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AN EFFICIENT SYNTHESIS OF *N*-BOC-*D*-DIPHENYLALANINE FROM A CHIRAL AZIRDINE-2-CARBOXYLATE

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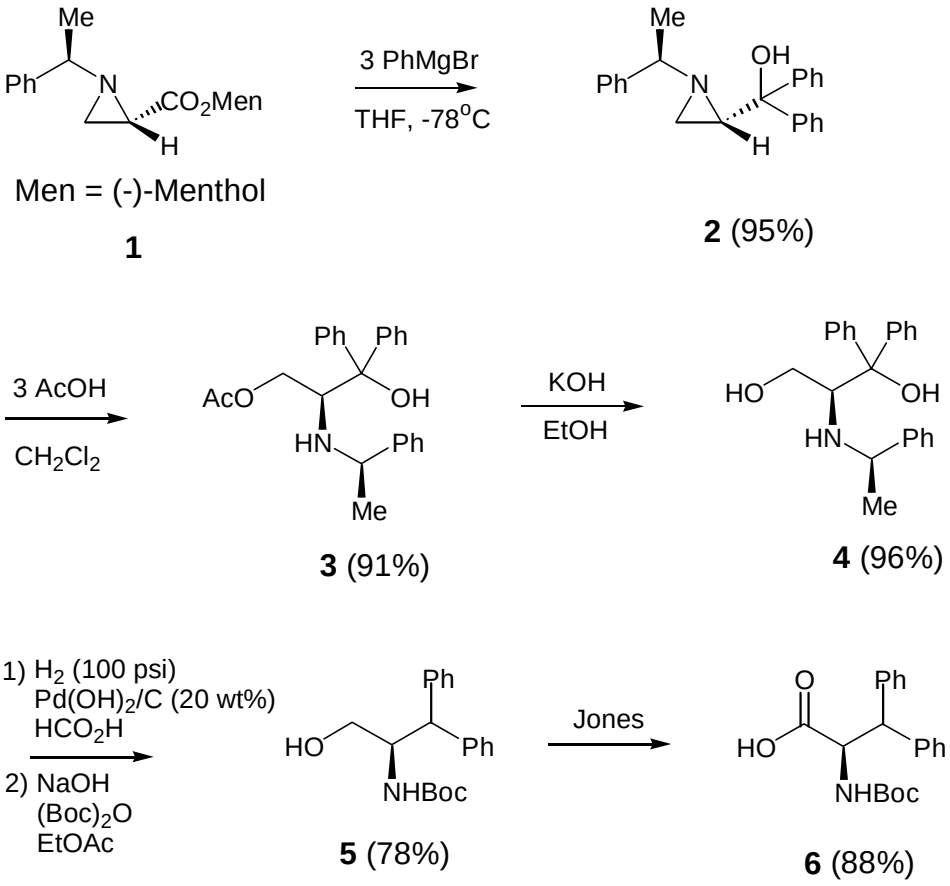
Abstract - *N*-Boc-*D*-diphenylalanine was prepared from a commercially available aziridine-2(*S*)-carboxylate through alkylation, regiospecific aziridine ring opening, and benzylic deoxygenation followed by oxidation in 57% overall yield.

Enantiomerically pure unnatural amino acids attract attentions from many fields for the syntheses of peptide-based biologically active compounds.[1] Especially peptide bearing diphenylalanine as a core unnatural amino acid possesses high biological activity.[2] The best-known examples are the analogs of angiotensin II with high binding affinities for rat uterus and brain receptors[3] because they have diphenylalanine instead of phenylalanine. Since peptidomimetics play important roles in both chemistry and biology,[4] the preparation of large quantities of diphenylalanine in enantiomerically pure form is an important issue. Enantiomerically pure diphenylalanine has been prepared by azidation of an enantiopure oxazolidinone,[5a] alkylation of a sultam-derived glycine imine,[5b] and modification of serine.[6,7] Therefore, we planned an efficient synthesis of enantiomerically pure *D*-diphenylalanine from a commercially available *N*-α-methylbenzyl substituted aziridine-2(*S*)-carboxylate.[8] Moreover, the methodology is liable to large scale synthesis and also the preparation of the enantiomeric form.

