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Asymmetric dihydroxylation route to a dipeptide isostere of a protease inhibitor: enantioselective synthesis of the core unit of ritonavir

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An enantioselective synthesis of the dipeptide isostere of ritonavir has been accomplished utilizing Sharpless asymmetric hydroxylation as the key step.

The utility of dipeptide isosteres in the design and synthesis of potent and selective HIV protease inhibitors has been well documented.[1] A number of peptidomimetic protease inhibitors in combination with reverse transcriptase inhibitors have now been approved for treatment of AIDS, and early indications are very promising.[2, 3] Ritonavir **1** is one such protease inhibitor which is potent, selective and clinically effective.[2a] Ritonavir consists of a unique dipeptide mimic **2** evolved from structure-based design strategies (Fig. 1).[4] Most syntheses of the ritonavir isostere start with N-protected L-amino acids and are therefore limited to natural amino acid-derived substitutents.[5] Herein we report an enantioselective synthesis of the ritonavir isostere utilizing the Sharpless' catalytic asymmetric dihydroxylation reaction as the key step.

As illustrated in Scheme 1, γ,δ-unsaturated ester **4** was prepared by addition of vinyl magnesium bromide to phenylacetaldehyde **3**, followed by Claisen rearrangement of the resulting allylic alcohol with triethyl orthoacetate in the presence of propionic acid at 145 °C.[6] Ethyl ester **4** was converted to lactone **5** utilizing Sharpless protocol.[7] Thus, ester **4** was treated with AD-mix-β and $MeSO_2NH_2$ in a mixture (1 : 1) of Bu^tOH and H_2O at 0 °C for 36 h and the resulting hydroxy ester was lactonized in the presence of a catalytic amount of AcOH in refluxing toluene for 6 h. The desired hydroxy lactone **5** was obtained in 87% yield after silica gel chromatography [$[\alpha]_D^{23}$ −58, (*c* 1.81, $CHCl_3$)]. The hydroxy lactone **5** was transformed into protected amino lactone derivative **6** in the following three steps sequence: (1) formation of the mesylate with MsCl and Et_3N in the presence of a catalytic amount of DMAP; (2) displacement of the mesylate with NaN_3 in DMF at 90 °C and (3) catalytic hydrogenation of the resulting azide over 10% Pd/C in EtOAc in the presence of Boc_2O (overall 73% yield). The benzyl side chain at C-2 in isostere **2** was installed by a stereoselective alkylation of lactone derivative **6** as described previously.[8] Thus, generation of the enolate of lactone **6** with LiHMDS in THF at −78 °C, and subsequent reaction with BnI afforded the alkylated product **7** as a single diastereomer along with a small amount (4%) of dialkylated product. Alkylated lactone **7** was separated (70% yield) by silica gel chromatography. Saponification of lactone **7** by LiOH followed by protection of the resulting hydroxy acid with TBDMSCl, imidazole in DMF afforded the TBDMS protected acid derivative **8**.[5a] Curtius rearrangement of the acid **8** with $(PhO)_2PON_3$ and Et_3N in refluxing toluene followed by addition of BnOH as described previously provided the Z-

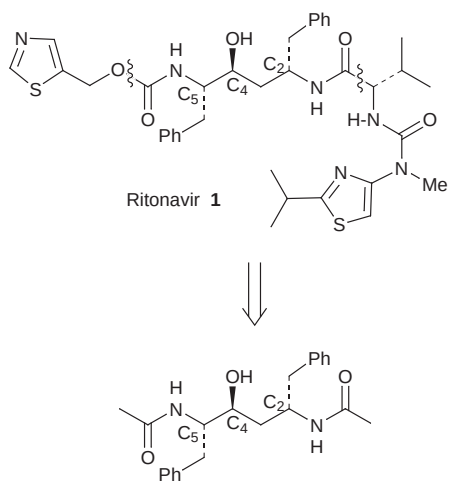
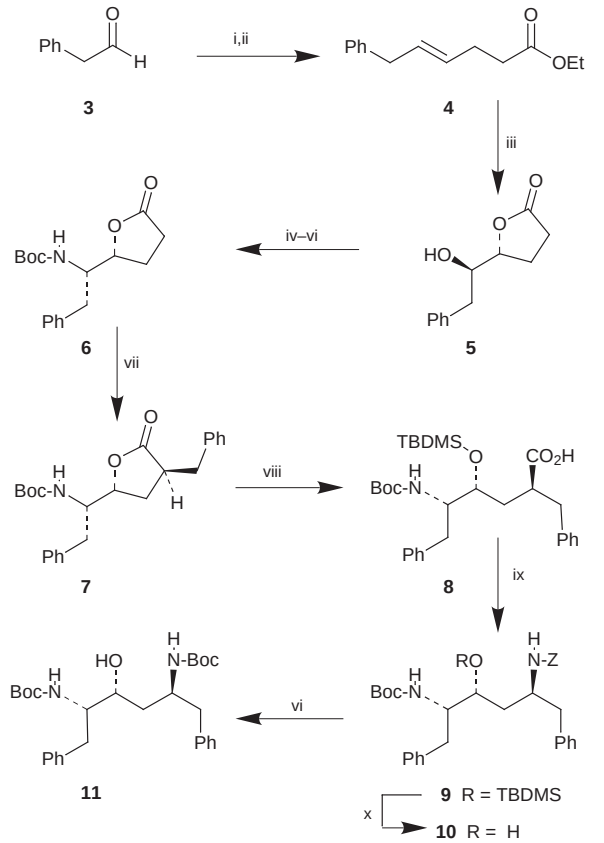
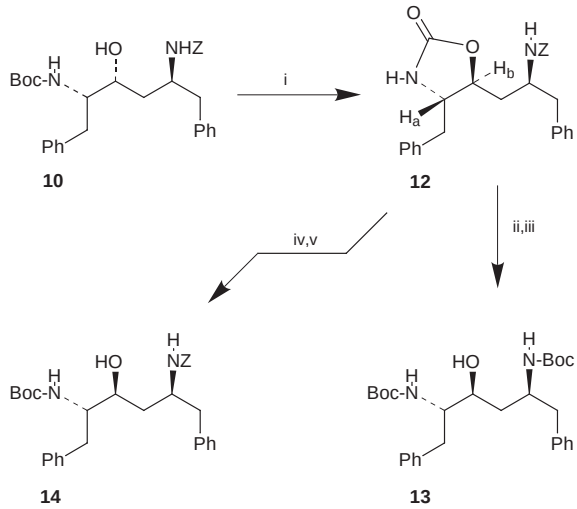


