Asymmetric Aldol Route to Hydroxyethylamine Isostere: Stereoselective Synthesis of the Core Unit of Saquinavir

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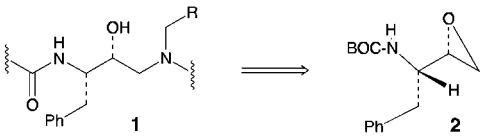
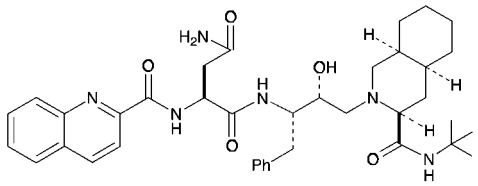
Hydroxyethylamine isosteres have been extensively utilized in the synthesis of potent and selective HIV protease inhibitors[1] including saquinavir,[2] a protease inhibitor recently approved by the U.S. Food and Drug Administration for the treatment of AIDS.[3] These dipeptide mimics are typically prepared by opening the corresponding protected aminoalkyl epoxides with amines. In connection with our study aimed at the design and synthesis of novel protease inhibitors, we required an enantioselective and efficient synthesis of a number of protected aminoalkyl epoxides that are not limited to amino acid derived substituents.[4] We describe here a convenient route to the versatile (1′*S*,2*S*)-(1′-((*tert*-butyloxycarbonyl)amino)-2-phenylethyl)oxirane (**2**) utilizing an asymmetric syn-aldol reaction and Curtius rearrangement sequence. The epoxide **2** was converted to the core unit of saquinavir[5] and other protease inhibitors.[1,2] The present synthesis is easily adaptable to a range of other dipeptide isosteres with a variety of designed side chain substituents.





3 Saquinavir

We planned to insert both of the asymmetric centers in hydroxyethylamine isostere **1** by Evans' asymmetric syn-aldol process.[6] The requisite chiral oxazolidinone **5** was prepared from hydrocinnamic acid and commercially available[7] (4*S*,5*R*)-indano[1,2-*d*]oxazolidin-2-one by standard protocol. Aldol reaction of the boron enolate of **5** with (benzyloxy)acetaldehyde in CH_2Cl_2 at −78 °C provided the syn-aldol product **6** as a single diastereomer in 88% yield after silica gel chromatography. Aldol reaction of (*S*)-(−)-benzyl-2-oxazolidinone-derived carboximide also provided comparable yield (83%) of syn-aldol product. The removal of the chiral auxiliary was effected by exposure to lithium hydroperoxide in aqueous THF at 0 °C for 1 h.[8] To incorporate the amine functionality, the resulting β-hydroxy acid was then subjected to Curtius rearrangement[9] with diphenylphosphoryl azide and triethylamine in refluxing benzene to provide the oxazolidinone **7** in 69% yield after chromatography. The oxazolidinone ring stereochemistry was assigned on the basis of the precedence that the Curtius rearrangement proceeds with retention of configuration of the migrating carbon atom. Indeed, the observed ^{1}H-NMR (400 MHz) coupling constant of vicinal protons ($J_{AB} = 8$ Hz) is consistent with a syn-stereochemical relationship.[10] Basic hydrolysis of oxazolidinone **7** with aqueous KOH at 70 °C afforded the corresponding syn-amino alcohol which was treated with di-*tert*-butyl dicarbonate in CH_2Cl_2 at 23 °C to furnish the BOC derivative **8** in 87% isolated yield (Scheme 1).

For conversion of **8** to the aminoalkyl epoxide **2**, the benzyl group was deprotected by catalytic hydrogenation of **8** over Pearlman's catalyst in ethyl acetate for 12 h. The resulting diol was efficiently converted to epoxide **2** in the following two-step sequence: (1) treatment of the diol with commercially available 1-(chlorocarbonyl)-1-methylethyl acetate in dry chloroform at 23 °C; (2) exposure of the corresponding chloroacetate derivative to an excess of NaOMe in THF for 4 h to provide the

