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Synthesis of the WXYZA′ Domain of Maitotoxin

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Abstract: A synthesis of the WXYZA′ domain (**7**) of the marine neurotoxin maitotoxin (**1**) is reported. The convergent synthetic strategy involves construction of key building blocks **11** and **12**, their coupling, and the elaboration of the resulting ester (**10**) to the target molecule through a ring-closing metathesis and a hydroxy dithioketal cyclization as the key steps. For the construction of fragment **11**, the Noyori reduction/Achmatowicz rearrangement and hydroxy epoxide opening technologies were applied (starting from furfuryl alcohol (**13**)), whereas for the synthesis of fragment **12**, a carbohydrate-based approach was adopted (starting from 2-deoxy-D-ribose (**14**)). The synthesized WXYZA′ domain (**7**) of maitotoxin (**1**) exhibited the expected ^{13}C NMR chemical shifts, supporting the originally assigned structure of the corresponding region of the natural product.

1. Introduction

In a preceding article,[1] we described the synthesis of the C′D′E′F′ fragment **6** (Figure 1) of maitotoxin (**1**, Figure 1), the largest and most toxic secondary metabolite ever isolated and characterized.[2,3] Herein, we report the construction of the WXYZA′ domain[4] **7** (Figure 1) of this molecule and confirm its original stereochemical assignment[3] through ^{13}C NMR comparison with the natural product. With this accomplishment, all the major domains of maitotoxin (**1**) have now been synthesized, including fragments **2**,[5] **3**,[6] **4**,[7] **5**,[8] **6**,[1] and **7** (present work) (Figure 1).

2. Results and Discussion

2.1. Retrosynthetic Analysis. The synthesis of the targeted WXYZA′ domain (**7**) of maitotoxin is complicated by the presence of the seven-membered ring and the 5 methyl groups on the periphery of its pentacyclic framework, not to mention its 12 stereogenic centers. Driven by our desire to devise a convergent synthetic strategy toward the targeted maitotoxin domain **7**, we disassembled the molecule retrosynthetically, as shown in Figure 2. Thus, disconnection at the indicated carbon−oxygen bond of **7** through a hydroxy dithioketal cyclization/methylation process[4b,8,9] unraveled hydroxy ketone **8** as a possible precursor. It was reasoned that the latter intermediate could arise from cyclic enol ether **9** through a

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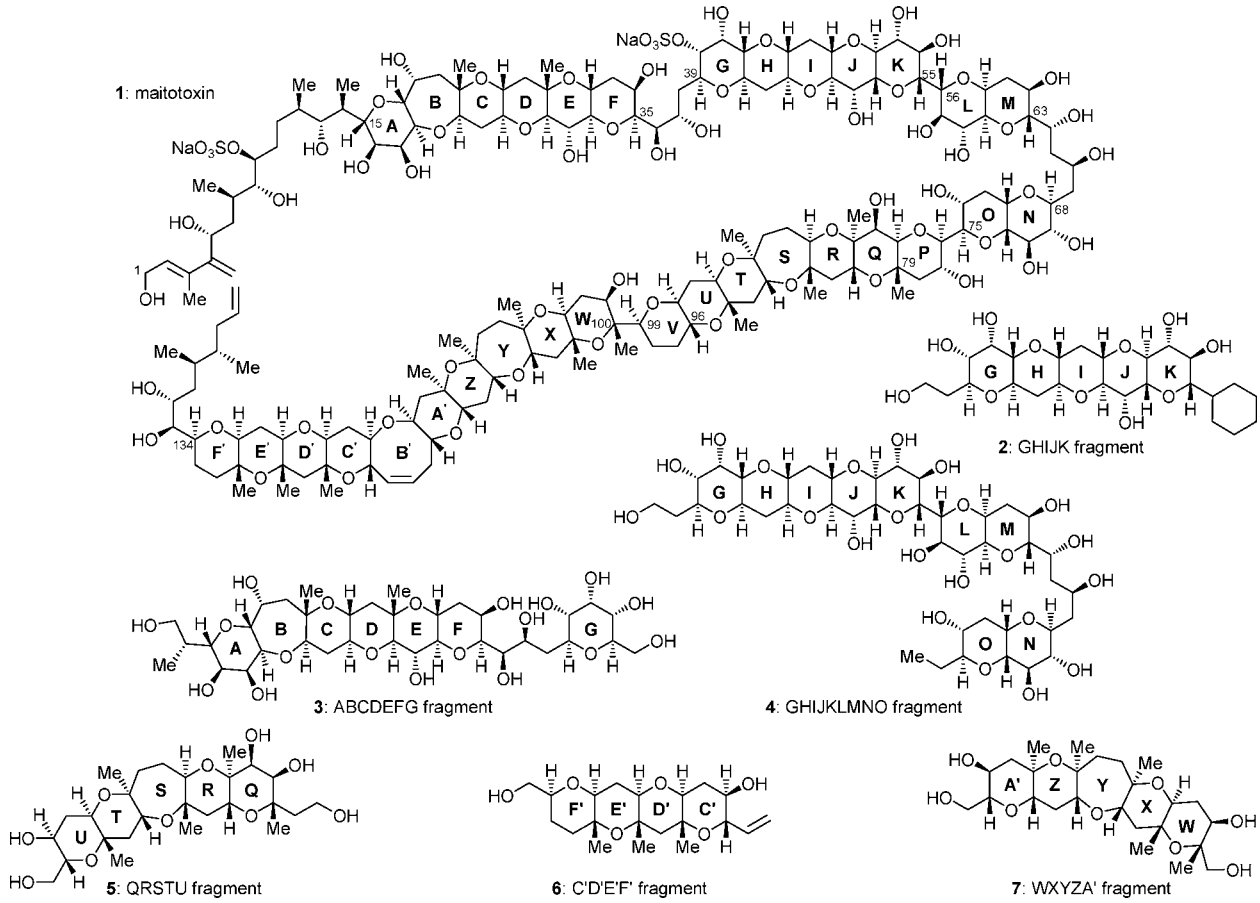

