Selective *N*-Methylation of Dehydroamino Acids and Peptides

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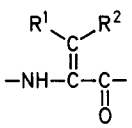
Unsaturated amino acid residues are found in many peptide natural products (e.g. **1a–d**) and often impart unusual conformational chemical or biological properties to the molecule. Selective methods for modifying the unsaturated residues, such as *N*-methylation of unsaturated amides in the presence of normal amide bonds, would be useful for the synthesis of this portion of the unsaturated peptides because *N*-methylated β-substituted amino acids (e.g. **2a–d**) are often difficult to prepare or use in peptide synthesis.



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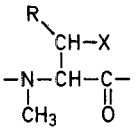

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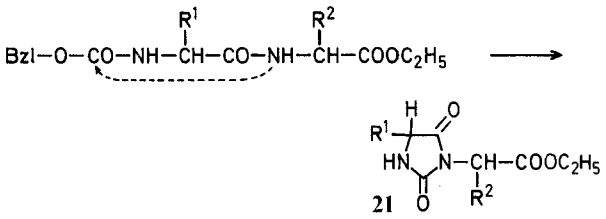
1	R^1	R^2	Occurrence
a	H	H	nisin[1]
b	CH_3	H	stendomycin[2]
c	CH_3	CH_3	phalloin[3]
d	C_6H_5	H	tentoxin[4]

2	X
a	Tos
b	Br
c	—SH
d	—S—C_6H_5

For the synthesis of the unsaturated cyclic tetrapeptide tentoxin[5] it was necessary to develop a method for selectively *N*-methylating a dehydrophenylalanine residue (**1d**) without methylating other amide bonds or causing base-catalyzed rearrangements. We report here the results of the study to develop this procedure and present evidence that the reaction proceeds cleanly and with retention of configuration about the double bond.

Treatment of Boc-dehydroamino acid methyl esters **3–10** with anhydrous potassium carbonate and methyl iodide in dimethylformamide or with potassium carbonate and dimethyl sulfate in acetonitrile gave the *N*-methylated products **11–18** in good yield (Table 1). The reagents must be carefully dried since water retards methylation and reduces purity and yield of product. Although the reaction can be conveniently monitored by N.M.R. and T.L.C., it was necessary with some larger peptides or hindered residues (e.g. **8**) to isolate and remethylate the product in order to achieve complete reaction.

Peptides containing glycine residues such as Cbz-Phe-Gly-OEt (**19**) and Cbz-Leu-Gly-OEt (**20**) were not methylated under these reaction conditions. These peptides are *N*-methylated (predominantly on the glycyl nitrogen) when stronger bases such as wet silver oxide[6] or sodium hydride are used. Strong base also is known to catalyze hydantoin formation (**21**) especially on Cbz-protected peptides (e.g. **19** or **20**) during either hydrolysis[7] or *N*-methylation[8]. No hydantoin formation was detected when peptides **19**, **20**, or **6–10** were subjected to our *N*-methylation conditions indicating that the procedure probably can be applied to many systems, including the natural substance, to prepare derivatives.



The effect of *N*-methylation on the double bond configuration was studied. Methyl esters of Boc-(*Z*)-dehydrobutyrine (**22**) and Boc-(*E*)-dehydrobutyrine (**23**) were prepared and the configurations assigned on the basis of the chemical shifts of the vinyl and methyl protons (Table 2). *Z*-Substituents of acylated amino acid esters are known to be deshielded with respect to the *E*-substituents[9]. *N*-Methylation of the *Z*-isomer **22** gave only (*Z*)-*N*-methyldehydrobutyrine methyl ester (**24**, 84%) while methylation of the *E*-isomer **23** gave only the corresponding (*E*)-*N*-methyl isomer **25** (89%). Similarly, methylation of the protected tetrapeptide **10** (*Z*-isomer) gave the *N*-methyl-*Z*-isomer **18** in 89% yield. The corresponding *E*-isomer was not methylated under these conditions and was recovered unchanged in high yield. These results established that *N*-methylation of dehydro residues under these conditions does not change the configuration about the double bond.

Potassium carbonate was pulverized and dried at 200° for 24 h before use. Methyl iodide and dimethylsulfate were filtered through alumina, distilled, and stored under argon. Acetonitrile was distilled from P_2O_5. Dimethylformamide was distilled from calcium hydride under reduced pressure and stored over molecular sieves. T.L.C. was run on silica gel G plates eluting with benzene (80)/ethyl acetate (20).