The synthesis of *N*-Boc-*D*-diphenylalanine was started from enantiomerically pure aziridine-2(*S*)-carboxylate (**1**) by performing a double Grignard additions to the ester to obtain the tertiary alcohol (**2**). This was accomplished by addition of aziridine-2(*S*)-carboxylate (**1**) to a freshly prepared solution of

phenylmagnesium bromide in THF at –78 ^{0}C, followed by aqueous work-up to provide the addition product (**2**) in 95% yield.[9] The aziridine ring C(3)-*N* bond was regiospecifically cleaved by treating the aziridine-2-methanol (**2**) with 3 equiv of AcOH in dichloromethane at room temperature to provide 3-acetyloxy-2-aminopropanol (**3**) in 91% yield.[10] The acetate (**3**) was then hydrolyzed quantitatively by treatment with KOH in ethanol to give the corresponding 2-amino-1,3-propanediol (**4**) in 96% yield. After optimization of these three steps form **1** to **4** could be obtained amino diol (**4**) by one simple recrystallization from hexane without isolation of compound (**2**) or (**3**) starting from enantiomerically pure aziridine-2(*S*)-carboxylate (**1**).

Scheme



In our synthesis, the deoxygenation of the tertiary benzylic hydroxyl group in **4** is a key step. Catalytic hydrogenation with atmospheric pressure of hydrogen in the presence of a nitrogen activating substance $(Boc)_2O$ provided *N*-Boc-diphenylalaninol (**5**) with the removal of the *N*-benzyl group and the reductive deoxygenation of the hydroxy group at the benzylic position. However, it took long time for the reaction

to be completed. The best result was obtained under 100 psi pressure of hydrogen in HCO_2H with 20 wt% of the Pearlman's catalyst.[6] Reductive deoxygenation of the benzylic hydroxy group and the removal of the *N*-benzyl group proceeded smoothly in 6 h at room temperature that was followed by the treatment with $(Boc)_2O$ to provide *N*-Boc-diphenylalaninol (**5**) in 78% yield. Oxidation of the primary alcohol (**5**) using Jones reagent furnished *N*-Boc-*D*-diphenylalanine (**6**) in 88% yield. The physical properties of **6** exactly matched with those of authentic data reported in the literature.[7] Using this protocol, *N*-Boc-*D*-diphenylalanine was obtained from the enantiomerically pure aziridine-2(*S*)-carboxylate (**1**) in 57% overall yield in 5 steps.

To summarize, we developed an efficient and practical method for the preparation of *N*-Boc-*D*-diphenylalanine from an enantiomerically pure aziridine-2(*S*)-carboxylate. This method makes it possible to prepare a variety of other aromatic amino acids easily by changing the nucleophile in the conversion of **1** to **2**. Since the aziridine-2(*R*)-carboxylate is also available, the preparation of *N*-Boc-*L*-diphenylalanine and its analogs is also possible using the same protocol.

EXPERIMENTAL

General: Flash chromatography was performed on a Tokyo Rikagikai EF -10 with Merck 230~400 mesh silica gel. Mps were determined on a Thomas-hoover capillary melting point apparatus and all melting points were not corrected. ^{1}H NMR spectra were obtained on a Varian Gemini 200 (200 MHz), Varian Gemini 300 (300 MHz) and Varian Gemini 500 (500 MHz) spectrometers. NMR spectral data were recorded in ppm (δ) related to tetramethylsilane ($\delta = 0.00$) as an internal standard unless stated otherwise. Elemental analysis was performed by Carlo Erba EA 1180 elemental analyzer. Optical rotations were obtained on Rudolph Autopol III. digital polarimeter. Data are reported as follow: $[\alpha]_D^{25}$(concentration g/100 mL, solvent). Solvents and liquid reagents were transferred using hypodermic syringes. All other reagents and solvents used were grade. All glassware was dried in an oven at 150 ^oC prior to use. Methylene chloride and triethylamine were dried from calcium hydride prior to use. Small and medium scale purifications were performed by flash chromatography.

