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An efficient chiral synthesis of (*R*)-*N*-[3-acetyl-4-(2-hydroxy-3-isopropylamino-propoxy)phenyl]-butanamide with high enantioselectivity

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***R*-Enantiomer of the β-receptor antagonist *N*-[3-acetyl-4-(2-hydroxy-3-isopropylamino-propoxy)phenyl] butanamide with high enantioselectivity was synthesized from cheap starting materials and enantiopure chiral reagent through an efficient, convenient and practical synthetic strategy. Title product was detected by ^{1}H NMR, ^{13}C NMR, and MS, and the enatiomeric excess was determined by chiral HPLC analysis using a chiracel AD-H column.**

chiral synthesis, enantioselectivity, enatiomeric excess, chiral HPLC analysis

1 Introduction

(+)-(*S*,*R*,*R*,*R*)-Nebivolol, a β_1-adrenergic receptor blocker, has been synthesized successfully by chiral pool of natural product in mild conditions in our group[1,2]. *N*-[3-Acetyl-4-(2-hydroxy-3-isopropylamino-propoxy)phenyl]-butanamide, acebutolol (Ac), is a selective β-adrenergic blocking drug used in the treatment of high blood pressure, abnormal heart rhythms and sometimes chest pain[3−9]. As same as other β-blockers, acebutolol is used in clinical practice as a racemic mixture, although it is well known that its β-blocking activity is mainly attributed to the *S*-enantiomer and its major metabolite, and *S*-diacetolol[10]. In addition, it has been reported that the enantiomers of adrenergic β-receptor blockers are greatly different not only in their pharmacodynamics but also in their pharmacokinetics[11−13]. Therefore, synthesis of acebutolol with high enantioselectivity remains an interesting field in recent years.

Acebutolol belongs to the scope of aryloxypropanol amine derivatives bearing a chiral carbon atom in its molecule. These aryloxypropanolamine derivatives are always cardioselective and the *S*-enantiomers are generally 50−500 times more effective than the *R*-enantiomers in their β-blocking activity. To date, several documents have reported the asymmetric synthesis of these compounds, such as atenolol[14,15], propranolol[16,17] and the title compound acebutolol[18]. Reported methods related to asymmetric resolution of the corresponding racemates, asymmetric lipase-catalyzed kinetic resolution or chiral pool methods, which possess many disadvantages, such as high costs, multiple steps, low overall yields and low optical purity. So, these methods are difficult to be applied to the large-scale industrial production. Herein, we report a convenient, practical and highly enantioselective synthesis of *R*-acebutolol from inexpensive starting material *p*-anisidine just in four steps. Enantiopure chiral reagent is used as starting material and the title product with high enatiomeric excess is obtained, which is an efficient chiral synthesis compared with chiral resolution methods.

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2 Experimental

2.1 General information and methods

^{1}H NMR spectra were recorded at 400 MHz (100 MHz for ^{13}C) at 20℃ unless otherwise stated. TMS was used as internal standard and $CDCl_3$ was used as solvent. Melting points were measured on an X-4 digital microscope melting point apparatus (Beijing Tech Instrument Co., Ltd.). IR spectra (KBr disks) were recorded on Bruker AC-300 FT or AV-400 FT instrument. Electron impact MS spectra were obtained on a JEOL JMS-HX 100 instrument. Chiralcel AD-H columns were purchased from Daicel Chemical Industries.

2.2 Synthesis of *N*-(4-methoxy-phenyl)-butanamide (5)

A round bottom flask equipped with a Dean-Stark trap was charged with *p*-anisidine (5.0 g, 0.04 mol), *n*-butyric acid (14.1 g, 0.16 mol) and toluene (40 mL). The mixture was refluxed at 140℃ for 8 h till the water was separated completely. The solvent and excess *n*-butyric acid was removed at the refluxed temperature by distillation then cooled to ambient temperature. The resulting crude product was washed with petroleum ether (3×100 mL) and recrystallized from EtOAc to give pure *N*-(4-methoxy-phenyl)-butanamide **5** as white powder. Yield: 6.74 g (86%); mp 87－88℃. IR (KBr): 3287, 2968, 1653, 1509, 1246, 832, 666 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.02 (t, J= 7.36 Hz, 3 H, CH_2CH_3), 1.77 (m, 2 H, CH_2CH_2), 2.33 (t, J= 7.36 Hz, 2 H, CH_2CH_2), 3.79 (s, 3 H, OCH_3), 6.86 (d, J= 8.92 Hz, 2 H, C_6H_4), 7.05 (s, 1 H, NH), 7.42 (d, J= 8.92 Hz, 2 H, C_6H_4).

