Pergamon

Tetrahedron Letters, Vol. 37, No. 50, pp. 9111-9114, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02098-9

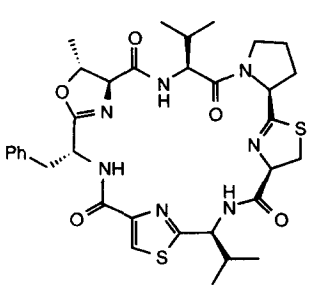
Total Synthesis of the Thiazoline-based Cyclopeptide Cyclodidemnamide

Christopher D J Boden, Mark C Norley and Gerald Pattenden*

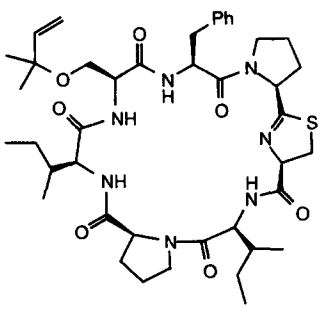
Department of Chemistry, Nottingham University, Nottingham NG7 2RD, England

Abstract: A total synthesis of the proposed structure **1** for cyclodidemnamide from the marine ascidian *Didemnum molle* is described, which features the novel double, sequential formation of chiral thiazoline and oxazoline rings as the key stratagem. Copyright © 1996 Elsevier Science Ltd

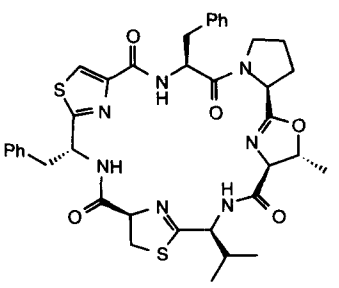
Cyclodidemnamide **1** is a newly described thiazoline-oxazoline containing 21-membered cyclopeptide which has been isolated from the marine ascidian *Didemnum molle*.[1] The compound, which is weakly toxic toward human colon tumor cells, is related structurally to other thiazoline-based cyclopeptides from marine organisms including mollamide **2**[2] and lissoclinamide 4 **3**.[3] Chiral thiazoline units of the type contained within the structures **1** → **3** are well known to be configurationally labile under a range of conditions.[4] We recently achieved the first synthesis of a thiazoline-containing cyclopeptide, *ie* lissoclinamide 4 **3**, whereby the thiazoline ring was produced simultaneously with an oxazoline ring *via* a novel, double cyclodehydration sequence from an appropriate cyclopeptide precursor as a final step.[5] We now illustrate further scope for this strategy towards thiazoline-containing cyclopeptides by describing a concise synthesis of the structure **1** reported for cyclodidemnamide.