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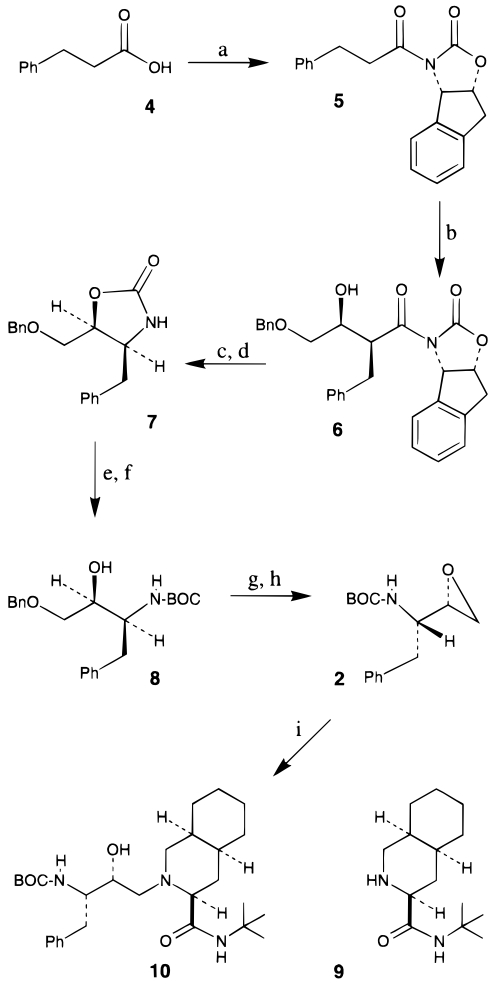
Scheme 1[a]



[a] Key: (a) Me_3CCOCl, Et_3N, THF, −15 to 0 °C, then *N*-lithio-(4*S*,5*R*)-indano[1,2-*d*]oxazolidin-2-one, −78 °C; (b) Bu_2BOTf, $(^iPr)_2NEt$, CH_2Cl_2, 0 °C, then $BnOCH_2CHO$, −78 to 23 °C; (c) LiOOH, THF:H_2O (1:1), 0 °C; (d) $(PhO)_2P(O)N_3$, Et_3N, PhH, 80 °C; (e) aqueous KOH, EtOH, 70 °C; (f) BOC_2O, CH_2Cl_2, 23 °C; (g) H_2, $Pd(OH)_2$, EtOAc; (h) $AcOC(Me)_2COCl$, $CHCl_3$, 23 °C, then NaOMe, THF, 0 to 23 °C; (i) amine **9**, ^iPrOH, 70 °C.

epoxide **2** in 56% yield (from **8**) after silica gel chromatography.[11] The epoxide **2** is the key intermediate for the synthesis of hydroxyethylene[12] and hydroxyethylamine isosteres.[1,2] For example, reaction of epoxide **2** with decahydroisoquinoline derivative **9** in 2-propanol at reflux furnished the hydroxyethylamine isostere **10** in 75% yield after chromatography. The peptide isostere **10** has been previously converted to saquinavir[5] and other potent inhibitors.[1,2]

In summary, we have developed a stereocontrolled route to aminoalkyl epoxide, an important intermediate for the synthesis of HIV protease inhibitors. The stereochemistry of both stereogenic centers was assembled unequivocally by asymmetric syn-aldol reaction. The present method should provide an enantioselective entry to other useful dipeptide isosteres that are not limited to amino acid derived side chain substituents. Application of this method in the synthesis of novel protease inhibitors is in progress.

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Experimental Section

All melting points are uncorrected. Analytical HPLC analyses were performed on a μBondapak C-18 column, 4.6 mm × 25 cm, 40% CH_3CN/H_2O as solvent, flow rate 2.0 mL/min. Anhydrous solvents were obtained as follows: methylene chloride, distillation from P_4O_{10}; tetrahydrofuran, distillation from sodium/benzophenone; pyridine, distillation from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240−400 mesh silica gel under a low pressure of 5−10 psi. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates.

***N*-(3-Phenylpropionyl)-(4*S*,5*R*)-indano[1,2-*d*]oxazolidin-2-one (5).** To a stirred solution of hydrocinnamic acid (**4**) (1 g, 6.65 mmol) in THF (15 mL) at −20 °C was added Me_3CCOCl (0.9 mL, 7.73 mmol) dropwise over a period of 5 min. After 10 min, Et_3N (1.2 mL, 8.64 mmol) was added and the resulting mixture was allowed to warm to −10 °C for 1 h. In a separate flask, commercial (4*S*,5*R*)-indano[1,2-*d*]oxazolidin-2-one (1.28 g, 7.31 mmol, Aldrich) was dissolved in dry THF (15 mL), the resulting solution was cooled to −78 °C, and to this solution was added n-BuLi in hexanes (2.5 M solution, 2.9 mL) over a period of 10 min. The cold solution was taken up in a syringe and added to the mixed anhydride prepared above. After the mixture was stirred for 30 min at −78 °C, the reaction was quenched with aqueous sodium bisulfate (1 N, 10 mL). The mixture was then concentrated under reduced pressure, and the residue was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with aqueous $NaHCO_3$ solution and then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% EtOAc/hexanes) to afford **5** (1.62 g, 79%) as a white solid (mp 168−170 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ, 7.57 (d, 1H, J = 7.2 Hz), 7.28 (m, 8H), 5.93 (d, 1H, J = 7 Hz), 5.27 (m, 1H), 3.37 (d, 2H, J = 3.5 Hz), 3.26 (m, 2H), 3.02 (m, 2H); IR (neat) 3050, 2926, 1778, 1698, 1377, 1175, 1120, 1048, 755 cm^{-1}; mass (CI) m/z 308 (M^+ + H). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.57; N, 4.55. Found: C, 73.84; H, 5.53; N, 4.70.

