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# β-LACTAM AS SYNTHETIC INTERMEDIATE: SYNTHESIS OF LEUCINE-ENKEPHALIN

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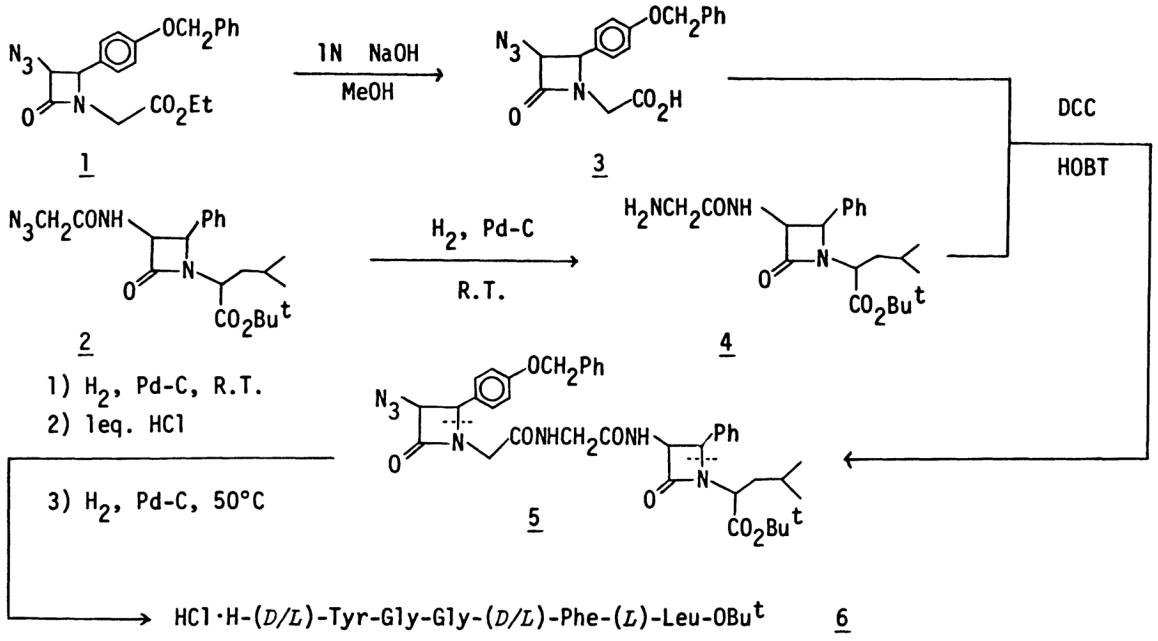
A method for oligopeptide synthesis via β-lactam intermediate has been successfully applied to the synthesis of a biologically active pentapeptide, leucine-enkephalin.

In preceding papers,[1-4] we have reported the entirely new method for peptide synthesis via β-lactam intermediate. The β-lactam method has been proved to have an advantage over conventional methods[5] in view of increased solubility and superior chromagraphic behavior on silica gel. Now, we have successfully applied the current method to the synthesis of a pentapeptide, leucine-enkephalin (Tyr-Gly-Gly-Phe-Leu) which possesses opioid activity.[6]

The β-lactam 1 is prepared by using our modified Bose's method[7] from N-(p-benzyloxybenzylidene)ethoxycarbonylmethylamine and azidoacetyl chloride in the presence of triethylamine in methylene chloride (84 %). The ester group in 1 was successfully saponified with 1 equivalent of 1 N sodium hydroxide in methanol to the free β-lactamcarboxylic acid 3 without touching the sensitive β-lactam ring (72 % after recrystallization from benzene-ethyl acetate). The β-lactam 2 was prepared by azidoacetylation (azidoacetyl chloride and N-methylmorpholine in chloroform) of the corresponding amino-β-lactam[8] (72 % after recrystallization from ether). The azide group in 2 was reduced under 1 atm of hydrogen on 5 % Pd-C in methanol at room temperature to give the amine 4 (100 %).

## SYNTHESIS OF LEUCINE-ENKEPHALIN



The acid 3 and the amine 4 were subjected to the coupling reaction by using DCC (dicyclohexylcarbodiimide) and HOBT (1-hydroxybenztriazole) in DMF (dimethylformamide). The coupling product 5 was purified on a silica gel column using ethyl acetate as eluent (98 % after purification).[9]

After the azide group of the bis-β-lactam 5 was reduced to the amino group under 1 atm of hydrogen on 10 % Pd-C in ethanol at room temperature and the amino group was protected as hydrochloride by adding 1 equivalent of 1N hydrochloric acid, the hydrogenolysis was carried out at 50°C to give a diastereomeric mixture of leucine-enkephalin t-butyl ester hydrochloride 6 (84 %).[10]

Now that we have established an efficient route to leucine-enkephalin via β-lactam intermediate, an investigation on the synthesis of optically pure enkephalin and its analogues is now actively under way.

References

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8. Azido-β-lactam (prepared from N-benzylidene[(*S*)-1-t-butoxycarbonyl-3-methyl]butylamine 7 and azidoacetyl chloride in the presence of triethylamine in methylene chloride) was reduced to the amino-β-lactam under 1 atm of hydrogen on 5 % Pd-C in methanol at room temperature (100 %). The Schiff base 7 was obtained by the condensation of (*L*)-leucine t-butyl ester with benzaldehyde.
9. IR(KBr) 3330, 2110, 1770, 1665, 1540 $cm^{-1}$. NMR($CDCl_3$) δ 0.61-1.08(m, 6H), 1.36, 1.47(s, 9H), 1.50-2.35(m, 2H), 2.91-4.50(m, 6H), 4.87-5.64(m, 6H), 6.76-7.53(m, 14H). Found: C, 64.58; H, 6.37; N, 13.41. Calcd. for $C_{39}H_{45}N_7O_7$; C, 64.72; H, 6.27; N, 13.55.
10. IR(KBr) 3300, 1730, 1660, 1550 $cm^{-1}$. NMR($CD_3OD$) δ 0.50-1.10(m, 6H), 1.45(s, 9H), 1.10-1.95(m, 2H), 2.70-4.50(m, 12H), 6.70-7.40(m, 9H). The product was also identified by comparing the HPLC chromatogram with that of authentically prepared HCl·H-(*D/L*)-Tyr-Gly-Gly-(*D/L*)-Phe-(*L*)-Leu-$OBu^t$. HPLC analysis was carried out using a column packed with TOYO SODA LS410K (ODS SIL) and MeOH-$H_2O$ as eluent.

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