 0 °C, 20 min, 98%. 9-BBN = 9-borabicyclo[3.3.1]nonane, Bn = benzyl, CSA = (±)-camphor-10-sulfonic acid, DET = diethyl tartrate, DIBAL-H = diisobutylaluminum hydride, DMP = Dess−Martin periodinane, DMSO = dimethyl sulfoxide, lut. = lutidine, NaHMDS = sodium bis(trimethylsilyl)amide, py = pyridine, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, THF = tetrahydrofuran, Ts = *p*-toluenesulfonyl.

the desired stereochemical arrangement by virture of the accompanying inversion of configuration at the Me-bearing stereocenter. With the Q ring cast, a four-step functionalization sequence of the growing molecule [(i) tosylation (TsCl, Et_3N, 97% yield) of the primary alcohol; (ii) benzylation (BnBr, NaO*t*-Bu, 100% yield) of the secondary alcohol; (iii) acetonide cleavage (CSA, 85% yield); and (iv) benzylidene formation ($PhCH(OMe)_2$, CSA, 75% yield)] gave fully protected intermediate **30**. Regioselective hydroboration/oxidation (9-BBN, aq H_2O_2/NaOH, 95% yield) of the vinyl group of **30**, followed by protection of the resultant primary alcohol (BnBr, NaO*t*-Bu, 86% yield) and regioselective opening of the benzylidene with DIBAL-H yielded alcohol **31**. Exposure of the latter compound (**31**) to KCN in DMSO at 80 °C, followed by silylation of the free alcohol (TBSOTf, 2,6-lut.), furnished nitrile **32** in 81% yield over the three steps. Reduction of nitrile **32** with DIBAL-H set the stage for installation of the substituted methylene unit, which was carried out with $CH_3CH_2PPh_3Br$ and NaHMDS (81% yield over the two steps)[19] to afford the corresponding olefin, whose desilylation with TBAF provided hydroxy pyran **34**. Finally, transformation of **34** to the desired tertiary alcohol Q fragment **10** was readily accomplished through oxidation with DMP (to afford ketone **35**, 95% yield for the two steps) followed by the addition of MeMgCl (98% yield). The exquisite stereocontrol observed in the last reaction was expected on steric grounds as revealed through manual molecular modeling.

Coupling of UT and Q Fragments 9 and 10. Union of the two key building blocks **9** and **10** was achieved as shown in Scheme 3. Our initial attempts to accomplish this task employing the Yamaguchi esterification and other standard coupling conditions failed to yield the desired product.[20] It was soon discovered, however, that by preforming the acid chloride of acid **9** using $(COCl)_2$ and catalytic amounts of DMF and adding to it the anion of tertiary alcohol **10** (formed with KHMDS), the desired ester **37** was formed in 65% yield (100% based on **10**).[21] At this point it was necessary to swap the two TBS groups for a cyclic silane [Si(*t*-Bu)$_2$] in order to augment the robustness of the growing substrate. Thus, desilylation of **37** with TBAF, followed by reprotection of the resultant diol **38** using *t*-Bu$_2$Si(OTf)$_2$ and 2,6-lutidine, afforded cyclic silane ester **39** in 94% yield over the two steps. The stage was now set for formation of the intended R ring enol ether. To that end, **39** was subjected to the Takai−Utimoto reaction to achieve both the olefination and ring-closing metathesis in one pot, furnishing enol ether **40** in 93% yield.[11j,k] Regioselective hydroboration of **40** and DMP oxidation of the resultant alcohol led to diastereomeric ketones **41** and **42** (90% combined yield). As anticipated from the diastereoselectivity of the hydroboration step, the undesired 86-*epi*-QRSTU ketone **41** was the major product (**41**:**42** ∼3:1 dr), due to shielding of the α-face of the enol ether substrate by the α-angular methyl group at C_{82}. Epimerization of the 86-*epi*-QRTSU ketone **41** to the desired diastereoisomer **42** was more problematic than expected. Thus, it was after considerable experimentation that we found conditions to accomplish this goal

