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# A New Highly-Enantioselective Synthetic Process for Producing (*S*)-2-Hydroxybutyric Acid Methyl Ester

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**Abstract:** (*S*)-2-aminobutyric acid being initial raw material, (*S*)-2-hydroxybutyric acid methyl ester was synthesized by means of a three step reaction of hydroxylation, salification and esterification. The product had a yield rate of 60.4%, purity of 99% and ee value higher than 99% by characterization of GC, HPLC and $^1$H NMR. This synthesis technique has advantages of high purity and ee value, low cost, short reaction time and mild reaction conditions so that it is suitable for production on industrial scale.

**Key words:** (*S*)-2-hydroxybutyric acid methyl ester; (*S*)-2-hydroxyl butyric acid; chiral drug intermediate; esterification
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## 0 Introduction

(*S*)-2-hydroxybutyric acid methyl ester is a very important chiral drug intermediate, which is easy to be converted into corresponding acid [1] and is widely used in medication, chemistry, food and cosmetic areas [2,3]. Structural units of hydroxyl ester with photo-activity exist in natural products in general. Therefore, it becomes a hot area in which photo-active hydroxyl ester and its derivants used as raw materials and natural organics with medication value are synthesized for new medicine development [4,5].

Presently, patients with high blood fat are as many as 160 million in mainland China [6]. Abnormal blood fat phenomenon is resulted from poor fat metabolism, which affects human health very much. It is not only the cause of cardiovascular and brain vascular diseases, atherosclerosis, coronary heart disease, stroke, etc.[7-9], but also has things to do with diabetes, nephropathy, hypertension, tumour, etc.. Therefore, to develop effective medicines that overcome human fat metabolism abnormality is not only of very significance, but is also very urgent. Peroxisome proliferator-activated receptor, PPAR, is a transcription divisor in human body for activating fat acid, which has wide organic distribution. And PPAR is also an important target standard for sugar adjustment and fat metabolism. Therefore PPAR plays an important role for fat synthesis and decompose and metabolism. PPAR exciting agent can be widely used for treating diseases such as hyperlipemia, diabetes effectively. Today, synthesis of PPAR new exciting agents becomes a hot

point for research of fighting against fat metabolism disorder [10]. (*S*)-2-hydroxybutyric acid methyl ester is a new pattern of PPAR exciting agent that also called (*R*)-K-13675 [11, 12], an important raw material and is widely used for synthesis of such medicines, of which the structural formula [13,14] see Fig. 1 (a).

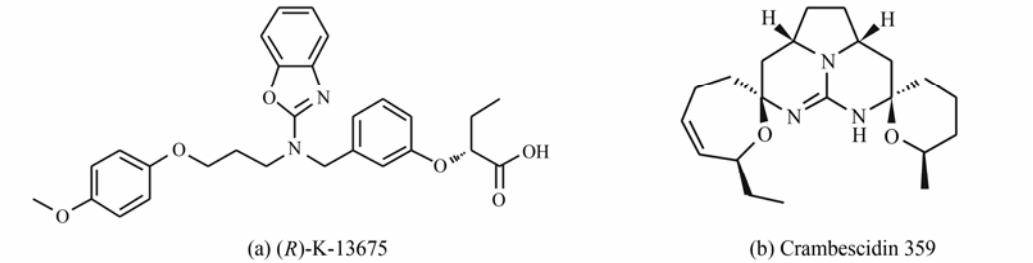



**Fig. 1 Structural formulas of two kinds of downstream products of (*S*)-2-hydroxybutyric acid methyl ester**

Aoki *et al* [15] found out that apentacyclic guanidine alkaloid contained in marine sponge had an inhibition function against K562 chronic myelogenous cells' growing up, which worked during the cell cycling period *S*. When myeloma cells were cured with such alkaloid at certain concentration for 24 h, p21 protein, which can promote apoptosis of cells, would be produced. After being cured for 48 h, the express amount of protein inside cells increased. p21 protein can combine proliferative cell antigen of tumour to inhibit DNA polymerase delta so that duplication of DNA was inhibited. p21 protein also inhibits phosphorylation of substrate of cell cyclin/cyclin dependent kinases, and further to inhibit cell cycle from G1 to *S*, resulting in blockage of tumour cell proliferation so that the cancer cells are in the apoptosis condition.

