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An efficient synthesis of 3(*S*)-aminopiperidine-5(*R*)-carboxylic acid as a cyclic β,γ′-diamino acid

Jin-Seong Park,[a] Chang-Eun Yeom,[a] Soo Hyuk Choi,[a] Yong Shik Ahn,[a] Sunggu Ro,[b,†] Young Ho Jeon,[b,†] Dong-Kyu Shin[b,†] and B. Moon Kim[a,*]

[a]*School of Chemistry & Molecular Engineering and Center for Molecular Catalysis, Seoul National University, Seoul 151-747, South Korea*

[b]*LG Life Science, PO Box 51, Yuseong, Science Town, Daejon 305-380, South Korea*

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Abstract—An orthogonally protected β,γ′-diamino acid **6** possessing conformationally-constrained ring system was synthesized as a novel cyclic amino acid analogue. This synthesis involves as key steps chemoselective enzymatic hydrolysis of *cis*-piperidine-3,5-dicarboxylic ester derivative followed by efficient kinetic resolution of the partially resolved half-acid to afford the C_1-symmetric piperidine-3,5-dicarboxylic acid monoester in high enantiomeric excess (>98% ee). The optically active half-acid was transformed to the cyclic amino acid via *Curtius*-type rearrangement.

A great deal of research has been devoted to the design and synthesis of new peptidomimetic building blocks.[1] In particular, novel conformationally constrained and optically active unnatural amino acids attract much attention since these compounds can be utilized as potential building blocks for biologically active molecules.[2] From our continuing effort in asymmetric syntheses of unnatural amino acids and peptide secondary structure mimetics possessing interesting biological activities, we have been interested in the 3,5-disubstituted piperidine ring system such as **A** and **B** in Figure 1. These substituted piperidine structures have been utilized as building blocks for ras farnesyl protein transferase inhibitors[3] and a scaffold for the preparation of optically active indole alkaloids.[4] The conformational constraint in these structures could play a significant role as a peptidomimetic template to nuclease hydrogen-bonding pattern mimicking the peptide secondary structure such as β-sheet[5] or turn motifs.[6] Especially compound **A** represents a conformationally constrained β,γ′-diamino acid derivative which may be of a particular value when two amino groups can be orthogonally protected. Due to these interesting perspectives, the optically active form of this cyclic unnatural amino acid has been the target of considerable synthetic efforts.[4,7] Reported herein is a new, efficient synthetic route for optically active *cis*-3,5-disubstituted piperidine derivatives.

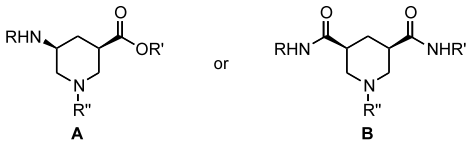

Figure 1.

Key features of our synthetic approach for enantiomerically enriched structures **A** and **B** involve chemoselective desymmetrization of σ-symmetrical dimethyl piperidine-3,5-dicarboxylate **3** through enzyme-mediated hydrolysis with PLE,[7b,7c,8] followed by kinetic resolution with a chiral amine such as α-phenylethylamine (α-PEA).[9]

As shown in Scheme 1, a ~3:2 mixture of stereoisomeric dimethyl *meso*-*N*-*t*-butyloxycarbonyl-3,5-piperidine-dicarboxylate **3** was prepared from 3,5-pyridine dicarboxylic acid **1** through esterification followed by hydrogenation under acidic conditions. Separation of the desired *cis*-isomer from the *cis*/*trans* mixture **3** was accomplished either through column chromatography on silica gel or simple recrystallization from *n*-hexane. It was assumed that *trans*-**3** would be less stable than *cis*-**3** due to its axial ester group. The crystalline com-

* Corresponding author. Tel.: +82-2-880-6644; fax: +82-2-872-7505; e-mail: kimbm@snu.ac.kr

† Present address: CrystalGenomics, Inc., Daeduk BioCommunity, 461-6, Jeonmin-dong, Yusung-gu, Daejeon 305-390, Korea.