2.3 Synthesis of *N*-(3-acetyl-4-hydroxyphenyl)-butanamide (3)

To a solution of **5** (10 g, 51.7 mmol) in CH_2Cl_2 (100 mL) at room temperature was added anhydrous $AlCl_3$ (14 g, 105 mmol), followed by slow addition of acetyl chloride (5.6 mL, 78.8 mmol) over 30 min with vigorous agitation. The mixture was stirred for 10 h then the supplement of anhydrous $AlCl_3$ (4.0 g, 30 mmol) and acetyl chloride (1.0 mL, 14.1 mmol) were added. After the reaction mixture was stirred at 25℃ for a further 25 h, ice water and 6 M HCl were added till the obtained solid was totally dissolved. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with 10% $NaHCO_3$ solution and water and dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation and the residue was recrystallized from EtOAC-toluene (5∶3, *V*/*V*) to give pure **3**, 9.9 g. Yield 87%; mp 121－122℃. IR (KBr): 3270, 3052, 1651, 1543, 1481, 1368, 1198, 819, 639 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.02 (t, J= 7.32 Hz, 3 H, CH_2CH_3), 1.76 (m, 2 H, CH_2CH_2), 2.34 (t, J= 7.36 Hz, 2 H, CH_2CH_2), 2.64 (s, 3 H, $COCH_3$), 6.94 (d, J= 8.88 Hz, 1 H, C_6H_3), 7.09 (s, 1 H, NH), 7.30 (m, 1 H, C_6H_3), 8.26 (d, J= 1.96 Hz, 1 H, C_6H_3), 12.1 (s, 1 H, OH).

2.4 (*R*)-2-(2,3-Epoxypropoxy)-5-butyramidoacetophenone (2)

The mixture of KOH (0.4 g, 7.1 mmol), benyltrimethylammonium chloride (0.01 g, 0.05 mmol) and water (10 mL) was stirred for 10 min and then cooled to 0℃ and *S*-epichlorohydrin (1.0 mL, 12.8 mmol) was added. After the reaction mixture was stirred at 0℃ for 9 h, the supplement of KOH (0.2 g, 3.6 mmol) and *S*-epichlorohydrin (0.5 mL, 6.4 mmol) was added. The reaction mixture was then stirred further at 0℃ for another 25 h. The precipitated solid was filtered, washed with water and dried under vacuum to give **2** (1.01 g, 81%) directly to be used in the next step without further purification. The pure product can be obtained through recrystallization in EtOAc. Mp 141－143℃. $[\alpha]_D^{20}$ –20.8 (*c* 0.013, methanol). IR (KBr): 3339, 2967, 2932, 1685, 1657, 1546, 1501, 1301, 1023, 811 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.00 (t, J= 7.36 Hz, 3H, CH_2CH_3), 1.76 (m, 2H, CH_2CH_2), 2.34 (t, J= 7.32 Hz, 2H, CH_2CH_2), 2.67 (s, 3H, $COCH_3$), 2.77 (m, 1H, CH_2CHO), 2.94 (m, 1H, CH_2CHO), 3.40 (m, 1H, CH_2CHO), 3.98 (m, 1H, $CH_2OC_6H_3$), 4.38 (m, 1H, $CH_2OC_6H_3$), 6.94－8.05 (m, 3H, C_6H_3), 7.40 (s, 1H, NH). MS (EI): *m*/*z* (%) 277, 151, 44.

