Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2013, 5(12):349-352

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Asymmetric synthesis of (2S)-propranolol using D-mannitol

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ABSTRACT

It is wildly known that racemic propranolol has dramatically side effects to cardiovascular patients. Thus, it's important to develop a new approach to synthesize the chiral propranolol. In present study, a novel synthetic route to chiral propranolol was carried out, using natural and cheap D-mannitol as starting material. The structures of all the synthesised compounds were confirmed by their IR, ^{1}H NMR spectral data, and the results of HPLC showed that enantioselectivities up to 99% ee and chemical yields up to 97% have been obtained.

Keywords: D-mannitol, (2S)-3-(1-naphthyloxy)-1,2-epoxypropane, (2S)-propranolol

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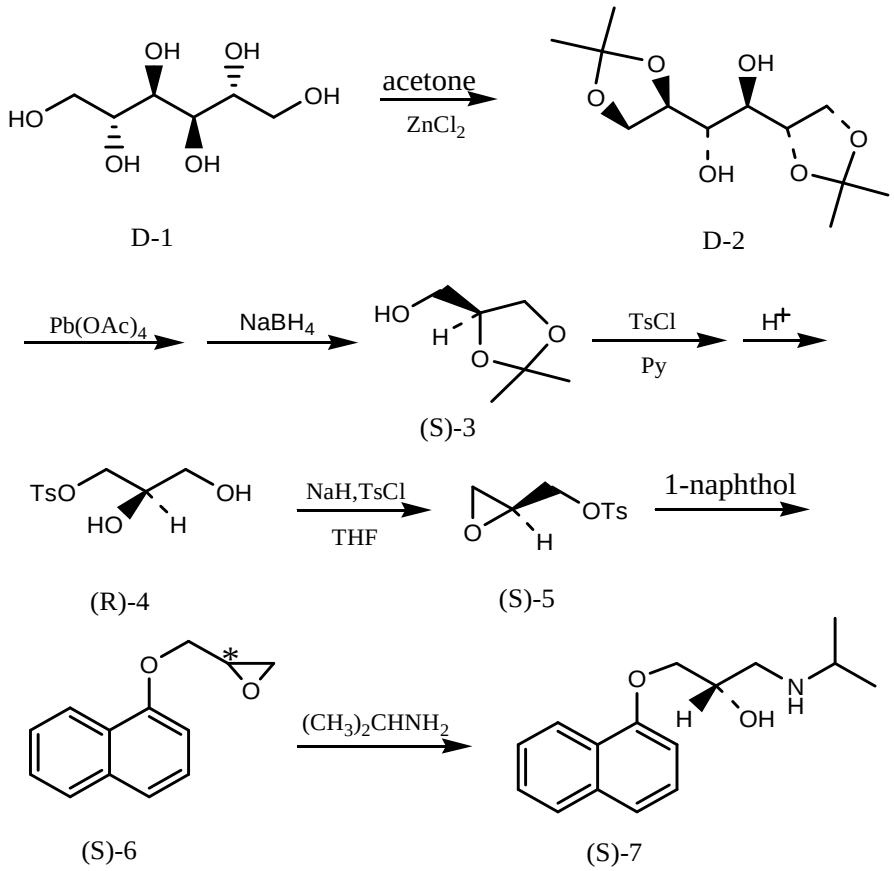
INTRODUCTION

Propranolol is a kind of β-blockers, which can be used to treat arrhythmia, angina, hypertension with good effect . It is reported that racemic propranolol is likely to cause loss of libido and impotence to male patients with a capacity of 40-320mg per day. The blockage of (2S) - propranolol is 100 times stronger than (2R) - propranolol [1]. Loss of libido and impotence to male patients and sex apathy of female patients are observed pronouncedly because of (2R) - propranolol`s side effects[2]. Therefore, the research of optimization about (2S)-propranolol synthesis is very important to enhance effectiveness, and reduce the dosage alleviating toxicity.

