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Novel stereospecific dehydration of β-hydroxy-α-amino acids using Martin's sulfurane

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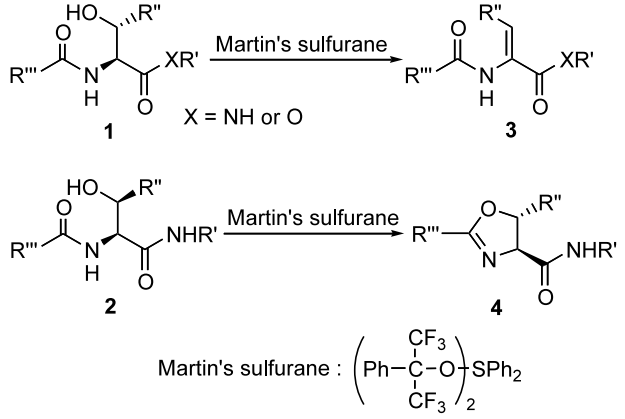
Abstract—The stereospecific dehydration of *threo*-*N*-acyl-β-hydroxy-α-amino acid derivatives was performed using Martin's sulfurane to give (*Z*)-α,β-dehydroamino acids, while *erythro*-*N*-acyl-β-hydroxy-α-amino acid amides were converted to 4,5-*trans*-oxazolines using analogous reaction conditions.

In the preceding communication,[1] we described the novel effective dehydrative elimination of *N*-acyl threonine ester using Martin's sulfurane (diphenyl bis(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propyl)sulfurane)[2] to provide the (*Z*)-Abu (2-amino-2-butenoic acid) moiety during the total synthesis of somamide A. We have further investigated the general aspects for the dehydrative reactions of β-hydroxy-α-amino acids using Martin's sulfurane. In this paper, we describe the stereospecific elimination of the *threo*-β-hydroxy-α-amino acid derivatives **1** to the dehydroamino acid derivatives **3** as well as the cyclodehydration to the 4,5-*trans*-oxazolines **4** from the *erythro*-*N*-acyl-β-hydroxy-α-amino acid amides **2** (Scheme 1).



Scheme 1.

As shown in Table 1, we initially attempted the dehydration of Boc-(*S*)-Phe-(*S*)-Thr-OAllyl (**5**) using (diethylamino)sulfur trifluoride (DAST, Et_2N-SF_3) with pyridine or triethylamine based on the Shanzer's conditions[3] to afford Boc-(*S*)-Phe-(*Z*)-Abu-OAllyl (**6**) in moderate yield (entries 1 and 2). In this reaction, the elimination of the intermediate $ROSF_2NEt_2$ derivative is likely to be sluggish with pyridine or triethylamine. Next, we applied two-step procedures that require DAST-Et_3N followed by exposure to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give **6** in higher yield (entry 3). It is noteworthy that the one-pot reaction of **5** using Martin's sulfurane without base smoothly occurred to produce **6** in 86% yield (entry 4). The dehydration of the threonine amide derivative **7** sluggishly proceeded even in the two-step protocol using DAST to give Boc-(*S*)-Phe-(*Z*)-Abu-(*S*)-Ala-OMe (**8**)[4] in 19% yield (entry 5). In contrast, the one-pot dehydration using Martin's sulfurane smoothly afforded **8** in 80% yield (entry 6). The other β-hydroxy-α-amino acid derivatives including *threo*-phenylthreonine, serine, and β-hydroxyvaline effectively underwent the dehydration to give the α,β-dehydroamino acid derivatives using Martin's sulfurane in good to excellent yields (entries 7–10). The noteworthy feature is that the reactions with Martin's sulfurane proceeded at room temperature for 1 h.

Remarkably, the threonine-thiazole moiety **17** was also smoothly eliminated to give the Thr-Abu-Thz fragment

Keywords: stereospecific dehydration; β-hydroxy-α-amino acid; Martin's sulfurane; dehydroamino acid; 4,5-*trans*-oxazoline.

