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Synthesis of the WXYZA' Domain of Maitotoxin

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1. Introduction

1.1. Ladderlike Polycyclic Ethers.

- A particularly diverse and celebrated set of marine biotoxins.
- Some of these compounds have been implicated as causative agents in many seafood-related poisonings, and also responsible for many of the massive fish kills.
- In 1981, the first disclosure of a member of this family (brevetoxin B, Figure 1 left).
- In 1992, the first total synthesis of a member of this family (hemibrevetoxin, Figure 1 right).

=> This lapse of time was not only to the structural complexity of these molecules, but also because of the lack of methods suitable for their construction.

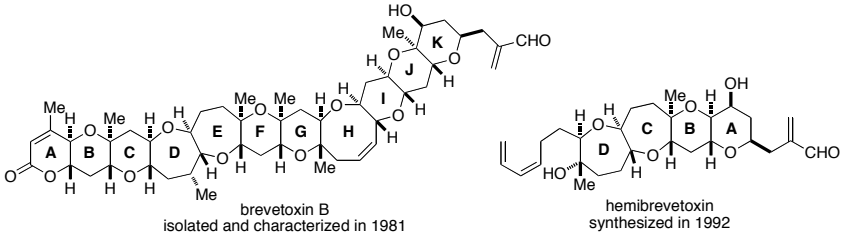


Figure 1. Structures of ladderlike polycyclic ethers, brevetoxin B and hemibrevetoxin.

1.2. About Maitotoxin.

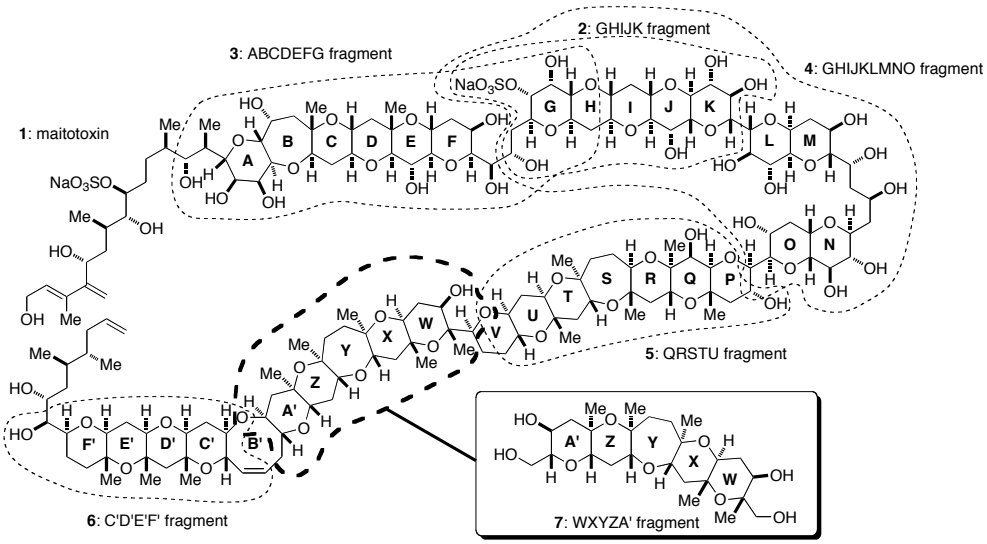
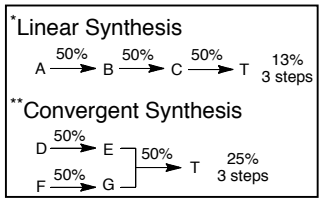


Figure 2. Structures of maitotoxin (**1**), previsouly synthesized maitotoxin domains GHIJK (**2**), ABCDEFG (**3**), GHIJKLMNO (**4**), QRSTU (**5**), and C'D'E'F' (**6**), and the targeted WXYZA' domain (**7**).

- The largest and most toxic, nonpolymeric natural product isolated and characterized to date. (MW: 3422, 32 rings, 99 elements of stereochemistry, LD_{50}: 50 ng/kg, mice, i.p.)

