Pergamon

Tetrahedron Letters, Vol. 35, No. 28, pp. 5023-5026, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01016-1

Synthesis and Stereochemical Confirmation of the *cis*-Fused L/M and N/O Ring Systems of Maitotoxin

Makoto Sasaki, Taro Nonomura, Michio Murata, and Kazuo Tachibana*

Department of Chemistry, School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract: Stereocontrolled synthesis of *cis*-fused 1,6-dioxadecalin system **1**, which corresponds to the L/M and N/O rings of maitotoxin, was accomplished. Comparison of its ^{1}H and ^{13}C NMR data with those of the natural toxin established the earlier stereochemical assignments.

Maitotoxin (MTX), with its molecular weight of 3422 Da, is one of the toxic principles of ciguatera food poisoning[1] and the most potent toxin except for a few proteins (LD_{50} 50 ng/kg, mouse, ip).[2] Recently, the full structure of MTX was elucidated to be a polyether containing 32 ether rings, and 28 hydroxyl and two sulfate groups, on the basis of extensive 2D NMR measurements and collisionally activated dissociation (CAD) MS/MS experiments on the whole MTX molecule and its degradation products (Figure 1).[2] The toxin molecule consists of both polycyclic ethers, most of which are *trans*-fused as is the case with brevetoxins[3] and ciguatoxins,[4] and acyclic portions like palytoxin.[5] A remarkable structural feature is the unconventional presence of two sets of *cis*-fused ether rings (rings L/M and N/O) in the middle region of the molecule. In this communication, we wish to report a stereoselective synthesis of the *cis*-fused 1,6-dioxadecalin system **1** which corresponds to both the L/M and N/O ring systems of MTX, and consequent confirmation of the exceptional stereochemical assignments for these *cis*-fused cyclic ethers (Figure 2).

Our synthesis of the bicyclic compound **1** started with methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **2**,[6] utilizing the obvious structural similarity with the L and N rings of MTX, and adopted as a key step the 6-endo selective epoxide opening with simultaneous ring closure reaction developed by Nicolaou *et al.*[7] Many applications of the method for the construction of tetrahydropyran systems have been reported;[8] however, cyclization of *trans*-epoxide with the preexisting *cis*-substitution on the 6-membered ring was not investigated.

Routine protecting group manipulations allowed the transformation of **2** into the allyl ether **3** in three steps (71% overall yield; Scheme I). *C*-Glycosidation[9] of the allyl ether **3** provided the expected axially substituted product **4** along with a minute amount of the corresponding β-isomer in 79% total yield in a ratio of 98:2.[10] Selective cleavage of the allyl ether was achieved with hydridotetrakis(triphenylphosphine)rhodium and trifluoroacetic acid in refluxing ethanol,[11] and alcohol **5** was obtained after chromatographic separation as a pure form in 65% yield. The alcohol **5** was protected as its *t*-butyldimethylsilyl (TBS) ether **6** in quantitative yield.

