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Stereoselective total synthesis of arenastatin A, a spongean cytotoxic depsipeptide

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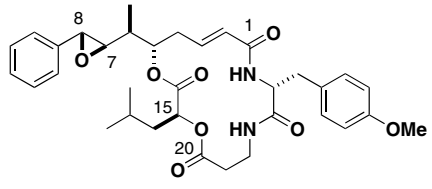
Abstract—A highly stereoselective total synthesis of arenastatin A, an extremely potent cytotoxic cyclic depsipeptide from marine sponge, was developed. The desired 7,8-β-epoxide in arenastatin A was constructed by asymmetric sulfur ylide-mediated epoxidation in good yield and highly stereoselective manner.

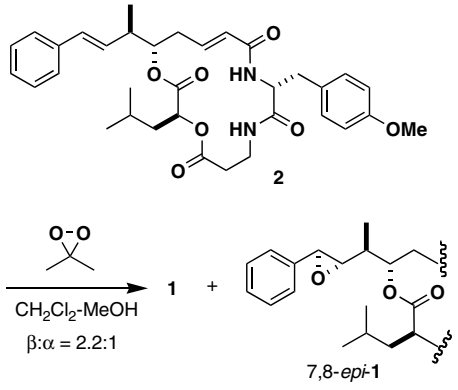
In the course of our search for bioactive substances from marine organisms, we isolated and characterized arenastatin A (**1**), a cyclic depsipeptide having an extremely potent antiproliferative activity against KB cells (IC_{50} 5 pg/mL), from the Okinawan marine sponge of *Dysidea arenaria*.[1] Thereafter, we achieved the first total synthesis of **1**,[2] and many synthetic studies toward **1** and its analogues have been reported so far, because of its synthetically attractive structure and potent biological activity (Fig. 1).[3]

Arenastatin A (**1**) has a 7*R*,8*R*-β-epoxy moiety on its molecule. Some structure–activity relationship (SAR) studies have revealed that the β-epoxy moiety plays critical role for the potent cytotoxic activity of **1**, and the α-epoxy isomer has no biological activity. However, the epoxy function in **1** is labile under acidic condition, so it should be introduced at the final stage of the synthesis. The most reliable method for the stereoselective construction of the 7,8-β-epoxide would be the epoxidation of the 7,8-*E*-olefin of **2** with dimethyldioxirane developed by our group (Scheme 1).[2a,4] However, the stereoselective ratio is β:α = 2.2:1, and reversed-phase HPLC separation should be needed to isolate pure product. Furthermore, the epoxidation with other bulky oxirane reagents gave 7,8-epoxide with poor or inverse selectivity. In the synthetic study of cryptophycin 52, a closely related depsipeptide, Moher and co-workers[4] reported that the selective (β:α = 5–9.5:1) introduction of the 7,8-β-epoxide to the acyclic intermediates has been performed by using Shi epoxidation. However,



arenastatin A (**1**)

Figure 1. Chemical structure of arenastatin A (**1**).



Scheme 1.

Keywords: Arenastatin A; Depsipeptide; Total synthesis; Asymmetric epoxidation.
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Shi epoxidation of the substrate having cyclic depsipeptide structure resulted in very low conversion, because of steric hindrance. Thus, another method for the construction of the 7,8-β-epoxide in a highly stereoselective manner is strongly needed from the viewpoint of synthetic utility and atom economy. Here, we present our new synthetic procedure for the stereoselective total synthesis of arenastatin A (**1**) by using asymmetric sulfur ylide-mediated epoxidation.[5]

The synthetic strategy was shown in Figure 2. An aryl moiety and a 7*R*,8*R*-epoxide of **1** could be introduced in one operation by the Corey–Chaycovsky reaction between a chiral benzyl sulfur ylide and an aldehyde **3** having cyclic depsipeptide structure. Compound **3** could be synthesized through the similar manner as our previous total synthesis of **1**,[2] that is, the successive condensation of the four segments A (**6**), B (**5**), C (**7**), and D (**8**).

