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SYNTHESIS OF 7-MEMBERED CYCLIC OXAMIDES: NOVEL HIV-1 PROTEASE INHIBITORS

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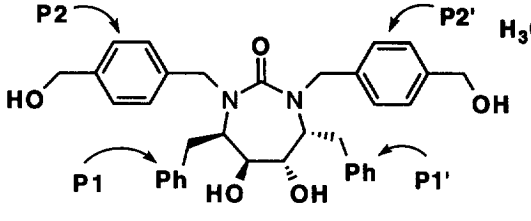
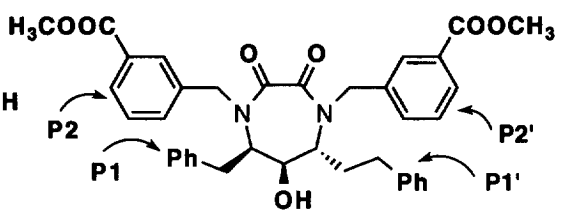
Summary: An intermediate with three chiral centers, constructed by two key reactions viz. asymmetric allylboration and Sharpless epoxidation, has been used for the synthesis of novel 7-membered cyclic oxamides.

Human Immunodeficiency Virus type-1 (HIV-1), the causative agent of Acquired Immunodeficiency Syndrome (AIDS), encodes for a specific proteinase (HIV-1 protease).[1-4] The aspartic protease is essential for replication of fully infectious virion particles. Inhibition of this enzyme is effective in chronically infected cells. Therefore, it is regarded as a promising approach for finding effective treatments for HIV infection.[1-4] Protein X-ray crystallography studies of the substrate based inhibitor and HIV-1 complex revealed the presence of a unique water molecule which is hydrogen bonded to the two carbonyls of the inhibitor and the flap residues of the enzyme.[5] We previously described successful incorporation of the structural water molecule in the cyclic urea (**1**) class of HIV-1 protease inhibitors.[6] Structural studies of DMP323 with HIV-1 protease revealed that the carbonyl of the cyclic urea moiety hydrogen bonds to the two flap residues (Ile50 and Ile50') of the enzyme while the diol moiety is hydrogen bonded to the two catalytic aspartic acid residues (Asp25 and Asp25').[6] Consequently, cyclic structures that contain complimentary groups to capture these important electrostatic interactions may function as good starting templates for anchoring optimum P1, P1', P2 and P2' groups.



1, DMP323



2, Cyclic Oxamide

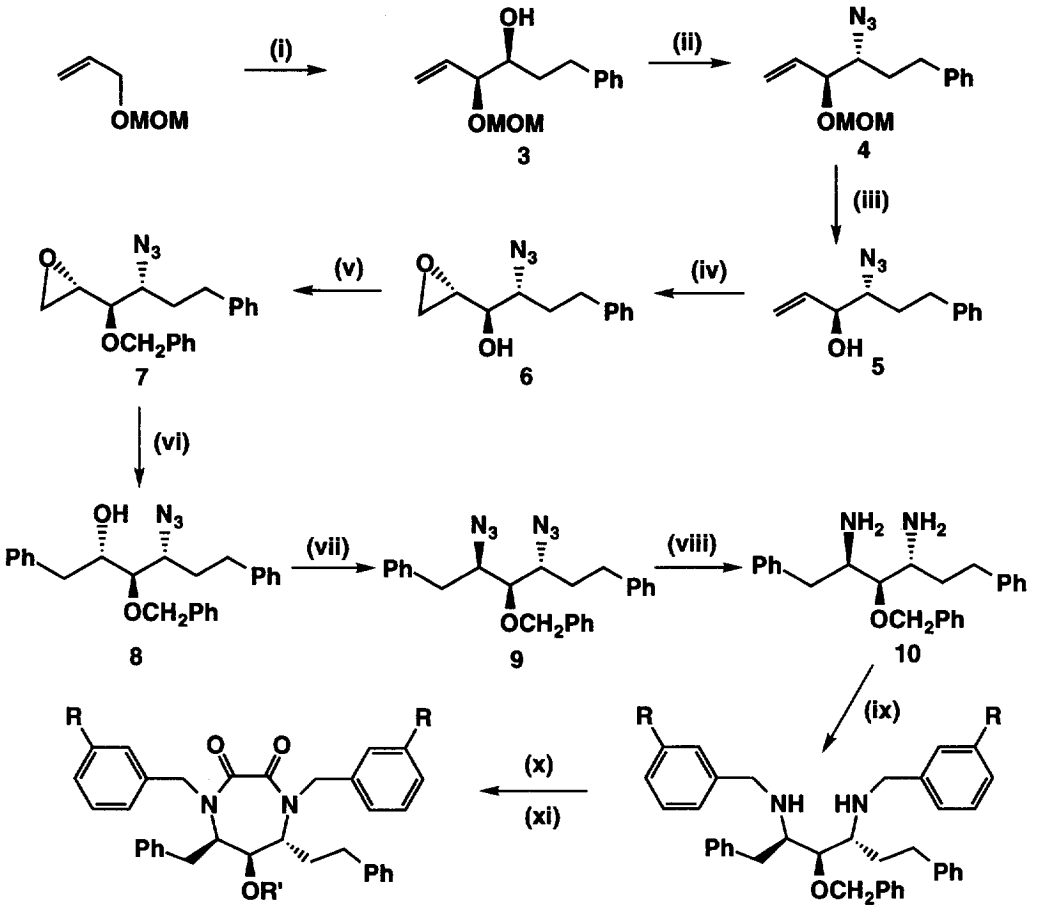
We were intrigued by an alternative cyclic structure in which there are two carbonyl groups for accepting two hydrogen bonds from Ile50 and Ile50' and a mono hydroxy group for providing hydrogen bonds to Asp25 and Asp25'. In this communication, we report the synthesis of cyclic oxamide (**2**) containing appropriate groups for electrostatic and van der Waals interactions complimentary to the active site of HIV-1 protease.

