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FACILE SYNTHESIS OF FOUR ISOMERS OF LINEAR TENTOXIN SEQUENCE BY USING N-CARBOXY DEHYDROPHENYLALANINE ANHYDRIDE

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Four isomers of protected dehydrotetrapeptides of linear tentoxin sequence, consisted of Gly, Ala, Leu, and ΔPhe residues, were readily synthesized by using N-carboxy dehydrophenylalanine anhydride.

In connection with the synthesis of dehydrooligopeptides (DHP), which were very important constituents or moieties of naturally occurring bioactive peptides containing one or more α-dehydroamino acid (DHA) residues,[1] we already reported the facile and novel synthesis of unique N-carboxy α-dehydroamino acid anhydride (ΔNCA)[2-4] and that of DHP by using the resulting ΔNCA. On the other hand, as a proof of the usefulness of the ΔNCA method developed by us, more recently,[5] Jacquier and Verducci have applied to the facile synthesis of tentoxin [⌐MeAla-Leu-MeΔPhe-Gly¬].[6,7]

In the present paper, we wish to report the convenient synthesis of all the four protected dehydrotetrapeptide isomers of linear tentoxin sequence lacking two N-methyl groups at Ala and ΔPhe residues.[8]

The coupling of N-carboxy dehydrophenylalanine anhydride (ΔPhe-NCA; 1), derived from (Z)-geometric N-benzyloxycarbonyl-ΔPhe-OH and $SOCl_2$,[2,4] with t-butyloxycarbonyl (Boc)-Leu-OH in the presence of dicyclohexylcarbodiimide (DCC) and pyridine in THF formed Boc-Leu-ΔPhe-NCA (2), which was then *in situ* treated with methanol in the presence of N-methylmorpholin (NMM) to give Boc-Leu-ΔPhe-OMe {3; yield 77%, colorless needles from hexane, mp 87-88 °C. IR (KBr): 1680, 1530 (-CONH-) cm^{-1}. NMR ($CDCl_3$): δ 7.30 (m, C_6H_5 + H, -CH=). $[\alpha]_D^{20}$ 41.5° (c 0.9 in MeOH)}. The subsequent treatment of 3 with successive HCl and Boc-Gly-Ala-OH by DCC/1-hydroxybenzotriazole (HOBt) in dichloromethane gave the expected protected Δ^4-dehydrotetrapeptide,[9] Boc-Gly-Ala-Leu-ΔPhe-OMe (4)

in a good yield.

On the other hand, the intermediate 2 was also coupled with H-Gly-OMe in the presence of NMM in THF to give Boc-Leu-ΔPhe-Gly-OMe {5; yield 60%, colorless needles from ethyl acetate-hexane, mp 134-135 °C. IR (KBr): 1685, 1525 (-CONH-) cm^{-1}. NMR ($CDCl_3$): δ 7.14 (1H, s, -CH=). $[\alpha]_D^{20}$ -32.7° (c 0.9 in MeOH)}. Subsequently, the treatment of 5 thus obtained with successive HCl and Boc-Ala-OH in dichloromethane by DCC/HOBt gave protected Δ^3-dehydrotetrapeptide, Boc-Ala-

