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A short approach to the synthesis of the ritonavir and lopinavir core and its C-3 epimer via cross metathesis

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ABSTRACT

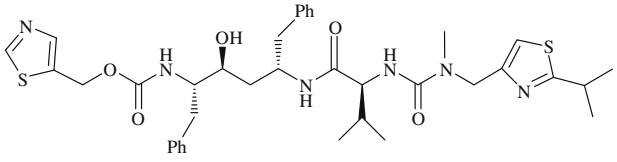
A short synthesis of hydroxyethylene dipeptide isostere, a core unit of the HIV-protease inhibitors ritonavir and lopinavir, its C-3 epimer and C_2 symmetric diamino diol is described. The crucial aspects of the synthesis are self-cross metathesis and exploitation of C_2-symmetric of the metathesis product **8** to obtain the required skeleton.

1. Introduction

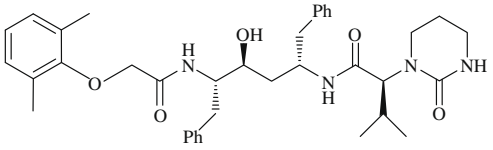
AIDS, a degenerative disease of the immune system, is one of the most challenging problems in medicine. Aspartyl protease plays a vital role not only in HIV but also in the development and propagation of several disease states.[1] The human immunodeficiency virus protease (HIV-PR) is an essential enzyme for the replication of the virus responsible for AIDS.

A number of peptidomimetic protease inhibitors in combination with reverse transcriptase inhibitors have now been approved for the treatment of AIDS.[2,3] Ritonavir **1**[4] and lopinavir **2**[4] (Fig. 1) are the protease inhibitors, which are selective, potent and clinically effective.[2a] Therefore several approaches have been developed for the synthesis of the core unit.[4] Both ritonavir **1** and lopinavir **2** consist of the unique dipeptide mimic **3** (Fig. 2) evolved from the structure-based design strategies.[5] The utility of dipeptide isosteres in the design and synthesis of potent and selective HIV protease inhibitors has been well documented.[6]

Incorporation of C_2 symmetry has become a useful paradigm in the design of active site inhibitors for HIV-1 protease (HIV PR) and has led to the design of a series of highly potent, C_2 symmetry-based diol containing inhibitors of HIV PR. The symmetric molecule inhibited both the protease activity and the acute HIV-1 infection in vitro, and was at least 10,000-fold more potent against HIV-1 protease than against related enzymes and appeared to be stable to degradative enzymes.[7] All diastereomers of the C_2-symmetric diaminodiol core **5** are active against HIV proteases[8] and the diol **5** is a basic structural motif of Kalanchosine[8b] which is an anti-inflammatory agent. Therefore several synthetic approaches have been developed to make this core unit. Due to the importance of this molecule, our interest in this area[4a] and the metathesis reaction,[9] we herein report a short and efficient synthesis of the ritonavir and lopinavir isostere and diamino diol compound **5** utilizing the self cross metathesis[10] as the key step.



Ritonavir **1**



Lopinavir **2**

Figure 1.

2. Results and discussion

As illustrated in Scheme 1, our synthesis started from commercially readily available L-phenyl alanine. L-Phenyl alanine was converted to its corresponding Boc-amino alcohol **6** easily using standard procedures. Alcohol **6** was subjected to Swern oxidation conditions using $(COCl)_2$, DMSO in CH_2Cl_2 to give the aldehyde, which was taken as such to the next step without purification. The one carbon extension of aldehyde to olefin compound **7** was unsuccessful under standard Wittig protocols. Finally olefin **7** was obtained using Takai–Nozaki[11] olefination conditions in 55% overall yield (for two steps). The key cross metathesis reaction of olefin **7** using Grubbs' second generation olefin metathesis catalyst

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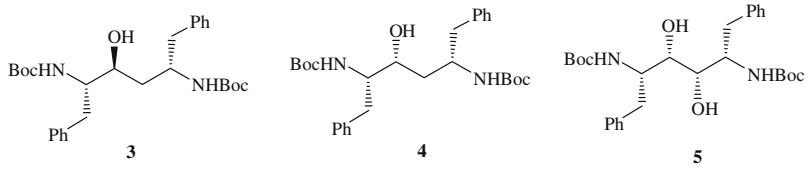
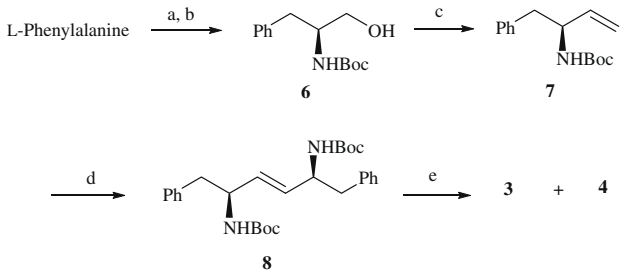


Figure 2.



