

Study on Synthesis of (R)-tert-butyl 2, 2-dimethyl-4-(prop-1-yn-1-yl)oxazolidine-3-carboxylate

Cheng Liang^{1,a}, Shuanglin Qin^{1,b}, Xiaoji Wang^{1,c*} and Shuangping Huang^{1,d*}

¹School of Pharmacy, Jiangxi Science and Technology Normal University, Jiangxi, 330013, China

^a1147764672@qq.com, ^bqinshuanglin0@163.com, ^{c*}13767101659@163.com, ^{d*}185544590@qq.com

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Abstract. (R)-tert-butyl 2,2-dimethyl-4-(prop-1-yn-1-yl)oxazolidine-3-carboxylate, an key intermediate of Biotin which is a water-soluble vitamin involved in an essential part of the metabolic cycle causing catalytic fixation of carbon dioxide in the biosynthesis of fatty acids, sugars, and α -amino acids, was synthesized from L-cystine in overall yield 41% through six steps, which included esterification, Boc protection, acetonization, reduction, Corey-Fuchs reaction.

Introduction

Biotin (vitamin H, Figure 1) is a known as a co-enzyme for carboxyl translocation reactions such as pyruvate carboxylase, acetyl-CoA carboxylase, and propionyl-CoA carboxylase. Biotin may exist in the apoenzyme of biotin-dependent enzymes. It has been widely used in medicine and also used in sports drinks, infant formula, milk and other healthy food [1]. So taking it appropriately is beneficial in our health and is good for the development of children and adults, through improved physical mechanisms that combat aging, disease and efficient mental capacity [2]. Since biotin plays an important role in many kinds of areas, its synthesis has arouse much attention. Here we described the synthesis of (R)-tert-butyl 2,2-dimethyl-4-(prop-1-yn-1-yl)oxazolidine-3-carboxylate serving as a potential intermediate for the synthesis of Biotin from the chiral material L-Serine.

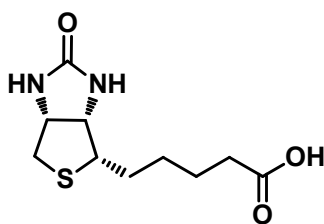
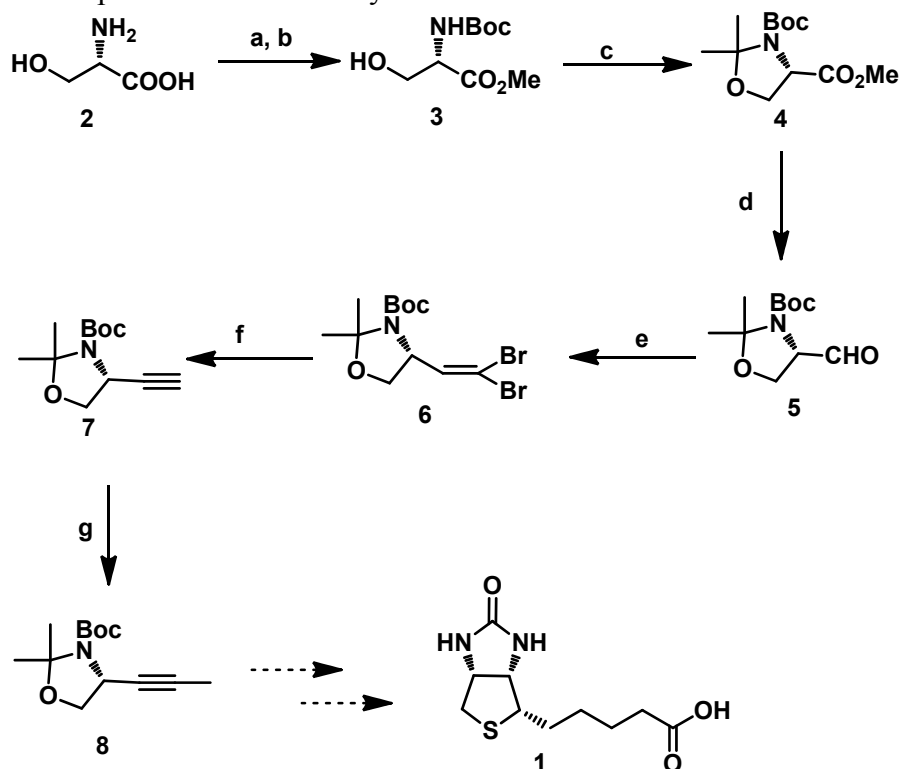