Regulations issued by the U.S. Food and Drug Administration (FDA) in 1992 required that new drugs with single enantiomers content can be permitted to sale. It is also required that toxicity, clinical results, pharmacological effects of each single isomer chiral content in drugs on sale must be carefully studied[3]. At present, just racemic propranolol is offered in the domestic market. (2S) - propranolol can be obtained by resolution of the racemate [4-7]. In particular, asymmetric catalysis has applied successfully in the synthesis of (2S) - propranolol in recent years [8-13], however, it has been unable to applied in commercial production for expensive catalysts and materials. In present study, a novel synthetic route to chiral propranolol was carried out, using natural and cheap D-mannitol as starting material. The structures of all the synthesised compounds were confirmed by their IR, ^{1}H NMR spectral data, and the results of HPLC showed that enantioselectivities of (2S) - propranolol up to 99% ee and chemical yields up to 97% have been obtained. The following is the synthetic route.



EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded on a VARIANINONA 500 spectrometer, operating at 500Hz for ^{1}H NMR and 125.65 Hz for ^{13}C NMR. ^{1}H NMR and ^{13}C NMR spectra were measured $CDCl_3$ as solvents. Chemical shifts are reported in ppm on the δ scale relative to TMS(δ=0.00 for ^{1}H NMR) or using residual $CHCl_3$ (δ=7.26 for ^{1}H NMR and δ=77.0 for ^{13}C NMR) as an internal reference, respectively. Column chromatography was performed with silica gel Merck 60(230-400 mesh ASTM). The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on Agilent 1100 HPLC systems. Powdered molecular sieve 4A (MS 4A) was dried at 180□ under reduced pressure for more than 6h prior to use.

Synthesis of 1,2;5,6-di-O-iso- propylidene-D-mannitol(D-2)

To a solution of zinc chloride (60g, 0.44mol) in acetone (300mL) was added D-mannitol(10g, 54.9mmol). After being stirred for 2h at room temperature, the reaction mixture was poured into a vigorously stirred mixture of saturated aqueous potassium carbonate . The whole mixture was stirred vigorously for 30 min at room temperature, the reaction mixture was diluted with ether and filtered to remove zinc carbonate. The filtrate was concentrated and extracted twice with hot petroleum ether, then cooled down and filtered to give (D-2) (10.7g, 40.125mmol; 75％) as a solid . mp117℃ ; $[\alpha]^{25}_D$=+22.4(c 5.175，CH_3OH) ； IR (KBr) 3275, 2986, 2940, 1425, 1357, 1261, 1213, 1150, 1075, 1020, 936, 860, 705 cm^{-1} ； ^{1}H NMR（$CDCl_3$）δ：1.36（6H, s）, 1.42（6H, s）,2.58（2H, s）, 3.7－4.2（8H, m）;

Synthesis of (S)-Glcerol-1,2-Acetonide((S)-3)

To a solution of D-2 (8g, 30mmol) in THF (40mL) was added dried lead(IV) acetate (13.4g, 30mmol). After being stirred for 30min at 0℃ and 1h at room temperature, the reaction mixture was filtered. The filtrate was added $NaBH_4$ (2.29g，0.061mol) in 4% aqueous NaOH (20mL). After being stirred for 30min at 0℃ and 2h at room temperature, the reaction mixture was quenched with ammonium chloride and concentrated to remove THF. The mixture was extracted with AcOEt , dried (Na_2SO_4), and concentrated to give the (S)-3（7.44g, 56.8mmol; 93％) as an oily residue. bp 80-90℃（20mmHg）; $[\alpha]^{25}_D$＝+11.3(c 5.175, CH_3OH); ^{1}H NMR（$CDCl_3$）δ：1.37（3H, s）, 1.44（3H, s）, 2.1（1H, s），3.5－4.2（5H, m）.

Synthesis of (R)-3-Tosyloxy-1,2-propanediol((R)-4)

To a solution of S-3 (7.2g, 55mmol) in pyridine (30mL) was added TsCl (10.4g, 55mmol) . After being stirred for 16h at 0℃ , the reaction mixture was diluted with Et_2O and washed with 1N HCl .The aqueous layer was separated, and the organic layer was washed with saturated aqueous $NaHCO_3$, dried ($NaSO_4$) , and concentrated to give the (R)-3 -Tosyloxy-Glcerol -1,2-propanediol (14.1, 49.2mmol, 91%). The condensates was added acetone (10mL) and 1N HCl (30mL) .After being stirred for 2h at 80℃, the reaction mixture was extracted with CH_2Cl_2 and concentrated to give (R)-4 (12.1g, 49.2mmol; 100%) as a solid. $[\alpha]^{25}_D$＝－9.3^0(c 4.99, CH_3OH) (99% ee) ; mp63－64℃; IR (KBr) 3342, 2963, 2369, 1926, 1568, 1495, 1360, 1173, 1097, 964, 814, 667 cm^{-1} ; ^{1}H NMR（$CDCl_3$）δ：1.93（2H, s）, 2.48（3H, s）, 3.62－4.12（5H, m），7.38－7.82 (4H, 2d, J＝8.31Hz).

