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A Novel Synthetic Method for Bepotastine, a Histamine H1 Receptor Antagonist

Tae Hee Ha,[†,*] Kwee-Hyun Suh,[†] and Gwan Sun Lee[†]

Department of Chemistry, Sungkunkwan University, Suwon 440-746, Korea
[†]Hanmi Research Center, Hwaseong 445-813, Korea. [*]E-mail: hahaha@hanmi.co.kr
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An efficient and alternative synthesis of enantiomerically pure (+)-(*S*)-4-(4-((4-chlorophenyl)(pyrid-2-yl)methoxy]piperidin-1-yl)butanoic acid, bepotastine (**1**) is described. The key resolution of (*R*/*S*)-bepotastine *l*-menthyl ester (**3**) is achived via diastereomeric salt crystallization using *N*-benzyloxycarbonyl-L-aspartic acid (NCbzLAA) as the resolving agent to provide (*S*)-bepotastine *l*-menthyl ester (***S*)-3**. Hydrolysis of (*S*)-bepotastine *l*-menthyl ester (***S*)-3** afforded the desired bepotastine (**1**) with good yields and enantiopurity (> 99%). Finally, bepotastine besilate (**4**) and bepotastine calcium (**5**) are achived by salt formation of bepotastine (**1**) with benzene sulfonic acid and calcium salt respectively. The reaction conditions were optimized to make suitable for commercial scale production.

Key Words : Bepotastine, Histamine H1 receptor antagonist, Diastereomeric salt, Resolving agent

Introduction

Bepotastine (**1**), (+)-(*S*)-4-(4-((4-chlorophenyl)(pyrid-2-yl)methoxy]piperidin-1-yl)butanoic acid, is a highly selective histamine H1-receptor antagonist, which is the most widely used medication in the treatment of allergic rhinitis and other allergic diseases, causes no side effects, such as sleepiness, and arrhythmia.[1] Bepotastine was launched in Japan in July 2000 by Tanabe Seiyaku and UBE Industries, LTD., and is currently being marketed under the brand name of Talion in the dosage of 10 mg tablets.[2] Bepotastine was originally disclosed as a racemate, but later, bepotastine having *S*-configuration, was known to be pharmacologically much more effective and less toxic than the corresponding *R*-enantiomer.[3] Accordingly, there have been attempts to convert bepotastine to an acid salt form having a high optical purity which is resistant to racemization. UBE Industries, LTD. has disclosed bepotastine benzenesulfonic acid salt, which is relatively stable and non-hygroscopic. However, bepotastine besilate salt (**4**) still has a drawback, which is that it undergoes slow racemization in high moisture conditions, such as 75% relative humidity. Several synthesis of (**2**) and bepotastine (**1**) have been reported.[4] (***S*)-2** is protected by a patent of substance and the synthetic method of (***S*)-2** is the use of expensive, a less commercially available resolving agent, (2*R*,3*R*)-2-hydroxy-3-(4-methoxy phenyl)-3-(2-nitro-5-chloro phenyl thio)propionic acid. With this issue in mind, we have endeavored to develop a novel synthetic method for overcoming the barrier of substance patent, and to achive non-hygroscopic salt, that is chemically or optically stable and a pharmaceutically acceptable salt. Herein, we are reporting an efficient and alternative synthesis of enantiomerically pure (+)-(*S*)-4-(4-((4-chlorophenyl)(pyrid-2-yl)methoxy]piperidin-1-yl)butanoic acid, bepotastine (**1**) and its new salt.

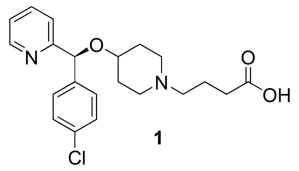


Figure 1. Structure of Bepotastine (**1**).

Experimental

The ^{1}H-NMR spectra were measured in $CDCl_3$ and DMSO-d_6 on a DPX-300 NMR spectrometer (300 MHz, Bruker); the chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as a KBr dispersion using MB-100 Infrared spectrometer (Bomem). The mass spectrum was recorded on an Esquire LC MS spectrometer (Bruker). The melting point were determined by using the capillary method on a IA 9000 series digital melting point apparatus (Fisher). The chiral HPLC analytical methods were developed using authentic racemic samples. The solvents and reagents were used without further purification.

