An Olefin Metathesis Based Strategy for the Construction of the JKL, OPQ, and UVW Ring Systems of Maitotoxin

K. C. Nicolaou,* M. H. D. Postema, E. W. Yue, and A. Nadin

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

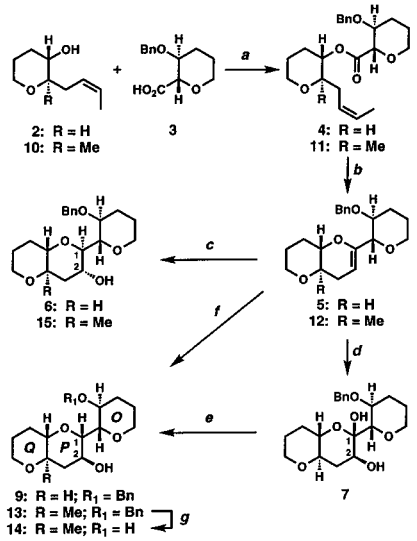
Received August 15, 1996

The structure of the most potent nonpeptidic substance known to man, the marine neurotoxin maitotoxin (**1**, Figure 1), has recently been elucidated.[1,2] Containing no less than 32 rings and 98 stereocenters, this structure presents an imposing challenge to synthetic chemistry and provides opportunities for invention and discovery both in chemistry and biology. Although considerably larger, this structure is reminiscent to that of brevetoxin B,[3] except for the carbon−carbon bonds bridging rings K and L, O and P, and V and W (see shaded areas, Figure 1). In this paper we wish to disclose the construction of these intriguing regions of maitotoxin (**1**) through application of our recently developed olefin metathesis[4] based strategy of cyclic ethers.[5] Specifically, we report the synthesis of the OPQ (**14**), UVW (**23**), and JKL (**29**) representing nine of maitotoxin's rings and 19 of its stereocenters (antipodal,[1] see Figure 1).

Our initial explorations of the olefin metathesis approach to these frameworks focused on the simplified OPQ ring system **9** (Scheme 1) lacking the methyl group at the PQ fusion. Thus, coupling of fragments **2**[6] and **3**[6] in the presence of 2-(chloromethyl)pyridinium iodide and 4-DMAP afforded ester **4**[7] (81%). Exposure of **4** to excess Tebbe reagent in THF, initially at 25 °C and then at reflux, led to cyclic enol ether **5** in 50% yield. Initial attempts to introduce the required hydroxyl group via hydroboration led predominantly to the wrong stereoisomer **6**[8] (epimeric at C-1 and C-2) with the desired product **9** being formed only as a minor component (**6**/**9** *ca*. 2:1, 93% combined yield). Attention was then turned to the Sharpless dihydroxylation[9] of **5** as a means to control the stereochemistry of the hydroxyl group at C-2, a reaction that led to some interesting observations: (a) while AD mix α gave exclusively compound **7** (95% yield) as expected, AD mix *β* led, unexpectedly, to a preponderance of the same isomer, **7**, [98% yield, *ca*, 13:1 ratio with its epimer **8** (see Scheme 2)] and (b) exposure of the minor isomer **8** to conditions similar to those of dihydroxylation reaction [K_2CO_3, $^tBuOH/H_2O$ (2:1), 25 °C] caused its complete isomerization to the desired isomer **7**. These observations can be explained by the mechanism shown in Scheme 2, by which the undesired isomer **8** is envisioned to undergo ring opening (to **16**), enolization (to **17**), and exclusive reclosure to the thermodynamically more stable isomer **7** (with both hydroxyl and pyran groups disposed equatorially in space, see box, Scheme 2). Dihydroxylation of **5** without a chiral ligand [OsO_4−NMO] gave **7** as the major product (**7**/**8** *ca*, 5:1). Reductive removal of the anomeric hydroxyl group from **7** (Scheme 1) was achieved with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$, affording the desired OPQ model system **9** (40% yield).[10]

