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Asymmetric Synthesis and Characterization of Pharmaceutical Important Drug (R)-Mexiletine

Sachin A. Khiste,[1] Nilesh Rathod, [2] Manisha Kodape,[3] Dnyaneshwar S. Wankhede*[1] ,Mahendra Lokhande*[4]

[1]School of Chemical Sciences, Swami Ramanad Teerth Marathwada University, Nanded-431606 (M.S.) India dswchem@yahoo.co.in

[2]Department of Chemistry, R.A. Arts S.M.K.C. Shri Rathi Science College, Washim 444505(M.S.) India

[3]Department of Chemistry, Sant Gadge Baba Amravati University, Amravati 444602 (M.S.) India

[*4]Department of Chemistry, Matoshri Nanibai Gharpalkar Science College, Babhulgaon, Dist.Yavatmal – 445101 (M.S.) India Mahendra8881@gmail.com1

Abstract

The synthesis of S-(R)-Mexiletine was carried out in six step in 38% overall yield. The introduction of chirality was demonstrated by the desymmetrization of glycerol, it results in spiroketal formation with reductive deoxigenation of hydroxyl moiety of epoxide. The Mitsunobu reaction is the main feature of the reaction. (R)-Mexiletine is the alternative drug used in the treatment of hypertension and as cardiotonics.

Keywords: Mitsunobu reaction, Spiroketal, Epoxide, Hypertension, Cardiovascular

1. Introduction

In 1980's, mexiletine is first developed clinical drug, which belong to the group Ib sodium channel blockers.[1] Mexiletine also clinically used as an antiarrhythmic, antimyotonic, analgesic, and pain relief oral drug in its racemic form.[2] However use of racemic mexiletine for clinical treatment is limited due to its side effect. Being (*R*)-mexiletine potent important than (S)-mexiletine as clinical drugs in life sciences, therefore an enantiomerically pure synthesis of (R)-mexiletine is highly challenging and active research area. Hence, this section describes the synthesis of (R)- mexiletine. As bit also used as β-adrenergic blocking agents and belong to class of medicines and also called as adrenergic inhibitors.[3]

The β-blockers are play key role to block only catecholamines hormones in brain, heart, and blood vessels that results the heart beats more slowly with less force. In addition, blood vessels relax and widen so that blood flows through them more easily.[4] Both of these actions are most important to reduce the blood pressure during heart-attack. In the view of medicinal purpose it is essential to synthesis and characterizes the β -adrenergic blocking agents.[5] Presently, many of the pharmaceuticals are marketing these antihypertensive drugs in the racemic forms, even though (R)- mexiletine are known to be 100-500 fold more effective than the I-isomer.[6] As or strategy involve the synthesis of (R)-mexiletine was used from glycerol by modified desymmetrization strategy. [7]

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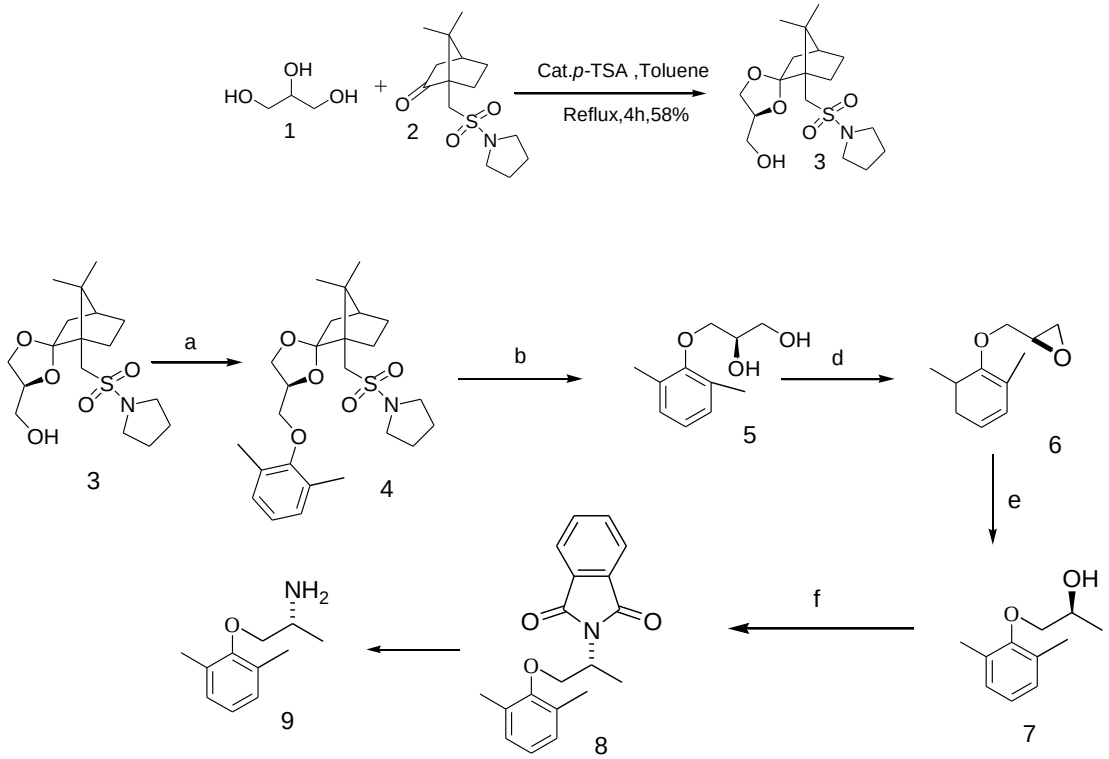

Scheme 2.