Synthesis of 4-[(4-Chlorophenyl)(2-pyridyl)methoxy] piperidine (2). 4-Chlorophenyl-2-pyridiylmethanol (300 g, 1.37 mol)[5] and 380 mL of triethylamine were added in 2500 mL of toluene and the reaction mixture was cooled at 0 °C, a solution obtained by dissolving methanesulfonyl chloride (187 g, 1.63 mol) in 500 mL of toluene was slowly added to the reaction mixture at 0 °C. The reaction mixture was stirred at rt for 1 h. The reaction mixture was washed with 2500 mL of water. The organic layer was dried with magnesium sulfate. Ethyl 4-hydroxypiperidine-1-carboxylate (167 g, 0.96 mol) and 485 mL of diisopropylethylamine were added to the reaction mixture and stirred at 80 °C for 3 h. The reaction mixture was washed with 2500 mL of water, 1500 mL of 1 N-HCl and 500 mL of brine, and dried with

magnesium sulfate. The solvent was removed under reduced pressure, to obtain 360 g (crude) of 4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidine-1-carboxylic acid ethyl ester as an oil. 3000 mL of isopropanol and NaOH (535 g, 13.4 mol) were added and the reaction mixture was refluxed for 12 h and the solvent was removed under reduced pressure. The reaction mixture was extracted with 3000 mL of ethyl acetate and washed with 1500 mL of water and 500 mL of brine and dried with magnesium sulfate. 100 g of fumaric acid (100 g, 0.86 mol) was added in the solution of extration and stirred at rt for 5 h. The solid precipitate was filtered and dried. The product was obtained 255 g (63%) in a fumaric acid salt form. 4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidine fumarate salt (250 g, 0.60 mol) was dissolved in the mixture of 1750 mL of dichloromethane and 1750 mL of water, NaOH (60 g, 1.50 mol) was added and stirred at rt for 10 min. The organic layer was separated and the solvent removed under reduced pressure. The product was obtained 179 g (yield: 99%) as a foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.5 (d, J = 3.9 Hz, 1H), 7.7 (t, J = 11.5 Hz, 1H), 7.5 (d, J = 7.8 Hz, 1H), 7.4 (d, J = 8.5 Hz, 2H), 7.3 (d, J = 4.2 Hz, 2H), 7.2 (m, 1H), 5.6 (s, 1H), 3.5 (m, 1H), 3.1 (m, 2H), 2.6 (m, 2H), 1.9 (m, 2H), 1.6 (m, 2H).

Synthesis of 4-Bromobutanoic Acid *l*-Menthyl Ester: Intermediate for (*R*/*S*)-Bepotastine *l*-Menthyl Ester (3). l-Menthol (146 g, 0.93 mol) and 148 mL of pyridine were dissolved in 1500 mL of dichloromethane, a solution obtained by dissolving 4-bromobutyryl chloride (172 g, 0.93 mol) in 200 mL of dichloromethane was slowly added to the reaction mixture and stirred at rt for 1 h. The reaction mixture was washed with 1000 mL of water, and the solvent was removed under reduced pressure. The product was obtained 270 g (97%) as an oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.7 (m, 1H), 3.5 (t, J = 10.6 Hz, 2H), 2.5 (t, J = 14.5 Hz, 2H), 2.2 (m, 2H), 2.0 (m, 1H), 1.9 (m, 1H), 1.7 (m, 2H), 1.5 (m, 1H), 1.3 (m, 1H), 1.1 (m, 3H), 0.9 (d, J = 6.5 Hz, 6H), 0.7 (d, J = 7.0 Hz, 3H); IR (KBr, cm^{-1}): 2956, 2928, 2870, 1729, 1456, 1370, 1251, 1205, 1177, 1129, 984.

Synthesis of (*R*/*S*)-Bepotastine *l*-Menthyl Ester (3). 240 g of (*R*/*S*)-4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidine (240 g, 0.79 mol) was dissolved in 2400 mL of acetone, 4-bromobutanoic acid *l*-menthyl ester (270 g, 0.88 mol) and K_2CO_3 (164 g, 1.19 mol) were sequentially added in the reaction mixture and refluxed for 7 h. The reaction mixture was filtered to remove insoluble solids, and the solvent was removed from the filtrate under reduced pressure. The product was obtained 420 g (99%) as an oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.5 (d, J = 4.1 Hz, 1H), 7.7 (t, J = 15.3 Hz, 1H), 7.5 (d, J = 7.8 Hz, 1H), 7.4 (d, J = 8.4 Hz, 2H), 7.3 (m, 2H), 7.2 (m, 1H), 5.6 (s, 1H), 4.7 (m, 1H), 3.5 (br s, 1H), 2.7 (m, 2H), 2.3(m, 4H), 2.1 (m, 1H), 2.0-1.6 (m, 11H), 1.5 (m, 1H), 1.4 (m, 1H), 1.2 (m, 3H), 0.9 (m, 6H), 0.7 (d, J = 5.0 Hz, 3H); IR (KBr, cm^{-1}): 2952, 2869, 2810, 1727, 1588, 1489, 1468, 1455, 1370, 1187, 1086, 984, 807, 768, 749.