Cyclic peptide **3** was synthesized as follows (Schemes 2, 3). First of all, segment A (**6**) was prepared with a known method.[6] Thus, Lewis acid-promoted allylation of aldehyde **9** gave a homoallylic alcohol **10**, as a mixture of the diastereomers in a 13/1 ratio. Removal of *p*-methoxybenzyl (MPM) group of **10** and subsequent protection of the primary hydroxyl group of **11** by *tert*-butyldiphenylsilyl (TBDPS) group afforded a desired segment A (**6**).

Segment A (**6**) was coupled with segment C (**7**), prepared from L-leucic acid,[2] to give segment AC (**12**) in 87% yield. Oxidative cleavage of the terminal olefin of **12** smoothly proceeded to give an aldehyde **4**, and subsequent Horner–Emmons reaction with segment B (**5**) afforded an α,β-unsaturated amide **13**. It revealed that the choice of base was important in this reaction. The results are summarized in Table 1. Thus, the use of NaH as a base (entry 1) resulted in disappointing yield of the desired product, and considerable amount of α,β-unsaturated aldehyde **14** was obtained as a byproduct. On the other hand, the Masamune–Roush condition[7] using DBU and LiCl (entry 2), which was developed for base-sensitive aldehydes, afforded **14** as a sole product. Among tested, the use of activated $Ba(OH)_2$[8] (entry 6) gave the best result to afford the coupling product **13** in 60% yield (three steps from **12**).

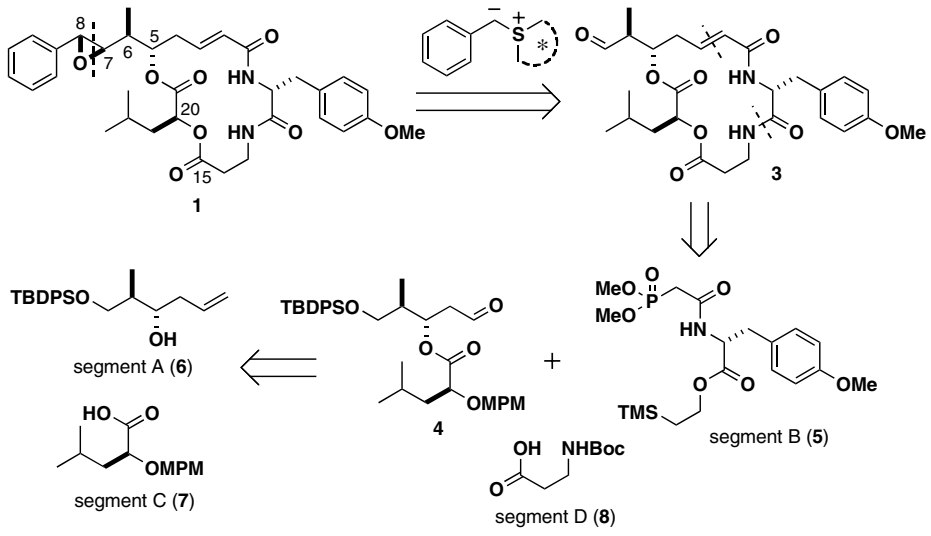
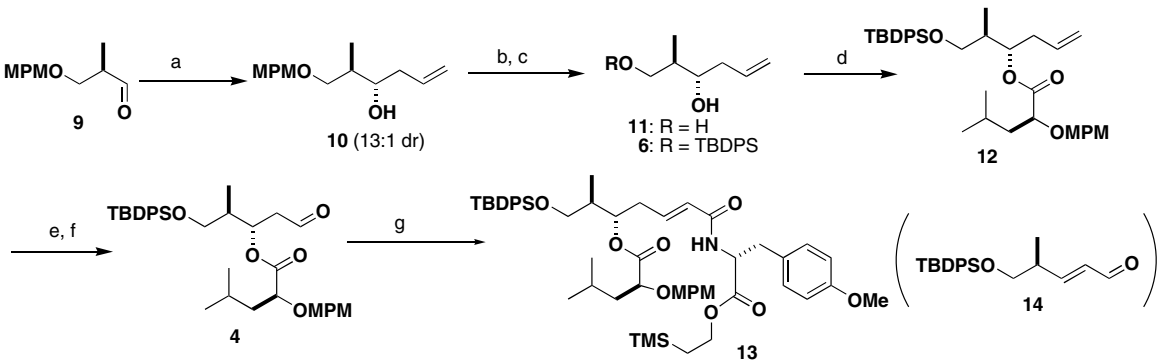
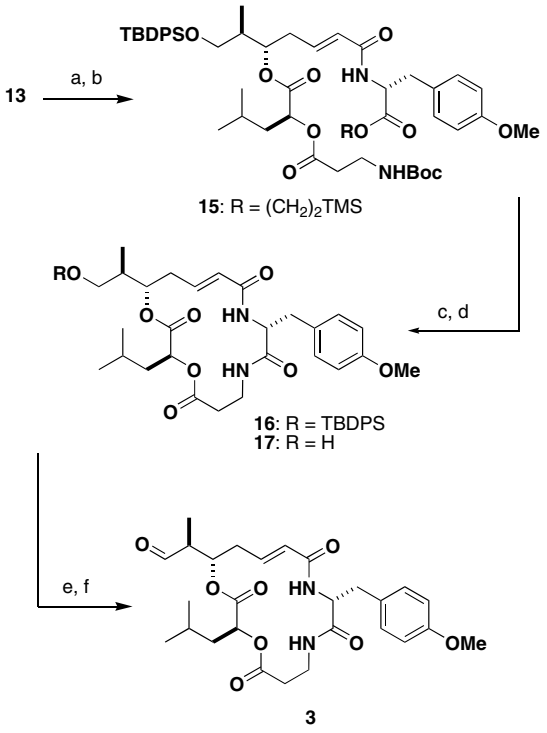


