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Total synthesis of the prenylated cyclopeptide trunkamide A, a cytotoxic metabolite from *Lissoclinum* sp.

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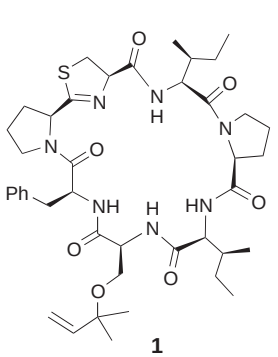
Abstract—A total synthesis of the doubly prenylated cyclic peptide trunkamide A of marine origin, and also its C45 epimer, is described.

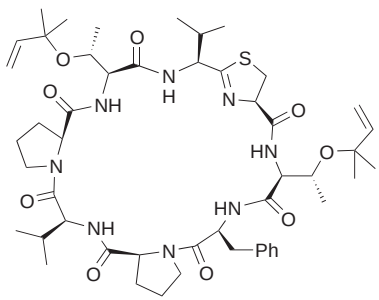
The marine environment has delivered a prodigious variety of structurally novel and biologically important secondary metabolites in recent years, many of which have lured chemists into their total synthesis and an evaluation of their potential as chemotherapeutic agents. Amongst some of the most intriguing marine natural products are heterocyclic based cyclic peptides produced by ascidians of the genus *Lissoclinum*.[1] These unusual compounds show structures which are based on the inclusion of thiazoline and oxazoline rings in their peptide backbone and, sometimes, modified by the presence of reverse prenyl units in their side chains; examples include mollamide **1**,[2] patellin 6 **2**,[3] and trunkamide A **3**.[3] Most of the cyclic peptides isolated from ascidians show moderate cytotoxicity, but trunkamide A is reported to have particularly pronounced and promising antitumour activity.[4] Synthetic work within the various families of natural cyclic peptides has been intense,[5] and recently we described the first synthesis of a reverse prenylated member, i.e. mollamide **1**.[5d] In continuation of our studies of the synthesis,[5] self assembly,[6] and ionophore properties[7] of novel marine cyclic peptides and their analogues, we now report a synthesis of trunkamide A **3a**, and of its C45 epimer **3b**.[8]

Following our successful synthesis of mollamide **1**, we designed a synthesis of the structure **3b** reported for naturally derived trunkamide A **3** using a similar strategy, whereby the thiazoline ring in the natural product was to be produced in the final step from the thioamide cyclic peptide **4**. The cyclic peptide **4** was to be derived from the heptapeptide **5** which, in turn, would be elaborated from the thioamide **6** and the prenylated amino acids **7** and **8** (Scheme 1).[9]

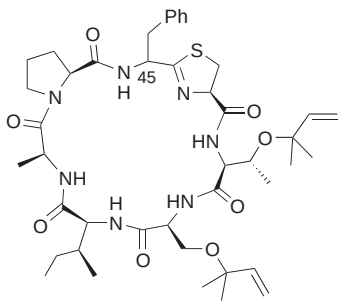
Thus the pentapeptide thioamide **6** was first prepared starting from serine methyl ester and proceeding via the thioamide **9** and then adding proline, alanine and isoleucine sequentially (Scheme 2). After removal of the Boc-protecting group in **6**, a coupling reaction with **7**



