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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 58.[1] A SYNTHESIS OF PATELLAMIDE A, A CYTOTOXIC CYCLIC PEPTIDE FROM A TUNICATE. REVISION OF ITS PROPOSED STRUCTURE

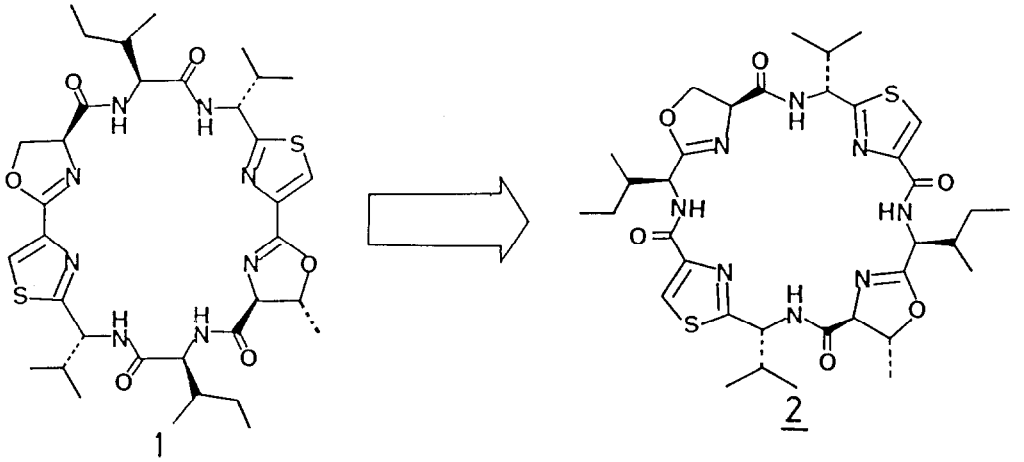
Yasumasa Hamada*, Makoto Shibata, and Takayuki Shioiri*

Faculty of Pharmaceutical Sciences, Nagoya City University,
Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

The real structure of patellamide A, a cytotoxic lipophilic cyclic peptide from a marine tunicate, has been unambiguously determined by the synthesis of both its proposed and revised structures.

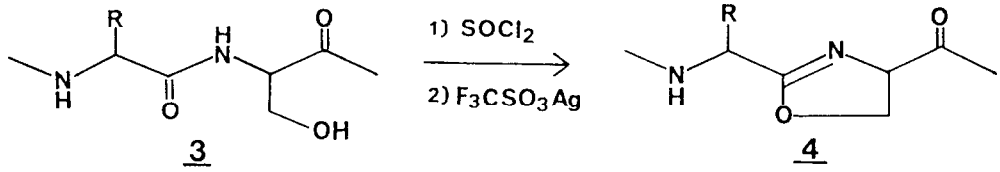
We have already revised the structures of patellamides B and C,[2] cytotoxic lipophilic cyclic peptides from a tunicate *Lissoclinum patella*, by their synthetic studies.[3]

Patellamide A is an analogous cytotoxic peptide isolated from the same tunicate and its structure has been proposed as **1**.[2] In this paper we wish to describe the revision of the proposed structure **1** to the alternative **2**, having the reverse order of each peptide bond, by the synthesis of both peptides.



1 **2**

Furthermore we have devised a novel method for the construction of the oxazoline skeleton **4** from serine peptides **3** by treatment of thionyl chloride followed by silver trifluoromethanesulfonate:



3 4

We first synthesized patellamide A with the proposed structure 1, as shown in Chart 1. The Boc group was employed for N^{α}-protection and deblocked with 4N hydrogen chloride in dioxane (room temp., 1h). Formation of peptide bonds was achieved by the use of diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$) in the presence of triethylamine in dimethylformamide.

Two tripeptides, Boc-L-aThr-L-Ile-D-(val)Thz-OMe (6) (mp 182-183°C, $[\alpha]_D^{23}$ -6.3°(c=0.25, MeOH)) and Boc-L-Ser-L-Ile-D-(val)Thz-OMe (7) (mp 164-166°C, $[\alpha]_D^{24}$ -5.6°(c=0.5, MeOH)) were respectively prepared in good yields from Boc-D-(val)Thz-OMe[4,5] via Boc-L-Ile-D-(val)Thz-OMe (5) (mp 114-115°C, $[\alpha]_D^{23}$ +15.4°(c=0.5, MeOH)). Alkaline hydrolysis of 6 afforded the carboxylic acid 8 (mp 211-213°C (dec), $[\alpha]_D^{24}$ +10.4°(c=0.25, DMF)), which was condensed with the amine hydrochloride 9 obtained from 7 to give the protected hexapeptide 10 (mp 183-196°C (dec)). Successive deblocking at the C- and N-terminals of 10, followed by cyclization with diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$)[3] afforded the cyclic peptide 11 (mp 189-191°C) in 55% yield. To construct the two oxazoline skeletons in 11, we employed the similar reaction conditions to those in the preparation of patellamides B and C[3] using thionyl chloride (4°C, 48h). However, the major product, obtained in 50% yield, was 12 (169-172°C), in which the simple chlorination occurred at the serine residue while the desired oxazoline ring was formed at the allothreonine residue. The expected patellamide A with the proposed structure 1 (mp 114-115°C) was also obtained but in only 15% yield.

