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Total synthesis of somamide A, an Ahp (3-amino-6-hydroxy-2-piperidone)-containing cyclic depsipeptide

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Abstract—The first total synthesis of somamide A (**1**), an Ahp (3-amino-6-hydroxy-2-piperidone)-containing cyclic depsipeptide, from the marine cyanobacterium *Lyngbya majuscula* is described. The efficient and stereospecific dehydration of the *N*-acyl threonine ester using Martin's sulfurane provided the (*Z*)-2-amino-2-butenoic acid residue. The macrolactamization using FDPP($Ph_2P(O)OC_6F_5$), the final installation of the Ahp moiety by oxidation with 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, and cyclization of the norvaline derivative to the cyclic hemiaminal afforded somamide A (**1**). © 2002 Elsevier Science Ltd. All rights reserved.

Marine cyanobacteria have proven to be exceptionally rich sources of structurally unique and biologically active natural products.[1] Somamide A (**1**) was isolated from assemblages of the marine cyanobacteria *Lyngbya majuscula* and *Schizothrix* sp. from the Fijian Islands.[2] The structure of this 19-membered macrocyclic depsipeptide is quite unique because it has a 3-amino-6-hydroxy-2-piperidone (Ahp) unit, a (*Z*)-2-amino-2-butenoic acid unit, and a sulfoxide function. The Ahp unit can be considered as a glutamate in

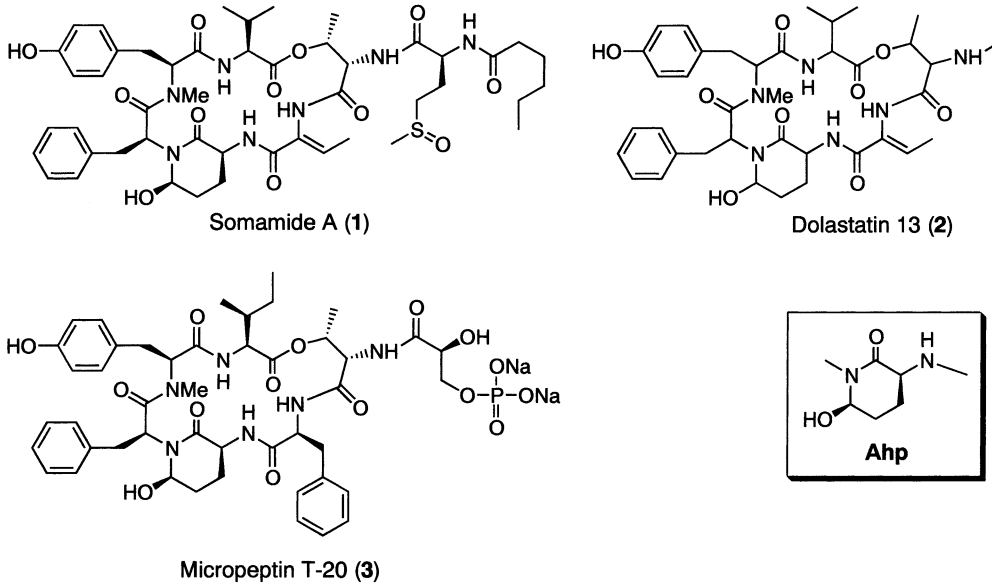

Figure 1. Somamide A (**1**), dolastatin 13 (**2**), micropeptin T-20 (**3**), and Ahp.

Keywords: total synthesis; cyclic depsipeptide; marine cyanobacteria; cyclic hemiaminal; dehydroamino acid.

