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NEW METHOD FOR THE SYNTHESIS OF DEHYDROTRIPEPTIDES, USING N-CARBOXY α-DEHYDROAMINO ACID ANHYDRIDE AS SYNTHON

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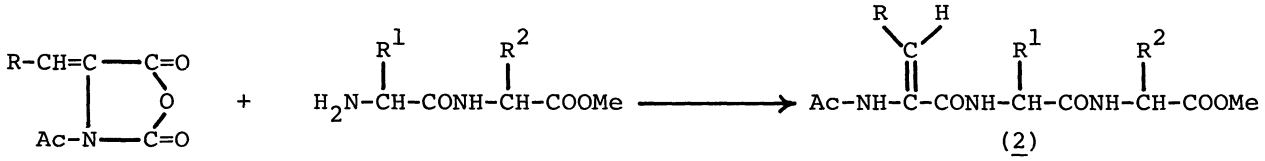
Various dehydrotripeptides, containing one or two α-dehydroamino acid residues, were readily synthesized by using N-carboxy α-dehydroamino acid anhydride as synthon of dehydropeptide unit.

Recently, much attention has been focused on the synthesis of dehydropeptide (DHP), containing one or more α-dehydroamino acid (DHA) residues, and the correlation between the structure and the bioactivity of DHP.[1-5]

So far, we have developed a few synthetic methods for DHP by the stepwise elongation of DHA with α-amino acid or another DHA[6] and by the β-elimination of peptide having a leaving group.[7] In the preceding paper,[8] we reported briefly the synthesis of N-carboxy α-dehydroamino acid anhydride (ΔNCA)[9] from N-benzyloxycarbonyl-DHA and the application of ΔNCA to the dehydrooligopeptide synthesis without using any coupling reagent. Here, we will report the very useful synthetic method for a variety of DHP by using N-acyl ΔNCA as synthon of DHA or DHP unit.

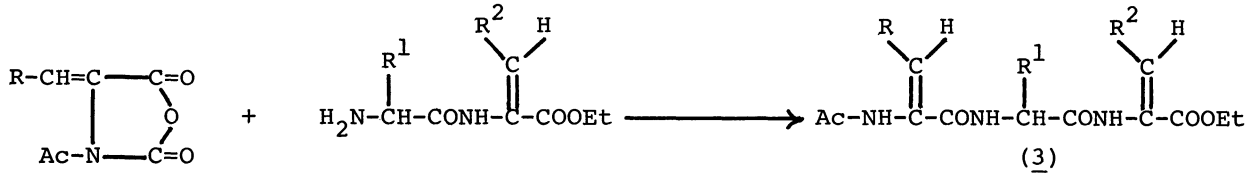
A solution of N-acetyl (Z)-ΔNCA (1), prepared by the acetylation of (Z)-geometric ΔNCA (0.3 mol) with acetyl chloride (0.4 mol) in THF (40 ml) by the usual way,[8] was treated with (L,L)-dipeptide methyl ester (0.3 mol) in THF (20 ml) at 0-10 °C for 1 hr. The resulting solution was made basic to pH 8-9 with triethylamine. After removal of solvent, the residue was dissolved in ethyl acetate (100 ml) and washed successively with 3% HCl, saturated $NaHCO_3$ aqueous solution, water, and then dried over anhydrous Na_2SO_4. The evaporation of ethyl acetate gave a crude solid residue, which was purified on a silica gel column using a mixture of benzene-acetone (10 : 1 v/v) as the eluent to give (Z,L,L)-dehydrotripeptide (2) as colorless needles.



Ac-ΔPhe-Leu-Val-OMe	82%	193-194 °C	$[\alpha]_D$ +16.2°
Ac-ΔBut-Phe-Val-OMe	95%	135-136 °C	$[\alpha]_D$ -38.3°
Ac-ΔPhe-Phe-Val-OMe	95%	158-159 °C	$[\alpha]_D$ -64.2°
Ac-ΔLeu-Ala-Val-OMe	80%	180-181 °C	$[\alpha]_D$ -22.2°

Treatment of 1 with (L,Z)-dehydrodipeptide ethyl ester[6] followed by similar

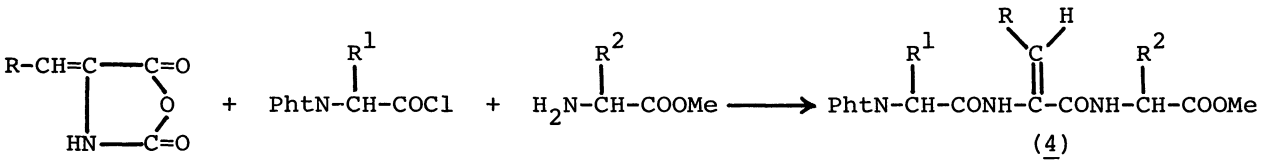
work-up gave (Z,L,Z)-dehydrotripeptide (3) as colorless needles.



(3)

Ac-ΔLeu-Phe-ΔLeu-OEt	60%	109-110 °C	$[\alpha]_D$	-45.9°
Ac-ΔLeu-Ala-ΔBut-OEt	71%	syrup	$[\alpha]_D$	-11.5°
Ac-ΔPhe-Leu-ΔVal-OEt	66%	198-200 °C	$[\alpha]_D$	+28.3°

On the other hand, to synthesize the tripeptide containing a DHA residue at center, ΔNCA was acylated with an equimolar phthalyl-(L)-amino acid chloride (0.3 mol) in the presence of triethylamine in THF (40 ml) at 5-10 °C for 1 hr, followed by the coupling with (L)-amino acid methyl ester at room temperature for 1.5 hr. After removal of solvent, the residue obtained was submitted to similar work-up to give (L,Z,L)-dehydrotripeptide (4) as colorless needles.



(4)

Pht-Leu-ΔBut-Phe-OMe	71%	151-152 °C	$[\alpha]_D$	-4.5°
Pht-Phe-ΔBut-Gly-OMe	77%	100-101 °C	$[\alpha]_D$	-113.4°
Pht-Gly-ΔLeu-Phe-OMe	78%	193-194 °C	$[\alpha]_D$	-20.2°

In conclusion, it was found that the ΔNCA method developed newly by us was very versatile and applicable to the various dehydropeptide synthesses by combination of α-amino acid and DHA. Further works including the analogous study are now in progress.

References

Specific rotation was measured in methanol (c 1.0) at 25 °C.

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9) In this paper, the symbol Δ indicates a double bond of DHA residue.

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