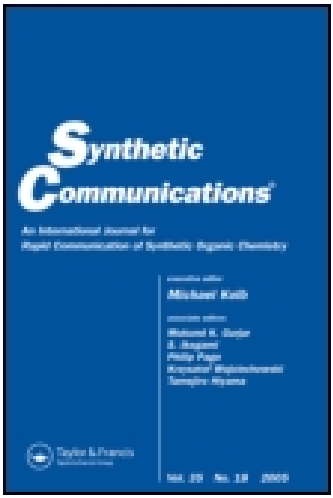

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Facile Synthetic Route to (2S,3S)-3-Amino-2-hydroxy-4-phen Acid and Its Derivatives, the Key Intermediates for HIV Protease Inhibitors

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Facile Synthetic Route to (2*S*,3*S*)-3-Amino-2-hydroxy-4-phenylbutyric Acid and Its Derivatives, the Key Intermediates for HIV Protease Inhibitors

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Abstract: A facile and efficient route to (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutyric acid and its derivative (4*S*,5*S*)-4-benzyl-5-hydroxymethyl oxazolidin-2-one is presented. N-phthaloyl protected L-phenylalanine **1** was treated with thionyl chloride followed by hydrogenation of the acyl chloride **2** on Pd/C, giving (*S*)-2-phthalimido-3-phenylpropionaldehyde **3**. Aldehyde **3** reacted with Nagata's reagent to afford 3-phthalimido-2-hydroxy-4-phenylbutyronitrile **4** as a diastereomeric mixture. After hydrolysis, protection, esterification, and reduction, **4** was transformed into the optically pure compound **7** in good yield.

Keywords: AHPBA, HIV protease inhibitors, Nagata's reagent, N-phthaloyl protecting group

INTRODUCTION

(2*S*,3*S*)-3-Amino-2-hydroxy-4-phenylbutyric acid (AHPBA)[1] and its derivative, (4*S*,5*S*)-4-benzyl-5-hydroxymethyl oxazolidin-2-one, are the chiral building blocks for the synthesis of HIV protease inhibitors such as saquinavir[2] and amprenavir.[3] To date, considerable efforts have been directed

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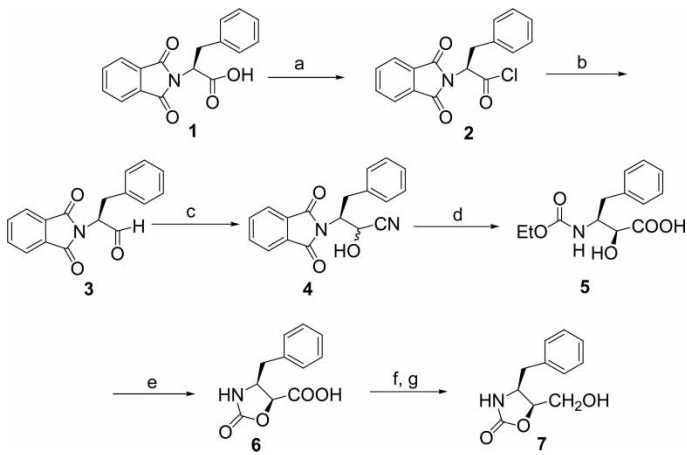
toward the synthesis of stereochemical pure (2*S*,3*S*)-AHPBA methyl ester and its derivatives.[4–9] Kottenhahn et al.[10] first reported a practical synthetic route suitable for the large-scale preparation of AHPBA. However, the synthetic methods described in literature[4,11] all started from the boc or di-benzyl protected 2-amino propionaldehyde, which underwent cyanohydrin reaction, and followed by a sequence of reactions to obtain the target compound **7**. Herein, as part of our research work concerning the synthesis of novel HIV protease inhibitors, we report a facile and efficient synthetic route to (4*S*,5*S*)-4-benzyl-5-hydroxymethyl oxazolidin-2-one (**7**) in good yield and >99% e.e.

RESULTS AND DISCUSSION

Our synthesis started from phthaloyl protected L-phenylalanine **1**, which was treated with thionyl chloride instead of oxalyl chloride,[2] affording (*S*)-phthaloyl phenylalanyl chloride **2**. Aldehyde **3** was obtained in 55% yield by catalytic hydrogenation of acyl chloride **2** on Pd/C (Scheme 1). It was reported that **2** could be also reduced to **3** with lithium tris-(t-butoxy)-aluminium hydride.[12]