1



2



3a; C45 *R*
3b; C45 *S*

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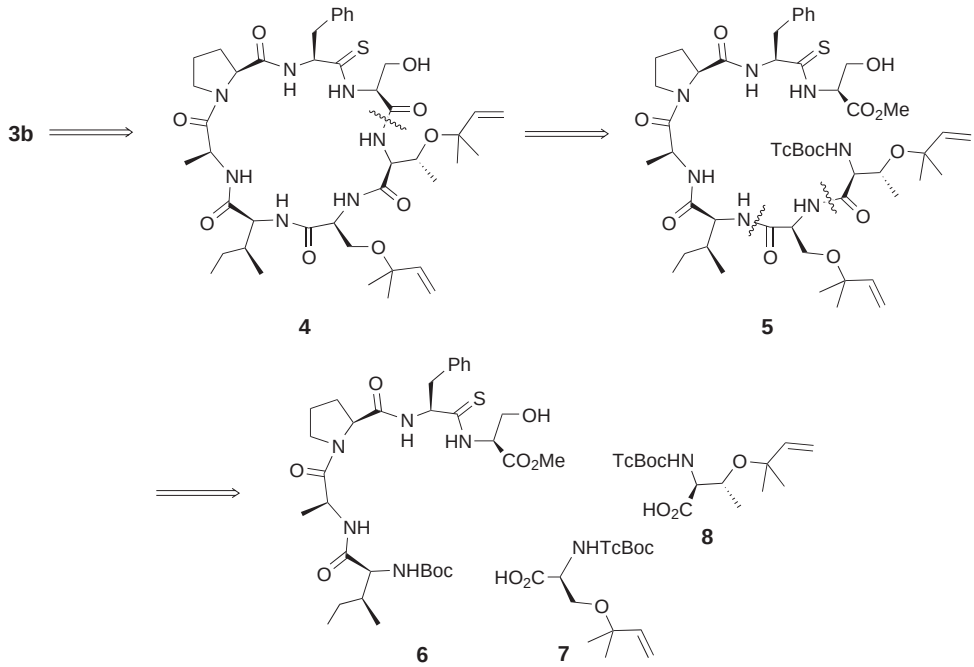
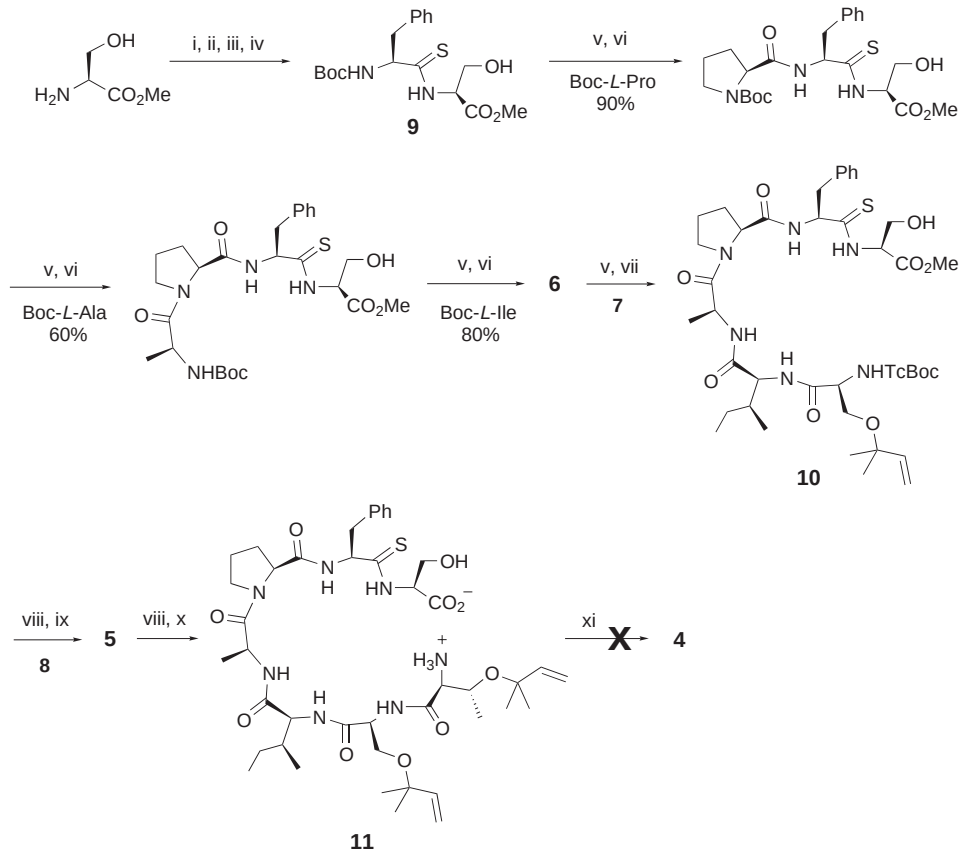


Scheme 1.



