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Total Synthesis and Revision of Stereochemistry of Cyclodidemnamide, a Novel Cyclopeptide from the Marine Ascidian *Didemnum molle*

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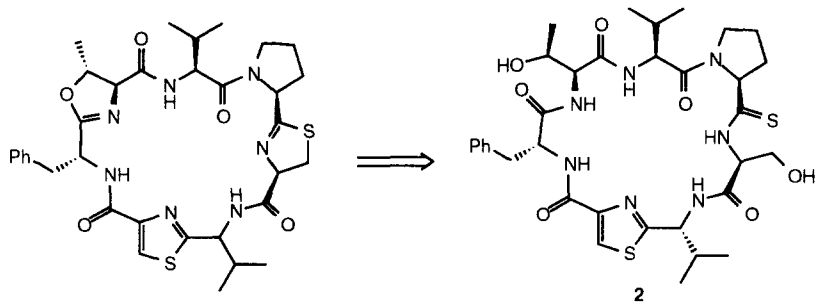
Abstract: A total synthesis establishes the structure and stereochemistry of the novel heterocycle-based cyclopeptide cyclodidemnamide isolated from the "sea squirt" *Didemnum molle* as **1b**, not **1a**.

The cyclopeptide cyclodidemnamide **1**, isolated from the sea squirt *Didemnum molle*,[1] is weakly toxic toward human colon tumor cells and has a structure which features an alternating sequence of five-membered heterocycles (*ie* oxazoline, thiazole, thiazoline and pyrrolidine) and hydrophobic amino acid residues.[2] Natural products accommodating chiral thiazoline units having the substitution pattern found in cyclodidemnamide are somewhat rare; furthermore, such chiral thiazoline units are well known to be configurationally labile[3] which has made their synthesis difficult. We recently developed a synthetic approach to chiral thiazoline- and oxazoline-containing cyclopeptides of the type **1**, whereby the heterocyclic rings were produced simultaneously *via* a double cyclodehydration sequence from an appropriate cyclopeptide precursor as a final step, *ie* **2** → **1**.[4] Indeed, we applied this strategy in a concise synthesis of the structure **1a** previously assigned to cyclodidemnamide from *D. molle*.[5]



1a L-Val (β-*i*-Pr)
1b D-Val (α-*i*-Pr)

2

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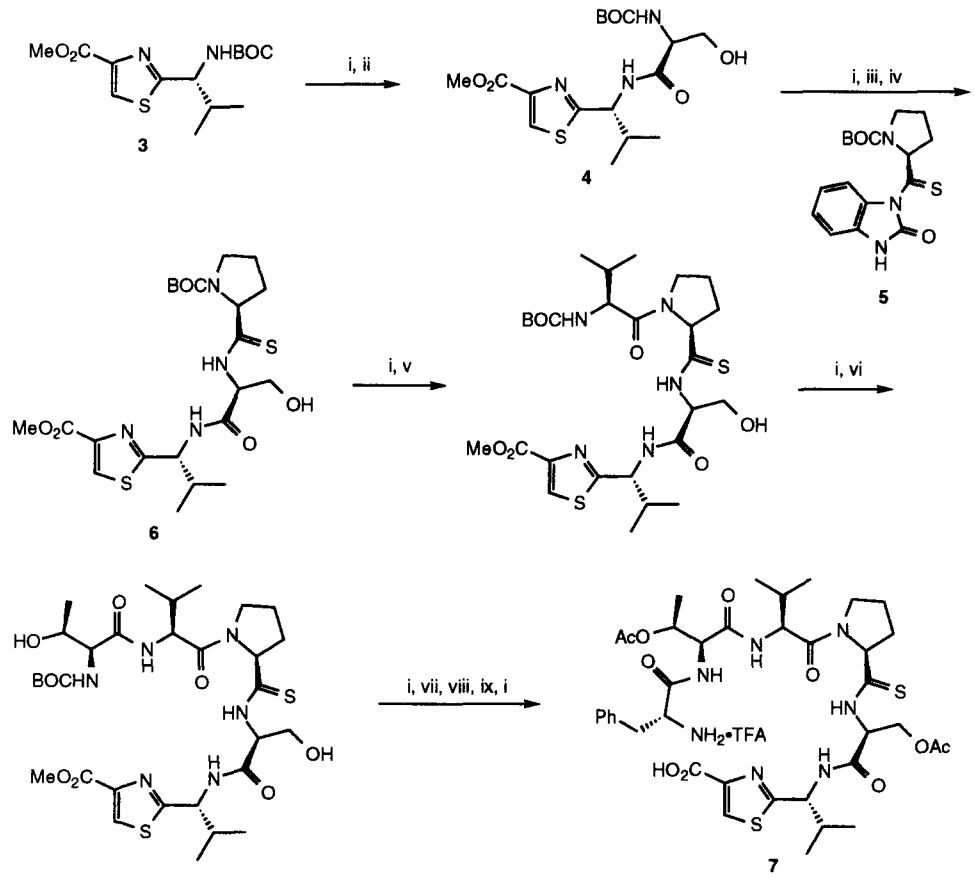
The NMR spectroscopic data recorded for the synthetic material and natural cyclodidemnamide however were significantly different. Re-evaluation and detailed comparison of the NMR data obtained for natural cyclodidemnamide and our synthetic material, together with knowledge of the known propensity with which chiral thiazoles and thiazolines can undergo racemisation during mild acid or base degradation of thiazole/thiazoline-based cyclopeptides, led us to suggest that naturally derived cyclodidemnamide has the stereostructure **1b**, which is epimeric at the valine-derived thiazole centre in structure **1**.[6] In order to vindicate this suggestion we have now synthesised structure **1b** and gratifyingly the molecule displays NMR data which are superimposable on those recorded for the natural product from *D. molle*.

