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Assymetric synthesis of (2*S*,3*R*)- and (2*S*,3*S*)-[2-^{13}C;3-^{2}H] glutamic acid

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ABSTRACT

We have developed a synthetic route for (2*S*,3*R*)- and (2*S*,3*S*)-[2-^{13}C;3-^{2}H] glutamic acids with high enantioselectivity. The key reactions in this synthesis are the asymmetric reduction of the 2,3-didehydroornithine derivative using the (*S*,*S*)-Et-DuPHOS-Rh catalyst and the oxidation of the δ-position by ruthenium catalysis.

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The replacement of ^{1}H by ^{2}H has been recognized as an efficient method for eliminating undesired peaks in ^{1}H nuclear magnetic resonance (NMR) spectra and for observing NMR signals against the relaxation caused by ^{1}H.[1] We recently proposed a novel labeling strategy, termed stereo-array isotope labeling (SAIL), for high-throughput NMR structure determination of proteins.[2] In the case of amino acid metabolism studies, the analysis of ^{13}C isotope shifts induced by H/^{2}H exchange in a $^{2}H_2O$ system is utilized.[3] In this study, we carried out the chemical synthesis of (2*S*,3*S*)- and (2*S*,3*R*)-[2-^{13}C;3-^{2}H] glutamic acids for metabolic analysis. Several groups have reported the stereoselective synthesis of glutamic acid derivatives labeled with deuterium at prochiral protons.[4] However, these synthetic routes were not suitable for regioselective ^{13}C labeling coupled with deuterium labeling because the starting ^{13}C-labeled materials were unavailable. We therefore wish to report the simple synthesis of (2*S*,3*S*)- and (2*S*,3*R*)-[2-^{13}C;3-^{2}H] glutamic acids via the asymmetric hydrogenation of a 2,3-didehydroamino acid derivative, prepared from commercially available materials. Generally, during the synthesis of glutamic acid labeled with deuterium at the β-position, the synthetic route involving the hydrogenation of the 2,3-didehydroglutamic acid derivative may be straightforward. To the best of our knowledge, the regioselective ^{13}C labeling of the 2,3-didehydroglutamic acid derivative can be achieved by using an α-oxoglutarate or a dehydroserine derivative as the starting material. This report describes a simple method for the synthesis of [2-^{13}C;3-^{2}H] glutamic acid, routed through ornithine as the key intermediate. Asymmetric hydrogenation of the [2-^{13}C;3-^{2}H] 2,3-didehydroornithine derivative,[5] which is derived from readily available [2-^{13}C] glycine and β-alanine, is carried out to yield an ornithine derivative labeled with deuterium at the β-position. This is stereoselectively followed by conversion of the derivative into the target [2-^{13}C; 3-^{2}H] glutamic acids by oxidation of the δ-position.

As shown in Scheme 1, the synthesis of (2*S*,3*R*)-[2-^{13}C;3-^{2}H] glutamic acid (**7**) commenced with the preparation of the stable isotope-labeled dehydroornithine derivative (**3**) using the Horner–Wadsworth–Emmons[6] reaction. The starting *N*-Boc-3-amino[1-^{2}H]propionaldehyde (**1**) was prepared by the reduction of the Weinreb amide[7] of *N*-Boc-β-alanine with lithium aluminum deuteride ($LiAlD_4$),[8] and was then condensed with phosphoryl[2-^{13}C]glycine ester (**2**)[9] in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give 2,3-didehydro[2-^{13}C;3-^{2}H]-ornithine (**3**) in 71% yield. Highly *Z*-selective olefination was observed when the reaction was conducted at −25 °C.

Asymmetric hydrogenation of the obtained dehydroornithine (**3**) was carried out under medium pressure (0.4 MPa) of hydrogen in the presence of (+)-1,2-bis[(2*S*,5*S*)-2,5-diethylphospholano]benzene (cyclooctadiene)rhodium(I) trifluoromethanesulfonate [(*S*,*S*)-Et-DuPHOS-Rh], because the DuPHOS family of catalysts is highly efficient for the hydrogenation of β-monosubstituted acetamidoacrylates, yielding a variety of amino acids with high enantioselectivities.[10] In our previous study, a DuPHOS-Rh catalyst was also employed for the asymmetric hydrogenation of dehydroserine derivatives.[11] The stereochemistry at the α- and β-positions of [2-^{13}C;3-^{2}H]ornithine (**4**) was determined after the final glutamic acid was obtained.