(2*S*,3*S*)-*N*-[(2-Benzyl-4-(benzyloxy)-3-hydroxybutanoyl)-(4*S*,5*R*)-indano[1,2-*d*]oxazolidin-2-one (6). To a stirred solution of **5** (800 mg, 2.6 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added dibutylboron triflate (3.4 mL, 3.38 mmol, Aldrich) followed by ethyldiisopropylamine (0.68 mL, 3.9 mmol). The resulting mixture was stirred at 23 °C for 1 h. The mixture was cooled to −78 °C, and a CH_2Cl_2 solution of (benzyloxy)acetaldehyde (780 mg, 5.2 mmol) was added. The mixture was stirred at −78 °C for 30 min and then warmed to 23 °C for 2 h. After this period, the reaction was quenched with pH 7.4 buffer solution (2.5 mL). The mixture was cooled to 0 °C, MeOH (7 mL) followed by a 2:1 mixture of MeOH and 30% H_2O_2 (6 mL) was added, and the resulting mixture was stirred for an additional 1 h. After this period, the reaction mixture was concentrated under reduced pressure and the residue was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution and brine and then dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was chromatographed over silica gel (35% EtOAc/hexanes) to provide **6** (1.07 g, 88%) as a white solid (mp 82−83 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.02−7.17 (m, 14 H), 5.72 (d, 1H, J = 7 Hz), 4.96 (m, 1H), 4.52 (m, 1H), 4.5 (s, 2H), 4.2 (m, 1H), 3.52 (d, 2H, J = 6.1 Hz), 3.25 (d, 2H, J = 5.2 Hz), 3.1 (d, 2H, J = 8 Hz), 2.63 (d, 1H, J = 4.4 Hz); IR (neat) 3510, 3055, 2921, 2857, 1693, 1361, 1119, 1027, 722 cm^{-1}; mass (CI) m/z 458 (M^+ + H), 440, 350, 176. Anal. Calcd for $C_{28}H_{27}NO_5$: C, 73.50; H, 5.94; N, 3.06. Found: C, 73.82; H, 6.35; N, 3.0.

(4*S*,5*S*)-4-Benzyl-5-((benzyloxy)methyl)oxazolidinone (7). To a stirred mixture of **6** (950 mg, 2.07 mmol) in 50% aqueous THF (4 mL) at 0 °C was added H_2O_2 (30%, 1 mL) followed by $LiOH\cdot H_2O$ (173 mg, 4.14 mmol). The resulting reaction mixture was stirred for 1 h at 0 °C, and the reaction was quenched with an aqueous Na_2SO_3 solution (1.5 M, 5 mL). The mixture was concentrated under reduced pressure, and the residue was diluted with brine and extracted with CH_2Cl_2 (2 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated to obtain 297 mg (82%) of chiral oxazolidinone. The aqueous layer was acidified to pH 1 with aqueous HCl (2 N) and extracted with EtOAc (2 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced

pressure to obtain a residue which was chromatographed over silica gel (65% EtOAc/hexanes) to afford the corresponding acid (465 mg).

The above acid (410 mg, 1.37 mmol) was dissolved in dry benzene (3 mL), and diphenylphosphoryl azide (450 mg, 1.64 mmol) followed by Et_3N (0.25 mL, 1.77 mmol) was added. The resulting mixture was heated at reflux for 4 h. After this period, the reaction was cooled to 23 °C and diluted with EtOAc (6 mL). The mixture was washed with a saturated aqueous $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure, and the residue was chromatographed over silica gel (25% EtOAc/hexanes) to afford **7** (374 mg, 69% from **6**) as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ, 7.02−7.33 (m, 10 H), 5.1 (br s, 1H), 4.84 (q, 1H, J = 6.5), 4.61 (s, 2H), 4.07 (m, 1H), 3.8 (d, 2H, J = 5.9 Hz), 2.95 (dd, 1H, J = 13.3, 3.5 Hz), 2.7 (dd, 1H, J = 13.3, 11.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 157.89, 137.28, 136.65, 129.02, 128.84, 128.47, 127.9, 127.8, 127.1, 76.3, 73.74, 67.15, 55.89, 35.9; IR (neat) 3278, 3065, 2922, 1671, 1385, 1234, 1071 cm^{-1}; mass (CI) m/z 298 (M^+ + H). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.83; H, 6.31; N, 5.12.

