Novel Statine Analogue Synthesized from L-Aspartic Acid

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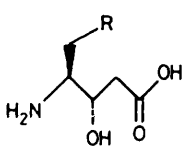
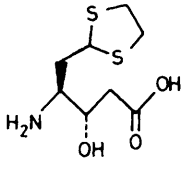
The incorporation of the novel statine analogue (**2**), synthesized *via* L-aspartic acid, into a tripeptide has led to a very potent renin inhibitor.

Pepstatin[1] is a natural peptide having the structure Iva-Val-Val-Sta-Ala-Sta, wherein statine (**1a**) (Sta) is (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid. Incorporation of statine into an appropriate peptide sequence has led to the discovery of potent human renin inhibitors.[2] Recently other hydrocarbon side chain analogues of statine such as (**1b**) (AHPPA)† and (**1c**) (ACHPA) have been synthesized.[3] The replacement of statine (**1a**) with (**1c**) in peptide analogues was reported to lead to much more potent renin inhibitors.[3] We report here the synthesis of the first statine analogue (**2**) containing a heterocyclic side chain *via* L-aspartic acid.

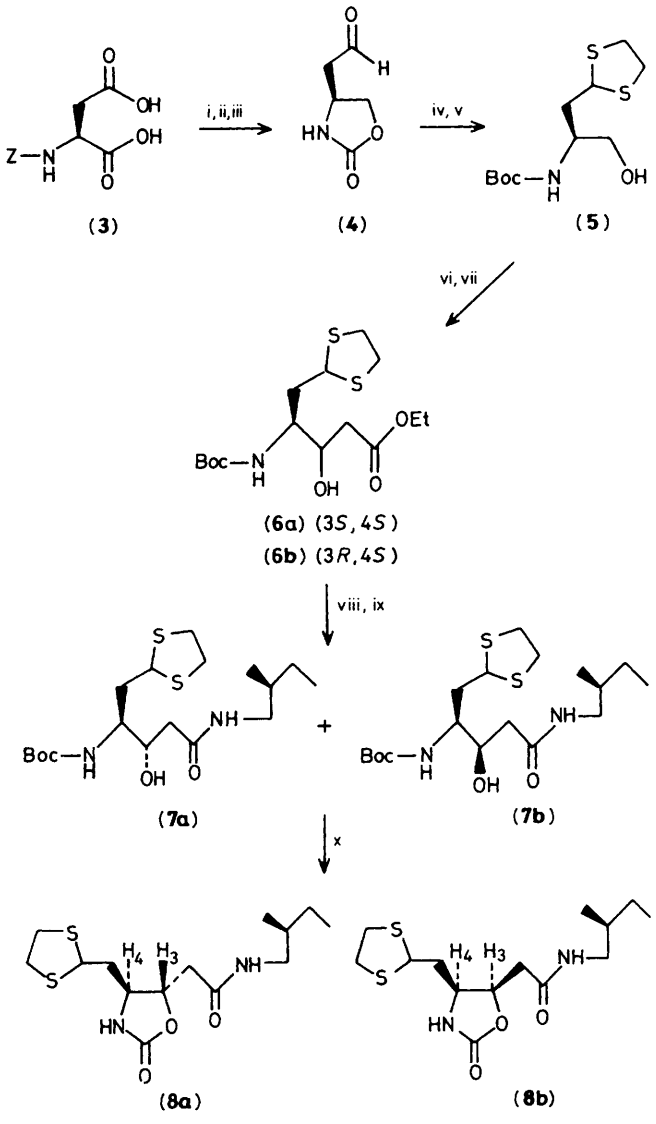


(**1**) **a**; R = Pr^i (Sta)
b; R = Ph (AHPPA)
c; R = cyclo-C_6H_{11} (ACHPA)



(**2**) (ADHPA)

† *Abbreviations:* AHPPA = (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid; ACHPA = (3*S*,4*S*)-4-amino-3-hydroxy-5-cyclohexylpentanoic acid; ADHPA = (3*S*,4*S*)-4-amino-3-hydroxy-5-(1,3-dithiolan-2-yl)pentanoic acid.



