Pergamon

Tetrahedron Letters, Vol. 36, No. 49, pp. 9007-9010, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01972-3

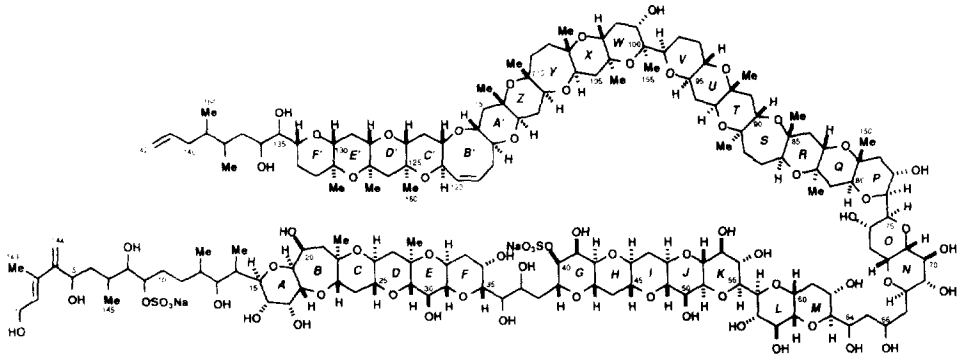
Synthetic Approach toward Complete Structure Determination of Maitotoxin. Stereochemical Assignment of the C63-C68 Acyclic Linkage

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. The relative configuration of carbons within the C63-C68 acyclic linkage of maitotoxin (MTX) was assigned by synthesis of stereodefined model compounds (**1a-1d**) and their comparison with MTX in ^{1}H and ^{13}C NMR spectra.

Maitotoxin (MTX), isolated from the dinoflagellate *Gambierdiscus toxicus*, is the most toxic and largest non-biopolymer known to date.[1,2] The toxin possesses a powerful ability to elevate the intracellular Ca^{2+} level of a wide range of cell types.[3] The gross chemical structure and stereochemistry of fused or directly connected ether rings were elucidated on the basis of extensive 2D/3D NMR measurements and negative FAB MS/MS experiments.[2] However, the relative configurations of the acyclic residues (C5-C15, C35-C39, C63-C68, and C134-C139) remained to be determined. Herein we report the relative configurations of the C63-C68 portion of MTX by comparison between stereodefined synthetic fragments and MTX in their NMR spectra.



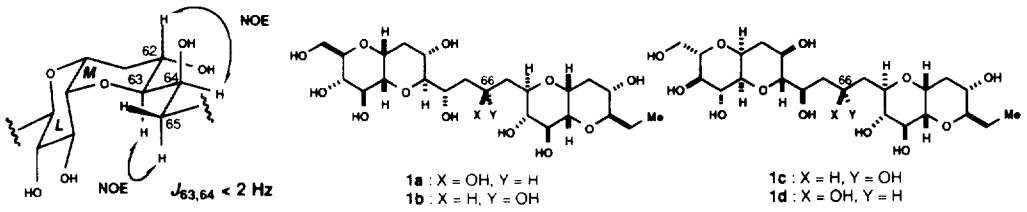
maitotoxin (MTX)

In order to realize this strategy of stereochemical determination, it was required to assume, and consequently shown, that the preferred conformation of an appropriately designed fragment with the natural

configuration in NMR solvent reflects that of the corresponding portion of MTX; the NMR characteristics of the fragment should therefore not significantly differ from those of the corresponding moiety of MTX.

We first attempted the stereochemical analysis of the acyclic region in question by the NOESY and Exclusive Correlation Spectroscopy (E.COSY)[4] of MTX in order to reduce the configurational candidates as targets of synthesis. Small coupling constant[5] between 63-H and 64-H and prominent NOEs between 62-H/64-H and 63-H/65-H allowed us to deduce the relative stereochemistry at the C63 and C64 positions as indicated in Figure 1; these NMR data suggested that carbon chain C61-C65 adopted the zigzag conformation with the orientation of hydrogen atoms being 1,2-*gauche* for 63-H/64-H. However, sever overlap of the cross peak signals prevented the detailed analysis for the C66-C68 portion of MTX, leaving the diastereomeric relations between C64/C66 and C66/C68 to be solved. Thus, we directed our effort to synthesize **1a**-**1d**, representing the four possible diastereomers at C56-C75 of MTX.[6]