According to Yoshifuji's procedure,[12] the conversion of ornithine (**4**) to glutamine (**5**) was performed using a catalytic amount of ruthenium dioxide and an excess of sodium periodate in a two-phase system of ethyl acetate and water. However, [2-^{13}C;3-^{2}H]glutamine (**5**) was obtained in only 38% yield because of the considerable side reaction yielding the cyclic compound **6**.

Hydrolysis of **5** was performed by refluxing it in 2 M HCl, and subsequent ion exchange treatment of the obtained glutamic acid hydrochloride with DOWEX 50WX8 afforded (2*S*,3*R*)-[2-^{13}C;3-^{2}H]

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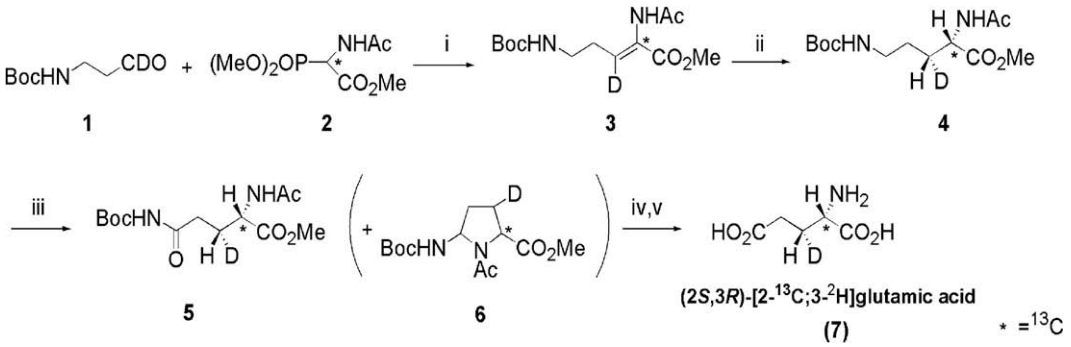


Scheme 1. Reagents and conditions: (i) DBU, CH_2Cl_2, −25 °C, 71%; (ii) (*S*,*S*)-Et-DuPHOS-Rh, benzene, H_2 (0.4 MPa), 84%; (iii) RuO_2, $NaIO_4$, ethyl acetate-H_2O, 38%; (iv) 2 M HCl reflux; (v) DOWEX 50WX8, 70% (2 steps).

glutamic acid (**7**) in 70% yield. The enantiopurity based on the α-position was determined to be 99% ee by high performance liquid chromatography (HPLC) analysis using a chiral column (MCIGEL CRS10W). Figure 1a shows the 300 MHz ^{1}H NMR spectrum of **7**. As compared to that of the unlabeled glutamic acid (Fig. 1d), the signal for the 3*R* proton disappears completely, indicating that **7** has *R* stereochemistry at the β-position. This stereochemical outcome can be attributed to the exclusive cis-addition of hydrogen to the α-re-face of deuterated (*Z*)-2,3-didehydroornithine (**3**), promoted by the (*S*,*S*)-Et-DuPHOS-Rh catalyst.

We next performed the asymmetric deuteration of 2,3-didehydro[2-^{13}C]ornithine (**9**), prepared from *N*-Boc-3-aminopropionaldehyde (**8**) and **2**, in 60% yield (Scheme 2), in order to obtain its isotopic stereoisomer, (2*S*,3*S*)-[2-^{13}C;3-^{2}H] glutamic acid (**13**). The (*S*,*S*)-Et-DuPHOS-Rh catalyst afforded [2-^{13}C;2,3-$^2H_2$]ornithine (**10**) in 98% yield with the (2*S*,3*S*)-configuration, which was confirmed after its conversion to glutamic acid.