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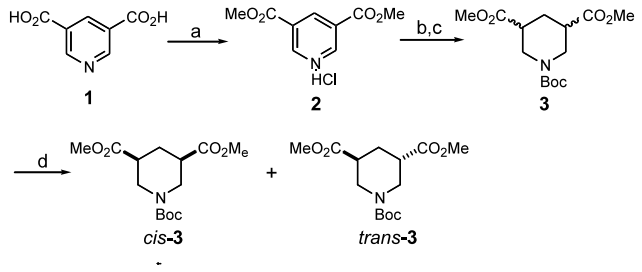
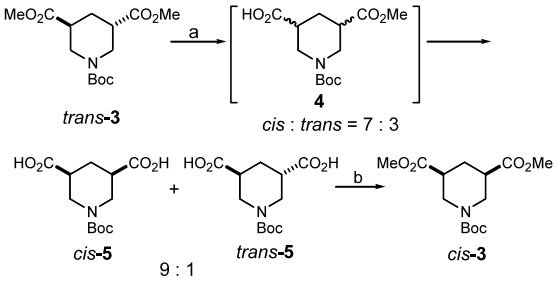


Scheme 1. a) HCl (g), MeOH; b) H_2 (50 atm), Pd/C, AcOH; c) Boc_2O, Et_3N, CH_2Cl_2; d) column chromatography or crystallization.

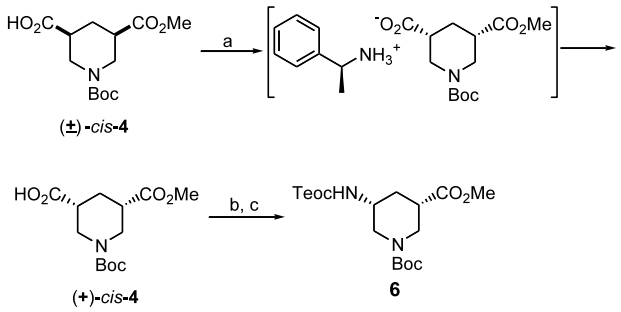


Scheme 2. a) K_2CO_3, trace H_2O, MeOH, reflux, 24 h; b) CH_3I, Cs_2CO_3, DMF.

pound was confirmed to be *cis*-**3** from the comparison of the ^1H NMR spectrum of dimethyl *cis*-*N*-benzyl-3,5-piperidinedicarboxylate derived from *cis*-**3** (TFA, CH_2Cl_2; PhCHO, $NaBH(OAc)_3H$, dichloroethane) with that reported in the literature.[7]

Computational study (HyperChem™) supported our hypothesis in that *cis*-**3** has about 2.1 kcal/mol lower energy for heat of formation than *trans*-**3**.

The transformation of *trans*-**3** to *cis*-isomer was successfully accomplished through isomerization during the hydrolysis of *trans*-**3** (Scheme 2). When *trans*-**3** was heated in MeOH in the presence of K_2CO_3 or Cs_2CO_3, a 9:1 mixture of *cis*- and *trans*-diacid **5** was obtained. This mixture was converted to the *cis*-enriched diester **3** quantitatively upon reaction with MeI in the presence of cesium carbonate.[10] The presence of a 7:3 mixture of



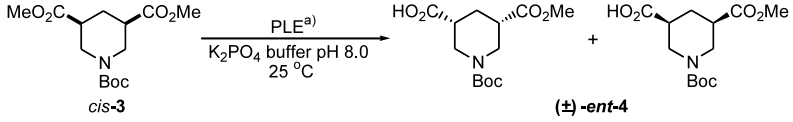
Scheme 3. a) (*S*)-PEA, EtOH, 70°C to rt; b) DPPA, Et_3N, benzene; c) 2-(trimethylsilyl)ethanol; d) Ac_2O, pyridine; e) LiOH, dioxane–water; f) $MeNH_2$, EDC, HOBT, CH_2Cl_2; g) HCl (g), EtOAc.

half-acid ester intermediate **4** was confirmed through HPLC analysis.

In order to desymmetrize the *meso*-diester *cis*-**3**, enzyme-catalyzed kinetic resolution was attempted.[7b] Following precedents in the literature for similar cases, pig liver esterase (PLE) was chosen for the catalyst and the desymmetrization results are listed in Table 1. Due to poor water solubility of the solid substrate *cis*-**3**, a small portion of surfactant (entry 1) or organic cosolvents such as MeCN or DMSO (entries 2 and 3, respectively) were used.[11] However, under any conditions, efficient kinetic resolution has not been achieved, giving only partially resolved half-acid **4** (Table 1). It was of note, however, that the hydrolysis exhibited complete chemoselectivity and the reaction stopped at the half-acid stage.

