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Cyclopeptides from Ascidians. Total Synthesis of Lissoclinamide 4, and a General Strategy for the Synthesis of Chiral Thiazoline-containing Macrocyclic Peptides.

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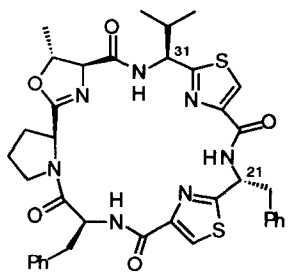
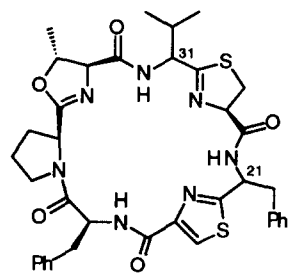
Abstract: In the first synthesis of a chiral thiazoline-containing macrocyclic peptide, a total synthesis of lissoclinamide 4 **2c**, produced by the marine tunicate *Lissoclinum patella*, is described.

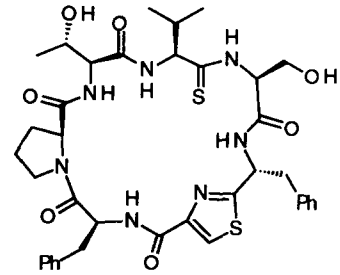
The marine environment is a rich source of novel and unusual secondary metabolites, many of which have already shown considerable promise for development as therapeutic agents. A particularly intriguing family of marine metabolites is the heterocycle-containing cyclopeptides known as lissoclinamides produced by the tunicate *Lissoclinum patella*.[1] These compounds show structures which feature an oxazoline ring, together with one or more thiazoles and/or thiazolines, derived from unusual amino acid residues incorporated into a cyclic heptapeptide. Although a large body of synthetic work towards marine cyclic peptides has already been reported[2] they remain a significant challenge, especially in the context of designing effective macrocyclisation prototcols and also developing procedures which avoid racemisation, both in the target molecules and in their precursors. This latter feature is especially important since a significant number of the structures previously assigned to marine cyclopeptides have needed to be corrected as a result of later synthetic investigations.[3]



1 (31*S*, 21*R*)



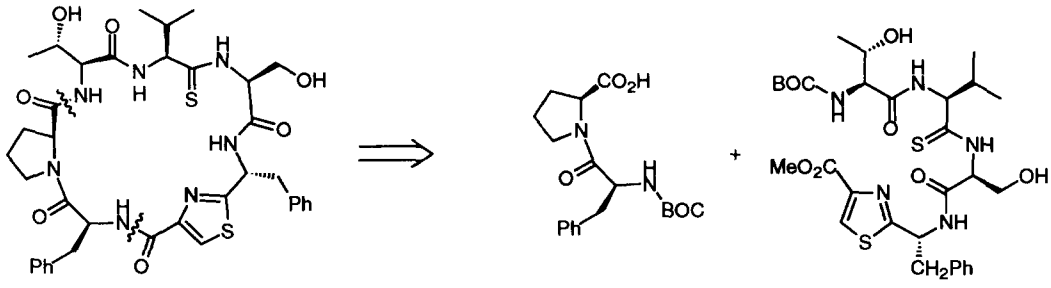
2a (31*R*, 21*S*) ; **2b** (31*R*, 21*R*)
2c (31*S*, 21*R*) ; **2d** (31*S*, 21*S*)



3

As part of an ongoing program of synthetic investigations into lissoclinamide cyclic peptides produced by *L. patella* we recently reported[4] the total synthesis of lissoclinamide 5 **1**, the stereostructure of which was shown to differ from that previously predicted at the C21- and C31- positions. The closely related set of four

diastereoisomeric compounds **2a-2d** are thought to comprise at least three other natural products, lissoclinamides 4,6 and 8, also isolated from *L. patella*.[5,6] The difficulty of forming the sensitive chiral thiazoline ring in **2** by total synthesis has, however, precluded the absolute determination of these centres. We report here the first total synthesis of lissoclinamide 4, which is shown to have the structure **2c**, and the development of a general method which should allow the synthesis of a range of thiazoline-containing macrocyclic peptides.