The obtained ornithine (**10**) was then subjected to ruthenium-catalyzed oxidation. Sheldon and co-workers pointed out that low pH has a detrimental effect on a catalytic system involving ruthenium tetroxide.[13] We found that keeping the pH mildly alkaline by adding aqueous sodium carbonate during the course of the reaction improved the chemical yield of the glutamine from 38% (for **5**) to 64% (for **11**).

The glutamine (**11**) was then deprotected to give (2*S*,3*S*)-[2-^{13}C;2,3-$^2H_2$] glutamic acid (**12**) in 82% yield. The enantiopurity of **12** with respect to the α-position was also confirmed by HPLC analysis to be 99% ee. Its ^{1}H NMR spectrum (Fig. 1b) confirmed that

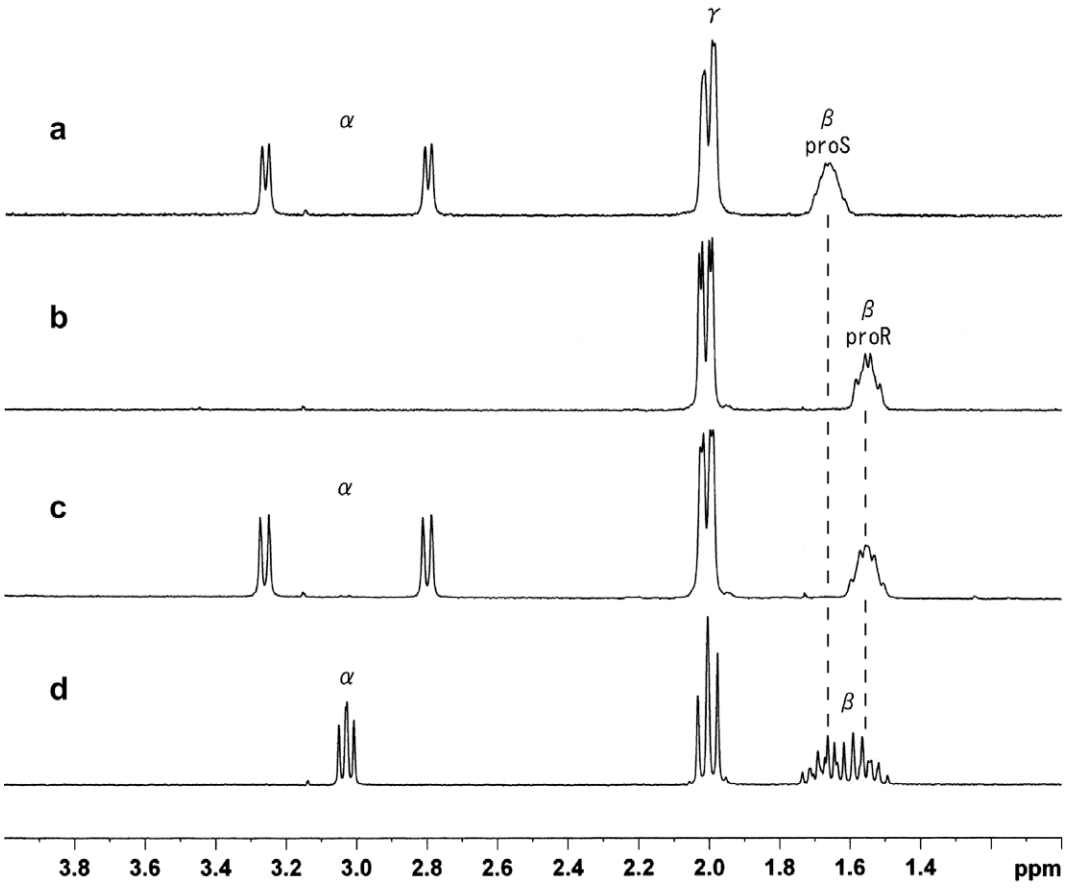
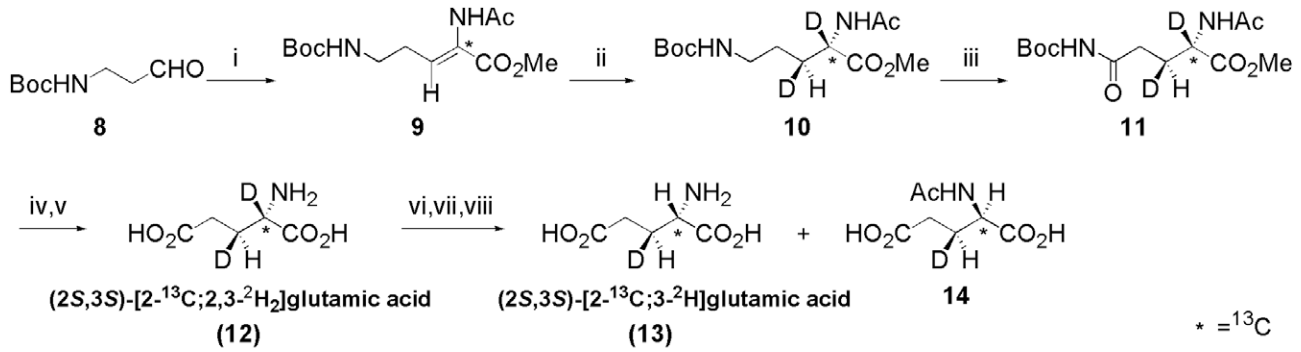