1

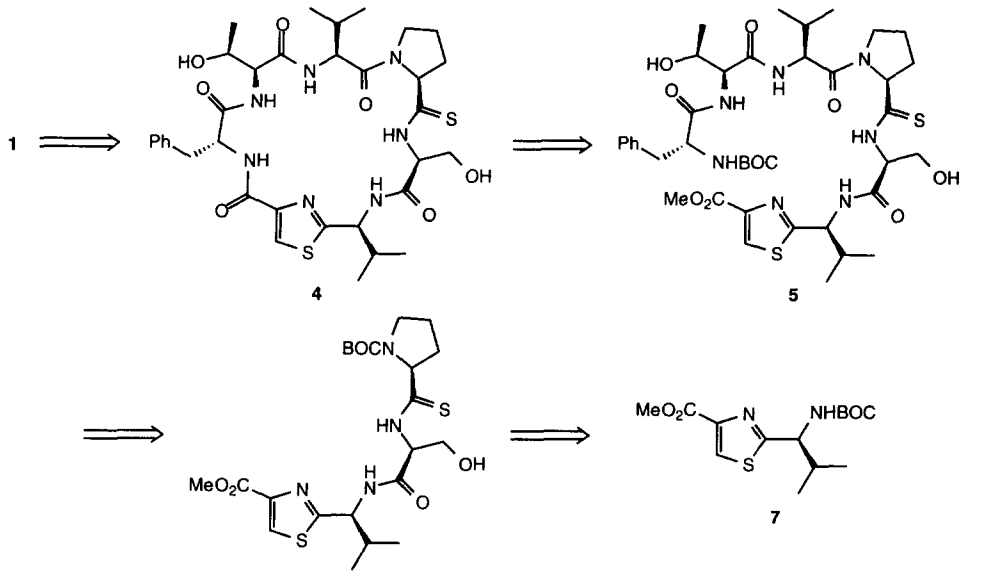


2

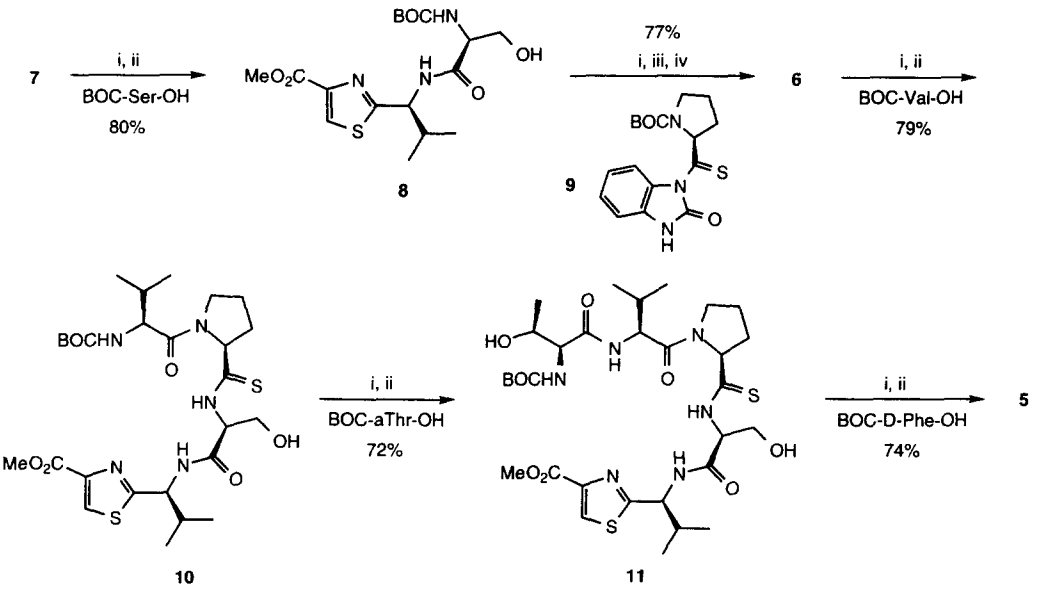


3

Thus, our synthetic strategy to cyclodidemnamide **1** was based on double cyclodehydration from the monothioamide-based cyclopeptide **4** which we planned to elaborate from the known substituted thiazole **7**[6] *via* **6** and **5** as key intermediates (Scheme 1).