2.5 (*R*)-*N*-[3-Acetyl-4-(2-hydroxy-3-isopropylamino-propoxy) phenyl]butanamide (1)

A mixture of 3 (1.01 g, 3.6 mmol), isopropylamine (6.0 mL, 70 mmol) and water (1 mL) was stirred at room temperature for 8 h. The excess of isopropylamine was removed by distillation and the residue was treated with water. The slurry obtained was acidified with 6 N HCl to pH 2.0. The resulting solution was then filtered. The filtrate was basified with 2 N NaOH to pH 12.0 and the precipitated solid was filtered, washed with water and dried under vacuum to give (*R*)-acebutolol **1** as white powder (0.98 g, 80%). The enatiomeric excess was determined by HPLC analysis using a chiracel AD-H col-

umn (eluent: *n*-hexane/ethanol/diethylamine = 90∶10∶0.1, flow rate: 1 mL/min, temperature: 35℃, retention time: 18.949 min). Mp 125—126℃. $[\alpha]_D^{20}$ –2.7 (*c* 0.05, methanol). IR (KBr): 3339, 2968, 1692, 1654, 1545, 1498, 1299, 1023, 822 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ= 1.02 (t, *J* = 7.36 Hz, 3H, CH_2CH_3), 1.13 (d, *J* = 6.08 Hz, 6H, $(CH_3)_2CH$), 1.78 (m, 2H, CH_2CH_2), 2.33 (t, *J* = 7.32 Hz, 2H, CH_2CH_2), 2.62 (s, 3H, $COCH_3$), 2.76 (m, 1H, $(CH_3)_2CH$), 2.94 (m, 2H, $NHCH_2$), 4.06 (m, 3H, $CHCH_2OC_6H_3$), 6.94—7.91 (m, 3H, C_6H_3), 7.37 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 13.9 (CH_2CH_3), 19.2 (CH_2CH_3), 23.1 ($(CH_3)_2CH$), 23.3 ($(CH_3)_2CH$), 31.8 ($(CH_3)_2CH$), 39.6 ($NHCH_2$), 49.1 ($COCH_3$), 49.3 ($NHCOCH_2$), 68.4 ($CHCH_2O$), 71.9 ($CHCH_2O$), 113.9 (C_6H_3), 122.0 (C_6H_3), 126.2 (C_6H_3), 128.2 (C_6H_3), 131.7 (C_6H_3), 154.8 (C_6H_3), 171.6 (NHCO), 199.3 (C_6H_3-$COCH_3$). MS (EI): *m*/*z* (%) 337, 222, 56.

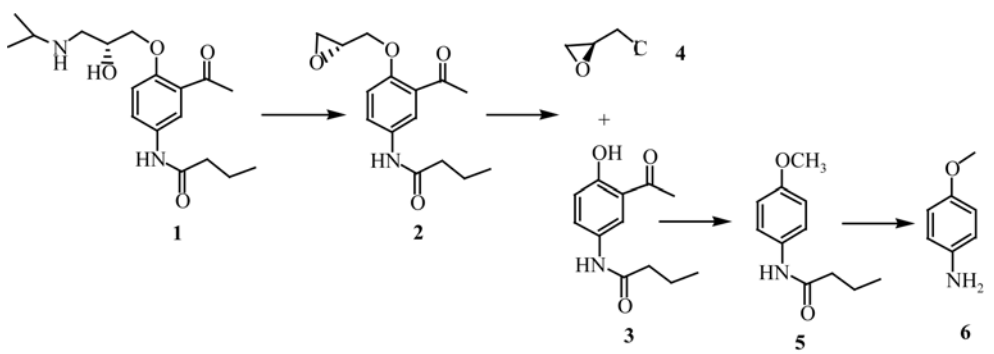
3 Results and dicsussion

The general retrosynthetic analysis is shown in Scheme 1. *R*-acebutolol **1** was obtained via an optically active glycidyl ether **2**, which was synthesized by the reaction of phenol **3** and enantiopure *S*-epichlorohydrin (>98% *ee*) in the presence of base. The key intermediate phenol **3** could be mainly prepared from the cheap material *p*-anisidine **6** through two simple steps, amidation with *n*-butyric acid and the subsequent Friedel-Crafts reaction[19]. It was noteworthy that the traditionally used Fries reaction with high cost and trouble post-treatment was avoided here. Therefore, our new synthetic method not only has the advantage of atom economy but also requires much less synthetic steps.