For the successful construction of (**2**) we needed an enantioselective synthesis of a key intermediate epoxide (**6**). The three chiral centers in epoxide (**6**) were constituted by asymmetric allylboration[7] and Sharpless epoxidation[8] as shown in **Scheme 1**. Addition of dihydrocinnamaldehyde to *in situ* generated (*Z*)-3-methoxymethoxyallyldiisopinocampheylborane[7(c)] provided alcohol (**3**) in 90% ee[9] after oxidative workup. Displacement of the secondary hydroxyl group in alcohol (**3**) under Mitsunobu reaction[10] conditions provided azide (**4**) in 88% yield. In order to set the stage for Sharpless epoxidation, the methoxymethyl ether (**4**) was hydrolyzed to alcohol (**5**) under acid catalyzed ether exchange conditions. Sharpless epoxidation of alcohol (**5**) afforded a single diastereomer (**6**) in 95% yield.[8] The minor enantiomer of (**5**) remains unreacted under these conditions and can be readily separated from epoxide (**6**) by chromatography. Consequently, enantiomeric purity of the key intermediate epoxide (**6**) is enriched[9] from 90% ee to 98% ee via the Sharpless epoxidation-kinetic resolution process.[8(b)] Benzylation of epoxy alcohol (**6**) was achieved without any Payne rearrangement[11] using conditions reported in the literature[12] to provide epoxide intermediate (**7**) in 80% yield. Addition of diphenylcuprate (derived from PhLi and CuCN) to the epoxide (**7**) furnished azido alcohol (**8**) in 82% yield.

The inversion of hydroxyl group in (**8**) under Mitsunobu reaction[10] conditions resulted in the formation of bisazide (**9**) in 89% yield. The competitive elimination product (15% isolated yield at 25 °C vs 6% isolated yield at -10 °C) during the inversion was minimized by carrying out the reaction at lower temperature. The bisazide (**9**) was reduced to diamine (**10**) under Staudinger reaction conditions.[13] Reductive amination[14] of 3-carbomethoxybenzaldehyde with diamine (**10**) furnished the intermediate (**11**) in 75% yield. Cyclization to oxamide (**12**), a key step in the reaction sequence, needed considerable experimentation. The most optimum conditions involved treatment of diamine (**11**) with freshly distilled oxalyl chloride at -40 °C. Cyclic oxamide (**12**) is formed in 50% yield. Reductive debenzylation in the presence of palladium hydroxide and hydrogen in ethyl acetate provided the target compound (**2**) in 80% yield. The overall yield of **2** from methoxymethyl allyl ether is 7.8 %.[15]

At ambient temperature, all ^{1}H NMR signals of oxamides (**2**) and (**12**) broaden presumably due to the high energy barrier of inversion of the ring system[16]. All signals coalesce and sharpen at a temperature above 90 °C to give well resolved ^{1}H NMR spectra. Cyclic oxamide (**2**) is a potent HIV protease inhibitor (Ki = 40 nM).

Scheme 1



(i) *s*-BuLi/ THF/ 15 min/ (+)-DIP-OMe/ 30 min/ -78 °C; BF_3Et_2O/ $PhCH_2CH_2CHO$/ -78 °C for 30 min then 0 °C for 30 min; NaOAc/ H_2O_2/ 18 h; 70%; (ii) Ph_3P/ EtOOCN=NCOOEt/ $(PhO)_2P(O)N_3$/ THF/ 0 °C 1 h then at 25 °C 2 h; 88%; (iii) 2M HCl in 1:1 Dioxane : CH_3OH/ 25 °C/ 18 h; 90%; (iv) D-Diisopropyl tartarate/ $Ti(OiPr)_4$/ *t*-BuOOH/ 4Å molecular sieves/ CH_2Cl_2/ -15 °C/ 36 h; 95%; (v) $PhCH_2Br$/ 10% TBAI / NaH/ THF/ 25 °C/ 1 h; 80%; (vi) PhLi/ CuCN/ THF/ 0 °C/ 4 h; 82%; (vii) Ph_3P/ EtOOCN=NCOOEt/ $(PhO)_2P(O)N_3$/ THF/ -10 °C/ 36 h; 89%; (viii) PPh_3/ THF/ H_2O/ 80 °C/ 4 h; 85%; (ix) $Na(OAc)_3BH$/ HOAc/ 3-COOMePhCHO/ $ClCH_2CH_2Cl$/ 25 °C/ 18 h; 75%; (x) ClCOOCCl/ Et_3N/ $CHCl_3$/ -40 °C then at 25 °C/ 18 h; 50%; (xi) 20% $Pd(OH)_2$/ H_2 35 psi/ EtOAc/ 10 h; 80%.

Protein X-ray structure of HIV-1 protease complex with cyclic urea indicated the importance of hydrogen bonding interactions amino acid residues Ile50, Ile50', Asp25, and Asp25' of the protease to the inhibitor. Structure based approaches have been useful for design of cyclic oxamides as potent HIV-1 protease inhibitors which are structurally diverse from cyclic ureas. We are continuing to use structural information on enzyme-inhibitor complexes for *de novo* design of enzyme inhibitors.

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