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Facile access to chiral β-homoglutamic acid from 3-cyclohexene-carboxylic acid

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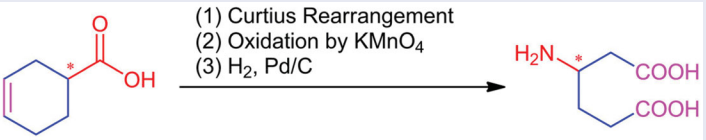
ABSTRACT

A convenient, safe, and effective synthetic protocol for the synthesis of chiral β-homoglutamic acid was described. The strategy started from 3-cyclohexenecarboxylic acid, followed by three steps classic reaction including Curtius Rearrangement, oxidative cleavage of alkene, and debenzylation by catalytic hydrogenation. The chiral β-homoglutamic acid was prepared with a high yield and high enantiomeric excess.

GRAPHICAL ABSTRACT



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KEYWORDS
β-Amino acids; β-homoglutamic acid; chiral; Curtius rearrangement; 3-cyclohexenecarboxylic acid

Introduction

β-amino acids have unique bioactivity, stability in peptide, and the ability to self-assembly into high-order structures. They have been used as very important scaffolds for peptide drugs and composites.[1] β-homoglutamic acid is one of the most important unnatural β-amino acids. In recent years, it has been widely used in the synthesis of new peptide drugs and the development of nanomaterials.[2] Research on its efficient synthetic method has also been gradually paid attention. There are currently two main strategies to obtain chiral β-homoglutamic acid. One is the use of optically pure chiral auxiliary reagents for chiral induction synthesis, such as the optically pure 2-tert-butyl-perhydropyrimidinone induction method reported by Snieckus,[3] and the D-gulose derived hydroxylamine induction method developed by Bode.[4] Although these methods can successfully prepare a variety of β-amino acid including chiral β-homoglutamic acid, the desired chiral auxiliary reagent is usually not easy to obtain, and the

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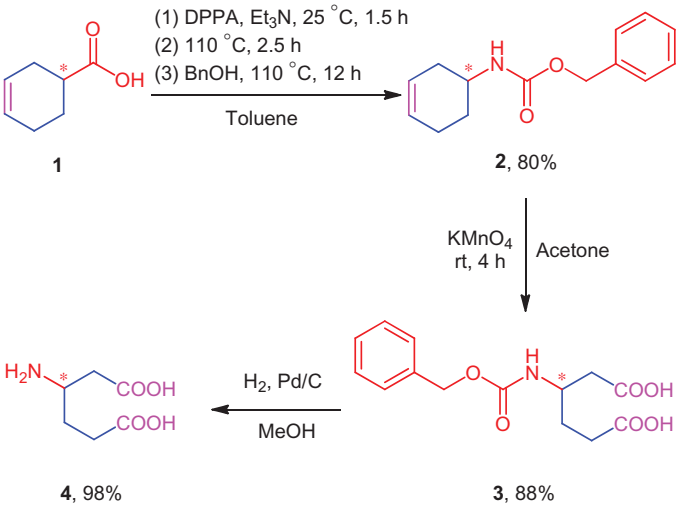

Scheme 1. A new synthetic route of optically pure β-homoglutamic acid.

preparation procedure is tedious and costly. The other route is using chiral glutamic acid as the starting material to prepare diazoketone with diazomethane at low temperature and then is rearranged to obtain β-homoglutamic acid.[2c,5] However, it is very dangerous to use easily exploded diazomethane, which requires reaction at low temperature and is not suitable for amplification.

Here, a new route for the synthesis of β-homoglutamic acid is illustrated. (Scheme 1) Chiral 3-cyclohexenecarboxylic acid (**1**) is used as a starting material. After a simple three-step reaction of Curtius Rearrangement, oxidative cleavage of alkene, and debenzylation by catalytic hydrogenation, chiral β-homoglutamic acid (**4**) can be obtained with a high yield.