Figure 1. 300 MHz ^{1}H NMR spectra of (a) (2*S*,3*R*)-[2-^{13}C;3-^{2}H]glutamic acid (**7**), (b) (2*S*,3*S*)-[2-^{13}C;2,3-$^2H_2$]glutamic acid (**12**), (c) (2*S*,3*S*)-[2-^{13}C;3-^{2}H]glutamic acid (**13**), and (d) unlabeled glutamic acid in NaOD–D_2O.



Scheme 2. Reagents and conditions: (i) **2**, DBU, CH_2Cl_2, −25 °C, 83%; (ii) (*S*,*S*)-Et-DuPHOS-Rh, benzene, D_2 (0.4 MPa), 98%; (iii) RuO_2, $NaIO_4$, Na_2CO_3, ethyl acetate–H_2O, 64%; (iv) 2 M HCl reflux; (v) DOWEX 50WX8, 82% (2 steps); (vi) 5 M NaOH, $(CH_3CO)_2O$, 38 °C; (vii) porcine kidney acylase I, pH 8, 37 °C; (viii) DOWEX 50WX8, (**13**): 39% (2 steps), (**14**):43%.

the regioselective and stereoselective incorporation of stable isotopes were accomplished. Finally, we carried out deuterium-hydrogen exchange at the α-position using a traditional racemization-resolution procedure.[14] Thus, **12** was treated with an excess of acetic anhydride in 5 M NaOH at 38 °C overnight. The optical resolution of the racemic *N*-acetylglutamic acid was effected through the L-directed deacetylation with porcine kidney acylase I to give (2*S*,3*S*)-[2-^{13}C;3-^{2}H] glutamic acid (**13**) in 39% yield, along with unreacted (2*R*,3*S*)-*N*-acetyl[2-^{13}C;3-^{2}H] glutamic acid (**14**) in 43% yield. The ^{1}H NMR spectrum of **13** (Fig. 1c) indicated the complete replacement of α-deuterium by a hydrogen atom.

In summary, we have achieved the asymmetric synthesis of (2*S*,3*R*)- and (2*S*,3*S*)-[2-^{13}C;3-^{2}H] glutamic acids with high enantioselectivity. The key reactions in this synthesis are the asymmetric hydrogenation or deuteration of the 2,3-didehydroornithine derivative using the (*S*,*S*)-Et-DuPHOS-Rh catalyst and the subsequent ruthenium-catalyzed δ-oxidation leading to the formation of the glutamine derivative. Further modification of the present procedure to obtain other labeled amino acids is now underway.

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