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Synthesis of Peptides Containing 2,3-Methanoaspartic Acid

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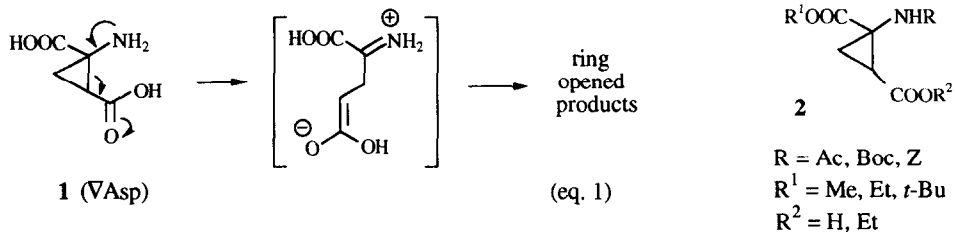
Abstract: Simple *N*-protected di- and tri-peptide methyl esters incorporating (±)-(*Z*)-2,3-methanoaspartic acid were prepared by oxidation of the corresponding (±)-(*Z*)-2,3-methanohomoserine-derived peptides.

Cyclopropane aminoacids are of broad interest as biological probes, enzyme inhibitors, and conformationally constrained analogues of native aminoacids.[1] The cyclopropane analogue of aspartic acid, 2,3-methanoaspartic acid (1-aminocyclopropane-1,2-dicarboxylic acid) (∇Asp), **1**, cannot be isolated in the free state[1b,1e,2] on account of the inherent instability of the 1-amino-2-carboxy system which undergoes spontaneous ring opening (eq. 1).[3] The only reported[4] preparation of **1** was recently shown to be an error.[2] It has been possible, however, to obtain stable *N*-acyl-∇Asp derivatives of general structure **2** in which the nitrogen lone pair is not available to promote ring opening.[1b,5-7] On this premise, the preparation of peptides containing ∇Asp would appear plausible, providing that this aminoacid is never the free *N*-terminal unit. An appropriate synthetic strategy calls for the use of a surrogate aminoacid, being a masked ∇Asp, from which this latter can be generated once the *N*-terminal function is safely (and permanently) in place. 2,3-Methanohomoserine (∇Hse) is a stable, conveniently available[6,8,9] cyclopropane aminoacid from which derivatives of type **2** can be prepared by oxidation.[1b,5] In this communication, we report on the successful application of this strategy for the preparation of some di- and tri-peptides containing a (±)-(*Z*)-∇Asp residue.



1 (∇Asp) (eq. 1)

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N-Protected di- and tri-peptide methyl esters **4-11** were prepared by standard methods using (±)-(*Z*)-∇Hse **3** as the ∇Asp surrogate (Scheme). Each peptide was oxidized at room temperature using sodium periodate and ruthenium trichloride in a CH_3CN-CCl_4-H_2O solvent system[10] to give the corresponding carboxylic acid **12-19** (eq. 2). Isolated product yields for this key step are given in the Table.[11]

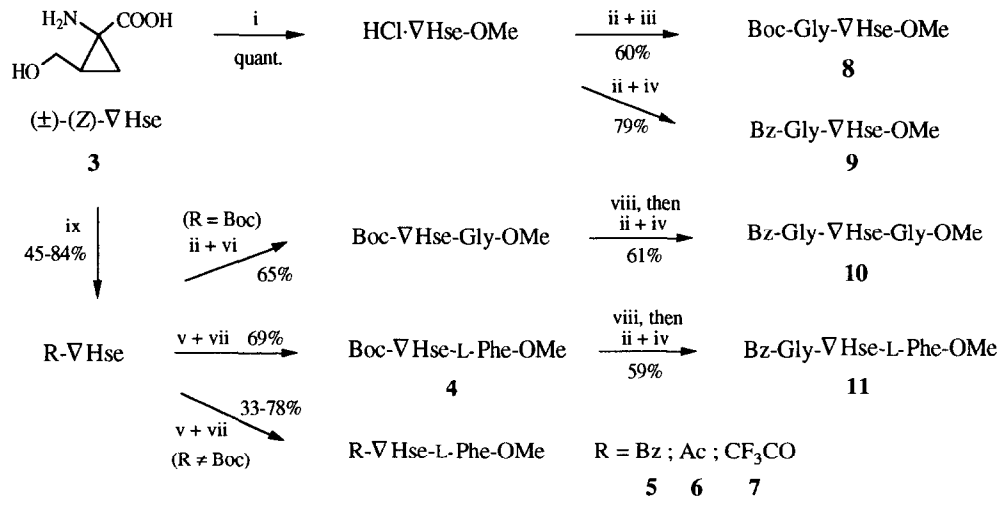
Dipeptides R-∇Asp-AA$_2$-OMe: The strategy was first applied to dipeptides **4-7**. The reactions of derivatives having benzoyl- and trifluoroacetyl-protected ∇Hse at the *N*-terminal proceeded well, giving **13** and **15** in 59% and 82% yield respectively. The lower isolated yield (36%) of the acetyl derivative **14** from **6** was partly due to problems encountered in the extraction procedure at the end of the reaction. In contrast with these amide derivatives, the Boc-protected dipeptide **12** was obtained from **4** in only 8% yield, accompanied by some unreacted starting material (*c.* 25%) and a number of other unidentified by-products. Although the poor reactivity of the carbamate is rather surprising, it does not really present a serious drawback: the most common use of an *N*-terminal Boc function is as a protecting group from which the free amine is subsequently liberated for further reaction, a sequence of events which would not be envisaged in the case of ∇Asp peptides for the reasons elaborated in the introduction.

