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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-

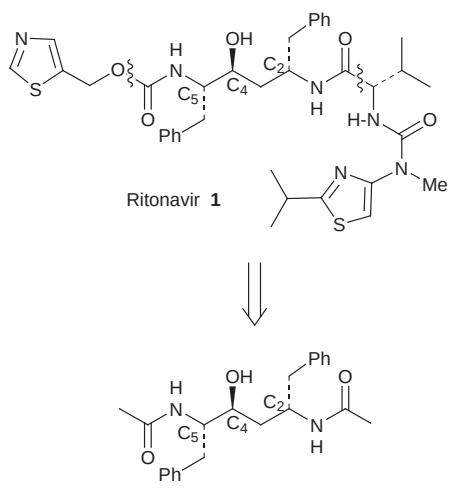
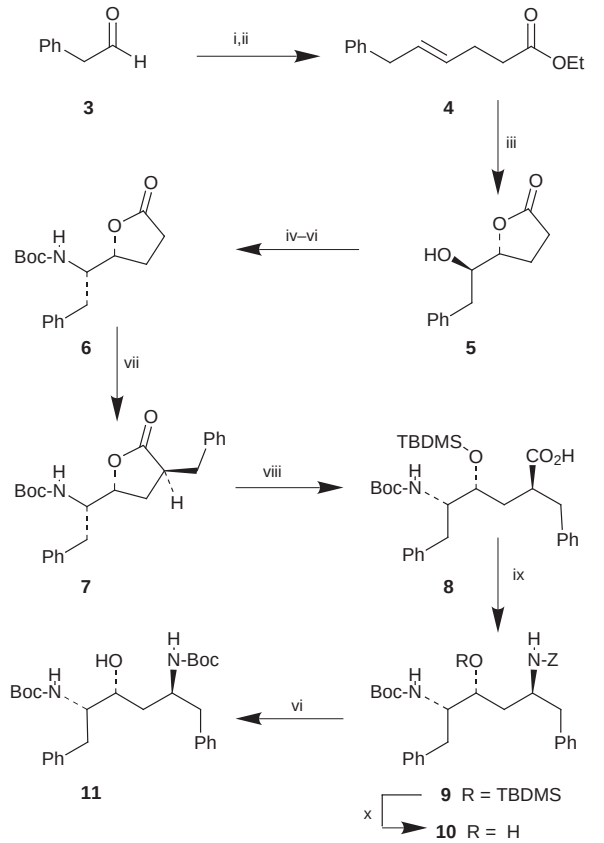
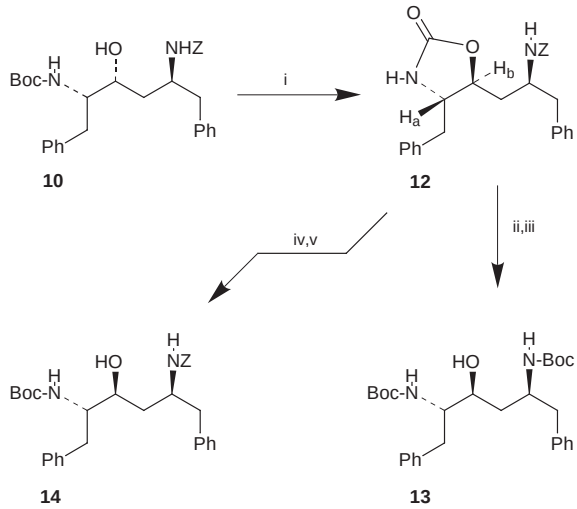



**Fig. 1** Dipeptide mimetic of ritonavir **1**




**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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14 In-house prepared saquinavir [ref. 2(*c*)] exhibited an $IC_{50}$ value of 1.6 nM in the same assay.

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