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Total synthesis of didmolamides A and B

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Abstract—The first total synthesis of didmolamides A (**1**) and B (**2**) has been accomplished by the solid phase assembly of thiazole-containing amino acids and commercially available Fmoc-protected amino acids. The synthesis of didmolamide B was also achieved in high yield using solution phase peptide synthesis. The thiazole-containing amino acid composing **1** and **2** was synthesized by a MnO_2 oxidation of a thiazoline, prepared from an Ala-Cys dipeptide using bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate. The final macrolactamization was accomplished efficiently by PyBOP and DMAP in solution.

Many oxazole and/or thiazole-containing macrolactams have been recently isolated from marine organisms.[1] Their activities, including cytotoxicity, multiple drug resistance pump inhibition, as well as their metal binding, and transport properties, have led to much synthetic interest.[2,3] Didmolamides A and B (Fig. 1), isolated from the marine ascidian *Didemnum molle* collected in Madagascar, were shown to be mildly cytotoxic with IC_{50} values of 10–20 μg/mL.[4] Recently, we reported a facile and efficient biomimetic synthesis of thiazolines accomplished by treating *N*-acylated cysteine substrates with bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate.[5] Thiazoles can in turn be obtained by oxidation of the thiazolines. Dendroamide A,[6] bistratamides E–J,[7] tenuecyclamides A–D[8] and their analogs have been efficiently synthesized by taking advantage of this methodology. In this letter, we report the total synthesis of didmolamides A (**1**) and B (**2**).

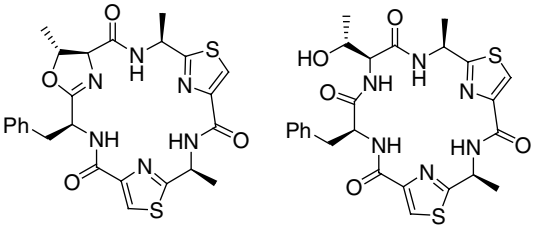

Figure 1. Line drawings of didmolamides A (**1**) and B (**2**).

The retrosynthetic analysis for didmolamide A (**1**) is shown in Figure 2. Disconnections at the amide bonds and oxazoline ring result in two commercially available amino acids and two identical thiazole-based amino acids (**3**).

The thiazole-containing amino acid (**3**) was synthesized as shown in Scheme 1. The synthesis commences with the protection of the carboxylic acid of *N*-Fmoc-*S*-trityl-L-cysteine as an allyl ester. Fmoc deprotection allows the resulting amine to be coupled with an active ester of *N*-Fmoc-L-alanine to afford the fully protected dipeptide **4** (84% overall, three steps). Bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate was utilized to convert the trityl protected cysteine-containing dipeptide **4** into thiazoline **5** (92%). Thiazoline **5** was oxidized to

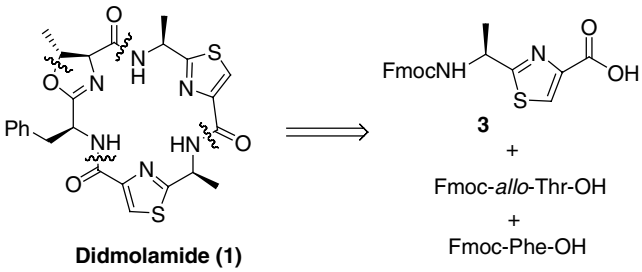

Figure 2. Retrosynthetic analysis for didmolamide A (**1**).