Currently, medicines such as apentacyclic guanidine alkaloid are greatly demanded in curing tumour diseases while it is limited to extract it from natural raw materials[16] .Therefore, an artificial process to extract such materials to satisfy the market needs becomes much more urgent. (*S*)-2-hydroxybutyric acid methyl ester, such as crambescidin 359 [17], of which the structural formula see Fig.1(b), is an important raw material for synthesis of such medicines. Therefore, an industrial-scale development for such products is an urgent need.

Being of a kind of chiral molecule, 2-hydroxybutyric acid methyl ester is divided into two types: *R* chiral and *S* chiral. The chiral medicine with biological activity may be synthesized from (*S*)-2-hydroxybutyric acid methyl ester, while (*R*)-2-hydroxybutyric acid methyl ester will affect the biological activity of the chiral medicines. In the synthesis process of (*S*)-2-hydroxybutyric acid methyl ester, high reaction temperature and low enantiomorphs selectivity, may result in formation of (*R*)-2-hydroxybutyric acid methyl ester which is difficult to be separated from (*S*)-2-hydroxybutyric acid methyl ester. The less the (*R*)-2-hydroxybutyric acid methyl ester contentis, the higher the ee value (ee expresses the overdose of an enantiomer against that of the other enantiomer) is. So that synthesis of (*S*)-2-hydroxybutyric acid methyl ester with high ee value is significantly important.

Today, there are mainly four processes for synthesis of (*S*)-2-hydroxybutyric acid methyl ester: ① As Rioz-Martinez *et al* reported [18], (*R*)-2-ethyl-3-oxobutanoate being raw material, (*S*)-2-hydroxybutyric acid methyl ester was obtained by processes of oxidation and prosthesis. The shortcoming of this method is long reaction time and low optical purity. ② As what reported by Farjad *et al* [19], 2-ketobutyric acid being raw material, (*S*)-2-hydroxybutyric acid methyl ester was obtained by processes of reduction and methylation. This method has a shortcoming of expensive test agents, great toxicity. ③ The following process was reported by Waldemar *et al* [20], methyl butyrate being raw material, (*S*)-2-hydroxybutyric acid methyl ester was obtained by means of oxidation and reduction. The shortcoming of this process is expensive test agents, low enantioselectivity. ④ According to Teodozyj *et al* [21], (*S*)-2-aminobutyric acid was used as raw material, (*S*)-2-hydroxybutyric acid methyl ester was obtained by means of acetoxylation and esterification. The shortcoming of this process is long reaction time and serious reaction conditions.

Here a kind of new approach for synthesis of (*S*)-2-hydroxybutyric acid methyl ester is introduced and (*S*)-2-hydroxybutyric acid methyl ester products with high purity and high ee value is expected to be obtainable.

# 1 Experiment

## 1.1 Agents, Instruments and Technique

1) Agents: (*S*)-2-aminobutyric acid, anhydrous methanol, sodium nitrite, sulfuric acid, sodium bicarbonate, potassium bicarbonate, anhydrous magnesium, sodium chloride, sodium methoxide, ethyl acetate and ether. The agents are all of AR degree.

2) Instruments: RY-1 digital melting point apparatus (made by Tianjin Analytical Instrument Factory), GC112A gas chromatograph (made by Shanghai Precision Scientific Instrument Co., Ltd), Hitachi L-2000 HPLC (made by Hitachi High-Technology Corporation), Chiralpak AD-H column (made by Daicel Medicine Chiral Technologies Co., Ltd), NMR Bruker 400M (made by Brucker Company, Germany). TRACE 2000 GC-MESS spectrometry (made by ThermoFinnigan).

3) Processing flow: The flow chart of route for synthesizing (*S*)-2-hydroxybutyric acid methyl ester see Fig. 2.