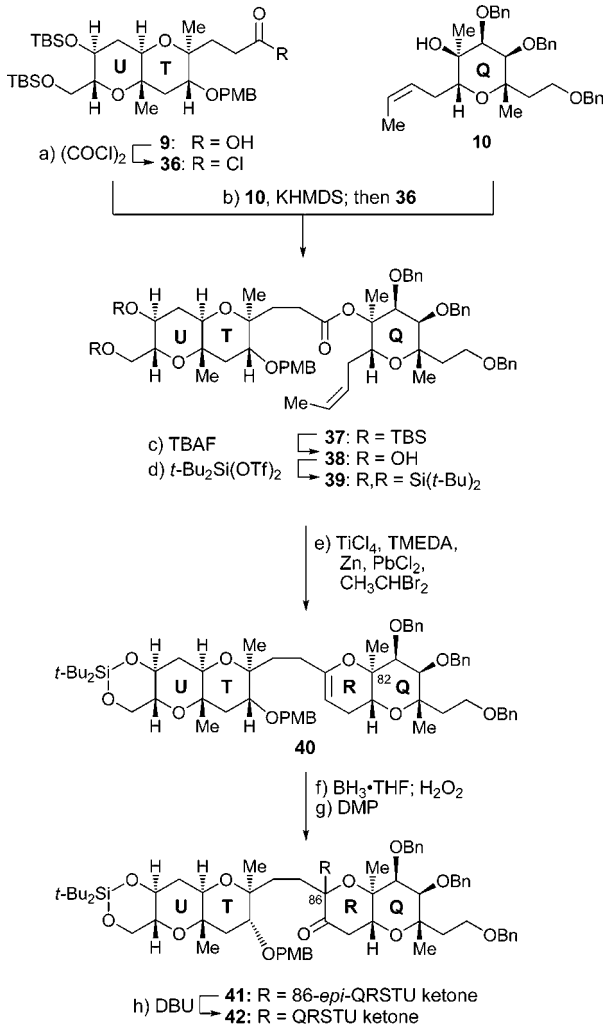
(18) (a) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189. For a mechanistic study on the water-promoted cyclization of epoxy alcohols, see: (b) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383. For an application of water-promoted epoxide-opening cascades toward total synthesis, see: (c) Van Dyke, A. R.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 4430. For a review on epoxide-opening cascades in water, see: (d) Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, *38*, 3175.

(19) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *Chem.—Eur. J.* **2006**, *12*, 1747.

(20) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822.

(21) Wilmouth, S.; Pellissier, H.; Santelli, M. *Tetrahedron* **1998**, *54*, 10079.

Scheme 3. Coupling of Fragments **9** and **10** and Synthesis of 86-*epi*-QRSTU Ketone **41** and QRSTU Ketone **42**[a]