Scheme 2. *Reagents*: (i) Boc-L-Phe, DCC, HOBt, DIPEA, DCM, 74%; (ii) TBSCl, imidazole, DMF, 90%; (iii) Lawesson's reagent, benzene, 80°C, 92%; (iv) TBAF, THF, 93%; (v) AcCl, MeOH; (vi) DCC, HOBt, DIPEA, DCM; (vii) EDC, HOBt, DIPEA, DCM, 72%; (viii) Cd/Pb, 1 M NH_4OAc/THF (1:1); (ix) EDC, HOBt, DCM, 78% (two steps); (x) 1 M NaOH, MeOH; (xi) DPPA, DIPEA, DMF.

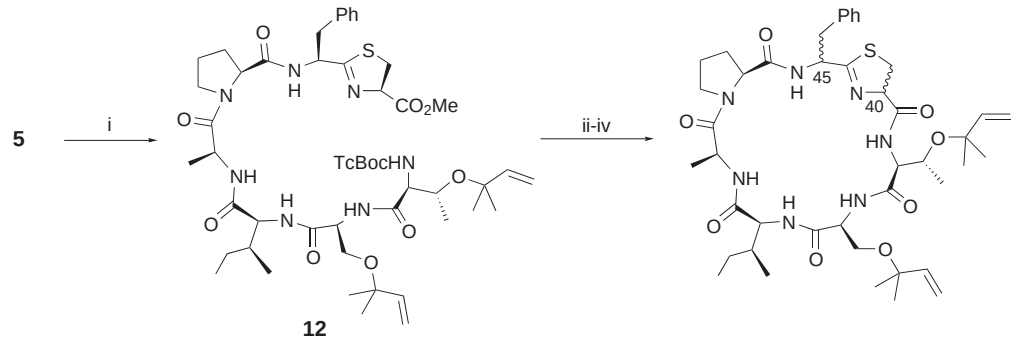
next produced **10**, which was then deprotected and the resulting free amine coupled with **8** leading to the advanced doubly prenylated precursor **5**.

After removal of the TcBoc and methyl ester protecting groups in **5**, we were disappointed to find that attempts to induce macrolactamisation of the zwitterion **11** lead-

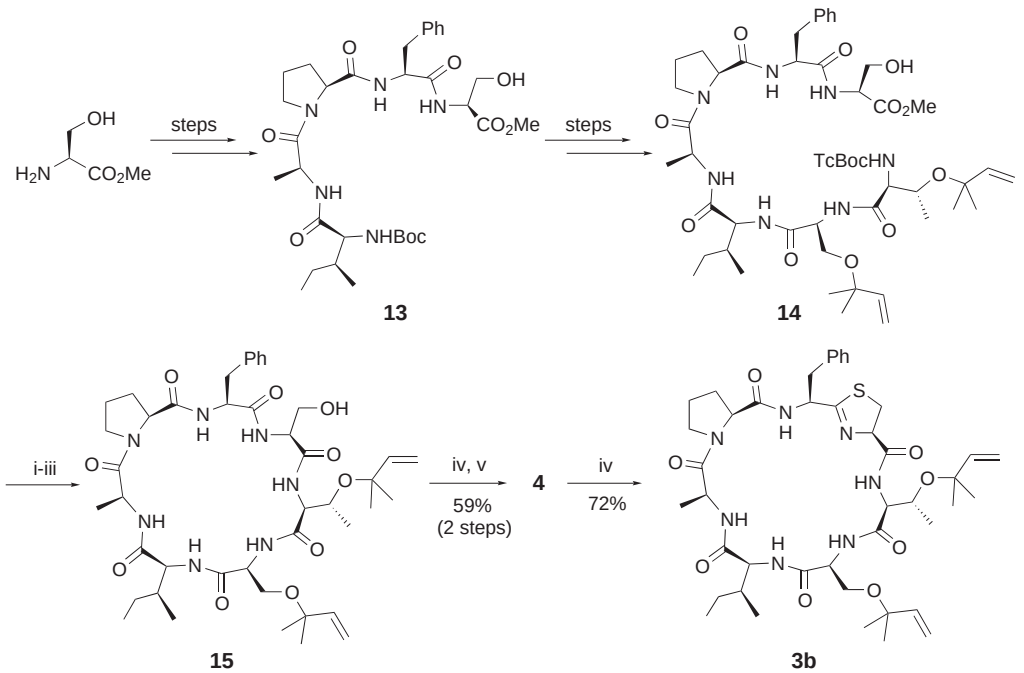
ing to **4** failed and, instead, only intractable material was recovered. We were persuaded that the thioamide bond in **11** and its proximity to the site of macrolactamisation was the likely cause of the problem. We therefore decided to synthesise the thiazoline ring in the target natural product prior to macrolactamisation, hence removing any possible interference. This was a somewhat risky decision since it is well documented that chiral thiazolines are prone to undergo isomerisation under a range of acid/base conditions.[10] In the event we would expect to lose the stereochemical integrity at C45 (and possibly C40) during any subsequent synthetic manipulations leading to the trunkamide target.

