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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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Abstract

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 substituents.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 MeSO₂NH₂ in a mixture (1:1) of Bu^tOH and H₂O 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 [$[\alpha]_D^{25}$ – 58, (*c* 1.81, CHCl₃)]. 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 Et₃N in the presence of a catalytic amount of DMAP; (2) displacement of the mesylate with NaN₃ in DMF at 90 °C and (3) catalytic hydrogenation of the resulting azide over 10% Pd/C in EtOAc in the presence of Boc₂O (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 278 °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)₂PON₃ and Et₃N in refluxing toluene followed by addition of BnOH as described previously provided the Z-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 Boc₂O and Et₃N 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 SOCl₂ 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–H₂O (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 Boc₂O and Et₃N in the presence of a catalytic amount of DMAP in THF followed by selective cleavage of the oxazolidinone ring by treatment with Cs₂CO₃ in PrⁱOH–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 (IC₅₀ 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. Financial support of this project was provided by the National Institutes of Health (GM 53386). We thank Ms Hanna Cho for the protease inhibition assay.

Notes and references

1. Thaisrivongs S, *Annu. Rep. Med. Chem.*, 1994, 29, 133; Darke PL and Huff JR, *Advances in Pharmacology*, ed. August JT, Anders M and Murad F, Academic Press, San Diego, 1994, 25, 399 and references cited therein. [PubMed: 8204507]
2. (a) Kempf DJ, Marsh KC, Denissen JF, McDonald E, Vasavononda S, Flentge CA, Green BG, Fino L, Park CH, Kong X-P, Ideburg NE, Saldivar A, Ruiz L, Kati M, Sham HL, Robins T, Ste,art KD, Hsu A, Plattner JJ, Leonard J and Norbeck D, *Proc. Natl. Acad. Sci. U.S.A.*, 1995, 92, 2484; [PubMed: 7708670] (b) Vacca JP, Dorsey BD, Schleif A, Levin RB, McDaniel SL, Darke PL, Zugay J, Quintero JC, Blahy OM, Roth E, Sardana VV, Schlabach AJ, Graham PI, Condra JH, Gotlib L, Holloay MK, Lin J, Chen I-, Vastag K, Ostovic D, Anderson PS, Emini EA and Huff JR, *Proc. Natl. Acad. Sci. U.S.A.*, 1994, 91, 4096; [PubMed: 8171040] (c) Roberts NA, Martin JA, Kinchington D, Broadhurst AV, Craig JC, Duncan IB, Galpin SA, Handa BK, Kay J, Krohn A, Lambert R, Merrett JH, Mills JS, Parkes KEB, Redsha, S, Ritchie AJ, Taylor DL, Thomas GJ and Machin PJ, *Science*, 1990, 248, 358 and references cited therein. [PubMed: 2183354]

3. Stein DS, Fish DG, Bilello JA, Preston SL, Martineau GL and Drusano GL, AIDS, 1996, 10, 485; [PubMed: 8724039] Schapiro JM, inters MA, Ste,art F, Efron B, Norris J, Kozal MJ and Merigan TC, Ann. Intern. Med, 1996, 124, 1039 and references cited therein. [PubMed: 8633817]
4. Erickson J, and Fesik S., *Annu. Rep. Med. Chem.*, 1992, 26, 271 and references cited therein.
5. (a) Ghosh AK, McKee SP, Thompson ,J, Darke PL and Zugay JC, J. Org. Chem, 1993, 58, 1025; [PubMed: 30310240] (b)Stuk TL, Haight AR, Scarpetti D, Allen MS, Menzia JA, Robbin TA, Parekh SI, Langridge DC, Tien J-H, Pariza RJ and Kerdesky FAJ, J. Org. Chem, 1994, 59, 4040.
6. Trust RI and Ireland RE, Org. Synth, 1988, Coll. Vol. 6, 606.
7. ,ang Z-M, Zhang X-L, Sharpless KB, Sinha SC, Sinha-Bagchi A and Keinan E, Tetrahedron Lett, 1992, 33, 6407;Sharpless KB, Amberg ., Bennani YL, Crispino GA, Hartung J, Jeong KS, K,ong H-L, Morika,a K, ,ang Z-M, Xu D and Zhang X-L, J. Org. Chem, 1992, 57, 2768.
8. Ghosh AK and Fidanze S, J. Org. Chem, 1998, 63, 6146; [PubMed: 11672244] Fray AH, Kaye RL and Kleinman EF, J. Org. Chem, 1986, 51, 4828 and references therein.
9. Shioiri T, Ninomiya K and Yamada S, J. Am. Chem. Soc, 1972, 94, 6203 [PubMed: 5054412] Grune,ald GL and Ye Q, J. Org. Chem, 1988, 53, 4021Ghosh AK and Liu ., J. Org. Chem, 1996, 61, 6175. [PubMed: 11667452]
10. Rich DH, Sun C-Q, Prasad JVN, Pathiasseril A, Toth MV, Marshall GR, Clare M, Mueller RA and Houseman K, J. Med. Chem, 1991, 34, 1225. [PubMed: 2002465]
11. Kempf DJ, Norbeck D., Codacovi L, ,ang XC, Kohlbrenner ,E, ,ideburg NE, Paul DA, Knigge MF, Vasavanonoda S, Craig-Kennard A, Saldivar A, Rosenbrook ., Jr, Clement JJ, Plattner JJ and Erickson J, J. Med. Chem, 1990, 33, 2687; [PubMed: 2213822] Ghosh AK, McKee SP and Thompson ,J, Tetrahedron Lett, 1991, 32, 5729. [PubMed: 30310242]
12. Ishizuka T and Kunieda T, *Tetrahedron Lett.*, 1987, 28, 4185Matsunaga H, Ishizuka T and Kunieda T, Tetrahedron, 1997, 53, 1275.
13. Toth MV and Marshall GR, *Int. J. Pept. Protein Res.* 1990, 36, 544. [PubMed: 2090647]
14. In-house prepared saquinavir [ref. 2(c)] exhibited an IC50 value of 1.6 nM in the same assay.

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

Scheme 1.

Reagents and conditions: i, $\text{CH}_2\text{NCHMgBr}$, Et_2O , 0°C , 57%; (ii) MeC(OEt)_3 , $\text{MeCH}_2\text{CO}_2\text{H}$ (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 , 278°C , 70%; viii, aq. LiOH , DME , 23°C , H_3O^+ , then imidazole, TBDMSCl , DMF , 23°C , quant. ix, $(\text{PhO})_2\text{PON}_3$, 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–H₂O (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%.