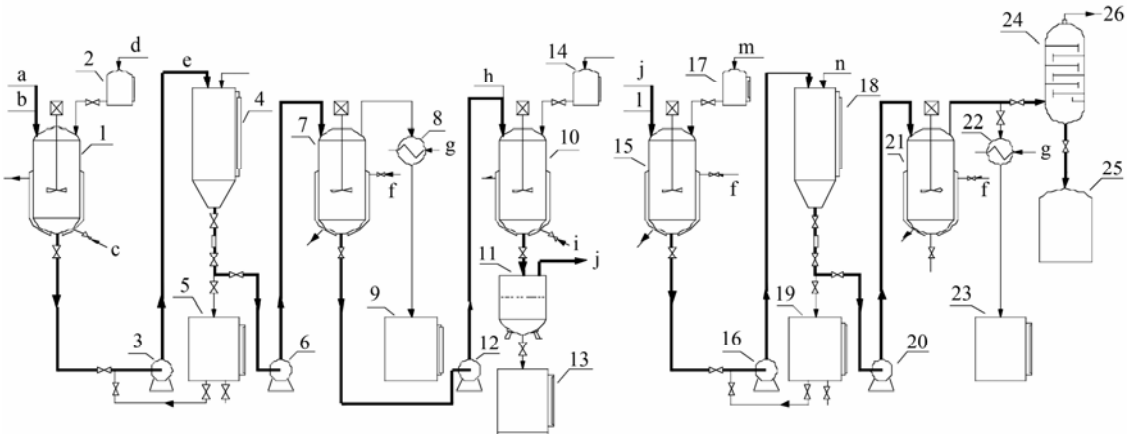



**Fig. 2 Flow chart of route for synthesizing (*S*)-2-hydroxybutyric acid methyl ester**

a: (*S*) -2-aminobutyric acid; b: dilute sulfuric acid; c: cooling medium; d: sodium nitrite solution; e: extracting agent; f: heating steam; g: cooling water; h: methanol; i: hot water; j: salification product; k: sodium methoxide-methanol solution; l: methanol; m: concentrated sulfuric acid solution; n: concentrated sulfuric acid solution

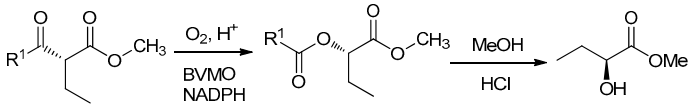
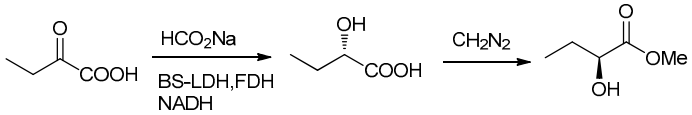
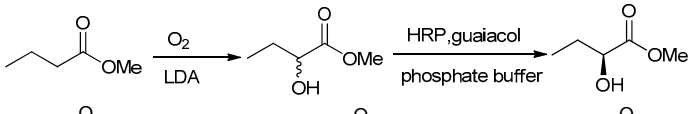
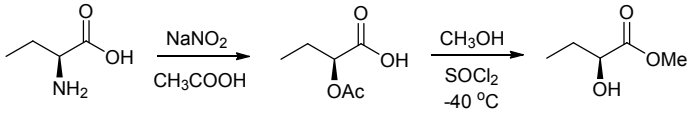
1: hydroxylation reaction kettle; 2, 14, 17: metering tank; 3, 6, 12, 16, 20: pump; 4, 18: extraction tank; 5, 19: liquid storage tank; 7, 21: distillation kettle; 8, 22: overhead condenser; 9, 13, 23: solvent recovery tank; 10: salification reaction kettle; 11: filter; 15: esterification reactor; 24: distillation tower; 25: product receiving tank; 26: vacuum pump

## 1.2 Route for Synthesizing (*S*)-2-Hydroxybutyric Acid Methyl Ester

Currently, there are mainly four types of synthetic route for producing (*S*)-2-hydroxy butyric acid methyl ester.

Four related routes of synthesizing (*S*)-2-hydroxybutyric acid methyl ester. Four present synthesis routes for producing (*S*)-2-hydroxybutyric acid methyl ester are given in Table 1.

**Table 1 Some synthesis routes for producing (*S*)-2-hydroxybutyric acid methyl ester**

| No. | Method | Synthetic route |
|---|---|---|
| 1 | Rioz-Martinez method[18] |  |
| 2 | Farjad method [19] |  |
| 3 | Waldemar method [20] |  |
| 4 | Teodozyj method [21] |  |



BVMO: Baeyer-Villiger monooxygenases; NADPH: nicotinamide adenine dinucleotide phosphate; BS-LDH: bacillus stearothermophilus; NADH: nicotinamide adenine dinucleotide; FDH: formate dehydrogenase; LDA：lithium diisopropylamide；HRP: horseradish peroxidase

The synthesis route adopted in this writing for producing (*S*)-2-hydroxybutyric acid methyl ester is shown in Fig. 3.