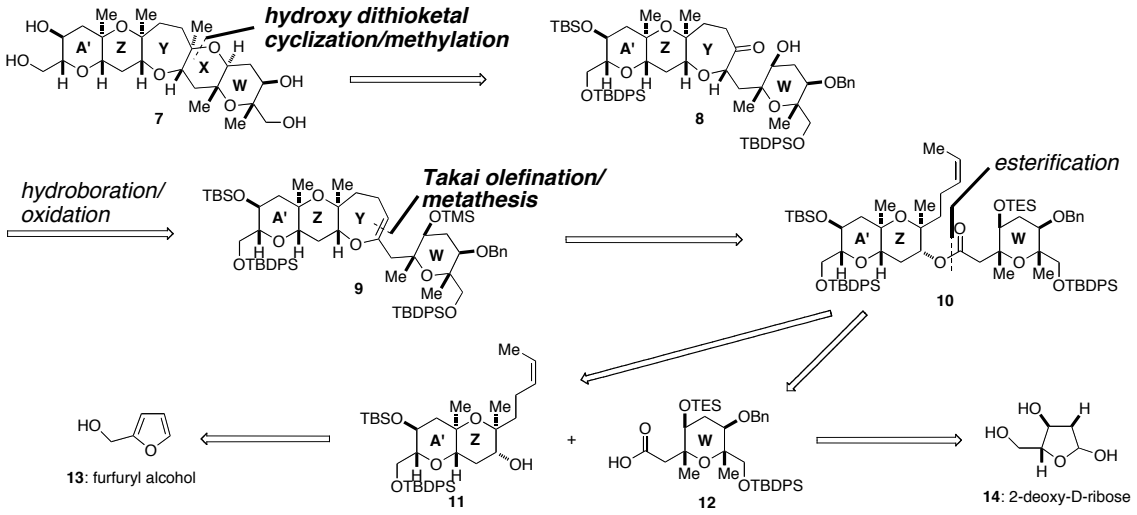
- Isolated in 1988 from a broth of the dinoflagellate (鞭毛虫) *Gambierdiscus toxicus* by Yasumoto and co-workers.
- In 1996, the complete characterization was accomplished by Kishi and Tachibana research groups.

1.3. This Work.



- Synthesis of WXYZA' domain of maitotoxin.
  - A linear synthesis,[*,1] and a convergent synthesis[**] of related domain[2] have reported.
- Convergent synthetic strategy through coupling of **11** and **12** (Scheme 1).
- All the major domains of maitotoxin have now been synthesized with this accomplishment (including the construction of C'D'E'F' domain at the same time).[3]
- Takai olefination/metathesis and hydroxy dithioketal cyclization are the key steps.

Scheme 1. Retrosynthetic analysis of the WXYZA' maitotoxin domain **7**.



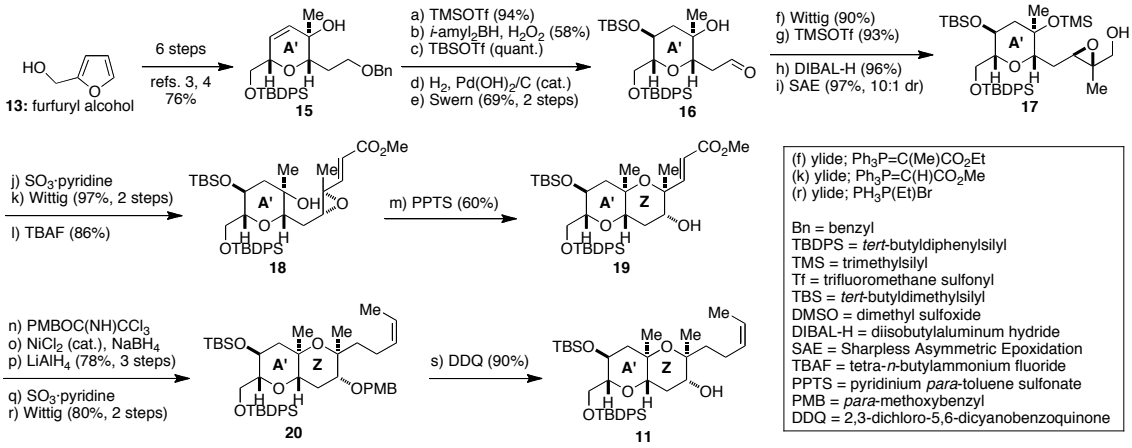
2. Results and Discussion

2.1. Construction of Building Blocks 11 and 12.

2.1.1. Synthesis of A'Z Ring Fragment 11 (Scheme 2).

- Compound **15** was successfully converted to **11** in 7.5% yield including;
  - Regio- and stereoselective hydroboration (step b, **15** to **16**).
  - Sharpless asymmetric epoxidation (SAE) (step i, **16** to **17**).
  - Parikh-Doering oxidations (steps j and q, **17** to **18** and **19** to **20**).

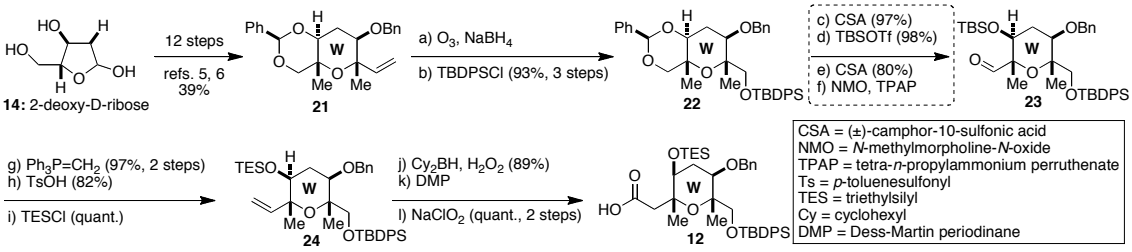
Scheme 2. Synthesis of A'Z ring fragment **11**.