Synthesis of (*S*)-Bepotastine *l*-Menthyl Ester · *N*-benzyloxycarbonyl-L-aspartate ((*S*)-3·NCbzLAA). (*R*/*S*)-Bepotastine *l*-menthyl ester (300 g, 0.57 mol) was dissolved in 3000 mL of ethyl acetate, *N*-benzyloxycarbonyl L-aspartic acid (152 g, 0.57 mol) and was added to the reaction mixture and stirred at rt for 12 h. The solid precipitate was filtered and dried. The first crude product was obtained 160 g (yield: 71%, optical purity: 89.7% ee) as a white crystal. 150 g of the first crude product was added to 1500 mL of ethyl acetate, and clearly dissolved by heating. The solution was slowly cooled to rt and stirred for 12 h to induce solid precipitation. The second crude product was obtained 130 g (yield: 87%, optical purity: 96.7% ee) as a white crystal by filtration and drying. 120 g of the second crude product was recrystallized from ethyl acetate by repeating the above procedure. The product was obtained 109 g (yield: 91%, optical purity: 99.5% ee) as a white crystal. Specific optical rotation: $[\alpha]_D^{24}$ −15.2 (c=1.0, MeOH); Melting point: 108-110 °C (degradation); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.5 (br s, 1H), 7.8 (t, J = 13.7 Hz, 1H), 7.5 (d, J = 7.3 Hz, 1H), 7.4-7.2 (m, 10H), 7.2 (m, 1H), 5.6 (s, 1H), 5.0 (s, 2H), 4.5 (m, 1H), 4.1 (m, 1H), 3.5 (br s, 1H), 2.9 (m, 2H), 2.6-2.3 (m, 5H), 2.2 (t, J = 12.0 Hz, 2H), 1.9-1.6 (m, 11H), 1.5 (m, 1H), 1.4 (m, 1H), 1.0 (m, 3H), 0.9 (m, 6H), 0.7 (d, J = 5.1 Hz, 3H); IR (KBr, cm^{-1}): 3412, 2956, 2928, 2870, 1725, 1592, 1491, 1455, 1435, 1389, 1227, 1191, 1068, 960, 772, 696, 673.

Synthesis of (*S*)-Bepotastine *l*-Menthyl Ester · *N*-Benzyloxycarbonyl-L-aspartic Acid ((*S*)-3·NCbzLAA). (*R*/*S*)-Bepotastine *l*-menthyl ester (100 g, 0.19 mol) was dissolved in 1000 mL of ethyl acetate, *N*-benzyloxycarbonyl-L-aspartic acid (51 g, 0.19 mol) was added to the reaction mixture and dissolved by heating at the boiling point of the solvent. The solution was cooled slowly to rt and 0.5 g of bepotastine *l*-menthyl ester·*N*-benzyloxycarbonyl-L-aspartate seeded and stirred for 12 h. The solid precipitate was filtered and dried. The product was obtained 55 g (yield: 73%, optical purity: 95.3% ee) as a white crystal.

Synthesis of (*S*)-Bepotastine *l*-Menthyl Ester ((S)-3). Bepotastine *l*-menthyl ester·*N*-benzyloxycarbonyl-L-aspartic acid complex (250 g, 0.31 mol) was added to the mixture of 1000 mL of ethyl acetate and 1250 mL of water and the pH of the reaction mixture was adjusted to 8.0 with saturated sodium bicarbonate to induce phase separation. The organic layer was separated and the solvent removed under reduced pressure. The product was obtained 162 g (yield: 98%, optical purity: 99.5% ee) as an oil. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.5 (br s, 1H), 7.7 (t, J = 13.7 Hz, 1H), 7.5 (d, J = 7.3 Hz, 1H), 7.4 (m, 2H), 7.3 (m, 2H), 7.2 (m, 1H), 5.6 (s, 1H), 4.7 (m, 1H), 3.5 (br s, 1H), 2.7 (m, 2H), 2.3 (m, 4H), 2.1 (m, 1H), 2.0-1.6 (m, 11H), 1.5 (m, 1H), 1.4 (m, 1H), 1.2 (m, 3H), 0.9 (m, 6H), 0.7 (d, J = 5.1 Hz, 3H); IR (KBr, cm^{-1}): 2953, 2869, 2811, 1728, 1588, 1489, 1469, 1456, 1434, 1370, 1253, 1188, 1108, 1086, 1015, 984, 807, 768, 749, 615.