The route suggested in this paper for synthesizing

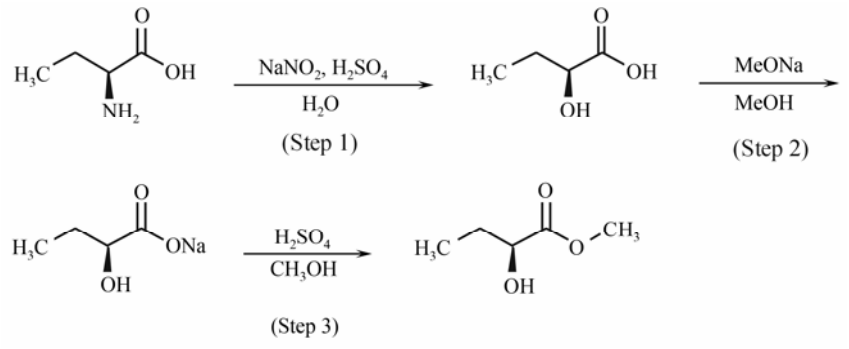



**Fig. 3 Synthesis route of (*S*)-2-hydroxybutyric acid methyl ester**

(*S*)-2-hydroxybutyric acid methyl ester is carried out in three steps below.

**Step 1** Synthesis of (*S*)-2- hydroxybutyric acid

41.2 g (0.40 mol) of (*S*)-2-aminobutyric acid was added into 1000 mL of 5% $H_2SO_4$ solution and stirred to uniformity, then cool it with ice bath to 0 ℃. 0.6 mol $NaNO_2$ solution was dissolved in 80 mL water, which was then dropped into the liquid in reaction. Continue stirring 1 hour and raise the temperature up to ambient and adjust pH to 2, stir for whole night. Then 360 g NaCl was added into the liquid in reaction and was then extracted with ether. The organic phase matter was rinsed with saturated NaCl solution (200 mL × 2) and dried with anhydrous magnesium. A chalky yellow liquid was obtained by filtrating the semi-finished product, which was then rotary-evaporated at reduced pressure to produce 36.1 g of chalky yellow liquid — (*S*)-2-hydroxybutyric acid, of which the yield is 86.8%. The final product was characterized as: $\delta$ 0.95 (t, 3 H, —$CH_3$), 1.80 (m, 2 H, —$CH_2$—), 2.98 (s, 1 H, —OH), 4.17 (t, 1 H, —CH<), 11.2 (s, 1 H, —COOH).

**Step 2** Synthesis of (*S*)-2-hydroxybutyric acid sodium salt

36.1 g of the (*S*)-2-hydroxybutyric acid obtained in the above process (0.35 mol) was dissolved in 70 mL of anhydrous methanol, to which 78.5 mL(0.39 mol) of MeONa/MeOH was slowly dropped. After dropping was finished the reaction temperature was raised to 50 ℃ so that the solid matters contained were dissolved totally then stirred for 30 min. The reaction temperature lowered to room temperature, continue stirring for 5.5 h. A white colored solid matter was gained after filtration, which was washed using EtOAc (150 mL × 2) and dried in a vacuum drier. The semi-final product, 40.5 g of white final product, is (*S*)-2-hydroxybutyric acid sodium salt. Yield rate: 92.6%, melting point: 132-134 ℃. The product was characterized to be $\delta$ 0.94 (t, 3 H,—$CH_3$), 1.79 (m, 2 H, —$CH_2$—), 2.96 (s, 1 H, —OH), 4.16 (t, 1 H, —CH< ).

**Step 3** Synthesis of (*S*)-2-hydroxybutyric acid methyl ester

40.5 g (0.32 mol) of (*S*)-2-hydroxybutyric acid sodium salt obtained in the above process was added to 300 mL of anhydrous methanol and stirred it to uniform. Then 100 mL of anhydrous methanol solution, in which 25 g (0.25 mol) of concentrated sulfuric acid was dissolved, was slowly dropped into the liquid in reaction, then let it flow back for 2 h while the temperature being raised up. The liquid in reaction was then cooled in an ice bath down to 0 ℃, then saturated $KHCO_3$ solution was added in until the liquid in reaction appeared to be slightly alkaline and then stirred for 30 min. The liquid in reaction was then extracted with ether, of which the matter of organic phase was rinsed with 200 mL of water and 200 mL of saturated NaCl solution successively and then dried with anhydrous magnesium. The intermediate product, a thin yellow liquid obtained by filtrating the liquid in reaction, is to be distilled at reduced pressure to obtain the final product — (*S*)-2-hydroxybutyric acid methyl ester, which is a colorless liquid. This process offered a yield rate of 75.2% and was characterized with $^1$H NMR ($CDCl_3$) as $\delta$ 0.95 (t, 3 H, —$CH_3$), 1.81 (m, 2 H, —$CH_2$—), 3.00 (s, 1 H, —OH), 3.77 (s, 3 H, —$OCH_3$), 4.17 (t, 1 H, —CH<).