Fig. 1 Dipeptide mimetic of ritonavir **1**



Scheme 1 *Reagents and conditions*: i, CH_2=$CHMgBr$, Et_2O, 0 °C, 57%; (ii) $MeC(OEt)_3$, $MeCH_2CO_2H$ (cat), 145 °C, 86%; (iii) AD-Mix-β, $MeSO_2NH_2$, Bu^tOH, H_2O, 0 °C, then PhMe, 115 °C, 87%; iv, MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C; v, NaN_3, DMF, 87%; vi, H_2, 10% Pd-C, Et_3N, Boc_2O, EtOAc, 23 °C, 84%; vii, LiHMDS, THF, BnI, −78 °C, 70%; viii, aq. LiOH, DME, 23 °C, H_3O^+, then imidazole, TBDMSCl, DMF, 23 °C, quant. ix, $(PhO)_2PON_3$, Et_3N, PhMe, then BnOH, 130 °C, 65%; x, TBAF, THF, 23 °C, 75%.



Scheme 2 *Reagents and conditions*: i, $SOCl_2$, THF, 23 °C, 73%; ii, KOH, EtOH–H_2O (1 : 1), 70 °C; iii, THF, Boc_2O, $NaHCO_3$, 23 °C, 52%; iv, Boc_2O, Et_3N, DMAP (cat), THF, 23 °C, 93%; v, Cs_2CO_3, Pr^iOH–MeOH (6 : 1), 23 °C, 60%.

derivative **9** (overall 65% yield from **7**).[9] Removal of the silyl group by treatment with TBAF in THF at 23 °C afforded the dipeptide isostere **10** with (4*R*)-configuration. Catalytic hydrogenation of **10** over 10% Pd/C in the presence of Boc_2O and Et_3N furnished the Boc derivative **11** in 72% yield after silica gel chromatography.

In the ritonavir isostere, the (4*S*)-configuration of the hydroxy group is known to be essential for effective enzyme inhibitory properties.[2a, 5, 10] Therefore, the C-4 hydroxy group stereochemistry was inverted as depicted in Scheme 2. Reaction of **10** with $SOCl_2$ in THF at 23 °C furnished the oxazolidinone **12** (73%). The vicinal coupling constant of oxazolidinone **12** is consistent with an *anti* stereochemical relationship (J_{AB} 4.8 Hz).[11] Treatment of the oxazolidinone **12** with KOH in EtOH–H_2O (1 : 1) resulted in the cleavage of the Z group and the oxazolidinone ring. Boc protection of the free amines afforded the biologically active dipeptide mimetic **13**. Differentially protected dipeptide mimic **14** was prepared by protection of oxazolidinone **12** with Boc_2O and Et_3N in the presence of a catalytic amount of DMAP in THF followed by selective cleavage of the oxazolidinone ring by treatment with Cs_2CO_3 in Pr^iOH–MeOH (6 : 1) at 23 °C for 6 h.[12] Consistent with the previous report, dipeptide mimic **11** with (4*R*)-hydroxy configuration has shown enzyme inhibitory potency (IC_{50} value) greater than 2 mM in the assay protocol developed by Toth and Marshall.[13, 14] Inversion of the C-4 hydroxy configuration of **10** resulted in derivatives **13** and **14** with inhibitory potencies of 118 nM and 75 nM respectively. Dipeptide isostere **14** has been previously converted to ritonavir and its derivatives.[2a]

In conclusion, we have developed an enantioselective synthesis of the core unit of ritonavir by utilizing Sharpless' catalytic asymmetric dihydroxylation reaction as the key step. The present route provides access to a diverse array of protease inhibitors containing designed functionalities. Synthesis and biological evaluation of novel protease inhibitors are currently in progress.

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