Facile Synthesis of Potent HIV-1 Protease Inhibitors containing a Novel Pseudo-symmetric Dipeptide Isostere

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A series of potent inhibitors of the HIV-1 protease containing a novel pseudo-symmetric dipeptide isostere **3** was synthesized *via* ring opening of a protected epoxide with various substituted hydrazines.

Human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS). One of the key steps in the replication cycle of the HIV is mediated by the HIV-protease, which is an aspartic protease encoded by the retrovirus. This proteolytic enzyme cleaves specific amide bonds (*e.g.* between Phe–Pro) in precursor gag and gag-pol polyproteins to form the mature proteins needed for the production of infectious viral particles.[1] X-Ray crystal structures have established that the HIV-1 protease is a C_2-symmetric aspartic protease consisting of two identical 99 amino acid subunits.[2] It was found that deactivation of this enzyme by site-directed mutagenesis leads to the formation of non-infectious virions.[3] Thus, HIV protease is an attractive target for the development of agents for treatment of HIV infection. Potent HIV-1 protease inhibitors containing both transition-state analogue dipeptide isosteres and symmetry-based inhibitor core units such as **1**[4] and **2**,[5] respectively, (Fig. 1) have been reported. We report here a series of potent HIV-1 protease inhibitors containing the novel dipeptide isostere **3**, in which C-2 in **2** is substituted by a nitrogen atom.

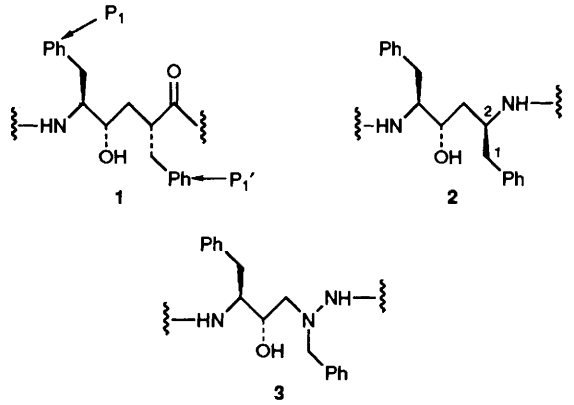
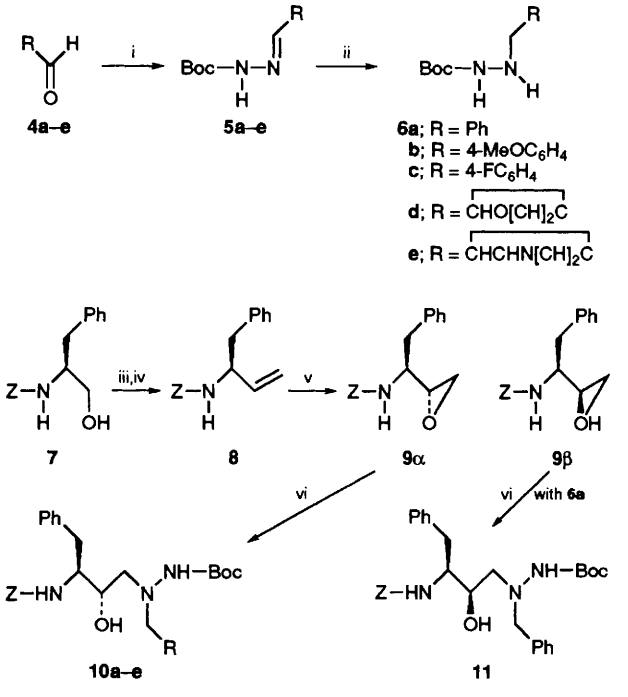


Fig. 1 Representative dipeptide isosteres incorporated in HIV-1 protease inhibitors



Scheme 1 *Reagents*: i, Boc-NH-NH_2; ii, H_2/Pd; iii, $(COCl)_2$–dimethylsulfoxide; iv, KH/methyltriphenylphosphonium bromide; v, MCPBA; vi, alumina/**6a–e**

Table 1 IC_{50} of the HIV-1 protease inhibitors

Compound	IC_{50}/nmol dm^{-3}
10a	5.1
10b	10
10c	13
10d	2.9
10e	104
11	150

As demonstrated by the compounds **10a–e**, this series of inhibitors nearly maintains the potency of the carbon series but is considerably easier to synthesize.

Condensation of aldehydes **4a–e** with Boc-protected hydrazine provided the corresponding hydrazones **5a–e** in 85–96% yield.[6] Hydrogenation of the hydrazones under medium pressure using 10% palladium on charcoal as the catalyst gave the substituted hydrazines **6a–e** in high yield. Oxidation of *Z*-L-phenylalaninol **7** using the Swern procedure[7] provided the corresponding aldehyde. The olefin **8** was synthesized by reaction of the aldehyde with the ylide generated from methyltriphenylphosphonium bromide and potassium hydride (75% yield).[8] Epoxidation of the olefin with *meta*-chloroperbenzoic acid (MCPBA) in methylene chloride at 0 °C produced the epoxides **9**α and **9**β in a ratio of ~9 : 1 (95% yield) as described for the similar Boc-protected olefin.[9] Alumina-catalysed epoxide opening[10] with the substituted hydrazine **6a** with a benzyl side-chain provided the corresponding dipeptide isosteres **10a** and **11**. Compound **10a** is a potent inhibitor of the HIV-1 protease with an IC_{50} of 5.1 nmol dm^{-3}. In contrast, compound **11** which was obtained from the β-epoxide is much less potent (IC_{50} = 150 nmol dm^3). Similarly, epoxide ring opening of **9**α with other substituted hydrazines **6b–e** provided the inhibitors **10b–e** with different P_1' side-chains. Their IC_{50}s are shown in Table 1. Two important aspects of the synthetic route to these potent HIV-1 protease inhibitors are worth noting: (*i*) the compounds **10a–e** are orthogonally protected at the two amino groups, offering the option of selective deprotection and coupling to selected amino acids to increase the potency of the resulting inhibitors; and (*ii*) the P_1' side-chain can be easily varied for structure–activity studies simply by choosing the appropriate aldehyde **4** for the synthesis of the corresponding substituted hydrazine **6**.

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