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Total synthesis of the putative structure of the marine metabolite trunkamide A

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Abstract

The structure assigned to trunkamide A, a cycloheptapeptide alkaloid isolated from the colonial ascidian *Lissoclinum* sp., was prepared via segment condensations and an efficient oxazoline–thiazoline interconversion. The novel reverse prenylated serine and threonine amino acid building blocks were obtained by Lewis acid assisted opening of aziridines. In light of this total synthesis, the structure of natural trunkamide A needs to be revised.

A large number of azole-containing cyclopeptide alkaloids have been isolated from marine organisms, in particular ascidians from the genus *Lissoclinum*, and shown to exhibit moderate to high cytotoxicity.[1] In addition to their biological activities, the novel structural features and metal-binding properties of Lissoclinum peptides have attracted considerable synthetic work.[2,3] Most recent attention has focused on 16–24-membered macrocycles such as lissoclinamide 7 with three to four oxazoline, thiazoline, oxazole, and thiazole heterocycles as part of the primary sequence.[1,2] However, related cyclopeptide alkaloids such as mollamide that incorporate a single azole heterocycle continue to be isolated.[4,5] Specifically, the *Lissoclinum* sp. metabolite trunkamide A was reported[4] in 1996 and subsequently shown to exhibit attractive antitumor properties.[6] The structure was assigned based on extensive NMR and degradation studies.[4] We now report the first synthesis of the putative structure of trunkamide A; in consideration of the synthetic material, the structure originally assigned for this marine metabolite has to be revised. Synthetic **1** has different NMR and chiroptical properties from the natural compound which most likely represents a stereoisomer of **1**.

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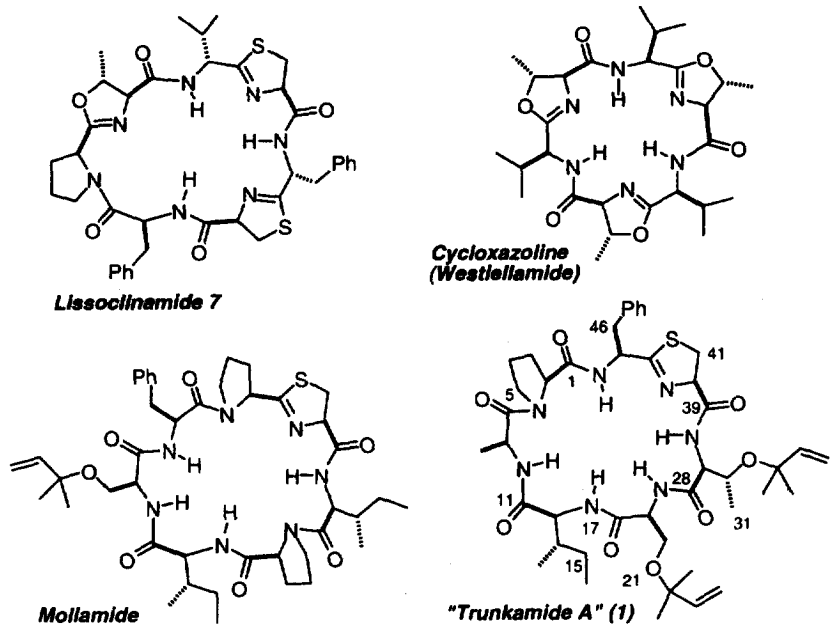
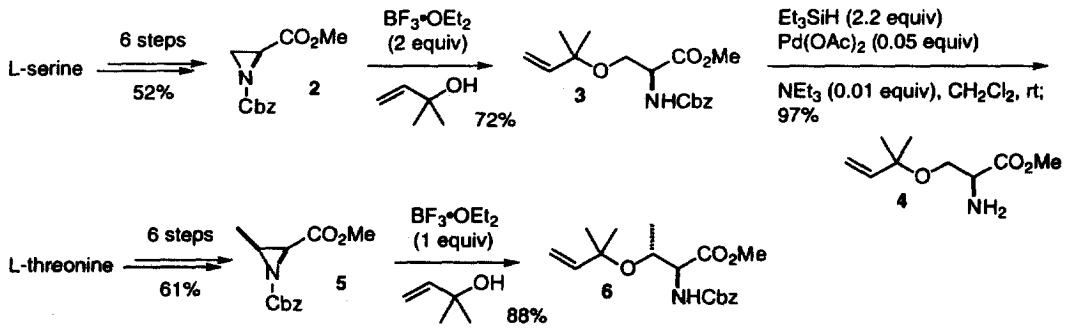