Figure 1. Structures of maitotoxin (**1**), previously synthesized maitotoxin domains GHIJK (**2**), ABCDEFG (**3**), GHIJKLMNO (**4**), QRSTU (**5**), and C′D′E′F′ (**6**), and the targeted WXYZA′ domain (**7**).

hydroboration/oxidation protocol. The seven-membered ring of tetracycle **9** was then disconnected through a postulated Takai olefination/metathesis sequence, revealing tricyclic ester **10** as its progenitor.[10] This ester was then disassembled to generate secondary alcohol **11** and carboxylic acid **12** as the required building blocks. Finally, these building blocks were traced back to furfuryl alcohol (**13**) and 2-deoxy-D-ribose (**14**), respectively, whose ready availability and low cost boded well for the devised synthetic strategy.

2.2. Construction of Building Blocks 11 and 12. The desired building block **11** was constructed in enantiopure form through a sequence featuring a Noyori reduction[11]/Achmatowicz rearrangement protocol[12] and a hydroxy epoxide opening (see Scheme 1).[13] Thus, furfuryl alcohol (**13**) was converted to A′ ring tertiary alcohol **15** in six steps and 76% overall yield, as described previously for a related system.[6,1] Following TMS protection of **15** (TMSOTf, 94% yield), the resulting product was regio- and stereoselectively hydroborated and converted to the corresponding alcohol (*i*-amyl$_2$BH, aq NaOH, H_2O_2, 58% yield plus 16% recovered starting material). This alcohol was sequentially silylated (TBSOTf, quant. yield) and debenzylated (H_2, 20% $Pd(OH)_2$/C) to afford the corresponding primary alcohol, which was oxidized ($(COCl)_2$, DMSO, Et_3N) to afford aldehyde **16** in 69% overall yield for the last two steps. Reaction of this aldehyde with stabilized phosphorane $Ph_3P{=}C(Me)CO_2Et$ gave the corresponding α,β-unsaturated ester in 90% yield. Following protection of the tertiary alcohol as a TMS ether (TMSOTf, 2,6-lut., 93% yield), the ester moiety of the resulting product was reduced with DIBAL-H to the corresponding allylic alcohol (96% yield), whose Sharpless asymmetric epoxidation[14] ((−)-DET, Ti(*i*-OPr)$_4$, *t*-BuOOH, 4 Å MS) gave epoxide **17** (97% yield) as a 10:1 inseparable mixture of epoxide diastereoisomers. Oxidation of this hydroxy epoxide to the corresponding epoxy aldehyde employing Parikh−Doering condi-