***N*-[(*R*)-α-Methylbenzyl]aziridine-2(*S*)-diphenylmethanol (2):** To a solution of *N*-[(*R*)-α-methylbenzyl]aziridine-2(*S*)-carboxylate (**1**) (413mg, 1.25 mmol) in 7 mL of THF with stirring and cooling at –78 ^0C was added PhMgBr (2.96 M, 1.27 mL, 3.76 mmol) in THF. The pale yellow mixture

was stirred for 2 h at –78 ºC and then quenched with 5 mL of water. The mixture was warmed to rt and the organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL x 5). The combined organic extracts were washed with 20 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. Purification by silica gel flash chromatography (EtOAc/n-Hexane, 50:50) gave 390 mg (95%) of the addition product (**2**) as a white solid. mp 86-88 ºC, $[\alpha]^{22}_D$ = +34.0º (*c* 0.53, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37-6.86 (m, 15H), 3.81 (br, 1H), 2.76 (q, *J*=6.6 Hz, 1H), 2.49 (dd, *J*=6.5, 3.6 Hz, 1H), 2.02 (d, *J*=3.6 Hz, 1H), 1.53 (d, *J*=6.5 Hz, 1H), 1.41 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 145.6, 143.6, 128.1, 128.0, 127.6, 127.3, 127.1, 126.9, 126.3, 126.1, 125.7, 74.0, 69.1, 45.7, 30.2, 22.9. Anal. Calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.60; H, 6.99; N, 4.21.

2(*S*)-{*N*-[(*R*)-α-Methylbenzyl]amino}-3-*O*-acetyl-1,1-diphenyl-1,3-propanediol (3): To a solution of *N*-[(*R*)-α-methylbenzyl]aziridine-2(*S*)-diphenylmethanol (**2**) (390 mg, 1.18 mmol) in 5.90 mL of methylene chloride was added 0.20 mL (3.54 mmol) of acetic acid. The mixture was stirred for 4 h at rt and then quenched with 2 mL of saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with methylene chloride (4 mL x 5). The combined organic extracts were washed with 2 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. Purification by silica gel flash chromatography (EtOAc/n-Hexane, 30:70) gave 446 mg (91%) of 2(*S*)-{*N*-[(*R*)-α-methylbenzyl]amino}-3-*O*-acetyl-1,1-diphenyl-1,3-propanediol (**3**) as yellow oil. $[\alpha]^{22}_D$ = +87.9º (*c* 1.00, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51-6.98 (m, 15H), 4.34 (dd, *J*=12.0, 3.6 Hz, 1H), 3.96 (dd, *J*=12.0, 5.8 Hz, 1H), 3.74 (dd, *J*=5.8, 3.6 Hz, 1H), 3.71 (q, *J*=6.6 Hz, 1H), 1.94 (s, 3H), 1.27 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 145.8, 144.7, 144.3, 128.6, 128.4, 128.3, 127.3, 127.2, 127.0, 126.8, 126.2, 125.9, 78.7, 64.5, 59.6, 55.1, 23.8, 20.6. Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.99; H, 7.29; N, 3.60.