With this chemoselective enzyme-mediated hydrolysis in hand, we have carried out the resolution of partially resolved **4** with fractional crystallization using α-PEA in good efficiency (Scheme 3).[12] Fractional crystallization was performed with both (*R*)-(+) and (*S*)-(−)-PEA. (*S*)-(−)-PEA favored (+)-*cis*-**4**, which was the major isomer of PLE-catalyzed hydrolysis products.[13] Repetitive crystallizations (five times) were carried out to yield product of over 98% ee. Enantiomeric excess of optically-active half-acid (+)-*cis*-**4** was determined through normal phase HPLC analysis (HP hypersil column, eluted with 1% *i*-PrOH in *n*-hexane, 1.0 mL/min) after derivatization with (−)- or (+)-PEA.

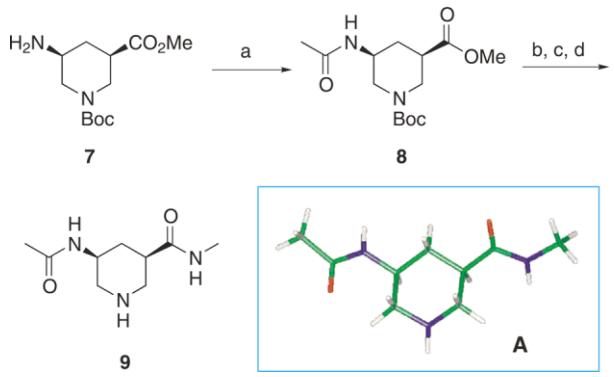
Table 1.



[a] 600 units of PLE / mmol of *cis*-**3**, [*cis*-**3**] = 0.03 M

Entry	Medium	Reaction time	Yield (%)	% e.e.[b]
1	2 drops Triton-X/50 mg of *cis*-**3**	4 days	48	18
2	20% DMSO/phosphate buffer	13 h	93	23
3	20% MeCN/phosphate buffer	12 h	96	28

[b] % e.e. was determined by HPLC spectra analysis of diastereomeric amide.



Scheme 4. a) Ac_2O, pyr; b) LiOH, THF–water; c) $MeNH_2$, EDC, HOBt, DMF; d) TFA, CH_2Cl_2.

The absolute stereochemistry of the product (+)-*cis*-**4** was determined by comparison of optical rotation of (3*S*)-*N*-*t*-butyloxycarbonyl-3-hydroxymethyl-1-piperidine derived from (+)-*cis*-**4** with literature data {$[\alpha]_{365}$ +60.7 (*c* 1, EtOH)}.[7b,14] This result revealed that half-acid (+)-*cis*-**4** resolved with (−)-PEA is equipped with a (3*S*,5*R*) absolute configuration as shown in Scheme 3. Optically active half-acid (+)-*cis*-**4** was converted into β,γ′-diamino acid derivative **6** through Curtius-type rearrangement.[15] Treatment of (+)-*cis*-**4** with diphenylphosphoryl azide (DPPA) and Et_3N in anhydrous benzene provided isocyanate intermediate, which was quenched with 2-(trimethylsilyl)ethanol to give orthogonally protected diamino acid **6** (Scheme 3).

For preliminary conformational analysis of compounds incorporating this unnatural cyclic amino acid unit, a pseudopeptide derivative **9** was prepared from free amine **7** through acetylation of the amine, hydrolysis of the methyl ester, coupling of the corresponding free carboxylic acid with methylamine followed by deprotection of the *N*-Boc group as shown in Scheme 4. Conformational search through molecular mechanics of the resulting compound **9** followed by optimization using ab initio calculation (HF/3-21G*, 41 conformations) and ^1H NMR studies in water (DQF-COSY, ROESY, and temperature variation experiment) indicate the extended β-strand structure **A** as depicted in Scheme 4.

In conclusion, we have developed an efficient method for the preparation of a conformationally constrained, unnatural β,γ′-diamino acid derivative **6**. We are currently investigating the possibility of constructing a combinatorial library toward various enzyme inhibitors including serine and aspartyl proteases from this interesting unnatural amino acid scaffold and the result will be reported in due course.