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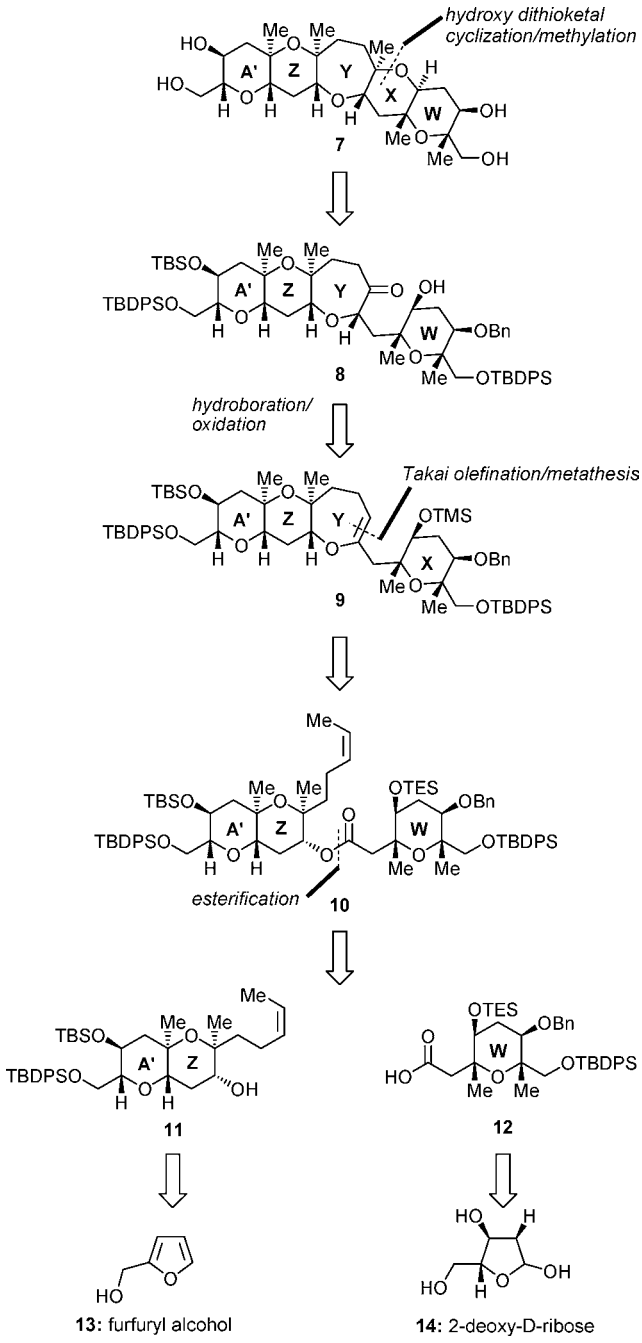
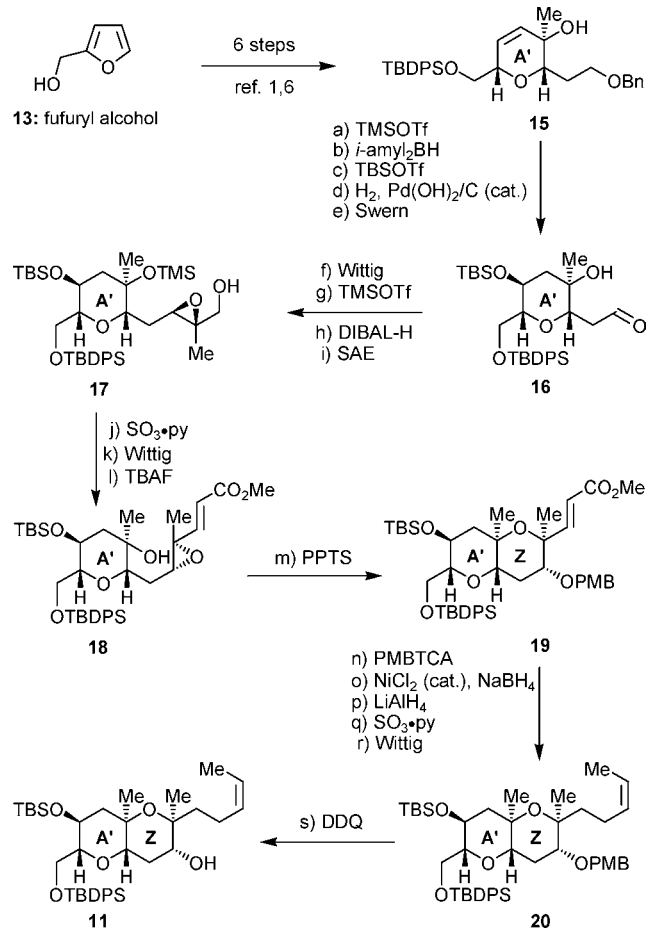


Figure 2. Retrosynthetic analysis of the WXYZA′ maitotoxin domain **7**.

tions[15] (SO_3·py, DMSO, Et_3N), followed by Wittig olefination ($Ph_3P{=}CHCO_2Me$, 97% yield for the two steps) and selective monodesilylation (TBAF, 86% yield), afforded olefinic hydroxy epoxide **18**, setting the stage for the fusion of the next tetrahydropyran ring system. Indeed, substrate **18** underwent regio- and stereoselective ring closure under the influence of PPTS in CH_2Cl_2 at 40 °C to generate A′Z ring system **19** in 60% yield.[16] The secondary hydroxyl group of the latter intermediate was then protected as a PMB ether (PMBOC-(NH)CCl_3, $La(OTf)_3$ (cat.)). Stepwise reduction of the α,β-unsaturated moiety of the so-obtained product ($NaBH_4$, $NiCl_2$·$6H_2O$ (cat.); $LiAlH_4$, 78% yield over the three steps), followed by Parikh−Doering oxidation (SO_3·py, DMSO, Et_3N) of the resulting primary alcohol, furnished the corresponding aldehyde, whose reaction with the ylide derived from Ph_3P(Et)Br and NaHMDS led to *Z* olefin **20** in 80% yield for the last two steps.[17] Finally, the PMB group was oxidatively cleaved from

Scheme 1. Synthesis of A′Z Ring Fragment **11**[a]



