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Stereochemical Assignment of the C35-C39 Acyclic Linkage in Maitotoxin: Completion of Stereochemical Determination of C15-C134

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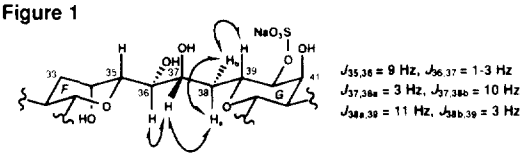
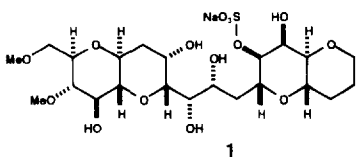
Abstract: The relative configuration of carbons within the C35-C39 acyclic linkage of maitotoxin (MTX) was assigned by synthesis of stereodefined model compound **1** and its comparison with MTX in ^{1}H and ^{13}C NMR spectra. This result completed stereochemical assignments of the whole molecule except for side chains.

In the preceding letter[1] we disclosed the relative configurations at the C63-C68 acyclic chain of maitotoxin (MTX), the largest and most toxic non-biopolymer known to date, by complementary use of organic synthesis and NMR spectroscopy. In this letter, we report determination of the relative stereochemistry at the C35-C39 residue of MTX using the similar but more simplified approach, and consequently connected stereochemical correlation from C15 through C134 of MTX.

Stereochemical analysis of the C35-C39 chain of MTX was carried out by the NOESY and E.COSY spectra of MTX. The relative magnitude of NOEs observed in the NOESY spectrum and $^{3}J_{H,H}$ data estimated from cross peaks in the NOESY and E.COSY spectra allowed us to deduce that the structure shown in Figure 1 as the most likely diastereomer; carbon chain C33-C41 adopted the zigzag conformation with the orientation of hydrogen atoms being 1,2-*anti* for 35-H/36-H, 1,2-*gauche* for 36-H/37-H, and as depicted for 37-H/38-H_2/39-H though the other diastereomers were not completely excluded. In order to confirm the assigned configurations, we chose a model compound **1** as the synthetic target corresponding to the C28-C46 of MTX.

Figure 1

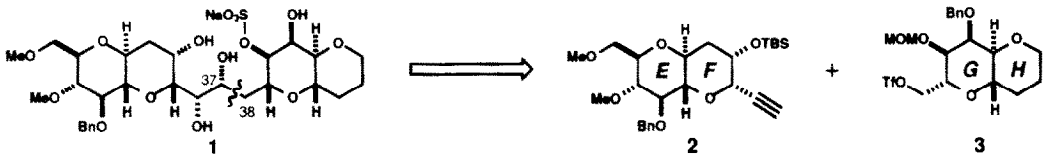




1

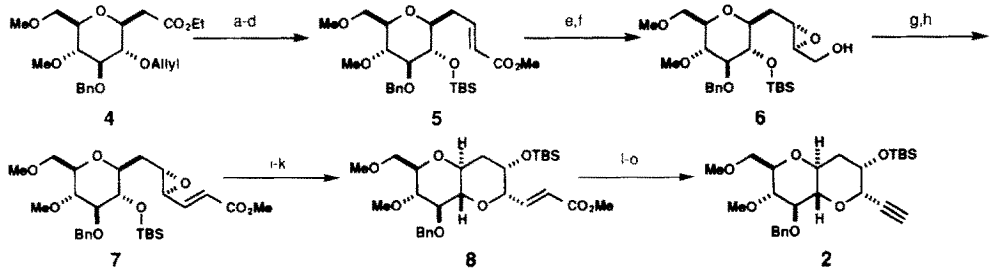
Retrosynthetic disconnection at the C37-C38[2] bond of **1** provides two fragments, the EF ring fragment **2** and the GH ring fragment **3** (Figure 2). Construction of the EF ring fragment **2** began with ester **4**[3] (Scheme 1). After replacement of the protective group in **4**, DIBALH reduction and Wittig elongation gave α,β-unsaturated ester **5** in high yield. DIBALH reduction of **5** to allylic alcohol and Sharpless asymmetric