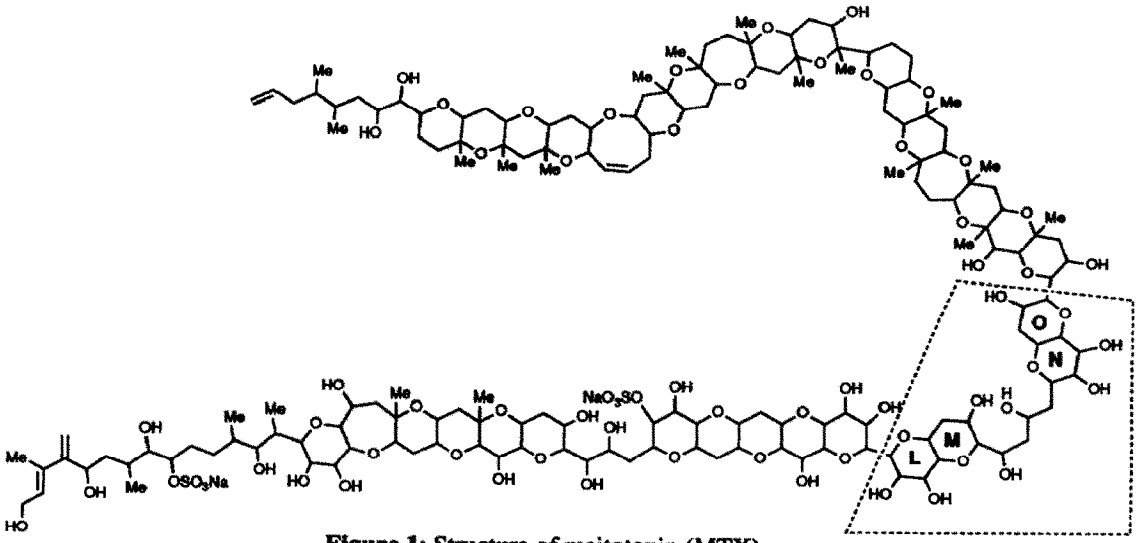


Figure 1: Structure of maitotoxin (MTX)