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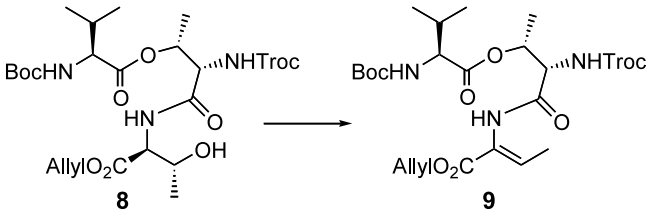
which the side chain carboxyl has been reduced to an aldehyde and the aldehyde cyclized with n+1 amide forms a cyclic hemiaminal that is arguably its most interesting structural feature. The Ahp unit was first described as a constituent of dolastatin 13 (**2**), a cytostatic agent from the sea hare *Dolabella auricularia*,[3] and has been found in several metabolites of blue-green algae, namely the cyanopeptolins,[4] micropeptins,[5] nostopeptins,[6] oscillapeptins,[7] symplostatin **2**,[8] etc. Most Ahp-containing metabolites have been discovered as protease inhibitors, and their unprecedented common structure can participate in converting the cyclic peptide into a bioactive conformation due to the conformationally restricted structure and hydrogen bonding with the free hydroxyl group in Ahp. Interests on the synthesis of biologically intriguing and structurally unique peptides[9] have led us to focus on the synthesis of the Ahp-containing cyclic depsipeptides, and we have already succeeded in the synthesis of micropeptin T-20 (**3**) as its putative structure having the Ahp unit.[10] In this paper, we describe the first total synthesis of somamide A (**1**), clearly demonstrating that our strategy for the construction of the Ahp moiety[10] is appropriate and reasonable (Fig. 1).

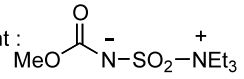
Our retrosynthetic approach is shown in Scheme 1. As shown in our previous paper,[10] the precursor of the Ahp can be the 5-hydroxynorvaline derivative **4**, which should be cyclized at the Abu (2-amino-2-butenoic acid)/norvaline site thus reducing the risk of racemization at the α-chiral center of the *C*-terminus during the macrolactamization. The macrocycle **4** was disconnected into the three fragments **5**–**7**.

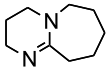
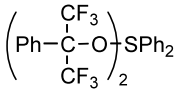
For the synthesis of the Abu-containing depsipeptide fragment **9**, we chose the stereospecific dehydrative elimination of the corresponding *N*-acyl threonine ester **8**. As shown in Table 1, we first attempted the formation of the cyclic sulfamidite from **8** using thionyl chloride, followed by stereospecific elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) according to the Wandless' method.[11] However, the elimination of the cyclic sulfamidite could only be achieved in low yield (20%) due to the further α-elimination of the other *O*-acyl threonine moiety (entry 1). An alternative one-pot procedure using thionyl chloride in the presence of

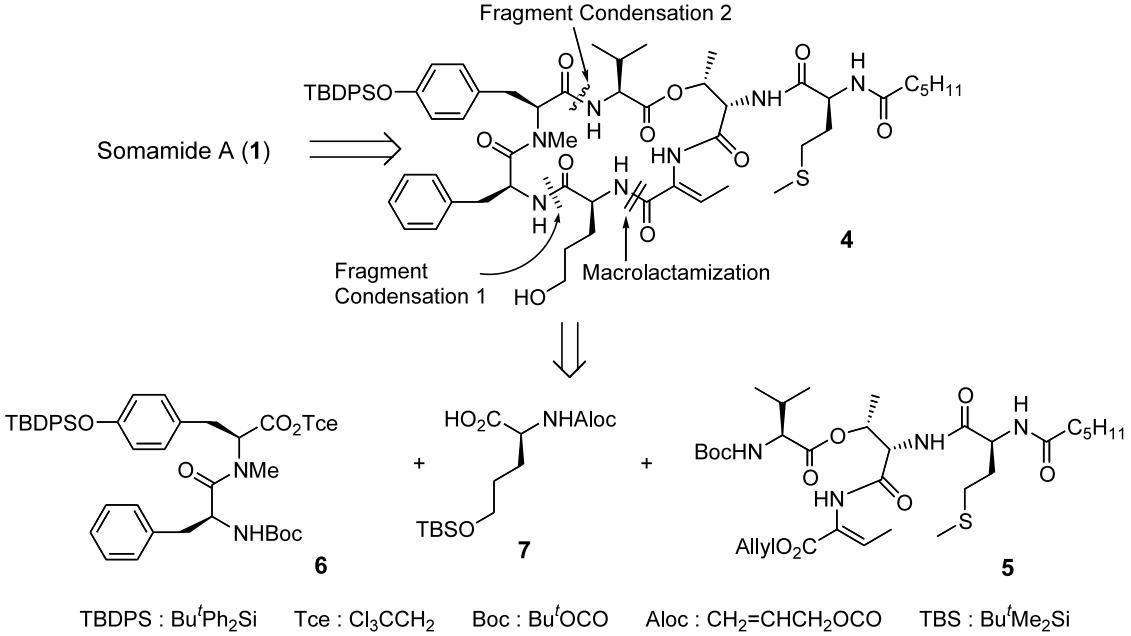
Table 1. Dehydrative elimination of the *N*-acyl threonine ester **8**