Figure 2



epoxidation using (+)-DET as a chiral auxiliary afforded hydroxyl epoxide **6**. Oxidation of **6** and subsequent Wittig reaction gave γ,δ-epoxy-α,β-unsaturated ester **7**, which was subjected to palladium-mediated cyclization developed by Hirama *et al.*[4] Treatment of **7** with TBAF and then with catalytic amounts of $Pd(PPh_3)_4$ and Ph_3P in one-pot, followed by silylation, provided the desired α,β-unsaturated ester **8** in 72% overall yield. Oxidative cleavage of the double bond of **8** followed by olefination gave dibromoolefin (82%), which upon sequential treatment with NaHMDS and *n*-BuLi led to the desired acetylene **2** (73%).[5]

Scheme 1[a]



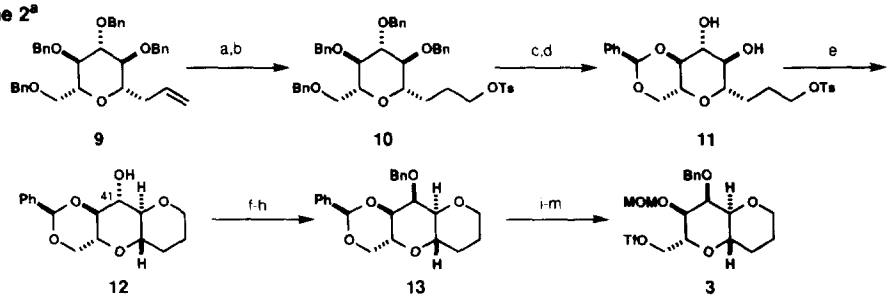
[a]Reagents and conditions: (a) $[Ir(COD)(Ph_2MeP)_2]PF_6$, THF, H_2, then I_2, H_2O, rt; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 93% (two steps); (c) DIBALH CH_2Cl_2, -78 °C; (d) $Ph_3P{=}CHCO_2Me$, PhH, rt, 97% (two steps); (e) DIBALH, CH_2Cl_2, -78 °C, 92%; (f) *t*-BuOOH, (+)-DET, $Ti(O\text{-}iPr)_4$, 4Å MS, CH_2Cl_2, -20 °C, quant.; (g) SO_3·Pyr, DMSO, Et_3N, CH_2Cl_2, 0 °C; (h) $Ph_3P{=}CHCO_2Me$, PhH, rt, 87% (two steps); (i) TBAF, THF, rt; (j) $Pd(PPh_3)_4$, Ph_3P, CH_2Cl_2, rt; (k) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 72% (three steps); (l) OsO_4, NMO, acetone-H_2O, rt; (m) $NaIO_4$, THF-H_2O, rt; (n) CBr_4, Ph_3P, CH_2Cl_2, 0 °C, 82% (three steps); (o) NaHMDS, *n*-BuLi, THF, -78 °C, 73%.

The synthesis of the GH ring fragment **3** is summarized in Scheme 2. Hydroboration of the known *C*-allyl tetra-*O*-benzyl-β-D-glucoside **9**[6] using 9-BBN was followed by tosylation to give **10**. Removal of the benzyl groups of **10** and subsequent protection of the resulting tetraol as its benzylidene acetal provided **11**. Exposure of **11** to KH in THF led to the formation of the ring H in 90% yield. Inversion at the C41 of **12** by an oxidation-reduction sequence gave compound **13** after benzylation, which was then converted to the fragment **3** in a straightforward way.