[a] Reagents and conditions: (a) TMSOTf (1.5 equiv), Et_3N (2.5 equiv), CH_2Cl_2, −78 °C, 1 h, 94%; (b) *i*-amyl$_2$BH (0.8 M in THF, 8.0 equiv), THF, −78 to 0 °C, 6 d; then 1 M aq NaOH, excess H_2O_2, 58% plus 16% recovered starting material; (c) TBSOTf (2.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 0 → 25 °C, 16 h, quant.; (d) H_2, 20% $Pd(OH)_2$/C (0.2 equiv), EtOH, 25 °C, 18 h; (e) $(COCl)_2$ (3.0 equiv), DMSO (4.0 equiv), Et_3N (8.0 equiv), CH_2Cl_2, −78 → 0 °C, 2 h, 69% over the two steps; (f) $Ph_3P{=}C(Me)CO_2Et$ (1.3 equiv), CH_2Cl_2, 25 °C, 90%; (g) TMSOTf (1.3 equiv), 2,6-lut. (2.0 equiv), CH_2Cl_2, 0 °C, 93%; (h) DIBAL-H (1.0 M in CH_2Cl_2, 3.0 equiv), CH_2Cl_2, −78 °C, 96%; (i) (−)-DET (0.25 equiv), Ti(O*i*-Pr)$_4$ (0.2 equiv), *t*-BuOOH (5.5 M in decane, 1.5 equiv), 4 Å MS, CH_2Cl_2, −20 °C, 17 h, 97% (ca. 10:1 dr); (j) SO_3·py (3.0 equiv), Et_3N (5.0 equiv), DMSO, CH_2Cl_2, 0 → 25 °C; (k) $Ph_3P{=}C(H)CO_2Me$ (1.5 equiv), CH_2Cl_2, 25 °C, 14 h, 97% over the two steps; (l) TBAF (1.0 M in THF, 1.1 equiv), THF, 0 °C, 86%; (m) PPTS (1.0 equiv), CH_2Cl_2, 40 °C, 60%; (n) PMBOC(NH)CCl_3 (1.5 equiv), $La(OTf)_3$ (0.05 equiv), PhMe, 25 °C, 6 h; (o) $NiCl_2$·$6H_2O$ (0.04 equiv), $NaBH_4$ (3.0 equiv), EtOH, 0 °C, 1 h; (p) $LiAlH_4$ (2.0 equiv), Et_2O, 25 °C, 78% over the three steps; (q) SO_3·py (3.0 equiv), Et_3N (5.0 equiv), DMSO, CH_2Cl_2, 0 → 25 °C; (r) Ph_3P(Et)Br (3.2 equiv), NaHMDS (0.6 M in THF, 3.0 equiv), THF, 0 °C, 80% over the two steps; (s) DDQ (2.0 equiv), phosphate-buffered saline, CH_2Cl_2, 0 °C, 2 h, 90%. Abbreviations: TMS = trimethylsilyl, Tf = trifluoromethane sulfonyl, TBS = *tert*-butyldimethylsilyl, DMSO = dimethyl sulfoxide, lut. = lutidine, DIBAL-H = diisobutylaluminum hydride, MS = molecular sieves, TBAF = tetra-*n*-butylammonium fluoride, PPTS = pyridinium *para*-toluene sulfonate, PMB = *para*-methoxybenzyl, NaHMDS = sodium bis(trimethylsilyl)amide, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone.

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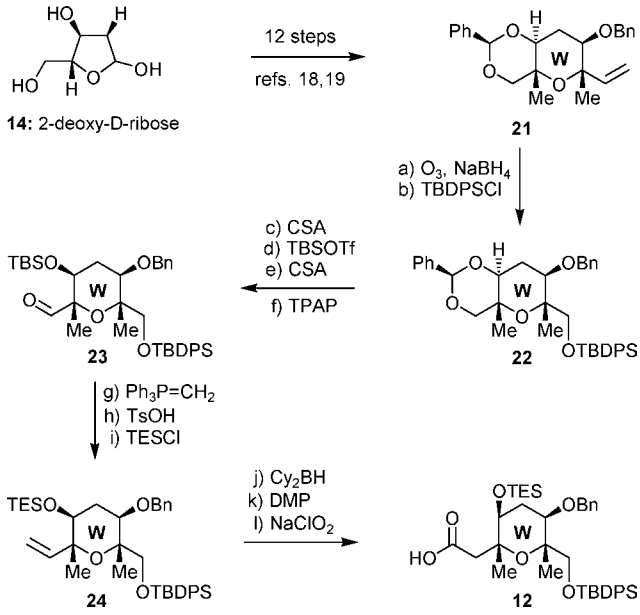
Scheme 2. Synthesis of W Ring Building Block **12**[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2/MeOH (5:1), −78 °C; then $NaBH_4$ (1.0 equiv), CH_2Cl_2/MeOH (5:1), −78 → 25 °C; (b) TBDPSCl (1.5 equiv), imidazole (3.0 equiv), CH_2Cl_2, 25 °C, 5 h, 93% over three steps; (c) CSA (0.25 equiv), MeOH/CH_2Cl_2 (4:1), 0 °C, 2 h, 97%; (d) TBSOTf (3.0 equiv), 2,6-lut. (4.0 equiv), CH_2Cl_2, 0 °C, 0.5 h, 98%; (e) CSA (0.2 equiv), MeOH, 0 °C, 1 h, 80%; (f) NMO (3.0 equiv), TPAP (0.05 equiv), 4 Å MS, CH_2Cl_2, 0 → 25 °C, 4 h; (g) Ph_3PCH_3Br (3.1 equiv), NaHMDS (0.6 M in PhMe, 2.9 equiv), THF, 0 → 25 °C, 4 h, 97% over the two steps; (h) TsOH·H_2O (6.0 equiv), MeOH/CH_2Cl_2 (3:1), 25 °C, 3 h, 82%; (i) TESCl, (2.0 equiv), imidazole (4.0 equiv), CH_2Cl_2, 25 °C, 1 h, quant.; (j) Cy_2BH (5.0 equiv), THF, 25 °C, 1 h; then 2 M aq NaOH, excess H_2O_2, 0 → 25 °C, 1 h, 89%; (k) DMP (1.5 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 3 h; (l) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 25 °C, 0.5 h, quant. over the two steps. Abbreviations: Bn = benzyl, TBAI = tetra-*n*-butylammonium iodide, TBDPS = *tert*-butyldiphenylsilyl, CSA = (±)-camphor-10-sulfonic acid, TPAP = tetra-*n*-propylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide, TES = triethylsilyl, Cy = cyclohexyl, DMP = Dess−Martin periodinane.