2. Results and discussion

a) 2, 6-dimethyl phenol, TPP, DIAD, THF, rt, 4h, 71%; b) MeOH, Conc. HCl, reflux, 10h, 96%; c) TPP, DIAD, THF, rt, 4h, yield 78%; d) LAH, THF, 0 ^{o}C-RT, 2 h, 96 %; e) Ph_3P, phthalimide, DIAD, THF, RT, 5 h, 84 %;f) $N_2H4.H_2O$, EtOH, reflux, 3 h, 83 %.

As classical desymmetrization strategy is usefull for the synthesis of (R)- mexiletine **9** by desymmetrization of glycerol by (R)-(-)-Camphor sulfonamide. Glycerol was first desymmetrized by Uang making use of (1*R*)-(-)-Camphorsulfonamide.[8] Our total synthesis is start by using D-10-Camphor sulphonic acid converted into D-10-Camphor sulphonyl chloride by using thionyl chloride. Then chloride converted to D-10-Camphor sulphonamide by simple nucleophilic displacement with pyrrolidine using DMAP as strong base. From this D-10-Camphor sulphonamide, spiroketal **3** formation is done by using glycerol and p-tolunesulphonic acid in benzene for 48 hr.[9] The formed spiroketal **3** was confirmed by the ^{1}H-NMR,^{13}C, IR spectra. The exo and endo of CH_2 observed at 2.30-2.36 as exo ddd, 1H, *J* = 3.5, 7.3 Hz. While endo coupling of proton is at 1.48- 1.52 d, 1H, *J* = 12.6 Hz. The CH_2 of methyl sulfonamide of two H observed at distinct position as one is at 2.65-2.70, 1H, *J* = 14.4 Hz and one H at 3.52-3.47, d, 1H, *J* = 14 Hz. While in literature the physical property of the compound is found to be gamy liquid but after carefully chromatographic separation of reaction mixture it is found that spiroketal is solid compound having melting point is 118-120^{0}C. After chromatographic separation the spiroketal shows the optical rotation $[\alpha]^{25}_{D}$ = -18.58 (c 9.9,$CHCl_3$) i.e. 99% optical purity as compared to lit. Value $[\alpha]^{25}_{D}$ = -11.8 (c 1, $CHCl_3$).

As in ^{13}C the absence C=O frequency indicating the ketal formation with ketal carbon at δ 115.25 and three glycerol carbon are fond at δ 64.41, 74.05, 60.75 Hz respectively. The free alcohol moiety was employed a typical Mitsunobu reaction with 2, 6-dimethyl phenol to get compound **4** having melting point is 146-148^{0}C,whose optical rotation is found to be $[\alpha]^{26}_{D}$= -30.8^{o} (c = 1 , CH_3OH)]. [10]

Then the compound **4** was deprotected by using methanolic HCl.[11] After deprotection we get diol **5**, the appearance of new aliphatic

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multiplet at δ 3.76-4.12, and the broad singlet for two hydroxyl group of diol at δ 2.93. The ^{13}C NMR spectrum showed signals at δ 11.74 and 20.14 for two CH_3 attached to the aromatic ring. The peak appears at δ 70.70 for the tertiary carbon bearing hydroxy group. The chiral diol under Mitsunobu reaction conditions afforded corresponding chiral epoxide. The optical rotation is observed $[\alpha]^{25}_{D}$=-30.5°(c=1.55,$CHCl_3$)],{Lit.33.9°(c=1.55, MeO H),}.[12] The ^{1}H NMR spectrum of an epoxide **6** compound showed disappearance of singlet for the hydroxyl group and appearance of multiplet of one proton at δ 2.91-2.93. The ^{13}C NMR spectrum shows the signal at δ 11.74, and 20.16 for two CH_3 attached to the aromatic ring and signal at δ 50.26 for tertiary carbon of an epoxide, which confirmed the formation of an epoxide compound. The reduction of an epoxide **6** using LAH in

a THF solvent, gives the chiral secondary alcohol **7** which on reaction with phthalimide Under Mitsunobu reaction condition, gives phthalate protected compound **8**. Finally deprotection of phthalate **8**, gives (*R*)-mexiletine

3. Conclusion

In summary, we have prepared a pharmaceutical acitve (R)- mexiletine 9 having overall yield 38% via desymmetrization of glycerol strategy using (1R)–(-)-10–camphorsulfonamide as chiral auxiliary. The enantiomeric purity found to be in the range of 90% ee.

7. References

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