An Efficient Synthesis of the Piperazinone Fragment of Pseudotheonamide A_1 *via* a Stereoselective Intramolecular Michael Ring Closure

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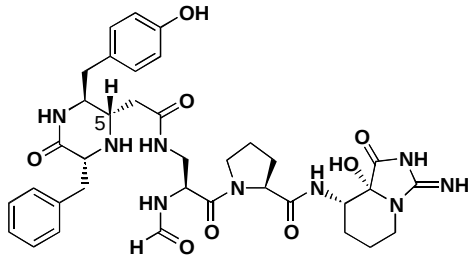
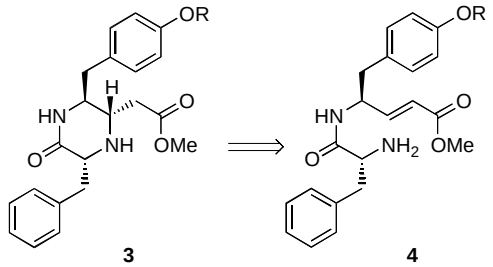
The stereoselective intramolecular Michael ring closure of the dipeptide efficiently gives the piperazinone fragment of pseudotheonamide A_1, a serine protease inhibitor from the marine sponge *Theonella swinhoei*.

Pseudotheonamides have been isolated by Fusetani and co-workers[1] from the marine sponge *Theonella swinhoei* collected off Hachijo-jima Island in Japan. They show interesting serine protease inhibitory activity. Pseudotheonamides A_1 (**1**) and A_2 (**2**) are the principal members of pseudotheonamides, and have a unique piperazinone ring system. The configuration of **1** at C_5 has proved to be *S* while that of **2** is *R*.



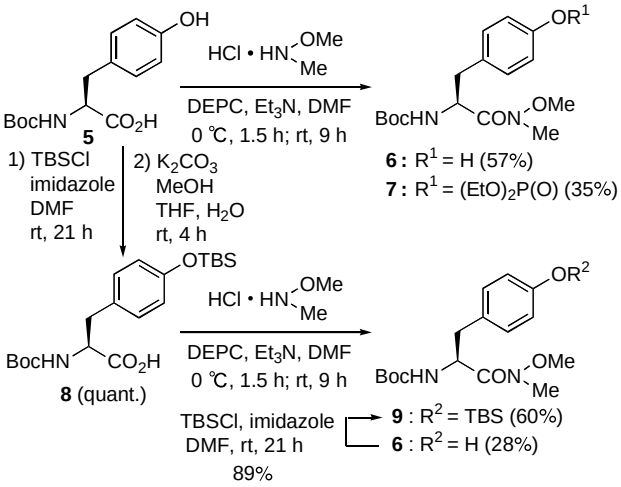
Pseudotheonamide A_1 (**1**)

We have been quite interested in the synthesis of structurally intriguing and biologically active peptides of aquatic origin,[2] and we already finished the total synthesis of cyclotheonamide B,[3] a macrocyclic analog of pseudotheonamides. Along this line, we now selected pseudotheonamide A_1 (**1**) as a synthetic target. We wish to report here an efficient synthesis of the piperazinone fragment as its protected form **3** (R=2,6-dichlorobenzyl, Cl_2Bzl).[4] The key step of our synthesis is the stereoselective intramolecular Michael ring closure of the dipeptide **4**,[5] shown in Scheme 1.



Scheme 1.

First, conversion of *tert*-butyloxycarbonyl(BOC)-L-tyrosine (**5**) to the corresponding Weinreb amide **6** by use of methoxy methyl amine and diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$)[6] afforded the desired **6** together with the O-phosphorylated one **7**,[7] as shown in Scheme 2. On the other hand, O-*tert*-butyldimethylsilyl(TBS)-L-tyrosine (**8**), prepared from **5**,[8] resulted in the formation of a mixture of the O-TBS derivative **9** and the O-deprotected one **6**. However, the latter was easily transformed to the former with TBSCl.

