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A novel application of a [3+2] cycloaddition reaction for the synthesis of the piperazinone rings of pseudotheonamides A_1 and A_2

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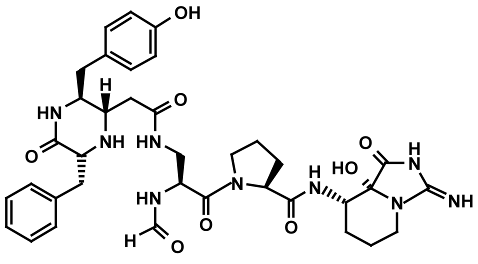
Abstract—A novel approach to synthesize the piperazinone ring system of pseudotheonamide A_1 and A_2 is described. The key step is the intramolecular [3+2] cycloaddition reaction of a suitably orientated azide and an α,β-unsaturated ester. © 2002 Elsevier Science Ltd. All rights reserved.

The four major classes of protease enzymes[1–4] (aspartic, serine, cysteine and metallo) selectively catalyze the hydrolysis of polypeptide bonds. Proteases of these classes are also crucial for disease propagation, and inhibitors of such proteases are emerging with promising therapeutic uses.[3,5] Among them, serine protease inhibitors are useful for the treatment of diseases like cancer,[6–8] viral infections (e.g. HIV,[9–11] hepatitis,[12,13] herpes[14,15]), and neurodegenerative disorders including Alzheimer's disease.[16] To be effective as biological tools, protease inhibitors must not only be very potent but also highly selective in binding to a particular protease.

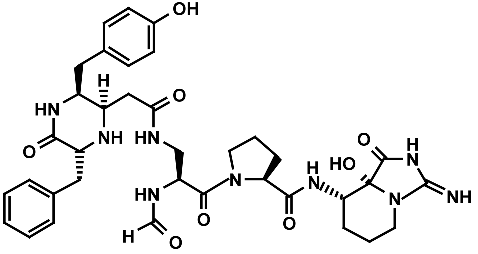
Recently, Fusetani and co-workers[17] have isolated pseudotheonamides from the marine sponge *Theonella swinhoe*, which possess potent serine protease inhibitor activity. Their absolute stereochemistry was determined by exhaustive spectroscopic studies coupled with chemical degradation. Interestingly, the mode of action of these natural products was elucidated by X-ray crystallographic studies of the complex between cyclotheonamide A and human α-thrombin or trypsin. Pseudotheonamides A_1 and A_2 are characterized by novel piperazinone and piperadinoiminoimidazolone ring systems. The novel structural features and pronounced inhibitory properties of pseudotheonamides A_1 and A_2 (Fig. 1) have attracted our attention for synthetic investigations.

Our retrosynthesis (Scheme 1) evolved from the strategy of disconnection of amide bonds leading to piperazinone derivative (**3**) and piperadinoiminoimidazolone (**4**), as key intermediates. This communication describes a first synthetic approach to obtain the *syn*- and *anti*-piperazinone moieties present in pseudotheonamides A_1 (**1**) and A_2 (**2**), respectively.

A dipolar cycloaddition reaction was chosen as the preferred strategy for controlling issues related to stereochemistry and regiochemistry.[18] For assembling the



pseudotheonamide A_1 [1]



pseudotheonamide A_2 [2]

Figure 1.

Keywords: azides; enamines; olefins; stereoselective; Dess–Martin reagents.