2(*S*)-{*N*-[(*R*)-α-Methylbenzyl]amino}-1,1-diphenyl-1,3-propanediol (4): To a solution of 2(*S*)-{*N*-[(*R*)-α-methylbenzyl]amino}-3-*O*-acetyl-1,1-diphenyl-1,3-propanediol (**3**) (430 mg, 1.04 mmol) in 5.20 mL of EtOH was added 70 mg (1.25 mmol) of KOH. The mixture was stirred for 2 h at rt and concentrated in *vacuo* and was treated with 3 mL of water. The organic layer was separated and the aqueous layer was extracted with methylene chloride (4 mL x 5). The combined organic extracts were washed with 2 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. Purification by silica gel

flash chromatography (EtOAc/n-Hexane, 30:70) gave 347 mg (96%) of 2(S)-{*N*-[(*R*)-α-methylbenzyl]amino}-1,1-diphenyl-1,3-propanediol (**4**) as a white solid. mp 78-80 ºC, $[\alpha]^{24}_{D}$= +13.1º (*c* 1.0, in $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-6.95 (m, 15H), 4.11 (br, 1H), 3.77 (m, 2H), 3.58 (dd, *J*=11.8, 4.7 Hz, 1H), 3.38 (m, 1H), 1.29 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 144.7, 144.2, 128.4, 128.3, 128.2, 127.1, 126.8, 126.7, 126.6, 125.6, 125.2, 80.9, 60.1, 59.8, 55.1, 23.9. Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.55; H, 7.29; N, 4.14.

***N*-Boc-diphenylalaninol (5):** To a solution of **4** (329 mg, 0.947 mmol) in 4.70 mL of HCO_2H was added $Pd(OH)_2/C$ (20 wt%) and the mixture was stirred with 100 psi pressure of hydrogen. The mixture was stirred for 6 h at rt, concentrated in *vacuo,* and then was treated with 2.50 mL of 1M aqueous NaOH. To the solution was added $(Boc)_2O$ (248 mg, 1.136 mmol) and 2.00 mL of EtOAc. The mixture was stirred for 4 h and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 mL x 4) and the combined organic extracts were washed with 2 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. Purification by silica gel flash chromatography (EtOAc/n-Hexane, 30:70) gave 250 mg (78%) of **5** as a white solid. mp 109-111 ºC, $[\alpha]^{25}_{D}$ = –22.2º (*c* 1.0, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.16 (m, 10H), 4.63 (m, 1H), 4.47 (br, 1H), 4.15 (d, *J*=10.7, 1H), 3.67 (d, *J*=9.2, 4.1 Hz, 1H), 3.47 (dd, *J*= 10.7, 4.1 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 142.0, 141.4, 128.8, 128.5, 128.4, 128.1, 126.8, 126.6, 79.7, 63.7, 54.9, 52.5, 28.2. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 72.85; H, 7.93; N, 4.49.

***N*-Boc-*D*-diphenylalanine (6):** To a solution of *N*-Boc-*D*-diphenylalaninol (**5**) (200 mg, 0.61 mmol) in 3.10 mL of acetone with cooling at 0 ºC was added 5.0 mL (1.83 mmol) of Jones reagent. Jones reagent was prepared from chromium(VI) oxide (1.87 g, 18.7 mmol), conc. H_2SO_4 (1.6 mL), and H_2O (5 mL) in acetone (20 mL) at 0 ^{0}C. After being stirred at 0 ºC for 4 h, the reaction was quenched by slow addition of 2-propanol at the same temperature, and stirring was continued for another 30 min. The reaction mixture was diluted with saturated $NaHCO_3$ solution, the volatiles were removed in *vacuo*, and the aqueous phase was then acidified with 1N HCl solution and extracted with EtOAc (3 mL x 4). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give analytically pure acid (**6**) as a white power (183 mg, 88%). mp 152-153 ºC, $[\alpha]^{25}_{D}$ = –35.8º (*c* 1.0, MeOH); lit.,[7] mp 149-151 ºC, $[\alpha]^{26}_{D}$ = –36.2º (*c* 1.0, in MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.15 (m, 10H), 5.08 (d, *J*=7.3 Hz, 1H), 4.48 (d, *J*=7.3 Hz, 1H).

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