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A FACILE SYNTHESIS OF ULICYCLAMIDE [1]

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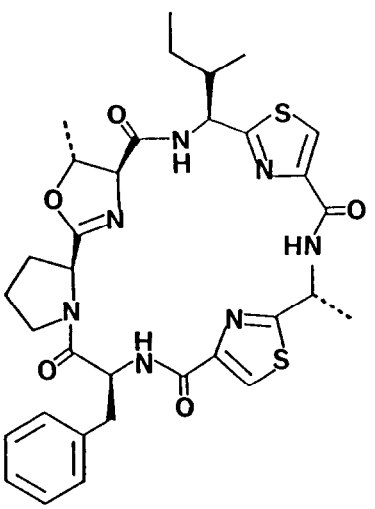
Abstract: Ulicyclamide (**1**), a cytotoxic cyclic peptide from a marine tunicate, has been efficiently synthesized by the solid-phase method using diethyl phosphorocyanidate for the coupling and trimethylsilyl triflate for the final deprotection.

Ulicyclamide (**1**) is one of cytotoxic cyclic peptides isolated from the tunicate *Lissoclinum patella*.[2] Its unique structure was determined by Ireland and coworkers,[2] and the synthesis by a conventional manner was reported by Schmidt and Gleich.[3] As part of an extensive synthetic study on cytotoxic cyclic peptides of marine origin,[1,4] we now wish to report a facile synthesis of **1** by the solid-phase method using diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$)[5] for the coupling and trimethylsilyl triflate (TMSOTf)[6] for the final deprotection.

The synthesis of **1** started from Boc-L-Pro-polystyrene resin,[7] to which Boc-L-Phe-OH, Boc-D-(ala)Thz-OH,[8] Boc-L-(ile)Thz-OH,[8] and Z-L-aThr(Bu^t)-OH were sequentially attached by use of DEPC-triethylamine in dimethylformamide, as shown in Chart I. Five equivalents of the protected amino acid, DEPC, and triethylamine (TEA) were used in each coupling, which was carried out with ice-



Ulicyclamide (1)

cooling for 0.5-2h, then at room temperature for 1-1.5h. Introduction of the thiazole amino acids[8] required longer reaction time (ice-cooling, 2h; room temp., more than 10h) under above conditions, but the use of 7.5-fold excess of triethylamine accelerated the reaction (ice-cooling, 2h; room temp., 1h). The general procedure for the solid-phase peptide synthesis is summarized in Table I.

Table I. General Procedure for the Solid-phase Synthesis

Step	Reagents and operations[a]	Mix times (min)	Step	Reagents and operations[a]	Mix times (min)
1	CH_2Cl_2 wash (3 times)	2	8	Protected amino acid in DMF[b]	5
2	50% TFA in CH_2Cl_2 (1 time)	30	9	DEPC (ice-cooling)	2
3	CH_2Cl_2 wash (3 times)	2	10	TEA (ice-cooling)	0.5-2h
4	EtOH wash (3 times)	2		(room temp.)	1-1.5h
5	DMF wash (3 times)	2	11	DMF wash (3 times)	2
6	TEA (10eq.) in DMF (1 time)	10	12	EtOH wash (3 times)	2
7	DMF wash (6 times)	2			

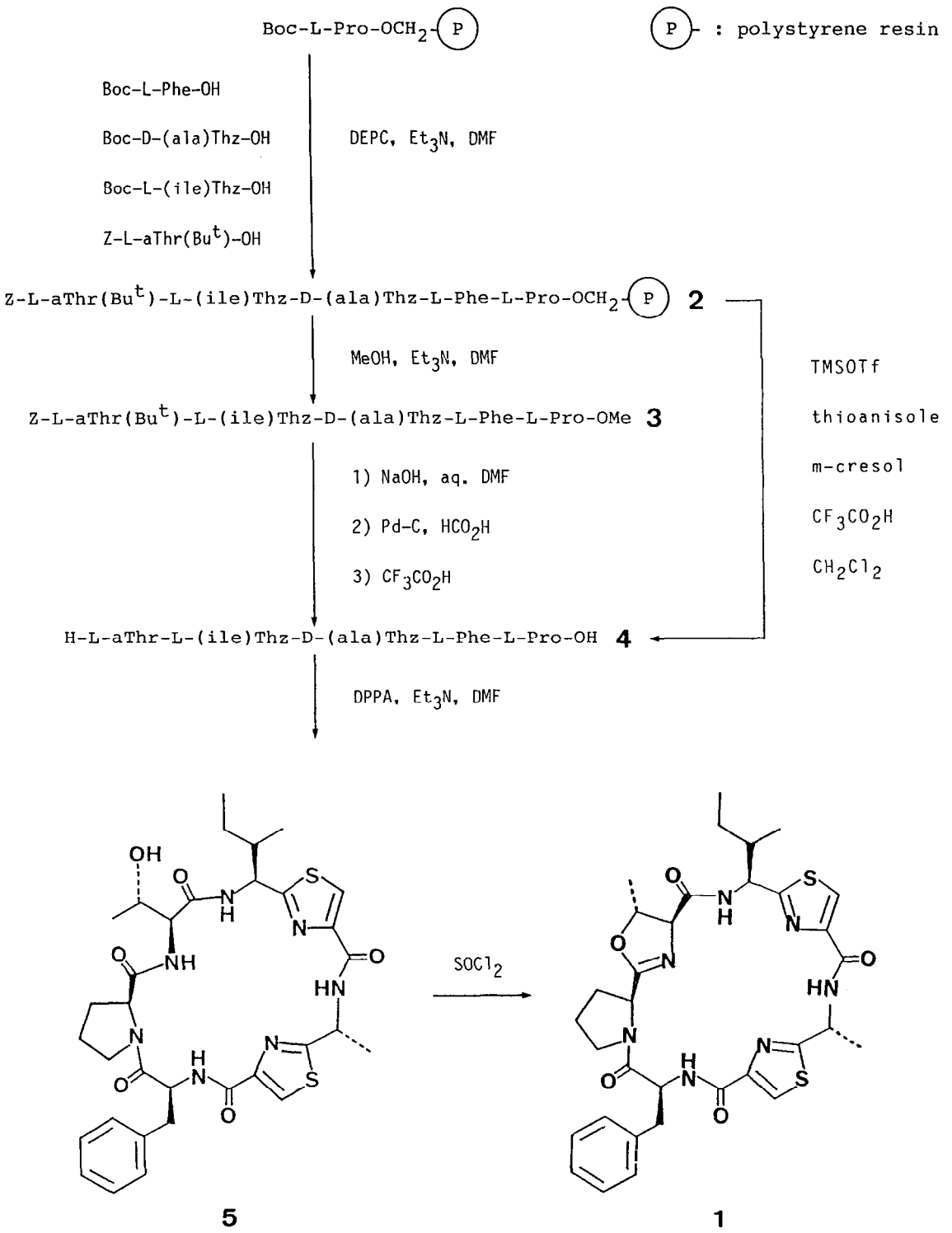
a) 5ml of solvent to 1g of resin was used for washing.
b) 2.5ml of solvent to 1g of resin was used.