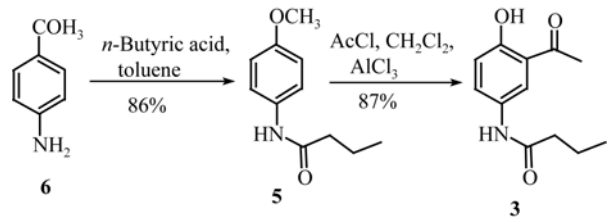
In order to obtain the key building block **3,** the cheap and commercially available starting material *p*-anisidine **6** was used (Scheme 2). **6** was converted to *N*-(4-methoxyphenyl)-butanamide **5** by the amidation reaction with *n*-butyric acid in an apparatus fitted with a Dean-Stark trap. Subsequently, Friedel-Crafts reaction of **5** with acetyl chloride in the presence of lewis acid gave the key intermediate phenol **3**, in which the acylation to the phenyl ring and deprotection of the phenolic hydroxyl proceeded in one step. Generally, **3** was obtained by a Fries reaction[20] which required high reaction temperature, many solvents and tedious post-treatment steps resulting in low overall yields. These disadvantages were overcome in our one step Friedel-Crafts reaction[19].

With the key intermediate **3** in hand, the stage was set for the preparation of optical acebutolol involving the construction of a carbon chiral center. Hietaniemi et al.[18] reported that the reaction of phenol **3** with a glycerol acetonide followed by hydrolysis, tosylation, and amination steps gave optical *R*-acebutolol **1** in less than 30% overall yield, which was tedious and did not accord with atom economy. Since racemic acebutolol can be obtained from **3** and racemic epicholorohydrin via two steps[21], we found that optical acebutolol could be synthesized from **3** and enantionpure epichlorohydrin which is commercially available or synthesized by Jacobson's[22] method (Scheme 3).

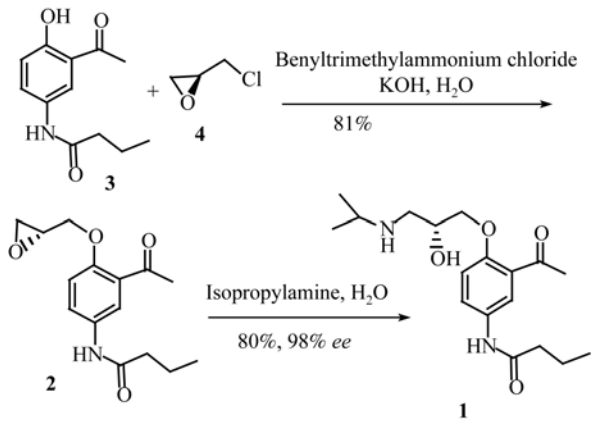
Phenol **3** was converted to an optically active glycidyl ether **2** by reaction with *S*-epichlorohydrin in water in the presence of potassium hydroxide at 0℃. We found that the best solvent used here was water, and alcoholic solvents would result in more by-products and loss of enatioselectivity, which was appropriately catering to the demand of green chemistry. Treatment of glycidyl ether **2** with isopropylamine gave *R*-acebutolo **1** in 80% yield with high enantiomeric excess (98%, *ee*). It was found that *R*-acebutolol was obtained when *S*-epichlorohydrin was used, which suggested that in the course of **3** to **2** phenoxide ion preferentially attacks the carbon of epoxide ring of **4** to form a new epoxide ring with leaving



Scheme 1



Scheme 2



Scheme 3

out chloride[23]. The temperature is an important factor for the stereoselectivity, and the reaction temperature of this step affected the optical purity significantly (Table 1). The higher optical purity of **1** was obtained as the reaction was performed at lower temperature. However, when the reaction temperature was reduced to under 0℃, it proceeded very slowly. Since the reaction mixture is an isopropylamine aqueous solution, it was not frozen at −5℃.

Table 1 The effect of temperature on optical purity of *R*-acebutolol

	T (℃) [a]	Yield (%) [b]	Optical purity of **1** [c]
1	25−30	88	91
2	10−20	85	93
3	0	81	98

a) All reactions were carried out at special temperature for 30−40 h; b) isolated yield of **2;** c) the optical purity was determined by chiral HPLC (chiralpak AD-H).

In conclusion, the synthesis of *R*-enatiomer of β-adrenergic receptor blocker acebutolol was studied. The synthetic strategy described here, using inexpensive starting materials and chiral reagent, is an efficient and practical method, and all the reactions were carried out under mild conditions. *S*-epichlorohydrin was used as chiral building block. It is proper to conclude that the *S*-enationmer of acebutolol can be obtained in the similar fashion to that of *R*-acebutolol with substitution of *S*-epichlorohydrin by *R*-epichlorohydrin.

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