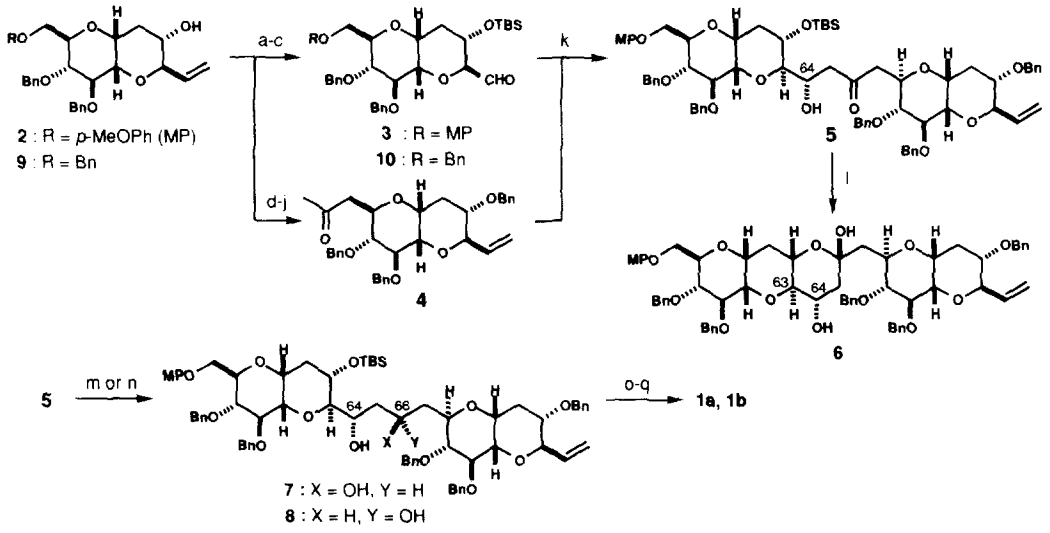
Figure 1



The synthesis of diastereomers **1a** and **1b** is summarized in Scheme 1. The C64-C65 bond[7] was constructed by an aldol coupling of aldehyde **3** and methyl ketone **4**, both prepared from a common bicyclic compound **2**.[8] Lithium enolate derived from **4** was reacted with **3** to provide, after chromatographic separation, the desired β-hydroxyketone **5** as the major adduct in 37% yield. The stereochemistry of the newly generated hydroxyl group at the C64 position was assigned by removal of the silyl group in **5** to provide hemiketal **6**, whose ^{1}H NMR data clearly showed the expected configuration at C64 ($J_{63,64}$ = 9 Hz). Reduction of **5** with Saksena-Evans reagent[9] led exclusively to the corresponding 64,66-*anti*-diol **7** in 97% yield, whereas 1,3-*syn*-selective reduction of **5** by the Narasaka-Prasad protocol[10] afforded 64,66-*syn*-diol **8** (51% yield).[11] Desilylation of **7** and **8** followed by oxidative cleavage of the *p*-methoxyphenyl (MP) group[12] and hydrogenolysis/hydrogenation furnished respective nonaols **1a** and **1b**. The remaining diastereomers **1c** and **1d** were prepared similarly starting from **4** and the antipode of **10**, which was derived from *ent*-**9**.[13]

As expected, all four diastereomers thus obtained showed different NMR profiles and only **1a** among these gave virtually identical ^{1}H and ^{13}C NMR data to those for the C63-C68 region of MTX (Table 1).[14] As seen from these data, the change in diastereomerism through a methylene affects the δ_C values significantly; the δ_C differences between MTX and any of **1b**-**1d** exceeded 0.5 ppm for the most carbons and 1 ppm for at least one. These results not only allowed for the configurational assignment of the C63-C68 region of MTX as depicted in **1a**, but also validated our first assumption on the conformational identity between MTX and its fragment.

Scheme 1[a]



[a]Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt; (b) OsO_4, NMO, THF-H_2O, rt, 87% (two steps); (c) $NaIO_4$, THF-H_2O, rt; (d) NaH, BnBr, THF-DMF, rt, 98%; (e) CAN, CH_3CN-H_2O, rt, 89%; (f) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 92%; (g) NaCN, DMSO, 70 °C, 92%; (h) DIBALH, CH_2Cl_2, -78 °C; (i) MeMgBr, THF, -30 °C, 54% (two steps); (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt, quant; (k) **4**, LDA, THF, -78°C, then **3**, 37%; (l) TBAF, THF, rt, quant; (m) $Me_4NBH(OAc)_3$, CH_3CN-AcOH, 0 °C to rt, 97%; (n) $NaBH_4$, Et_2BOMe, THF-MeOH, -78 ° to 0 °C, 51%; (o) TBAF, THF, rt, (p) CAN, CH_3CN-H_2O, (q) H_2, $Pd(OH)_2$/C, MeOH, **1a**, 69% (three steps), **1b**, 92% (three steps).

Table 1. ^1H and ^{13}C NMR chemical shifts of C63-C68 regions in MTX and **1a-1d**.[a]

	MTX		1a		1b		1c		1d	
position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
63	3.15	76.5	3.15	76.4	3.22	75.2	3.16	76.3	3.20	75.2
64	4.02	66.4	4.02	66.2	4.02	67.2	4.01	66.1	4.00	67.1
65	1.49	41.8	1.50	41.9	1.66	39.9	1.44	40.6	1.70	41.3
	1.72		1.72		1.72		1.79		1.70	
66	3.85	65.7	3.85	65.7	3.91	68.5	3.90	67.2	3.83	66.4
67	1.40	40.5	1.42	40.3	1.53	39.5	1.55	40.2	1.44	39.8
	1.85		1.85		1.91		1.88		1.84	
68	3.64	70.7	3.63	70.7	3.57	72.0	3.54	71.9	3.62	70.7

a) The spectra were all measured in CD_3CN-D_2O (1:1).