Synthesis of (*S*)-bepotastine (1). Bepotastine *l*-menthyl (150 g, 0.28 mol) was dissolved in the mixture of 500 mL of ethanol and 500 mL of water, 34 g of sodium hydroxide (34 g, 0.85 mol) was added and stirred at rt for 10 h. After adding water, the resulting mixture was washed with ethyl ether, and 300 mL of 3N HCl was added to the aqueous

solution, which was extracted with dichloromethane. The organic layer was separated and the solvent removed under reduced pressure. The product was obtained 102 g (yield: 92%, optical purity: 99.5% ee) as a foam. MS: *m/z* 389.1 [M+H]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.6 (d, *J* = 5.7 Hz, 1H), 7.7 (t, *J* = 13.5 Hz, 1H), 7.4 (d, *J* = 7.9 Hz, 1H), 7.4-7.2 (m, 5H), 5.6 (s, 1H), 3.8 (br s, 1H), 3.0 (t, *J* = 12.7 Hz, 2H), 2.5 (m, 2H), 2.3 (m, 2H), 1.9 (m, 4H).

Synthesis of (*S*)-Bepotastine Besilate (4). Bepotastine (50 g, 0.13 mol) was dissolved in 500 mL of acetonitrile, and benzenesulfonic acid monohydrate (20 g, 0.11 mol) was added to the reaction mixture. Bepotastine besilate (0.5 g, 1.28 mmol) was seeded in the reaction mixture and stirred at rt for 12 h. The solid precipitate was filtered and dried. The product was obtained 38 g (yield: 64%, optical purity: 99.5% ee) as a pale white crystalline powder. Melting point: 161-163 °C. Water: 0.2% (Karl-Fischer water determination). MS: *m/z* 389.1 [M+H]; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.2 (br s, 1H), 8.5 (d, *J* = 4.1 Hz, 1H), 7.8 (t, *J* = 7.7 Hz, 1H), 7.6 (m, 3H), 7.4 (m, 4H), 7.3 (m, 4H), 5.7 (s, 1H), 3.7 (br s, 2H), 3.3 (br s, 3H), 3.1 (br s, 2H), 2.3 (t, *J* = 14.1 Hz, 2H), 2.2 (m, 1H), 2.0 (m, 1H), 1.8 (m, 3H), 1.7 (m, 1H); IR (KBr, cm^{-1}): 3422, 2996, 2909, 2735, 2690, 2628, 1719, 1592, 1572, 1488, 1470, 1436, 1411, 1320, 1274, 1221, 1160, 1123, 1066, 1031, 1014, 996, 849, 830, 771, 759, 727, 693, 612, 564.

Synthesis of (*S*)-Bepotastine Calcium Salt (5). Bepotastine (50 g, 0.13 mol) was dissolved in 28 mL of 5 N aqueous sodium hydroxide solution and 25 mL of water, a solution obtained by dissolving 20 g of calcium chloride in 250 mL of water that was slowly added to the reaction mixture and stirred at rt for 12 h. The solid precipitate was filtered and dried. The product was obtained 45 g (yield: 86%, optical purity: 99.5% ee) of the title compound as a white crystalline powder. Water: 4.4% (Karl-Fischer water determination, a theoretical value of dihydrate 4.23%); Melting point: 238-240 °C (degradation); MS: *m/z* 389.1 [M+H]; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.4 (d, *J* = 4.6 Hz, 1H), 7.8 (t, *J* = 15.2 Hz, 1H), 7.5 (d, *J* = 7.8 Hz, 1H), 7.4 (m, 4H), 7.2 (t, *J* = 12.2 Hz, 1H), 5.6 (s, 1H), 3.5 (m, 1H), 2.6 (m, 2H), 2.2 (t, *J* = 14.4 Hz, 2H), 1.9 (m, 4H), 1.8 (m, 2H), 1.6 (m, 4H); IR (KBr, cm^{-1}): 3338, 2945, 2825, 1589, 1562, 1490, 1471, 1432, 1412.9, 1308, 1116, 1092, 1061, 1014, 994, 808, 776, 750.

