Tetrahedron Letters 50 (2009) 1482–1484

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Kosuke Okuma [a,b], Akira M. Ono [a], Seiji Tsuchiya [a], Makoto Oba [b], Kozaburo Nishiyama [b], Masatsune Kainosho [c,d], Tsutomu Terauchi [a,*]

[a] SAIL Technologies Inc., 1-1-40, Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, Japan
[b] Department of Materials Chemistry, Tokai University, 317 Nishino, Numazu, Shizuoka 410-0395, Japan
[c] Graduate School of Science, Structural Biology Research Center, Nagoya University, Furo-cho, Chikusa-ku 464-8601, Japan
[d] Graduate School of Science, Tokyo Metropolitan University, 1-1 Minami-osawa, Hachioji, Tokyo 192-0397, Japan

ARTICLE INFO

Article history:
Received 12 December 2008
Accepted 13 January 2009
Available online 19 January 2009

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.

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.

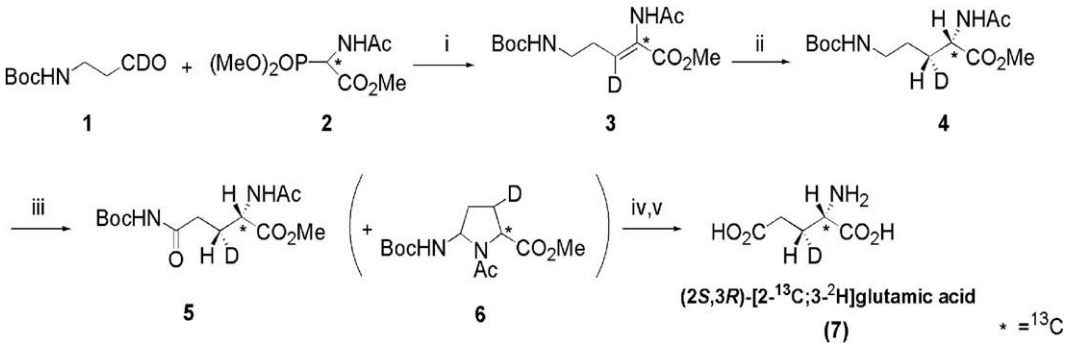
Asymmetric hydrogenation of the obtained dehydroornithine (**3**) was carried out under medium pressure (0.4 MPa) of hydrogen in the presence of (+)-1,2-bis[(2*S*,5*S*)-2,5-diethylphospholano]benzene (cyclooctadiene)rhodium(I) trifluoromethanesulfonate [(*S*,*S*)-Et-DuPHOS-Rh], because the DuPHOS family 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]

* Corresponding author. Tel.: +81 45 508 7651; fax: +81 45 508 7652.
E-mail address: terauchi@sail-technologies.com (T. Terauchi).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.01.062



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

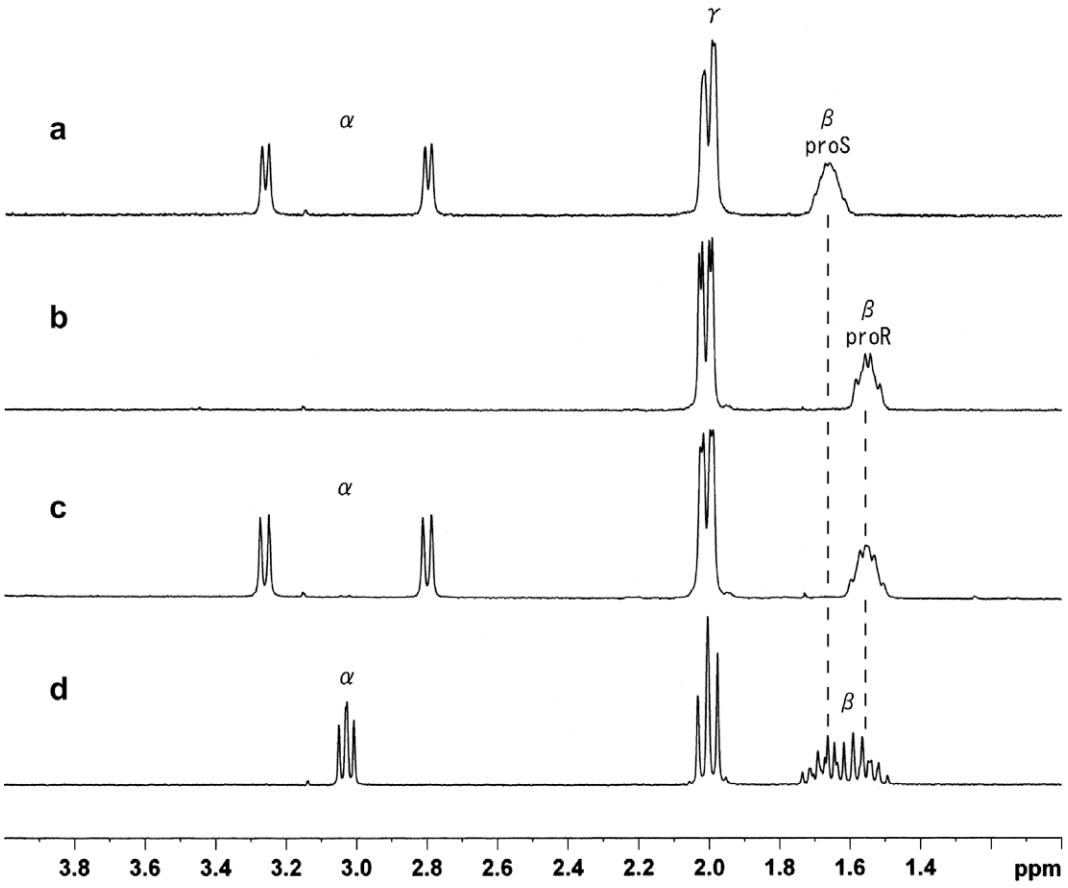
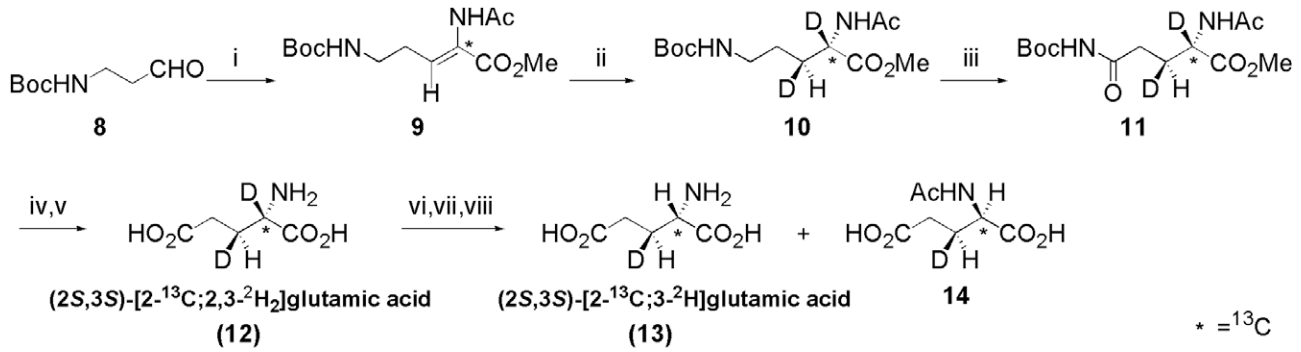


