SYNTHESIS OF OPTICALLY ACTIVE 2-PIPERIDYLGlyCINE

Hyun-kyu Chung, Hyung-woo Kim, and Kyoo-Hyun Chung*

Department of Chemistry, Inha University, Inchon 402-751, Korea

Abstract - Both chiral threo- and erythro-2-piperidylglycines were synthesized from racemic 2-[(N-benzyloxycarbonyl)piperidin-2-yl]ethanoic acid. (4S,5S)-4-Methyl-5-phenyl-2-oxa-zolidinone was used as a chiral auxiliary in the resolution and azidation.

Many of \( \alpha,\beta \)-diamino acids have displayed various biological activities.\(^1\) Streptolutin [1, 2-amino-2-(5-chloropiperidin-2-yl)ethanoic acid], one of \( \alpha,\beta \)-diamino acids, is the parent amino acid of antitumor agent DKP 593A (2). The agent was isolated from the soil microorganism, \textit{Streptomyces griseoluteus} and reported to be effective against certain solid tumors.\(^2\) The antitumor agent has been synthesized as a racemic mixture.\(^3\) Streptolutine has three chiral centers whose configurations are (R) at C-2', (S) at C-5' and C-2, thus the stereochemical relationship between C-2' and C-5' is \textit{trans}, and that of C-2' and C-2 is \textit{threo}. In the attempted synthesis of streptolutin, the corresponding \textit{erythro} isomer was formed as a major compound.\(^5\)

2-Piperidylglycine [3, 2-amino-2-(piperidin-2-yl)ethanoic acid] has been studied as a model compound in the preparation of analogs of streptolutin and DKP 593A.\(^6\)–\(^8\) Heating 7-amino-7-carboxy-8-oxo-1-azabicyclo[4.2.0]octane in 5 M HCl gave a 2:1 mixture of \textit{threo}- and \textit{erythro}-2-piperidylglycines.\(^7\) Hydrogenation of ethyl 2-piperidinyldiene-N-(ethoxycarbonyl)glycinate on 10% Pd/C gave the corresponding \textit{erythro}-glycine derivative.\(^8\)

In the azidation at the C-2 position of a 2-(piperidin-2-yl)ethanoate, an \textit{erythro}-azide is always predominant over a \textit{threo} isomer.\(^9\) In the meantime, a few compounds related to 2-piperidylglycine were
optically resolved. Pig liver esterase catalyzed enantioselectively the hydrolysis of racemic methyl 2-(N-acetylpyrrolidin-2-yl)ethanoate or acetate of 2-(N-acetylpyrrolidin-2-yl)ethanol to give the corresponding acid or alcohol in 7-24% ee. 2-Piperidineethanol was also resolved through recrystallization of d-10-camphorsulfonate salt.

Evans chiral imide enolates have been used in alkylation, aldol condensation and azidation. So we thought that a chiral auxiliary may be utilized to obtain chiral 2-(pyrrolidin-2-yl)ethanoic acid from the racemate and to introduce amino group diastereoselectively at the C-2 position. In this note, we described the synthesis of chiral threo- and erythro-2-pyrrolidylglycines using (4S,5S)-4-methyl-5-phenyl-2-oxazolidinone as a chiral auxiliary.

Racemic 2-[(N-benzoxycarbonyl)pyrrolidin-2-yl]ethanoic acid (4) was reacted with (4S,5S)-4-methyl-5-phenyl-2-oxazolidinone to give diastereomeric carboxamide (5). By column chromatography, the mixture of 5a and 5b was separated without any difficulty. When (5)-4-benzyl-2-oxazolidinone was used as a chiral auxiliary to prepare a carboxamide, the resulting mixture of two diastereoisomers was difficult to be separated by column chromatography.

The stereochemistry of the pyrrolidine ring was determined by comparison with the known optical rotation. Chiral 2-(pyrrolidin-2-yl)ethanoic acid (6) was prepared by the following sequence; hydrolysis of carboxamide (5) by LiOH·H₂O followed by hydrogenolysis of the resulting acid on 10% Pd/C. The [a]₀ values of 6, derived from one of 5 having lower RF value, was +31.2°. Because the [a]₀ values of (S)-2-(pyrrolidin-2-yl)ethanoic acid (6b) was reported to be +33.5°, the compound having lower RF value was assigned to be 5b and the other one was 5a in a mixture of 5 (Scheme 1).