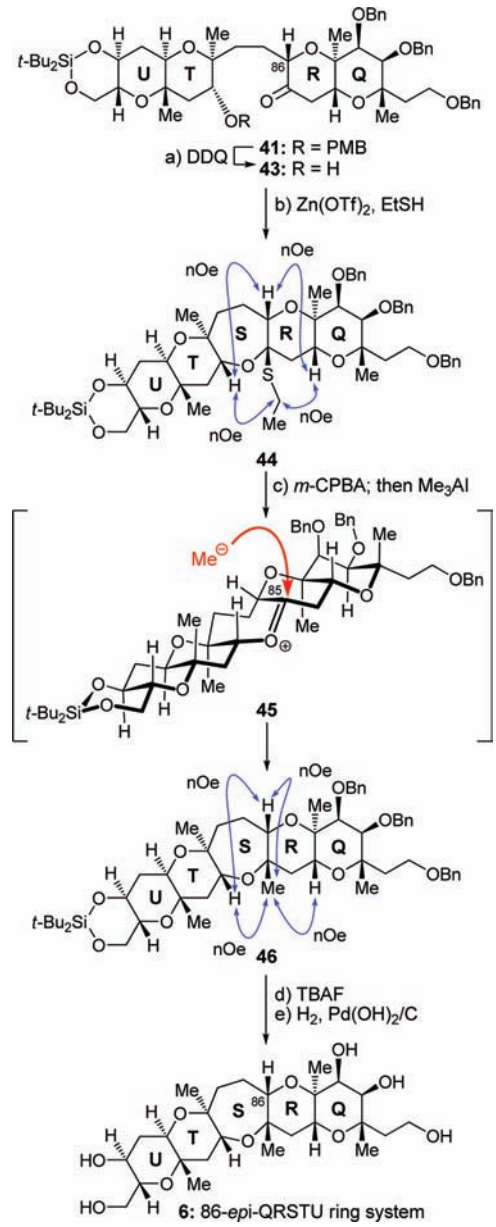


[a] Reagents and conditions: a) acid **9** (1.4 equiv), $(COCl)_2$ (2.1 equiv), DMF (0.1 mol %), PhH, 25 °C, 2 h; b) alcohol **10** (1.0 equiv), KHMDS (1.4 equiv), THF, 0 °C, 15 min; then **36** (1.5 equiv), THF, 0 °C, 30 min, 65% (100% based on **10**); c) TBAF (3.0 equiv), THF, 25 °C, 1.5 h; d) *t*-$Bu_2Si(OTf)_2$ (1.5 equiv), 2,6-lut. (3.0 equiv), THF, 25 °C, 1 h, 94% over the two steps; e) $TiCl_4$ (33 equiv), TMEDA (190 equiv), THF (228 equiv), Zn (71 equiv), $PbCl_2$ (3.9 equiv), CH_2Cl_2, 25 °C, 20 min; then **39** (1.0 equiv), CH_3CHBr_2 (32 equiv), CH_2Cl_2, 60 °C, 1 h, 93%; f) BH_3•THF (1.0 M in THF, 10 equiv), THF, 0 °C, 14 h; then H_2O_2 (35% aq, 15 equiv), NaOH (3.0 M aq, 15 equiv), 25 °C, 5 h; g) DMP (2.0 equiv), $NaHCO_3$ (4.0 equiv), CH_2Cl_2, 25 °C, 30 min, 90% over the two steps (~3:1 dr **41**:**42**); h) K_2CO_3 (2.0 equiv), EtOH, 25 °C, 3 h, 89%. KHMDS = potassium bis(trimethylsilyl)amide, TMEDA = *N*,*N*,*N*′,*N*′-tetramethyl-ethane-1,2-diamine.

(K_2CO_3, EtOH, 25 °C, strictly anaerobic).[22] Pleasantly, this protocol channeled the undesired epimer (**41**) to the thermodynamically favored QRSTU ketone **42** in 89% yield.

Synthesis of 86-*epi*-QRSTU, QRSTU, and 85-*epi*-QRSTU Ring Systems of Maitotoxin. With ample quantities of the QRSTU ketones **41** and **42** readily available, the drive toward the synthesis of the QRSTU ring system **4** of maitotoxin was undertaken. As it turned out, the developed route to QRSTU system **4** also delivered its diastereoisomers, 85-*epi*-QRSTU and 86-*epi*-QRSTU ring systems **5** and **6**. Our first foray en route to the desired goal was directed toward the 86-*epi*-QRSTU ring system **6**, starting from

Scheme 4. Synthesis of 86-*epi*-QRSTU Ring System **6**[a]