(1*S*,2*S*)-1-[*N*-(*tert*-Butyloxycarbonyl)amino]-1-benzyl-3-(benzyloxy)propan-2-ol (8). To a stirred solution of **7** (252 mg, 0.84 mmol) in 50% aqueous EtOH (1 mL) at 23 °C was added solid KOH (190 mg, 3.5 mmol), and the mixture was heated at 70 °C for 3 h. After this period, the mixture was cooled to 23 °C and neutralized to pH 7 with dilute HCl. The mixture was concentrated under reduced pressure, and to the residue were added CH_2Cl_2 (1 mL) and di-*tert*-butyl dicarbonate (368 mg, 1.7 mmol). The resulting mixture was stirred at 23 °C for 2 h. After this period, saturated NH_4Cl solution was added and the mixture was extracted with ethyl acetate (2 × 5 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure. The residue was purified by silica gel chromatography (35% EtOAc/hexanes) to afford **8** (266 mg, 87%) as a white soild (mp 107−109 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ, 7.02−7.28 (m, 10H), 4.73 (d, 1H, J = 7.8 Hz), 4.55 (s, 2H), 3.94 (m, 1H), 3.86 (m, 1H), 3.56 (d, 2H, J = 5.7 Hz), 2.95 (br d, 1H, J = 4.2 Hz), 2.87 (d, 2H, J = 6.3 Hz), 1.35 (s, 9H); IR (neat) 3356, 3045, 2989, 2830, 2790, 1689, 1527, 1366, 1018 cm^{-1}; mass (CI) m/z 372 (M^+ + H), 316, 272. Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.14; H, 7.86; N, 3.77. Found: C, 70.83; H, 8.10; N, 4.03.

2(*S*)-[1′-(*S*)-*N*-((*tert*-Butyloxycarbonyl)amino)-2-phenylethyl]oxirane (2). To a stirred solution of **8** (250 mg, 0.69 mmol) in EtOAc (1.5 mL) was suspended $Pd(OH)_2$ (15 mg), and the mixture was hydrogenated under a balloon filled with hydrogen for 12 h. The reaction mixture was then filtered through a pad of Celite, and the Celite pad was washed with MeOH (2 mL). The filtrate was concentrated under reduced pressure to obtain a residue which was purified by flash chromatography over silica gel (80% EtOAc/hexanes) to provide the diol (180 mg, 96%) as an oil.

To a stirred solution of the above diol (175 mg, 0.64 mmol) in dry chloroform (1 mL) at 0 °C was added 1-(chlorocarbonyl)-1-methylethyl acetate (137 mg, 0.83 mmol). The resulting mixture was stirred at 23 °C for 3 h. After this period, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and the mixture was extracted with EtOAc (2 × 3 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The resulting residue was dissolved in dry THF (2 mL), and the solution was cooled to 0 °C. To this solution was added solid NaOMe (51 mg, 0.64 mmol), and the reaction mixture was stirred for 4 h at 23 °C. The reaction was then quenched with a saturated NH_4Cl solution (3 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed over silica gel (25% EtOAc/hexanes) to afford the title epoxide **2** (94 mg, 56%) as an amorphous solid (mp 123−124 °C); $[\alpha]^{23}_D$ −6.6 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2−7.4 (m, 5H), 4.45 (br s, 1H), 3.68 (m, 1H), 2.9 (dd, 1H, J = 13.7, 3.8 Hz), 2.9 (m, 2H), 2.81 (t, 1H, J = 4.2 Hz), 2.75 (br s, 1H), 1.37 (s, 9H).

***N*-*tert*-Butyl-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-((*tert*-butyloxycarbonyl)amino)butyl]decahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (10).** A mixture of epoxide **2** (85 mg, 0.32 mmol) and decahydroisoquinoline **9** (92 mg, 0.38 mmol) in 2-propanol (2 mL) was heated at reflux for 2 h. The reaction mixture was cooled to 23 °C and then concentrated under reduced pressure. The residue was flash chromatographed over silica gel (35% EtOAc/hexanes) to provide the title hydroxyethylamine isostere **10** (121 mg, 75%) as a semisolid: $[\alpha]^{23}_D$ −58 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 5H), 5.83 (s, 1H), 4.88 (d, 1H, J = 7 Hz), 3.9−3.58 (m, 3H), 3.08 (t, 1H, J = 11 Hz), 2.9 (m, 2H), 2.65 (dd, 1H, J = 14.7, 6.2 Hz), 2.62 (d, 1H, J = 11.7 Hz), 2.26 (m, 2H), 1.94 (q, 1H, J = 11.7 Hz), 1.85−1.2 (m, 11H), 1.3 (s, 18H); mass (CI) m/z 502 (M^+ + H).

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