

## WHAT IS THE STRUCTURE OF THE PATELLAMIDES?<sup>1</sup>

Ulrich Schmidt\*, Roland Utz and Peter Gleich

Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität  
Stuttgart, Pfaffenwaldring 55, D-7000 Stuttgart 80

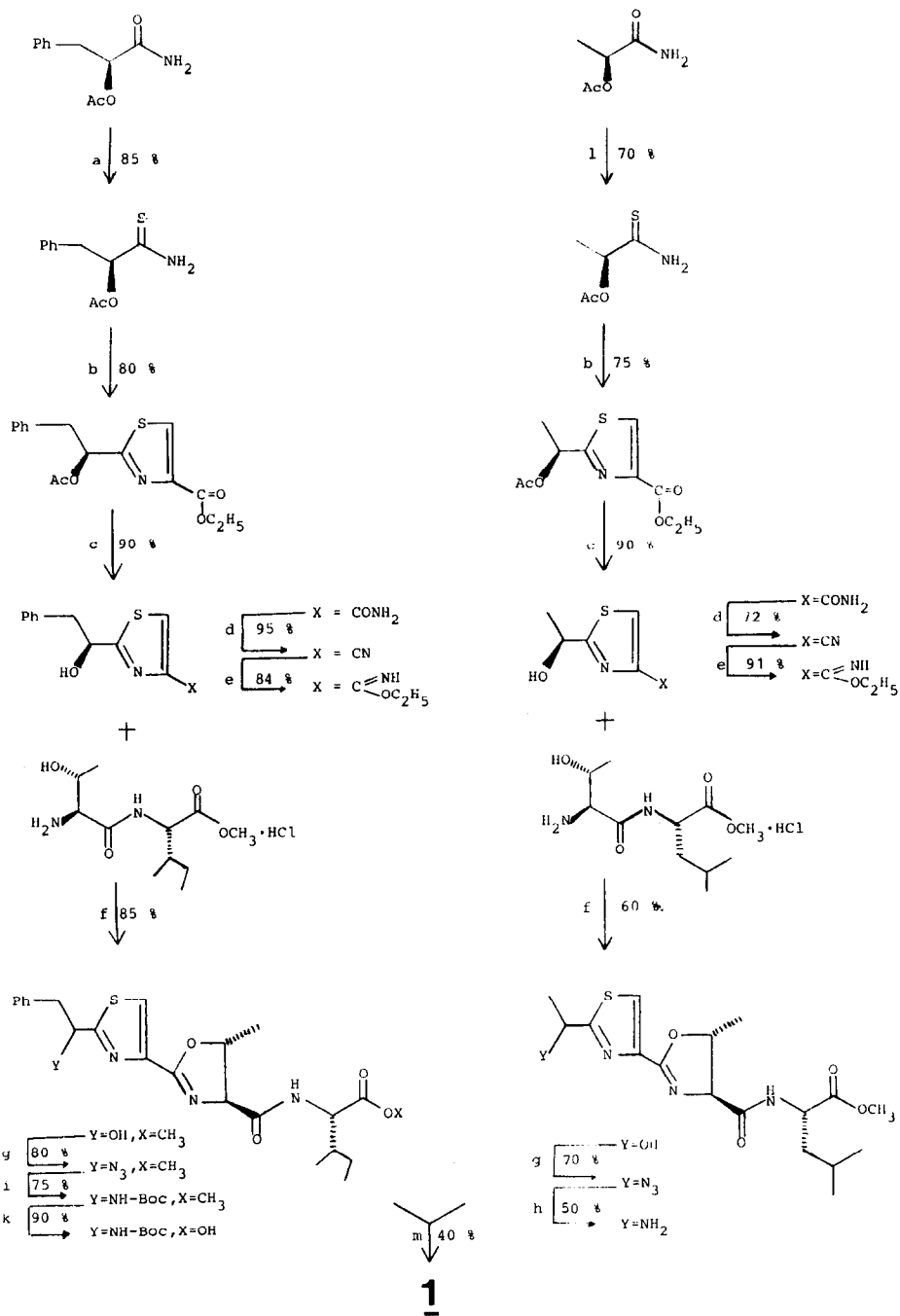
Abstract. The compound with the structure (2) elucidated for patellamide B was synthesized and found to be not identical with that cyclopeptide. A new proposition for the structure of patellamide B is given.