Scheme 1



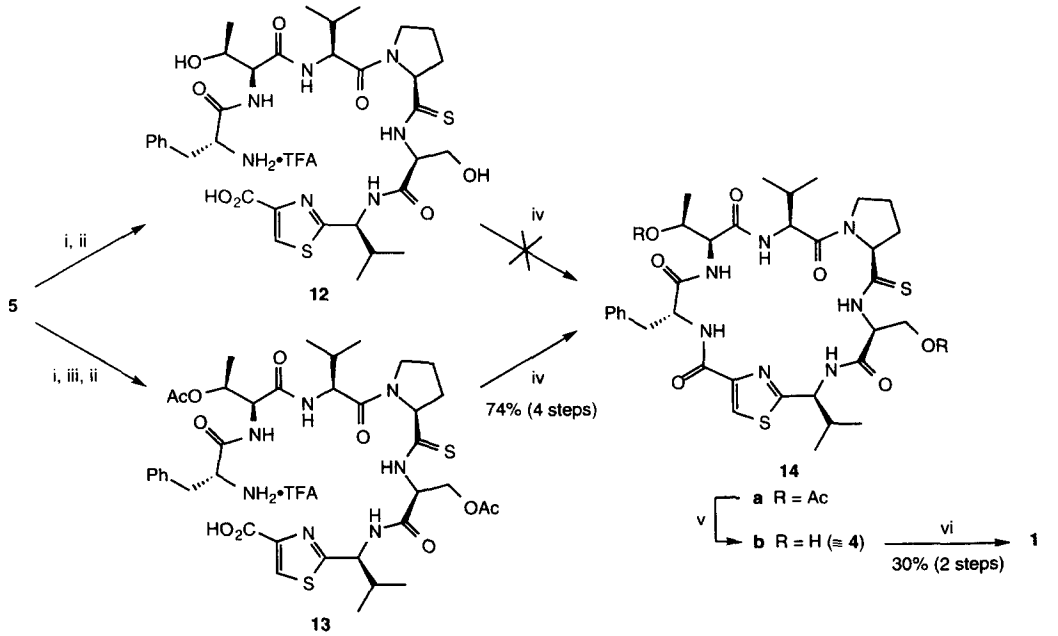
i, 50% TFA-CH_2Cl_2, 0°C, 1 h; ii, DCC, HOBt, *i*-Pr_2NEt, CH_2Cl_2, 0°C → r.t., 18 h;
iii, aq. $NaHCO_3$-CH_2Cl_2; iv, **9**, DMF, 0°C → r.t., 18 h

Scheme 2

The BOC group in the thiazole **7** (>97% ee) was first removed and the resulting amine was next coupled with BOC-Ser-OH in the presence of DCC-HOBt giving rise to the tripeptide **8** (Scheme 2). The

monothiotetrapeptide **6** was now elaborated from the tripeptide **8** following removal of the BOC group and coupling of the free amine with the thioacylating reagent **9**[7]. BOC-deprotection of **6**, by the usual method, and coupling of the resulting amine with BOC-Val-OH next produced the pentapeptide **10**, which was elaborated in a similar manner to the hexapeptide **11** (using BOC-aThr-OH) and finally to the key heptapeptide precursor **5** (using BOC-D-Phe-OH).

Saponification of the heptapeptide ester **5** using NaOH in THF-MeOH and removal of the BOC group next provided the amino acid **12** in readiness for macrocyclisation to the cyclopeptide **4** (Scheme 3). However attempts to macrocyclise **12** using our favoured DPPA or FDPP reagents failed to provide any of the corresponding cyclopeptide; instead degradation occurred and a number of unidentified products were produced. Suspecting that the free hydroxy groups in **12** were principally responsible for this sensitivity towards the reagents used in its cyclisation, we decided to convert them into their corresponding acetate derivatives prior to macrocyclisation. Thus, the *bis*-acetate **13** was produced from **5**, and this underwent clean macrocyclisation in the presence of DPPA (*i*-Pr_2NEt, DMF, 0°C → r.t.) to produce the cyclopeptide **14a** in a satisfying 74% overall yield from **5**. Saponification of the acetate groups in **14a** using K_2CO_3 in MeOH then provided the key penultimate precursor **4** (≡ **14b**) in our synthesis in essentially quantitative yield. Treatment of the cyclopeptide **14b** with Burgess' reagent[8] in refluxing THF for 2h then resulted in double, simultaneous cyclisation to the thiazoline and oxazoline rings producing the cyclodidemnamide structure **1** in an acceptable 30% yield.



i, aq. NaOH, THF-MeOH (3:1), 0°C, 1 h; ii, 50% TFA-CH_2Cl_2, 0°C, 1 h;
iii, Ac_2O, Et_3N, cat. DMAP, DMF, r.t., 2 h; iv, DPPA, *i*-Pr_2NEt, DMF, 0°C → r.t., 3 days;
v, aq. K_2CO_3, MeOH, 0°C, 1 h; vi, Burgess' reagent, THF, Δ, 2 h