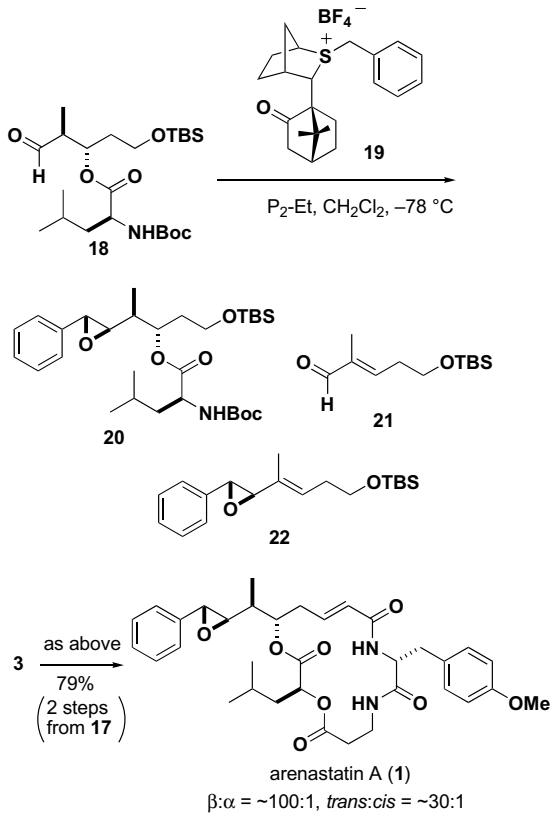
Figure 2. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) allyltributylstannane, $SnCl_4$, CH_2Cl_2, −78 °C, 75%, 13:1 dr; (b) HCl/MeOH, reflux, 80%; (c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 95%; (d) **7**, EDCI·HCl, DMAP, CH_2Cl_2, 87%; (e) OsO_4, NMO, THF/pH 7.0 buffer; (f) $NaIO_4$, THF/pH 7.0 buffer; (g) **5**, $Ba(OH)_2$, THF/H_2O (40:1), 60% (three steps).