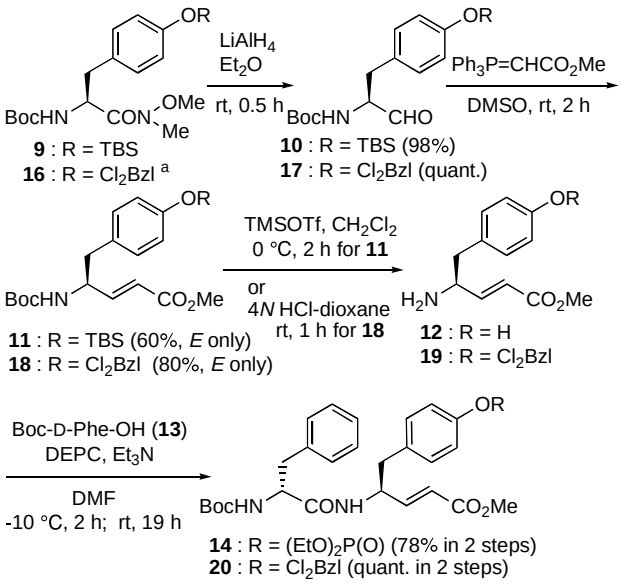


Scheme 2.

Reduction of **9** with lithium aluminum hydride gave the aldehyde **10**, which underwent the Wittig olefination with methoxycarbonylmethylenetriphenylphosphorane to give the (*E*)-α,β-unsaturated ester **11** as a sole isolable product, as shown in Scheme 3. Removal of the both Boc and O-TBS functions with trimethylsilyl trifluoromethanesulfonate (TMSOTf), followed by the coupling of the resulting amino compound **12** with Boc-D-phenylalanine (**13**) smoothly proceeded to yield the dipeptide **14** whose phenolic O-function was phosphorylated. Although the phosphoryl group might work as a protective group, it is not tolerant under alkaline conditions and its deprotection seemed to be rather difficult at some stages of the synthesis of pseudotheonamide A_1 (**1**). Thus we decided the change of the protective group, and the group we selected was the 2,6-dichlorobenzyl one.

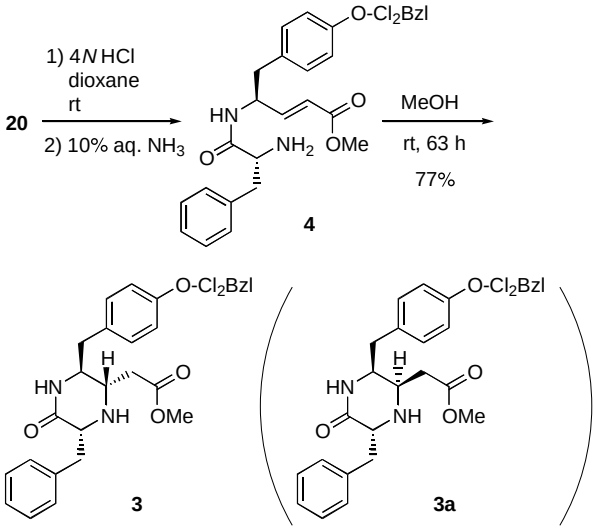
O-2,6-Dichlorobenzyl(Cl_2Bzl)-Boc-L-tyrosine (**15**) was converted to the Weinreb amide **16**, which was reduced with lithium aluminum hydride to give the aldehyde **17**. The Wittig olefination with the phosphorane, acidic treatment of the resulting α,β-unsaturated ester **18**, followed by the coupling of the deprotected amine **19** with Boc-D-phenylalanine (**13**) efficiently afforded the α,β-unsaturated ester **20** (Scheme 3).

After acidic removal of the Boc group followed by neutralization, the intramolecular Michael ring closure of the resulting dipeptide **4** was investigated under several reaction conditions. So far, the reaction at room temperature in methanol gave the best result, and the required piperazinone derivative **3**



[a] Prepared from O-2,6-dichlorobenzyl-Boc-L-tyrosine (**15**).[8]

Scheme 3.



Scheme 4.

was obtained in 77% yield,[9,10] (Scheme 4). The diastereoisomer **3a**, a component of pseudotheonamide A_2 (**2**), was also obtained under some reaction conditions. Addition of triethylamine to methanol increased this diastereoisomer **3a** (**3**, 46%; **3a**, 41%).

Interestingly, the intermolecular Michael addition of the α,β-unsaturated ester **18** with D-phenylalanine trimethylsilylethyl ester (**21**), prepared from **13**, did not proceed at all under analogous reaction conditions to give the Michael adduct **22**, as shown in Scheme 5.

Thus, we could establish a convenient route to the piperazinone ring component of pseudocyclotheonamide A_1 by use of an intramolecular Michael ring closure as the key step. The method developed here will offer the general procedure for the construction of the piperazinone skeleton. The total synthesis of pseudotheonamide A_1 (**1**) is now under way.