Figure 1. 300 MHz ^{1}H NMR spectra of (a) (2*S*,3*R*)-[2-^{13}C;3-^{2}H]glutamic acid (**7**), (b) (2*S*,3*S*)-[2-^{13}C;2,3-$^2H_2$]glutamic acid (**12**), (c) (2*S*,3*S*)-[2-^{13}C;3-^{2}H]glutamic acid (**13**), and (d) unlabeled glutamic acid in NaOD–D_2O.



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.

Acknowledgments

We are grateful to A. Shirai for mass spectrum analyses. This work has been supported by the Core Research for Evolutional Science and Technology (CREST) of the Japan Science and Technology Agency (JST).

References and notes

1. Butter, W. T.. *Science* **1968**, *161*, 795–798; Markley, J. L.; Putter, I.; Jardetzky, O. *Science* **1968**, *161*, 1249–1251.
2. Kainosho, M.; Torizawa, T.; Iwashita, Y.; Terauchi, T.; Ono, A.; Güntert, P. *Nature* **2006**, *440*, 52–57.
3. García-Martín, M. L.; García-Espinosa, M. A.; Ballesteros, P.; Bruix, M.; Cerdán, S. *J. Biol. Chem.* **2002**, *227*, 7799–7807.
4. Dietrich, P.; Young, D. W. *Tetrahedron Lett.* **1993**, *34*, 5455–5458; (b) Oba, M.; Terauchi, T.; Hashimoto, J.; Tanaka, T.; Nishiyama, K. *Tetrahedron Lett.* **1997**, *38*, 5515–5518.
5. Baldwin, J. E.; Merritt, K. D.; Schofield, C. J. *Tetrahedron Lett.* **1993**, *34,24*, 3919–3920.
6. Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99.
7. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
8. Blaney, P.; Grigg, R.; Rankovic, Z.; Thornton-Pett, M.; Xu, J. *Tetrahedron* **2002**, *58*, 1719–1737.
9. (a) Mazurkiewicz, R.; Kuźnik, A.; Grymel, M.; Październiok-Holewa, A. *ARKIVOK* **2007**, *vi*, 193–216; (b) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53–60; (c) Oba, M.; Ueno, R.; Fukuoka, M.; Kainosho, M.; Nishiyama, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1603–1609.
10. (a) Burk, M. *J. Acc. Chem. Res.* **2000**, *33*, 363–372; (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125–10138; (c) Stammers, T. A.; Burk, M. J. *Tetrahedron Lett.* **1999**, *40*, 3325–3328; (d) Jones, S. W.; Palmer, C. F.; Paul, J. M.; Tiffin, P. D. *Tetrahedron Lett.* **1999**, *40*, 1211–1214; (e) Debenham, S. D.; Debenham, J. S.; Burk, M. J.; Toone, E. J. *J. Am. Chem. Soc.* **1997**, *119*, 9897–9898; (f) Rizen, A.; Basu, B.; Chattopadhyay, S. K.; Dossa, F.; Frejd, T. *Tetrahedron: Asymmetry* **1998**, *9*, 503–512; (g) Hiebl, J.; Kollmann, H.; Rovenszky, F.; Winkler, K. *J. Org. Chem.* **1999**, *64*, 1947–1952.
11. Terauchi, T.; Kobayashi, K.; Okuma, K.; Oba, M.; Nishiyama, K.; Kainosho, M. *Org. Lett.* **2008**, *10*, 2785–2787.
12. Yoshifuji, S.; Tanaka, K.; Nitta, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2994–3001.
13. Gonsalvi, L.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **2002**, 202–203.
14. Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; John Wiley and Sons: New York, 1961.