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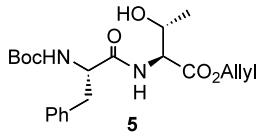
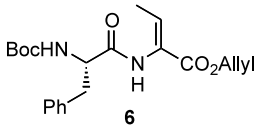
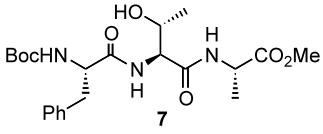
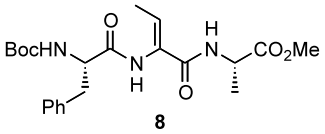
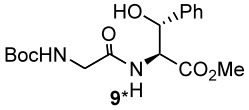
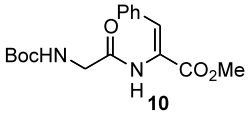
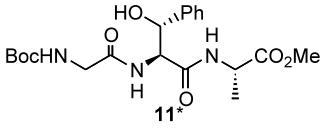
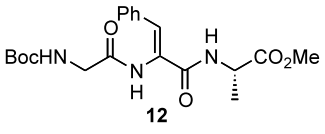
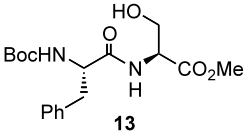
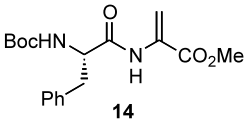
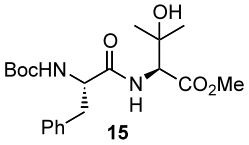
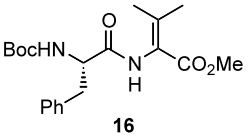
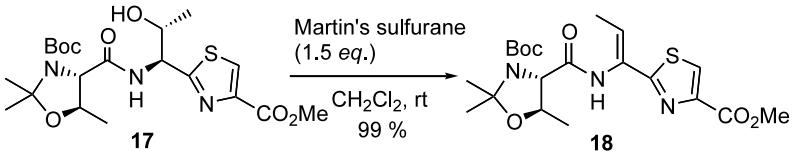
Table 1. Dehydrative elimination of the *N*-acyl-β-hydroxy-α-amino acid esters or amides

entry	substrate	product	reaction conditions	yield
1	 **5**	 **6**	DAST (1.5 *eq.*), Et_3N (3 *eq.*) CH_2Cl_2, -20 °C ~ rt	50 %
2	**5**	**6**	DAST (1.5 *eq.*), pyridine (3 *eq.*) CH_2Cl_2, 0 °C ~ rt	30 %
3	**5**	**6**	1) DAST (1.5 eq.), Et_3N (3 eq.) CH_2Cl_2, -20 °C ~ rt 2) DBU (1.5 eq.) CH_2Cl_2, rt	80 %
4	**5**	**6**	Martin's sulfurane (1.5 *eq.*) CH_2Cl_2, rt	86 %
5	 **7**	 **8**	1) DAST (1.5 eq.), Et3N (3 eq.) CH_2Cl_2, -20 °C ~ rt 2) DBU (1.5 eq.) CH_2Cl_2, rt	19 %
6	**7**	**8**	Martin's sulfurane (3 *eq.*) CH_2Cl_2, rt	80 %
7	 **9***H	 **10**	Martin's sulfurane (1.5 *eq.*) CH_2Cl_2, rt	96 %
8	 **11***	 **12**	Martin's sulfurane (1.5 *eq.*) CH_2Cl_2, rt	52 %
9	 **13**	 **14**	Martin's sulfurane (1.5 *eq.*) CH_2Cl_2, rt	70 %
10	 **15**	 **16**	Martin's sulfurane (1.5 *eq.*) CH_2Cl_2, rt	88 %

* Racemic threo-phenylthreonine derivative



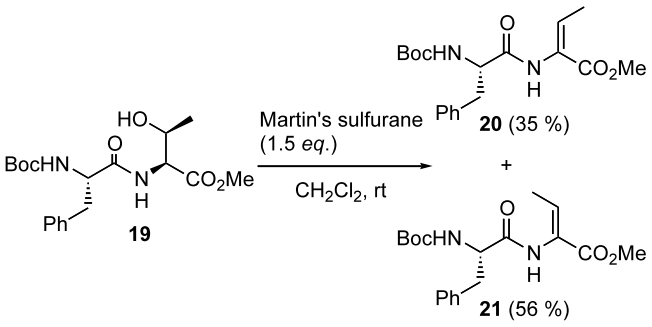
17 18

Scheme 2.