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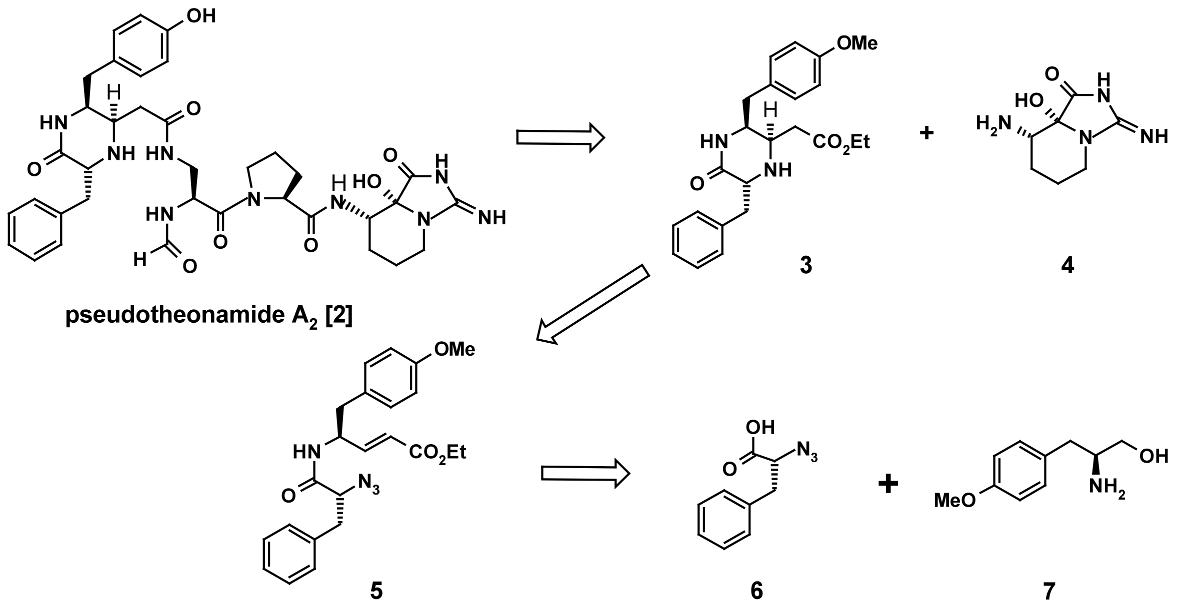


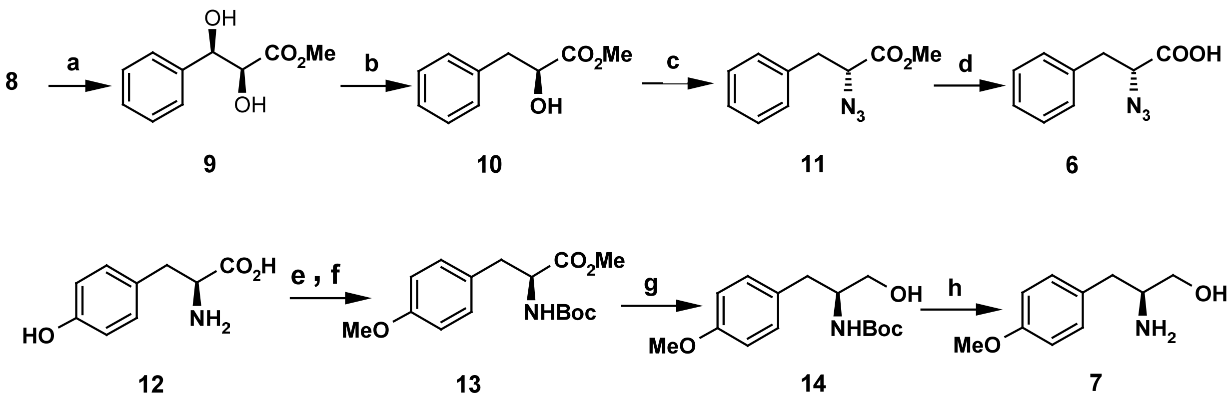
Scheme 1. Retrosynthetic analysis of pseudotheonamide A_2.

functional groups, the cycloaddition reaction between an azide and an α,β-unsaturated ester was selected for investigation.[19] It is pertinent to mention that methods to synthesize the piperazinones, substituted at position C-3 are found in the literature,[20] however, the corresponding 3,5-disubstituted compounds are rather rare.