Fig. 1 Biotin

A practical route of (R)-tert-butyl 2,2-dimethyl-4-(prop-1-yn-1-yl)oxazolidine-3-carboxylate (8) was synthesized from the low-cost material L-Serine, illustrated in Scheme 1. Commercially available compound L-serine was first transformed into the protected methyl ester (4) and the latter was then reduced to the aldehyde by DIBAL-H. The reaction employed for the preparation of (4) involved the protection of the amino acid using di-tert-butyl dicarbonate, esterification with methanol and thionyl chloride, and protection of hydroxyl and amine group with 2,2-dimethoxypropane under the acid catalysis of boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$). Ester (4) was transformed into the aldehyde using the strategy of half-reduction with DIBAL-H by controlled condition [3]. This strategy of DIBAL-H reduction was more convenient compared with that through reduced by lithium aluminum hydride and following Swern oxidation using DMSO and COCl_2 in the presence of diisopropylethylamine [4] which provided (5) in good yield (overall yield 85% from L-Serine). Alkyne (7) was synthesized via a Corey-Fuchs reaction [5]. The modified procedure we used, in the presence of Et_3N at low temperature, provided an efficient transformation to (6). Conversion into (7) was accomplished simply by treating with 2 equiv of n-BuLi at -78°C . Next terminal alkyne (8) was

synthesized using potassium iodide, 2.5 equiv of HMPA and 1.2 equiv of n-BuLi at -78°C. With (8) in hand, we will attempt to finish the total synthesis of Biotin in the future.



a) SOCl_2 , MeOH; b) Boc_2O , Et_3N , DCM; c) 2,2-dimethoxypropane, $\text{BF}_3 \cdot \text{OEt}_2$, acetone; d) DIBAL-H, DCM; e) PPh_3 , CBr_4 , Et_3N , DCM, -60°C; f) n-BuLi, THF, -78°C to -15°C; g) n-BuLi, THF, CH_3I , HMPA, -78°C to rt.

Fig. 2 Synthesis of Key intermediate of Biotin
(R)-tert-butyl 2,2-dimethyl-4-(prop-1-yn-1-yl)oxazolidine-3-carboxylate (8)

Experiment

NMR spectra were recorded on a BRUKER AV-400MHz NMR(Nuclear Magnetic Resonance). High-resolution FAB mass spectra (HR-FABMS) were recorded on a Finnigan MAT 95 mass spectrometer. Optical rotations were recorded on a Perkin-Elmer 343 Polarimeter. All solvents are refined by standard method.

(S)-methyl 2-(tert-butoxycarbonylamino)-3-hydroxypropanoate (3)

A solution of L-serine (2) (8.4 g, 80 mmol) in methanol (400 mL) is cooled to 0°C, and thionyl chloride (9.52 mL, 120 mmol) is added dropwise. The solution is slowly heated to reflux and then refluxed overnight. After that, the solution is allowed to cool to room temperature and the solvent is removed under reduced pressure to give crude methyl serinate hydrochloride (12.2 g, 98% yield) as a white crystalline solid that is used without further purification.

A solution of methyl serinate hydrochloride (12.0 g, 80 mmol) in dichloromethane (400 mL) is cooled to 0°C, and triethylamine (24.53 mL, 176 mmol) is added, and stirred for 5 min. Then, di-tert-butyl dicarbonate (18.83 mL, 88 mmol) is added dropwise. After 10 min of additional stirring, the ice-water bath is removed and the suspension is stirred overnight at room temperature. The solvent is removed under reduced pressure and saturated aqueous bicarbonate solution (250 mL) is added. The aqueous phase is extracted with dichloromethane. The combined organic phases are washed with brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. Purification with flash chromatography on silica gel eluting with (1:1) petroleum ether-ethyl acetate gives N-Boc-L-serine methyl ester (3) (14.2 g, 99% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ : 1.44 (s, 9H), 3.01 (br s, 1H), 3.80 (s, 3H), 3.79 (dd, 1H, $J = 11, 3.3$), 3.92 (br d, 1H, $J = 8.1$), 4.31-4.37 (m, 1H), 5.55 (br d, 1H, $J = 7.5$).

(S)-3-tert-butyl-4-methyl-2,2-dimethyloxazolidine-3,4-dicarboxylate (4)

To a solution of N-Boc-L-serine methyl ester (3) (14.0 g, 63.89 mmol) in acetone (300 mL) is added 2,2-dimethoxypropane (86.3 mL, 701.6 mmol) and boron trifluoride etherate (BF₃·OEt₂) (0.61 mL, 4.8 mmol) at 0°C. The resulting orange solution is stirred at room temperature overnight. The solvent is removed under reduced pressure. Saturated aqueous sodium bicarbonate solution (250 mL) is added, and the aqueous layer is extracted with diethyl ether. The combined organic phases are washed with brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue is purified with flash chromatography on silica gel eluting with (6:1) petroleum ether-ethyl acetate to give oxazolidine methyl ester (4) (14.8 g, 93% yield) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃, 75°C) δ: 1.38 (s, 9 H), 1.50 (br s, 3 H), 1.83 (br s, 3 H), 3.33 (s, 3 H), 3.70 (m, 1 H), 3.81 (dd, 1 H, *J* = 8.8, 3.2), 4.26 (m, 1 H).