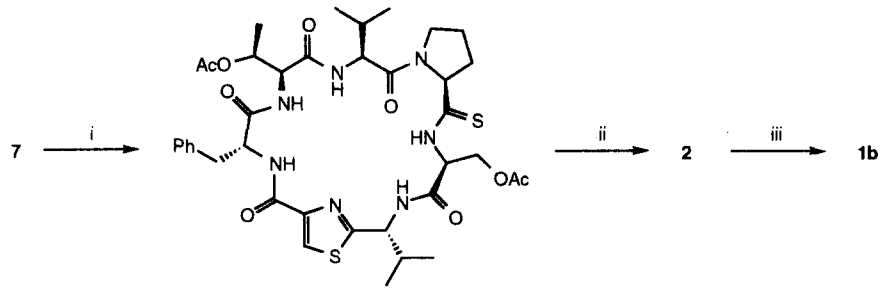
Thus, the strategy we followed[5] for synthesising the monothioamide-based cyclopeptide precursor **2** began with the known D-valine-derived thiazole **3**[7] and proceeded *via* (i) the monothiotetrapeptide **6** derived from coupling of the amine produced from the tripeptide **4** with the thioacylating agent **5**,[8] and (ii) the heptapeptide amino acid salt **7**, as key intermediates (Scheme 1).



Reagents: i, 50% TFA-CH_2Cl_2, 0°C, 1 h; ii, BOC-Ser-OH, DCC, HOBt, *i*-Pr_2NEt, CH_2Cl_2, 0°C → r.t., 18 h, 91%; iii, aq. $NaHCO_3$-CH_2Cl_2; iv, **5**, DMF, 0°C → r.t., 18 h, 56%; v, BOC-Val-OH, DCC, HOBt, *i*-Pr_2NEt, CH_2Cl_2, 0°C → r.t., 18 h, 68%; vi, BOC-aThr-OH, DCC, HOBt, *i*-Pr_2NEt, CH_2Cl_2, 0°C → r.t., 18 h, 73%; vii, BOC-D-Phe-OH, DCC, HOBt, *i*-Pr_2NEt, CH_2Cl_2, 0°C → r.t., 18 h, 71%; viii, aq. NaOH, THF-MeOH (3:1), 0°C, 1 h; ix, Ac_2O, Et_3N, cat. DMAP, DMF, r.t., 2 h

Scheme 1

Macrocyclisation of **7** in the presence of DPPA (*i*-Pr_2NEt, DMF, 0°C → r.t.) next produced the cyclopeptide **8** in 59% yield (Scheme 2).[9] Saponifacation of the acetate groups in **8** using K_2CO_3 in MeOH then provided the pivotal penultimate thioamide cyclopeptide **2**. Finally, treatment of **2** with Burgess' reagent[10] resulted in facile, double cyclodehydration to the thiazoline and oxazoline rings producing the cyclodidemnamide structure **1b** in 28% yield. The synthetic cyclopeptide showed ^1H and ^{13}C NMR spectra which were superimposable on those recorded for naturally derived cyclodidemnamide.[1]