Scheme 3. Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, PhSH, CH_2Cl_2, −45 °C, 71%; (b) **8**, EDCI·HCl, DMAP, CH_2Cl_2, 98%; (c) TFA, CH_2Cl_2, 0 °C; (d) DPPA, $NaHCO_3$, DMF, 61% (two steps); (e) HF-pyridine, THF, 84%; (f) Dess–Martin periodinane, CH_2Cl_2.



Scheme 4.

Table 1. Conditions of Horner–Emmons reaction between **4** and **5**

Entry	Base	Yield[a] (%)
1	NaH	33
2	LiCl, DBU	Decomp.
3	*t*-BuOK	Decomp.
4	*n*-BuLi, DMSO	55
5	$Ba(OH)_2$ (2.0 equiv)	56
6	$Ba(OH)_2$ (0.8 equiv)	60

[a] Isolated yield of **13** in three steps from **12**.

Removal of the MPM group of **13** using PhSH and $BF_3{\cdot}Et_2O$ and subsequent condensation with segment D (**8**) using the conventional method[2a] afforded **15** in good yield. Finally, removal of both (trimethylsilyl)ethyl group and *tert*-butoxycarbonyl (Boc) group by trifluoroacetic acid (TFA) and subsequent intramolecular macrocyclization using diphenylphosphoryl azide (DPPA) furnished a cyclic depsipeptide **16**. Removal of the TBDPS protecting group and Dess–Martin oxidation gave a desired aldehyde **3** (Scheme 3).

In the final stage of the synthesis, that is, the introduction of the aryl moiety and 7*R*,8*R*-epoxide, we used asymmetric Corey–Chaycovsky reaction mediated by D-camphor-derived chiral sulfide, which has been developed by Aggarwal's group.[5] In order to optimize the reaction condition, the condensation between aldehyde **18** and sulfur ylide, which was generated by deprotonation from sulfonium salt **19** using phosphazene base P_2–Et, was examined (Scheme 4). In the case using stoichiometric amount, α,β-unsaturated aldehyde **21** was obtained as a sole product, which was produced by β-elimination of the leucine moiety from **18**. The use of increased amount of the sulfur ylide tended to give a desired epoxide **20** together with an epoxide **22**, which was produced from **21** and sulfur ylide. The ^1H NMR spectrum and HPLC analysis of **20** revealed that epoxide **20** was obtained as almost single stereoisomer! The stereochemistry of **20** was ascertained by NOESY experiment. However, even in the optimized reaction condition, the desired epoxide **20** was obtained in low yield (~25%), and the β-elimination reaction could not be avoided.

Fortunately, the same reaction using cyclic peptide **3** as a substrate proceeded smoothly to give arenastatin A (**1**) in good yield (79%, two steps from **17**). The side product derived from the elimination of the ester moiety was not detected, probably because of the stability of the cyclic structure in **3**. The HPLC analysis of the reaction product revealed that the reaction proceeded with excellent stereoselectivity (β:α = ~100:1, trans:cis = ~30:1).[2a,9] Recently, Sherman and co-workers[10] reported that the stereoselective epoxidation of the 7,8-*E*-olefin in the cyclic precursor of cryptophycin 2 was succeeded by using cryptophycin CYP450 epoxidase, which was obtained by overexpression of the cyanobacterial gene in *Escherichia coli*.

In summary, we developed a convergent synthetic procedure of arenastatin A (**1**) by using asymmetric sulfur

ylide-mediated epoxidation as a key step. This method provided a highly stereoselective construction of the 7*R*,8*R*-β-epoxide moiety in **1**.

Acknowledgment

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