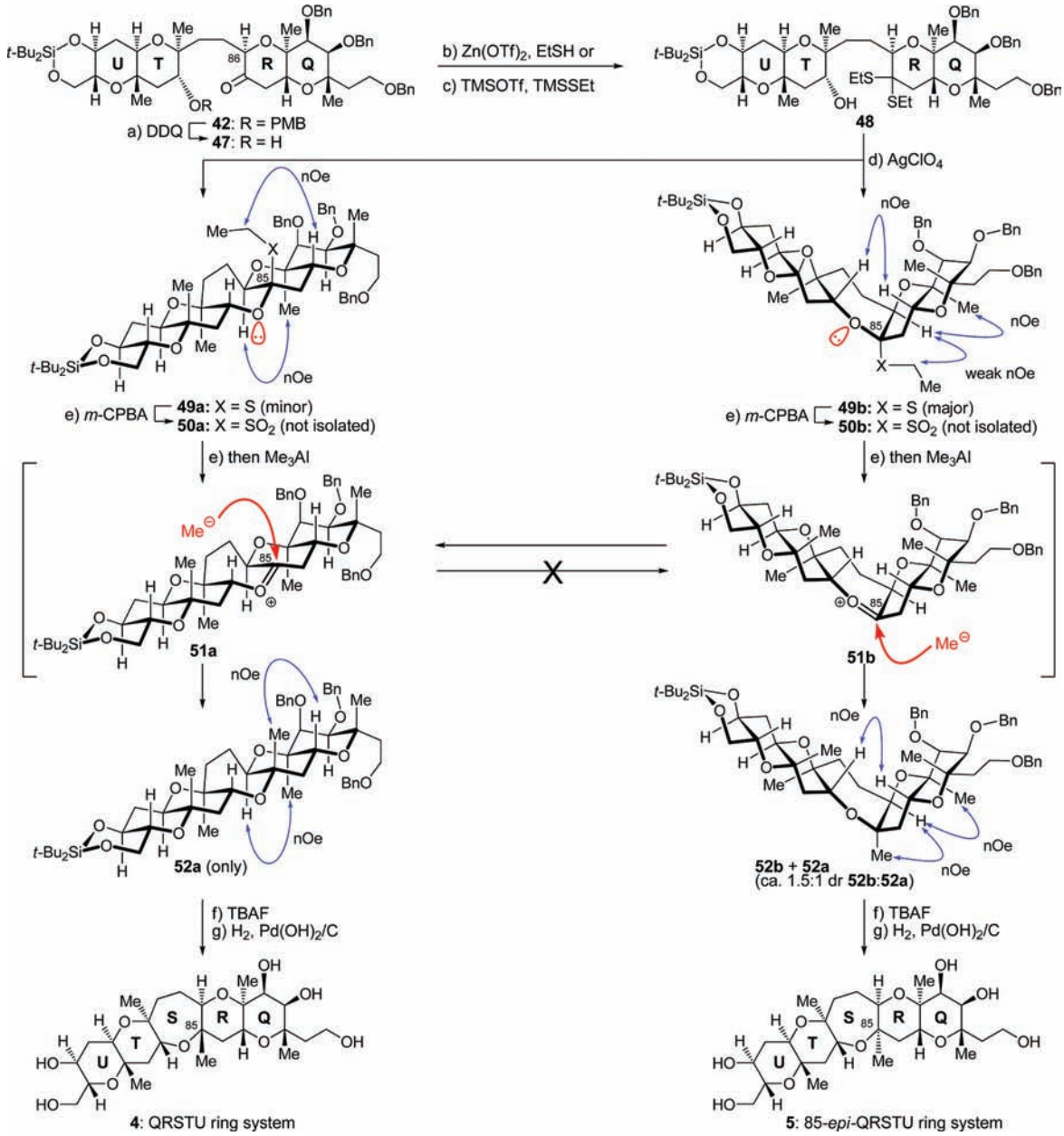
[a] Reagents and conditions: a) DDQ (2.0 equiv), CH_2Cl_2:H_2O (20:1), 0 °C, 3 h, 83%; b) $Zn(OTf)_2$ (2.0 equiv), EtSH (48 equiv), CH_2Cl_2, 25 °C, 3 h, 77%; c) *m*-CPBA (5.0 equiv), CH_2Cl_2, 0 °C, 20 min; then Me_3Al (2.0 M in heptanes, 10 equiv), 0 °C, 30 min, 93%; d) TBAF (5.0 equiv), THF, 25 °C, 19 h, 98%; e) H_2, 20% $Pd(OH)_2$/C (50% w/w), THF, 25 °C, 17 h, 100%. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, *m*-CPBA = *m*-chloroperbenzoic acid.

the initially obtained 86-*epi*-QRSTU ketone **41** in order to scout the road ahead since it was readily available. In addition to the preparation for the final drive toward the QRSTU ring system **4**, the construction of the 86-*epi*-QRSTU system would also allow for its NMR spectroscopic comparisons with the primary target of our investigation (i.e., QRSTU ring system **4**) and maitotoxin, thereby providing further support (or lack thereof) of the originally assigned structure of that region of the natural product.

Scheme 4 depicts the synthesis of the targeted 86-*epi*-QRSTU ring system **6** from 86-*epi*-QRSTU ketone **41**. Thus, exposure of **41** to DDQ furnished hydroxy ketone **43** (83% yield), whose treatment with EtSH in the presence of $Zn(OTf)_2$ induced

(22) For an example of a similar isomerization, see: (a) Crimmins, M. T.; McDougall, P. J.; Ellis, J. M. *Org. Lett.* **2006**, *8*, 4079.

