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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 thiazolecontaining 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. © 2005 Elsevier Ltd. All rights reserved.

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



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

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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).

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<sub>3</sub>CN; (c) HBTU, HOBt, DIEA, *N*-Fmoc-Ala-OH; (d) Ph<sub>3</sub>PO, Tf<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C; (e) activated MnO<sub>2</sub>; (f) Pd(OAc)<sub>2</sub>, PS–PPh<sub>3</sub>, PhSiH<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>.

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**.<sup>9</sup>

The solid phase synthesis of 1 on Wang resin is depicted in Scheme 2.<sup>10</sup> 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<sub>2</sub>Cl<sub>2</sub>. 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<sub>2</sub>Cl<sub>2</sub>/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%).<sup>2b,11</sup> Its <sup>1</sup>H and <sup>13</sup>C NMR spectra are identical to those reported in the literature.<sup>4</sup>

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), 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 e



Scheme 3. Solid phase synthesis of didmolamide B (2). 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), DIEA (3 equiv), N-Fmoc-Thr(Trt)-OH (2 equiv, 0.5 M in DMF), 2 h; (e) HBTU (2 equiv), HOBt (2 equiv), DIEA (3 equiv), DIEA (3 equiv), N-Fmoc-Thr(Trt)-OH (2 equiv), 0.5 M in DMF), 2 h; (e) HBTU (2 equiv), HOBt (2 equiv), DIEA (3 equiv), DIEA (3 equiv), N-Fmoc-Thr(Trt)-OH (2 equiv), 95% TFA in CH<sub>2</sub>Cl<sub>2</sub>, 3 h; (g) PyBOP (2 equiv), DMAP (2 equiv), DIEA (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, DMF.

cleavage of the peptide from the Wang resin using TFA. Didmolamide B (2) was obtained as a white foam. Its  $^{1}$ H and  $^{13}$ C NMR spectra were reported in an undefined

mixture of CDCl<sub>3</sub> and CD<sub>3</sub>OD, however, upon request the author provided the <sup>1</sup>H spectrum in DMSO- $d_6$ , which is very similar to our spectra excepting the amide



Scheme 4. Solution phase synthesis of didmolamide B (2). Reagents and conditions: (a) Diethylamine, CH<sub>3</sub>CN; (b) 3, HBTU, HOBt, DIEA; (c) *N*-Fmoc-Thr(Trt)-OH, HBTU, HOBt, DIEA; (d) *N*-Fmoc-Phe-OH, HBTU, HOBt, DIEA; (e) Pd(OAc)<sub>2</sub>, PS–PPh<sub>3</sub>, PhSiH<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (f) PyBOP, DMAP, DMF/CH<sub>2</sub>Cl<sub>2</sub> (1/2); (g) TFA, PhSH, CH<sub>2</sub>Cl<sub>2</sub>.

resonances and the Thr hydroxyl resonance, which may be shifted owing to the presence of  $H_2O$  in their sample.<sup>4</sup>

In order to ensure the integrity of didmolamide B (2), its total synthesis was also accomplished in solution (Scheme 4). The carboxylic acid 3 was coupled with the free amine derived from 6 (generated by removing the Fmoc group with diethylamine) utilizing HBTU and HOBt in the presence of DIEA (Scheme 4). The amide-linked bisheterocycle 8 was obtained in 95% yield. Compound 8 was coupled sequentially with *N*-Fmoc-*O*-trityl-L-threonine and *N*-Fmoc-L-phenylalanine employing HBTU/HOBt/DIEA affording 9 (91%) and 10 (94%), respectively.

Deprotecting the Fmoc group in 10 using diethylamine followed by removal of the allyl ester protecting group using a palladium catalyst, generated from  $Pd(OAc)_2$ and polymer-supported triphenylphosphine, gave the amino acid macrolide precursor.<sup>9</sup> The macrolactamization was mediated by PyBOP and DMAP yielding 11 in 88% yield. After removing the trityl group from the threonine residue in 11, didmolamide B (2) was obtained. The properties of this compound were identical to those of didmolamide B (2) synthesized using a solid phase strategy.

In summary, 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 Fmoc-protected  $\alpha$ -amino acids. The synthesis of didmolamide B was also achieved using solution phase peptide synthesis (48% overall yield). The crucial thiazole amino acid (3) was synthesized by a MnO<sub>2</sub> 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 all cases.

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## Supplementary data

Experimental details and NMR data for compounds 1–11. Supplementary data associated with this article can

be found, in the online version, at doi:10.1016/j.tetlet. 2005.02.097.

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