The Transformation of Tryptophan to Aspartic Acid in Peptides

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The tryptophan side chain is transformed by *in situ* generated ruthenium(VIII), to that of aspartic acid, in good yields; a multi-step degradation sequence is suggested on the basis of the transformations of tetrahydrocarbazole to adipic acid, valine to isobutyric acid, and phenylalanine to phenylacetic acid.

In this communication, we report the effective transformation of Bz-Trp-OMe (**1**), Z-Trp-OMe (**3**), Bz-Trp-Leu-OMe (**5**) and Bz-Trp-Phe-OMe (**7**) to, respectively, Bz-Asp-OMe (**2**), Z-Asp-OMe (**4**), Bz-Asp-Leu-OMe (**6**), and Bz-Asp-Phe-OMe (**8**) (*N*-protected aspartame, the sweetening agent), with complete chiral retention.†

Bz–Trp–OMe → Bz–Asp–OMe
(**1**) (**2**)

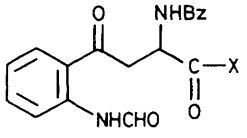
Z–Trp–OMe → Z–Asp–OMe
(**3**) (**4**)

Bz–Trp–Leu–OMe → Bz–Asp–Leu–OMe
(**5**) (**6**)

Bz–Trp–Phe–OMe → Bz–Asp–Phe–OMe
(**7**) (**8**)

Z = $PhCH_2OC(O)$

When (**1**) was treated with 2.2 mol % of Ru^{VIII} reagent in the presence of 18 equiv. periodate in H_2O–MeCN–CCl_4 for 60 h,[1] (**2**) (69%), (**9**) (7%), and benzamide (6%) were produced.‡§ Under similar conditions, a 65% yield of (**4**) was obtained from (**3**).



Bz = COPh

(**9**) X = OMe

(**10**) X = –NH–CH(CH$_2$Ph)–CO$_2$Me

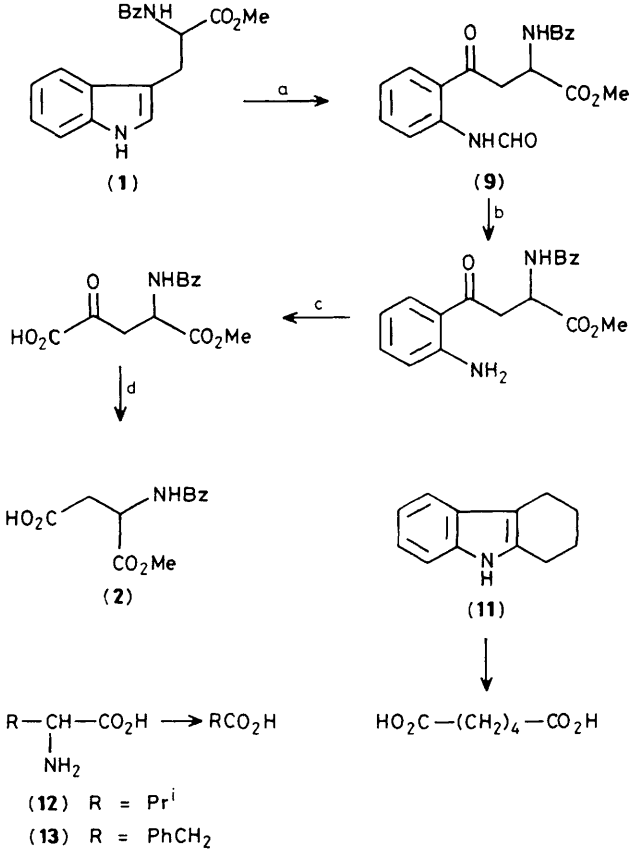
† All amino acids used were of the L-configuration. Wherever possible, i.r., n.m.r., and mass spectra, and optical rotation of products were compared with those of authentic samples and were found to be identical. Spectral and analytical data in excellent agreement with those expected were obtained for all compounds.

‡ In a typical procedure, (**1**) (5 mmol) in MeCN (20 ml) was added to a mixture of CCl_4–H_2O (1:2, 60 ml), $NaIO_4$ (90 mmol), and $RuCl_3 \cdot 3H_2O$ (2.2 mol %), sealed and shaken for 60 h. After filtration the aqueous layer was extracted with EtOAc (3 × 25 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated, and the residue was digested with saturated $NaHCO_3$ (40 ml) for 3 h then extracted with EtOAc (3 × 20 ml). The EtOAc extract, on evaporation, followed by chromatography on silica gel with C_6H_6–EtOAc (7:3), as eluent gave (**9**) (m.p. 94—95 °C); further elution with C_6H_6–EtOAc (1:1) gave benzamide. The $NaHCO_3$ extract was adjusted to pH 3 with 1 M H_2SO_4, saturated with NaCl, then extracted with EtOAc (3 × 20 ml). When dried and evaporated, this extract yielded (**2**), m.p. 125—127 °C (from EtOAc–hexane).

§ In blank experiments no (**2**) was formed in the absence of Ru^{VIII}.

The Trp → Asp transformation has been accomplished in a peptide environment and also selectively, under specific conditions, in the presence of a Phe residue, which has already been demonstrated to undergo oxidation to Asp with Ru^{VIII}.[2] Thus, whilst (**5**) is smoothly transformed to (**6**) (58% yield), (**7**), under similar conditions but for only 8 h, gave (**8**) selectively (66% yield). The latter reaction also produced the interesting dipeptide (**10**) (13%). Parallel studies with dipeptides using Phe as the reference enable us to infer that the Trp → Asp peptide modification can be effected, provided Cys and Met are absent.[3]

The (**1**) → (**2**) transformation proceeds in four stages, as shown in Scheme 1. The reaction of (**1**) with only 2 equiv. of periodate gave (**9**) (47%) and no (**2**). Under the IO_4^-–Ru^{VIII} conditions which effected the (**1**) → (**2**) transformation, compound (**9**) was in turn transformed to (**2**) in 97% yield. These results support the proposed step (a). In view of the known inertness of the Ru^{VIII} species towards amido groups containing substrates such as present in (**1**) and (**9**), the proposed hydrolytic step (b) is reasonable and is supported by the finding that tetrahydrocarbazole (**11**) is transformed to



Scheme 1

adipic acid in 60% yields, under conditions of the (**1**) → (**2**) transformation. The oxidative decarboxylation proposed as the last step (d) was tested by attempting to effect a one-step conversion of α-amino acids into lower carboxylic acids by oxidation, since these substrates are usually transformed first to α-keto acids. This was achieved: Val (**12**) was transformed to isobutyric acid (66%) under the general oxidation conditions and Phe (**13**) to phenylacetic acid (43%) in a shorter reaction (8 h).

Tryptophan-containing cyclic and acyclic peptides play a vital role in several biological processes and the efficient method presented here for the transformation of this residue to aspartic acid suggests interesting possibilities for the ready preparation of modified peptides.

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References

1 P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936.
2 S. Ranganathan, D. Ranganathan and S. Bamezai, *Proc. Indian Acad. Sci., (Chem. Sci.)*, 1984, **93**, 687.
3 The other amino acid partners in these investigations were Tyr, His, Pro, Met, and Cys (S. Ranganathan, D. Ranganathan, and D. Bhattacharyya, unpublished work).