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A Concise and Enantioselective Synthesis of Novel HIV-1 Protease Transition State Mimics

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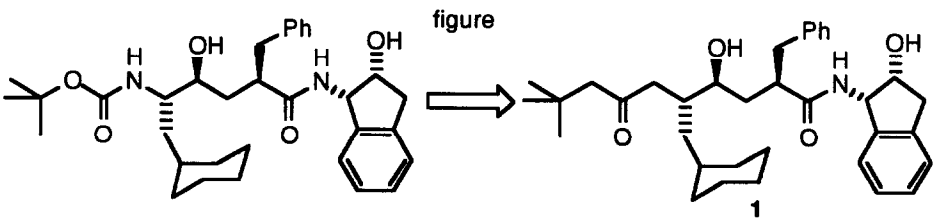
Abstract: Novel HIV-1 protease inhibitors have been prepared in a enantioselective manner via an Evans asymmetric aldol, Claisen rearrangement and iodolactonization. X-ray crystallographic analysis was used to confirm the absolute configuration of the newly created stereogenic centers.

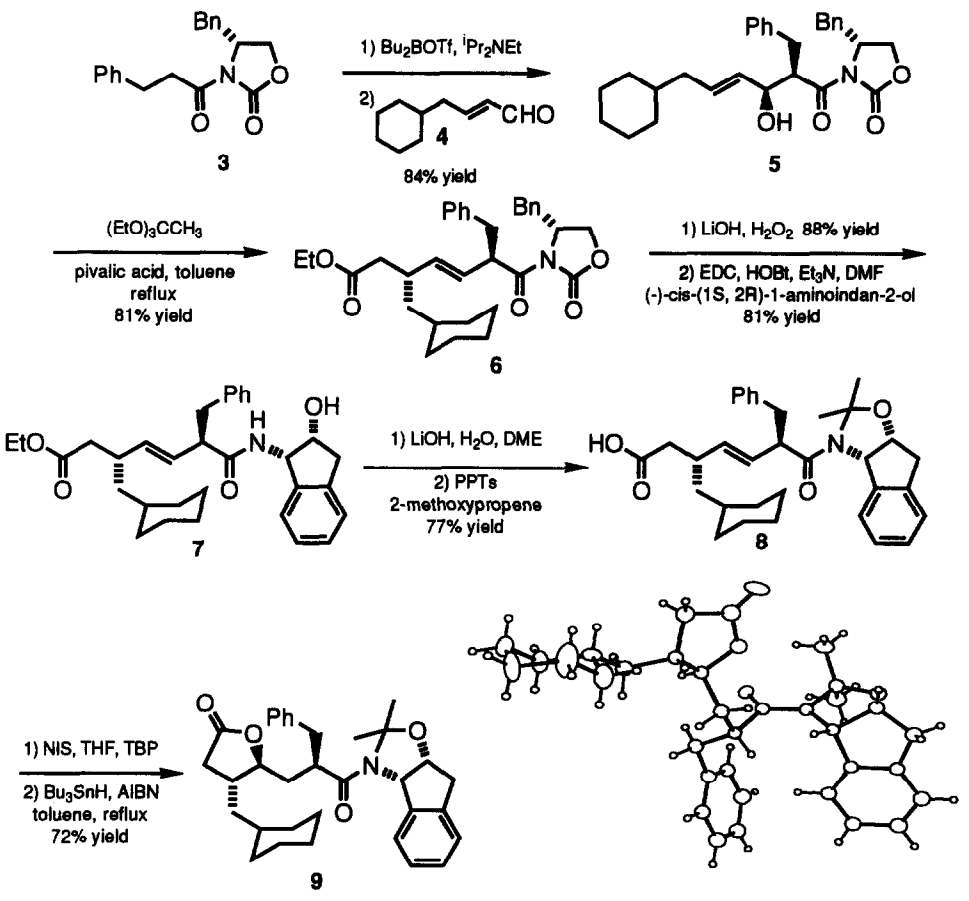
The alarming spread of human immunodeficiency virus type 1 (HIV-1), the etiologic agent of the acquired immunodeficiency syndrome (AIDS),[1] has initiated an urgent quest to comprehend and control this disease. This has led to the discovery of a virally encoded homodimeric aspartyl protease,[2] which is responsible for processing the *gag* and *pol* gene products that allow for the organization of core structural proteins. Inhibition of this enzyme prevents the maturation and replication of the virus in cell culture[3] and thus has become a primary target for drug intervention. A series of potent hydroxyethylene dipeptide isostere inhibitors of HIV-1 protease has been previously described by researchers in these laboratories.[4] Although these molecules are highly effective HIV-1 protease inhibitors, they lack the necessary pharmacokinetic profile required for drug therapy. One method to improve the pharmacokinetic profile[5] is to reduce the peptide character of these molecules, and thereby improve oral absorption and reduce biliary clearance. Therefore, we reasoned that replacement of the carbamate moiety of those inhibitors with a ketone (figure) should eliminate one area of vulnerability to enzymatic degradation. In this Letter we describe a facile enantioselective synthesis to achieve this end.