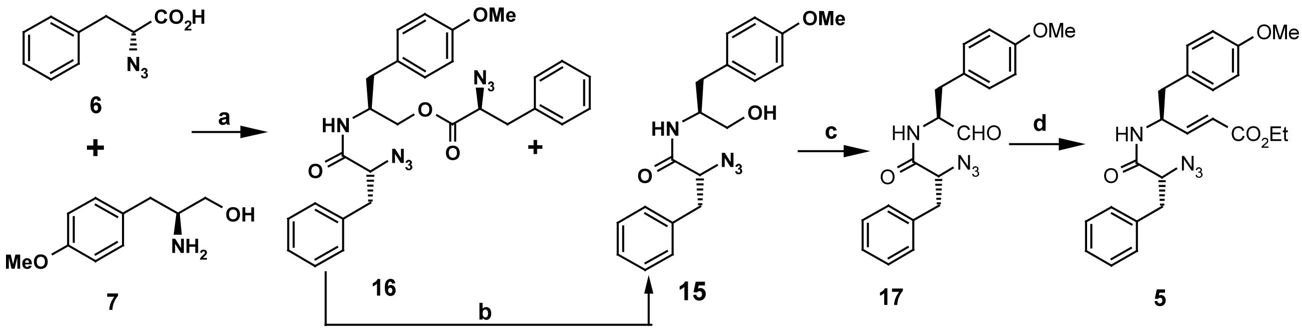
Our first concern was the preparation of the (*R*)-α-azido acid (**6**) for which an efficient and practical synthetic route was contemplated involving well known reactions.[21] Accordingly, the asymmetric dihydroxylation of methyl cinnamate (**8**) using $(DHQD)_2$–PHAL as a chiral ligand proceeded in 92% yield and 98% ee (HPLC).[22,23] The resulting (2*S*,3*R*)-dihydroxy derivative (**9**) was subjected to reduction of the benzylic hydroxyl group with Raney® Ni in refluxing ethanol to give the (2*S*)-hydroxy derivative (**10**) as the exclusive product. Nucleophilic displacement of the mesylate with sodium azide in DMF at 60°C followed by saponification with LiOH in methanol provided the desired (*R*)-α-azido acid (**6**) (Scheme 2).

p-Methoxyphenylalaninol (**7**) was prepared (Scheme 2) following standard reaction conditions.[24]

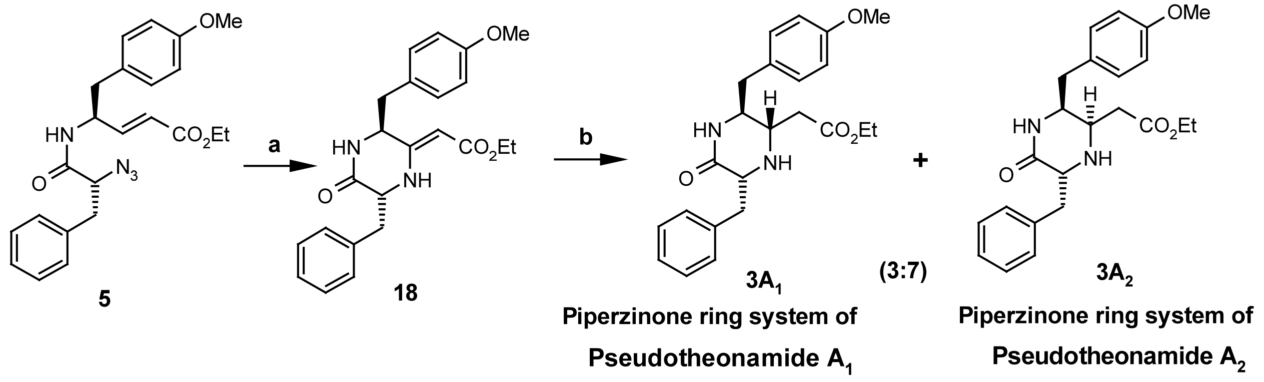
The coupling reaction (Scheme 3) of *p*-methoxyphenylalaninol (**7**) with the (*R*)-α-azido acid (**6**) promoted with DCC–HOBT in CH_2Cl_2 provided the required dipeptide (**15**) along with the dipeptide ester (**16**) as a minor component. Subsequent hydrolysis of **16** with LiOH in methanol gave an additional quantity of **15**. The resulting alcohol was then exposed to Dess–Martin periodinane oxidation to obtain the aldehyde **17**. The crude aldehyde **17** was subjected to a two carbon homologation with (ethoxycarbonylmethylene)triphenylphosphorane to furnish the α,β-unsaturated ester (**5**) (Scheme 3) in 92% overall yield.