entry	reaction conditions	yield
1	1) $SOCl_2$ (1.5 *eq.*), Et_3N (3 *eq.*), CH_2Cl_2, -50 °C 2) DBU (2 *eq.*), 0 °C	20 %
2	$SOCl_2$ (1.5 *eq.*), Et_3N (20 *eq.*), CH_2Cl_2, -78 °C ~ rt	25 %
3	Burgess reagent (1.5 *eq.*), Et_3N (3 *eq.*), rt ~ reflux	trace
4	DAST (1.5 *eq.*), Et_3N (3 *eq.*), CH_2Cl_2, -20 °C	51 %
5	Martin's sulfurane (1.5 *eq.*), CH_2Cl_2, rt	63 %

Troc : Cl_3CCH_2OCO Burgess reagent : 

DBU :  Martin's sulfurane : 



TBDPS : Bu^tPh_2Si Tce : Cl_3CCH_2 Boc : Bu^tOCO Aloc : $CH_2{=}CHCH_2OCO$ TBS : Bu^tMe_2Si

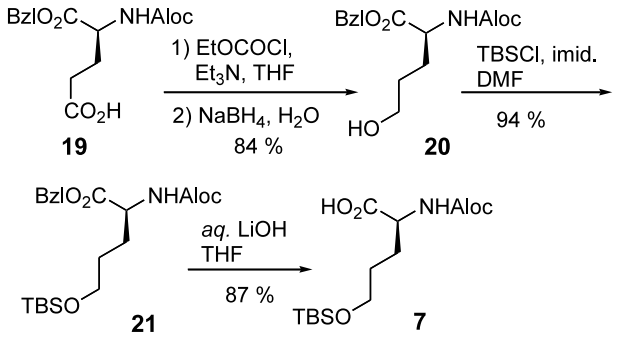
Scheme 1.

excess triethylamine also gave the Abu fragment **9** in low yield (entry 2). Burgess reagent[12] was also ineffective for this dehydrative elimination (entry 3). We next applied the Shanzer's one-pot protocol[13] from **8** using (diethylamino)sulfur trifluoride (DAST, Et_2N–SF_3) with triethylamine as the dehydrative agent to afford **9** in 51% yield (entry 4). Interestingly, the efficient and stereospecific elimination of **8** was achieved by using Martin's sulfurane (diphenyl bis(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propyl)sulfurane)[14] to produce **9** in 63% yield (entry 5).