figure



1

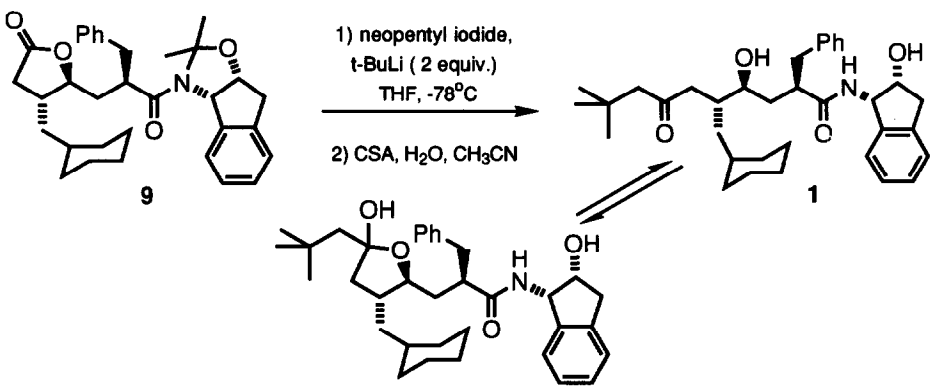
Scheme 1



Our effort to synthesize a carbon replacement analog (scheme 1) of the tert-butyl carbamate began with the condensation of known aldehyde[6] **4** and oxazolidinone **3** using dibutylboron triflate and diisopropyl ethyl amine following the Evans protocol.[7] Silica gel chromatography provided the desired aldol product **5**[11] ($[\alpha]^{20}_D$ -8.5 (c 0.79, $CHCl_3$), oil) in 84% yield with >10:1 diastereoselectivity. A stereoselective Claisen rearrangement utilizing triethylorthoacetate and a catalytic amount of pivalic acid[8] afforded optically pure ester **6**[11] ($[\alpha]^{20}_D$ -74 (c 1.19, $CHCl_3$), oil) in 81% yield. A chemoselective hydrolysis[9] of the chiral auxiliary using lithium hydroperoxide provided the carboxylic acid ($[\alpha]^{20}_D$ -3.7 (c 0.9, $CHCl_3$), oil).[11] The free acid, isolated in 90% yield, was then condensed under standard peptide coupling conditions ([1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), 1-hydroxybenzotriazole (HOBt), Et3N) with (-)-*cis*-(1S,2R)-1-aminoindan-2-ol[12] to afford ester amide **7** ($[\alpha]^{20}_D$ -19.8 (c 1.22, $CHCl_3$), mp 96-97°C).[11] Careful hydrolysis of ethyl ester **7**, followed by protection of the hydroxyl amide with 2-methoxypropene and a catalytic amount of pyrdinium p-tolunesulfonic acid (PPTs) provided acid **8** ($[\alpha]^{20}_D$ 0.47 (c 100, $CHCl_3$), mp 109-111°C)[11] in 77% overall