Scheme 5. Completion of the Synthesis of Maitotoxin QRSTU Ring System **4** and 85-*epi*-QRSTU Ring System **5**[a]



[a] Reagents and conditions: a) DDQ (2.0 equiv), CH_2Cl_2:H_2O (20:1), 0 °C, 3 h, 87%; b) $Zn(OTf)_2$ (2.0 equiv), EtSH (48 equiv), CH_2Cl_2, 25 °C, 3 h, 83%; or c) TMSOTf (2.0 equiv), TMSSEt (3.0 equiv), CH_2Cl_2, −78 °C, 3 h, 95%; d) $AgClO_4$ (3.0 equiv), $NaHCO_3$ (3.0 equiv), SiO_2, 4 Å MS, $MeNO_2$, 25 °C, 1.5 h, 72%, 3:1 dr **49b**:**49a**; e) *m*-CPBA (4.0 equiv), CH_2Cl_2, 0 °C, 2 h; then Me_3Al (2.0 M in hexanes, 8.0 equiv), −78 °C, 12 h, then 0 °C, 1 h, 95%, ∼1:0.8 dr **52a**:**52b** from mixture of ∼3:1 dr **49b**:**49a**; 92% **52a** (only) from **49a**; 94%, ∼1.5:1 dr **52b**:**52a** from **49b**; f) TBAF (5.0 equiv), THF, 25 °C, 14 h, 87% from **52a**, 92% from **52b**; g) H_2, 20% $Pd(OH)_2$/C (50% w/w), THF, 25 °C, 12 h, **4**: 100%, **5**: 87%.

the desired ring closure,[23] forming mixed *O*,*S*-ketal **44** as a single diastereoisomer in 77% yield. The indicated configurations at the RS ring junction were based on the observed nOes (see structure **44**, Scheme 4). The required C_{85}-Me group was then introduced into the growing molecule through a one-pot, two-step procedure involving oxidation of **44** to the corresponding sulfone with *m*-CPBA, followed by addition of Me_3Al to oxonium intermediate **45** from the less sterically hindered convex face to afford methylated polycyclic system **46** in 93% overall yield.[10a] The indicated stereochemical arrangement around the C_{85}−C_{86} ring junction within **46** was confirmed through the observed nOes (see structure **46**, Scheme 4). With all five angular methyl groups installed in their intended positions around the targeted maitotoxin framework, intermediate **46** was then converted to the desired 86-*epi*-QRSTU ring system **6** by global deprotection, achieved through sequential desilylation (TBAF, 98% yield) and debenzylation [H_2, $Pd(OH)_2$, 100% yield].

With the accomplishment of the synthesis of 86-*epi*-QRSTU ring system **6** came intelligence and confidence for the final drive toward the QRSTU ring framework (i.e., **4**) of maitotoxin. Scheme 5 summarizes the rather adventurous chemistry that led not only to this targeted fragment (**4**), but also to its diastere-

(23) (a) Nicolaou, K. C.; Veale, C. A.; Hwang, C.-K.; Hutchinson, J.; Prasad, C. V. C.; Ogilvie, W. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *130*, 304. (b) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019.

oisomer, 85-*epi*-QRSTU ring system **5**. Thus, treatment of QRSTU ketone **42** with DDQ liberated hydroxy ketone **47** (87% yield), which upon reaction with EtSH in the presence of $Zn(OTf)_2$ furnished hydroxy dithioketal **48** in 83% yield. An improved yield (95%) of **48** was obtained with TMSSEt in the presence of TMSOTf.[24] Exposure of the latter compound to our previously developed cyclization conditions ($AgClO_4$, $NaHCO_3$, $MeNO_2$)[10] led to a mixture of C_{85} diastereomeric closed *O,S*-mixed ketals **49b** and **49a** (~3:1 dr) in 72% combined yield. Chromatographic separation of **49a** and **49b** allowed for their configurational assignments as shown based on NMR spectroscopic analysis (see nOes, Scheme 5).