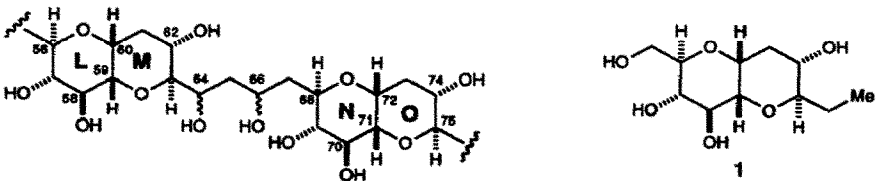


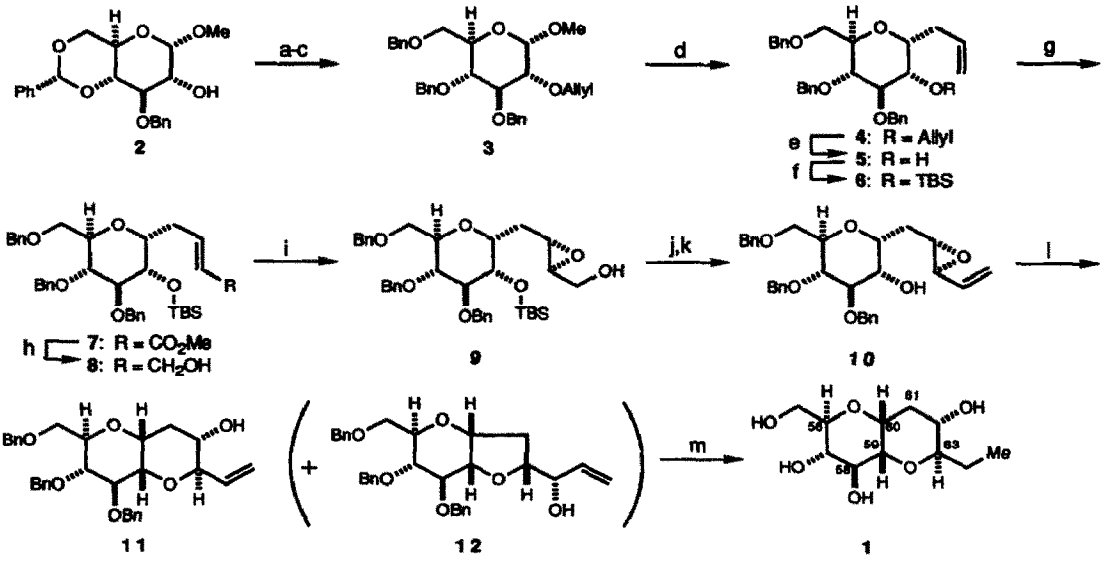
Figure 2

Ozonolysis of the terminal olefin of **6** followed by Wittig olefination using methyl (triphenylphosphoranylidene)acetate provided *trans*-α,β-unsaturated ester **7** in 60% overall yield. Diisobutylaluminum hydride (DIBAL) reduction of **7** provided allylic alcohol **8** in 90% yield, which was subjected to Katsuki-Sharpless asymmetric epoxidation using (+)-diethyl tartarate[12] to afford epoxy alcohol **9** in 92% yield. Oxidation of the primary hydroxyl of **9** to the aldehyde with SO_3·pyridine followed by Wittig methylenation (92% overall yield) and deprotection of the silyl group provided epoxy alcohol **10** in 98% yield, setting the stage for the crucial acid-catalyzed cyclization. Treatment of **10** with 0.1 equiv of camphorsulfonic acid in dichloromethane at -20 °C to room temperature for 4 h gave rise to *cis*-fused 1,6-dioxadecalin **11**[13,14] in 75% yield along with undesired tetrahydrofuran **12**[15] (5% yield). Finally, hydrogenolysis/hydrogenation of **11** was carried out on Pearlman's catalyst to yield tetraol **1**. The coupling constant $J_{59,60}$ of 5.8 Hz and NOEs between 56-H/61-H, 58-H/63-H, and 59-H/60-H observed for **1** are consistent with the assigned *cis*-fused 1,6-dioxadecalin skeleton.

Examination of the chemical shifts in the ^1H and ^{13}C NMR spectra of **1** thus obtained showed that the observed NMR data matched well with those of MTX (Table I). Especially, the ^1H and ^{13}C NMR signals around the ring-fusion, namely, C58(70)-C61(73), of **1** correspond extremely well to those of MTX. Moreover, the coupling constants $J_{56(68),57(69)}$, $J_{57(69),58(70)}$, $J_{61(73),62(74)}$, and $J_{62(74),63(75)}$ of **1** agreed well with those of MTX. Thus, the formerly proposed *cis*-fused L/M and N/O ring systems of MTX[2] were

confirmed to be represented by structure **1**. Further synthetic approaches toward determination of the relative stereochemistry at the C64 and C66 positions of MTX (Figure 2) are currently in progress.

Scheme I[a]



[a]**Reagents and conditions:** (a) NaH, CH_2=$CHCH_2Br$, THF-DMF, rt, 84%; (b) *p*-TsOH, MeOH-CH_2Cl_2, rt, quant.; (c) NaH, BnBr, THF-DMF, 0 °C to rt, 84%; (d) CH_2=$CHCH_2TMS$, TMSOTf, CH_3CN, rt, 79%; (e) $(Ph_3P)_4RhH$, CF_3CO_2H, EtOH, reflux, 45 min, 65%; (f) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0 °C, quant.; (g) (1) O_3, MeOH, -78 °C then Me_2S, rt; (2) Ph_3P=$CHCO_2Me$, PhH, 50 °C, 60%; (h) DIBAL, CH_2Cl_2, -78 °C, 90%; (i) *t*-BuOOH, (+)-DET, $Ti(O$*i*$-Pr)_4$, 4Å molecular sieves, CH_2Cl_2, -25 °C, 92%; (j) (1) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (2) $Ph_3P^+CH_3Br^-$, KHMDS, THF, 0 °C to rt, 92%; (k) *n*-Bu_4NF, THF, rt, 98%; (l) camphorsulfonic acid, CH_2Cl_2, -20 °C to rt, **11**: 75%, **12**: 5%; (m) H_2, $Pd(OH)_2$/C, MeOH, rt, 97%.