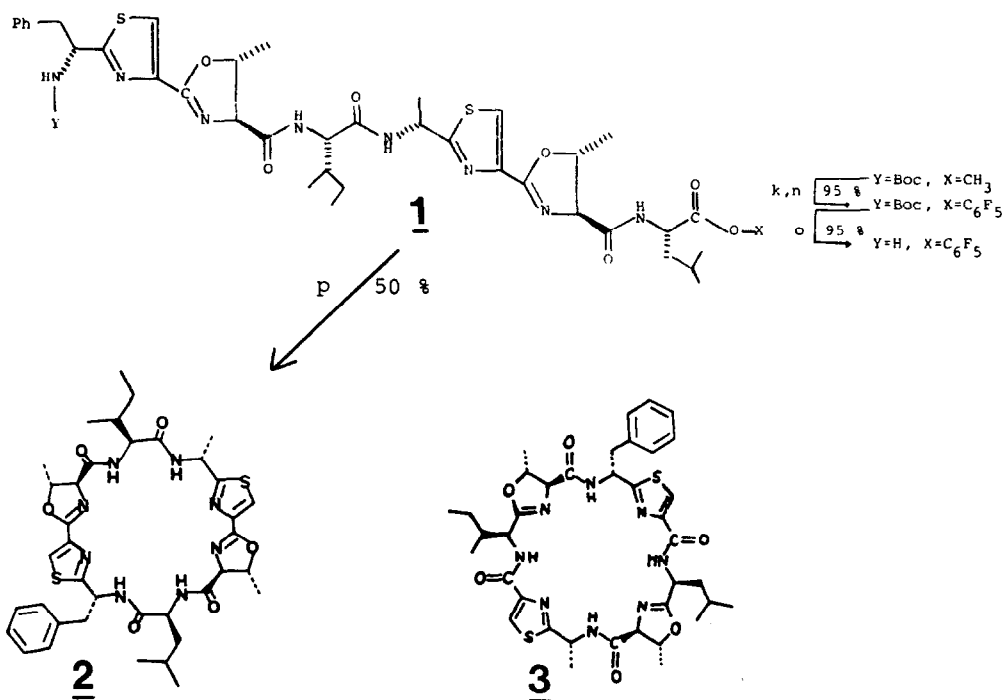
A group of antineoplastic cyclopeptides from *Lissoclinum patella* - a marine invertebrate - which contain thiazole amino acids and oxazoline carboxylic acids was isolated and elucidated in the last few years<sup>2-6</sup>.

The first total synthesis<sup>7</sup> in this field was performed a few months ago by the construction of ulicyclamide containing oxazoline and thiazole components which are separated by an amino acid. For 3 compounds of this group - the patellamides A-C - a sequence with fused oxazoline-thiazoles seemed to be logical because no homoallylic coupling of the protons at the C-4 of the oxazolines was observed. Structure 2 was therefore proposed for patellamide B<sup>3</sup>.

We synthesized this compound with structure 2 by a clear way (scheme). The two (R)-(aminoalkyl)thiazoles were constructed by the method we developed in the synthesis of do-lastatin isomers<sup>8</sup> and ulicyclamide<sup>7</sup>. The combination of the two oxazoline-thiazole fragments without extensive racemisation in moderate yield could be achieved only by DCCD/CuCl<sub>2</sub><sup>9</sup>. The cyclopeptide 2 was formed by cyclisation of the ω-aminopentafluoro-phenyl ester 1 under high dilution conditions<sup>10</sup> and isolated by medium pressure chromatography.