Having established the viability of the metathesis approach to these systems, we then set out to assemble the three maitotoxin fragments OPQ (**14**, Scheme 1), UVW (**23**, Scheme 3), and JKL (**29**, Scheme 4). Construction of **14** began with olefinic compound **10**[11] and followed the sequence depicted in Scheme 1. In this instance, the ring closure of ester **11** proceeded via metathesis to afford cyclic system **12** in 54% yield, whereas hydroboration of the latter at −78 → 0 °C proved both efficient and stereoselective, furnishing **13** (78%) plus its C-1, C-2 stereoisomer (**15**, R = CH_3, 11%). Apparently, the

Scheme 1. Synthesis of OPQ Ring Systems **9** and **14**.[a]



[a] Reagents and conditions: (a) for **2** + **3** → **4**; 2-(chloromethyl)pyridinium iodide (1.5 equiv), Et_3N (3.0 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 3 h, 81%; for **10** + **3** → **11**, DCC (1.5 equiv), 4-DMAP (0.5 equiv), CH_2Cl_2, 25 °C, 3 h, 85%; (b) for **4** → **5**, Tebbe reagent (4.0 equiv), THF, 25 °C, 0.5 h, then Δ, 4 h, 50%; for **11** → **12**, same conditions as for **4** → **5**, 54%; (c) BH_3 (10 equiv), THF, 0 °C, 5 h, then 3 N NaOH (50 equiv), H_2O_2 (50 equiv), 93%; (d) AD mix α (2.0 equiv), $MeSO_2NH_2$ (3.0 equiv), *t*-BuOH−H_2O (1:1), 0 °C, 36 h, 98%; (e) Et_3SiH (3.0 equiv), $BF_3{\cdot}Et_2O$ (1.1 equiv), CH_2Cl_2, 0 °C, 2 h, 35%; (f) for **12** → **13**, BH_3 (10 equiv), THF, 0 °C, 4 h, then 3 N NaOH (50 equiv), H_2O_2 (50 equiv), 89%; (g) H_2, Pd/C (0.3 wt equiv), EtOH, 25 °C, 3 h, 91%. 4-DMAP = 4-(dimethylamino)pyridine; DCC = 1,3-dicyclohexylcarbodiimide; Tebbe reagent = $Cp_2TiCH_2ClAlMe_2$; THF = tetrahydrofuran.

(1) Just prior to submission of this work, the absolute configuration of maitotoxin was reassigned as that shown in Figure 1 which is opposite to the previously adopted[2] absolute stereochemistry and to that of the reported fragments OPQ (**14**), UVW (**23**), and JKL (**29**): (a) Sasaki, M.; Matsumori, N.; Maruyama, T.; Nonomura, T.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem.* **1996**, *108*, 1782. Nonomura, T.; Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem.* **1996**, *108*, 1786. (b) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946. We thank Professor Y. Kishi for a preprint of this article.

(2) (a) Murata, M.; Naoki, H.; Matsunaga, S.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1994**, *116*, 7098. (b) Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1995**, *36*, 9007. (c) Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 9011. (d) Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1994**, *35*, 5023.

(3) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773. (b) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855.

(4) (a) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (c) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634.

(5) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565.

(6) Compounds **2**, **3**, **24**, and **25** were synthesized from D-glucal as described in the Supporting Information.

(7) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials. All compounds are optically pure.

(8) Stereochemical assignments were made by 2-D NMR spectroscopy on the intermediates or the corresponding acetates.

(9) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483 and references cited therein.

(10) Overreduction of lactol **7** to a triol was a major side reaction.

(11) Compounds **10**, **18**, and **19** were synthesized from 1,4-butanediol as described in the Supporting Information.