20 with DDQ to afford targeted building block A′Z ring system **11** in 90% yield.

The construction of building block **12** was accomplished from W ring system **21** (synthesized from 2-deoxy-D-ribose (**14**) in 12 steps and 39% overall yield as previously described),[18,19] as summarized in Scheme 2. Thus, reductive ozonolytic cleavage of the terminal olefin (O_3, $NaBH_4$) and reaction of the resulting primary alcohol with TBDPSCl and imidazole furnished fully protected intermediate **22** in 93% overall yield. Methanolysis of the benzylidene acetal of **22** under acidic conditions (CSA, MeOH/CH_2Cl_2) then generated the corresponding diol (97%). To differentiate between the two hydroxyl groups of the latter intermediate, it was necessary to employ a two-step procedure involving bis-silylation (TBSOTf, 2,6-lut., 98% yield) and selective monodesilylation (CSA (cat.), MeOH, 0 °C, 80% yield). The resulting primary alcohol was then oxidized with NMO-TPAP (cat.)[20] to afford aldehyde **23**. Wittig-type methylenation of the latter compound ($Ph_3P{=}CH_2$, 97% yield for the last two steps) and exchange of protecting groups on the secondary alcohol (TsOH·H_2O, 82% yield; TESCl, quant. yield) led to derivative **24**. This protecting group switch was dictated by subsequent steps (see below). It should also be noted that attempts to prepare the TES-protected derivative from the diol obtained from benzylidene **22** through bis-TES protection/monodesilylation proved less efficient than the sequence involving the TBS group. Finally, conversion of the terminal olefin of **24** to the desired carboxyl moiety was accomplished through the standard three-step sequence involving hydroboration (Cy_2BH; aq NaOH, H_2O_2, 89% yield) and oxidation (DMP followed by Pinnick, quant. yield for the two steps).[21,22]

2.3. Coupling of Building Blocks and Completion of the Synthesis of the WXYZA′ Maitotoxin Domain 7. The union of fragments **11** and **12** and the elaboration of the resulting product to the targeted WXYZA′ domain **7** of maitotoxin are summarized in Scheme 3. Thus, coupling of alcohol **11** and carboxylic acid **12** under the influence of the Shiina reagent[23] (MNBA, Et_3N, DMAP) afforded the corresponding ester in 84% yield. The Takai ring-closing olefination/metathesis of the W ring TES-protected olefinic ester **25a** proved problematic as it did earlier with the corresponding TBS-protected derivative (**25d**) (which was prepared from aldehyde **23** (Scheme 2)). Neither substrate served well under conditions expected to induce the desired cyclization ($TiCl_4$, TMEDA, Zn, $PbCl_2$, CH_3CHBr_2; see Table 1, entries 1−3),[10,17,24] with starting material being the only recoverable compound. Additionally, the method previously developed by us[10f,g] to accomplish similar transformations employing the Tebbe reagent[25] proved unsuccessful in this instance, leading only to extensive decomposition. We reasoned that the difficulty in this reaction arose from the bulkiness of the substituent on the W ring hydroxyl moiety. We, therefore, opted to exchange the TES group of **25a** for a TMS group and a hydrogen. In contrast to our inability to selectively remove the TBS group from the originally synthesized TBS-protected derivative (**25d**), the desired cleavage of the TES group from the TES-protected substrate (**25a**) proceeded smoothly in the presence of the other three silyl protecting moieties. Indeed, this was the reason we were forced to switch from the TBS-protected series of intermediates to their TES-protected counterparts (**23** → **24**, Scheme 2; see above). The exchange of the TES group in **25a** to a TMS group in **25c**