Lithium anion generated from **2** was reacted with triflate ester **3**, furnishing the desired alkyne **14** in 70% yield (Scheme 3).[7] Desilylation and Red-Al® reduction[8] of the resulting homopropargyl alcohol, followed by benzylation, furnished *E*-olefin **15** ($J_{36\text{-}H,37\text{-}H}$ = 16 Hz) in 29% over three steps. Osmylation of **15** followed by benzylation yielded an approximately 5:1 diastereomeric mixture with **16** being the major product (94% yield) as predicted by the empirical rule developed by Cha *et al.*[9] The stereochemistry of **16** was eventually established unambiguously on the basis of the long-range carbon-proton coupling constants ($^{2,3}J_{C,H}$) and $^3J_{H,H}$ data of **1**.[10]

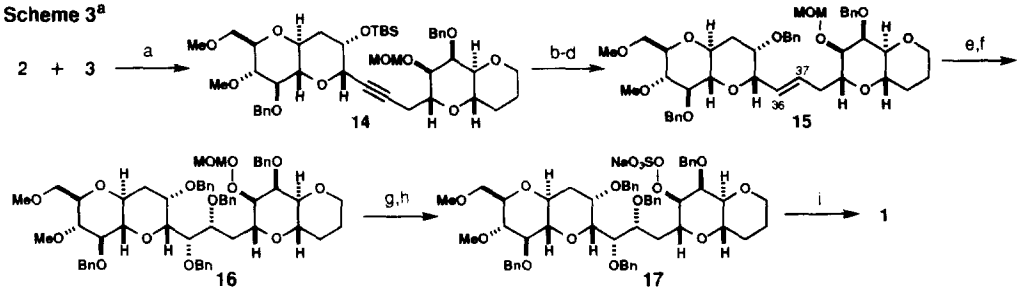
Removal of the MOM group in **16** with TMSBr[11] provided alcohol, which was converted to the sodium sulfate **17**, by exposure to SO_3·NMe_3 complex in pyridine and exchange of the counterion.[12] Finally, debenzylation of **17** gave the targeted sulfate **1**.[13]

Scheme 2[a]



[a]Reagents and conditions: (a) 9-BBN, THF, rt, then 3M NaOH, 30% H_2O_2, rt; (b) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 84% (two steps); (c) H_2, $Pd(OH)_2$/C, EtOAc-MeOH, rt; (d) $PhCH(OMe)_2$, *p*-TsOH, CH_2Cl_2-DMF, rt, 87% (two steps); (e) KH, THF, rt, 90%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt; (g) L-Selectride, CH_2Cl_2, -78 °C, quant. (two steps); (h) NaH, BnBr, TBAI, DMF, 94%; (i) *p*-TsOH, CH_2Cl_2-MeOH, rt, qu (j) MMTrCl, *i*-Pr_2NEt, CH_2Cl_2, rt, quant.; (k) NaH, MOMCl, DMF, rt; (l) PPTS, CH_2Cl_2-MeOH, 89% (two steps); (m) Tf_2O, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, -20 °C, 94%.

Scheme 3[a]



[a]Reagents and conditions: (a) **2**, *n*-BuLi, THF-HMPA, -78 °C, then **3**, 70%; (b) TBAF, THF, rt; (c) Red-Al®, Et_2O, rt; (d) NaH, BnBr, TBAI, DMF, 29% (three steps); (e) OsO_4, NMO, acetone-H_2O, rt, 94% (ca. 5:1); (f) NaH, BnBr, TBAI, DMF, rt, 75%; (g) TMSBr, CH_2Cl_2, 4Å MS, -20 °C, 94 (h) SO_3·NMe_3, pyridine, rt, 50%; (i) H_2, $Pd(OH)_2$/C, MeOH, 48%.

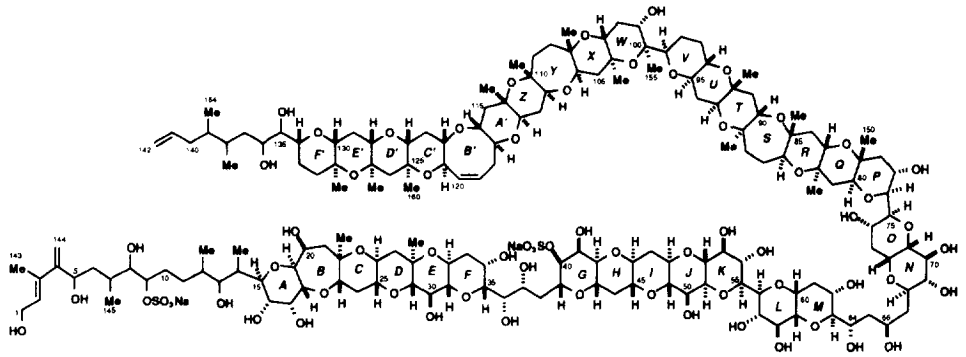
Comparing the ^1H and ^{13}C NMR data of **1** with those of MTX, the observed chemical shifts and $^3J_{H,H}$ data of **1** in the acyclic region in question matched extremely well with those of MTX (Table 1). Considering the difference observed among the NMR data for the diastereomers at the C63-C68 region,[1] we could confirm the above proposed relative stereochemical assignment for the C35-C39 portion as shown in Figure 1.