As expected from our synthetic studies on patellamides B and C,[3] this synthetic patellamide A with the proposed structure 1 was not identical with natural patellamide A, kindly donated by Professor Ireland, on a TLC behavior[6] as well as IR and NMR[7] spectral comparisons.

Therefore, we immediately started the synthesis of patellamide A with the revised structure 2, which was considered on the basis of the structural revision of patellamides B and C.[3]

Analogously to the synthesis of 1, two peptide fragments were selected as building blocks to construct the full peptide skeleton, as shown in Chart 2. Thus, Boc-D-(val)Thz-OMe was converted to two tripeptides, Boc-L-Ile-L-aThr-D-(val)Thz-OMe (15) (mp 188-189°C, $[\alpha]_D^{23}$ -11.8°(c=0.49, MeOH)) and Boc-L-Ile-L-Ser-D-(val)Thz-OMe (16) (mp 112-113°C, $[\alpha]_D^{22}$ +17.0°(c=0.51, DMF)), via Boc-L-aThr-D-(val)Thz-OMe (13) (mp 139-140°C, $[\alpha]_D^{22}$ +16.4°(c=0.69, MeOH)) and Boc-L-Ser-D-(val)Thz-OMe (14) (mp 138-139°C, $[\alpha]_D^{22}$ +19.8°(c=1.0, MeOH)), respectively. After saponification of 15 and removal of the Boc group from 16, the fragment coupling of the resulting 17 (mp 201-203°C, $[\alpha]_D^{24}$ -12.4°(c=0.3, MeOH)) and 18 smoothly proceeded by the DEPC method to give the hexapeptide 19 (mp 232-235°C (dec), $[\alpha]_D^{23}$ +26.0°(c=0.51, DMF)). Sequential treatment of 19 with sodium hydroxide, hydrogen chloride,

Chart 1. Synthesis of Patellamide A with the Proposed Structure 1

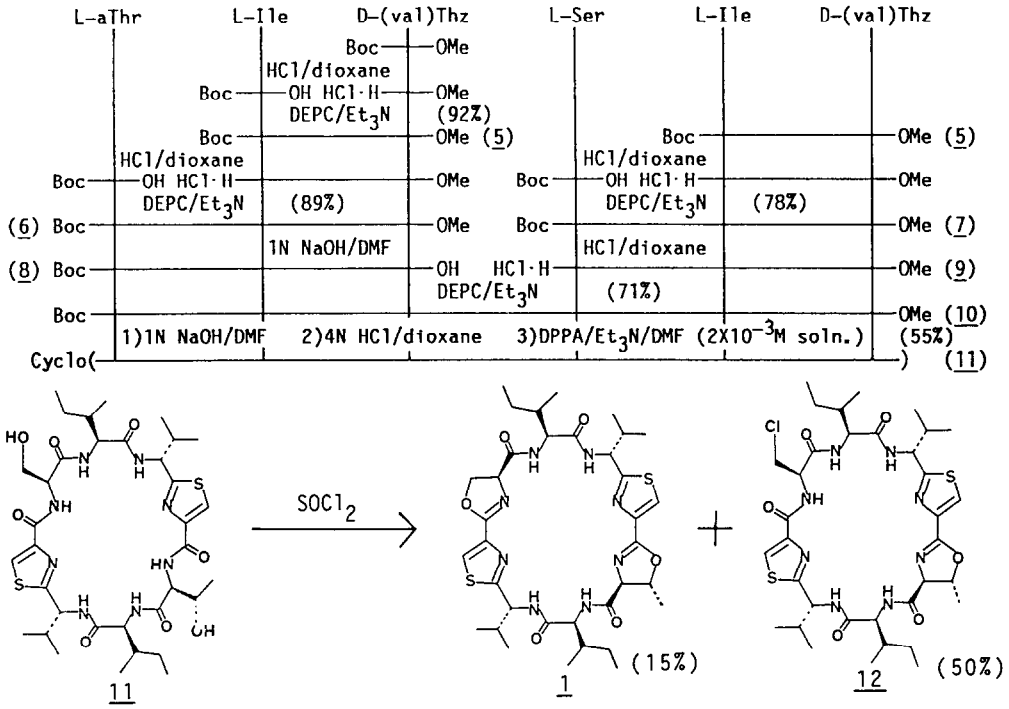
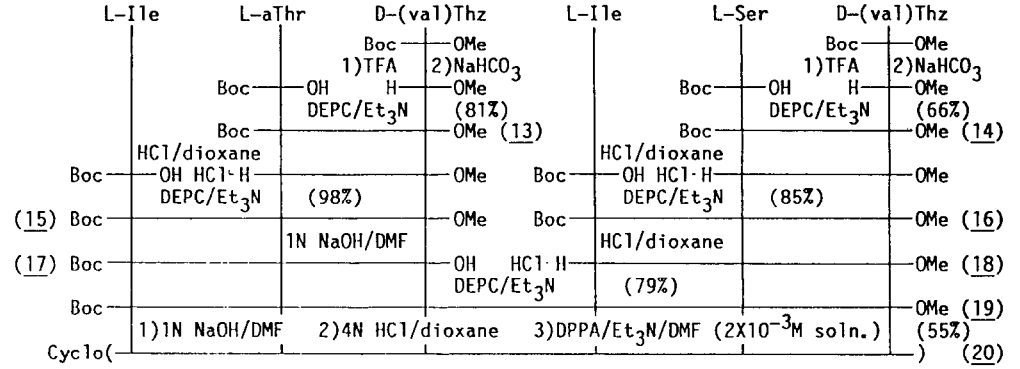
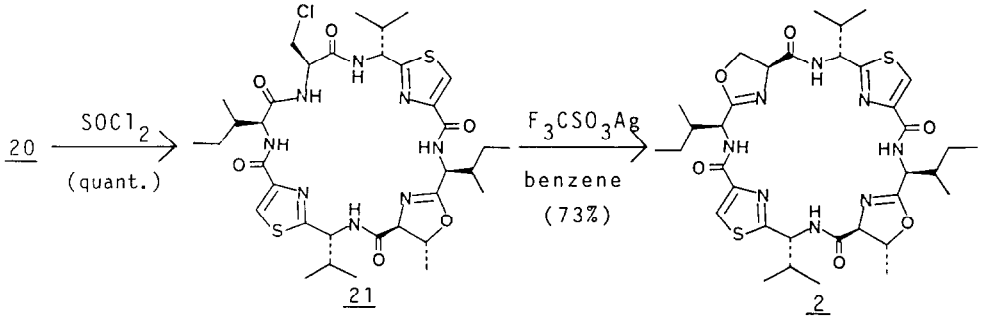