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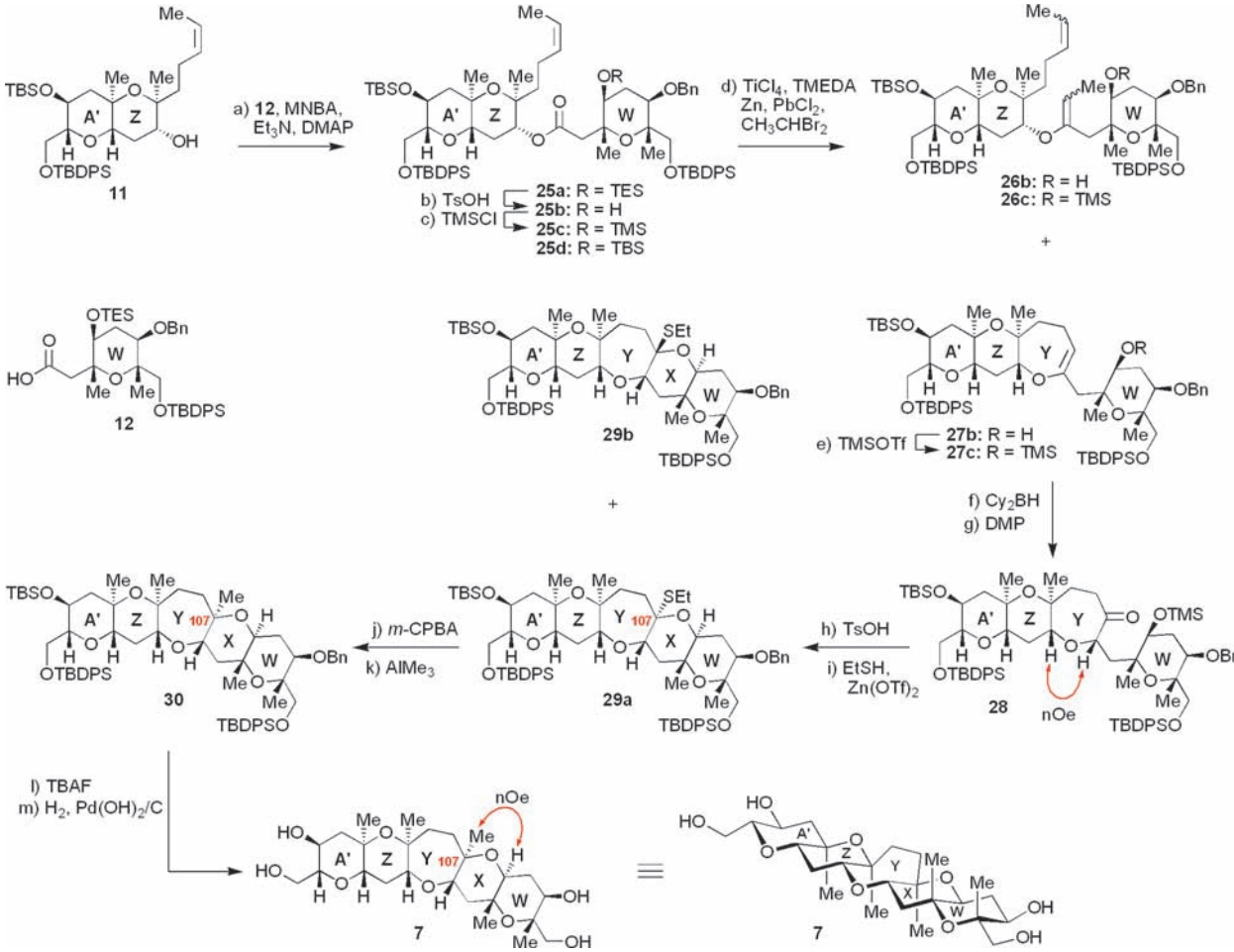
Scheme 3. Coupling of Fragments **11** and **12** and Synthesis of the WXYZA′ Domain of Maitotoxin (**7**)[a]



[a] Reagents and conditions: (a) **12** (1.0 equiv), MNBA (1.05 equiv), Et_3N (2.7 equiv), DMAP (0.1 equiv), 4 Å MS, PhMe, 25 °C, 10 min; then **11** (1.0 equiv), 13 h, 84%; (b) $TsOH \cdot H_2O$ (2.0 equiv), $MeOH/CH_2Cl_2$ (3:1), 0 °C, 40 min, 93%; (c) TMSCl (1.2 equiv), imidazole (3.0 equiv), CH_2Cl_2, 25 °C, 1 h, 96%; (d) from **25c**: $TiCl_4$ (1.0 M in CH_2Cl_2, 87.5 equiv), TMEDA (503 equiv), Zn (189 equiv), $PbCl_2$ (10.2 equiv), CH_3CHBr_2 (84.9 equiv), THF, CH_2Cl_2, 0 → 65 °C, 76%, 1.8:1 **26c**/**27c**; from **25b**: $TiCl_4$ (1.0 M in CH_2Cl_2, 50 equiv), TMEDA (285 equiv), Zn (110 equiv), $PbCl_2$ (5.0 equiv), CH_3CHBr_2 (50 equiv), THF, CH_2Cl_2, 0 → 65 °C, 84%, 1:3.9 **26b**/**27b**; (e) TMSOTf (3.0 equiv), 2,6-lut. (4.0 equiv), CH_2Cl_2, 0 °C, 1 h, quant.; (f) Cy_2BH (15 equiv), THF, 25 °C, 6 h; then 1 M aq NaOH, excess H_2O_2, 14 h, 71%; (g) DMP (3.0 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 0 → 25 °C, 3 h, 89%; (h) $TsOH \cdot H_2O$ (0.1 equiv), $MeOH/CH_2Cl_2$ (3:1), 0 °C, 30 min, 79%; (i) $Zn(OTf)_2$ (5.0 equiv), CH_2Cl_2/EtSH (5:1), 25 °C, 16 h, 65% (2.5:1 dr); (j) *m*-CPBA (4.0 equiv), CH_2Cl_2, −78 → −30 °C, 2.5 h; (k) $AlMe_3$, (40 equiv), −78 → 0 °C, 1 h, quant.; (l) TBAF (1.0 M in THF, 5.0 equiv), THF, 25 → 40 °C, 13 h, 81%; (m) H_2, 20% $Pd(OH)_2/C$ (0.2 equiv), EtOH, 25 °C, 18 h, quant. Abbreviations: MNBA = 2,6-methylnitrobenzoyl anhydride, TMEDA = tetramethylethylenediamine, *m*-CPBA = *meta*-chloroperoxybenzoic acid.