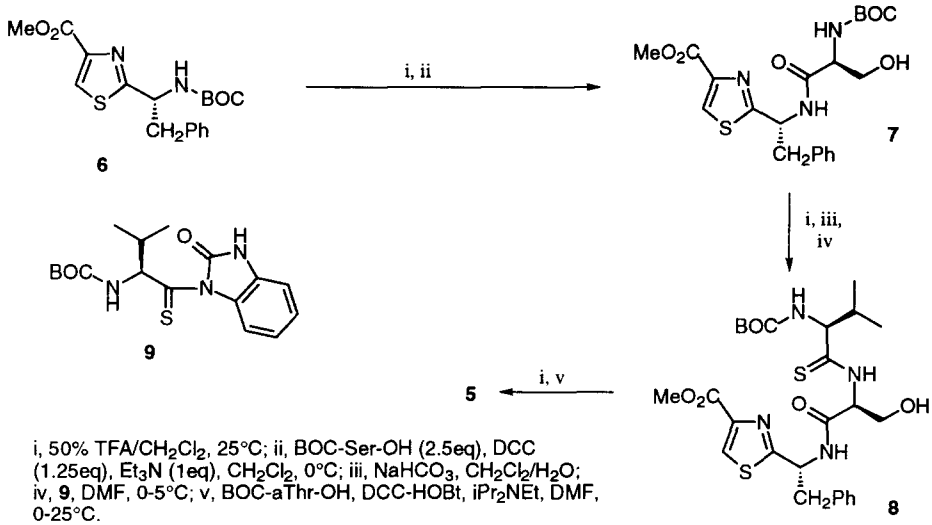
3 **4** **5**

Scheme 1

Recent work has shown that the desired thiazoline subunits in cyclopeptides can be synthesised by dehydration of the corresponding serine-derived hydroxy thioamides.[7] Given that the reagents and conditions required to carry out this transformation are identical to those required for the formation of the methyl oxazoline subunits in **1** and **2**, it seemed natural to envisage the formation of the thiazoline and oxazoline rings in **2** from a suitable dihydroxy precursor **3**, via a double cyclodehydration sequence in the final step. We therefore decided to synthesise **3**, which we undertook via the synthetic pathway indicated in Scheme 1.

The experience of both ourselves and others[2,3] with the synthesis of thiazole-containing cyclic peptides had indicated that macrolactamisation via a thiazole carboxyl group is an effective way of forming the large ring, avoiding as it does any problems of racemisation in the ring closure step. Similarly, the resistance of carboxyl-activated proline to base-catalysed racemisation makes the Pro-aThr bond the optimum site for fragment condensation, giving us the fragments **4** (which is synthesised by standard methods) and **5** as the initial targets.

