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TOTAL SYNTHESIS OF ULITHIACYCLAMIDE[1]

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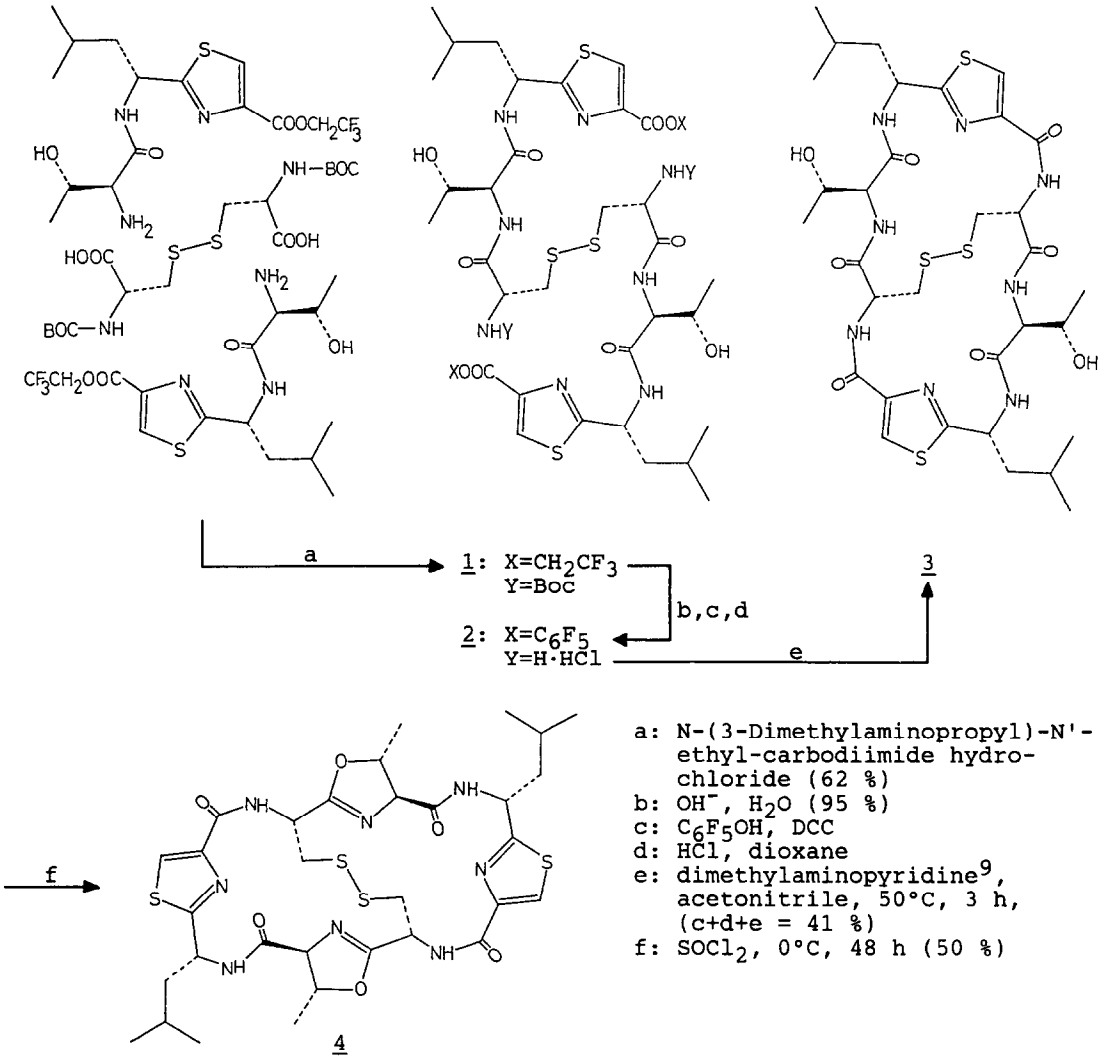
Abstract: The total synthesis of ulithiacyclamide (4) by twofold ring closure reaction of the bifunctional pentafluorophenyl ester 2 is described.

Several cytotoxic and cancerostatic cyclopeptides which contain unique thiazole amino acids and oxazoline amino acids have been isolated from marine animals in the last few years.
The first total synthesis of a cyclopeptide with thiazole amino acids was performed by our preparation[2] of the 16 structural isomers of dolastatin 3[3]. In the field of cyclopeptides with both thiazole amino acids and oxazoline amino acids we firstly synthesized ulicyclamide[4]. Now we describe the total synthesis of ulithiacyclamide, which contains two thiazole amino acids, two oxazoline amino acids and a symmetric disulfide bridge. This cyclopeptide was isolated from the ascidian Lissoclinum patella and elucidated by C.Ireland and P.J.Scheuer[5]. It is the most potent antitumor constituent of this tunicate and seems to be biosynthesized from two leucines, two threonines and four cysteines.
The (R)-2-(1-amino-3-methylbutyl)-4-thiazolecarboxylic acid was formed by our synthesis[6] of chiral (aminoalkyl)thiazolecarboxylic acids from (S)-leucine. All our attempts failed to construct the cyclopeptide via S-protected cysteines[7]. Though a cyclopeptide with a 2-fold rotation axis is synthesized most simply by cyclodimerisation, this way bears the disadvantage, that the first bond must be formed in an intermolecular reaction and the second by an intramolecular one. The first bond formation requires high concentration and the second one high dilution. These difficulties are off set if the two bonds are formed in the cystine derivative 2.
Because the two rings to be formed are 17-membered, the ring closure reactions should be performed in moderate dilution. From our experience high dilution is not necessary for the construction of flexible cyclopeptides. The synthesis of the educt for the ring closure reaction is described in the scheme. The rings were formed with the bifunctional pentafluorophenyl ester 2. The cyclopeptide 3 is polar and difficult to purify. It was transformed into ulithiacyclamide (4) by $SOCl_2$[8]. The spectra data (N.M.R.,H.R.M.S.) of the synthetic product and the natural product are completely identical.



a: N-(3-Dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride (62 %)
b: OH^-, H_2O (95 %)
c: C_6F_5OH, DCC
d: HCl, dioxane
e: dimethylaminopyridine[9], acetonitrile, 50°C, 3 h, (c+d+e = 41 %)
f: $SOCl_2$, 0°C, 48 h (50 %)

References and Notes

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