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TOTAL SYNTHESIS AND STRUCTURE DETERMINATION OF PATELLAMIDE B[1]

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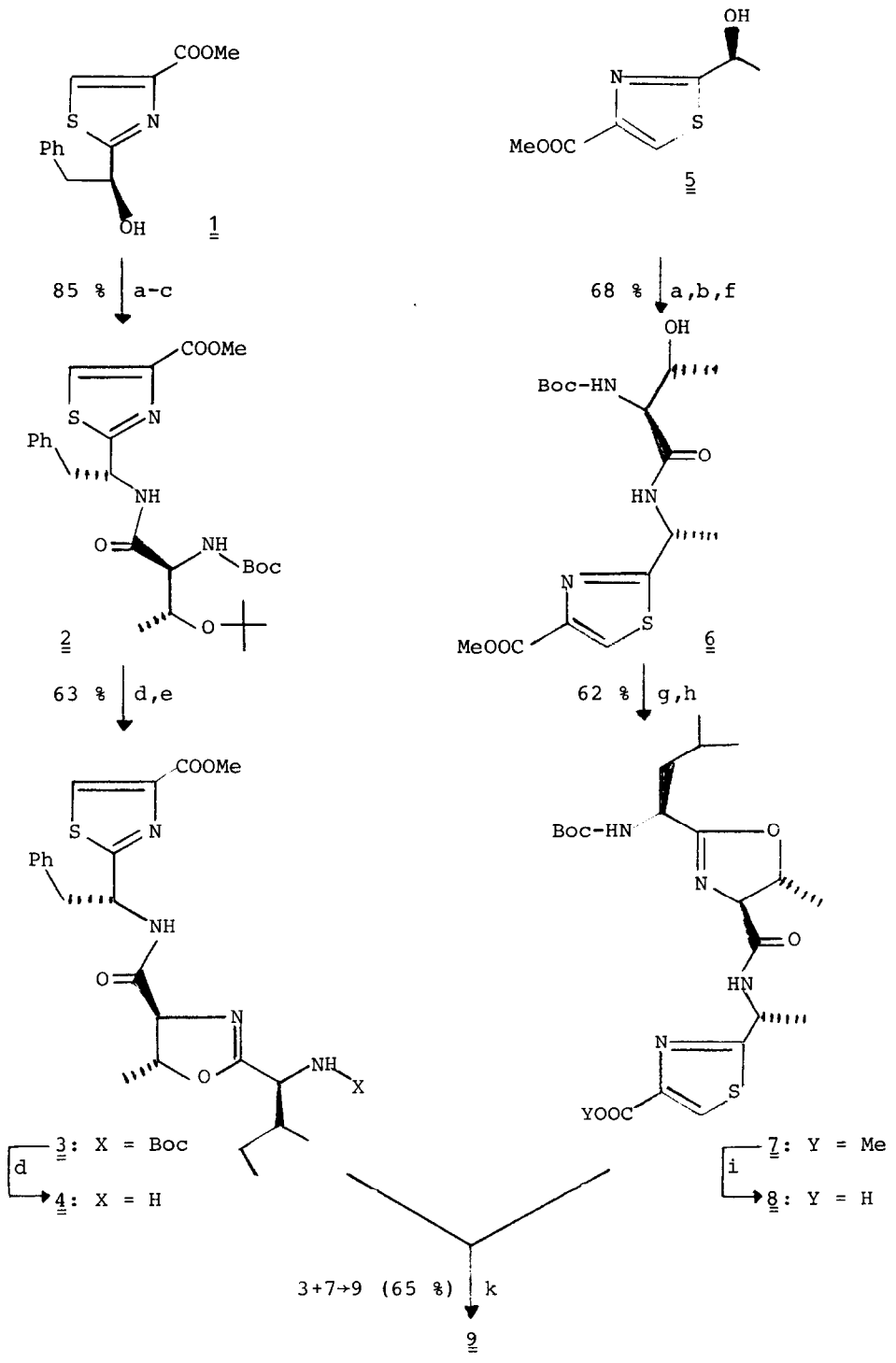
Abstract. The total synthesis of patellamide B, 12, is described, which confirms the corrected structure.

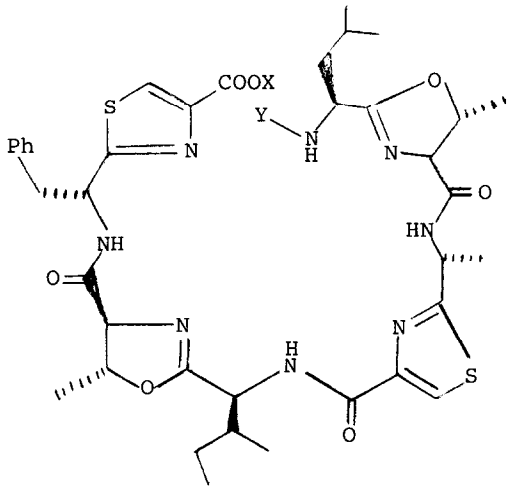
A group of antineoplastic cyclopeptides from Lissoclinum patella, a marine invertebrate, which contains thiazole amino acids and oxazoline carboxylic acids has been isolated and elucidated in the last few years[2-6].