Results and discussion

(*S*)-3-Cyclohexene formic acid is the starting material for the synthesis of Edoxaban[6] (An anticoagulant drug as important as Fondaparinux[7] and Idraparinux[8]), which is obtained by the resolution of optically pure α-methylbenzylamine. There are bulk commodities supplied by tonnage in the market with low price. 3-Cyclohexene formic acid has one more carbon than β-homoglutamic acid. The carboxyl group of the chiral carbon link can be converted into amino group just by Curtius rearrangement, and the stereo configuration can be maintained.[9] As to olefin double bonds, it is very easy to be oxidized and cleaved into adipic acid to form the whole framework of β-homoglutamic acid. Therefore, we took the chiral cyclohexene carboxylic acid (**1**) as the starting material, and obtained chiral cbz-3-cyclohexene amine (**2**) in 80% yield through the optimized one-pot Curtius rearrangement reaction. Then, we used potassium permanganate to oxidize cbz-3-cyclohexene amine (**2**) at room temperature in 88% yield and 99% enantiomeric excess (ee) obtaining CBZ protected β-homologic acid (**3**). And finally CBZ was removed by catalytic hydrogenation at 5% Pd/C for 12 h to obtain near-quantitative yield of β-homoglutamic acid (**4**).

Experimental section

All commercial reagents were used as received without further purification unless otherwise stated. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded using a 400 MHz spectrometer. Chemical shifts were reported in parts per million (ppm), using $CDCl_3$ ($\delta_H = 7.26$, $\delta_C = 77.12$) or DMSO-d6 ($\delta_H = 2.50$, $\delta_C = 39.9$) or D_2O ($\delta_H = 4.79$) as internal standards. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). High-resolution mass spectra (HRMS) were obtained by the ESI ionization sources using TOF MS technique. Melting point was obtained on a micromelting point apparatus.

Procedure for the synthesis of (S)-benzyl cyclohex-3-en-1-ylcarbamate ((S)-2)

To a solution of (*S*)-cyclohex-3-enecarboxylic acid (10.0 g, 79 mmol) in toluene (100 mL) was added 8.8 g TEA (87 mmol) and 22.9 g DPPA (83 mmol). The mixture was stirred at 25 °C for 1.5 h under N_2 atmosphere. Then, it was warmed to 110 °C and stirred for another 2.5 h. BnOH (9.4 g, 87 mmol) was added to the mixture and the resulting mixture was stirred at 110 °C for 12 h. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by recrystallization (ethyl acetate/n-hexane = 1/10) to obtain (*S*)-benzyl cyclohex-3-en-l-ylcarbamate ((***S***)-**2**) 14.6 g. Yield 80%; white solid; mp 58-59 °C (lit.[10] 54–56 °C); $[\alpha]_D^{30}$ −26.4 (c 1.0, MeOH) (lit.[10] $[\alpha]_D^{25}$ −17.1 (c 0.36, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.37 (m, 5H), 5.57–5.69 (m, 2H), 5.10 (s, 2H), 4.80 (s, 1H), 3.88 (s, 1H), 2.37–2.42 (m, 1H), 2.07–2.20 (m, 2H), 1.84–1.94 (m, 2H), 1.52–1.61 (*m*, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 136.6, 128.5, 128.2, 128.1, 127.0, 124.3, 66.5, 46.2, 31.9, 28.3, 23.5. HRMS (ESI) *m*/*z* calculated for $[M + Na]^+$: 254.1157; found: 254.1154.

Using (*R*)-cyclohex-3-enecarboxylic acid as the starting material, (*R*)-Benzyl cyclohex-3-en-1-ylcarbamate ((*R*)-**2**) was synthesized by the same method as (***S***)-**2**. Yield 79%, mp 57-58 °C, $[\alpha]_D^{30}$ +26.3(c 1.0, MeOH) .