Hence, treatment of the heptapeptide thioamide **5** with Burgess' reagent resulted in cyclodehydration leading to the corresponding substituted thiazoline **12** (Scheme 3). Removal of the protecting groups from **12** followed by macrolactamisation of the resulting ω-amino acid, and chromatography, successfully produced the cyclopeptide structure. However, as anticipated, analysis of the material obtained clearly showed the presence of a mixture of diastereoisomeric products. One of these separated diastereoisomers, however, showed NMR spectroscopic data which were identical with those reported for natural trunkamide A, whereas another showed NMR data corresponding to those reported for the C45 epimer **3b** of trunkamide A.[3,8]

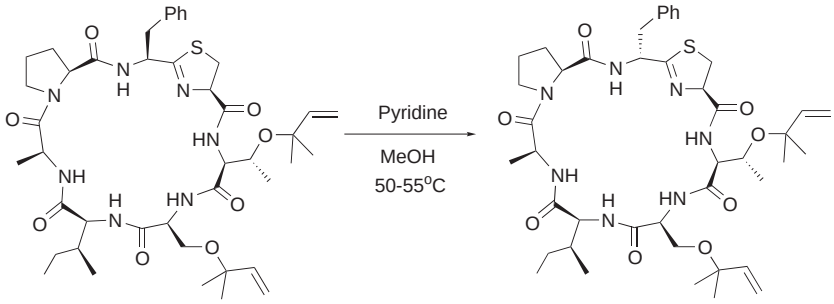
Encouraged by this outcome, we speculated that if we replaced the problematic thioamide bond in **11** with an amide bond then our original macrocyclisation strategy, cf. **5**→**4** (Scheme 1), may prove more successful and allow us access to diastereomerically pure material. Hence, we decided to synthesise the heptapeptide **14** and examine its macrocyclisation (Scheme 4). Thus, starting from serine methyl ester, the heptapeptide **14** was prepared by the sequential addition of phenylalanine, proline, alanine and isoleucine, to give **13**, followed by the addition of the two reverse prenylated amino acids **7** and **8**.



Scheme 3. *Reagents*: (i) Burgess' reagent, THF, 65°C, 92%; (ii) Cd/Pb, 1 M NH_4OAc/THF (1:1), 93%; (iii) 1 M NaOH, MeOH; (iv) DPPA, DIPEA, DMF.



Scheme 4. *Reagents*: (i) Cd/Pb, 1 M NH_4OAc/THF (1:1), 98%; (ii) TBAH, THF, 0°C; (iii) DPPA, DIPEA, DMF, 35% (two steps); (iv) DAST, DCM; (v) H_2S, Et_3N, MeOH.



Scheme 5.