The first total synthesis[7] 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 was described by Ch.Ireland et al[3].

We synthesized[8] the compound 13 with the structure proposed for patellamide B by a clear way. As the cyclopeptide 13 of our synthesis was not identical with patellamide B, the structure of the latter and presumably of patellamide A and C had to be corrected.

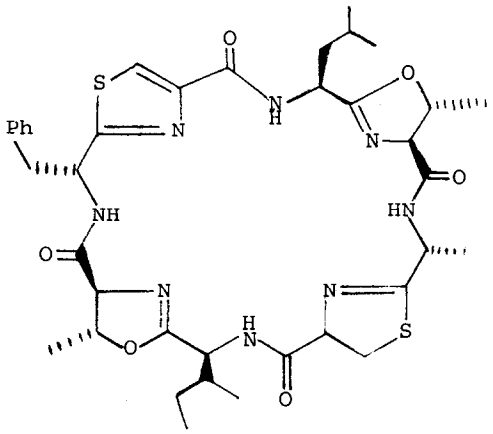
As a result of our experience with the NMR spectra of fused oxazoline thiazoles and after a critical trial of the NMR spectra described[3] for the tripeptides which were obtained by mild hydrolysis of patellamide B, we proposed[8] 12 with separated oxazoline and thiazole components to be the structure of patellamide B and analogous structures for patellamides A and C.
The total synthesis of the cyclopeptide 12 by a clear way was achieved in our laboratory in the last few weeks according to the following scheme:


COOMe
S
N
Ph
OH
1
85 % a-c
2
63 % d,e
3: X = Boc
d
4: X = H
OH
N
S
MeOOC
5
68 % a,b,f
6
62 % g,h
7: Y = Me
i
8: Y = H
3+7→9 (65 %) k
9

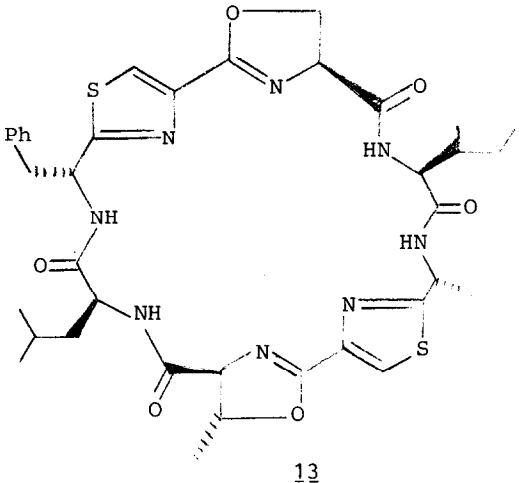


9: X = Me; Y = Boc
i,l → 10: X = C_6F_5; Y = Boc
d → 11: X = C_6F_5; Y = H

9 → 12 | m
20 %



12



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a: Diethylazodicarboxylate/$P(Ph)_3$/HN_3, r.t., 3 h; b: Pd/H_2; c: Boc-Thr-(tBu)-OH/DCCD, -20°C→r.t., 1 d; d: CF_3COOH, 0°C, 1 h; e: Boc-isoleucine imidic ester·HCl/CH_2Cl_2 reflux 2 d; f: Boc-Thr-OH/DCCD, -20°C→r.t., 1 d; g: HCl/$CHCl_3$;, h: Boc-leucine imidic ester/HCl, reflux 3 d; i: NaOH/dioxane/H_2O, r.t., 1 h; k: diphenyl phosphorazidate/ Et_3N/ dioxane, 0°C, 14 h; l: C_6F_5OH/DCCD/dioxane, 0°C→r.t., 1 d; m: dioxane/EtOH/4-pyrrolidinopyridine, 95°C, high dilution, 4 h.

The synthetic product was identical with authentic material (^{1}HNMR, MS, HPLC) in every respect which proved the structure 12 for patellamide B and analogous structures for patellamide A and C. We informed Prof. Ireland that the published structures of the patellamides were not correct. By the help of 2D COSY 45 NMR he thereupon corrected[9] the structure in accordance with our proposal[8]. Our synthesis is described as follows: The (S)-2-(1-hydroxyalkyl)-4-thiazolecarboxylic esters 1 and 5 were prepared as described by us[7,8], but with improved yields and converted via Mitsunobu reaction with inversion into the azides and by following hydrogenation into the amines. The so obtained compounds were acylated with protected threonine to give 2 and 6. After cleavage of the protecting groups the amino alcohols were condensed with Boc-leucine imidic ester and Boc-isoleucine imidic ester respectively to the oxazoline compounds 3 and 7. After hydrolysis of the ester group of 7 and cleavage of the Boc group of 3 the two components 4 and 8 were connected to form the linear peptide 9. Saponification of the ester group, conversion into the pentafluorophenyl ester and cleavage of the Boc group furnished the linear educt for the ring closure reaction[10] under high dilution condition to patellamide B, 12, which could be isolated and purified by medium pressure chromatography.
The main difficulty of this synthesis results from the high sensitivity and lability of the oxazoline ring derived from isoleucine.

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