FDMS proves the molecular formula C<sub>38</sub>H<sub>48</sub>N<sub>8</sub>O<sub>6</sub>S<sub>2</sub>. The 250 MHz <sup>1</sup>H-NMR spectrum is in complete accordance with the structure 2, but differs entirely from the data of the patellamide B spectrum. Therefore the structures of at least patellamide B and presumably of patellamide A and C have to be corrected.





- a: 1. TFAA/Py, 0°C, 10 min; 2. H<sub>2</sub>S/NEt<sub>3</sub>, r.t., 1 d  
 b: Ethylbromopyruvate, EtOH  
 c: Methanol/NH<sub>3</sub>, r.t., 4 d  
 d: TFAA/Py, 0°C, 10 min  
 e: EtOH/NaOEt, r.t., 1 d  
 f: CH<sub>2</sub>Cl<sub>2</sub>, r.t., 1 d  
 g: Diethylazodicarboxylate/P(Ph)<sub>3</sub>/HN<sub>3</sub>, r.t., 1 h  
 h: Pd/H<sub>2</sub>  
 i: (Boc)<sub>2</sub>O  
 k: NaOH/dioxane/H<sub>2</sub>O, r.t., 5 h  
 l: Lawesson's reagent, dioxane, r.t. 2 d  
 m: DCCD/CuCl<sub>2</sub>, 0°C→r.t., 3 d  
 n: C<sub>6</sub>F<sub>5</sub>OH/DCCD, 1 d  
 o: CF<sub>3</sub>COOH, 0°C, 25 min  
 p: Pyrrolidinopyridine/dioxane, 3 h

**2**: <sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>, TMS): δ = 7.93(s,1H), 7.89(d,J=9Hz,1H), 7.87(s,1H), 7.84(d,J=9Hz,1H), 7.66(d,J=8Hz,1H), 7.60(d,J=7.5Hz,1H), 7.21(m,3H), 7.01(m,2H), 5.67(ddd,J=8,7.5,4.5Hz,1H), 5.48(dq,J=7.5,7Hz,1H), 4.99(dq,J=7.5,6Hz,1H), 4.91(dq,J=8.5,6Hz,1H), 4.63(m,1H), 4.61(dd,J=9,4.5Hz,1H), 4.48(d,J=8.5Hz,1H), 4.34(d,J=7.5Hz,1H), 3.31(dd,J=13.5,4.5Hz,1H), 3.17(dd,J=13.5,7.5Hz,1H), 2.06(m,1H), 1.78(m,1H), 1.65(d,J=6Hz,3H), 1.63(d,J=6Hz,3H), 1.60(d,J=7Hz,3H), 1.38(m,2H), 1.23(m,2H), 0.84(d,J=7Hz,3H), 0.82(d,J=6.5Hz,3H), 0.80(d,J=6.5Hz,3H), 0.76(t,J=7.5Hz,3H)

It is remarkable that the spectra of all cyclopeptides with undoubtedly separated oxazoline and thiazole components contain signals as doublets for the oxazoline methyl group at  $\delta = 1.46-1.51$  (ascidiacyclamide<sup>6</sup>:  $\delta$  1.49; ulicyclamide<sup>2,5</sup>:  $\delta$  1.44; three further cyclopeptides<sup>5</sup> from *Lissoclinum patella*:  $\delta = 1.46, 1.51, 1.46$ ). In contrast the signals of the oxazoline methyl group of peptides with fused oxazoline-thiazoles show chemical shifts of  $\delta = 1.6$  (cyclopeptide 2 and all intermediates with fused oxazoline-thiazoles in the scheme). - Because the signals of the oxazoline methyl groups in the patellamides A-C were described at  $\delta = 1.41, 1.44, 1.45$  and  $1.47$ , a structure of these cyclopeptides with fused oxazoline-thiazoles seems to be improbable. - Moreover, the two tripeptides obtained in the mild hydrolysis of patellamide B cannot have the proposed structure<sup>3</sup>, as the signals of the methoxyprotons in the methyl thiazolecarboxylates have a chemical shift of about  $\delta = 4.0$  compared with an observed shift of  $\delta = 3.78$ . - We propose 3 to be the structure of patellamide B and analogous structures for patellamides A and C.

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