After our failure to induce macrocyclisation from the thioamide heptapeptide **5** we were delighted to find that, following removal of the TcBoc and methyl ester protecting groups in **14**, macrocyclisation proceeded smoothly and provided the cyclopeptide **15** in 35% yield (Scheme 4). The macrocycle **15** was then elaborated to the trunkamide structure **3b** using a strategy described by Wipf et al.[8,11] Hence cyclodehydration of **15** to the corresponding oxazoline, and subsequent thiolysis with H_2S led to the thioamide cyclic peptide **4** which, on reaction with DAST gave **3b** in 72% yield. The cyclic peptide **3b** was identical in all respects with the trunkamide structure reported by Uto and Wipf[8] but differed significantly with spectroscopic data reported by Bowden et al. for natural trunkamide A.[3,12a] Following the report of Uto and Wipf revealing the correct structure of trunkamide A, i.e. **3a** rather than **3b**,[5a] we then decided to attempt to synthesise this epimeric structure. Instead of carrying out a new total synthesis of natural trunkamide A from D- rather than L-phenylalanine, however, we planned to effect conversion of *epi*-trunkamide A **3b** into trunkamide A **3a** by selective epimerisation of the incorrect C45 stereocentre. Indeed, we found that when **3b** was treated with methanolic pyridine at 50–55°C it was slowly converted into trunkamide A **3a** with no detectable formation of any other diastereoisomer (Scheme 5). The data for our synthetic trunkamide[12b] were identical in every respect with those reported for the natural product[3] and those reported by Uto and Wipf.[5a]

