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Synthesis and Characterization of Pharmaceutical Important Drug S-Xibenlol Very Useful as a Cardiovascular Drug

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ABSTRACT

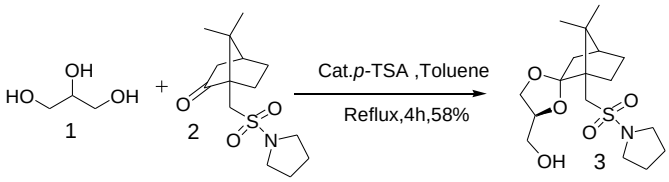
The synthesis of S-Xibanolol was carried out in six step in 34% overall yield. The introduction of chirality was demonstrated by the desymmetrization of glycerol, it results in spiroketal formation with camphorsulfonamide. The Mitsunobu reaction and desymmetrization is the main feature of the reaction. Xibenlol is the alternative drug used in the treatment of hypertension and as cardiotonics.

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

I. INTRODUCTION

The large number of β-adrenergic blocking agents is used as β-blockers, which belong to class of medicines and also called as adrenergic inhibitors. The clinically useful β-blocker are used for lowering of blood pressure antihypertensive, antiarrhythmics and cardiotonics.[1]

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.[2] 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.[3] Presently, many of the pharmaceuticals are marketing these antihypertensive drugs in the racemic forms, even though (S)-isomers are known to be 100-500 fold more effective than the I-isomer.[4] As or strategy involve the synthesis of S-Xibenlol On a similar line, Hsu etal. demonstrated the desymmetrization of glycerol by spiroketal formation with camphorsulfonamide.[5] Thus, by entrapping the 1,2-diol functionality one can broaden the scope of glycerol to use as a chiral source in asymmetric synthesis. Marzi et al. used this strategy for the synthesis of (R)-carnitine from glycerol by modified desymmetrization strategy. [6]



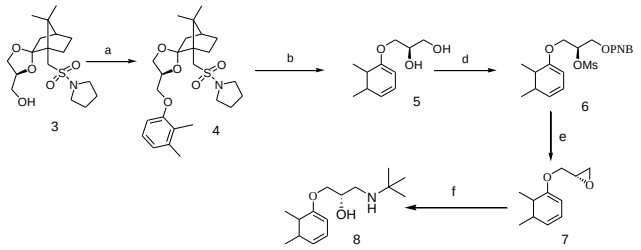
II. METHODS AND MATERIAL [Page Layout]

Synthesis of (S)- Xibenolol:

To a solution of epoxide (0.1g, 2.5 mmol) in water (10 mL) was added slowly the amine (0.295 g, 25 mmol). The whole reaction mixture was stirred at room temperature. Reaction was monitored by TLC and the reaction stopped after 7h. The excess isopropyl amine and the dichloromethane were removed under reduced pressure to dryness. The residue thus obtained was dissolved in water and extracted with EtOAc (25 mL x 2). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. Purification was carried out by flash column chromatography (230-400 mesh silica) using EtOAc-petroleum ether (75:25) as a solvent system to give (S)-Xibenolol. Yield: 515 mg (98 %); white sticky solid; $[\alpha]_D^{25}$= -25.81 (c 1, $CHCl_3$) (lit. $[\alpha]_D^{25}$= -25.4 (c 1, $CHCl_3$)); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (s, 9H),

2.14 (s, 3H), 2.27 (s, 3H), 2.85 (dd, *J*=8 Hz, 1H), 3.01 (dd, *J*=3 Hz, 1H), 3.91 (dd, *J*=6 Hz, 1H), 4.19 (dd, *J*=5 Hz, 1H), 4.60 (s, 2H), 6.66 (d, *J*=8 Hz, 1H), 6.74 (d, *J*=7 Hz, 1H), 7.02 (t, *J*=8 Hz, 1H); ^{13}C NMR (50 Hz, $CDCl_3$): δ 11.78, 20.14, 26.43, 45.51, 55.58, 66.31, 70.20, 109.07, 122.84, 124.94, 125.97, 137.78, 156.28; Anal. Calcd for C15H25NO2: C, 71.67; H, 10.03; N, 5.57. Found: C, 71.71; H, 10.07; N, 5.49 %.