Since we expected (on the basis of steric grounds) the diastereoselectivity in the next step (i.e., oxidation to the corresponding sulfone and subsequent reaction with Me_3Al) to proceed through an oxonium species, thereby erasing the C_{85} stereocenter and delivering the desired methylated product, we moved forward with a mixture of epimers **49b** and **49a** (~3:1 dr). Thus, oxidation of this mixture with *m*-CPBA, followed by addition of Me_3Al to the resulting reaction mixture furnished,[25] to our surprise, a diastereomeric mixture of pentacycles **52a** (β-85-Me) and **52b** (α-85-Me) as a ~1:0.8 dr mixture (95% combined yield), with desired product **52a** as the major isomer. Various changes in reaction temperature, solvent, and stoichiometry of Me_3Al did not improve the diastereoselectivity of this reaction. Chromatographic separation of **52a** and **52b** led to their configurational assignments through NMR spectroscopic analysis (see nOes, Scheme 5). The fact that the diastereomeric ratio of the obtained products did not reflect the diastereomeric ratio of the starting mixture was intriguing. Faced with this unexpected result, we proceeded to subject each diastereoisomer (i.e., **49a** and **49b**) to the methylation conditions (*m*-CPBA; then Me_3Al) individually in order to shed light on the diastereoselectivity of this methylation process. While the reactions of both **49a** and **49b** proceeded in equally high yield as with the mixture, their selectivities were surprising. Thus, whereas thioketal **49b** (major) led to a mixture of methylated products **52b**:**52a** (~1.5:1 dr), diastereoisomer **49a** (minor) gave exclusively the desired methylated diastereoisomer **52a**.[26] These results suggest that the methylation reaction of the corresponding sulfones (i.e., **50a** and **50b**) proceeds through a more complex mechanism than assumed (i.e., through nucleophilic attack by a methyl anion on a common oxonium intermediate). On the basis of the inspection of manual molecular models of **49a,b**−**51a,b** we propose the following speculative mechanism to explain these observations. Thus, sulfone **50a** is exclusively and rapidly converted to oxonium species **51a**, which is also rapidly and exclusively converted to methylated product **52a** (TLC analysis). In contrast, sulfone **50b** is sluggishly converted to oxonium species **51b** (TLC analysis as compared to **50a**), whose strained nature forces it to undergo a ring flip into the more comfortable oxonium **51a** (thermodynamically more stable) at a rate comparable to that of its methylation to give **52b**. The surmised rate differences of formation of oxonium species **51a** and **51b** from the two diastereomeric sulfones may be explained by the alignment of the lone pair of electrons from the oxygen atom in relation to the σ^* orbital of the C−S bond in **50a** (antiparallel) and **50b** (nonantiparallel). The reaction of sulfone **50b** leading to both **52b** and **52a** (~1.5:1 dr) is, therefore, a consequence of leakage of oxonium species **51b** to **51a**, whereas the reverse conversion of **51a** to **51b** does not occur due to the thermodynamic stability of the former species. Whereas the methylation rates of oxonium species **51a** and **51b** may or may not be a factor in the observed diastereospecificity (or lack thereof) of these reactions, the rates of formation of these oxonium species from the corresponding sulfones are unlikely to influence the diastereoselectivities of their methylation.

Table 1. Chemical Shifts (δ, ppm) of C_{79} to C_{96} and C_{150} to C_{154} for Maitotoxin (MTX, **1**) and QRSTU Ring Systems **4**, **5**, and **6** and Differences Between Each of the Latter Three Compounds and MTX (**1**) ($\Delta\delta$, ppm)[a]

carbon	δ for MTX (**1**) (ppm)	δ for **4** (ppm)	difference ($\Delta\delta$, ppm)	δ for **5** (ppm)	difference ($\Delta\delta$, ppm)	δ for **6** (ppm)	difference ($\Delta\delta$, ppm)
150	19.8	19.4	0.4	19.3	0.5	19.5	0.3
79	75.4	79.8	−4.4	79.7	−4.3	79.9	−4.5
80	81.4	72.5	8.9	72.4	9.0	72.3	9.1
81	74.8	76.2	−1.4	76.7	−1.9	76.0	−1.2
151	15.2	14.5	0.7	13.7	1.5	19.1	−3.9
82	76.4	75.9	0.5	75.6	0.8	75.6	0.8
83	64.7	64.1	0.6	62.5	2.2	64.1	0.6
84	41.0	41.3	−0.3	41.1	−0.1	35.6	5.4
152	16.5	16.4	0.1	28.8	−12.3	24.9	−8.4
85	78.4	78.0	0.4	77.4	1.0	77.8	0.6
86	74.1	74.1	0.0	74.2	−0.1	83.8	−9.7
87	25.9	26.1	−0.2	24.6	1.3	32.1	−6.2
88	38.6	38.9	−0.3	36.3	2.3	43.2	−4.6
153	19.5	19.7	−0.2	16.1	3.4	16.4	3.1
89	79.5	79.4	0.1	80.0	−0.5	78.3	1.2
90	72.1	71.8	0.3	74.5	−2.4	71.9	0.2
91	43.2	43.2	0.0	43.5	−0.3	43.0	0.2
154	16.0	15.7	0.3	16.3	−0.3	15.6	0.4
92	75.0	74.0	1.0	74.1	0.9	74.0	1.0
93	71.9	71.2	0.7	71.3	0.6	71.3	0.6
94	32.0	34.9	−2.9	35.1	−3.1	35.0	−3.0
95	80.2	67.3	12.9	67.4	12.8	67.3	12.9
96	71.4	76.5	−5.1	76.5	−5.1	76.5	−5.1