Acknowledgements

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8. In contemporaneous studies Uto and Wipf described a total synthesis of the stereostructure **3b** assigned to trunkamide A by Bowden et al.[3] However, the spectroscopic data recorded for the synthetic and natural materials did not correlate; Uto, Y.; Wipf, P. *Tetrahedron Lett.* **1999**, *40*, 5165. In a subsequent report these authors showed that **3a** was the correct stereostructure for natural trunkamide A (Ref. 5a).
9. The amino acids **7** and **8** were synthesised by Lewis acid-mediated ring openings of chiral aziridines prepared from homochiral serine methyl ester and threonine methyl ester, respectively, using a procedure described by Okawa et al.; Nakajima, K.; Neya, M.; Okawa, K.; Yamada, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3049 (see also Refs. 5a and d).
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12. Satisfactory spectroscopic and mass spectrometry data were obtained for all new compounds.
(a) Data for synthetic **3b**: $[\alpha]_D$ −10 (*c* 0.50, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.45 (1H, d, $J=7.1$ Hz), 8.17 (1H, d, $J=7.1$ Hz), 7.56 (1H, d, $J=7.0$ Hz), 7.30 (1H, d, $J=5.5$ Hz), 7.18–7.14 (3H, m), 7.12–7.07 (2H, m), 6.26 (1H, d, $J=10.0$ Hz), 5.96 (1H, dd, $J=17.6$ and 10.8 Hz), 5.76 (1H, dd, $J=17.6$ and 10.9 Hz), 5.32 (1H, dd, $J=17.5$ and 0.4 Hz), 5.30 (1H, dd, $J=10.8$ and 0.7 Hz), 5.17 (1H, dd, $J=10.8$ and 0.9 Hz), 5.14 (1H, dd, $J=17.5$ and 0.9 Hz), 5.07–4.97 (2H, m), 4.85 (1H, app d, $J=7.5$ Hz), 4.68–4.58 (1H, masked dq), 4.67 (1H, dd, $J=10.0$ and 3.2 Hz), 4.61 (1H, dd, $J=6.8$ and 5.5 Hz), 4.47 (1H, app dt, $J=6.5$ and 2.9 Hz), 4.00 (1H, dq, $J=6.5$ and 5.2 Hz), 3.91 (1H, dd, $J=9.3$ and 2.3 Hz), 3.67 (1H, dd, $J=11.4$ and 9.5 Hz), 3.62 (1H, app t, $J=11.3$ Hz), 3.51 (1H, dd, $J=9.3$ and 3.4 Hz), 3.47–3.35 (2H, m), 3.22 (1H, dd, $J=14.0$ and 5.4 Hz), 2.95 (1H, dd, $J=14.1$ and 5.8 Hz), 2.59–2.55 (1H, m), 2.46–2.40 (1H, m), 2.01–1.84 (2H, m), 1.68–1.60 (1H, m), 1.51 (3H, s), 1.42 (3H, s), 1.36–1.26 (2H, m), 1.29 (3H, s), 1.26, (6H, s), 1.19 (3H, d, $J=6.7$ Hz), 0.97 (3H, d, $J=6.2$ Hz), 0.95 (3H, app t, $J=6.4$ Hz); δ_C (100 MHz, $CDCl_3$) 172.6 (s), 171.8 (s), 170.7 (s), 170.4 (s), 170.3 (s), 169.8 (s), 169.2 (s), 142.7 (d), 142.2 (d), 136.4 (s), 129.6 (d), 128.2 (d), 126.8 (d), 115.8 (t), 115.1 (t), 77.9 (s), 77.8 (d), 76.0 (s), 67.3 (d), 62.0 (t), 59.7 (d), 57.6 (d), 56.4 (d), 56.1 (d), 53.6 (d), 47.8 (d), 47.3 (t), 40.5 (t), 36.5 (d), 35.8 (t), 29.8 (t), 27.4 (q), 25.9 (q), 25.7 (q), 25.5 (q), 25.2 (t), 23.9 (t), 18.9 (q), 18.4 (q), 16.2 (q), 12.2 (q); HRMS (ES) m/z calcd for $C_{43}H_{63}N_7NaO_8S$ ($[M+Na]^+$): 860.4357; found: 860.4321; (b) Data for synthetic **3a**: $[\alpha]_D$ −21 (*c* 0.26, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 7.97 (1H, d, $J=6.4$ Hz), 7.56 (1H, d, $J=7.8$ Hz), 7.29–7.21 (4H, m), 7.17 (1H, d, $J=7.7$ Hz), 7.15–7.12 (2H, m), 6.32 (1H, d, $J=9.6$ Hz), 5.93 (1H, dd, $J=17.6$ and 10.8 Hz), 5.75 (1H, dd, $J=17.6$ and 10.9 Hz), 5.28 (1H, dd, $J=17.5$ and 0.6 Hz), 5.25 (1H, dd, $J=10.8$ and 0.7 Hz), 5.17–5.11 (1H, masked ddd), 5.16 (1H, dd, $J=10.9$ and 0.9 Hz), 5.12 (1H, dd, $J=17.5$ and 0.9 Hz), 4.93 (1H, app t, $J=9.6$ Hz), 4.63–4.56 (3H, m), 4.51 (1H, dq, $J=6.5$ and 5.7 Hz), 4.39 (1H, app t, $J=6.0$ Hz), 4.04 (1H, dq, $J=6.5$ and 5.1 Hz), 3.91 (1H, dd, $J=9.1$ and 2.1 Hz), 3.73 (1H, dd, $J=11.3$ and 9.7 Hz), 3.64 (1H, dd, $J=11.2$ and 9.7 Hz), 3.55–3.49 (2H, m), 3.46 (1H, dd, $J=9.1$ and 3.2 Hz), 3.25 (1H, dd, $J=13.9$ and 5.7 Hz), 2.95 (1H, dd, $J=14.0$ and 5.9 Hz), 2.40–2.33 (1H, m), 2.27–2.22 (1H, m), 1.96–1.87 (3H, m), 1.49 (3H, s), 1.39 (3H, s), 1.35–1.18 (2H, m), 1.27 (3H, s), 1.25 (3H, s), 1.22 (3H, d, $J=6.6$ Hz), 1.07 (3H, d, $J=6.5$ Hz), 0.96 (3H, d, $J=6.9$ Hz), 0.94 (3H, app t, $J=7.4$ Hz); δ_C (100 MHz, $CDCl_3$) 173.3 (s), 171.1 (s), 170.9 (s), 170.6 (s), 170.2 (s), 170.1 (s), 168.7 (s), 142.7 (d), 142.1 (d), 135.7 (s), 129.7 (d), 128.4 (d), 127.2 (d), 115.8 (t), 115.0 (t), 78.2 (d), 77.9 (s), 76.0 (s), 67.3 (d), 62.3 (t), 60.0 (d), 57.9 (d), 56.5 (d), 55.4 (d), 52.8 (d), 47.8 (d), 47.1 (t), 39.9 (t), 36.5 (d), 36.4 (t), 28.6 (t), 27.4 (q), 25.8 (q), 25.8 (q), 25.7 (q), 25.6 (t), 23.8 (t), 18.6 (q), 18.1 (q), 16.1 (q), 12.0 (q); HRMS (ES) m/z calcd for $C_{43}H_{63}N_7NaO_8S$ ($[M+Na]^+$): 860.4357; found: 860.4320.