Scheme 2. (a) $(DHQD)_2$–PHAL, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, OsO_4, *t*-BuOH:H_2O (2:1), 0°C, 11 h, 92%; (b) Raney Ni, ethanol (degassing), reflux, 3 h, 81%; (c) (i) MsCl, Et_3N, CH_2Cl_2, 0°C–rt, 4 h; (ii) NaN_3, DMF, 60°C, 6 h, 86% (two steps); (d) LiOH, MeOH, rt, 1 h, 94%; (e) Boc_2O, KOH, dioxane:H_2O (1:1), rt, 6 h, 92%; (f) Me_2SO_4, K_2CO_3, acetone, reflux, 7 h, 90%; (g) LiCl, $NaBH_4$, EtOH:THF (2:1), 4 h, 87%; (h) 15% HCl, EtOAc, 0°C–rt, 1 h, 86%.



Scheme 3. (a) DCC, HOBT, CH_2Cl_2, 0°C–rt, 16 h, 82%; (b) LiOH, MeOH, rt, 30 min, 94%; (c) Dess–Martin periodinane, CH_2Cl_2, rt, 7 h; (d) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 12 h, 92% (two steps).



Scheme 4. (a) Et_3N (catalytic), toluene, reflux, 7 h, 56%; (b) $NaCNBH_3$, MeOH, 5% HCl, 0°C, rt, 2 h, 90%.

Our next plan was to optimize the cycloaddition reaction of the azido group on the double bond followed by elimination of nitrogen to give the enamine system. Satisfactory results were obtained when compound **5** was heated under reflux in toluene containing a catalytic amount of triethylamine.[25,26] The structure of **18** was established by ^1H NMR, ^{13}C NMR and mass spectroscopic analysis.

Finally, reduction of the enamine bond of **18** was carried out with sodium cyanoborohydride[27] in methanol while maintaining the pH at 4 with intermittent addition of 5% HCl to give a 3:7 mixture of piperazinones (**3A₁**) and (**3A₂**), which were easily separated by silica gel column chromatography. The structure and relative stereochemistries of $\mathbf{3A_1}$ and $\mathbf{3A_2}$ were determined by NMR studies.[28] For example, in the ^1H NMR spectrum of $\mathbf{3A_1}$, the peak corresponding to the proton Tyr H_β, appeared at δ 3.00, and showed coupling with the Tyr $H\gamma$ (proton attached to the γ-carbon relative to the carbonyl group of ester) with $J = 9.0$ Hz indicating the *trans* relationship. NOE studies on $\mathbf{3A_1}$ showed the interaction of Tyr H_β with Phe H_α confirming the *syn* geometry of the piperazinone ring system. In addition, ^{13}C NMR and mass spectral data further substantiated the assigned structure of compound $\mathbf{3A_1}$. In a similar manner the structure of the other diastereomer was established as $\mathbf{3A_2}$. It is pertinent to mention that catalytic hydrogenation over Pt–C in methanol at 50 psi provided $\mathbf{3A_2}$ in a 9:1 diastereomeric ratio.

In conclusion, we have demonstrated the applicability of an intramolecular 1,3-dipolar cycloaddition reaction of an azide with an α,β-unsaturated ester for the synthesis of the 3,5-disubstituted piperazinone ring system present in pseudotheonamide A_1 and A_2. Our work represents a first synthesis of the piperazinone ring system present in pseudotheonamides A_1 and A_2 (Scheme 4). The synthesis of pipradinoiminoimidazolone **4** leading to the total synthesis of pseudotheonamides A_1 and A_2 is in progress.