Dipeptides R-AA$_1$-∇Asp-OMe: The dipeptides **16** and **17** were obtained from their ∇Hse precursors **8** and **9** respectively in about 50% yield. It was useful to note that no problem was encountered with the *N*-terminal Boc protecting group of **8**, located in this case one aminoacid residue away from the reacting centre.

Tripeptides R-AA$_1$-∇Asp-AA$_3$-OMe: Since both above dipeptide combinations worked satisfactorily, the extention to tripeptide derivatives with ∇Asp as the internal unit seemed likely to succeed. This was indeed the case, and the oxidation reactions of **10** and **11** gave the expected products **18** and **19** respectively, again in around 50% yield.

These results demonstrate that stable, small peptides containing a (±)-(*Z*)-∇Asp unit can be prepared conveniently by oxidation of the corresponding (±)-(*Z*)-∇Hse precursors under mild conditions.[12] The synthetic strategy may also find a use in the preparation of larger peptides; the compatibility of a removable *N*-terminal protecting group (in Boc-AA$_1$-∇Asp- fragments) and differentiated carboxylate functions (a *C*-terminal ester and a free acid ∇Asp side-chain) should facilitate the incorporation of these small peptide units into larger systems. We are currently investigating the application of this strategy to the synthesis of conformationally restrained analogues of selected Asp-containing peptides of biological interest.

General procedure for oxidation reactions. A solution of the (±)-(*Z*)-∇Hse-containing peptide (5 mmol) in a mixture of carbon tetrachloride (15 mL), acetonitrile (15 mL) and water (23 mL) was treated with sodium periodate (3.3 g; 15 mmol) and ruthenium trichloride (15 mg) and the orange suspension was stirred vigorously at room temperature. After 2-5 h (tlc monitoring) the reaction mixture was diluted with dichloromethane (50 mL), the organic phase collected, and the residual aqueous phase washed with more dichloromethane (3 × 50 mL). Combined organic extracts were dried over magnesium sulfate, decolorized with activated charcoal and filtered through celite. The filtrate was evaporated and the resulting crude product was purified by chromatography or crystallization as required.



Reagents: i. HCl/MeOH; ii. HOBt, DCC, Et_3N, DMF; iii. Boc-Gly; iv. Bz-Gly; v. HCl·L-Phe-OMe; vi. HCl·Gly-OMe; vii. IIDQ, Et_3N, DMF or CH_2Cl_2; viii. excess TFA; ix. Boc_2O/NaOH *or* Ac_2O/NaOH *or* BzCl/NaOH *or* TFAA

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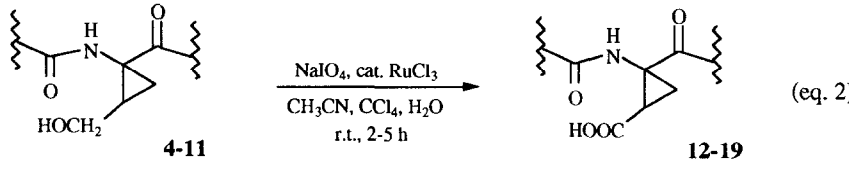

(eq. 2)

TABLE. Oxidation reactions (eq. 2)

Substrate	Product	Yield (%)
Boc-∇Hse-L-Phe-OMe **4**	Boc-∇Asp-L-Phe-OMe **12**	8
Bz-∇Hse-L-Phe-OMe **5**	Bz-∇Asp-L-Phe-OMe **13**	59
Ac-∇Hse-L-Phe-OMe **6**	Ac-∇Asp-L-Phe-OMe **14**	36
CF_3CO-∇Hse-L-Phe-OMe **7**	CF_3CO-∇Asp-L-Phe-OMe **15**	82
Boc-Gly-∇Hse-OMe **8**	Boc-Gly-∇Asp-OMe **16**	45
Bz-Gly-∇Hse-OMe **9**	Bz-Gly-∇Asp-OMe **17**	51
Bz-Gly-∇Hse-Gly-OMe **10**	Bz-Gly-∇Asp-Gly-OMe **18**	42
Bz-Gly-∇Hse-L-Phe-OMe **11**	Bz-Gly-∇Asp-L-Phe-OMe **19**	62

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11. All new compounds presented herein showed satisfactory spectral and/or analytical data. Peptides **4-7**, **11-15** and **19** were obtained as 1:1 diastereomeric mixtures and caracterized as such. No epimerization was observed in the described procedures.
12. The Sharpless system (ref. 10) was the most convenient. Among some alternative oxidizing systems (Cr^{VI} reagents; $KMnO_4$), Jones' reagent gave **15** from **7** in 45% yield. Others were less efficient or failed completely.

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