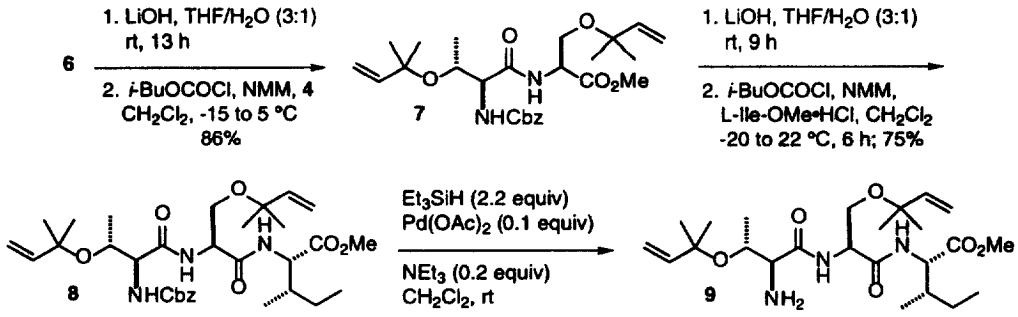
Trunkamide A and the structurally related patellins as well as other marine cyclopeptides contain serine and threonine residues that are modified as dimethyl allyl ('reverse prenyl') ethers.[5,7] For the preparation of these unusual side-chain unsaturated amino acids, we applied a Lewis-acid assisted ring-opening of activated aziridine derivatives **2** and **5**,[8] which were obtained in six steps and 52–61% yield according to literature protocols[9] (Scheme 1). Treatment of **2** with an excess of 1,1-dimethyl allyl alcohol in the presence of 2 equiv. of $BF_3 \cdot OEt_2$ provided the serine derivative **3** in 72% yield. Chemoselective deprotection of the Cbz group was readily accomplished by exposure to Et_3SiH and catalytic $Pd(OAc)_2$ in 97% yield.[10] In an analogous fashion, the threonine derivative **6** was obtained.[11]



Scheme 1.

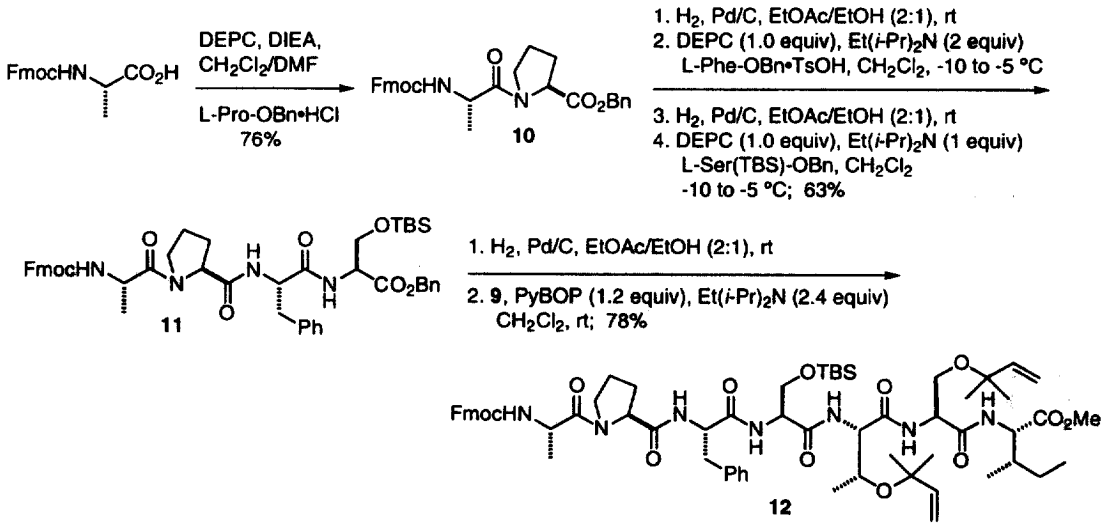
After ester saponification, the reverse prenylated threonine derivative **6** was coupled to the amine **4** under mixed anhydride conditions to give dipeptide **7** in 86% yield. Subsequent C-terminal chain extension followed by selective *N*-deprotection provided tripeptide segment **9** (Scheme 2).

For the preparation of the tetrapeptide segment of **1**, Fmoc-protected L-alanine was condensed with L-proline benzyl ester using the DEPC reagent (Scheme 3).[12] Iterative removal of the benzyl protective group followed by peptide coupling with L-phenylalanine and side-chain silylated L-serine led to tetrapeptide **11** in 48% overall yield based on Fmoc-alanine. Segment condensation with amine **9** proceeded smoothly to the fully protected heptapeptide **12**. The stage was now set for a macrolactamization



Scheme 2.

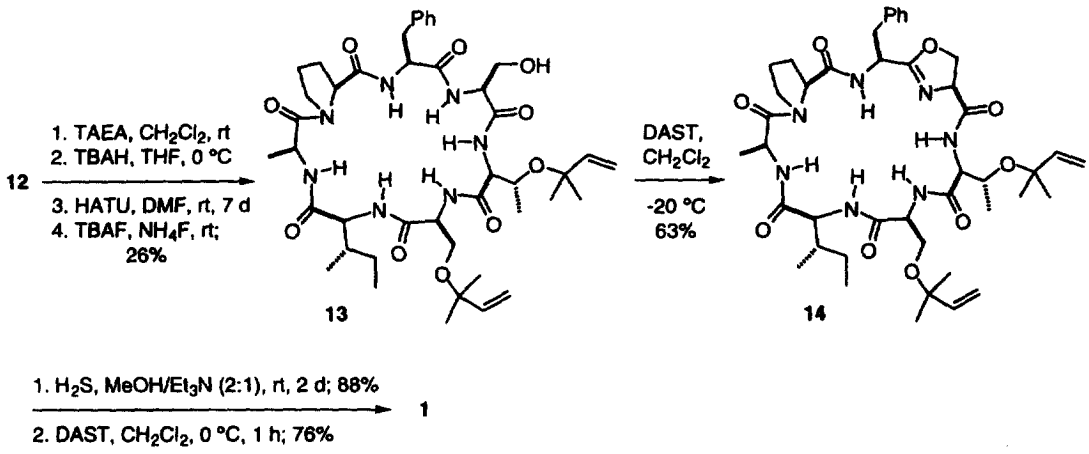
between the amine function of the N-terminal alanine residue and the isoleucine carboxylate. We had previously experimented with other *seco*-peptide precursors, but obtained only very low yields for the macrocyclization step.