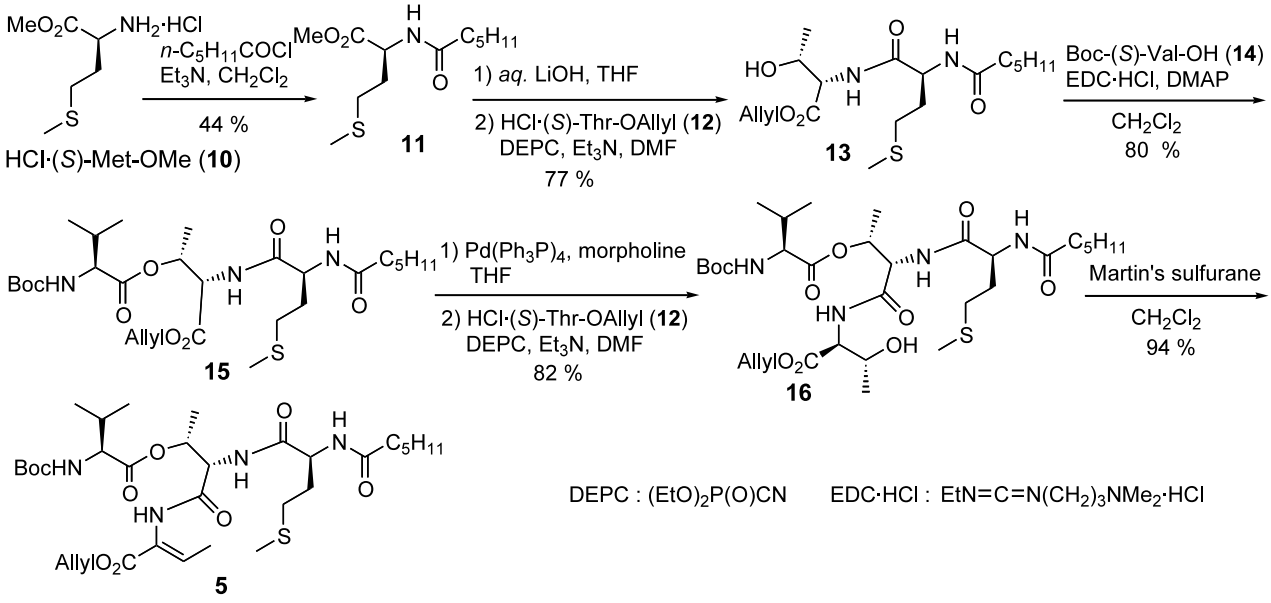
Since the deprotection of the Troc group in **9** led to complex mixtures, the synthesis of the depsipeptide fragment **5** was started by installation of the side chain. Treatment of HCl·(*S*)-Met-OMe (**10**) with hexanoyl chloride gave the *N*-acyl methionine **11**, which was hydrolyzed and then coupled with HCl·(*S*)-Thr-OAllyl (**12**) using diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$)[15] to afford the side chain-containing threonine **13** in 77% yield. Esterification of the threonine hydroxy group with Boc-(*S*)-Val-OH (**14**) using *N*-ethyl-*N*′-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC·HCl) gave the ester **15** in 80% yield, which was treated with $Pd(Ph_3P)_4$ in the presence of morpholine, followed by coupling with HCl·(*S*)-Thr-OAllyl (**12**) using DEPC to afford the *N*-acyl threonine ester **16** in 82% yield. The new Martin's sulfurane mediated elimination of the *N*-acyl threonine ester **16** led to the formation of the depsipeptide fragment **5** in 94% yield (Scheme 2).[16]

The dipeptide **6** was prepared from Boc-(*S*)-*N*-MeTyr(TBDPS)-OTce (**17**) through acidic removal of the Boc group followed by coupling with Boc-(*S*)-Phe-OH (**18**) using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BopCl)[17] in 76% yield (Scheme 3).

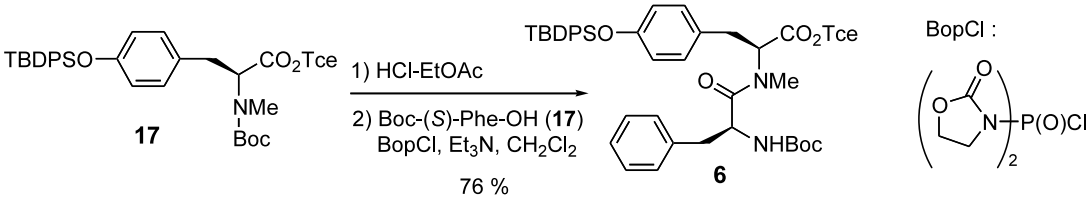
The 5-hydroxynorvaline derivative **7** was obtained from Aloc-(*S*)-Glu-OBzl (**19**) by reduction of the side chain carboxyl group via the mixed anhydride, protection of the resulting primary alcohol with TBSCl, and hydrolysis of the benzyl ester (Scheme 4).



