# Synthesis of (2*S*,5*S*,4*R*)-2,5-Diamino-3,3-difluoro-1,6-diphenylhydroxyhexane: The Core Unit of a Potent HIV Proteinase Inhibitor

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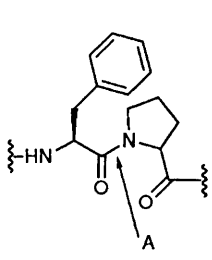
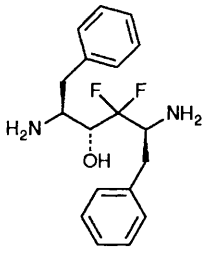
The coupling of the novel pseudo-symmetrical dipeptide mimic **1a**, synthesized *via* Boc-L-phenylalaninol, with Z-L-valine led to a very potent inhibitor of the HIV proteinase.

Human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS). One of the key steps in the replication cycle of this virus is when HIV-1 proteinase, the proteolytic enzyme encoded by the retrovirus, cleaves specific amide bonds (*e.g.* between Phe–Pro) in precursor *gag* and *gag-pol* polyproteins to form the mature proteins needed for production of infectious viral particles.[1] It is found that deactivation of this enzyme by site directed mutagenesis leads to the formation of non-infectious virions.[2] Thus, HIV proteinase is a potential target for the development



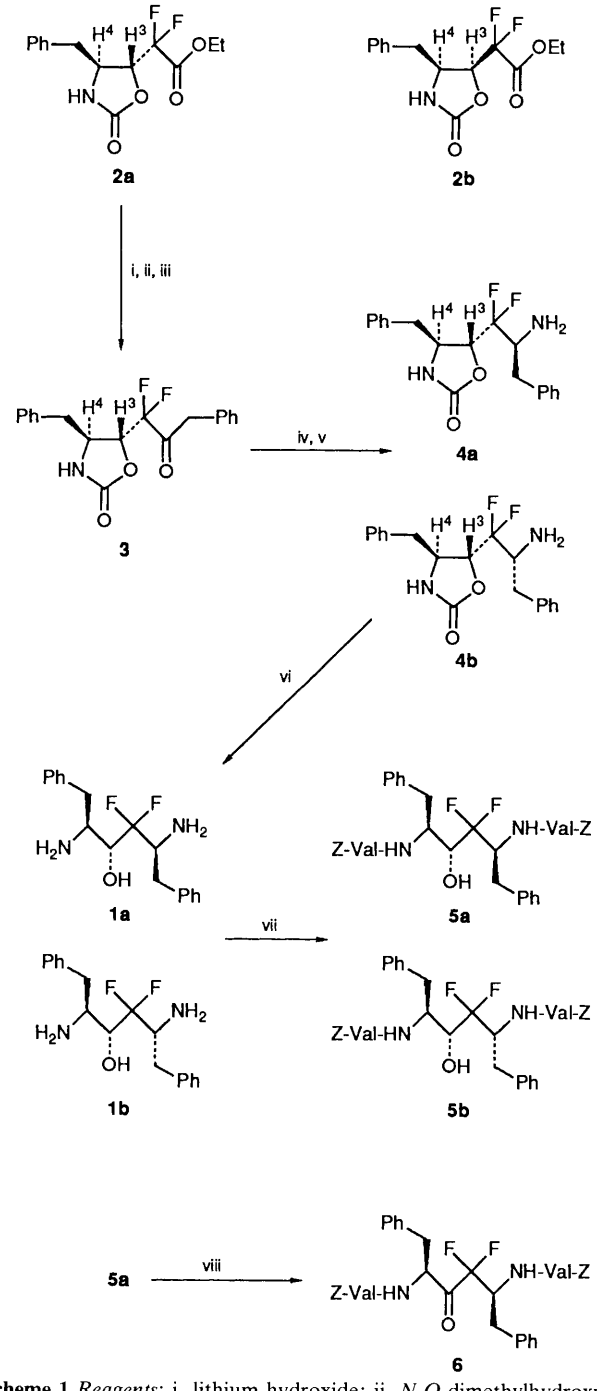
A: Phe–Pro amide bond of substrate that is cleaved by HIV-1 proteinase



**1a**

of antiviral agents for the treatment of AIDS. A variety of transition state peptidomimetic inhibitors of HIV-1 proteinase have been described.[3] X-ray crystal structures have established that the HIV proteinase is a symmetrical aspartic proteinase consisting of two identical 99 amino acid subunits.[4] Recently, two classes of C-2 symmetric HIV-1 proteinase inhibitors have been shown to exhibit potent antiviral activity.[5] We report here the synthesis of a novel pseudo-symmetrical transition state mimic of the Phe–Pro cleavage site: (2*S*,5*S*,4*R*)-2,5-diamino-3,3-difluoro-1,6-diphenylhydroxyhexane **1a**, the core unit of a potent HIV proteinase inhibitor.

