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AMINO-ALCOHOL DIPEPTIDE ANALOGUES: A SIMPLE SYNTHESIS OF A VERSATILE ISOSTERE FOR THE DEVELOPMENT OF PROTEINASE INHIBITORS

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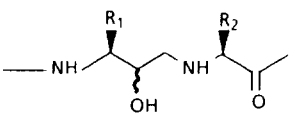
Summary Two simple approaches to an amino-alcohol isostere of proteolytically-cleavable dipeptide sequences are described; this isostere is incorporated into stereochemically-defined tetrapeptide analogues.

We[1] and others[2] have shown that replacement of the cleavable amide bond of appropriate peptide substrates by a novel amino-alcohol isostere (-Ψ-(CH(OH)CH2)-), (1) is a versatile approach to potent inhibitors of proteinases as diverse as renin[1,3], angiotensin converting enzyme[2], and enkephalin aminopeptidase[4]



(1)

Synthetic approaches to isostere (1) have recently been described[5]; this report prompts us to disclose our short and simple alternative approaches to peptide analogues containing this unit which were developed as a result of our interest in inhibitors of human renin These approaches proved to be applicable to a wide range of α-substituents R_1 and R_2

The approaches we adopted are illustrated by the synthesis of (9) and (10) as shown in the Scheme In the generally applicable Route 1, the dipeptide isostere is assembled separately then incorporated into the peptide sequence Thus, brief warming of a solution of the keto-iodide (2) and 2 equivalents of

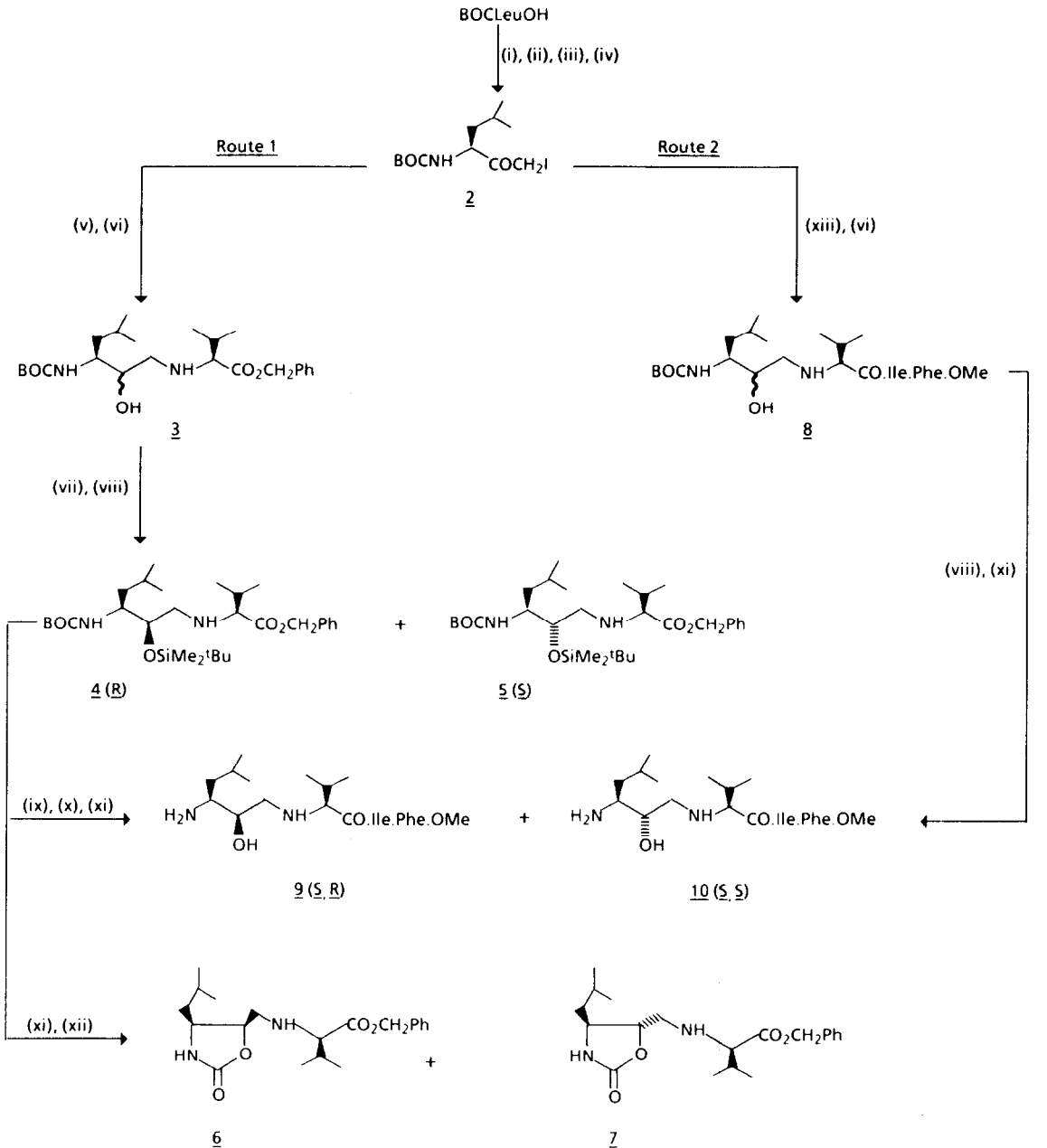
valine benzyl ester in dry tetrahydrofuran gave, in high yield[6], the desired amino-ketone, which was reduced in situ to the diastereoisomeric amino-alcohols (3). These were converted into the t-butyldimethylsilyl ethers (4) and (5) which were easily separable by column chromatography. The absolute configuration of the separate diastereoisomers was deduced from difference n.O.e. data obtained from their oxazolidinone derivatives (6) and (7)[7] and confirmed[8] by X-ray crystallographic analysis of their complexes with endothiapepsin at 2.2 Å resolution. The key intermediate silyl ethers (4) and (5) were conveniently elaborated to (9) and (10) by standard peptide coupling techniques followed by simultaneous deprotection of the hydroxyl and terminal amino functions. The overall yield of this process was high (ca 85%) and protection of the weakly basic (pKa ca. 5.0) in-chain secondary amine during the coupling reactions was found to be unnecessary, allowing a choice of N- or C- terminal elaboration of (4) or (5) following removal of the relevant blocking groups.