Scheme 3.

After deprotection of the Fmoc group in **12** with tris(2-aminoethyl)amine (TAEA)[13] and methyl ester cleavage with tetrabutylammonium hydroxide (TBAH),[14] macrolactamization with HATU[15] followed by desilylation with TBAF provided cycloheptapeptide **13** in 26% yield (Scheme 4).[16] After cyclodehydration of the serine residue in **13** with DAST to the oxazoline **14**,[17] we applied our oxazoline → thiazoline interconversion sequence for the conversion of **14** to the target heterocycle **1**.[2e,18] While all spectroscopic data for synthetic **1** were consistent with the structural assignment,[19] there were significant differences in ^1H and ^{13}C NMR spectra and a major difference in the $[\alpha]_D$ measured for **1** and the corresponding data reported for the natural product.[4]

In conclusion, we have developed an efficient strategy toward the total synthesis of the putative structure of trunkamide A and for the preparation of its unusual reverse prenylated serine and threonine amino acid building blocks. The structure of this natural product has to be revised in light of our synthetic work, and we suspect that natural trunkamide A is a stereoisomer of **1**, most likely at the readily epimerizable C(40) or C(45) centers.



Scheme 4.

Acknowledgements

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16. HPLC analysis of the constituent amino acids after hydrolysis of synthetic **1** and derivatization according to Marfey's procedure (Adamson, J. G.; Hong, T.; Crivici, A.; Lajoie, G. *Anal. Biochem.* **1992**, *202*, 210) confirmed the presence of L-Ile. Accordingly, macrolactamization proceeded without racemization.
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19. Synthetic **1**: $[\alpha]_D$ −10.4 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.38 (d, 1H, *J*=6.9 Hz), 8.10 (d, 1H, *J*=7.0 Hz), 7.49 (d, 1H, *J*=7.0 Hz), 7.22 (d, 1H, *J*=5.6 Hz), 7.12–7.08 (m, 3H), 7.02–6.98 (m, 2H), 6.19 (d, 1H, *J*=10.0 Hz), 5.88 (dd, 1H, *J*=10.8, 17.5 Hz), 5.68 (dd, 1H, *J*=10.9, 17.5 Hz), 5.25 (d, 1H, *J*=17.5 Hz), 5.22 (d, 1H, *J*=10.6 Hz), 5.09 (d, 1H, *J*=11.0 Hz), 5.06 (d, 1H, *J*=18.4 Hz), 4.97–4.90 (m, 2H), 4.78 (d, 1H, *J*=7.8 Hz), 4.59 (dd, 1H, *J*=2.9, 10.0 Hz), 4.53 (m, 2H), 4.40–4.38 (m, 1H), 3.91 (p, 1H, *J*=5.9 Hz), 3.83 (dd, 1H, *J*=1.5, 9.0 Hz), 3.62–3.52 (m, 2H), 3.43 (dd, 1H, *J*=3.2, 9.2 Hz), 3.41–3.24 (m, 2H), 3.15 (dd, 1H, *J*=5.5, 14.0 Hz), 2.87 (dd, 1H, *J*=5.7, 14.1 Hz), 2.51–2.47 (m, 1H), 2.37–2.34 (m, 1H), 1.93–1.89 (m, 1H), 1.86–1.80 (m, 1H), 1.58–1.50 (m, 2H), 1.43 (s, 3H), 1.34 (s, 3H), 1.24–1.17 (m, 3H), 1.21 (s, 3H), 1.18 (s, 3H), 1.11 (d, 3H, *J*=6.6 Hz), 0.92–0.84 (m, 6H), 0.82–0.78 (m, 1H); ^{13}C NMR δ 172.8, 171.9, 170.8, 170.5, 169.9, 169.3, 142.8, 142.4, 136.5, 129.7, 128.3, 127.0, 115.9, 115.2, 77.9, 77.4, 76.2, 67.4, 62.1, 59.8, 57.7, 56.5, 56.2, 53.7, 47.9, 47.4, 40.7, 36.6, 35.9, 29.9, 27.5, 26.0, 25.9, 25.6, 25.3, 24.0, 19.1, 18.5, 16.3, 12.3; HRMS (FAB) *m/z* calcd for $C_{43}H_{63}N_7O_8NaS$ ($[M+Na]^+$): 860.4357; found: 860.4314.