18[5] of micrococcin P_1 using this one-pot method (Scheme 2).[6]

Unfortunately, the treatment of the *N*-acyl *allo*-threonine ester **19** with Martin's sulfurane did not lead to the stereospecific elimination, but gave a mixture of *E* (**20**, 35%) and *Z* (**21**, 56%) isomers in the Abu residues (Scheme 3).

Interestingly, we observed that the *allo*-threonine residues in the peptide sequences could be converted to the corresponding 4,5-*trans*-oxazolines without compet-



Scheme 3.

ing formation of the Abu moiety under the one-pot Martin's sulfurane dehydrative conditions.[7] As shown in Table 2, this novel cyclodehydration protocol is suitable for the various *allo*-threonine-containing peptides (entries 1, 2). Especially, cyclodehydration of the cyclic peptide **26** using Martin's sulfurane provided the biologically active marine natural product, *cis*,*cis*-ceratospongamide (**27**)[8] in 81% yield (entry 3).

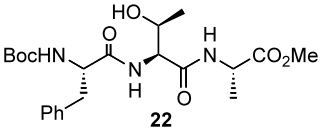
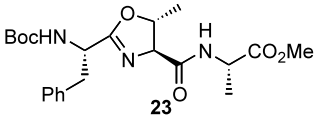
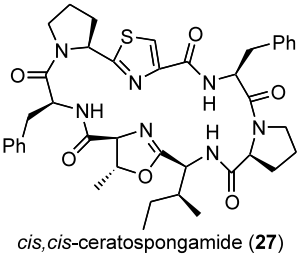
Furthermore, one of the noteworthy stereospecific feature of the method was well demonstrated by treatment of Boc-(*S*)-Phe-(*S*)-*a*Thr-(*S*)-Thr-OMe (**28**) with Martin's sulfurane, causing the oxazoline formation at the *a*Thr site and the dehydrative elimination at the Thr site to give the oxazoline-Abu product **29** in excellent yield (Scheme 4).

The plausible mechanism for the stereospecificity in this dehydrative reaction is shown in Scheme 5. The stereospecific formation of the (*Z*)-dehydroamino acids **3** from the *threo*-hydroxy amino acid derivatives **1** will proceed through the formation of the Martin's sulfurane intermediates **30a** followed by *trans* E_2 elimination from the antiperiplanar conformation, while these *threo* substrates did not undergo cyclization to the *cis*-oxazolines **4a** due to the less favorable formation of the sterically crowded intermediates **30b**.

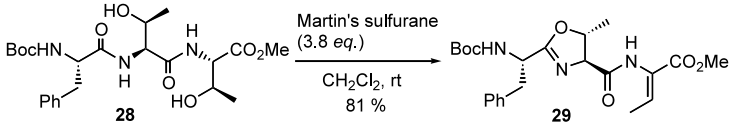
Similarly, the (*E*)-isomer **3a** would be a product expected to be formed from the *erythro* substrates **2b** if a *trans* E_2 elimination occurs as in the case of the reaction of **19** with Martin's sulfurane (Scheme 3). The (*Z*)-isomer **21** formed in this reaction might arise from isomerization of the thermodynamically less favored (*E*)-isomer **20**.[9] On the other hand, the *N*-*allo*-threonine amides **2a** will predominantly undergo cyclization to give the sterically favored *trans*-oxazolines **4** through the intramolecular S_N2 attack of the amide carbonyl groups, because of the lower acidity of the α-proton in the *allo*-threonine residues.