Alternatively, Route 2 illustrates a synthetically more direct procedure to (1)-containing analogues which is only suitable when there is no risk of peptide side-chain alkylation by the keto-iodide; this procedure gives similar yields to Route 1 in cases where the final peptide analogues are easily separable. Thus, reaction of the keto-iodide (2) with the tripeptide, H.Val.Ile.Phe.OMe, and in situ reduction of the intermediate amino-ketone gave the tetrapeptide analogue (8) as a mixture of diastereoisomers which were separated by column chromatography and deprotected to give (9) and (10) directly. This methodology has been applied to the synthesis of many (1)-containing tetrapeptide analogues and is general for diverse R_1 and R_2 side-chains.

The application of either of these synthetic approaches should therefore provide rapid access to a wide range of inhibitory proteinase substrate analogues. Indeed, some (1)-containing tetrapeptide derivatives have proved to be potent inhibitors of human renin; full experimental details and structure-biological activity studies will be published elsewhere.

Acknowledgements

We thank Dr D.E. Farrant for the n.O.e. data.



Reagents
(i) ^{i}BuOCOCl, NMM, Et_2O; (ii) CH_2N_2; (III) HBr, EtOAc; (iv) NaI, Me_2CO; (v) H.Val.OCH_2Ph, THF, 40°C; (vi) $NaBH_4$, MeOH; (vii) ^{t}BuMe$_2$SiCl, DMAP, DMF, Et_3N; (viii) Chromatographic Separation on Silica; (ix) H_2, Pd; (x) $^{i}Pr_2NH$, H.Ile.Phe.OMe.HCl, HOBT, EtN = C = N$(CH_2)_3NMe_2$.HCl, (xi) HCL, MeOH; (xii) $COCl_2$, Et_3N, CH_2Cl_2, -10°C; (xiii) H. Val.Ile.Phe.OMe, THF, 40°C;

Scheme

References and Notes

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6 The equivalent keto-chlorides or keto-bromides required higher reaction temperatures and gave markedly reduced yields. The keto-iodides, available from the chlorides by iodide exchange, were, in most cases, stable crystalline solids. The use of solvents of higher dielectric constant also gave reduced yields.

7 'H difference n.O.e. measurements, performed on oxazolidinones derived from (9) and (10), were consistent with these assignments.

8 S.I. Foundling, T.L. Blundell and J. Cooper, manuscript in preparation.

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