Procedure for the synthesis of (S)-3-(((benzyloxy)carbonyl)amino)hexanedioic acid ((S)-3)

A solution of (***S***)-**2** (10 g, 43.4 mmol) in acetone (500 ml) was slowly added 250 mL of 0.5 M potassium permanganate aqueous solution dropwise at 0 °C. After the addition, the reaction was continued at room temperature, and detected by TLC until the reaction was complete. Sodium thiosulfate was added to quench the excess potassium permanganate, and then the solution was adjusted to pH < 2 with 3 M hydrochloric acid, and stirring was continued for 20 min. Acetone was distilled off under reduced pressure, and the aqueous phase was extracted three times with 250 mL of ethyl acetate. The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain crude product, which was then purified by recrystallization (ethyl acetate/n-hexane = 1/1)to obtain (***S***)-**3** 11.3 g. Yield 88%; white solid; ee value 99% ((*S*)-major)[11]; mp 182–183 °C; $[\alpha]_D^{30}$−9.8 (c 1.0, MeOH) . ^{1}H NMR (400 MHz, DMSO) δ 12.14 (s, 2H), 7.29–7.38 (m, 5H), 7.22 (d, $J = 8.6$ Hz, 1H), 5.00 (*s*, 2H), 3.75–3.86 (*m*, 1H), 2.34–2.40 (*m*, 2H), 2.20 (*t*, $J = 7.5$ Hz, 2H), 1.67–1.79 (*m*, 1H), 1.52–1.63 (*m*, 1H). ^{13}C NMR (100 MHz, DMSO)

δ 174.6, 172.8, 156.1, 137.7, 128.8, 128.2, 128.1, 65.6, 47.9, 40.0, 30.7, 29.9. HRMS (ESI) m/z calculated for $[M+Na]^+$: 318.0948; found: 318.0950.

Using (***R***)-**2** as the starting material, (*R*)-3-(((benzyloxy)carbonyl)amino)hexanedioic acid ((*R*)-**3**) was synthesized by the same method as (***S***)-**3**. Yield 87%; white solid; ee value 99% ((*R*)-major)[11]; mp 182–183 °C; $[\alpha]_D^{30}$ + 10.0 (c 1.0, MeOH) .

Procedure for the synthesis of L-3-aminohexanedioic acid (L-4)

(***S***)-**3** (10 g, 33.9 mmol) was dissolved in 100 mL of methanol and was added 0.5 g of 10% Pd/C, replaced the air with hydrogen, and stirred under 15 psi H_2 for 10 h at room temperature. Then, the catalyst was filtered out and the reaction solution was concentrated under reduced pressure to obtain L-**4** 5.35 g, Yield 98%; white solid; mp 188–190 °C (lit.[3] 200–202 °C); $[\alpha]_D^{30}$+30.7 (c 0.4, H_2O) (lit.[3] $[\alpha]_D^{20}$+29.3 (c 0.37, H_2O)). ^{1}H NMR (400 MHz, D_2O) δ 3.50–3.54 (*m*, 1H), 2.59–2.63 (*m*, 1H), 2.39–2.51 (*m*, 3H), 1.86–1.93 (*m*, 2H). ^{13}C NMR (100 MHz, D_2O) δ = 178.3, 176.7, 48.5, 37.4, 30.9, 27.6. HRMS (ESI) m/z calculated for $[M-H]^-$: 160.0610; found: 160.0616.

Using (*R*)-**3** as the starting material, D-3-aminohexanedioic acid (D-**4**) was synthesized by the same method as L-**4**. Yield 97%; white solid; mp 190–192 °C; $[\alpha]_D^{30}$−36.0 (c 0.4, H_2O).

Conclusions

We have developed a novel route for the synthesis of chiral β-homoglutamic acid. We believe that these observations should further increase the potential application of β-homoglutamic acid in the design and synthesis of drugs and the development of new materials.

HPLC, ^{1}H and^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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