Acknowledgements

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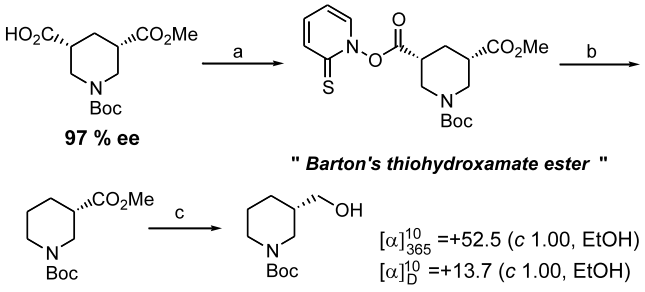
10. *General procedure for epimerization of trans-**3** to cis-**3***: To a solution of *trans*-diester in methanol (5 mL/mmol) was added 3 equiv. of K_2CO_3 and the mixture was refluxed for 24 h. The reaction progress was monitored through HPLC analysis. Filtration followed by concentration of the mixture afforded a yellowish residue. To a solution of the resulting residue in DMF (5 mL/mmol) were added 3.1 equiv. of CH_3I and 3 equiv. of K_2CO_3 and the mixture was stirred at room temperature for 12 h. The crude mixture was filtered, concentrated in vacuo and purified on a silica gel chromatographic column (10% EtOAc in hexane) to provide *cis*-**3** (85% yield) as a white solid: TLC R_f=0.61 (1:2 EtOAc:hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.36 (br, 2H), 3.70 (s, 6H), 2.71 (br, 2H), 2.48 (br, 2H), 2.43 (m, 2H), 1.70 (q, J=12.8 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (150 MHz) 173.2, 154.7, 80.7, 52.3, 45.7, 41.1, 30.5, 28.7; IR (neat) ν 1736, 1697, 1426, 1170 cm^{-1}; HRMS calcd for $C_{14}H_{23}NO_6$ [M+1] 302.1604, found 302.1605.
11. *General procedure for PLE-catalyzed hydrolysis of cis-**3***: *cis*-diester-**3** was suspended in 0.1 M aq. KH_2PO_4 (30 mL/mmol) solution of pH 8.0 containing CH_3CN (6 mL/mmol). To the stirred suspension was added PLE (600 units/mmol) at 25°C in one portion and the pH was maintained by addition of 2N aq. NaOH solution as needed. Stirring was continued at 25°C for 12 h. After complete consumption of *cis*-**3**, the resulting mixture was filtered via a Celite pad, acidified with 2N HCl solution and the aqueous layer was extracted five times with EtOAc. The combined extracts were dried over anhydr. $MgSO_4$, filtered and concentrated to afford the partially resolved *cis*-**4** (96% yield, 28% ee) as a white solid.
12. *General procedure for fractional crystallization*: Partially resolved *cis*-**4** (28% ee) was dissolved in hot ethanol (70°C, 1 mL/mmol) and 1.01 equiv. of (*S*)-(−)-1-phenylethylamine was added dropwise with caution. The solution was cooled to room temperature and allowed to stand for 24 h, which resulted in the precipitation of a salt. The salt was dissolved again in hot EtOH (70°C), cooled to room temperature and allowed to stand for 24 h. After repeating the same process three times, the resulting salt was dissolved in water, acidified with satd aquiv $KHSO_4$ solution and extracted three times with EtOAc. The combined extracts were dried (anhydr. $MgSO_4$), filtered and concentrated to afford the (+)-*cis*-**4** (55% yield, >98% ee) as a white crystalline solid: mp 155–156°C, $[\alpha]_D^{26}$ +5.4 (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.37 (br, 2H), 3.71 (s, 3H), 2.73 (br, 2H), 2.65–2.35 (br, 3H), 1.72 (q, J=12.6 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (150 MHz) δ 177.8, 173.3, 154.9, 81.1, 61.3, 52.4, 45.6, 41.0, 30.4, 28.7, 14.5; HRMS calcd for $C_{13}H_{22}NO_6$ [M+1] 288.1447, obsd 288.1441.
13. Preparation of (−)-*cis*-**4** was possible through employing (*R*)-(+)-PEA following the same fractional crystallization process.
14. The synthetic scheme for determination of optical rotation is as follows (Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479):



a) 1) $ClCO_2Et$, NMP, CH_2Cl_2, 2) 2-mercaptopyridine *N*-oxide, Et_3N, THF; b) *t*-BuSH, W-lamp, C_6H_6; c) $LiBH_4$, THF.

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