Scheme 1. Reagents and conditions: (a) (i) AcCl, MeOH, reflux, 3 h; (ii) $(Boc)_2O$, TEA, THF, rt, 7 h (95% for two steps); (b) LiCl, $NaBH_4$, EtOH, THF, rt, 16 h 82%; (c) (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 2 h then TEA; (ii) Zn, CH_2I_2, Ti $(O^iPr)_4$, THF, rt, 1 h, 55% (for two steps); (d) 10 mol % Grubbs' second generation catalyst, CH_2Cl_2, 40 °C, 14 h, 87%; (e) BH_3–SMe_2, H_2O_2, NaOH, THF, 0 °C to rt, 8 h, 70%.

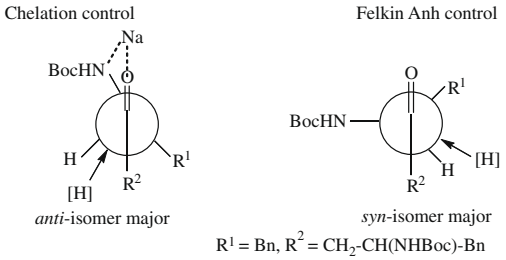
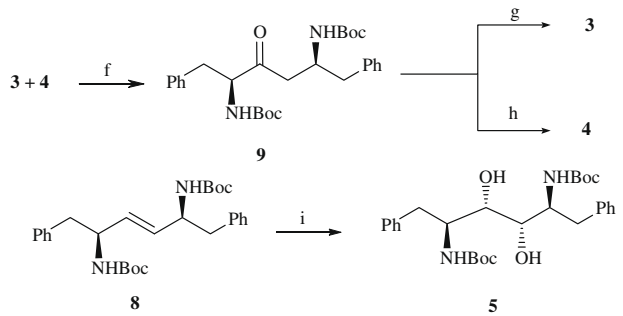


Figure 3.

(10 mol %) afforded C_2-symmetric dimer **8**[4i] as the *E*-isomer exclusively, whereas a first generation Grubbs' catalyst failed to give the product in our hand.[12] Although alkene **8** was synthesized by Gurjar et al. using Julia olefination, it involves more steps using reagents such as *n*-butyllithium, Na/Hg amalgam and Na in liquid ammonia, which resulted in low yields of the product. Therefore their approach has limitation to large scale synthesis. Hydroboration of olefin **8** with $BH_3{\cdot}SMe_2$ in THF gave the required alcohols **3** and **4** in a 3.8:1 ratio as a separable mixture; its spectroscopic data are in good agreement with the reported values.[4l]

In order to obtain good diastereoselectivity in the formation of **3** and **4**, an oxidation and reduction protocol was applied to the mixture of **3** and **4** (Scheme 2). Dess–Martin periodinane oxidation of the secondary alcohol function of **3** and **4** in CH_2Cl_2 led to ketone **9**. Reduction of the **9** with $NaBH_4$ in MeOH gave *anti*-alcohol **4** as the major isomer in a 9:1 ratio. The formation of the major *trans*-isomer can be explained by a chelation control model consistent with Hoffman's explanation of the reduction of α-amino ketone[16] (Fig. 3). Reduction with $ZnBH_4$ in THF afforded the *syn*-alcohol **3** as the major isomer in an 8:2 ratio, which can be explained by a Felkin Anh model[16] (Fig. 3). To obtain the C_2 symmetric diol, we subjected olefin **8** to dihydroxylation[4i] under Sharpless asymmetric conditions[13] with an AD Mix-β in *t*-BuOH/H_2O (1:1) to afford the *anti*-diol



Scheme 2. Reagents and conditions: (f) Dess–Martin periodinane, CH_2Cl_2, 0 °C to rt, 3 h, 80%; (g) $ZnBH_4$, THF, 0 °C to rt, 5 h, 75%; (h) $NaBH_4$, MeOH, 0 °C to rt, 3 h, 80%; (i) AD mix-β, H_2O/*t*-BuOH (1:1) 0 °C, 12 h, 85%.