With (*S*)-2-phthalimido-3-phenylpropionaldehyde **3** in hand, it was then treated with diethylaluminum cyanide in toluene at −78°C, and the adduct 2-hydroxy-3-phthalimido-4-phenylbutyronitrile **4** was obtained in 80% yield as a (2*S*,3*S*)-**4** and (2*R*,3*S*)-**4** mixture in a ratio of 2.6:1. The crude mixture **4** was used without purification. After hydrolysis of the cyanohydrins **4**, (2*RS*,3*S*)-AHPBA were afforded, which was protected once again with ethyl



Scheme 1. Reagents and conditions: (a) $SOCl_2$, CH_2Cl_2, reflux, 12 h; (b) 10% Pd/C, H_2, 40–50°C, 20 h; (c) Et_2AlCN, toluene, −78°C; (d) i) 25% HCl, reflux, 24 h; ii) 40% NaOH, ClCOOEt, pH = 7–8; (e) 3M NaOH, rt, 4 h; (f) CH_3 OH, H^+, reflux, 4.5 h; (g) $NaBH_4$, CH_3OH.

chloroformate to yield (2*RS*,3*S*)-3-ethoxycarbonylamino-2-hydroxy-4-phenylbutyric acid. The diastereomeric enrichment was achieved by recrystallization of the acids from toluene, giving (2*S*,3*S*)-3-ethoxycarbonylamino-2-hydroxy-4-phenylbutyric acid **5** as a stereochemically pure compound in 54.5% yield in two steps. In comparison with other methods, our approach to AHPBA and its derivatives features phthaloyl used as the protecting group of α-amino aldehyde **3** in cyanidation with Nagata's reagent, and hydrolysis, deprotection, and reprotection of **4** could be processed in one pot; thus, hydroxy acid **5** was obtained via a more convenient route.

(2*S*,3*S*)-3-Ethoxycarbonylamino-2-hydroxy-4-phenylbutyric acid **5** was then treated with 3 M of NaOH for 8 h, affording (4*S*,5*S*)-4-benzyl-2-oxo-oxazolidine-5-carboxylic acid **6** in 68.5% yield. After esterification of **6** and reduction of the resulting ester with $NaBH_4$ in methanol, the target compound (4*S*,5*S*)-4-benzyl-5-hydroxymethyl oxazolidin-2-one **7** was obtained in 74.5% yield and >99% e.e. value. The configuration of compound **7** was established by comparing the coupling constant ($J_{4,5} = 8$ Hz) and IR absorption of carbonyl group (1731 cm^{-1}).[6] To determine the e.e. value of compound **7**, we also prepared the enantiomer of **7**, (4*R*,5*R*)-4-benzyl-5-hydroxymethyl oxazolidin-2-one from (*R*)-phthaloyl phenylalanine via the same approach.

EXPERIMENTAL

General Procedures

Melting points were measured on a Buchi 510 apparatus and are uncorrected. Elemental analyses were performed on a Carlo-Erba 1106 instrument. Infrared spectra were obtained on a Nicolet Magna 750 spectrometer. NMR spectra were measured on Bruker AMX-400 spectrometer with tetramethylsilane as internal standard. Chemical shifts are reported in δ (ppm) and coupling constants in Hz. Specific rotations were measured on a Perkin-Elmer 241 MC. Mass spectra were determined on a Varian MAT-95 mass spectrometer.

(*S*)-Phthaloyl Phenylalanyl Chloride (**2**)

(*S*)-Phthaloyl phenylalanine **1** (5.9 g, 0.02 mol) was dissolved in dichloromethane (60 mL), and thionyl chloride (12 mL) was added to by one portion. The solution was heated under mild reflux for 12 h. After cooling to rt, the solution was concentrated in vacuum to dryness. The crude product was dissolved in dichloromethane (6 mL), and petroleum ether (30 mL) was added to the solution dropwise. The white solid was precipitated. The solid was filtered and washed with petroleum ether (20 mL) and dried in vacuum, giving **2** (5.0 g, 80%) as a white solid. Mp 79–82°C, $[\alpha]_D^{20} = -231$°C (c 1.4, benzene); lit.[13] Mp 82–83°C, $[\alpha]_D^{20} = -200$°C (c1.4, benzene).