Typical *N*-Methylation procedures are given below.

Methyl *t*-Butoxycarbonyl-*N*-methyldehydrovalinate (13):
Potassium carbonate (227 mg, 1.65 mmol) and methyl iodide (0.15 ml) were added to a solution of methyl *t*-butoxycarbonyldehydrovalinate (**5**; 109 mg, 0.48 mmol) in dimethylformamide (1.5 ml) in a pressure bottle. The mixture was stirred vigorously for 72 h under an inert atmosphere at 25°, then diluted with chloroform, and filtered. The solvent was removed by evaporation in vacuo and the residue distilled (Kugelrohr) to give the *N*-methylated product as a colorless oil; yield: 94 mg (84%); b.p. 85°/0.3 torr.

$C_{12}H_{21}O_4$	calc.	C 59.24	H 8.70	N 5.76
(243.3)	found	59.22	8.74	6.00

Methyl *t*-Butoxycarbonyl-alanyl-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycinate (18):
Potassium carbonate (110 mg, 0.8 mmol) and methyl iodide (1.0 ml) were added to a solution of methyl *t*-butoxycarbonyl-alanyl-leucyl-(*Z*)-dehydrophenylalanylglycinate (**10**; 58 mg, 0.108 mmol) in dimethylformamide (4 ml) in a pressure bottle. The reaction mixture was stirred vigorously for 72 h, diluted with ethyl acetate, and filtered. The filtrate was washed with water, 1 *N* citric acid

Table 1. *N*-Methylation of Protected Amino-acid and Peptide Esters

	Educt[a]		Product[a]	Yield (%)
(3)	Cbz-ΔAla-OMe	(11)	Cbz-MeΔAla-OMe	79
(4)	Boc-ΔAla-OMe	(12)	Boc-MeΔAla-OMe	84
(5)	Boc-ΔVal-OMe	(13)	Boc-MeΔVal-OMe	84
(6)	Boc-Ala-ΔAla-OMe	(14)	Boc-Ala-MeΔAla-OMe	76
(7)	Boc-Ala-ΔBut-OMe[b,c]	(15)	Boc-Ala-MeΔBut-OMe[b,c]	85
(8)	Boc-Ala-ΔVal-OMe	(16)	Boc-Ala-MeΔVal-OMe	82
(9)	Boc-MeAla-Leu-ΔAla-Gly-OMe	(17)	Boc-MeAla-Leu-MeΔAla-Gly-OMe	71
(10)	Boc-MeAla-Leu-(Z)-ΔPhe-Gly-OMe	(18)	Boc-MeAla-Leu-(Z)-MeΔPhe-Gly-OMe	89

[a] Satisfactory microanalysis, T.L.C., N.M.R., and I.R. data were obtained.
[b] But = Butyrine or aminobutanoic acid.
[c] Both *E* and *Z* isomers.

Table 2. ^{1}H-N.M.R. Data of Protected Dehydrobutyrine Esters and their Methylation Products[a]

Butyrine Derivative	δ_{N-H}	$\delta_{\beta-H}$	$\delta_{\gamma-H}$
Boc-(*Z*)-ΔBut-OMe (**22**)	6.52	6.78 (q, J = 7.5 Hz)	2.05 (d, J = 7.5 Hz)
Boc-(*E*)-ΔBut-OMe (**23**)	6.04	6.67 (q, J = 7.2 Hz)	1.81 (dd, J = 0.09/7.2 Hz)
Boc-(*Z*)-MeΔBut-OMe (**24**)	—	6.08 (q, J = 7.2 Hz)	2.02 (d, J = 7.2 Hz)
Boc-(*E*)-MeΔBut-OMe (**25**)	—	6.70 (q, J = 7.2 Hz)	1.78 (d, J = 7.2 Hz)

[a] Chemical shifts are expressed in ppm relative to internal TMS. The spectra were obtained with a Bruker-HX90E spectrometer in deuteriochloroform.

solution, water, sodium hydrogen carbonate solution, water, dried ($MgSO_4$), and evaporated in vacuo to give the *N*-methylated product; yield: 53 mg (89%); oil.

$C_{28}H_{42}N_4O_7$	calc.	C 61.52	H 7.74	N 10.27
(546.7)	found	61.82	7.68	10.47

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