S0002-7863(96)02862-4 CCC: $12.00

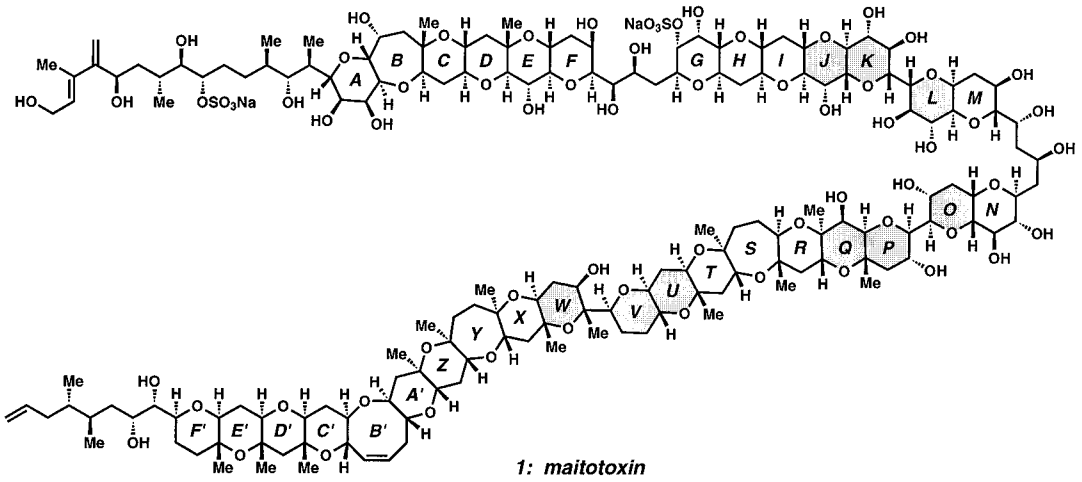
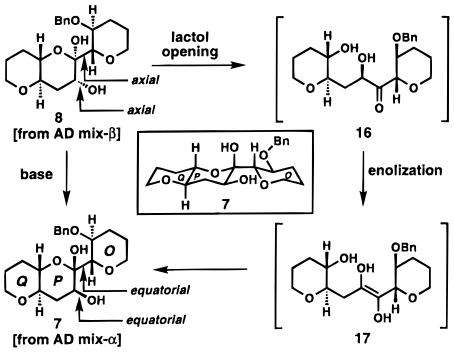
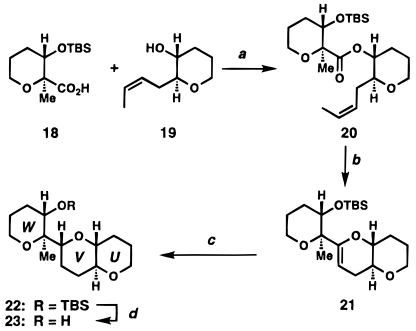


Figure 1. Structure of maitotoxin (**1**).

Scheme 2. Proposed Mechanism for the Isomerization of the OPQ Ring System (**8** → **7**)



Scheme 3. Synthesis of UVW Ring System **23**[a]



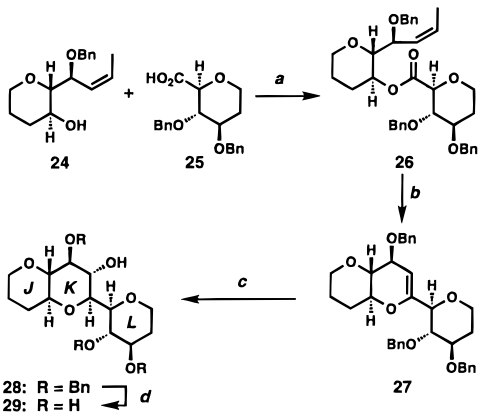
[a] Reagents and conditions: (a) DCC (1.5 equiv), 4-DMAP (0.5 equiv), CH_2Cl_2, 25 °C, 3 h, 93%; (b) Tebbe reagent (4.0 equiv), THF, 25 °C, 0.5 h, then Δ, 4 h, 36%; (c) TFA (1.5 equiv), Et_3SiH (3.0 equiv), CH_2Cl_2, 0 °C, 6 h, 80%; (d) TBAF (1.5 equiv), THF, 25 °C, 2 h, 91%. TFA = trifluoroacetic acid; TBAF = tetra-*n*-butylammonium fluoride.

methyl group in **12** directs the stereochemical outcome of the hydroboration reaction in favor of the desired isomer **13**. Hydrogenolysis of the benzyl ether in **13** gave, in 91% yield, the targeted OPQ ring system **14**.