Reagents: i, DPPA, *i*-Pr_2NEt, DMF, 0°C → r.t., 3 days, 59% (4 steps); ii, aq. K_2CO_3, MeOH, 0°C, 1 h; iii, Burgess' reagent, THF, Δ, 2 h, 28% (2 steps)

Scheme 2

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References:

1. Toske, S. G.; Fenical, W. *Tetrahedron Lett.* **1995**, *36*, 8355.
2. For other similar natural cyclopeptides see: (a) Carroll, A. R.; Bowden, B. F.; Coll, J. C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1994**, *47*, 61. (b) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; van den Brenk, A. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1349. (c) Schmitz, F. J.; Ksetbati, M. B.; Chang, J. S.; Wang, J. L.; Hossain, M. B.; van der Helm, D.; Engel, M. H.; Serban, A.; Silfer, J. A. *J. Org. Chem.* **1989**, *54*, 3463. (d) Hawkins, C. J.; Lavin, M. F.; Marshall, K. A.; van den Brenk, A. L.; Watters, D. J. *J. Med. Chem.* **1990**, *33*, 1634.
3. (a) Konigsberg, W.; Hill, R. H.; Craig, L. C. *J. Org. Chem.* **1961**, *26*, 3867. (b) Hirotsu, Y.; Shiba, T.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1870. (c) Yonetani, K.; Hirotsu, Y.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3302.
4. Boden, C. D. J.; Pattenden, G. *Tetrahedron Lett.* **1995**, *36*, 6153.
5. Boden, C. D. J.; Norley, M. C.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 9111.
6. The full details of these comparative spectroscopic data will be reported in a full paper.
7. Boden, C. D. J.; Pattenden, G.; Ye, T. *Synlett*, **1995**, 417.
8. Zacharie, B.; Sauvé, G.; Penney, C. *Tetrahedron* **1993**, *49*, 10489.

9. Satisfactory spectroscopic and mass spectrometry data were obtained for all new compounds. Spectroscopic data for **8**: δ_H (500 MHz, $CDCl_3$): 8.32 (1H, d, J = 8.4), 8.21 (1H, d, J = 7.4), 7.95 (1H, s), 7.87 (1H, d, J = 7.4), 7.30-7.20 (5H, m), 6.78 (1H, d, J = 9.1), 6.49 (1H, d, J = 8.9), 5.44 (1H, app. dt, J = 2.8, 7.6), 5.28 (1H, dq, J = 3.3, 6.6), 5.03 (2H, m), 4.88 (1H, app. dt, J = 5.9, 8.7), 4.77 (1H, dd, J = 7.8, 12.3), 4.72 (1H, dd, J = 3.2, 8.9), 4.50 (1H, dd, J = 3.3, 7.4), 4.40 (1H, dd, J = 2.8, 12.3), 3.78-3.68 (2H, m), 3.39 (1H, dd, J = 5.9, 14.4), 3.08 (1H, dd, J = 9.0, 14.4), 2.46 (1H, m), 2.39 (1H, m), 2.18 (1H, m), 2.07 (3H, s), 2.04 (3H, s), 2.02-1.92 (2H, m), 1.80 (1H, m), 1.36 (3H, d, J = 6.6), 1.04 (3H, d, J = 6.8), 0.88 (3H, d, J = 6.7), 0.84 (3H, d, J = 6.7), 0.12 (3H, d, J = 6.8)); δ_C (125 MHz, $CDCl_3$): 205.0 (s), 173.3 (s), 172.4 (s), 171.8 (s), 170.2 (s), 168.1 (s), 167.6 (s), 165.0 (s), 162.4 (s), 149.1 (s), 136.9 (s), 129.7 (d), 128.8 (d), 127.0 (d), 123.5 (d), 69.8 (d), 69.3 (d), 63.7 (t), 59.3 (d), 57.8 (d), 56.1 (d), 54.1 (d), 53.7 (d), 48.3 (t), 35.0 (t), 33.7 (d), 33.0 (t), 30.7 (d), 24.7 (t), 21.2 (q), 21.0 (q), 20.2 (q), 19.5 (q), 18.9 (q), 16.3 (q), 14.7 (q).

10. Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397.