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An enantioselective synthesis of (*R*)-4-piperidinylglycine

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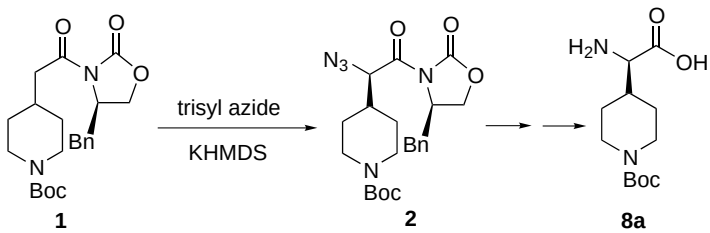
Abstract—An efficient process for the synthesis of (*R*)-*N*-*t*-Boc-4-piperidinylglycine **8a**, an unnatural amino acid, via enantioselective rhodium-catalyzed hydrogenation of the Cbz-enamide **5a** is described. Subsequent deprotection of **8a** affords unprotected (*R*)-4-piperidinylglycine **9** in good yield.

1. Introduction

(*R*)-4-Piperidinylglycine **9**, an unnatural amino acid, is an important building block for the synthesis of novel pharmaceutical drugs, such as matrix metalloproteinase inhibitors[1] and thrombin inhibitors.[2] Racemic piperidinylglycine[2] was synthesized by hydrogenation of an enamide substrate whose structure is similar to **5a**. Enantiomerically pure (*R*)-*N*-*t*-Boc-4-piperidinylglycine **8a**, a derivative of **9**, can be prepared in 8 steps by employing Evans' asymmetric azidation[3] with (*R*)-(+)-4-benzyl-2-oxazolidinone **1** as the chiral auxiliary and trisyl azide as the electrophile (Scheme 1).[1] This strategy works very well for the preparation of small quantities of **8a**. On scale up, we found this approach lengthy and unsafe due to the handling of large quantities of trisyl azide, which liberated a significant amount of energy upon heating. To address this safety issue and to reduce the number of synthetic steps, we investigated an alternative synthesis of enantiomerically pure (*R*)-*N*-*t*-Boc-4-piperidinylglycine **8a**.

Syntheses of *O*- and *S*-containing heterocyclic, unnatural amino acids with high enantiomeric excess by rhodium-catalyzed asymmetric hydrogenation have been reported by Burk.[4] In his study, *N*-acetyl-enamides were used as the hydrogenation precursors. Excellent enantiomeric purity has been reported in the synthesis of heterocyclic amino acids containing *N*-Cbz protected enamides.[5,6] To synthesize (*R*)-*N*-*t*-Boc-4-piperidinylglycine **8a**, an *N*-containing heterocyclic amino acid, we decided to investigate asymmetric hydrogenation utilizing *N*-Cbz-enamide **5a**. This would allow selective deprotection after the asymmetric hydrogenation and avoid the harshly acidic conditions, which are incompatible with the Boc-protecting group, but are required for the *N*-acetyl group removal.[7] Herein, we report the synthesis of (*R*)-*N*-*t*-Boc-4-piperidinyl-



Scheme 1. Evans asymmetric azidation and amino acid synthesis.

