

Novel Statine Analogue Synthesized from L-Aspartic Acid

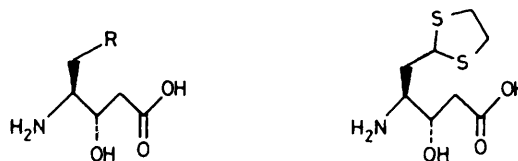
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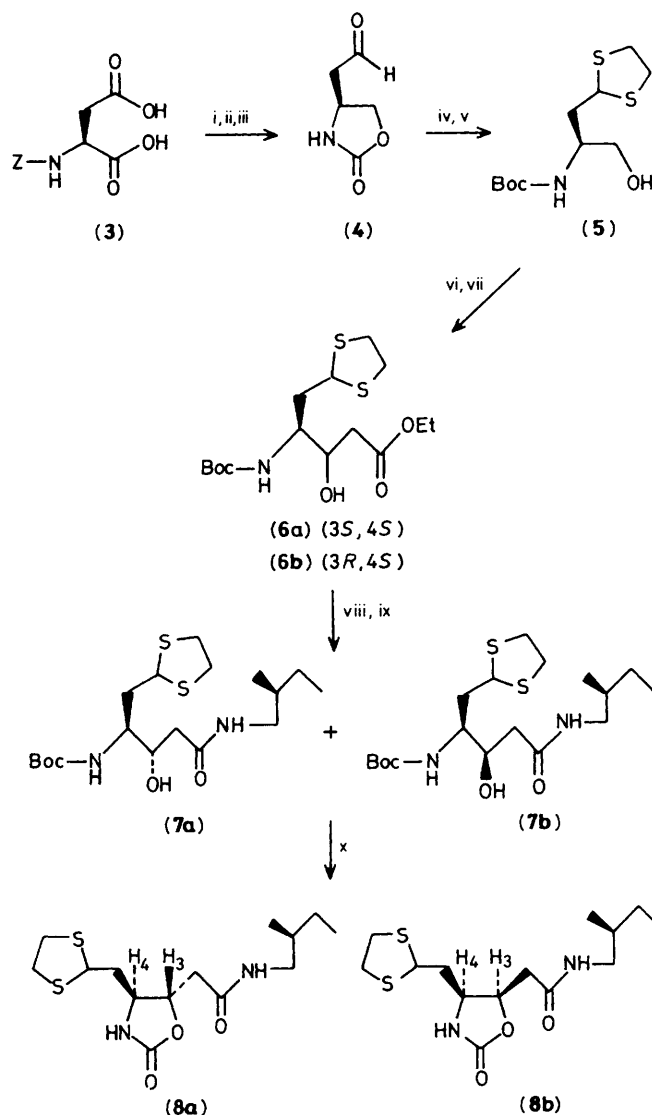
The incorporation of the novel statine analogue (**2**), synthesized *via* L-aspartic acid, into a tripeptide has led to a very potent renin inhibitor.

Pepstatin¹ 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.



[†] 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.



Scheme 1. Reagents: i, $\text{BH}_3 \cdot \text{THF}$; ii, NaH-DMF ; iii, PDC; iv, $\text{HSCH}_2\text{CH}_2\text{SH-BF}_3 \cdot \text{Et}_2\text{O}$; v, Ba(OH)_2 then $(\text{Boc})_2\text{O}$; vi, $(\text{COCl})_2$ -dimethyl sulphoxide DMSO; vii, $\text{LiCH}_2\text{CO}_2\text{Et}$; viii, LiOH ; ix, (2S)-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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$, followed by opening of the oxazolidinone ring with

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

Ba(OH)_2 in dioxane-water and protection of the free primary amine with di-*t*-butyl dicarbonate $[(\text{Boc})_2\text{O}]$ provided alcohol (5) (54%, 3 steps). Oxidation of the primary alcohol to the corresponding aldehyde using the Swern⁴ method, followed by aldol condensation with lithioethyl acetate⁵ 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 data⁶ for the oxazolidinones of (3S,4S)-statine [δ 4.50 ($J_{3,4}$ 5.0 Hz, H-3)] and (3R,4S)-statine [δ 5.10 ($J_{3,4}$ 8.8 Hz, H-3)]. This established the stereochemistry of (7a) as (3S,4S) and (7b) as (3R,4S). Deprotection of (7a) and coupling to the dipeptide Boc-Phe-His-OH using dicyclohexylcarbodiimide-hydroxybenzotriazole (HOBt) in DMF gave the tripeptide (12).

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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