Table I. Selected ^1H and ^{13}C NMR data of **1** and MTX.[a]

1			**MTX**					
position	δ_H (pattern)	δ_C	position	δ_H (pattern)[b]	δ_C	position	δ_H (pattern)[b]	δ_C
56 (68)	3.47 (ddd, 9.8, 5.4, 2.2)	74.3	56	3.69 (d, 9.5)	70.6	68	3.64 (-)	70.7
57 (69)	3.20 (dd, 9.8, 9.3)	71.4	57	3.50 (t, 9)	70.3	69	3.06 (t, 8.5)	75.4
58 (70)	3.98 (dd, 10.9, 9.3)	68.4	58	3.98 (t, 9)	68.8	70	3.95 (t, 9)	68.5
59 (71)	3.56 (dd, 10.9, 5.8)	75.2	59	3.62 (dd, 8.5)	75.2	71	3.64 (-)	75.9
60 (72)	3.99 (ddd, 12.0, 5.8, 4.8)	70.9	60	4.01 (-)	71.2	72	3.97 (-)	71.0
61 (73)	1.93 (ddd, 11.5, 4.8, 4.6)	32.7	61	1.97 (-)	32.4	73	2.02 (-)	32.8
	1.81 (ddd, 12.0, 11.5, 10.6)			1.83 (q, 11.5)			1.91 (q, 11.5)	
62 (74)	3.30 (ddd, 10.6, 9.7, 4.6)	69.1	62	3.65 (-)	65.8	74	3.73 (-)	64.7
63 (75)	3.21 (ddd, 9.7, 7.4, 2.8)	75.5	63	3.15 (d, 9)	76.5	75	3.50 (d, 10)	71.5

a) The spectra were all measured in CD_3CN-D_2O (1:1).
b) The coupling constants were estimated by cross peaks shown in the NOESY or the high-resolution COSY spectra.