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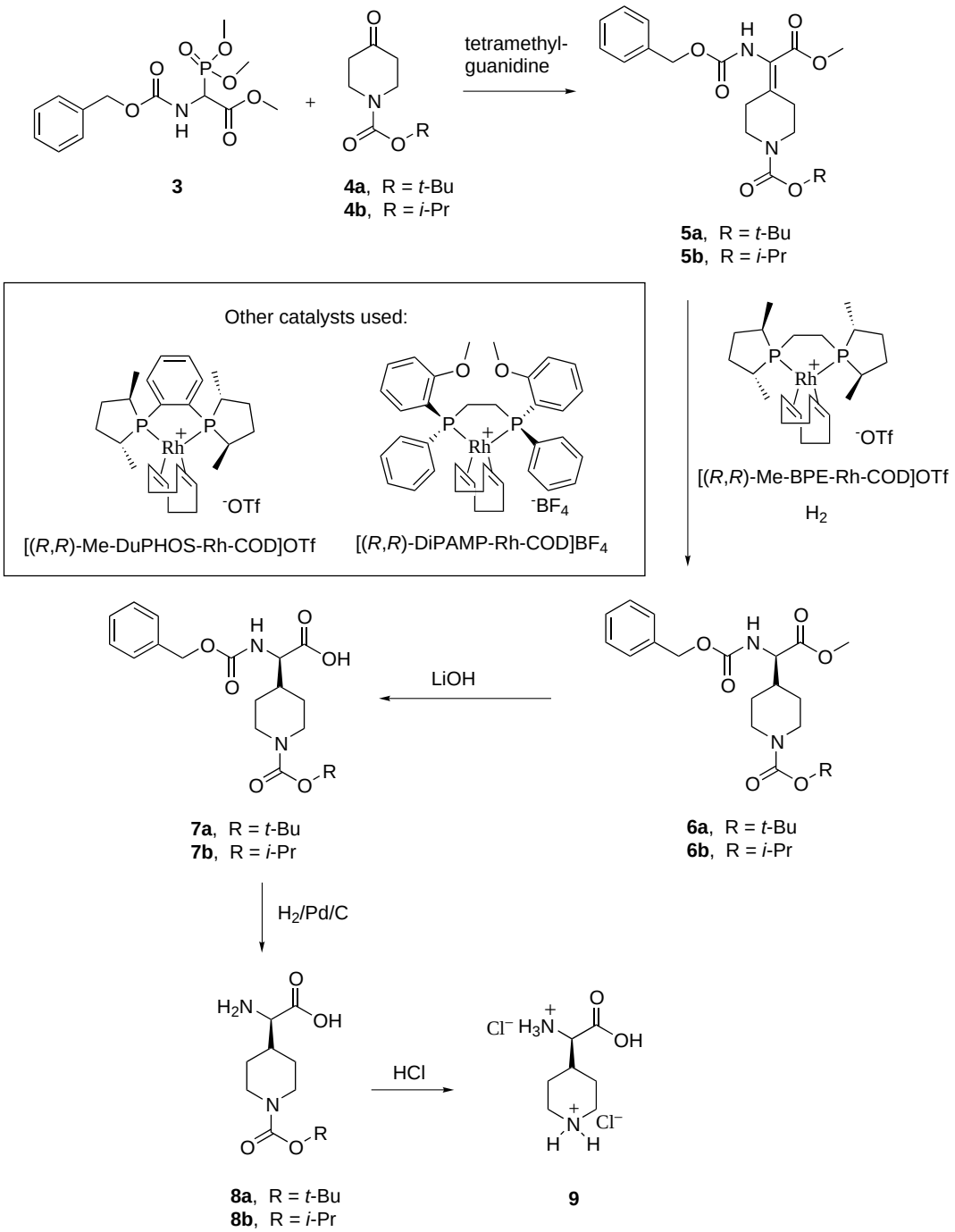
glycine **8a** and (*R*)-4-piperidinylglycine **9** via a highly enantioselective, rhodium-catalyzed hydrogenation reaction.

2. Results and discussion

Cbz-enamide **5a** was prepared from commercially available *N*-Cbz-phosphonoglycine trimethyl ester **3** and *N*-*t*-Boc-4-piperidone **4a** in 61% yield using the Schmidt protocol.[8] Enamide **5a** was recrystallized from a mixture of ethyl acetate and hexane to obtain a highly pure (>99% by HPLC) substrate. The high purity ensured the elimination of any contaminants that may poison the rhodium catalyst.[7b] Asymmetric hydrogenation of enamide **5a** in the presence of [(*R*,*R*)-Me-BPE-Rh-COD]OTf catalyst (2 mol%) at 90 psi generated the (*R*)-enantiomer[9] of protected 4-piperidinylglycine **6a** with 94% e.e. in 99.8% yield. Asymmetric hydrogenation of **5a** with two other commercially available rhodium catalysts led to the amino acid with much lower enantiomeric purity: [(*R*,*R*)-Me-DuPHOS-Rh-COD]OTf gave the (*R*)-enantiomer with 60% e.e. and [(*R*,*R*)-DiPAMP-Rh-COD]BF_4 afforded the (*S*)-enantiomer with 20% e.e. (Scheme 2).



Scheme 2. Asymmetric synthesis of (*R*)-4-piperidinylglycine.