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

All that remained to reach the targeted QRSTU maitotoxin segment **4** was removal of the protecting groups from intermediate **52a**. This task was easily accomplished through removal of the silyl groups (TBAF, 87% yield) and hydrogenolysis of the benzyl ethers [H_2, $Pd(OH)_2$ cat., 100% yield] of the latter intermediate, furnishing the much sought after QRSTU ring system **4**. The epimeric 85-*epi*-QRSTU ring system **5** was similarly generated from epimeric intermediate **52b** (TBAF, 92% yield; H_2, $Pd(OH)_2$ cat., 87% yield).

Comparison of the ^{13}C NMR Chemical Shifts of QRSTU Ring Systems 4, 5, and 6 with Those Corresponding to the Same Region of Maitotoxin. Having obtained maitotoxin diastereomeric fragments QRSTU (**4**), 85-*epi*-QRSTU (**5**) and 86-*epi*-QRSTU (**6**) through synthesis, we welcomed the opportunity to compare their ^{13}C NMR spectral data with those of the QRSTU domain of the natural product, as a means of securing further support for the originally assigned structure of the natural product.[27,28] Table 1 lists the ^{13}C NMR chemical shifts (δ, ppm) for these three QRSTU ring systems (i.e., **4**, **5** and **6**) together with those of the corresponding domain of natural maitotoxin [MTX (**1**)] and their differences ($\Delta\delta$, ppm).[3c] Figure 3 graphi-

(24) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.
(25) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989.
(26) For the use of $AgClO_4$-promoted cyclization of dithioketals to form *O,S*-ketal oxepanes followed by an oxidation/methylation procedure that gives similar diastereoselectivities, see: (a) Torikai, K.; Yari, H.; Murata, M.; Oishi, T. *Heterocycles* **2006**, *70*, 161. (b) Torikai, K.; Yari, H.; Mori, M.; Ujihara, S.; Matsumori, M.; Murata, M.; Oishi, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6355.
(27) Gallimore, A. R.; Spencer, J. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4406.
(28) Nicolaou, K. C.; Frederick, M. O. *Angew. Chem., Int. Ed.* **2007**, *46*, 5278.