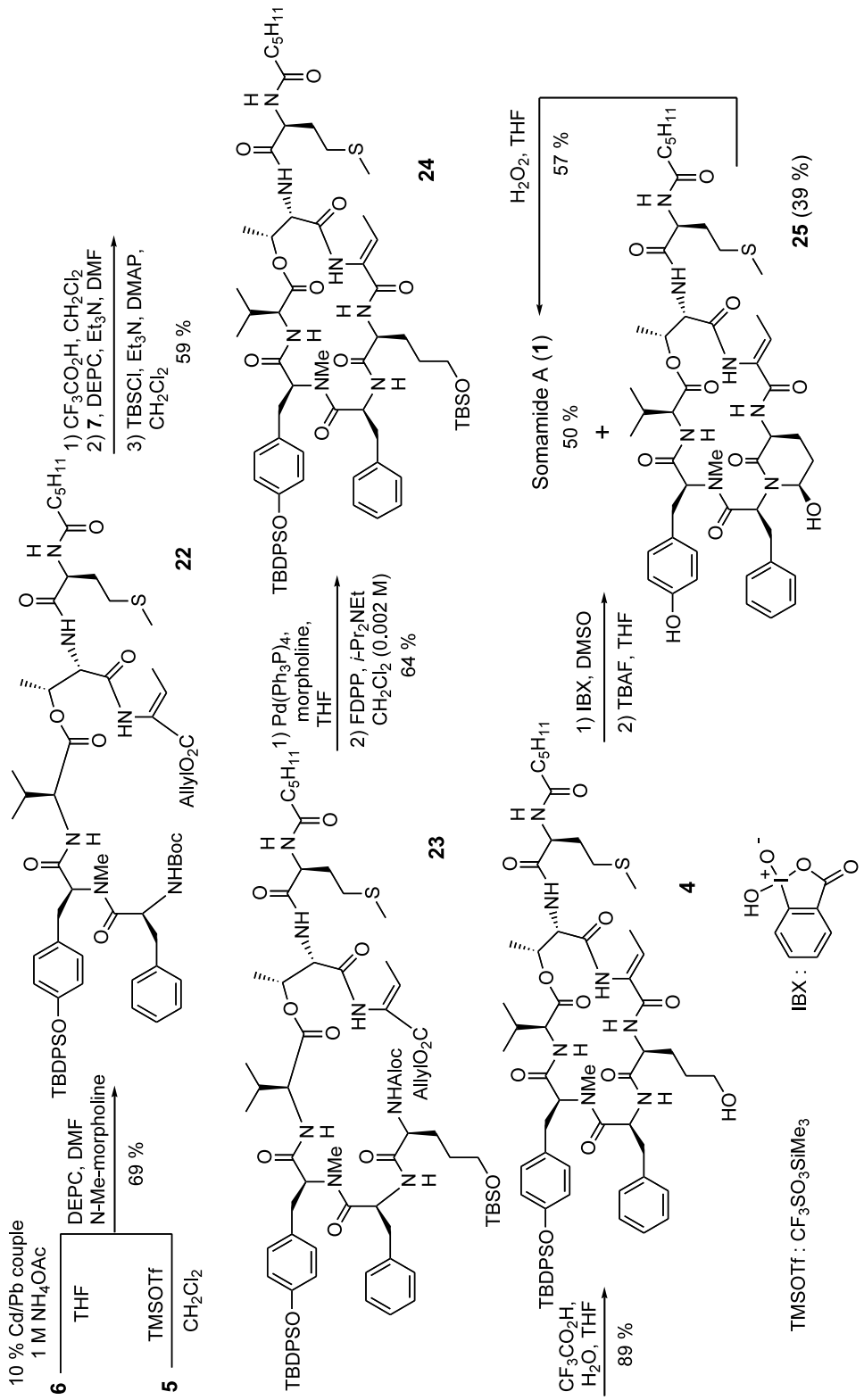
Scheme 4.