Saponification of the protected piperidinylglycine **6a** with aqueous LiOH solution produced carboxylic acid **7a** in 98% yield. Chiral-HPLC analysis of **7a** indicated a slightly lower enantiomeric purity (90% e.e.), which suggested partial epimerization of amino ester **6a** under the hydrolysis conditions. Further hydrogenolysis of **7a** to remove the Cbz-protecting group was achieved via the standard protocol (H_2, Pd/C, 50 psi, rt) to obtain the crude (*R*)-*N*-*t*-Boc-4-piperidinylglycine **8a** in quantitative yield. The enantiomeric purity of the crude amino acid **8a** was enriched by stirring it in methanol, then collecting the solid by filtration to furnish the desired (*R*)-*N*-*t*-Boc-4-piperidinylglycine **8a**. This extraction procedure resulted in excellent enantiomeric purity (98% e.e.) and an 82% yield. The augmentation of the enantiomeric excess was caused by a lower solubility of **8a** in methanol than that of its racemate.[10] Furthermore, (*R*)-piperidinylglycine **9** can be obtained easily in 79% yield by removing the *t*-Boc group from **8a** with a solution of HCl generated in situ with trimethylsilyl chloride and methanol.[11]

Asymmetric hydrogenation of the isopropyl carbamate analogue **5b** using [(*R*,*R*)-Me-BPE-Rh-COD]OTf at 45°C and a hydrogen pressure of 70 psi produced the protected amino acid **6b** with 84% e.e. Subsequent deprotection of the methyl ester and Cbz groups afforded *N*-4-isopropoxycarbonyl-piperidinylglycine **8b**. An attempt to enrich the enantiomeric purity of **8b** by stirring it in methanol (same procedure as used for **8a**) was unsuccessful and resulted in a much lower e.e. (57%). On the other hand, enriched enantiomeric purity (95% e.e.) was found in the mother liquor of **8b**, suggesting higher solubility of the enantiomer **8b** in methanol. These results demonstrate that a small variation in functionality within piperidinylglycine causes a reversal in its solubility, and consequently its enantiomeric excess. The nature of the enantiomeric mixture determines whether or not it can be extracted with solvent to increase its enantiomeric purity.[10]

3. Conclusion

In conclusion, we have developed a highly efficient process for the synthesis of (*R*)-*N*-*t*-Boc-4-piperidinylglycine **8a**, via rhodium-catalyzed asymmetric hydrogenation, in four steps and 49% overall yield starting from commercial *N*-α-Cbz-phosphonoglycine trimethyl ester **3** and *N*-Boc-4-piperidone **4a**. The enantiomeric purity of **8a** can be enriched from 90 to 98% e.e. with excellent recovery (82%) by a simple extraction procedure.[10] For the synthesis of amino acid **9** via asymmetric hydrogenation, we found *t*-butoxycarbonyl enamide **5a** to be the preferred prochiral substrate because it provided a much higher enantiomeric purity than isopropoxycarbonyl enamide **5b**. Our synthetic sequence is four steps shorter than the previously reported[1] synthesis and has been employed effectively for the synthesis of a large quantity (~500 g) of amino acid **8a**.

4. Experimental

N-α-Cbz-phosphonoglycine trimethyl ester **3** was purchased from Aldrich and *N*-Boc-4-piperidone **4a** from Lancaster. Chiral rhodium catalysts: [(*R*,*R*)-Me-BPE-Rh-COD]OTf, [(*R*,*R*)-Me-DuPHOS-Rh-COD]OTf and [(*R*,*R*)-DiPAMP-Rh-COD]BF_4 were purchased from Strem Chemicals Inc. Proton magnetic resonance spectra were recorded on either a Brüker ARX300, DPX300 or a DRX500 FT-NMR spectrometer. Chiral HPLC analyses were performed on a Waters HPLC system with a 996 PDA detector and Daicel columns. All the elemental analyses were performed by Robertson Microlit Labs (Madison, NJ).

4.1. 4-(Benzyloxycarbonylamino-methoxycarbonyl-methylene)-piperidine-1-carboxylic acid *tert*-butyl ester 5a