Scheme 1. Determination of the Stereochemistry in the Pyrrolidine Ring.

\[
\begin{align*}
4 \text{ (R=Cbz)} & \quad 6 \text{ (R=H)} \\
\text{(Chirality of C-2 in the pyrrolidine ring, a:R, b:S)}
\end{align*}
\]

Reaction conditions: (a) i) pivaloyl chloride, Et₃N, ii) (4S,5S)-4-methyl-5-phenyl-2-oxazolidinone, n-BuLi; (b) i) separation, ii) LiOH·H₂O₂; (c) H₂, 10% Pd/C.

Carboxamide (5a) was treated with KHMDS and 2,4,6-trisopropylbenzenesulfonyl azide (trisyl azide) to give azide (7a) which has S chirality at the C-2', since the stereochemistry was governed by the methyl
and phenyl groups of the oxazolidinone. As a result, the threo isomer was in hand. The reaction of azido carboxamide (7a) with LiOH-H,O gave azido acid (8a), which was hydrogenated on 10% Pd/C to afford threo-2-piperidylglycine (3a). The threo stereochemistry was confirmed by comparing its 

\[ ^1\text{H} \text{NMR spectra in} \ 2\text{M} \text{DCI/D}_2\text{O with spectra for threo- and erythro-2,3-diaminobutanoic acids.} \]

Since azide (7b), derived from carboxamide (5b), was difficult in separation from the unreacted 5b upon azidation, other methodology was employed to synthesize erythro-2-piperidylglycine (3b). Carboxamide (5b) was converted to ethyl ester (9b) which was reacted with trisyl azide to give a mixture of erythro-azide (10b) and the enantiomer of 10a in a ratio of 3.5 : 1.9 Perpendicular model was suggested to explain the erythro preference in the azidation.15 Ester (10b) was purified by flash column chromatography and was converted to erythro-2-piperidylglycine (3b) by the above mentioned method. The erythro stereochemistry was also confirmed by its 

\[ ^1\text{H} \text{NMR spectrum (Scheme 2).} \]

**Scheme 2. Synthesis of Chiral 2-Piperidylglycine.**

![Scheme 2. Synthesis of Chiral 2-Piperidylglycine.](image)

Reaction conditions: (a) KHMDS, trisyl azide; (b) LiOH,H,O; (c) H, 10% Pd/C; (d) NaOEt, EtOH; (e) LiOH.

**EXPERIMENTAL**

All chemicals were reagent grade (Aldrich Chemical Co.) and were used as purchased without further purification. \[ ^1\text{H} \text{and} \ ^{13}\text{C} \text{NMR spectra were recorded on a Varian Gemini 2000 (200MHz) spectrometer in} \ \text{CDCl}_3 \text{unless otherwise stated. Optical rotations were recorded on a Perkin-Elmer polarimeter 241. Melting points were determined on a Yamato MP-21 and were uncorrected. Elemental analysis was performed by a Xytel EA-1110 at Inha University.} \]