Racemization Reaction of (*R*)-Bepotastine *l*-Menthyl Ester Isomer Major. Bepotastine *l*-menthyl ester mixture (150 g, 0.28 mol, (*S*)-3:(*R*)-3 = 40:60) was dissolved in 150 mL of acetic acid and refulxed for 3 h. 150 mL of water was added to the resulting mixture and extracted with 300 mL of ethyl acetate and whshed with 150 mL of saturated aquous $NaHCO_3$ solution. The organic layer was washed with 150 mL of brine, dried, and removed under reduced pressure. The product was obtained 141g (94%, (*S*)-3:(*R*)-3 = 49.8: 50.2) as an oil.

Effect of Storage Condition on the Optical Purity. The bepotastine bezenesulfonic acid salt and the bepotastine calcium salt obtained by synthetic method in experimental part were respectively exposed to a condition of 60 °C and 75% relative humidity (R.H.) for 4 weeks in either an open or a closed storage condition. The optical purities of respective bepotastine salts were determined. The results are shown in Table 1.

Table 1. Effect of storage condition on the isomer purity

Bepotastine salt	Isomer purity (%)		
	Initial	60 °C, 75% R.H. for 4 weeks	
		opened	closed
Besilate	99.9	95.5	97.3
Calcium	99.9	99.9	99.9

Table 2. Solubility test of bepotastine salt

Bepotastine salt	Saturation solubility (mg/mL)		
	H_2O	pH 1.2[a]	pH 6.8[b]
Besilate	21.6	45.0	28.1
Calcium	3.6	43.2	61.6

[a]NaCl (2.0 g), HCl (7.0 mL) and H_2O (993 mL). [b]KH_2PO_4 (0.2 mol/L, 250 mL), NaOH (0.2 mol/L, 118 mL) and H_2O (632 mL)

Solubility Test. The saturation solubility of the bepotastine bezenesulfonic acid salt and the bepotastine calcium salt obtained by synthetic method in experimental part were analyzed using H_2O, pH 1.2 and pH 6.8 buffer solutions. The pH 1.2 and pH 6.8 buffer solution simulate the gastric juice and intestinal juice, respectively. The results are shown in Table 2.

Results and Discussion

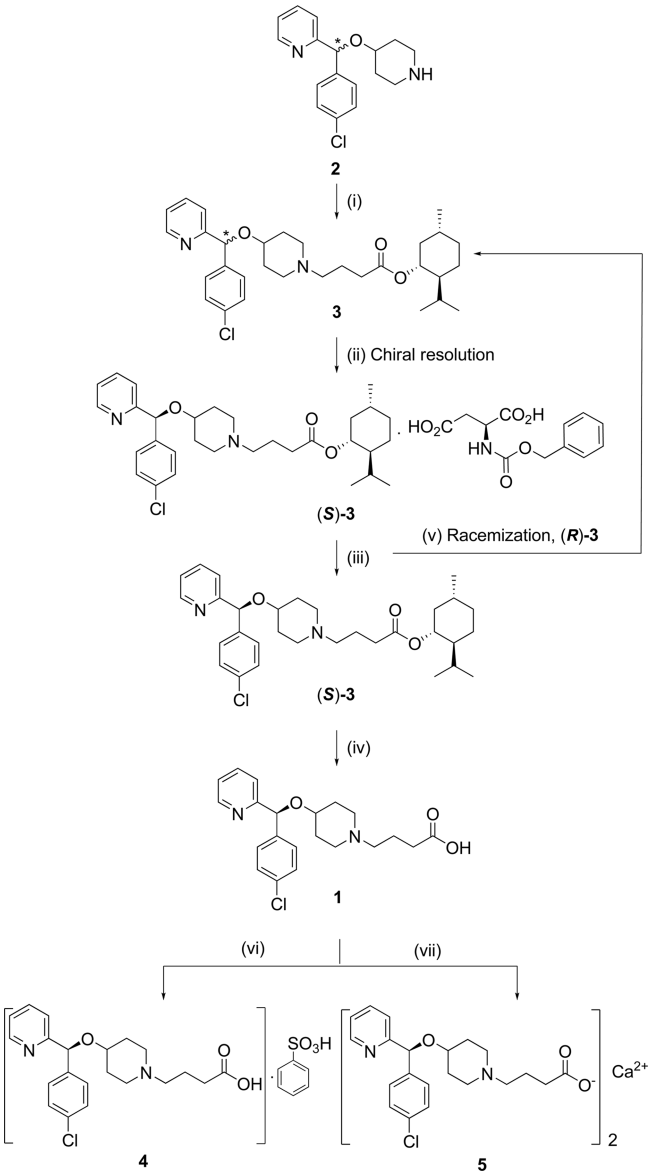
The first our process efforts focused on the direct resolution of (*S*)-bepotastine (**1**) from (*R*/*S*)-bepotastin using commerciallly available chiral resolving agents,[6] such as chiral acids (camphorsulfonic acid, malic acid, mandelic acid, tartaric acid, dibenzoyl tartaric acid, di-*p*-toluoyl tartaric acid, *N*-benzyloxycarbonyl L-aspartate) and chiral bases (methylbenzylamine, 2-amino-1-butanol, quinine, cinchonidine) because they are zwitteric molecules, that contain both a positive and a negative charge.