References and Notes

1. Yasumoto, T.; Bagnis, R.; Vernoux, J. P. *Bull. Jpn. Sci. Fish.* **1976**, *42*, 359.
2. (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.
3. (a) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J. C.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773. (b) Shimizu, Y.; Chou, H.-N.; Bando, H.; Duyne, G. V.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514.
4. (a) Murata, M.; Legrand, A.-M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380. (b) Lewis, R. J.; Sellin, M.; Poli, M. A.; Norton, R. S.; MacLeod, J. K.; Sheil, M. M. *Toxicon* **1991**, *29*, 1115. (c) Murata, M.; Legrand, A.-M.; Scheuer, P. J.; Yasumoto, T. *Tetrahedron Lett.* **1992**, *33*, 525. (d) Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1993**, *34*, 1975. (e) Lewis, R. J.; Norton, R. S.; Brereton, I. M.; Eccles, C. D. *Toxicon* **1993**, *31*, 637. (f) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.
5. (a) Uemura, D.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Tetrahedron Lett.* **1981**, *22*, 2781. (b) Moore, R. E.; Barolini, G. *J. Am. Chem. Soc.* **1981**, *103*, 2491. (c) Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, K. K.; Ko, S. S.; Leder, T.; McWhorter, Jr., W. W.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369.
6. Boons, G.-J.; Castle, G. H.; Case, J. A.; Grice, P.; Ley, S. V.; Pinel, C. *Synlett.* **1993**, 913.
7. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.
8. For example, see: (a) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558. (b) 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. (c) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517.
9. Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
10. The ratio was determined by HPLC analysis (YMC A024 SIL column, 10 x 300 mm; eluent, 1:10 ethyl acetate-hexane ; UV 254 nm; flow rate, 1 mL/min; t_R, **4**, 10.9 min; β-isomer, 8.7 min).
11. Ziegler, F. E.; Brown, E. G.; Sobolov, S. B. *J. Org. Chem.* **1990**, *55*, 3691.
12. Katsuki, T.; Sharpless, K. B.; *J. Am. Chem. Soc.* **1980**, *102*, 5976.
13. The numbering of compounds used in this paper corresponds to that of the L/M ring of MTX
14. Selected data for compound **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94 (1H, ddd, *J* = 12.3, 10.1, 9.0 Hz, 61-H), 2.06 (1H, ddd, *J* = 12.3, 5.5, 4.3 Hz, 61-H), 3.48 (1H, ddd, *J* = 9.0, 7.7, 4.3 Hz, 62-H), 3.63 (1H, dd, *J* = 9.0, 8.1 Hz, 57-H), 3.64 (1H, dd, *J* = 10.4, 2.3 Hz, 55-H), 3.70 (1H, dd, *J* = 10.4, 4.2 Hz, 55-H), 3.74 (1H, ddd, *J* = 9.1, 4.1, 2.3 Hz, 56-H), 3.89 (1H, brdd, *J* = 7.7, 6.3 Hz, 63-H), 4.00 (1H, dd, *J* = 8.1, 5.3 Hz, 59-H), 4.05 (1H, dd, *J* = 8.1, 8.1 Hz, 58-H), 4.13 (1H, ddd, *J* = 10.1, 5.5, 5.3 Hz, 60-H), 4.49 (1H, d, *J* = 12.2 Hz, C*H*$_2$Ph), 4.51 (1H, d, *J* = 11.0 Hz, C*H*$_2$Ph), 4.58 (1H, d, *J* = 12.1 Hz, C*H*$_2$Ph), 4.71 (1H, d, *J* = 11.2 Hz, C*H*$_2$Ph), 4.82 (1H, d, *J* = 10.9 Hz, C*H*$_2$Ph), 4.83 (1H, d, *J* = 11.2 Hz, C*H*$_2$Ph), 5.33 (1H, brd, *J* = 10.6 Hz, CH=C*H*$_2$), 5.36 (1H, brd, *J* = 17.5 Hz, CH=C*H*$_2$), 5.83 (1H, ddd, *J* = 17.3, 10.6, 6.3 Hz, C*H*=CH$_2$), 7.15-7.34 (15H, m, 3 x Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.2, 68.5, 68.9, 69.1, 72.7, 73.5, 73.8, 74.6, 76.88, 76.96, 77.4, 119.1, 127.67, 127.69, 127.85, 127.95, 128.35, 128.39, 138.0, 138.2, 138.3; FABMS m/z 539 $(M+Na)^+$.
15. The structure of compound **12** was confirmed by conversion to the corresponding acetate **13** under usual conditions. **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.97 (1H, ddd, *J* = 13.2, 8.6, 5.8 Hz, 61-H), 2.05 (3H, s, Ac), 2.12 (1H, ddd, *J* = 13.2, 6.8, 6.8 Hz, 61-H), 3.58-3.63 (3H, m, 55-H$_2$ and 57-H), 3.76 (1H, m, 56-H), 3.78 (1H, dd, *J* = 8.9, 5.7 Hz, 58-H), 3.95 (1H, dd, *J* = 5.8, 5.8 Hz, 59-H), 4.00 (1H, ddd, *J* = 8.6, 6.8, 4.8 Hz, 62-H), 4.44 (1H, d, *J* = 12.2 Hz, C*H*$_2$Ph), 4.45 (1H, d, *J* = 11.1 Hz, C*H*$_2$Ph), 4.52 (1H, d, *J* = 12.2 Hz, C*H*$_2$Ph), 4.62 (1H, ddd, *J* = 6.8, 5.8, 5.8 Hz, 60-H), 4.68 (1H, d, *J* = 11.7 Hz, C*H*$_2$Ph), 4.80 (1H, d, *J* = 11.1 Hz, C*H*$_2$Ph), 4.84 (1H, d, *J* = 11.7 Hz, C*H*$_2$Ph), 5.25 (1H, brd, *J* = 10.7 Hz, CH=C*H*$_2$), 5.30 (1H, brd, *J* = 17.3 Hz, CH=C*H*$_2$), 5.42 (1H, dd, *J* = 6.3, 4.8 Hz, 63-H), 5.82 (1H, ddd, *J* = 17.3, 10.7, 6.3 Hz, C*H*=CH$_2$); FABMS m/z 581 $(M+Na)^+$.

(*Received in Japan* 21 *April* 1994)