Chart 2. Synthesis of Patellamide A with the Revised Structure 2





and DPPA afforded the cyclic peptide **20** (mp >300°C) in 55% yield. Treatment of **20** with thionyl chloride (4°C, 48h) quantitatively afforded the mono oxazoline peptide **21** (mp 257-259°C). No spot of the desired **2** containing two oxazoline rings was detected on a TLC plate. However, the formation of the oxazoline ring at the serine residue was achieved by refluxing a mixture of **21** and silver trifluoromethanesulfonate (3eq) in benzene for 6h. The product (**2**, mp 228-229°C (from benzene), $[\alpha]_D^{24}$ +140.7°(c=0.27, CH_2Cl_2)), thus obtained in 73% yield,[8] was completely identical with natural patellamide A[2,9] by IR, ^{1}H- and ^{13}C-NMR spectral analyses as well as a TLC behavior.

The results described above have unambiguously established the real structure of patellamide A as **2**, but not **1** as proposed. Furthermore, silver trifluoromethanesulfonate in combination with thionyl chloride has been proven to be useful for the construction of the oxazoline ring from serine peptides.

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References and Notes

1) For Part 57, see Y. Hamada, A. Kawai, and T. Shioiri, Chem. Pharm. Bull., submitted.

2) (a) C.M. Ireland, A.R. Durso,Jr., R.A. Newman, and M.P. Hacker, J. Org. Chem., **47**, 1807 (1982); (b) J.E. Biskupiak and C.M. Ireland, J. Org. Chem., **48**, 2302 (1983).

3) Y. Hamada, M. Shibata, and T. Shioiri, Tetrahedron Lett., in press.

4) Y. Hamada, S. Kato, and T. Shioiri, Tetrahedron Lett., **26**, 3223 (1985).

5) For abbreviation of the thiazole amino acid, see G.R. Petitt, Y. Kamano, P. Brown, D. Gust, M. Inoue, and C.L. Herald, J. Am. Chem. Soc., **104**, 905 (1982).

6) Rf Values on TLC (silica gel, Merck Art 5715, MeOH:$CHCl_3$=1:15), 0.42 for synthetic patellamide A (**1**) and 0.50 for natural one.

7) ^{1}H-NMR(δ) for patellamide A:

	Oxazoline-CH_3	Thiazole-5-H
Synthetic(**1**)	1.64 (3H, d, J=6Hz)	7.91 (2H, s)
Natural	1.48 (3H, d, J=6Hz)	7.83 (2H, s)

8) The starting **21** was recovered in 14% yield.

9) No melting point is recorded in the literature,[2] and the reported specific rotation is $[\alpha]_D$ +113.9°(c=0.27, CH_2Cl_2).

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