5 exclusively; its spectroscopic data were in good agreement with the reported values.[14] Compounds **3** and **5** were selectively converted to ritonavir and lopinavir and other derivatives using reported procedures.[4k,n,14b]

3. Conclusions

In conclusion, we demonstrated a short synthesis of phe-phe hydroxyethylene isostere **3**, a core unit of ritonavir and lopinavir, its C-3 epimer **4** and diol **5** from C_2 symmetric dimer **8,** which was obtained from a single monomer using self-metathesis, hydroboration and sharpless asymmetric dihydroxylation.

4. Experimental section

TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^1H NMR and ^{13}C NMR spectra were recorded using Varian Gemini-200 MHz or Bruker Avance-300 MHz spectrometer. ^1H NMR data are expressed as chemical shifts in ppm followed by multiplicity (s-singlet; d- doublet; t- triplet; q- quartet and m- multiplet), number of proton(s) and coupling constant(s) *J* (Hz). ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA).

4.1. (*S*)-*tert*-Butyl 1-phenylbut-3-en-2-yl carbamate 7

To a stirred solution of oxalyl chloride (0.7 mL, 8.0 mmol) in dry CH_2Cl_2 (5 mL) under nitrogen atmosphere, was added DMSO (1.13 mL, 16 mmol) slowly at −78 °C and stirred for 30 min at −78 °C. Alcohol **6** (1.0 g, 3.9 mmol) in dry CH_2Cl_2 (10 mL) was added slowly over 10 min and stirred further for 2 h after which Et_3N (3.35 mL, 24.0 mmol) was added. The temperature was slowly raised to room temperature over 20 min and the reaction mixture was diluted with CH_2Cl_2 (50 mL). The organic layer was washed with brine and water, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator to give the aldehyde,

which was used as such for the next reaction without any purification.

To the stirred suspension of Zn (2.4 g, 36.10 mmol) in freshly dried THF was added CH_2I_2 (1.61 mL, 20.0 mmol) at 25 °C. After 30 min of stirring, Ti (O^iPr)$_4$ (4.0 mL, 4.0 mmol, 1 M solution in THF) was added and the resulting mixture was stirred at 25 °C for 30 mins. A solution of aldehyde (1.0 g, 4.0 mmol) in THF (10 mL) was added dropwise after being stirred for 1 h and the reaction mixture was diluted with ether (20 mL), washed with 1 M HCl (2 × 20 mL), $NaHCO_3$ (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate, 4:1) to afford compound **7** (0.48 g, 55% for two steps) as a white solid. Mp: 71–73 °C; $[\alpha]_D^{25} = +13.8$ (*c* 0.5, $CHCl_3$), {lit[15] $[\alpha]_D^{25} = 15.0$ (*c* 0.6, $CHCl_3$)}; IR ν_{max} 3339, 3025, 2978, 1682, 1527, 1358, 1169, 1018, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ .4 (s, 9H), 2.82 (m, 2H), 4.38 (br s, 2H), 5.08 (dd, *J* = 11.7, 17.3 Hz, 2H), 5.77 (m, 1H), 7.11–7.29 (m, 5H); ^{13}C NMR (50 MHz) in $CDCl_3$: δ 155.1, 137.9, 137.3, 129.4, 128.3, 126.3, 114.6, 79.2, 53.4, 41.3, 28.2; ESIMS: 248 (M^++H).