Table 1. Optimization of the Utimoto−Takai Olefination/Metathesis Sequence[a]

						yield (%)		
entry	substrate	R	solvent	time (h)	temp[b] (°C)	**27**	**26**	**25**
1	**25d**	TBS	CH_2Cl_2	1.0	65			90
2	**25d**	TBS	THF	1.0	65			100
3	**25a**	TES	CH_2Cl_2	5.0	65			80
4	**25c**	TMS	CH_2Cl_2	1.0	65	27	49	
5	**25b**	H	CH_2Cl_2	2.0	60	24		36
6	**25b**	H	CH_2Cl_2	6.0	60	20		30
7	**25b**	H	THF	1.5	65	67	17	
8	**25b**	H	THF	1.0	65	62	20	
9	**25b**	H	PhMe	3.0	80	20		48

[a] Reactions were carried out on a 0.02 → 0.18 mmol scale. Yields refer to chromatographically and spectroscopically homogeneous materials. [b] Oil bath temperature.

was carried out through the intermediacy of the free alcohol **25b** ($TsOH \cdot H_2O$, $MeOH/CH_2Cl_2$, **25b**, 93% yield; then TMSCl, imid., **25c**, 96% yield). Pleasantly, exposure of substrate **25c** to the same Takai reaction conditions as mentioned above for **25a** and **25d** led to a mixture of bis-olefins **26c** (four geometrical isomers) and cyclic enol ether **27c** (76% combined yield, ca. 1.8:1 ratio), in which, however, undesired products **26c** were predominating (Table 1, entry 4). Chromatographic separation of the mixture led to bis-olefin products **26c** (49% yield, four geometrical isomers) and cyclic enol ether **27c** (27% yield) and allowed recycling of the bis-olefin (**26c**) through ozonolysis/Wittig olefination (to afford starting material **25c**, 50% overall yield). Through further prep-TLC purification (multiple elutions), the mixture of bis-olefins **26c** was separated into two pairs of isomers, each consisting of a single geometrical isomer at the trisubstituted olefinic bond (enol ether) and a mixture at the disubstituted olefinic bond (ca. 6:1 ratio). On the basis of the chemical shift of the enol ether proton (δ = 4.77 ppm, 600 MHz, C_6D_6), the less polar isomer (**26c′**) was assigned the *Z* geometry and the more polar isomer (**26c″**, δ = 5.36−5.31 ppm, 600 MHz, C_6D_6) the *E* geometry. Attempts to convert the mixture of bis-olefin **26c** directly to cyclic enol ether **27c** through olefin metathesis with Grubbs' second generation catalyst,[26]

Table 2. C_{99} to C_{118} and C_{155} to C_{159} Chemical Shifts (δ) for Maitotoxin (MTX, **1**) and the WXYZA′ Ring System **7** and Their Differences ($\Delta\delta$, ppm)[a]

carbon	δ for MTX (**1**) (ppm)	δ for (**7**) (ppm)	difference ($\Delta\delta$, ppm)
118	31.5	63.0	−31.5
117	84.7	86.2	−1.5
116	76.6	65.9	10.7
115	46.7	48.9	−2.2
159	21.7	21.8	−0.1
114	74.1	73.8	0.3
113	83.8	82.5	1.3
112	30.3	30.3	0.0
111	87.7	87.6	0.1
110	79.6	79.1	0.5
158	23.5	23.2	0.3
109	40.4	40.4	0.0
108	39.1	39.1	0.0
107	79.6	79.6	0.0
106	84.6	84.5	0.1
157	18.3	18.4	−0.1
105	42.8	42.6	0.2
104	74.6	74.8	−0.2
156	20.2	20.3	−0.1
103	72.6	72.7	−0.1
102	31.0	31.8	−0.8
101	74.7	69.3	5.4
100	78.8	79.3	−0.5
155	19.5	21.0	−1.5
99	87.8	69.3	18.5

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

Hoveyda−Grubbs' second generation catalyst,[27] and Schrock's catalyst[28] failed, presumably due to steric congestion around the reactive sites of the substrate. Gratifyingly, however, substrate **25b**, bearing a free hydroxyl group on the W ring, was found to be a better substrate for the Takai cyclization to generate the desired enol ether (**27b**). Thus, through a judicious choice of solvent[29] and reaction time (see Table 1, entries 5−9), product **27b** was successfully forged in 67% yield, together with a small amount of the corresponding bis-olefin **26b** (17% yield, Table 1, entry 7). After installing a TMS group on the free hydroxyl group of **27b** (TMSOTf, 2,6-lut., quant.), regioselective hydroboration of the resulting enol ether (**27c**) with Cy_2BH and oxidation of the so-obtained borane (aq NaOH, H_2O_2) afforded the corresponding alcohol (71% yield) as a single diastereoisomer. The latter compound was then oxidized with DMP to furnish ketone **28** in 89% yield. The syn stereochemical assignment of the newly generated stereocenter was supported by the indicated NOE (see structure **28**, Scheme 3). Selective methanolysis of the TMS group from **28** ($TsOH\cdot H_2O$ (cat.), $MeOH/CH_2Cl_2$) led to the corresponding hydroxy ketone (79% yield), whose cyclization in the presence of EtSH and $Zn(OTf)_2$ afforded a mixture of *S*,*O*-acetals **29a** and **29b** (**29a**/**29b** ca. 2.8:1, 50% combined yield), plus 36% recovered starting material (**28**), which could be recycled (bringing the yield of **29ab** after three iterations to 65%).[16,4b] Oxidation of **29a** and **29b**, individually or as a mixture, with excess *m*-CPBA (CH_2Cl_2, −30 °C), followed by addition of excess $AlMe_3$ at −78 °C in the same pot, led to protected WXYZA′ pentacyclic system **30** in quantitative yield.[9a,4b] That this reaction proceeded with stereoselective installation of the methyl group at C_{107} was confirmed through NOE studies on the ultimate product (i.e., **7**; see below). Finally, deprotection of the latter intermediate (TBAF, 25 → 40 °C, 81% yield; H_2, 20% $Pd(OH)_2$/C (cat.), quant. yield) furnished the desired WXYZA′ maitotoxin domain **7**, whose shown stereochemical assignment at C_{107} was confirmed by the indicated NOE (see structure **7**, Scheme 3).