Scheme 2.



Scheme 3.


10 % Cd/Pb couple
1 M NH4OAc
THF
DEPC, DMF
N-Me-morpholine
69 %
6
5
TMSOTf
CH2Cl2
TBDPSO
NHBoc
AllylO2C
22
1) CF3CO2H, CH2Cl2
2) 7, DEPC, Et3N, DMF
3) TBSCl, Et3N, DMAP, CH2Cl2
59 %
1) Pd(Ph3P)4, morpholine, THF
2) FDPP, i-Pr2NEt CH2Cl2 (0.002 M)
64 %
NHAloc
23
24
CF3CO2H, H2O, THF
89 %
1) IBX, DMSO
2) TBAF, THF
4
H2O2, THF
57 %
Somamide A (1)
50 %
25 (39 %)
TMSOTf : CF3SO3SiMe3
IBX :

Scheme 5.

With the required building blocks in hand, the fragment condensation was initiated by deprotection of the Tce ester[18] in **6** and the Boc group in **5**, followed by coupling of the two deprotected fragments using DEPC to give **22** in 69% yield. After acidic removal of the Boc group in **22**, condensation with the norvaline derivative **7** and reprotection of the partially deprotected OH group with TBSCl produced the linear depsipeptide **23** in 59% yield. Treatment of **23** with $Pd(Ph_3P)_4$ in the presence of morpholine caused simultaneous removal of the *C*-terminus allyl ester and the *N*-terminus Aloc group, and then the macrolactamization using pentafluorophenyl diphenylphosphinate (FDPP, $Ph_2P(O)OC_6F_5$)[19] afforded the macrocyclic depsipeptide **24** in 64% yield. Finally, the construction of the Ahp moiety was performed by the strategy described in our previous paper.[10] After removal of the TBS group in **24**, treatment of the resulting primary alcohol **4** using 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX)[20] in DMSO gave a mixture of the aldehyde and further oxidized methionine sulfoxide, which were immediately exposed in TBAF to produce the Ahp moiety through the deprotection of the TBDPS group in Tyr and cyclization to the hemiaminal. After separation, the major product (50% yield) was somamide A (**1**), which was completely identical in all respects with spectra provided for the natural product.[21] The minor component **25** (39% yield) was slowly oxidized at the methionine residue under exposure to ambient atmosphere and characterized by conversion to somamide A (**1**) using *aq*. hydrogen peroxide in 57% yield. Therefore, our results indicate that the minor component **25** might be a true natural product and somamide A (**1**) is an artifact (Scheme 5).

In summary, we have accomplished the first total synthesis of somamide A (**1**), and demonstrated that our strategy for the construction of the Ahp moiety is suitable to the synthesis of the Ahp-containing natural products. Furthermore, we have found that Martin's sulfurane is a powerful agent for the dehydrative elimination of the *N*-acyl β-hydroxy-α-amino acid esters to the α,β-dehydroamino acid esters.[22]

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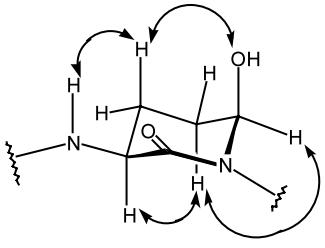
21. The relative stereochemistry for the Ahp residue has been confirmed from the ROESY correlations shown below (Ref. 8).



22. The details will be reported in the following paper: Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **2002**, *43*, 8679–8682.