1,1-Dimethylethyl (S)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (5)

To a stirred solution of oxazolidine methyl ester (4) (14.0 g, 54.0 mmol) in CH₂Cl₂ (300 mL) cooled to -78 °C was added DIBAL-H (80.0 mL, 1M in THF, 80.1mmol) dropwise. The solution was stirred at -78 °C for 1 h, and the reaction was quenched by the addition of sat. aq potassium sodium tartrate soln (130 mL). Then, the mixture was warmed to r.t. and filtered through a pad of Celite, and the residue was washed with sat. aq NaCl. The resulting mixture was extracted with CH₂Cl₂. The organic extract was concentrated to obtain the crude product, which was purified with flash chromatography on silica gel eluting with (5:1) petroleum ether-ethyl acetate to give 12.1 g (88% yield) of the aldehyde (5) as a colorless oil: ¹H NMR (400 MHz, CDCl₃, 70°C) δ: 1.32 (s, 9 H), 1.41 (br s, 3 H), 1.57 (br s, 3H), 3.58 (d, 1 H, *J* = 7.6), 3.66 (d, 1 H, *J* = 7.6), 3.91 (m, 1 H), 9.23 (br s, 1 H).

(S)-2,2-Dimethyl-3-(tert-butoxycarbonyl)-4-(2,2-dibromoethenyl)oxazolidine(6)

CBr₄ (16.9 g, 50.9 mmol) is dissolved in CH₂Cl₂ (500 mL) and cooled to -20°C. Then a solution of PPh₃ (13.2 g, 50.4 mmol) in CH₂Cl₂ (500 mL) is added slowly. The mixture is stirred for another 30 min and then cooled to -60 °C. A solution of (5) (12.1 g, 50.0 mmol) and Et₃N (35.4 g, 25.2 mmol) in CH₂Cl₂ (200 mL) is added slowly. After addition, the mixture is kept stirring at -60 °C for 30 min, and then stirred at room temperature overnight. The solution is diluted with pentane and then filtered. The filtrate is evaporated under reduced pressure, and the residue is purified with flash chromatography on silica gel eluting with (50:1) petroleum ether-ethyl acetate to give 8.8 g (77%) of (6) as a white solid: ¹H NMR (300 MHz, 50 °C) δ: 6.36 (d, 1H, *J* = 8.1 Hz), 4.57 - 4.43 (m, 1H), 4.11 (dd, 1H, *J* = 6.6, 9.3Hz), 3.67 (dd, 1H, *J* = 9.3, 2.7 Hz), 1.61 (s, 3H), 1.51 (s, 3H), 1.48 (s, 9H).

(S)-2,2-Dimethyl-3-(tert-butoxycarbonyl)-4-ethynyloxazolidine (7)

To a solution of (6) (8.0 g, 20.7 mmol) in THF (150 mL), is added n-BuLi (23.0 mL, 36.6 mmol) slowly at -78 °C. After stirring for 30 min, the mixture is heated to -15°C and stirred for another 15 min. After that, the reaction is quenched with aq. NaOH (0.01 M). After extraction, drying, and evaporation of the solvent, the crude residue is purified with flash chromatography on silica gel eluting with (50:1) petroleum ether-ethyl acetate to give 5.6 g (70%) of (7) as a colorless oil: ¹H NMR (CDCl₃, T=60°C) δ 4.65–4.6(m, 1H), 4.12 (dd, 1H, *J*=8.8, 6.0 Hz), 3.97(dd, 1H, *J*=8.8, 2.4 Hz), 3.11 (d, 1H, *J*=2.2 Hz), 1.63 (s, 3H), 1.53 (s, 9H), 1.51 (s, 3H).

(R)-tert-butyl 2,2-dimethyl-4-(prop-1-yn-1-yl)oxazolidine-3-carboxylate (8)

To a solution of alkyne (7) (5.0 g, 22.2 mmol) in THF (45 mL) added n-BuLi (2.3 g, 13.3 mmol) at -78°C. After stirring for 1 h and then HMPA was added in the solution, after stirring for 10min, the CH₃I was added. The reaction was stirred for 1h, then warmed the solution at 0°C to room temperature and stirred for overnight. After extraction, drying, and evaporation of the solvent, the crude residue is purified with flash chromatography on silica gel eluting with (100:1) petroleum ether-ethyl acetate to give 3.65 g (73%) of (8) (1.75g, 85% yield) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ: 1.40 (s, 9 H), 1.50 (s, 6 H), 1.71 (s, 3 H), 3.80-4.0 (m, 2 H), 4.50 (t, 1 H).

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References

- [1] Kou H, Oizumi J. Determination of free biotin in plasma by liquid chromatography with fluorimetric detection J. Journal of Chromatography A. 413 (1987) 247–250.
- [2] Subhash, P. C, Pradeep, B. L, Prakash, N. C, Tetrahedron: Asymmetry. 24 (2013) 1473-1479.
- [3] Chihui, A, Jon,A. J, Shawn, P.W, Adam, T. H, Amos, B. S. J. Org. Chem. 78 (2013) 4278-4296.
- [4] Mancuso, A. J, Huang, S. L, Swern, D. J. Org. Chem. 43 (1978) 2480.
- [5] Chung, J. Y. L, Wasicak, J. T. Tetrahedron. Lett. 31 (1990) 3957.