2.4. Comparison of the ^{13}C NMR Chemical Shifts of the WXYZA′ Ring System 7 with Those Corresponding to the Same Region of Maitotoxin. Having obtained the WXYZA′ fragment **7** through synthesis, we took the opportunity to compare its ^{13}C NMR spectral data with those of the WXYZA′ domain of the natural product as a means of providing further evidence for the correctness of the originally assigned structure of the natural product.[30,31] Table 2 lists the ^{13}C NMR chemical shifts (δ, ppm) for the WXYZA′ ring system **7**, together with those of the corresponding domain of natural maitotoxin (MTX (**1**)) and their differences ($\Delta\delta$, ppm).[3d] As seen from the small deviations between these values, which are also depicted graphically in Figure 3, there is excellent agreement between the two sets of chemical shifts for the two structures, except for those carbons residing at the edges of these domains due to the drastically different structural motifs at these locations. The average chemical shift deviation ($\Delta\delta$, ppm) for C_{102} to C_{115} and C_{155} to C_{159} is 0.36 ppm, with the largest difference being 2.2 ppm. These findings are in line with those reported by the Nakata group for a related domain of maitotoxin[4a] and provide further support for the originally assigned structure of this region of the natural product.

3. Conclusion

The described chemistry culminated in a convergent synthesis of the WXYZA′ domain (**7**) of maitotoxin (**1**), allowing a ^{13}C NMR chemical shift comparison of its carbons with those of the corresponding carbons of the same region of the natural product and ultimately providing further support for the originally assigned structure of the natural product. The construction of this target molecule was based primarily on synthetic technologies previously developed in these laboratories and incorporating improvements reported from other groups. Specif-

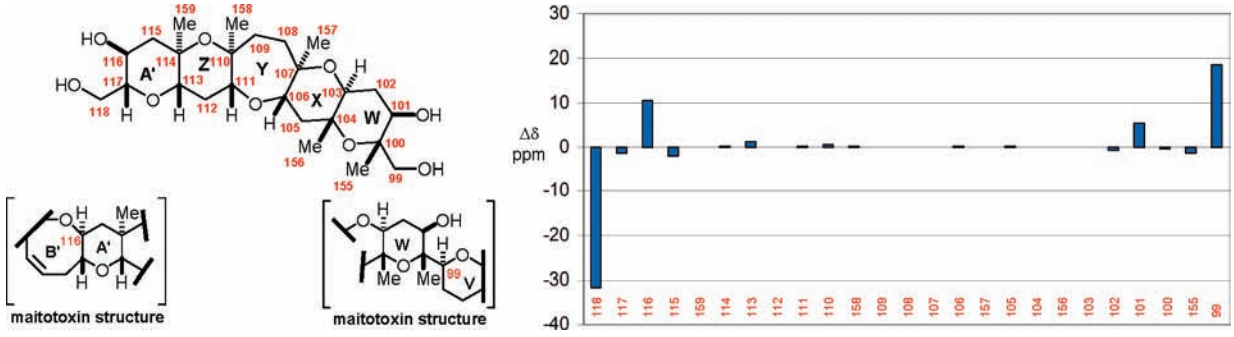


Figure 3. Graphically depicted ^{13}C chemical shift differences ($\Delta\delta$, ppm) for each carbon between C_{99} to C_{118} and C_{155} to C_{159} for maitotoxin (**1**) and the WXYZA′ ring system **7**.

ically, a Noyori reduction/Achmatowicz rearrangement-based tetrahydropyran synthesis,[5,12,32] a hydroxy epoxide opening,[13] a metathesis-based ring closure,[10b−h,17,24] and a hydroxy dithioketal cyclization/methylation were employed.[4b,9a,b,16,33] With this domain (**7**) of maitotoxin now synthesized, a set of six large domains (i.e., **2**−**7**, Figure 1) of this neurotoxin has been completed.[1,5–8] With appropriate modifications, the developed routes to these fragments can, in principle, deliver suitable fragments, whose coupling and further elaboration may lead to even larger domains of the natural product. Biological investigations with these molecules may provide further understanding of the mechanism of action of maitotoxin and other members of the polyether marine biotoxin class.[34]

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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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