A 12-L, four-necked, round-bottomed flask equipped with a mechanical stirrer and 1-L pressure equalizing addition funnel was charged with *N*-α-Cbz-phosphonoglycine trimethyl ester **3** (470 g, 1.42 mol) and EtOAc (2.5 L) under nitrogen purge. Tetramethylguanidine (214 g, 1.84 mol) was added and the solution was stirred for 30 min at rt. A solution of piperidone **4a** (424 g, 2.13 mol) in EtOAc (2.5 L) was added via the addition funnel over 60 min. The solution was stirred at rt for 42 h until **3** was consumed (HPLC). The mixture was cooled to 10°C and 5% aqueous citric acid solution (2.8 L) was added. The mixture was stirred for 15 min and the aqueous layer was separated. The organic solution was washed with 0.25N HCl (2.8 L), H_2O (2.0 L), dried over $MgSO_4$, filtered and concentrated under vacuum to give an oil. The oil was dissolved in EtOAc (0.5 L) and stirred with hexane (2.0 L) in order to initiate precipitation. The crude product was collected by filtration and recrystallized from a mixture of ethyl acetate:hexane (1:4, 2.0 L) to yield **5a** as a white solid (353 g, 61%): mp 101.5–102.6°C; IR (KBr) 3312, 2972, 1725, 1703, 1684, 1512, 1477, 1451, 1426, 1365, 1327, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.49–6.30 (m, 5H), 6.17 (br s, 1H), 5.13 (s, 2H), 3.76–3.68 (m, 3H), 3.56–3.40 (m, 4H), 2.92–2.78 (m, 2H), 2.39 (t, $J=5.9$ Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 155.1, 147.6, 136.4, 128.9, 128.8, 128.7, 128.6, 120.6, 80.2, 67.8, 53.3, 44.2, 43.43, 30.8, 30.1, 28.9, 28.8. Anal. calcd for $C_{21}H_{28}N_2O_6$: C, 62.36; H, 6.98; N, 6.93. Found: C, 62.43; H, 7.07; N, 6.83%.

4.2. 4-((*R*)-Benzyloxycarbonylamino-methoxycarbonyl-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester 6a

A 5-L high-pressure bottle was charged with enamide **5a** (60 g, 148 mmol) and previously degassed MeOH (3.0 L) under a nitrogen purge. This colorless solution was charged with [(*R*,*R*)-Me-BPE-Rh-COD]OTf catalyst (2 g, 3 mmol). The resulting mixture was subjected to a vacuum, then refilled with nitrogen for three cycles. The mixture was placed under vacuum and refilled with hydrogen for an additional three cycles. The solution was stirred under 90 psi of hydrogen gas at rt for 72 h. The mixture was flushed with nitrogen

and concentrated under vacuum. The residue was dissolved in ethyl acetate (500 mL) and filtered through silica gel (50 g) to remove the catalyst. The cake was rinsed with ethyl acetate (500 mL). The organic solution was concentrated under vacuum to afford **6a** as an oil (60 g 100%): R_f=0.36 (hexane/EtOAc 1/1); $[\alpha]_D^{25}$ −20.7 (c=1.05, $CHCl_3$); IR (KBr) 3323, 2950, 1691, 1529 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.32–7.42 (m, 5H), 5.32 (d, J=8.7 Hz, 1H), 5.12 (s, 2H), 4.33–4.44 (m, 1H), 4.08–4.21 (m, 2H), 3.77 (s, 3H), 2.57–2.76 (m, 2H), 1.85–2.02 (m, 1H), 1.40–1.70 (m, 2H), 1.46 (s, 9H), 1.19–1.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 171.8, 156.0, 154.6, 136.0, 128.5, 128.2, 128.1, 79.5, 67.1, 57.8, 52.3, 43.4, 39.6, 28.3, 27.1. Anal. calcd for $C_{21}H_{30}N_2O_6$: C, 62.05; H, 7.44; N, 6.89. Found: C, 61.99; H, 7.09; N, 7.04. Chiral HPLC: 94% e.e. (Chiralcel OD column, hexane/IPA/TFA 9/1/0.1%, flow rate 1.5 mL/min; (*S*)-enantiomer, R_t=7.21 min; (*R*)-enantiomer, R_t=10.0 min).[12]

4.3. 4-((*R*)-Benzyloxycarbonylamino-carboxy-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester 7a