The yield rates of the 3 steps were 86.8%($R_1$), 92.6%($R_2$), and 75.2%($R_3$), respectively.

The target products' total yield rate ($R$)= $R_1 \times R_2 \times R_3$= 86.8%×92.6%×75.2% =60.4%.

### 1.3 Superficial Characteristics of Synthesis Products' Structure

(*S*)-2-hydroxybutyric acid methyl ester is characterized by mass spectra. MS (EI): *m/z* [$M^+$] calcd for $C_5H_{10}O_3$: 118.06; found: 118.05.

Figure 4 shows the $^1$H NMR diagram of the synthesized products, of which the chemical shift at the multi-peaks of ($\delta$) 0.95 and $\delta$ 1.81 are the hydrogen characteristic peak for —$CH_2CH_3$, while the peak at $\delta$ 3.00 is the hydrogen characteristic peak for —OH, and that at $\delta$ 3.77 is hydrogen characteristic peak for —$OCH_3$, while the multi-peak at $\delta$ 4.17 is hydrogen characteristic peak for —CH<.

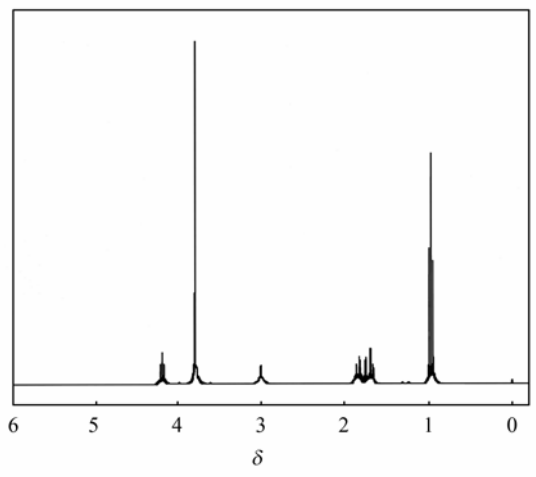



**Fig. 4 $^1$H NMR spectrogram of (*S*)-2-hydroxybutyric acid methyl ester**

### 1.4 Purity Measurement

Figure 5 shows GC spectrogram of (*S*)-2-hydroxybutyric acid methyl ester, from which it can be seen that a very strong product-absorbing peak at 2.8 min, whose peak area is 99.1% and there is only a very small impurity peak at 2 min.

Because (*S*)-2-hydroxybutyric acid methyl ester does not have an absorbing peak within the wave length

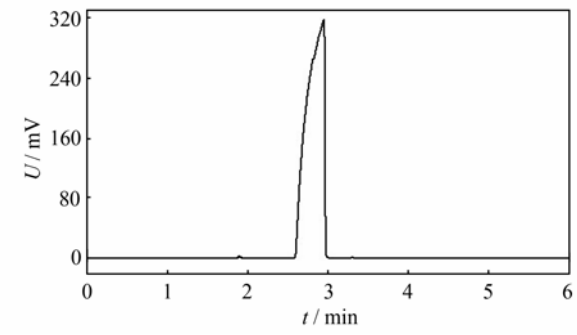



**Fig. 5 GC spectrogram of (*S*)-2-hydroxybutyric acid methyl ester**

range of the HPLC detection, ee value cannot be measured by means of HPLC. Therefore, in this method the derivates (1-methoxy-1-oxobutan-2-yl and 4-nitrobenzoate) were obtained by adding a functional group. The ee value of (*S*)-2-hydroxybutyric acid methyl ester was measured indirectly by means of measuring out the ee value of 1-methoxy-1-oxobutan-2-yl and 4-nitrobenzoate (see Fig. 6), for which the steps are as follows: 40 mg of (*S*)-2-hydroxybutyric acid methyl ester was added into 1 mL of pyridina, which was then cooled down to 0 ℃ in ice bath. And 63 mg (0.34 mmol) of paranitrobenzoyl chloride was added into the pyridina solution and heat it up to room temperature, stir it for 0.5 h then stop stirring. The liquid in reaction was extracted with 30 mL of EtOAc. The organic phase matter was then rinsed with 10 mL HCl (4 mol/L), 10 mL water and 10 mL saturated NaCl solution and then dried with anhydrous magnesium to obtain a slight yellow liquid, which turned into a yellow colored liquid by means of rotary evaporation at reduced pressure. The yellow liquid was further purified in a process called thin layer chromatographic separation and was measured with HPLC to have an ee value as high as beyond 99%. ee value is calculated as follows:

$$\text{ee value} = (A_S - A_R) / (A_S + A_R) \times 100\%$$

$$= (99.57\% - 0.42\%) / (99.57\% + 0.42\%) \times 100\%$$

$$= 99.15\%$$

Where, $A_S$ represents the content of S-isomer, $A_R$ represents the content of R-isomer.