\[ (4S,5R)-3-[2-[(N-Benzoyloxycarbonyl)piperidin-2-yl]-1-oxoethyl]-4-methyl-5-phenyl-2-oxazolidinone \ (5). \] To a solution of 2-[(N-benzyloxycarbonyl)piperidin-2-yl]ethanoic acid (4, 2.73 g, 9.83 mmol) in THF (25 mL) was added triethylamine (1.30 mL, 12.8 mmol) and pivaloyl chloride (1.30 mL, 10.8 mmol) at -
The slurry was stirred at -78 °C for 10 min and 0 °C for 50 min and then recooled to -78 °C. In a separate flask a solution of (4S,5S)-4-methyl-5-phenyl-2-oxazolidinone (6.80 g, 10.8 mmol) in THF (15 mL) was cooled to -78 °C. To this solution was added 1.6 M n-BuLi in hexane (13.5 mL, 21.6 mmol). The metalted oxazolidinone was added via cannula to the white slurry prepared as described above. The resulting slurry was stirred for 15 min at -78 °C, warmed to rt, and then stirred for 1.5 h. The reaction was quenched by sodium bisulfate (1.19 g, 4.00 mmol). THF was removed in vacuo, and the mixture was diluted with water and extracted with CH2Cl2 (40 mL x 3). The extract was dried over Na2SO4, and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc/n-hexane) gave 5a (1.50 g, 35%) and 5b (0.86 g, 20%). 5a: mp 93 °C-95 °C (EtOAcln-hexane). 1H NMR δ 0.79 (d, J = 6.5 Hz, 3H, CH3), 1.40-1.90 (m, 6H, H-3", H-4", H-5"), 2.93-3.20 (m, 2H, H-2'), 3.32-3.55 (m, 1H, H-6aM), 4.02-4.24 (m, 1H, H-be"), 4.24-4.48 (m, 1H, H-4), 4.85-5.00 (m, 1H, H-2e"), 5.10-5.17 (m, 2H, benzyl), 5.52-5.68 (m, 1H, H-5), 7.10-7.45 (m, 10H, Ph); 13C NMR δ 168.7, 153.8, 151.6, 135.5, 131.8, 126.87, 126.83, 126.14, 125.6, 124.0, 77.2, 65.2, 53.1, 46.4, 38.0, 34.8, 27.4, 23.6, 17.3, 12.8; [α]20D +3.3° (c 2.0, CHCl3). Anal. Calcd for C29H40N2O5: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.74; H, 6.48; N, 6.49.

5b (oil): 1H NMR δ 0.79 (d, J = 4.0 Hz, 3H, CH3), 1.33-1.85 (m, 6H, H-3", H-4", H-5"), 3.05-3.35 (m, 1H, H-6a"), 4.00-4.20 (m, 1H, H-6e"), 4.58-4.80 (m, 1H, H-4), 4.85-5.08 (m, 1H, H-2e"), 5.08 (bs, 2H, benzyl), 5.58 (d, J = 7.2 Hz, 1H, H-5), 7.15-7.50 (m, 10H, Ph); 13C NMR δ 168.9, 153.7, 151.4, 135.3, 131.7, 126.8, 126.2, 125.9, 124.1, 77.4, 65.2, 53.1, 46.4, 38.0, 34.5, 27.4, 23.5, 17.2, 12.4; [α]20D -24.2° (c 2.0, CHCl3). Anal. Calcd for C29H40N2O5: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.74; H, 6.48; N, 6.49.

(3(2S),3(2(2R)),4S,5S)-3-[2-Azido-2-((N-benzyloxycarbonyl)piperidin-2-yl)-1-oxoethyl]-4-methyl-5-phenyl-2-oxazolidinone (7a). To a solution of 5a (1.00 g, 2.29 mmol) in THF (15 mL) at -78 °C was added dropwise 0.5M KHMDS in toluene (5.5 mL, 2.75 mmol). The solution was stirred for 30 min and treated with a precooled solution of trisyl azide (0.78 g, 2.52 mmol) in THF (5 mL) via cannula. The mixture was stirred for 5 min at -78 °C and then quenched by rapid addition of acetic acid (0.66 mL, 4.80 mmol). After the white slurry was stirred for 2 h at rt, it was diluted with CH2Cl2. The mixture was washed with water, and the water layer was extracted with CH2Cl2 (50 mL x 3). Combined organic layer was dried over Na2SO4, and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc/n-hexane) gave an oil (0.744 g, 68%). 1H NMR δ 0.89 (d, J = 6.5 Hz, 3H, CH3), 1.35-1.95 (m, 6H, H-3", H-4", H-5"), 3.05-3.35 (m, 1H, H-6a"), 4.00-4.20 (m, 1H, H-6e"), 4.35-4.52 (m, 1H, H-4), 4.73-4.90 (m, 1H, H-2e"), 5.00-5.35 (m, 2H, benzyl), 5.35-5.57 (m, 1H, H-2"), 5.69 (d, J = 7.2 Hz, H-5), 7.15-7.50 (m, 10H, Ph); 13C NMR δ 169, 153.7, 151.4, 135.3, 131.7, 127.1, 126.9, 126.2, 125.7, 124.1, 77.6, 65.6, 61.7, 53.8, 46.4, 38.9, 28.0, 24.5, 17.8, 12.9; [α]20D +8.44° (c 2.9, CHCl3). HRMS (FAB+)
calcd for C_{33}H_{39}N_2O_2(MH^+) \ 478.2090, found \ 478.2089.