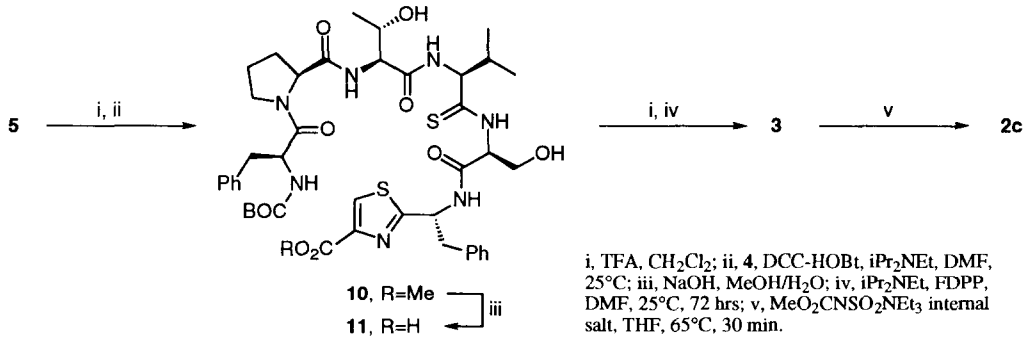
The synthesis of **5** was carried out in an essentially linear fashion, starting from the substituted thiazole **6**, which was prepared as previously described (Scheme 2).[8] Removal of the BOC group in **6** followed by coupling with BOC-Ser-OH using the symmetrical anhydride method gave the intermediate **7** in a gratifying 91% yield. Tripeptide **7** was next acidolysed with TFA to remove the BOC group, and the free amine isolated by extraction from aqueous bicarbonate. Coupling of this amine with the thioacylating reagent **9**[9] gave the endo-monothiotetrapeptide **8** in a satisfactory overall yield of 74%, without detectable signs of racemisation. BOC-deprotection of **8** by the usual method and coupling of the resulting amine with BOC-*allo*-threonine then gave **5** in an acceptable 71% yield; further deprotection and coupling with **4** gave the endo-monothioheptapeptide **10**, again in good yield (77%).



i, 50% TFA/CH_2Cl_2, 25°C; ii, BOC-Ser-OH (2.5eq), DCC (1.25eq), Et_3N (1eq), CH_2Cl_2, 0°C; iii, $NaHCO_3$, CH_2Cl_2/H_2O; iv, **9**, DMF, 0-5°C; v, BOC-aThr-OH, DCC-HOBt, iPr_2NEt, DMF, 0-25°C.

Scheme 2

The heptapeptide ester **10** was saponified to the acid **11** using 1M NaOH in aqueous methanol, and removal of the BOC group followed by cyclisation using FDPP[10] gave the desired macrocycle **3** in a modest 32% yield. Similar macrocyclisation yields have been obtained with other lissoclinamides,[2g,8] suggesting that the problems of macrocyclisation are neither accentuated nor ameliorated by the "opening" of one of the hetero-rings. The final conversion of **3** into **2c** was carried out using 2.2 equivalents of Burgess reagent[7] in refluxing THF for 30 minutes, giving the desired product in 61% yield, contaminated with ca. 5% of an unidentified isomer. As attempts by us to form simpler non-macrocyclic valine-derived thiazolines by this method have also given traces of other diastereoisomers, [8] this is perhaps not too surprising. Purification by HPLC gave **2c** as a white foam ($[\alpha]_D^{25}$ +43.2°, c=1.3, $CHCl_3$; literature[5,6] $[\alpha]_D^{25}$ +45°, c=0.7, $CHCl_3$). The PMR and CMR spectra recorded for synthetic **2c** overlapped with those published for lissoclinamide 4. The epimer at C21 **2d** was also synthesised, starting from the enantiomer of **6**; however, this did not appear to be either lissoclinamide 6 or lissoclinamide 8.



i, TFA, CH_2Cl_2; ii, **4**, DCC-HOBt, iPr_2NEt, DMF, 25°C; iii, NaOH, $MeOH/H_2O$; iv, iPr_2NEt, FDPP, DMF, 25°C, 72 hrs; v, $MeO_2CNSO_2NEt_3$ internal salt, THF, 65°C, 30 min.

Scheme 3

In summary, we have shown that the structure of lissoclinamide 4 is **2c** and not **2a** as previously suggested,[5,6] and by formation of the chiral thiazoline unit in the final step we have opened the way to a general method for the synthesis of the lissoclinamides and of related thiazoline-containing peptide macrocycles. The failure of our synthetic **2d** to overlap with either lissoclinamide 6 or 8 suggests that these compounds are either the **2a** and **2b** isomers, or else epimers at some other chiral centre(s). This hypothesis will be tested in due course as part of our continuing synthetic studies of the lissoclinamides.[11]

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