Removal of the peptide from the resin **2** was achieved by methanolysis in dimethylformamide in the presence of triethylamine to give the fully protected pentapepide **3** in 56% yield from the starting resin. Sequential deprotection by alkaline hydrolysis (1N NaOH aq.-DMF, ice-cooling, 2h), catalytic transfer hydrogenation (5% Pd-C in HCO_2H, room temp., 21h), then acid treatment (CF_3CO_2H, room temp., 1h) afforded the linear pentapeptide **4**. Treatment of **4** with diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$; 2eq.) and triethylamine (1eq.) in dimethylformamide under high dilution conditions (ca. 1mM soln.) at 0-5°C for 3 days, then at room temperature for 1 day afforded the cyclic pentapeptide **5** in 30% yield from **3**.

More conveniently, the peptide resin **2** was treated by the method of Yajima[6] with 2M trimethylsilyl triflate in methylene chloride (30eq.)-1M thioanisole in trifluoroacetic acid (30eq.) in the presence of m-cresole (30eq.) in an ice-bath for 2h, followed by chromatography on a Dowex 50W×4 column using 5% aqueous pyridine. The crude peptide **4** thus obtained was subjected to cyclization with DPPA as above to give the cyclic pentapeptide **5**, $[\alpha]_D^{22}$ -9.07° (c=0.24, $CHCl_3$), in 22% yield from the resin **2**.

Final construction of ulicyclamide (**1**) was achieved by treatment of **5** with thionyl chloride at 0-5°C for 30h, giving **1** quantitatively. Identity of the synthetic sample, mp 126-134°C (hot plate), $[\alpha]_D^{22}$ +51.0° (c=0.46, CH_2Cl_2),[9] with the natural one, mp 124-132°C (hot plate), $[\alpha]_D^{25}$ +35.7° (c=2.3, CH_2Cl_2),[2a] was established by comparisons of their spectra (IR, ^1H- and ^{13}C-NMR, and mass) as well as TLC behavior.

Chart I.


Boc-L-Pro-OCH2-(P)
(P)- : polystyrene resin
Boc-L-Phe-OH
Boc-D-(ala)Thz-OH
Boc-L-(ile)Thz-OH
Z-L-aThr(But)-OH
DEPC, Et3N, DMF
Z-L-aThr(But)-L-(ile)Thz-D-(ala)Thz-L-Phe-L-Pro-OCH2-(P) 2
MeOH, Et3N, DMF
Z-L-aThr(But)-L-(ile)Thz-D-(ala)Thz-L-Phe-L-Pro-OMe 3
1) NaOH, aq. DMF
2) Pd-C, HCO2H
3) CF3CO2H
TMSOTf
thioanisole
m-cresol
CF3CO2H
CH2Cl2
H-L-aThr-L-(ile)Thz-D-(ala)Thz-L-Phe-L-Pro-OH 4
DPPA, Et3N, DMF
SOCl2
5
1

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References and Notes:

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6. N. Fujii, A. Otaka, O. Ikemura, K. Akaji, S. Funakoshi, Y.Hayashi, S. Yamada, and H. Yajima, Chem. Commun., in press.
7. Prepared from Boc-Pro-OCs and chloromethylated polystyrene resin (divinylbenzene 2%, 200-400 mesh); Pro content=0.43 mmol/g.
8. For N- and C-protected thiazole amino acids (Boc-(ama)Thz-OMe), see Y. Hamada, M. Shibata, T. Sugiura, S. Kato, and T. Shioiri, J. Org. Chem., in press. Boc-(ama)Thz-OH was obtained by alkaline hydrolysis of Boc-(ama)Thz-OMe with 1N aqueous sodium hydroxide (1.2eq.) in dioxane-water (1:1) at room temperature for 0.5h.
9. The value of $[\alpha]_D^{25}$ +59° (c=0.43, CH_2Cl_2) for the synthetic **1** has been reported in ref. 3.

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