Keywords: Didmolamides; Bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate; Thiazoline; Thiazole.
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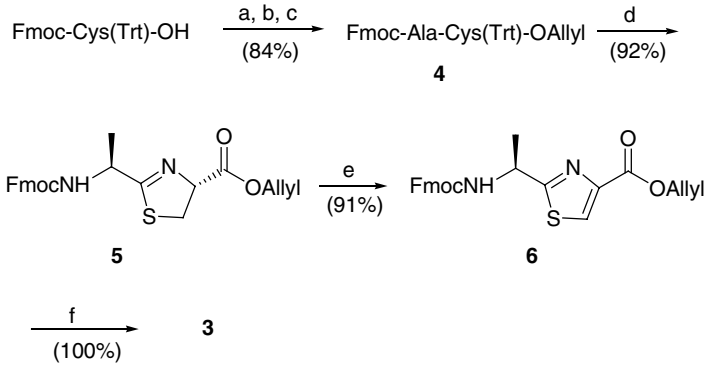
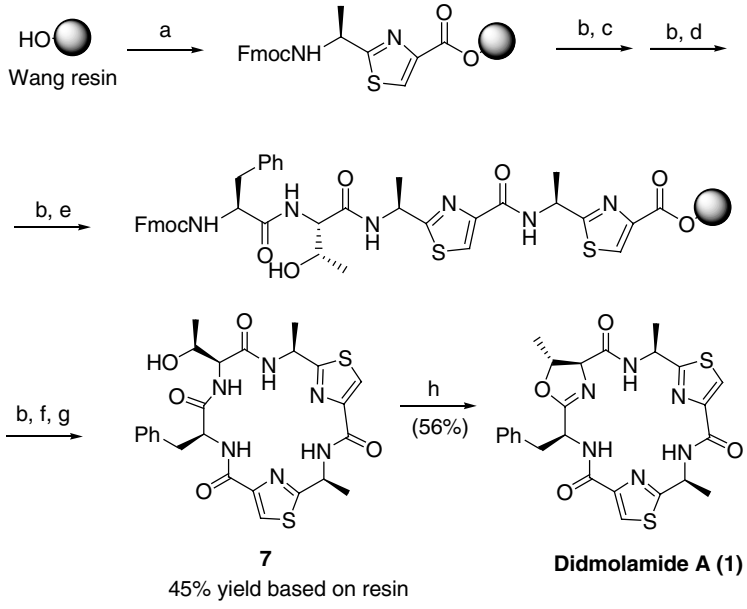


Scheme 1. Synthesis of the thiazole-containing amino acid **3**. Reagents and conditions: (a) HBTU, HOBt, DIEA, allyl alcohol; (b) diethylamine, CH_3CN; (c) HBTU, HOBt, DIEA, *N*-Fmoc-Ala-OH; (d) Ph_3PO, Tf_2O, CH_2Cl_2, −20 °C; (e) activated MnO_2; (f) $Pd(OAc)_2$, PS–PPh_3, $PhSiH_3$, CH_2Cl_2.

thiazole **6** employing activated manganese oxide (91%; >97% ee). Removal of the allyl ester protecting group using a palladium catalyst, generated from $Pd(OAc)_2$ and polymer-supported triphenylphosphine, afforded the amino acid **3**.[9]

The solid phase synthesis of **1** on Wang resin is depicted in Scheme 2.[10] The first coupling between the resin and thiazole amino acid **3** utilizing HBTU and HOBt in the presence of DIEA was performed for 8–12 h to ensure completion of ester bond formation. Removal of the Fmoc group was accomplished with 20% piperidine in DMF (1 h). Subsequent amide bond formation between the resin bound amine and the next thiazole-based amino acid residue (**3**) of the growing chain was enabled using HBTU/HOBt (2 h). After sequentially coupling *N*-Fmoc-*allo*-threonine and *N*-Fmoc-L-phenylalanine to the resin-bound peptide utilizing HBTU and HOBt in the presence of DIEA, the terminal Fmoc group was removed and the thiazole containing triamide was cleaved from the Wang resin using 95% TFA in CH_2Cl_2. Removal of the solvent yielded the amino acid macrolactamization precursor, which was transformed into the macrolactam **7** using a combination of PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) and DMAP (4-dimethylaminopyridine) in CH_2Cl_2/DMF (v/v: 2/1). Didmolamide A (**1**) was obtained as a white semisolid after refluxing the macrolactam **7** and the Burgess reagent in THF (56%).[2b,11] Its ^1H and ^{13}C NMR spectra are identical to those reported in the literature.[4]

Didmolamide B (**2**) was synthesized utilizing the same approach (Scheme 3), minus the treatment of the macrolactam with Burgess reagent. The *O*-trityl protecting group on the threonine residue was removed during



Scheme 2. Solid phase synthesis of didmolamide A (**1**). Reagents and conditions: (a) HBTU (2 equiv), HOBt (2 equiv), DIEA (3 equiv), **3** (2 equiv, 0.5 M in DMF), 8–12 h; (b) 20% piperidine in DMF, 1 h; (c) HBTU (2 equiv), HOBt (2 equiv), DIEA (3 equiv), **3** (2 equiv, 0.5 M in DMF), 2 h; (d) HBTU (2 equiv), HOBt (2 equiv), DIEA (3 equiv), *N*-Fmoc-*allo*-Thr-OH (2 equiv, 0.5 M in DMF), 2 h; (e) HBTU (2 equiv), HOBt (2 equiv), DIEA (3 equiv), *N*-Fmoc-Phe-OH (2 equiv, 0.5 M in DMF), 2 h; (f) 95% TFA in CH_2Cl_2, 3 h; (g) PyBOP (2 equiv), DMAP (2 equiv), DIEA (2 equiv), CH_2Cl_2, DMF; (h) Burgess reagent, THF, reflux.