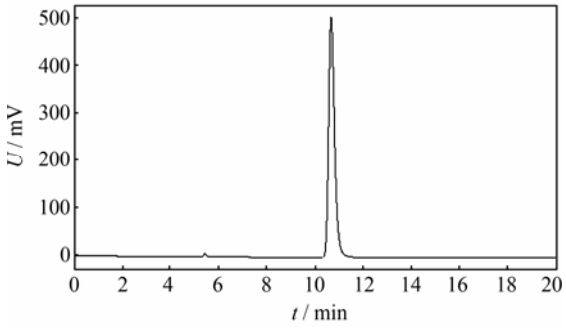



**Fig. 6 HPLC of 1-methoxy-1-oxobutan-2-yl and 4-nitrobenzoate, derivant of (*S*)-2-hydroxybutyric acid methyl ester**

## 2 Discussion

### 2.1 Selection of the Best Reaction Condition for Hydroxylation

Hydroxylation is the first step of synthesis reaction.

Because it is easy to initiate a side reaction for diazo compound at high temperature and the diazotization reaction in the process of hydroxylation releases heat violently so that thereaction temperature must be strictly controlled when sodium nitrite is being dropped into the liquid in reaction ($t \leqslant 5$ ℃). After dropping is completed it should be kept at a low temperature for 1 h to guarantee that the reaction of diazo compound is carried out perfectly at low temperature. The pH value should be controlled within 2-3.

Hydroxylation reaction goes on in an acidic condition. We observed and studied the effect chloride acid, acetic acid and sulphuric acid, as reaction mediums, on the purity of (*S*)-2-hydroxybutyric acid. When chloride acid and acetic acid are chosen reaction mediums, the product contains more impurities. Therefore, adoption of sulphuric acid in the synthesis process can reduce impurities to certain extent.

In addition, the molar ratio between (*S*)-2-aminobutyric acid and $NaNO_2$ affects yield significantly. Figure 7 shows the different yield rate of (*S*)-2-aminobutyric acid given by the two materials at different molar ratios.

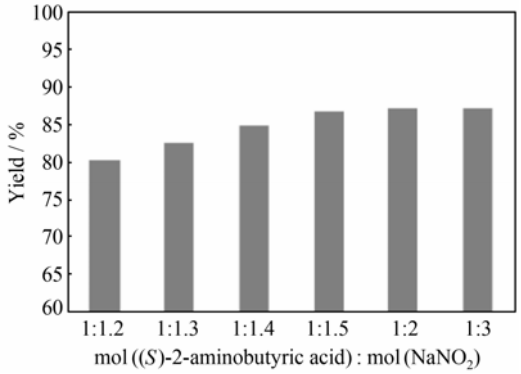



**Fig. 7 Effect of molar ratio between (*S*)-2-aminobutyric acid and $NaNO_2$ on yield rate of hydroxylation reaction**

Figure 7 concludes that when molar ratio between (*S*)-2-aminobutyric acid and $NaNO_2$ mol((*S*)-2-aminobutyric acid) : mol ($NaNO_2$) = 1:1.5, the yield rate of the reaction is higher. When consumption of $NaNO_2$ increases, the yield rate does not increase significantly. Considering cost factor, it is suggested that the suitable reaction condition be chosen as follows: mol ((*S*)-2-aminobutyric acid) : mol($NaNO_2$)=1:1.5.

## 2.2 Effect of Salt Forming Reaction on Product Quality

There is a big amount of oily impurities in hydroxylation reaction, the salt forming reaction (the second step of the synthesis) converted (*S*)-2-hydroxybutyric acid into (*S*)-2-hydroxybutyric acid sodium, then the impurities can be removed by filtration using filter paper (for amount used in the laboratory). After such impurities are removed, the purity of (*S*)-2-hydroxy butyric acid methyl ester produced in the esterification reaction reaches as high as 99%. Should it would not be done by means of the salt forming traction to carry out the esterification for (*S*)-2-aminobutyric acid, the product purity would be lower than 96.5% and ee value would be lower than 95.5%. Therefore, the salt forming reaction raised the purity of (*S*)-2-hydroxybutyric acid methyl ester by 2.5% and ee value by 3.5%.