(*S*)-2-Phthalimido-3-phenylpropionaldehyde (**3**)

Chloride **2** (1.37 g, 4.36 mmol) was hydrogenated in toluene (40 mL) in the presence of 1,2-butylene oxide (0.95 mL) and Pd/C (10%, 130 mg). The suspension was stirred at 40–50°C for 17 h until absorption of hydrogen was stopped. The mixture was filtered and the filtrate was washed with saturated sodium bicarbonate (2 mL × 3) and water (2 mL × 3). The organic layer was concentrated in vacuum to provide the desired aldehyde **3** as a yellowish solid, which was used without further purification. Recrystallization from dichloromethane/petroleum ether afforded **3** as a white solid (662 mg, 55%). Mp 101–104°C, $[\alpha]_D^{20} = -266°$C (c 0.5, benzene); lit.[13] Mp 110–113°C, $[\alpha]_D^{20} = -207°$C (c 0.5, benzene). ^{1}H NMR ($CDCl_3$): δ 9.8 (s, 1H), 7.10–7.20 (m, 5H), 7.70 (m, 2H), 7.80 (m, 2H), 5.0 (dd, $J = 5.5$, 10.7 Hz, 1H), 3.60 (dd, $J = 5.5$, 14.1 Hz, 2H), 3.30 (dd, $J = 10.7$, 14.1 Hz, 2H); EI-MS m/z (%): 279 (M^+, 8), 251 (100), 91 (56).

2-Hydroxy-3-phthalimido-4-phenylbutyronitrile (**4**)

Aldehyde **3** (280 mg, 1.0 mmol) was dissolved in anhydrous toluene (30 mL) and cooled to −78°C under argon. To the solution was added diethylaluminum cyanide (1.2 mL, 1 M in toluene, 1.2 mmol) dropwise over 10 min. The mixture was stirred at this temperature for 20 h, and then saturated aqueous ammonium chloride (10 mL) was added to quench the reaction. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine and water and dried over anhydrous Na_2SO_4. The solid obtained after removal of the solvent was recrystallized from dichloromethane/petroleum ether, affording **4** as a white solid (245 mg, 80%). After separation with preparative TLC, two diastereomeric isomers (2*S*,3*S*)-**4** and (2*R*,3*S*)-**4** were obtained, respectively. The diastereoselection (2.6:1) of cyanohydrin **4** was measured by ^{1}H NMR.

(2*S*,3*S*)-2-Hydroxy-3-phthalimido-4-phenylbutyronitrile: Mp 133–135°C. ^{1}H NMR ($CDCl_3$): δ 7.10–7.20 (m, 5H), 7.70 (m, 2H), 7.80 (m, 2H), 5.15 (dd, $J = 5.2$, 1.6 Hz, 1H), 4.80 (m, $J = 5.2$, 1.6, 4.0 Hz, 1H), 4.10 (s, 1H), 3.40 (ABXsystem, $J = 4.0$, 1.2 Hz, 2H); EI-MS m/z(%): 306 (M^+, 3), 279 (16), 251 (100), 250 (90), 232 (76), 91 (30); IR (KBr, cm^{-1}): 3494.4, 1774.2, 1390.4, 1365.4, 1107.0, 721.3.

(2*R*,3*S*) hyphen;2-Hydroxy-3-phthalimido -4-phenylbutyronitrile: Mp 155–157°C. ^{1}H NMR ($CDCl_3$): δ 7.10–7.20 (m, 5H), 7.80 (m, 2H), 7.90 (m, 2H), 5.40 (d, $J = 11.2$ Hz, 1H), 4.80 (m, $J = 4.8$, 8.0 Hz, 1H), 4.75 (dd, $J = 4.8$ Hz, 1H), 3.30 (dd, $J = 8.0$, 5.6 Hz, 1H), 3.10 (dd, $J = 8.0$, 5.6 Hz, 1H); EI-MS m/z (%): 306 (M^+, 3), 279 (16), 251 (100), 250 (90), 232 (76), 91 (30); IR(KBr, cm^{-1}): 3349.8, 1770.4, 1697.1, 1402.0, 1375.0, 1110.8, 721.3.

(2*S*,3*S*)-3-Ethoxycarbonylamino-2-hydroxy-4-phenylbutyric Acid (**5**)

Cyanohydrin **4** (2.0 g, 6.54 mmol) was suspended in 25% HCl (30 mL) and the mixture was heated to reflux for 17 h. The reaction mixture was then cooled to 0°C and stirred for 2 h. After filtration, the filtrate was adjusted to pH 7–8 with 40% aqueous solution of NaOH. To the solution was added ethyl chloroformate (0.9 mL, 9.41 mmol) and 40% aqueous solution of NaOH alternately to maintain pH value of the reaction mixture at 7–8. The mixture was stirred at rt for an additional 2 h, then adjusted to pH 1 with concentrated hydrochloric acid. The mixture was extracted with ethyl acetate (30 mL × 3). The organic layer was washed with water and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil and which was crystallized from toluene to afford **5** (0.95 g, 54.5%) as a white crystal. Mp 137–139°C (Lit.[10] Mp 138–140°C), $[\alpha]_D^{20} = -0.5^\circ$ (c 0.56, methanol); ^{1}H NMR (DMSO): δ 7.0–7.3 (m, 5H), 3.6–4.0 (m, 4H,), 2.65 (d, $J = 6.9$ Hz, 2H), 1.0 (t, $J = 7.2$ Hz, 3H); EI-MS m/z (%): 267 (M^+, 8), 222 (10), 192 (100), 176 (80), 120 (68), 91 (100); IR(KBr, cm^{-1}): 307.4, 1737.6, 1687.4, 1552.4, 1274.7, 1049.1, 752.1, 702.0. Anal. calcd. for $C_{13}H_{17}NO_5$: C, 58.40; H, 6.37; N, 5.24. Found: C, 58.52; H, 6.40; N, 5.30.