Table 1. ^1H and ^{13}C data[a] of C35-C39 regions in MTX and **1**.

	MTX		1	
position	δ_H	δ_C	δ_H (*J*)	δ_C
35	3.65	81.0	3.64 (dd, 8.9, 1.4)	80.4
36	3.96	73.1	3.93 (dd, 8.9, 1.8)	72.9
37	4.50	67.3	4.47 (ddd, 11.0, 2.7, 1.8)	67.5
38	1.68	37.4	1.68 (ddd, 13.6, 9.6, 2.7)	37.3
	2.69		2.64 (brdd, 13.6, 11.0)	
39	4.32	72.3	4.29 (m)	71.9

[a]The spectra were all measured in CD_3OD-C_5D_5N (1:1).

Since the stereochemical correlations for the other acyclic linkages such as rings K/L, O/P, and V/W have been revealed on the basis of NMR data with the aid of molecular mechanics calculations,[14] the present result, together with the preceding one,[1] completed the relative stereochemistry from C15 to C134 of MTX, covering all the junctions between the cyclic structures. Further spectroscopic and synthetic studies toward the complete absolute configuration of MTX are currently in progress and will be reported in due course.



Complete Stereochemical Assignments of C15-C134 in maitotoxin

Acknowledgment: This work was supported in part by Grant-in-Aid from the Ministry of Education, Science, and Culture of Japan.

References and Notes

1. Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron Lett.*, preceding paper in this issue.
2. The numbering of compounds in this paper corresponds to that of maitotoxin.
3. Compound **4** was prepared from 1,2,5,6-diisopropylidene-α-D-glucose in ten steps: (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) NaH, MeI, DMF, 97%; (7) HCl, AcOH, 57%; (8) Swern oxidation; (9) $LiCH_2CO_2Et$, THF; (10) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_3CN, 87% (three steps).
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10. Selected $^3J_{H,H}$ and $^{2,3}J_{C,H}$ of **1**: ^3J(37-H, 38-H_a) = 2.7, ^3J(37-H, 38-H_b) = 11.0, ^3J(38-H_a, 39-H) = 9.6 , ^3J(38-H_b, 39-H) = 1.2, ^2J(C-37, 38-H_a) = -1, ^2J(C-37, 38-H_b) = -6, ^3J(C39, 38-H_a) = -7, and ^3J(C-39, 38-H_b) = -1 Hz. $^{2,3}J_{C,H}$ data were obtained by the hetero half-filtered TOCSY (HETLOC) spectrum. The dihedral angle dependency of long-range carbon-proton coupling constants ($^{2,3}J_{C,H}$), coupled with that of $^3J_{H,H}$ data, allowed for the unambiguous determination of the relative configuration and conformation of the acyclic compounds: Matsumori, N.; Murata, M.; Tachibana, K. *Tetrahedron*, in press. For HETLOC, see: (a) Otting, G.; Wuthrich, K. *Quart. Rev. Biophys.* **1990**, *23*, 39-96. (b) Kurz, M.; Schmieder, P.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1329-1331. (c) Wollborn, U.; Willker, W.; Leibfritz, D. *J. Magn. Reson. Ser. A.* **1993**, *103*, 86-89.
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12. At this stage, the undesired diastereomer, produced in the OsO_4 oxidation, was separated by SiO_2 column chromatography.
13. Under these conditions, desulfation occurred and the corresponding pentaol was obtained in 47% yield.
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