## 2.3 Selection of Esterification Conditions

During esterification reaction (the third step of synthesis reaction), reaction time length affects the reaction product significantly. Figure 8 provides the yield rate and ee value for different reaction duration.

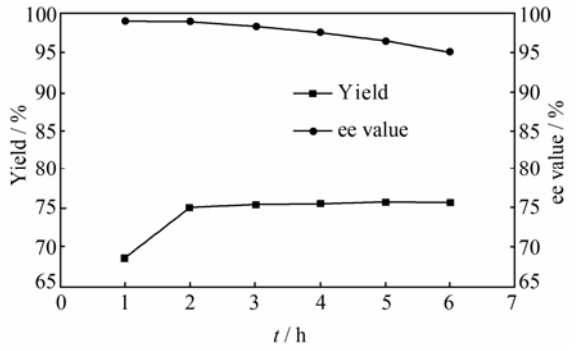



**Fig. 8 Effect of reaction duration on esterification reaction**

From Fig. 8, it can be known that yield rate increases with reaction time elongation. However, ee value reduces with reaction duration going longer. Figure 8 shows when reaction time is 2 h, yield rate is 75.2%, ee value ⩾ 99%. When reaction time beyond 2 h, ee value reduced significantly, which does not satisfy demand of high ee value. Therefore, 2 h for esterification reaction is suitable.

Due to high boil point of (*S*)-2-hydroxybutyric acid methyl ester and its heat-sensitivity, it is easy to convert into its optical isomers. Therefore, the product should be distilled in a high vacuum condition. In this technique, the distilling pressure is 65 Pa with temperature being 35 ℃.

## 2.4 Comparison between Some Approaches for Synthesis

Comparison between the synthesis introduced here and the other synthesis approach for (*S*)-2-hydroxybutyric acid methyl ester please see Table 2.

**Table 2 Comparison between several synthesis approaches for synthesizing (*S*)-2-hydroxybutyric acid methyl ester**

| Method | *t* /h | Yield /% | ee value /% | Reaction characteristics |
|---|---|---|---|---|
| Rioz-Martinez method [18] | 48 | 60 | 92 | Long reaction time, low ee value |
| Farjad method [19] | — | 73 | 99 | Highly toxic and expensive methylation reagent ($CH_2N_2$) |
| Waldemar method [20] | — | 50 | 97 | Low yield, corrosive and expensive oxidation reagents (LDA) |
| Teodozyj method [21] | 49 | 62 | — | Long reaction time, the esterification reaction temperature is very low (–40 ℃) |
| Our method | 21 | 60.4 | ⩾99 | High ee value, short reaction time, moderate yield (meet the production requirements), mild reaction conditions (0 ℃⩽ *T*＜100 ℃) |

## 3 Conclusion

1) (*S*)-2-aminobutyric acid being initial raw material, (*S*)-2-hydroxybutyric acid methyl ester with high ee value is synthesized in reactions of three steps. The result of $^1$HNMR characteristic test proves that the synthesized product is (*S*)-2-hydroxybutyric acid methyl ester. GC result proves that the purity of the product reached 99%. HPLC result shows its ee value is beyond 99%.

2) By proposed method, the best reaction condition to synthetise (*S*)-2-hydroxybutyric acid methyl ester is as follows: Reaction medium of hydroxylation is dilute sulphuric acid. Molar ratio mol((*S*)-2-aminobutyric acid): mol($NaNO_2$)=1∶1.5, duration of esterification reaction= 2 h, distillation pressure for (*S*)-2-hydroxybutyric acid methyl ester is 65 Pa at 35 ℃. This condition provided high yield rate, purity and ee value.

3) This synthesis approach also has advantages of short reaction period, low cost of raw materials and agents, mild reaction conditions and is suitable for production at industrial scale.

## References


[1] Coppola G M, Schuster H F. *In α-Hydroxy Acids in Enantioselective Synthesis* [M]. Weinhein: Wiley-VCH, 1997.

[2] Kozono I. *Process for Production of* 2*-Hydroxy Esters*: 2007018221 [P]. Japan, 2007-02-15.

[3] Fujiwara N, Nakagawa K, Kinoshita Y, *et al*. *Process for Production of Cyanohydrin Compound*, *and Process for Production of α-Hydroxyester Compound*: 2009054356 [P]. Japan, 2009-04-30.

