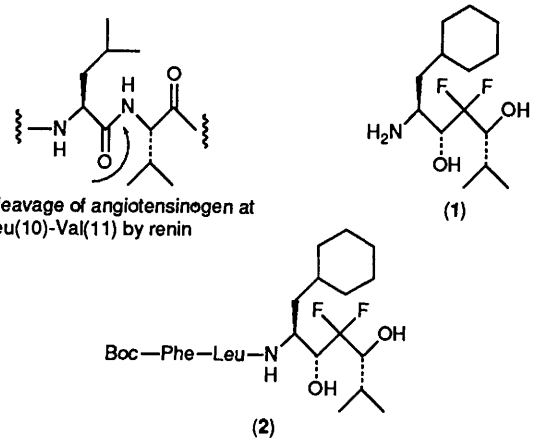
Synthesis of 6(*S*)-Amino-7-cyclohexyl-4,4-difluoro-3(*R*),5(*R*)-dihydroxy-2-methylheptane, a Novel Dipeptide Mimic

Hing L. Sham,* Cheryl A. Rempel, Herman Stein, and Jerome Cohen

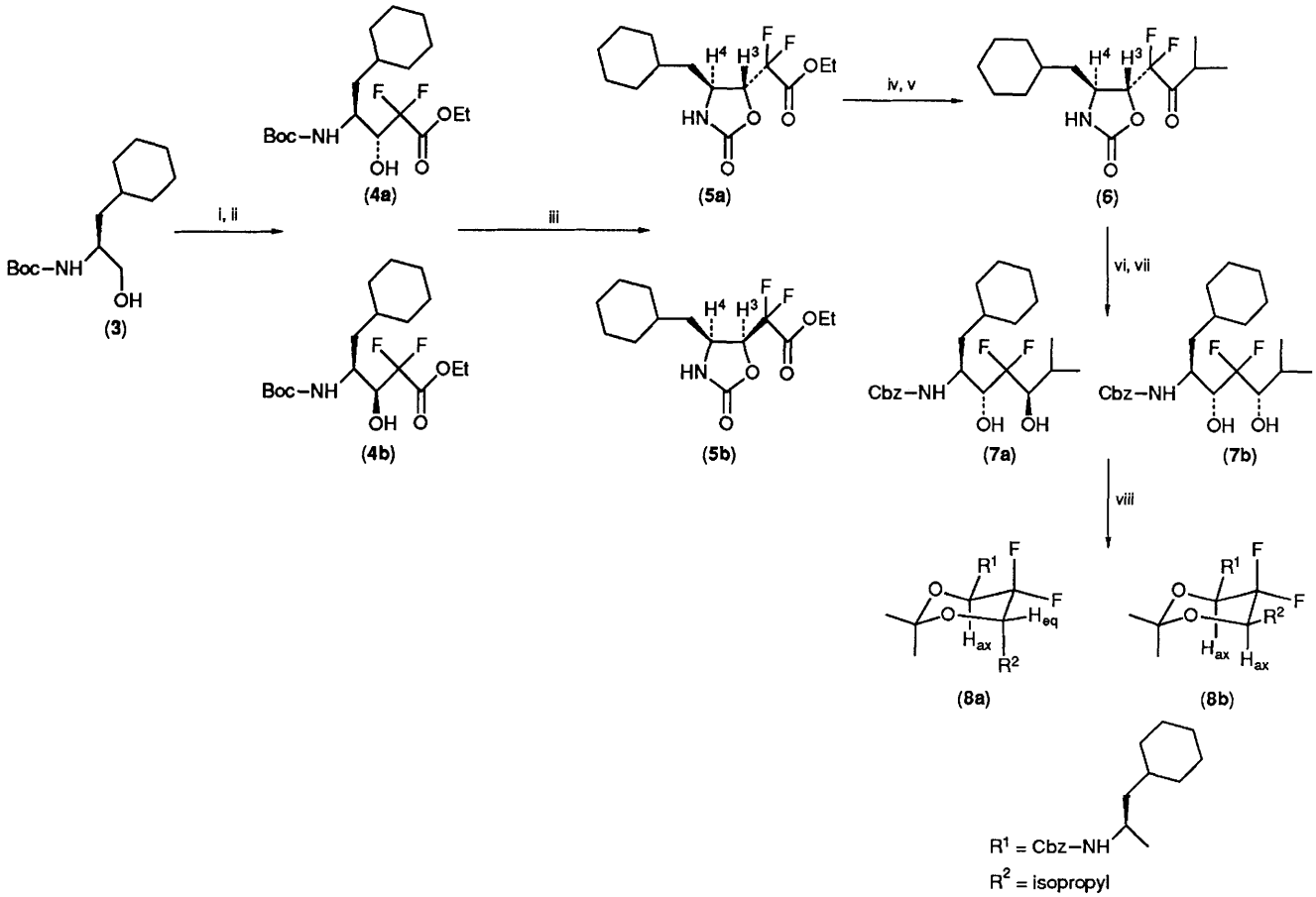
Abbott Laboratories, Pharmaceutical Discovery Division, Abbott Park, Illinois 60064-3500, USA

The incorporation of the novel dipeptide mimic (**1**), synthesized *via* Boc-L-cyclohexylalaninol (Boc = t-butoxycarbonyl), into a dipeptide sequence has led to a very potent renin inhibitor.