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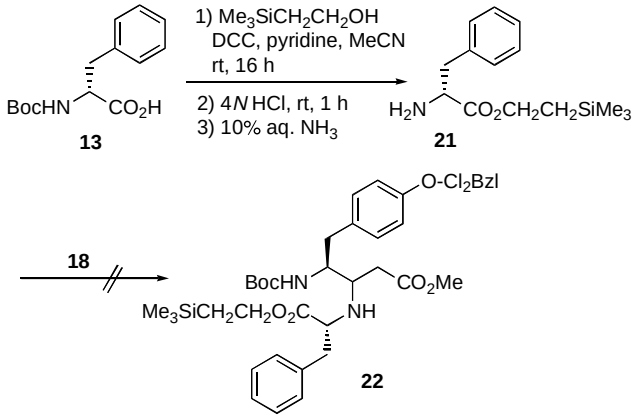

Scheme 5.

Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

1 Y. Nakao, A. Masuda, S. Matsunaga, and N. Fusetani, *J. Am. Chem. Soc.*, **121**, 2425 (1999).
2 T. Shioiri and Y. Hamada, *Synlett*, **2001**, 184.
3 J. Deng, Y. Hamada, T. Shioiri, S. Matsunaga, and N. Fusetani, *Angew. Chem., Int. Ed. Engl.*, **33**, 1792 (1994); J. Deng, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, **37**, 2261 (1996).
4 N. Irako and T. Shioiri, the 121st Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, March 2001, Abstr., Vol. 2, p 52.
5 The possibility of the intramolecular Michael addition of the amino group of phenylalanine to the vinylogous tyrosine residue was already suggested.[1] For a piperazinone synthesis through the Michael addition, see also D. A. Goff and R. N. Zuckermann, *Tetrahedron Lett.*, **37**, 6247 (1996).
6 S. Takuma, Y. Hamada, and T. Shioiri, *Chem. Pharm, Bull.* **30**, 3147 (1982) and references therein.
7 The phenolic O-phosphorylation by use of DEPC was already known: A. Guzmán and E. Diaz, *Synth. Commun.*, **27**, 3035 (1997).
8 T. Shioiri, T. Imaeda, and Y. Hamada, *Heterocycles*, **46**, 421 (1997).
9 The piperazinone **3** will be more stable than its isomer **3a**, from which the stereochemical assignment of both isomers will be deduced in addition to spectral evidence. **3**: IR ν_{max} (CHCl3) cm^{-1}: 3378, 2951, 1732, 1667, 1510, 1439, 1240, 1017, 756. ^{1}H-NMR (TMS/CD_3OD, 500 MHz) δ 2.26(dd, J = 16.1, 9.1 Hz, 1H), 2.56(dd, J = 6.7, 14.3 Hz, 1H), 2.61(dd, J = 16.1, 3.1 Hz, 1H), 2.66(dd, J = 14.0, 9.1 Hz, 1H), 2.81–2.86(m, 2H), 3.19–3.28(m, 1H), 3.34–3.39(m, 2H), 3.43(s, 3H), 5.16(s, 2H), 5.16(s, 2H), 6.89(d, J = 8.5 Hz, 2H), 7.07(d, J = 8.8 Hz, 2H), 7.10–7.34(m, 8H); **3a**: IR ν_{max}(neat) cm^{-1}: 3326, 2857, 1732, 1661, 1510, 1439, 1240, 1177, 1017, 765. ^{1}H-NMR (TMS/CD_3OD, 500 MHz) δ 2.41(dd, J = 15.2, 9.8 Hz, 1H), 2.47(dd, J = 15.2, 5.0 Hz, 1H), 2.64(d, J = 7.3 Hz, 2H), 2.81(dd, J = 13.7, 9.8 Hz, 1H), 3.05(dd, J = 13.7, 3.4 Hz, 1H), 3.40–3.44(m, 1H), 3.51(s, 3H), 3.55(dd, J = 9.8, 3.4 Hz, 1H), 3.60(dt, J = 7.3, 3.7 Hz, 1H), 5.18(s, 2H), 6.90(d, J = 8.8 Hz, 2H), 7.07(d, J = 8.8 Hz, 2H), 7.10–7.80(m, 8H).
10 Alkaline hydrolysis of **3** smoothly afforded the corresponding carboxylic acid.