Among these, resolution with di-toluoyl-L-tartaric acid in ethanol and ethyl acetate mixture although successful, diastereomeric salt yield is very low at only about 5-10%. These results on direct resolution of (*R*/*S*)-bepotastine were very discouraging.

Therfore, we explored an alternative synthetic route, that of the introduction of functional groups of (*R*/*S*)-bepotastin, such as amide and ester, to enhance the resolution efficiency. We found a suitable compound for the resolution which is (*R*/*S*)-bepotastine *l*-menthyl ester (**3**).

N-akylation of compound (**2**) with 4-chlorobutanoic acid *l*-menthyl ester or 4-bromobutanoic acid *l*-menthyl ester under basic conditions was readily converted to the compound (**3**) in good yield (> 95%).

The compound (**3**) with a commercially available *N*-benz-



Scheme 1. Synthesis of bepotastine *l*-menthyl ester *N*-benzyloxycarbonyl-L-aspartic acid complex (**3**), bepotastine besilate (**4**) and bepotastine calcium (**5**). Reagents and conditions; i) 4-bromobutanoic acid *l*-menthyl ester, K_2CO_3, acetone, reflux, 7 h, 95-99%; ii) *N*-benzyloxycarbonyl-L-aspartic acid (NCbzLAA), ethyl acetate, rt, 12 h, 71-73%; iii) Ethyl acetate/H_2O, $NaHCO_3$, 97-99%; iv) EtOH:H_2O = 1:1, NaOH, rt, 12 h, 3.0 N-HCl Neutralization, 92-95%; v) AcOH, reflux, 12 h, racemization 97-100%; vi) Bezensulfonic acid, acetonitrile, rt, 12 h, 64-67%; vii) NaOH, H_2O, $CaCl_2$, rt, 12 h, 86-89%.

yloxycarbonyl-L-aspartate (NCbzLAA) as a resolving agent, was conveniently converted to (*S*)-3·NCbzLAA complex by diastereomeric crystallization in ethyl acetate. The compound (***S*)-3** was easily converted to bepotastine (**1**) by hydrolysis under basic conditions in good yield (> 95%).

The compound (***R*)-3** was also converted to compound **3** by racemization in acetic acid medium in good yield (> 99%).

Bepotastine (**1**) was converted to bepotastine besilate (**4**) or bepotastine calcium (**5**) by salt formation. In addition, the compound (**5**) was also confirmed as a pharmaceutically acceptable new salt and suitable for an active pharmaceutical ingradient through the test of optical purity change in high humidity storage conditions and solubility.

Finally, the reaction conditions were optimized to make suitable for commercial scale production.

Conclusion

In conclusion, we have developed an efficient, alternative, and industrially scaleable process for the production of (+)-(*S*)-4-{4-[(4-chlorophenyl) (2-pyridyl) methoxy]piperidino} butyric acid, bepotastine (**1**), a histamine H1-receptor antagonist, and its pharmaceutically acceptable salts (bepotastine besilate (**4**) and bepotastine calcium (**5**)) from the (***S*)-3** via diastereomeric crystallization of the racemic compound (**3**) using *N*-benzyloxycarbonyl-L-aspartic acid (NCbzLAA).

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