4.2. *tert*-Butyl (2*S*,5*S*,*E*)-1,6-diphenylhex-3-ene-2,5-diyl dicarbamate 8

Olefin **7** (0.65 g, 2.63 mmol) was dissolved in dry CH_2Cl_2 (10 mL). Grubbs' second generation catalyst (0.22 g, 0.26 mmol) was added. The reaction mixture was stirred at 40 °C for 14 h, then concentrated under reduced pressure and the residue was purified by column chromatography using ethyl acetate: petroleum ether (3:7) to afford the compound **8** (0.21 g, 87%) as a white solid. Mp: 132–136 °C; $[\alpha]_D^{25} = -12.3$ (*c* 1.2, $CHCl_3$); I.R ν_{max} 3371, 3027, 2978, 1689, 1526, 1251, 1170, 700; ^{1}H NMR ($CDCl_3$, 200 MHz) δ .4 (s, 18H), 2.76 (m, 4H), 4.31 (br s, 4H), 5.41 (br s, 2H), 7.0–7.28 (m, 10H); ^{13}C NMR (75 MHz) in $CDCl_3$: δ 155, 137.3, 130.7, 129.6, 128.3, 126.4, 79.4, 52.7, 41.6, 28.3; ESIMS: 489 (M^++Na); HRMS: calcd for $C_{28}H_{38}N_2O_4$ $[M+Na]^+$ 489.2729, found 489.2739.

4.3. *tert*-Butyl (2*S*,3*S*,5*S*)-3-hydroxy-1,6-diphenylhexane-2,5-diyl dicarbamate 3 and *tert*-butyl (2*S*,3*R*,5*S*)-3-hydroxy-1,6-diphenylhexane-2,5-diyl dicarbamate 4

To the solution of **8** (0.2 g, 0.42 mmol) in THF (5 ml), $BH_3.Me_2S$ (0.1 ml, 0.51 mmol) was added dropwise at −10 °C. Stirring was continued for 8 h at room temperature. The reaction was quenched by the addition of 10% NaOH (1 mL) followed by 30% H_2O_2 (2 mL) at 0 °C and then the reaction mixture was allowed to return to room temperature, and stirring was continued for another 2 h. The reaction mixture was extracted with ethyl acetate (2 × 50 mL) and water (50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/petroleum ether (1:3) to afford compound **3** (0.12 g, 50%) as a white solid. Further elution with ethyl acetate/petroleum ether (1:3) afforded compound **4** (0.035 g, 20%) as a white solid. *Compound* **3**: Mp: 192–196 °C; $[\alpha]_D^{25} = -14.25$ (*c* 1, $CHCl_3$). IR (KBr); ν_{max} 3369, 2977, 1688, 1528, 1170, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.3–1.4 (s, 18H), 1.55–1.65 (m, 2H), 2.6–2.9 (m, 4H), 3.6–3.7 (m, 2H), 3.85 (m, 1H), 4.5 (br s, 1H), 4.8 (d, 1H). 7.05–7.4 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.35, 38.5, 39.76, 41.62, 50.12, 56.0, 69.97, 79.26, 79.6, 126.24, 126.44, 128.41, 129.34, 129.41, 137.58, 138.54, 155.93, 156.14; ESIMS: 485$[M+1]^+$; HRMS: calcd for $C_{28}H_{40}N_2O_5$ $[M+Na]^+$ 507.2834, found 507.2838. *Compound* **4**: Mp: 156–160 °C; $[\alpha]_D^{25} = -11.2$ (*c* 0.5, $CHCl_3$); IR (KBr): ν_{max} 3309, 2976, 2930, 1665, 1535, 1275, 1168, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 9H), 1.39 (s, 9H), 1.62 (m, 2H), 2.72–2.93 (m, 4H), 3.47 (m, 1H), 3.76 (m, 1H), 4.11 (m, 1H), 4.3 (br s, OH), 4.4 (d, *J* = 8.6 Hz, 1H), 4.55 (d, *J* = 9.45 Hz, 1H). 7.1–7.4 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.26, 35.44, 39.67, 41.4, 47.94, 55.11, 69.24, 79.0, 79.95, 126.0, 126.56, 128.25, 128.51, 129.19, 129.51, 137.34, 138.12, 155.63, 157.1; ESIMS: 485 $[M+1]^+$; HRMS: calcd for $C_{28}H_{40}N_2O_5$ $[M+Na]^+$ 507.2834, found 507.2845.