III. RESULTS AND DISCUSSION [Page Style]



Scheme 2. a) 2, 3-dimethyl phenol, TPP, DIAD, THF, rt, 4h, 71%; b) MeOH, Conc. HCl, reflux, 10h, 96%; c) (i) p-nitrobenzoyl chloride, pyridine, CH_2Cl_2, (ii) MsCl, Et_3N, CH_2Cl_2, rt, 10 min, over all yield 78%; d) NaOH, dioxane, 70^{o}C, 18h, 85%; e) tert-butyl amine, water, RT, 7 h, 98 %.

The 1,2 – amino alcohol functionality is present in wide variety of natural products and biologically active N-isopropyl -3-(aryloxy)-2-hydroxypropylamines. S-Xibenolol belongs to class-III antiarrhythmic compounds. The two enantiomeric forms of Xibenool are equiactive in their effect on the cardiac action potential duration (APD), whereas the L-enantiomer is about 20 times more potent than the D-form as a β – blocker. In the present work we synthesized (*S*)/(*R*) S-Xibenolol **8** by desymmetrization of glycerol by (*R*)-(-)-Camphor sulfonamide. Glycerol was first desymmetrized according to a procedure described by Uang making use of (1*R*)-(-)-Camphorsulfonamide as the chiral auxiliary in this only one spiroketal is formed confirming the hydrogen bonding is only driving force for the observed diastereoselectivity.[7] The bulkiness of the sulfonamide played secondary role and only correct (*S*) confirmation is observed which is established by Francesco De Angelis, which one would be an ideal key intermediate for the synthesis of S-Xibenolol 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..[8]

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 primary alcohol moiety of Glycerol is employing a typical Mitsunobu reaction with 2, 3-dimethyl phenol to get ether **4** is an white solid compound having melting point is 127-129 97^{0}C,whose optical rotation is found to be $[\alpha]^{26}_D$= -19.8^o (c = 1 , CH_3OH)]. [9]

Then deprotection is the next step, which is done by two ways. That is CAN mediated and another one is using methanolic HCl.[10] We observe that by CAN mediated deprotection gives high optical rotation as compare to methanolic HCl.[11] After deprotection we get diol **5**, the appearance of new aliphatic 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. Further successive protection of primary alcohol by *p*-nitrobenzyl chloride and mesylation of secondary alcohol to get **6** 78% (overall yield), {$[\alpha]^{26}_D$= -8.0^o (c=1, $CHCl_3$)}. The mesylated product gets hydrolyzed in basic condition to afford the *S*-epoxide by SN^2 way. The optical rotation is observed

$[\alpha]^{25}_{D}$=-30.5°(c=1.55,$CHCl_3$)],{Lit.33.9°(c=1.55,MeOH),}.[12] The ^{1}H NMR spectrum of an epoxide **7** 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. Finally, an epoxide was treated with excess of tert-butyl amine in the presence of catalytic amount of water at room tempreture for 7h, afforded the (*S*)-Xibenolol **8** in a 98 % yields. The 1H NMR spectrum of Xibenolol showed a singlet at δ 1.26 for nine methyl proton of tert-butyl group and two singlet for three proton each at δ 2.14 and δ 2.27, respectively, for the two methyl group attached to the aromatic ring. The multiplet in the region δ 2.85-3.05 for the one proton represents the carbon bearing the secondary hydroxyl group.

IV. CONCLUSION

In summary, we have prepared a pharmaceutical acitve (S)- Xibenolol having overall yield 34% via desymmetrization of glycerol strategy using (1R)–(-)-10–camphorsulfonamide as chiral auxiliary. The enantiomeric purity found to be in the range of 87-89% ee in comparison with the literature value.

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