yield for the two steps. Formation of the isopropylidene aminal served a variety of purposes. First, it greatly enhanced the yield and selectivity of the iodolactonization process. Second, it temporarily removes two acidic protons that proved to be detrimental in the penultimate step. From analysis of local conformational control about the trans olefin, (i.e., sp^2-sp^3 carbon-carbon bonds are eclipsed)[13] one would predict the acid moiety to cyclize from the β face of the olefin. After much experimentation, acid **8** was found to cyclize selectively utilizing the modified conditions of Hoover and Damon[10] (N-iodosuccinimide (NIS), 4,4'-thiobis(2-tert-butyl-6-methylphenol) (TBP) in THF, dark). The iodide ($[\alpha]^{20}_D$ 0.23 (c 1.0, $CHCl_3$), foam)[11] was obtained in near quantitative yield as a 6:1 mixture of trans:cis lactones as determined by ^1H NMR. In practice, the labile iodide was reduced immediately, affording lactone **9**[11] as the major product in 72% overall yield. Crystallization of the lactone from diethyl ether provided material ($[\alpha]^{20}_D$ 0.32 (c 0.87, $CHCl_3$), mp 149-150°C) suitable for single crystal X-ray analysis.[14] This analysis confirmed that the iodolactonization provided the "trans" lactone as predicted by conformational analysis. Incorporation of optically pure (-)-*cis*-(1S,2R)-1-aminoindan-2-ol confirmed the absolute stereochemistry at C2(R), C4(S) and C5(R) as well.

Scheme 2



Initially, attempts to complete the synthesis of target ketone **1** via the Weinreb amide were unsuccessful. However, treatment of lactone **9** with the anion generated from neopentyl iodide and *tert*-butyl lithium at -78°C in THF provided the desired product as a mixture of isomeric lactols. Deprotection of the isopropylidene aminal with a catalytic amount of camphorsulfonic acid (CSA) (H_2O:CH_3CN; 1:1) afforded the desired ketone **1**[11] also as an equilibrium mixture of ketone and lactols, as shown in Scheme 2. This methodology is currently being expanded to include other carbon nucleophiles to optimize binding in the P2 pocket of the protease.

In summary, a ten step stereoselective synthesis has been accomplished which provided the desired ketone in 9% overall yield. The synthesis proved to be enantioselective in that the initial absolute stereochemistry provided by the aldol condensation was exploited to control two distal stereogenic centers, and flexible in regard to the potential for substituting a variety of hydrophobic groups to fill the P2 binding pocket of the HIV-1 protease. The pharmacokinetic profile and HIV-1 protease inhibition of this compound will be disclosed in due course.

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References and Notes

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11. The structure assigned to each new compound is in accord with its infrared, 400-MHz ^{1}H NMR spectra, as well as parent ion high-resolution mass spectrometry and or C, H, and N combustion analysis.
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14. Crystal structure details: $C_{33}H_{41}NO_4$, M_r = 515.70, monoclinic space group $P2_1$, a = 13.202 (2), b = 8.130 (2), c = 14.731 (2) Å, β= 112.280 (8)°, V = 1463.1 Å^3, Z = 2, D_{calc} = 1.171 g cm^{-3}, monochromatized radiation λ(Cu K_α) = 1.54184 Å, m = 0.57 mm^{-1}, $F(000)$ = 556, T = 296 K. Data collected on a Rigaku AFC5R diffractometer to a $2q$ limit of 130° with 1019 observed data, at the $I \geq 3\sigma(I)$ level, out of 2727 measured. Structure solved using direct methods and refined using full-matrix least-squares on F using 202 parameters. The non-hydrogen atoms were refined with a mixture of isotropic and anisotropic thermal displacements. Hydrogen atom contributions included in calculations. Final agreement statistics are: R = 0.065, wR = 0.050, S = 1.90, $(\Delta/\sigma)_{max}$ = 0.004. Weighting scheme is $1/\sigma^2(F)$. Maximum peak height in a final difference Fourier map is 0.27(5) eÅ^{-3} with no chemical significance. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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