4.4. *tert*-Butyl (2*S*,5*S*)-3-oxo-1,6-diphenylhexane-2,5-diyl dicarbamate 9

To the stirred solution of alcohol mixtures **3** and **4** (0.2 g, 0.41 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Dess–Martin periodinane (0.26 g, 0.61 mmol) and stirred for 3 h. The reaction mixture was diluted with ether (20 mL) followed by washing with saturated $NaHCO_3$ solution (2 × 25 mL) and brine (2 × 25 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/petroleum ether (2:8) to afford the keto compound **9** (0.16 g, 80%) as a white solid. Mp: 145–148 °C; $[\alpha]_D^{25} = +15.5$ (*c* 2.0, $CHCl_3$); IR (KBr): ν_{max} 3370, 3028, 2980, 1687, 1517, 1251, 1170, 700; ^{1}H NMR (300 MHz, $CDCl_3$): δ .4 (s, 18H), 2.45–3.0 (m, 6H), 4.05 (m, 1H), 5.03 (d, 1H), 7.05–7.28 (m, 10H); ESIMS: 505 $[M+Na]^+$; HRMS: calcd for $C_{28}H_{38}N_2O_5$ $[M+Na]^+$ 505.2678, found 505.2671.

4.5. Reduction with $ZnBH_4$

4.5.1. *tert*-Butyl (2*S*,3*S*,5*S*)-3-hydroxy-1,6-diphenylhexane-2,5-diyldicarbamate 3

To a stirred suspension of $NaBH_4$ (0.018 g, 0.4 mmol) in dry THF (15 mL) was added anhydrous $ZnCl_2$ (0.035 g, 0.24 mmol) solution in THF (3 mL) at 0 °C and stirred overnight. The solid in the reaction mixture was allowed to settle for 4 h and the clear solution was used for the reaction.

To a stirred solution of ketone **9** (0.1 g, 0.20 mmol) in dry THF (2 mL) was added the above prepared $Zn(BH_4)_2$ (3 mL, mmol) solution at 0 °C and stirred for 5 h after which the reaction was quenched with saturated solution of NH_4Cl (2 mL). Next, THF was removed under vacuum and the residue was extracted with ethyl acetate (2 × 10 mL). The organic portion was separated, dried over anhydrous Na_2SO_4 and concentrated. Silica gel column purification (hexane/ethyl acetate 4:1) of the residue gave the *syn* alcohol **3** (50 mg, 60%) as the major isomer and the *anti*-isomer **4** (12 mg, 15%) in an 8:2 ratio as a white solid.

4.6. Reduction with $NaBH_4$

4.6.1. *tert*-Butyl (2*S*,3*R*,5*S*)-3-hydroxy-1,6-diphenylhexane-2,5-diyldicarbamate 4

To a stirred solution of ketone **9** (0.1 g, 0.41 mmol) in dry MeOH (2 mL) was added $NaBH_4$ at 0 °C and stirred for 3 h. Next, MeOH was removed under vacuum and the residue was treated with saturated aqueous solution of NH_4Cl (2 mL) and extracted with ethyl acetate (2 × 10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated. Silica gel column purification (hexane/ethyl acetate 3:1) of the residue gave the *anti*-alcohol **4** (65 mg, 72%) as the major isomer and the *syn*-isomer (7 mg, 10%) as a solid in a 9:1 ratio.

4.6.2. *tert*-Butyl (2*S*,3*S*,4*S*,5*S*)-3,4-dihydroxy-1,6-diphenylhexane-2,5-diyl dicarbamate 5

To a stirred solution of compound **8** (0.1 g, 1.63 mmol) in a 1:1 mixture of ^{t}BuOH and water (5 mL) was added Ad-mix-β (0.3 g) at 0 °C and stirred for 12 h. After completion of the reaction Na_2SO_3 (0.5 g) was added to the reaction mixture and extracted into ethyl acetate (2 × 10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and the solvent was concentrated under re-

duced pressure. The crude product was purified by column chromatography using ethyl acetate/petroleum ether (2:8) to afford diol compound **5** (0.70 g, 85%) as a white solid. Mp: 181–185 °C. $[\alpha]_D^{25} = -12.2$ (*c* 0.5, $CHCl_3$) {lit[14b] $[\alpha]_D^{25} = -13.4$ (*c* 1.0, CH_2Cl_2}; IR (KBr): ν_{max} 3345, 2977, 1661, 1537, 1275, 1168, 1020; ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 18H), 2.96 (dd, J = 4.5, 13.97 Hz, 2H), 3.15–3.25 (m, 4H), 4.03 (m, 2H), 4.39 (m, 4H), 7.15–7.3 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 36.24, 50.68, 70.09, 80.22, 126.49, 128.58, 129.81, 137.0, 156.94; ESIMS: 523$[M+Na]^+$; HRMS: calcd for $C_{28}H_{40}N_2O_6$ $[M+Na]^+$ 523.2784, found 523.2794.

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