A 5-L flask equipped with a mechanical stirrer was charged with amino ester **6a** (151 g, 371 mmol) and MeOH (1.7 L). The solution was cooled to 5°C. A solution of 1N LiOH (557 mL, 557 mmol) was added and the mixture was allowed to warm to rt, then stirred for 20 h. The reaction mixture was neutralized to pH 7 with 1N $KHSO_4$ solution and concentrated under vacuum. The resulting aqueous solution was adjusted to pH 2 with 2N $KHSO_4$ and extracted with EtOAc (3×800 mL). The combined organic layers were washed with brine (1 L), dried over $MgSO_4$, filtered through Celite, and concentrated under vacuum to give **7a** as a foamy white solid (142 g, 98%): $[\alpha]_D^{25}$ −18.6 (c=1.07, $CHCl_3$); IR (KBr) 3327, 2977, 2931, 1695, 1531, 1479, 1367, 1243, 1164 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.30–9.20 (br s, 1H), 7.30–7.40 (m, 5H), 5.49 (d, J=8.7 Hz, 1H), 5.13 (s, 2H), 4.34–4.50 (m, 1H), 4.03–4.30 (m, 2H), 2.57–2.80 (m, 2H), 1.95–2.09 (m, 1H), 1.46 (s, 9H), 1.22–1.78 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1, 156.7, 155.4, 136.4, 129.0, 128.7, 128.5, 80.5, 67.7, 58.1, 44.0, 39.7, 28.8, 27.3. Anal. calcd for $C_{20}H_{28}O_6N_2$: C, 61.21; H, 7.19; N, 7.14. Found: C, 60.98; H, 6.93; N, 7.14%. Chiral HPLC: 90% e.e. (Chiralcel OD, hexane/IPA/TFA 9/1/0.1%, flow rate 1.5 mL/min; (*S*)-enantiomer, R_t=5.72 min; (*R*)-enantiomer, Rt=8.54 min).[12]

4.4. 4-((*R*)-Amino-carboxy-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester 8a

A 2.5-L Parr bottle was charged with 5% Pd/C (50% wet, 16.0 g) under a nitrogen atmosphere. A solution of amino acid **7a** (75 g, 190 mmol) in EtOH:H_2O (2:1, 1.5 L) was added under a nitrogen purge. The mixture was hydrogenated under 50 psi hydrogen gas at rt for 16 h. The mixture was flushed with nitrogen and filtered. The catalyst cake was rinsed with EtOH (400 mL). The organic solution was concentrated under vacuum until a grey solid was obtained (49 g, 100%). The grey solid was suspended in MeOH (750 mL), stirred at 60°C for 2 h, cooled to 0°C, and stirred for an additional 1 h. The solid was collected by filtration and rinsed with cold (5°C) MeOH (200 mL). The solid was dried at 60°C under vacuum (2 mm Hg) to obtain 40 g (82%) of **8a**, as an off-white solid: $[\alpha]_D^{25}$ −4.2 (c=0.51, H_2O); ^1H NMR (500 MHz, D_2O): δ 4.18 (m, 2H), 3.68 (d, J=4.9 Hz, 1H), 2.76–2.92 (m, 2H), 2.09–2.21 (m, 1H), 1.74–1.83 (m, 1H), 1.64–1.72 (m, 1H), 1.48 (s, 9H), 1.25–1.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 156.4, 81.7, 58.9, 43.6, 37.0, 27.6, 26.9. Anal. calcd for $C_{12}H_{22}N_2O_4$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.67; H, 8.35; N, 10.79. Chiral HPLC: 98% e.e. (Crownpak CR$^+$, perchloric acid pH 1.5/MeOH 85/15, flow rate 1 mL/min; (*R*)-enantiomer, R_t=14.0 min; (*S*)-enantiomer, R_t=23.4 min).[12]

4.5. (*R*)-Amino-piperidin-4-yl-acetic acid dihydrochloride 9

A 50-mL flask equipped with a magnetic stirrer was charged with Boc-protected amino acid **8a** (0.16 g, 0.6 mmol) and MeOH (15 mL). Trimethylsilyl chloride (2.0 g, 18.4 mmol) was added to the suspension in one portion. The resulting solution was stirred at rt for 3 h. The reaction mixture was concentrated at 25°C under vacuum (2 mm Hg) to give **9** as a foamy white solid (0.11 g, 79%): $[\alpha]_D^{25}$ −18.3 (c=1.05, H_2O); IR (KBr) 3416, 2926, 1740, 1597, 1512, 1215 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 3.80 (d, J=4.8 Hz, 1H), 3.33–3.48 (m, 2H), 2.84–3.01 (m, 2H), 2.10–2.29 (m, 1H), 1.81–2.01 (m, 2H), 1.58–1.78 (m, 1H), 1.38–1.57 (m, 1H); MS: m/z 157 (M^+−1). Anal. calcd for $C_7H_{16}Cl_2N_2O_2$: C, 36.38; H, 6.98; N, 12.12. Found: C, 36.96; H, 7.38; N, 11.63%.

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