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22. Enantiomeric purity of **9** was verified by HPLC analysis (compared with the racemic **9**). HPLC conditions: column, CHIRAL CELL OJ; mobile phase, isopropyl alcohol: hexane (10:90); flow rate, 1 mL/min; UV detection at 254 nm.
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28. All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and/or elemental analysis. Selected spectral data of some of the important compounds are given below: compound **15**: IR (neat) 1665 (C=O), 2114 (N_3), 3402 (OH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.69 (dd, 1H, J=8.0, 14.4 Hz), 2.79 (dd, 1H, J=6.6, 14.4 Hz), 3.06 (dd, 1H, J=5.9, 14.4 Hz), 3.27 (dd, 1H, J=4.8, 14.4 Hz), 3.46 (m, 2H), 3.78 (s, 3H), 4.04 (m, 1H), 4.18 (dd, 1H, J=4.8, 5.9 Hz), 6.29 (d, 1H, J=6.4 Hz), 6.79 (d, 2H, J=8.0 Hz), 7.03 (d, 2H, J=8.0 Hz), 7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.0, 38.4, 52.7, 55.0, 63.2, 65.4, 114.1, 127.2, 128.6, 129.2, 129.5, 130.1, 136.1, 158.5; MS: m/z 355 (M$^+$+1). Compound **18**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, 3H, J=7.1 Hz), 2.89 (m, 3H), 3.28 (m, 2H), 3.78 (s, 3H), 3.89 (m, 1H), 4.10 (q, 2H, J=7.1 Hz), 4.57 (s, 1H), 6.82 (m, 3H), 7.03 (d, 2H, J=7.1 Hz), 7.10–7.40 (m, 5H), 8.68 (s, 1H); ^{13} C NMR (50 MHz, $CDCl_3$) δ 14.4, 38.0, 42.7, 54.6, 55.0, 58.5, 80.6, 114.0, 126.8, 127.0, 128.5, 129.3, 131.0, 136.1, 156.7, 159.0, 170.0; MS: m/z 394 (M$^+$). Compound **3A$_2$**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, 3H, J=7.2 Hz), 2.52 (dd, 2H, J=5.5, 15.1 Hz), 2.53 (dd, 1H, J=10.2, 15.1 Hz), 2.62 (dd, 1H, J=9.6, 15.1 Hz), 2.74 (dd, 1H, J=4.1, 13.8 Hz), 3.32 (dd, 1H, J=3.0, 13.8 Hz), 3.65 (m, 1H), 3.76 (dd, 2H, J=2.8, 9.6 Hz), 3.81 (s, 3H), 4.07 (m, 2H), 5.66 (s, 1H), 6.88 (d, 2H, J=8.3 Hz), 7.09 (d, 2H, J=8.3 Hz), 7.22–7.35 (m, 6H). Compound **3A$_1$**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, 3H, J=6.2 Hz), 2.36 (dd, 1H, J=10.2, 13.7 Hz), 2.42 (dd, 1H, J=7.5, 15.0 Hz), 2.67 (dd, 1H, J=2.5, 15.0 Hz), 2.82 (dd, 1H, J=10.0, 13.7 Hz), 2.94 (dd, 1H, J=2.5, 12.5 Hz), 3.00 (dt, 1H, J=2.5, 9.0, 12.5 Hz), 3.38 (dt, 1H, J=2.5, 10.0, 12.5 Hz), 3.43 (dd, 1H, J=2.5, 12.5 Hz), 3.63 (dd, 1H, J=3.5, 9.0 Hz), 3.82 (s, 3H), 4.01 (q, 2H, J=6.25 Hz), 5.57 (s, 1H), 6.88 (d, 2H, J=8.0 Hz), 7.08 (d, 2H, J=8.0 Hz), 7.29 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 29.8, 37.1, 37.7, 38.6, 55.2, 55.25, 58.2, 59.8, 60.8, 114.8, 126.6, 128.6, 129.4, 130.2, 138.2, 159.1, 170.7; MS: m/z 397 (M$^+$+1).