2.1.2. Synthesis of W Ring Building Block 12 (Scheme 3)

- 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.

Scheme 3. Synthesis of W ring building block **12**.



2.2. Coupling of Building Blocks and Completion of the Synthesis of Domain 7.

- Coupling of alcohol **11** and carboxylic acid **12** under the influence of the Shiina reagent afforded the corresponding ester **25a** in 84% yield.
- Takai ring-closing olefination/metathesis of the olefinic ester **25** proved problematic.
  - TES-protected olefinic ester **25a** and TBS-protected analogue **25d** did not serve well under conditions expected to induce the desired cyclization.
  - Reaction with Tebbe reagent (acts as a stronger lewis acid than Takai reagent) led to decomposition of the substrate.
  - The authors reasoned bulkiness of the

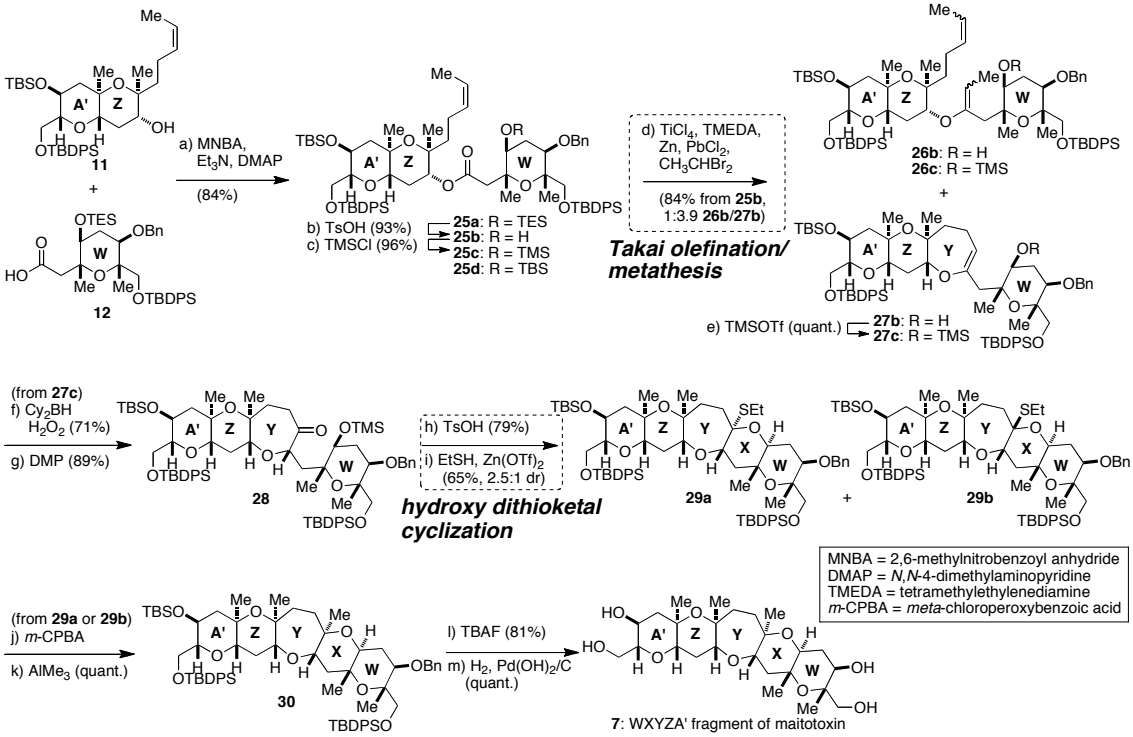
Table 1. Optimization of the Utimoto-Takai olefination/metathesis sequence

entry	substrate	R	solvent	time (h)	temp (°C)	yield (%) 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

substituent of the W ring hydroxyl moiety affects the cyclization.

- Finally the reaction proceeded well with non-protected substrate **25b** with a suitable choice of the solvent and the reaction time.

Scheme 4. Coupling of fragments **11** and **12** and synthesis of the WXYZA' domain of maitotoxin (**7**).



- After selective methanolysis of the TMS group of **28**, cyclization in the presence of EtSH and $Zn(OTf)_2$ afforded a mixture of *S*,*O*-acetals **29a** and **29b**.

3. Conclusions

- A convergent synthesis of WXYZA' domain of maitotxin was achieved in 0.75% overall yield in 36 longest linear steps from fufuryl alcohol **13** through Takai olefination metathesis and a hydroxy dithioketal cyclization as the key steps.
- With appropriate modifications, the developed synthetic routes may lead to even larger domains of the natural product.

4. References

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1) Oishi, T.; Hasegawa, F.; Torikai, K.; Konoki, K.; Matsumori, N.; Murata, M. *Org. Lett.* **2008**, *10*, 3599.
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