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SYNTHESIS OF 1,3-DIAMINO-2-HYDROXYPROPANE DERIVATIVES AS PSEUDOSYMMETRIC HIV PROTEASE INHIBITORS

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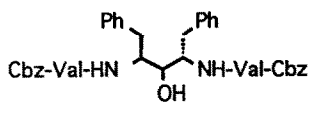
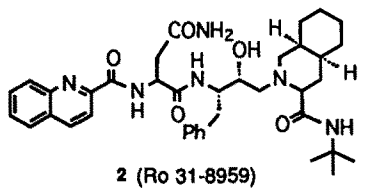
Abstract. A facile synthesis of a series of potential pseudosymmetric HIV-protease inhibitors containing 1,3-diamino-2-hydroxypropane moiety is described.

Human immunodeficiency virus type 1 (HIV-1) protease is the key enzyme involved in processing viral polyproteins into smaller mature viral proteins.[1] Inhibition of the HIV protease results in the production of immature, noninfectious particles making this enzyme essential for viral replication.[2] Development of protease inhibitors has, therefore, become a very promising strategy for the treatment of acquired immunodeficiency syndrome (AIDS). X-ray crystallography has revealed that HIV protease belongs to the aspartyl protease family and exists as a C2-symmetirc homodimeric structure.[3] Synthesis of symmetric or pseudosymmetric inhibitors may offer the advantage of simplicity of chemical synthesis and specificity towards retroviral proteases over other human aspartyl proteases, e.g. renin. This strategy has been elegantly employed initially by Kempf et al.[4] and more recently by Bone[5] and Humber.[6] In this report, we describe a facile synthesis of pseudosymmetric HIV protease inhibitors containing 1,3-diamino-2-hydroxypropane moiety as a transition state isostere of the substrate scissile peptide bond.

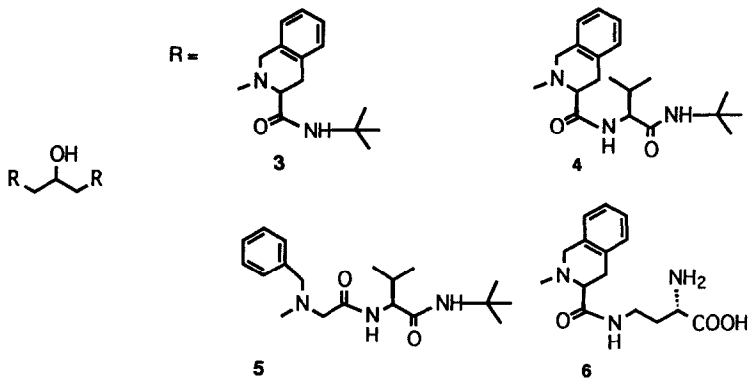
Peptidomimetics **1**[4] and **2**[7] contain the 1,3-diamino-2-hydroxypropane moiety and are reported to be very potent HIV-1 protease inhibitors. Based on the structure of **2** we have proposed pseudosymmetric inhibitors **3** - **5**. In addition, Our computer modeling study using reported X-ray crystal structure of HIV-1 protease[3] also highlighted potential polar interactions at the edges of the cleft in the enzyme, the inhibitor **6** with two charged groups in both ends was therefore prepared.