Scheme 3

Although the synthetic cyclodidemnamide showed closely similar data in its ^{13}C NMR spectrum with those obtained for the natural product, their corresponding ^{1}H NMR spectra showed significant differences.[9] These differences led us to the conclusion that formula **1** does not reflect accurately the stereostructure for cyclodidemnamide isolated from the marine ascidian *Didemnum molle*. On the assumption that the amino acid sequence in the natural product is secure, the known propensity with which chiral thiazole and thiazoline units undergo racemisation would lead us to suggest that natural cyclodidemnamide has a stereostructure which is epimeric at the valine-derived thiazole centre in structure **1**. Further synthetic work is now in progress to vindicate this proposition.

Acknowledgements: We thank Professor W Fenical for providing NMR spectra for naturally derived cyclodidemnamide, and for helpful correspondence. We also thank the EPSRC for support of this work.

References:

1. Toske, S. G.; Fenical, W. *Tetrahedron Lett.* **1995**, *36*, 8355.
2. 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.
3. (a) 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. (b) 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. (c) Hawkins, C. J.; Lavin, M. F.; Marshall, K. A.; van den Brenk, A. L.; Watters, D. J. *J. Med. Chem.* **1990**, *33*, 1634.
4. (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.
5. Boden, C. D. J.; Pattenden, G. *Tetrahedron Lett.* **1995**, *36*, 6153.
6. Boden, C. D. J.; Pattenden, G.; Ye, T. *Synlett*, **1995**, 417.
7. Zacharie, B.; Sauvé, G.; Penney, C. *Tetrahedron* **1993**, *49*, 10489.
8. Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397.
9. Satisfactory spectroscopic and mass spectrometry data were obtained for all new compounds. Data for synthetic **1**: δ_H (500 MHz, $CDCl_3$): 8.41 (1H, d, J = 7.9), 7.97 (1H, s), 7.48 (1H, d, J = 7.5), 7.25 (5H, m), 7.08 (1H, d, J = 7.5), 5.15 (1H, dd, J = 9.8, 1.9), 5.12 (1H, m), 4.91 (1H, t, J = 7.2), 4.83 (1H, quintet, J = 6.3), 4.66 (1H, dd, J = 9.9, 2.6), 4.35 (1H, t, J = 7.5), 4.03 (1H, d, J = 6.3), 3.70 (1H, m), 3.64 (1H, dd, J = 11.2, 1.9), 3.52 (1H, m), 3.51 (1H, app. t, J = 10.6), 3.25 (1H, dd, J = 13.7, 5.7), 3.18 (1H, dd, J = 13.7, 6.5), 3.03 (1H, m), 2.32 (1H, m), 2.17 (1H, m), 2.00 (2H, m), 1.80 (1H, m), 1.39 (3H, d, J = 6.3), 1.07 (3H, d, J = 6.5), 0.76 (3H, d, J = 6.7), 0.72 (3H, d, J = 6.7), 0.14 (3H, d, J = 6.4); δ_C (125 MHz, $CDCl_3$): 180.5 (s), 171.2 (s), 171.0 (s), 170.6 (s), 169.9 (s), 169.3 (s), 160.8 (s), 147.3 (s), 135.8 (s), 129.7 (d), 128.5 (d), 127.2 (d), 124.9 (d), 82.0 (d), 77.5 (d), 73.9 (d), 63.1 (d), 60.2 (d), 54.2 (d), 48.3 (d), 47.8 (t), 39.6 (t), 36.9 (t), 31.2 (d), 30.7 (d), 30.2 (t), 25.5 (t), 21.9 (q), 20.4 (q), 20.3 (q), 20.2 (q), 14.6 (q); MS (FAB), *m/z* (%): 716 (M^+ + Na, 55), 694 (M^+ + H, 100), 597 (14), 415 (13), 356 (6), 285 (18); HRMS, *m/z* for $C_{34}H_{44}N_7O_5S_2$ (M^+ + H), calc: 694.2845; found: 694.2813.

(*Received in UK* 1 *October* 1996; *revised* 23 *October* 1996; *accepted* 25 *October* 1996)