In summary, we have demonstrated that Martin's sulfurane is a useful reagent for the dehydrative elimination of *threo*-β-hydroxy-α-amino acid derivatives and cyclodehydration of *erythro*-*N*-acyl β-hydroxy-α-amino amides to 4,5-*trans*-oxazolines. Since Martin's sulfurane is a mild and neutral dehydrative agent, this one-pot protocol would be compatible with a wide

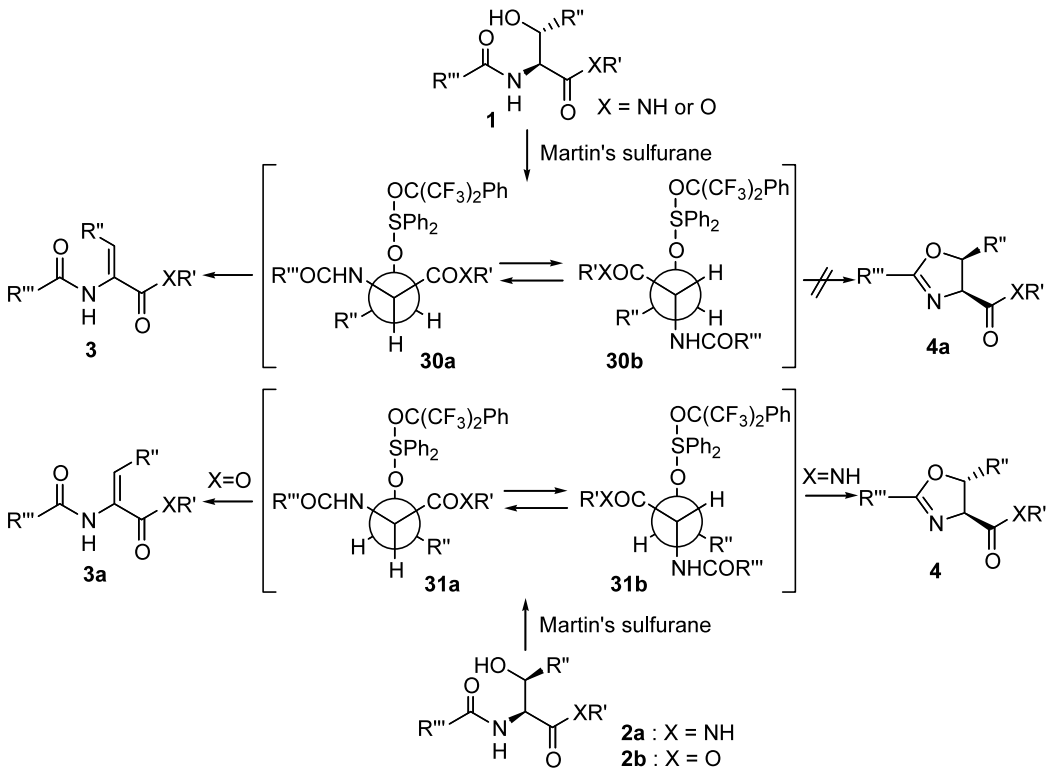
Table 2. Cyclodehydration of the *erythro*-*N*-acylthreonine amides with Martin's sulfurane

entry	substrate	product	yield
1	 **22**	 **23**	94 %
2	Boc-(*S*)-Ile-(*S*)-*a*Thr-(*S*)-Phe-(*S*)-Pro-Thz-OMe (**24**)	Boc-(*S*)-Ile-*trans*-oxazoline-(*S*)-Phe-(*S*)-Pro-Thz-OMe (**25**)	79 %
3	cyclo(-(*S*)-Phe-(*S*)-Pro-(*S*)-Ile-(*S*)-*a*Thr-(*S*)-Phe-(*S*)-Pro-Thz-) (**26**)	 *cis*,*cis*-ceratospongamide (**27**)	81 %

Reaction conditions: Martin's sulfurane (3 *eq.*), CH_2Cl_2, rt.



Scheme 4.



Scheme 5.

range of functional groups and applicable to the synthesis of natural products.

Acknowledgements

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7. For the cyclodehydration of β-hydroxy amides to oxazolines, see: Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett*. **2000**, *2*, 1165–1168, and references cited therein.
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