[4] Hasegawa J, Nagashima N. *In Steroselective Biocatalysis* [M]. New York: Marcel Dekker, 2000.

[5] Christopher G M, Patrick J M, Harri L W, *et al*. A synthesis of crambescidin 359 [J]. *Tetrahedron Letters*, 2003, **44**: 251-254.

[6] Liu C Y. Community management of hypertension in patients with high cholesterol report [J]. *China Health Care & Nutrition*, 2014, **3**: 1428-1429(Ch).

[7] Wu Q S, Lin J X, Zhang W L, *et al*. Research on abnormally elevated blood fat levels in adults [J]. *International Medicine & Health Guidance*, 2014, **15**(20): 2258-2262(Ch).

[8] Wang C, Yan L. Prevent treatment of dyslipidemia in the elderly [J]. *Chin J Endocrinol Metab*, 2014, **11**(30): 1035-1038(Ch).

[9] Stone N J, Robinson J, Lichtenstein A H, *et al*. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American college of cardiology/American heart association task force on practice guidellnes [J]. *J Am Coll Cardiol*, 2014, **63**(25): 2889-2934.

[10] Zhou J D. PPAR and chronic diseases [J]. *Chemistry of Life*, 2001, **21**(1): 80-83(Ch).

[11] Yukiyoshi Y, Kazutoyo A, Tsutomu T, *et al*. Design and synthesis of highly potent and selective human peroxisome proliferator-activated receptor α agonists [J]. *Bioorganic & Medicinal Chemistry Letters*, 2007, **17**: 4689-4693.

[12] Yukiyoshi Y, Kazutoyo A, Minoru K, *et al*. Enantioselective synthesis of the PPARα agonist (*R*)-K-13675 via

(*S*)-2-hydroxybutyroctone [J]. *Synthesis*, 2008, **7**: 1017-1022.

[13] Yukiyoshi Y, Shinichiro O, Kimiyuki S. Synthesis of highly deuterium-labeled (*R*)-K-13675, PPARα agonist, for use as an internal standard for low-level quantification of drugs in plasma [J]. *Bioorganic & Medicinal Chemistry*, 2009, **17**:1911-1917.

[14] Yukiyoshi Y,Takaaki A, Minoru K, *et al*. A practical synthesis of the PPARα agonist, (*R*)-K-13675, staring from (*S*)-2-hydroxybutyroctone [J]. *Tetrahedron*, 2008, **64**: 8155-8158.

[15] Aoki S, Kong D, Matsui K, *et al*. Erythroid differentiation in K562 chronic myelogenous cells induced by crambescidin 800, a pentacyclic guanidine alkaloid [J]. *Anticancer Res*, 2004, **24**(4): 2325-2330.

[16] Ning Z J, Han Y F, Pan X Q. The pharmacological effect of chiral drugs types and preparation technology [J]. *Medical Innovation of China*, 2009, **6**(25): 194-196(Ch).

[17] Christopher G M, Patrick J M, Harri L W, *et al*. Synthetic studies towards ptilomycalin A: Total synthesis of crambescidin 359 [J]. *Tetrahedron*, 2007, **63**: 11771-11780.

[18] Rioz-Martinez A, Marco W F, Vicente G, *et al*. Dynamic kinetic resolution of *α*-substituted *β*-ketoesters catalyzed by Baeyer-Villiger monooxygenases: Access to enantiopure *α*-hydroxy esters [J]. *Angew Chem Int Ed*, 2011, **50**: 8387-8390.

[19] Farjad A, Eiman H, Christine L, *et al*. An unusual matrix of stereocomplementarity in the hydroxylation of monohydroxy fatty acids catalyzed by cytochrome P450 from *Bacillus megaterium* with potential application in biotransformation [J]. *Chem Commun*, 1999, **20**: 2049-2050.

[20] Waldemar A, Rainer T, Peter S, *et al*. Kinetic resolution of chiral *α*-hydroperoxy esters by horseradish peroxidase-catalyzed enatioselective reduction to *α*-hydroxy esters [J]. *Tetrahedron Asymmetry*, 1995, **6**(5): 1047-1050.

[21] Teodozyj K, Marvin J. Reactions of *α*-hydroxy carbonyl compounds with azodicarboxylates and triphenylphosphine: Synthesis of *α*-N-hydroxy amino acid derivatives [J]. *Journal of Organic Chemistry*, 1987, **52**: 4978-4984.

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