Z = benzyloxycarbonyl; Boc = t-butoxycarbonyl

Scheme 1. *Reagents:* i, BH_3·THF; ii, NaH–DMF; iii, PDC; iv, $HSCH_2CH_2SH$–BF_3·Et_2O; v, $Ba(OH)_2$ then $(Boc)_2O$; vi, $(COCl)_2$–dimethyl sulphoxide DMSO); vii, $LiCH_2CO_2Et$; viii, LiOH; ix, (2*S*)-methylbutylamine–DCC; x, HCl then $COCl_2$ in toluene.

Reduction of *N*-protected L-aspartic acid (**3**) with BH_3·tetrahydrofuran (THF) gave the corresponding diol which was treated with NaH in dimethylformamide (DMF) to give exclusively the 5-membered oxazolidinone alcohol. The primary alcohol was oxidized to the aldehyde (**4**) using pyridinium dichromate (PDC) in CH_2Cl_2 (70%, 3 steps). Reaction of (**4**) with ethanedithiol in CH_2Cl_2 with catalytic amounts of BF_3·Et_2O, followed by opening of the oxazolidinone ring with $Ba(OH)_2$ in dioxane–water and protection of the free primary amine with di-t-butyl dicarbonate $[(Boc)_2O]$ provided alcohol (**5**) (54%, 3 steps). Oxidation of the primary alcohol to the corresponding aldehyde using the Swern[4] method, followed by aldol condensation with lithioethyl acetate[5] provided the protected statine analogues (**6a**) and (**6b**) as a mixture of diastereoisomers (60%) which were not readily separable. Hydrolysis of the ethyl ester and coupling of the resulting carboxylic acid to (*S*)-2-methylbutylamine provided (**7a**) and (**7b**) (1.5 : 1) which were readily separated by silica gel column chromatography. The absolute stereochemistry of the hydroxy group of these two diastereoisomers was established as follows: separate deprotection of (**7a**) and (**7b**) and cyclization with phosgene gave the corresponding oxazolidinones (**8a**) and (**8b**). The 300 MHz ^1H n.m.r. spectrum ($CDCl_3$) of (**8a**) [δ 4.60 ($J_{3,4}$ 4.8 Hz, H-3)] and (**8b**) [δ 5.08 ($J_{3,4}$ 8.5 Hz, H-3)] compared well with the reported data[6] for the oxazolidinones of (3*S*,4*S*)-statine [δ 4.50 ($J_{3,4}$ 5.0 Hz, H-3)] and (3*R*,4*S*)-statine [δ 5.10 ($J_{3,4}$ 8.8 Hz, H-3)]. This established the stereochemistry of (**7a**) as (3*S*,4*S*) and (**7b**) as (3*R*,4*S*). Deprotection of (**7a**) and coupling to the dipeptide Boc-Phe-His-OH using dicyclohexylcarbodiimide–hydroxybenzotriazole (HOBt) in DMF gave the tripeptide (**12**).

Table 1. Human renin inhibition by tripeptides containing statine and statine analogues (**1b**), (**1c**), and (**2**).

Tripeptide	I.C.$_{50}$ (10^{-9} M)
(**9**) Boc-Phe-His-Sta-(*S*)-2-methylbutylamine	70
(**10**) Boc-Phe-His-AHPPA-(*S*)-2-methylbutylamine	80
(**11**) Boc-Phe-His-ACHPA-(*S*)-2-methylbutylamine	4
(**12**) Boc-Phe-His-ADHPA-(*S*)-2-methylbutylamine	1

Comparison of (**12**) with analogous tripeptides containing previously reported statine analogues (**1a**,**b**,**c**) showed (Table 1) that the tripeptide (**12**) containing the novel statine analogue (**2**), synthesized *via* L-aspartic acid, was the most potent renin inhibitor. The use of the versatile intermediate (**4**) for the synthesis of other novel amino acids is under investigation.

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