Synthesis of (2S)-Goycidyl tosylate（(S)-5)

To a solution of (R)-4 (1.23g, 5mmol) in THF (20mL) was added NaH (0.48g, 20mmol) in THF (20mL). After being stirred for 2h at 0℃ and 10h at room temperature, the reaction mixture was added TsCl (1.0g, 5.25mmol) in THF (10mL). After being stirred for 1h at 0℃ and 10h at room temperature, the reaction mixture was diluted with hexane and filtered over a Celite pad. The filtrate was concentrated to give (S)-5 (1.08g, 4.75mmol; 95%) as a solid. $[\alpha]^{25}_D$ ＝+17.5°(c 2.13, $CHCl_3$) (99% ee) ; mp46-48℃; IR (KBr) 3075, 3000, 2935, 1598, 1362, 1195, 1180, 965, 915, 815, 775, 666, 558cm^{-1}; ^{1}H NMR($CDCl_3$)δ：2.44（3H，s ）, 2.59（1H, dd, J＝1.8, 4.5Hz）, 2.81（1H, m）, 3.16－3.20（1H, m）, 3.95（1H, dd, J＝3.9, 10.5Hz）, 4.25（1H, dd, J＝1.8, 9Hz），7.35（2H, d, J＝6.4Hz）, 7.80（2H, d, J=6.8Hz）.

Synthesis of (2S)-3-(1-naphthyloxy)-1,2-epoxypropane((S)-6)

To a solution of (S)-5 (1.523g, 6.7mmol) in THF (5mL) was added NaH (0.20g, 8mmol) and naphthol (1.01g. 7mmol) in THF (20mL). After being stirred for 4h at room temperature, the reaction mixture was filtered over a Celite pad and concentrated to give a residue which was then purified by silica gel flash chromatography (EtOAc/hexane, 4:6) to give (S)-6 (1.27g, 6.35mmol; 95%) as a slurry . $[\alpha]^{25}_D$=+32.9°(c 1.0, MeOH) (99% ee) ; IR (KBr) 1597, 1514, 1457, 1366, 1270, 1177, 1062, 1042, 1013, 889, 756, 710, 662 cm^{-1} ; ^{1}H NMR($CDCl_3$)，δ：2.86－2.97（2H, m, epoxide CH_2）, 3.50－4.42（3H, m, $ArOCH_2CH$）, 6.80－8.31（7H, m, aromatic hydrogen).

Synthesis of (2S)-propranolol ((S)-7)

To a mixture (S)-6 (0.8g, 4.0mmol) in isopropylamine (3.4mL, 40mmol) was added H_2O (0.34mL) .After being stirred for 4h under reflux, the reaction mixture was diluted with H_2O and extracted with Et_2O .The combined organic layers were washed with 1N aqueous NaOH , and saturated aqueous NaCl ,dried (Na_2SO_4) , and concentrated to give (S)-7 (1.01g, 3.4mmol; 97%) as yellow solid. $[\alpha]^{25}_D$= - 9.7°(c 1.5, EtOH) (99% ee); mp 71-73℃; IR (KBr) 3270, 2980, 2800, 1582, 1508, 1459, 1401, 1268, 1207, 1104, 997, 914, 879, 787, 764, 622 cm^{-1} ; ^{1}H NMR($CDCl_3$)δ：1.1（6H, J＝6.2Hz）, 1.9（2H, br s）, 2.9（3H, m）, 6.8－8.3（7H, m）.

CONCLUSION

We have successfully carried out a novel synthetic route to chiral propranolol using natural and cheap D-mannitol as starting material. The results of HPLC showed that enantioselectivities of (2S) - propranolol up to 99% ee and chemical yields up to 97% have been obtained. The synthetic route to chiral propranolol has been able to applied in commercial production.

Acknowledgment

We are grateful to the support from the National Natural Science Foundation (grant No U1204307) and also to GuangZhou University for the IR spectral analysis and Zhong Shan University for the ^{1}H NMR spectral analysis.

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