(2S,2(2R))-2-Azido-[(N-benzyloxycarbonyl)piperidin-2-yl]ethanoic acid (8a). To a solution of 7a (0.68 g, 1.42 mmol) in a mixture of THF and water (3:1, 15 mL) was added slowly LiOH (0.12 g, 2.88 mmol) and H_2O_2 (35%, 1.38 g, 14.2 mmol). The reaction mixture was stirred for 1 h, and quenched by sodium bisulfate (1.97 g, 14.2 mmol). THF was removed \textit{in vacuo}, and the resulting mixture was diluted by water, acidified to pH 1-2 with 1.0N HCl, and extracted with ethyl acetate (30 mL x 3). The combined organic extracts were dried, and concentrated \textit{in vacuo}. Purification of the residue by column chromatography (10% MeOH/CH_2Cl_2) gave a solid (0.41 g, 82%). mp 134°C-135°C (CH_2Cl_2/ n-hexane); \textit{H NMR} δ 1.40-1.86 (m, 6H, H-3', H-4', H-5'), 2.80-2.89 (m, 1H, H-6a'), 4.07-4.25 (m, 2H, H-6e', H-2), 4.62-4.80 (m, 1H, H-2a'), 5.11-5.28 (m, 2H, benzyl), 7.34 (s, 5H, Ph); \textit{13C NMR} δ 19.0, 20.7, 24.7, 26.2, 39.8, 51.9, 61.0, 67.7, 127.9, 128.0, 136.3, 156.0, 173.5; [α]_D^20 -21.0° (c 0.5, CHCl_3). Anal. Calcd For C_{34}H_{37}N_2O_3: C 56.60, H 5.70, N 17.60. Found: C 56.03, H 6.08, N 17.41.

(2S,2(2R))-2-Amino-2-(piperidin-2-yl)ethanoic acid (3a). To a solution of 8a (0.12 g, 0.38 mmol) in MeOH (15mL) was added 10% Pd/C (0.012 g). The black slurry was stirred under hydrogen at atmospheric pressure for 1 h. The slurry was then filtered through celite, and the filtrate was concentrated \textit{in vacuo}. The residue was recrystallized from MeOH/Et,O to give a solid (0.049 g, 81%). mp 204°C-205°C; \textit{H NMR} (2.0M DCl/D_2O) δ 1.18-1.82 (m, 6H, H-3', H-4', H-5'), 2.78-2.89 (m, 1H, H-6e'), 2.80-3.27 (m, 1H, H-2a'), 3.44-3.48 (m, 1H, H-2), 4.20 (d, J = 3.3 Hz, 1H, H-2); \textit{13C NMR} (2.0M DCl/D_2O) δ 18.6, 18.8, 20.6, 44.2, 50.6, 52.9, 164.9; [α]_D^20 +22.1° (c 0.24, 1.0N HCl). Anal. Calcd For C_{18}H_{31}N_2O: C 53.15, H 8.92, N 17.71. Found: C 53.24, H 8.89, N 17.66.

Ethyl (2S,2(2S))-2-[(N-benzyloxycarbonyl)piperidin-2-yl]ethanoate (9b). To a precooled solution of 5b (1.83 g, 4.19 mmol) in EtOH (10 mL) was added slowly NaOEt (0.294 g, 4.19 mmol) in EtOH (5 mL). The reaction mixture was stirred for 2 h and the EtOH was removed \textit{in vacuo}. The residue was added into water and extracted with CH_2Cl_2. The organic layer was dried, filtered, and concentrated \textit{in vacuo} to give an oil. Purification of the crude product by column chromatography (20% EtOAc/n-hexane) gave an oil (1.04 g, 81%). \textit{H NMR} δ 1.21 (t, J=7.2 Hz, 3H, CH_3), 1.35-1.95 (m, 6H, H-3', H-4', H-5'), 2.52-2.65 (m, 2H, H-2), 2.78-2.96 (m, 1H, H-6a'), 3.95-4.15 (m, 1H, H-6e'), 4.07 (q, J = 7.4 Hz, 2H, -OCH_3), 4.72-4.86 (m, 1H, H-2'), 5.13 (br s, 2H, benzyl); \textit{13C NMR} δ 12.4, 17.0, 23.5, 26.5, 33.6, 37.8, 46.5, 58.2, 65.3, 126.1, 126.2, 126.8, 135.3, 153.7, 169.6; [α]_D^20 -7.2° (c 2.1, CHCl_3); MS (EI) m/z 305 (M^+).