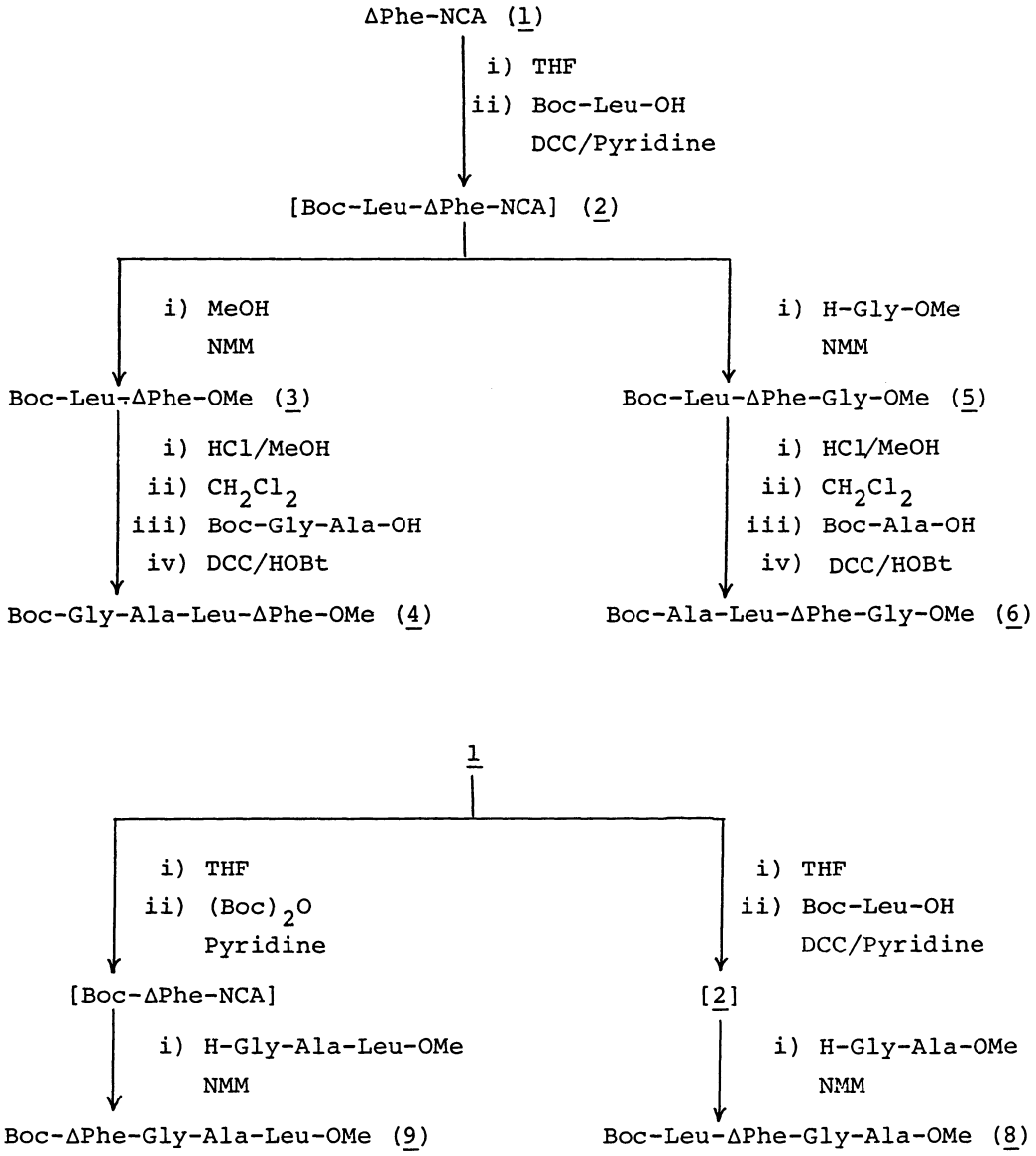

Chart 1.

Leu-ΔPhe-Gly-OMe (6) in a good yield.

Furthermore, the direct coupling of 2 with H-Gly-Ala-OMe in the presence of NMM was achieved to give protected Δ^2-dehydrotetrapeptide, Boc-Leu-ΔPhe-Gly-Ala-OMe (8) in a good yield. On the other hand, after the acylation of the starting material 1 with $(Boc)_2O$ in the presence of pyridine in THF by the usual method, Boc-ΔPhe-NCA thus formed was subsequently *in situ* coupled with H-Gly-Ala-Leu-OMe in the presence of NMM to give the desired protected Δ^1-dehydrotetrapeptide, Boc-ΔPhe-Gly-Ala-Leu-OMe (9) in a 65% yield.

Table 1. Protected dehydrotetrapeptides (4, 6, 8, 9)

Compound No.	Yield %	Mp °C	NMR, δ in DMSO-d_6 -CH=	NMR, δ in DMSO-d_6 =C-NH-	$[\alpha]_D^{20}$ (c 1.0)[d]
Δ^4-Dehydrotetrapeptide (4)	75	183-185[a]	7.22s	9.62s	-9.5°
Δ^3-Dehydrotetrapeptide (6)	80	178-179[b]	7.22s	9.60s	-70.1°
Δ^2-Dehydrotetrapeptide (8)	82	82-84[c]	7.07s	9.69s	-80.8°
Δ^1-Dehydrotetrapeptide (9)	65	74-76[c]	6.96s	8.67s	9.8°

a) Colorless needles from ethyl acetate. b) Colorless needles from chloroform-isopropyl ether. c) Colorless needles from ethyl acetate-hexane. d) Recorded in methanol.

As mentioned above, all the isomers of protected dehydrotetrapeptides of the linear tentoxin sequence were first synthesized here in good yields. The four routes to 4, 6, 8, and 9 respectively are closely illustrated in Chart 1. In addition, the yields, melting points, NMR spectral data, and the specific rotations of the four isomers are summarized in Table 1. The appearance of all the new protected dehydrooligopeptides thus obtained are colorless needles and in particular, interestingly, the sign of the specific rotation between 4 and 9 was entirly reversed.

The structure of all the new compounds were characterized spectroscopically and gave satisfactory results in elemental analysis.

In conclusion, it is note worthy that the ΔNCA method developed here is very useful for the synthesis of DHP and that the DHA moiety can be introduced freely into the desired position of some peptides whenever we want.

Further work including the hydrolysis of methyl ester by 5% LiOH and the deprotection of Boc group by CF_3COOH was successful. The detailed results will be published elsewhere.

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9) In this paper, the symbols Δ^1, Δ^2, Δ^3, and Δ^4 indicate the position number of double bond of DHA residue from the N-terminus in sequence.

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