The synthesis of the UVW system **23** is outlined in Scheme 3. Thus, DCC-mediated esterification of **18**[11] with **19**[11] furnished ester **20** (93%), which upon reaction with excess Tebbe reagent resulted in the formation of cyclic enol ether **21** in 36% yield. Exposure of **21** to Et_3SiH in the presence of CF_3COOH gave stereoselectively the saturated system **22** (80%), desilylation of which afforded the desired compound **23** (91%).

A sequence along similar lines (Scheme 4) resulted in the preparation of the JKL ring system **29**. Thus, coupling of **24**[6] with **25**[6] led to ester **26** (88% yield), whose olefination−metathesis (**26** → **27**) required the use of dimethyltitanocene[12,13] (20%, unoptimized).[14] Finally, stereoselective hydroboration of **27** led almost exclusively (>20:1 ratio) to the desired isomer

Scheme 4. Synthesis of JKL Ring System **29**[a]



[a] Reagents and conditions: (a) DCC (1.5 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 3 h, 88%; (b) Cp_2TiMe_2 (10 equiv), THF, Δ, 12 h, 20%; (c) BH_3 (10 equiv), THF, 0 °C, 2 h, then 3 N NaOH (50 equiv), H_2O_2 (50 equiv), 77% (4% of C-1, C-2 isomer); (d) H_2, Pd/C (0.4 wt equiv), EtOH, 25 °C, 6 h, 98%.

28 (77%), deprotection of which was achieved via hydrogenolysis, furnishing the targeted JKL ring framework **29** (98%).

Through this chemistry, the ester−olefin metathesis reaction has proven itself as a powerful strategy for rapid construction of complex cyclic polyether frameworks.[15] Specifically, this methodology appears to offer a potential solution[16] to the assembly of maitotoxin's JKL, OPQ, and UVW regions and, together with our previous work[17] on brevetoxin B, may even provide a possible synthetic pathway to maitotoxin (**1**) itself.

Acknowledgment. We thank Drs. Dee H. Huang and Gary Siuzdak for their NMR and mass spectroscopy assistance, respectively. Financial support provided by the National Institutes of Health (USA), the NSERC (MHDP), The Skaggs Institute of Chemical Biology, Merck, DuPont-Merck, Pfizer, Hoffmann La-Roche, and Amgen.

Supporting Information Available: Schemes for the synthesis of compounds **2**, **3**, **10**, **18**, **19**, **24**, and **25** and listing of selected data for compounds **11**−**14**, **20**−**23**, and **26**−**29** (17 pages). See any current masthead page for ordering and access instructions.

JA962862Z

(12) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(13) Klauss, K.; Bestian, H. *Justus Liebigs Ann. Chem.* **1962**, *654*, 8.
(14) The use of Tebbe reagent gave only unidentified decomposition products. It was assumed that enol ether **27** was unstable to the Lewis acidic reaction conditions.[4a,5]
(15) For a recent review on this topic, see: Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, D. D. *Chem. Rev.* **1995**, *95*, 1953.
(16) For a palladium-mediated approach to these systems, see: Nicolaou, K. C.; Sato, M.; Miller, N. D.; Gunzner, J. L.; Renaud, J.; Untersteller, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 889.
(17) For reviews, see: (a) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 588. (b) Nicolaou, K. C. *Aldrichimica Acta* **1993**, *26*, 62.