The oxazolidinones **2a** and **2b** as shown in Scheme 1 can be synthesized in 60% overall yield starting with Boc-L-phenylalaninol† using previously reported procedures.[6] The absolute stereochemistry of the hydroxy group of these two diastereoisomers was established by high-field NMR spectroscopy. The 300 MHz $^1$H NMR spectrum ($CDCl_3$) of **2a** [δ 4.74 ($J_{3,4}$ 5.8 Hz, 3-H)] and **2b** [δ 5.15 ($J_{3,4}$ 8.5 Hz,3-H)] compared well with the reported data[7] for the oxazolidinones of (3*S*,4*S*)-statine [δ 4.50 ($J_{3,4}$ 5.0 Hz, 3-H)] and (3*R*,4*S*)-statine [δ 5.10 ($J_{3,4}$ 8.8 Hz, 3-H)]. Hydrolysis of the ethyl ester in **2a**, followed by reaction with *N,O*-dimethylhydroxylamine and dicyclohexylcarbodiimide (DCC) gave the corresponding amide (2 steps, 95%). Reaction of the amide[8] with benzylmagnesium bromide in tetrahydrofuran (THF) at 0 °C provided ketone **3** in 88% yield. Formation of the oxime of **3** followed by hydrogenation with Raney nickel as catalyst in ethanol gave the two diastereoisomeric amines **4a** and **4b** in a ratio of *ca.* 1 : 1 in 62% yield. The two diastereoisomers were readily separated by silica gel chromatography. The absolute stereochemistry of the amino group of these two diastereoisomers was established by a single crystal X-ray crystallographic study of **4b**.‡ Hydrolysis of the oxazolidinone ring in **4a** and **4b** with barium hydroxide in dioxane–water provided the corresponding diamines **1a** and **1b** in 95% yield. Coupling to the amino acid Z-L-valine† using DCC in dimethylformamide (DMF) gave the compounds§ **5a** and **5b**. Compound **5a** is a potent inhibitor of HIV-1 proteinase with $K_i$ = 1.0 nmol dm$^{-3}$. The less symmetrical compound **5b** is much less active ($K_i$ > 100 nmol




**Scheme 1** *Reagents*: i, lithium hydroxide; ii, *N,O*-dimethylhydroxylamine hydrochloride–DCC; iii, benzylmagnesium bromide; iv, hydroxylamine hydrochloride–pyridine; v, $H_2$–Raney nickel; vi, $Ba(OH)_2$; vii, Z-Val-OH–DCC; viii, $Na_2Cr_2O_7$–AcOH

† Abbreviations: Z = benzyloxycarbonyl; Val = valine; Boc = t-butyloxycarbonyl

‡ *Crystal data*: $C_{19}H_{20}F_2O_2N_2$, **4b**: monoclinic, space group $P2_1$ (No. 4), $a$ = 5.33(3), $b$ = 11.360(2), $c$ = 14.010(4) Å, β = 98.79(4)°, $U$ = 870.3(5) Å$^3$, $Z$ = 2, $D_c$ = 1.322 g cm$^{-3}$. 1168 Unique reflections were measured by the ω-2θ scan technique to 2θ = 110.1° on a Rigaku AFCSR diffractometer, using Cu-Kα radiation. An empirical absorption connection was applied (μ = 8.1 cm$^{-1}$). 1134 Reflections with $I > 3\sigma(I)$ were used in the refinement to $R$ = 0.031, $R_w$ = 0.040. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ All new compounds have satisfactory spectral data and elemental analysis.

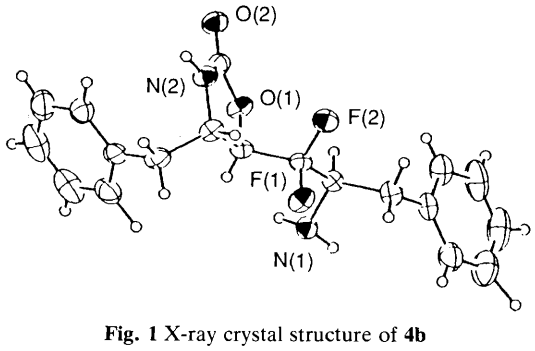



**Fig. 1** X-ray crystal structure of **4b**

$dm^{-3}$). Oxidation[9] of compound **5a** to the corresponding difluoroketone **6** provided an even more potent inhibitor of HIV-1 proteinase ($K_i$ = 0.1 nmol $dm^{-3}$). This is probably because the difluoroketone in its hydrated form truly mimics the tetrahedral transition state during the hydrolysis of a regular amide bond.

In conclusion, a synthesis of **1a** which is an excellent transition state mimic of the Phe–Pro cleavage site of the HIV proteinase is described. Incorporation of **1a** as the core unit of a small molecule resulted in a very potent inhibitor of HIV-1 proteinase.

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