1



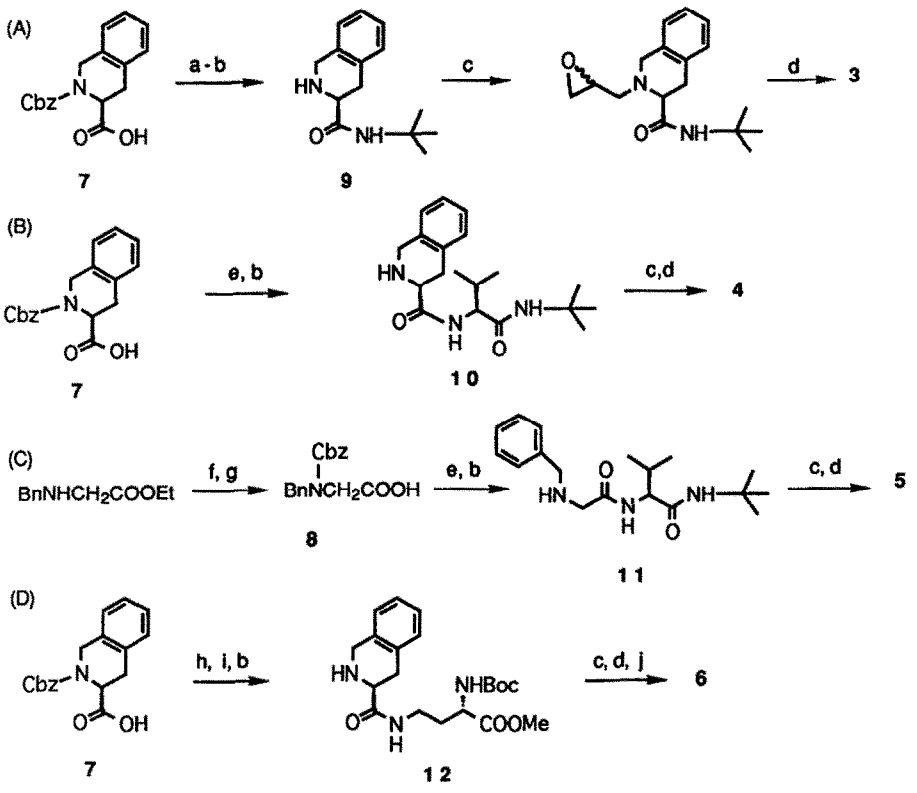
2 (Ro 31-8959)



The synthesis of these potential inhibitors is outlined in Scheme 1. The Cbz-protected tetrahydroisoquinoline-3-carboxylic acid **7**[8] or N-benzyl glycine **8** were coupled to t-butylamine or N-t-butylvalinamide using mixed anhydride[9] or diphenylphosphoryl azide.[10] Removal of the Cbz group of the resulting peptides by catalytic hydrogenolysis gave **9** - **11**, respectively, in high yields. The p-nitrophenol ester of **7** reacted with N^{a}-Boc-Orn-OH[11] in the presence of triethylamine to give a dipeptide, which on exposure to diazomethane followed by removal of the Cbz group provided amine **12**. These secondary amines, **9** - **12**, reacted with epibromohydrin in the presence of triethylamine and sodium iodide to produce a mixture of inseparable diastereomers of the epoxides (35-57% yields).[12] It is worth noting that primary amines, such as Phe-Val-NH-t-Bu, failed to react with epibromohydrin to give the desired products. Instead, a triethylamine adduct resulting from the attack of triethylamine at the epoxide was obtained. Attempts to prevent the side reaction by using the hindered base, diisopropylethylamine, gave mainly recovered starting material. The mixture of the epoxides obtained after the epibromohydrin reaction readily reacted with the secondary amines using lithium perchlorate[13] as catalyst to afford compounds **3**-**5** in good yields. In the case of **6**, the final product was accomplished by sequential deprotection of the ester and Boc groups, and purification by chromatography on a revere phase C18 column.

Compounds **3**-**6** prepared were evaluated *in vitro* for inhibition of HIV-1 protease.[14] None of these compounds showed activity even at concentration of 10^{-6} M.

Scheme 1



a) *t*-BuOCOCl, N-methylmorpholine; *t*-BuNH$_2$, 84%; b) H$_2$/ Pd/C; c) epibromohydrin, Et$_3$N, NaI ; d) **9-12**, LiClO$_4$, CH$_3$CN; e) DPPA, Val-NH-*t*-Bu, 82%-quant.; f) Cbz-Cl, Et$_3$N, 33%; g) 1 N NaOH; H$^+$, 95%; h) DCC, p-nitrophenol, 94%; i) N$^{\alpha}$-Boc-Orn-OH, Et$_3$N; CH$_2$N$_2$, 75%; j) 1 N NaOH; 4N HCl, 21%.

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