(4*S*,5*S*)-4-Benzyl-2-oxo-oxazolidine-5-carboxylic Acid (**6**)

Acid **5** (1.2 g, 5.4 mmol) was added in one portion to 0.75 M of NaOH solution (40 mL). After stirring at rt for 9 h, the solution was adjusted to pH 7 with concentrated hydrochloric acid and concentrated in vacuum to about 10 mL. The pH of the residue was further adjusted to 1 with concentrated hydrochloric acid, and the mixture was extracted with CH_2Cl_2 (20 mL × 3). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuum. The residue was dissolved in ethyl acetate, and the product was precipitated by the addition of toluene. After stirring for 2 h, the solid was collected by suction to afford **6** (0.68 g, 68.5%) as a white solid. Mp 174–176°C, $[\alpha]_D^{20} = -110^\circ$C (c 0.48, methanol). Lit.[10] Mp 172–174°C, $[\alpha]_D^{20} = -106.2^\circ$C (c 1.0, methanol). ^{1}H NMR (CD_3COCD_3): δ 7.2–7.4 (m, 5H), 5.2 (d, $J = 8.8$ Hz, 1H), 4.5 (ddd, $J = 3.6$, 8.8, 3.2 Hz, 1H), 3.0 (dd, $J = 3.6$, 10.4 Hz, 1H), 2.6 (dd, $J = 10.4$, 3.2 Hz, 1H); EI-MS m/z (%): 222 (M + 1, 4), 203 (12), 130 (42), 92 (100). IR (KBr, cm^{-1}): 3330.5, 2843.9, 1758.8, 1670.1, 1392.4, 1278.6, 1081.9, 713.5; Anal. calcd. for $C_{11}H_{11}NO_4$: C, 59.70; H, 4.97; N, 6.33. Found: C, 59.95; H, 5.07; N, 6.36.

(4*S*,5*S*)-4-Benzyl-5-hydroxymethyl Oxazolidin-2-one (**7**)

To a solution of acid **6** (0.53 g, 2.40 mmol) in anhydrous methanol (20 mL) was added sulfuric acid (0.5 mL), and the mixture was refluxed for 4 h. After cooling to rt, the solution was adjusted to pH 7 with 40% NaOH solution. The aqueous solution was concentrated under vacuum. To the

residue was added water (10 mL), and the mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried and evaporated in vacuum to afford methyl ester of acid **6** as an oil. To the solution of the methyl ester in anhydrous methanol (20 mL) was added sodium borohydride (0.14 g, 3.6 mmol) portion wise under stirring at room temperature. The reaction was monitored by TLC. At the end of the reaction, the mixture was adjusted to pH 7 with 25% hydrochloric acid and concentrated to dryness in vacuum. Water (10 mL) was added to the residue, and the mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuum to afford the crude product as a white solid, which was recrystallized from ethyl acetate/petroleum ether to afford the target compound **7** (0.37 g, 74.5%) with e.e. value of more than 99% (chiral OD column, hexane/iPrOH = 3/7, 215 nm, 0.9 mL/min). Mp 164–166°C, $[\alpha]_D^{20} = -76.4°C$ (c 0.36, methanol). Lit.[10] Mp 166–168°C, $[\alpha]_D^{20} = -79.4°C$ (c 1.0, methanol). ^1H NMR ($CDCl_3$): δ 7.2–7.4 (m, 5H), 4.95 (s, 1H), 4.80 (m, 1H), 4.2 (m, 1H), 4.0 (m, 2H), 3.0 (dd, $J = 13.5$, 3.6 Hz, 1H), 2.8 (dd, $J = 13.5$, 11.0 Hz, 1H); EI-MS m/z (%): 208 (M + 1, 6), 192 (42), 178 (44), 162 (36), 148 (44), 130 (45), 116 (88), 92 (100); IR(KBr, cm^{-1}): 3347.9, 3263.0, 2931.3, 1731.8, 1398.2, 1259.3, 1039.5, 738.6; Anal. calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.28; N, 6.76. Found: C, 63.90; H, 6.30; N, 6.86.

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