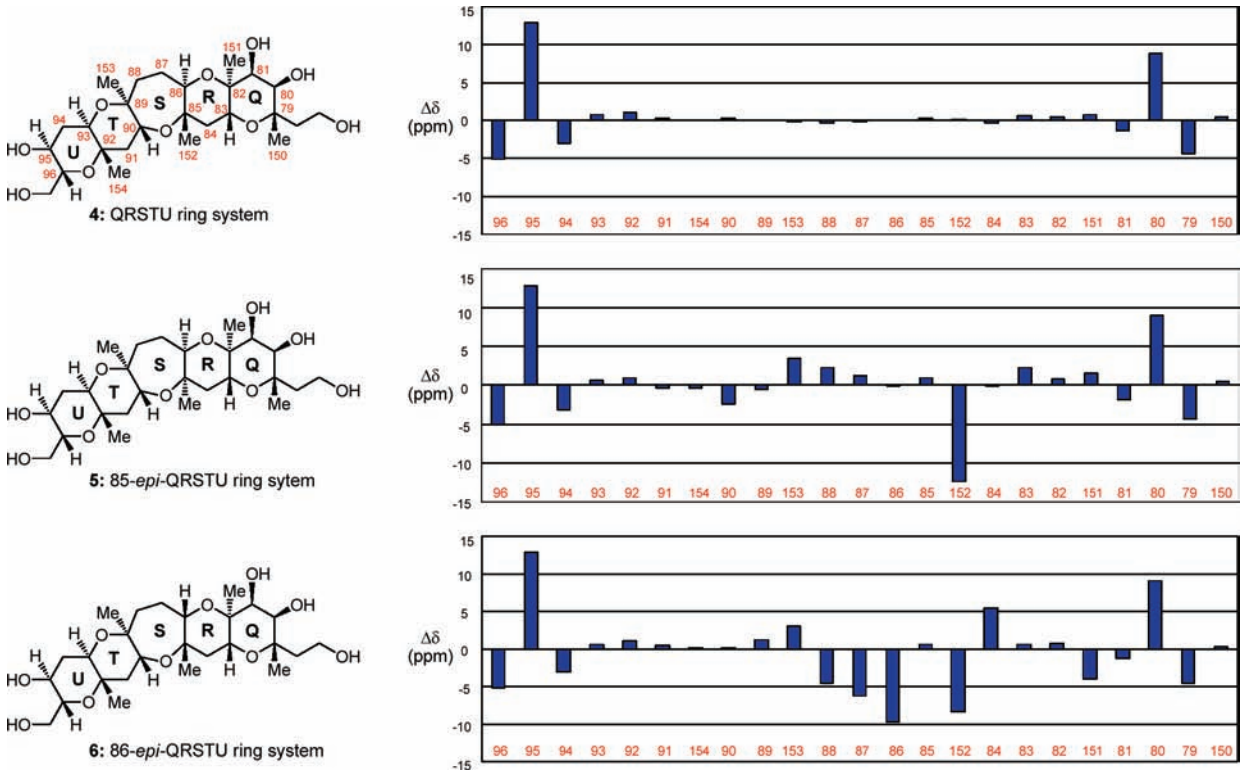


Figure 3. Graphically depicted ^{13}C chemical shift differences ($\Delta\delta$, ppm) for each carbon between C_{79} to C_{96} and C_{150} to C_{154} for maitotoxin (**1**) and QRSTU ring systems (**4**, top), 85-*epi*-QRSTU (**5**, middle), and 86-*epi*-QRSTU (**6**, bottom).

cally presents these differences for each diastereomeric structure (**4**, **5** and **6**) with maitotoxin (**1**) (carbons C_{79} to C_{96} and C_{150} to C_{154}). As seen from these graphs, the structure resembling maitotoxin the most is that of **4**, with the average difference ($\Delta\delta$) for carbons C_{81} to C_{94} and C_{150} to C_{154} being 0.54 ppm, and a maximum difference ($\Delta\delta$) for a given carbon being 2.9 ppm (C_{94}). The carbons at the two edges of the molecule (i.e., C_{79}, C_{80}, C_{95}, C_{96}) were excluded from the comparisons due to the rather drastic structural differences between their neighboring groups from those surrounding the same structural domain (i.e., QRSTU) of the natural product. In contrast, diastereoisomers **5** and **6** demonstrated significant variations from maitotoxin, with an average difference ($\Delta\delta$) of 1.9 ppm and 2.7 ppm, respectively, and maximum difference ($\Delta\delta$) for a given carbon of 12.3 ppm (C_{152}) and 9.7 ppm (C_{86}), respectively. Interestingly, the carbons exhibiting the maximum differences from the natural product are those residing either on (C_{86}) or adjacent (C_{152}) to the RS ring junction of these diastereoisomers. These findings provide compelling support for the correctness of the originally assigned structure of the QRSTU domain of maitotoxin as represented by QRSTU ring system **4** (Figure 3, top).

Conclusion

The described chemistry provided access to the QRSTU fragment **4** of maitotoxin (**1**) and its diastereoisomers 85-*epi*-QRSTU (**5**) and 86-*epi*-QRSTU (**6**) fragments for biological and chemical investigations. The unique synthetic challenge posed by this pentamethylated pentacycle was successfully met through a convergent strategy that relied on our previously developed hydroxy dithioketal cyclization methodology[10] to forge the oxepane ring of the molecule and install the final methyl group. Comparison of the ^{13}C NMR spectroscopic data of the synthesized QRSTU ring systems with those of maitotoxin led to further support for the originally assigned Yasumoto−Kishi−Tachibana structure of this most complex secondary metabolite.[2−6] Significantly, QRSTU ring system **4** and its precursors are appropriately functionalized at their two ends for further elaboration and coupling with suitably activated neighboring ring systems of maitotoxin for the purposes of constructing larger domains of the natural product.

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

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