The inhibition of the enzyme renin, which cleaves its natural substrate angiotensinogen (a large protein) at the Leu(10)–Val(11) amide bond, is an important area for study of blood pressure regulation.[1] Over the past decade, several transition state mimics of the Leu–Val scissile bond have been reported and these include statine,[2a] hydroxyethylene isosteres,[2b] amino glycols,[2c] and fluoroketones.[2d] We report here the synthesis of a novel transition state mimic of Leu(10)–Val(11): 6(*S*)-amino-7-cyclohexyl-4,4-difluoro-3(*R*),5(*R*)-dihydroxy-2-methylheptane (**1**).



Oxidation of Boc-L-cyclohexylalaninol (**3**) (Boc = t-butoxycarbonyl) by the Swern method[3] provided the corresponding aldehyde which, when reacted with ethyl bromodifluoroacetate and activated zinc under sonicating conditions,[4] gave the difluorostatine (**4a**) and its β-isomer (**4b**) in a ratio of 2:1 in 70% yield. The absolute stereochemistry of the hydroxy group of these two diastereoisomers was established as follows: separate deprotection of (**4a**) and (**4b**) and cyclization with phosgene gave the corresponding oxazolidinones (**5a**) and (**5b**). The 300 MHz ^{1}H NMR spectrum ($CDCl_3$) of (**5a**) [δ 4.60 ($J_{3,4}$ 4.5 Hz, H-3)] and (**5b**) [δ 5.05 ($J_{3,4}$ 8.5 Hz, H-3)] compared well with the reported data[2a] 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)]. Hydrolysis of the ethyl ester in (**5a**), followed by reaction of the resulting carboxylic acid



Scheme 1. *Reagents*: i, $(COCl)_2$–dimethyl sulphoxide; ii, Zn, ethyl bromodifluoroacetate; iii, HCl then $COCl_2$ in toluene; iv, lithium hydroxide; v, isopropyl-lithium; vi, sodium borohydride; vii, $Ba(OH)_2$ then Cbz-NOS; viii, 2-methoxypropene/*p*-TsOH.

with isopropyl-lithium[5] in tetrahydrofuran provided the ketone (**6**) in 72% yield (two steps). Reduction of the ketone with sodium borohydride in methanol at 0 °C, followed by hydrolysis of the oxazolidinone ring and protection of the amino function with *N*-(benzyloxycarbonyloxy)succinimide (Cbz-NOS) provided the alcohols (**7a**) and (**7b**) in the ratio of 9 : 1 in 70% overall yield. The relative stereochemistry of the two hydroxy groups in (**7a**) and (**7b**) was established by synthesizing the corresponding acetonides (**8a**) and (**8b**) by reaction with 2-methoxypropene catalysed by *p*-MeC_6H_4-SO_3H (*p*-TsOH). The 2D-NOE NMR experiment was done on (**8a**) and (**8b**). No NOE effect was observed between the axial and equatorial hydrogens in (**8a**) and a definite NOE effect was observed between the two axial hydrogens in (**8b**). Removal of the benzyloxycarbonyl (Cbz) protecting group in (**7a**) gave the novel dipeptide mimic (**1**) which was coupled to Boc-Phe-Leu-OH using dicyclohexylcarbodiimide in *N,N*-dimethylformamide to give compound (**2**).† Compound (**2**) is a very potent inhibitor of human renin (IC_{50} 6.5×10^{-10} M).

† All new compounds gave satisfactory spectral data and elemental analysis.

In conclusion, a stereoselective synthesis of (**1**), which is an excellent dipeptide mimic of the Leu(10)–Val(11) cleavage site of angiotensinogen is described. Incorporation of (**1**) in a short peptide sequence resulted in a very potent inhibitor of human renin.

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References

1 I. A. Reid, *Arch. Intern. Med.*, 1986, **145**, 1475.
2 (a) D. H. Rich and E. T. Sun, *J. Med. Chem.*, 1980, **28**, 27; (b) M. Szelke, D. M. Jones, B. Atrash, A. Hallet, and B. Leckie, in 'Peptides, Structure and Function,' eds. D. H. Rich and V. J. Hruby, 1983, p. 579; (c) J. R. Luly, N. Maung, A. Fung, and J. J. Plattner, *J. Med. Chem.*, 1988, **31**, 2264; (d) H. L. Sham, H. Stein, C. Rempel, J. Cohen, and J. J. Plattner, *FEBS Lett.*, 1987, **220**, 299.
3 K. Omura and D. Swern, *Tetrahedron*, 1978, **34**, 1651.
4 S. Thaissivongs, D. Pals, W. M. Kati, S. R. Turner, L. Thomasco, and W. Watt, *J. Med. Chem.*, 1986, **29**, 2080.
5 C. G. Knudsen and H. Rapoport, *J. Org. Chem.*, 1983, **48**, 2260.