Acknowledgment: We are grateful for Professor Takeshi Yasumoto, Tohoku University, for valuable discussions. This work was supported in part by Grant-in-Aid from the Ministry of Education, Science, and Culture of Japan.

References and Notes

1. (a) Yokoyama, A.; Murata, M.; Oshima, Y.; Iwashita, T.; Yasumoto, T. *J. Biochem.* **1988**, *104*, 184-187. (b) Murata, M.; Iwashita, T.; Yokoyama, A.; Sasaki, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1992**, *114*, 6594-6596.
2. (a) Murata, M.; Naoki, H.; Iwashita, T.; Matsunaga, S.; Sasaki, M.; Yokoyama, A.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 2060-2062. (b) Murata, M.; Naoki, H.; Matsunaga, S.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1994**, *116*, 7089-7107. (c) Satake, M.; Ishida, S.; Yasumoto, T.; Murata, M.; Utsumi, H.; Hinomoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 7019-7020.
3. Takahashi, M.; Ohizumi, Y.; Yasumoto, T. *J. Biol. Chem.* **1982**, *257*, 7287-7289.
4. Griesinger, C.; Sørensen, W.; Ernst, R. R. *J. Magn. Reson.* **1987**, *75*, 474-492.
5. Coupling constants were estimated from cross peaks in the NOESY and E.COSY spectra of MTX.
6. A model system was previously synthesized to confirm relative configurations within the *cis*-fused L/M and N/O rings: Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1994**, *35*, 5023-5026.
7. The numbering of compounds in this paper corresponds to that of MTX.
8. Compound **2** was prepared in 19 steps from 1,2,5,6-diisopropylidene-α-D-glucose as previously reported[6] with some modifications: (1) NaH, BnBr, THF-DMF, quant.; (2) HCl, MeOH; (3) $PhCH(OMe)_2$, TsOH, CH_2Cl_2, 66% (two steps); (4) NaH, AllylBr, THF-DMF, 84%; (5) TsOH, MeOH-CH_2Cl_2, quant.; (6) *p*-MeOPhOH, DEAD, Ph_3P, THF, 85%; (7) NaH, BnBr, THF-DMF, 95%; (8) CH_2=$CHCH_2TMS$, TMSOTf, CH_3CN, 72%; (9) $HRh(PPh_3)_4$, TFA, EtOH, 91%; (10) TBSOTf, 2,6-lutidine, CH_2Cl_2, quant.; (11) OsO_4, NMO, THF-H_2O; (12) $NaIO_4$, THF-H_2O; (13) Ph_3P=$CHCO_2Me$, PhH, 87% (three steps); (14) DIBALH, CH_2Cl_2, 93%; (15) *t*-BuOOH, $Ti(O\textit{i}\text{-}Pr)_4$, (+)-DET, 4Å MS, CH_2Cl_2, 93%; (16) SO_3·Pyr, Et_3N, DMSO-CH_2Cl_2, (17) Ph_3P=CH_2, THF, 89% (two steps); (18) TBAF, THF, 95%; (19) CSA, CH_2Cl_2, 72%.
9. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578.
10. (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233-2238. (b) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155-158.
11. The stereochemistry of 1,3-*syn*-diol **8** was unambiguously established by conversion to the corresponding acetonide. Selected ^1H NMR data ($CDCl_3$, 500 MHz) of acetonide of **8**: $J_{64,65eq}$ = 3, $J_{64,65ax}$ = 12, $J_{65eq,66}$ = 3, and $J_{65ax,66}$ = 12 Hz.
12. (a) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291-6294. (b) Petitou, M.; Duchaussoy, P.; Choay, J. *Tetrahedron Lett.* **1988**, *29*, 1389-1392.
13. *Ent*-**9** was synthesized from L-glucose according to the previously reported method.[6]
14. $^3J_{H,H}$ data of the C63-C68 portion of **1a** in CD_3CN-D_2O (1:1): $J_{63,64}$ = 0.9, $J_{64,65a}$ = 4.1, $J_{64,65b}$ = 10.2, $J_{65a,66}$ = 10.2, $J_{65b,66}$ = 3.3, $J_{66,67a}$ = 9.3, $J_{66,67b}$ = 3.1, $J_{67a,68}$ = 3.1, and $J_{67b,68}$ = 9.2 Hz. These data suggested the carbon chain C63-C68 adopted the zigzag conformation.

(*Received in Japan* 13 *September* 1995; *accepted* 13 *October* 1995)