Ethyl (2S,2(2S))-2-azido-[(N-benzyloxycarbonyl)piperidin-2-yl]ethanoate (10b). The procedure outlined above for the azidation of 5a was followed employing 9b. The crude product (10b) was purified by column chromatography (20% EtOAc/n-hexane) to give an oil (45%). \textit{H NMR} δ 1.20 (t, J = 7.0 Hz, 3H, CH_3), 1.40-2.02 (m, 6H, H-3', H-4', H-5'), 2.85-3.05 (m, 1H, H-6a'), 4.09 (q, J = 7.0 Hz, 2H, OCH_3),
3.98-4.10 (m, 1H, H-6e'), 4.53-4.68 (m, 1H, H-2e'), 5.10 (m, 2H, benzyl), 7.25-7.40 (m, 5H, Ph); \(^{13}\)C NMR 12.3, 17.3, 23.1, 24.4, 37.9, 50.2, 59.0, 60.3, 65.7, 126.3, 126.8, 134.9, 153.9, 167.6; [\(\alpha\)]\(^{20}\)_D +19.8° (c 2.3, CHCl\(_3\)); MS (CI) m/z 347 (M+).

\((2S,2(2S))-2\)-Azido-[(N-benzyloxycarbonyl)piperidin-2-yl]ethanoic acid (8b). To a solution of 10b (0.469 g, 1.42 mmol) in a mixture of THF and water (3:1, 15 mL) was added slowly LiOH (0.12 g, 2.83 mmol) at 0°C. the reaction mixture was stirred for 1 h, and THF was removed in vacuo. The resultant was diluted by water, acidified to pH 1-2 with 1.0N HCl, and extracted with ethyl acetate. The combined organic extracts were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. Purification of the residue by column chromatography (10% MeOH/CH\(_2\)Cl\(_2\)) gave an oil (0.42 g, 84%). \(^{1}\)H NMR \(\delta\) 1.40-1.95 (m, 6H, H-3', H-4', H-5'), 2.96-3.08 (m, 1H, H-6a'), 4.06-4.20 (m, 2H, H-6e', H-2), 4.52-4.64 (m, 1H, H-2a'), 5.03-5.17 (m, 2H, benzyl), 7.34 (br s, 5H, Ph); \(^{13}\)C NMR \(\delta\) 17.0, 22.8, 23.3, 50.4, 58.7, 66.3, 126.2, 126.9, 134.5, 154.5, 170.8; [\(\alpha\)]\(^{20}\)_D −6.9° (c 1.8, CHCl\(_3\)). Anal. Calcd For C\(_{19}\)H\(_{18}\)N\(_4\)O\(_2\): C 56.60, H 5.70, N 17.60. Found: C 56.03, H 6.08, N 17.41.

\((2S,2(2S))-2\)-Amino-2-(piperidin-2-yl)ethanoic acid (3b). The procedure outlined above for 3a was followed employing 8b. mp 234°C-235°C (MeOH/Et\(_2\)O); \(^{1}\)H NMR (2.0 M DCI/D\(_2\)O) \(\delta\) 1.12-1.63 (m, 6H, H-3', H-4', H-5'), 2.64-2.75 (m, 1H, H-6a'), 3.10-3.20 (m, 1H, H-6e'), 3.30-3.47 (m, 1H, H-2a'), 4.00 (d, \(J = 6.4\) Hz, 1H, H-2); \(^{13}\)C NMR (2.0 M DCI/D\(_2\)O) \(\delta\) 18.5, 22.8, 43.6, 51.2, 52.7, 164.9; [\(\alpha\)]\(^{20}\)_D −10.0° (c 0.05, 1.0 N HCl). Anal. Calcd For C\(_{14}\)H\(_{14}\)N\(_2\)O: C 53.15, H 8.92, N 17.71. Found: C 53.24, H 8.89, N 17.66.

ACKNOWLEDGMENT

We thank OCRC-KOSEF and the Korea Science and Engineering Fund (No 97-03-01-01-5-L) for partial financial support.

REFERENCES


Received, 12th July, 1999