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Synthetic approaches towards the synthesis of beta-blockers (betaxolol, metoprolol, sotalol, and timolol)

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Abstract: Numerous efficient synthetic methodologies have been elaborated for the synthesis of β-blockers since the introduction of propranolol (a beta-blocker) in 1968. In this review, focus is placed on the more concise asymmetric and bioenzymatic synthetic approaches attempted towards the synthesis of beta-blockers (betaxolol, metoprolol, sotalol, and timolol).

Key words: Beta-blockers, cardiovascular activity, antiglaucoma agent, biotransformations

1. Introduction

Beta-blockers[1,2] have gained a remarkable place worldwide to treat several cardiovascular disorders such as hypertension, angina pectoris, cardiac arrhythmia, and open angle glaucoma.[3,4] Beta-blockers also demonstrate efficacy to control adolescent and childhood disorders such as migraine headaches, dysrhythmias, anxiety, and behavioral disorders.[5]

Increased systolic and diastolic blood pressure can cause hypertension, which then can damage the renal, cardiac, and brain blood vessels.[6] Beta-blockers block the action of the sympathetic nervous system of the heart, thus reducing stress on the heart. Beta-blockers block beta-adrenergic substances such as epinephrine (adrenaline) in the autonomic nervous system. They control the increase in blood pressure and thus inhibit the damage to blood vessels.[3,4,7] Beta-blockers are incorporated in a wide range of clinical applications because they block the adverse effects of catecholamines on β-adrenergic receptors.[8]

Most of the racemic beta-blocker drugs are effective because their (S)-enantiomer shows great structural similarities to the adrenergic hormone noradrenaline, whereas the (R)-enantiomer is responsible mostly for side effects.[9,10] (S)-betaxolol (**1**)[8] (Figure 1) demonstrates beta-blocking activity as a strong antiglaucoma agent.[11–13]

Metoprolol (**2**) (β_1-blockade of catecholamines) (Figure 1) is widely used in the treatment of angina and hypertension.[14] Metoprolol shows great potential to treat sympathetic nervous system disorders. Modified and derived drugs of metoprolol are emphasized[15,16] due to their rapid elimination and low oral bioavailability.[17]

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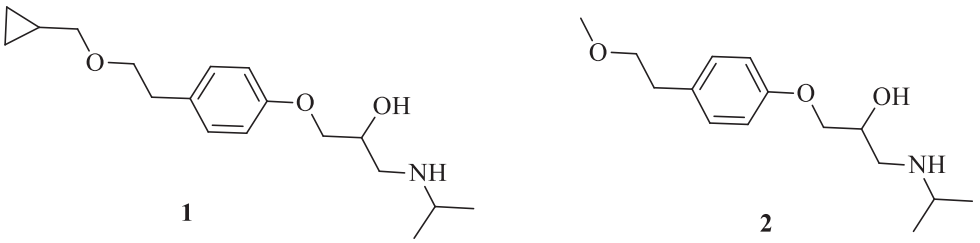


Figure 1. Structures of betaxolol and metoprolol beta-blockers.

Sotalol (**3**) (Figure 2) is most effective in reentrant verticular arrhythmia and belongs to class III of antiarrythmic drugs.[18–21] These drugs also have applications in the treatment of asthma, bronchitis, and congestive heart failure.[22] The l-enantiomer of sotalol demonstrates 20 times more beta-blocker activity as compared to $d-$enantiomer.[23,24]

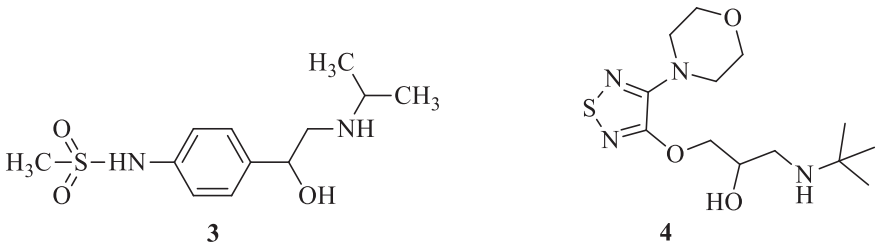


Figure 2. Structures of sotalol and timolol beta-blockers.

Timolol (**4**) (Figure 2) (or amphiphilic prodrugs such as nadolol[25]) has also been found to be effective in hypertension and angina pectoris.[26,27] When administrated to the eyes, timolol exhibits the capability to lower intraocular pressure, which is the base of its use to treat glaucoma.[28]

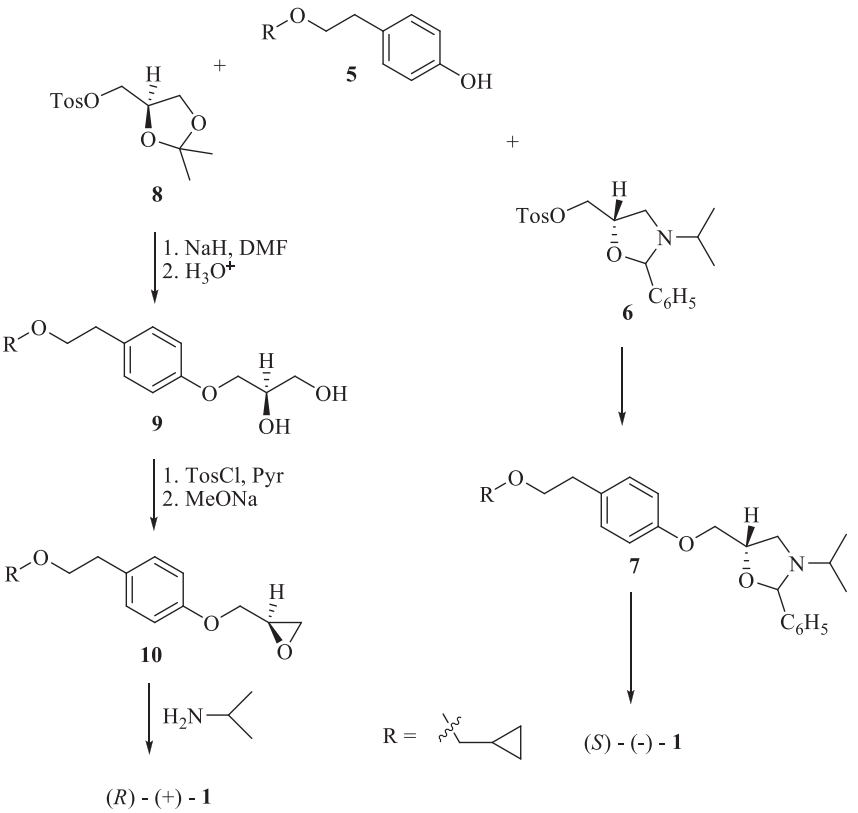
2. Review of the literature

2.1. Synthesis of betaxolol

Considering the significance of beta-blockers, Manoury et al.[29] explained the synthesis of betaxolol by selective benzylation of phenolic alcohol of 4-hydroxyphenethanoic acid. Reduction of the ethanoic acid group was followed by alkylation with (bromomethyl)cyclopropane. Deprotection with H_2 followed by treatment with isopropylamine furnished the betaxolol.

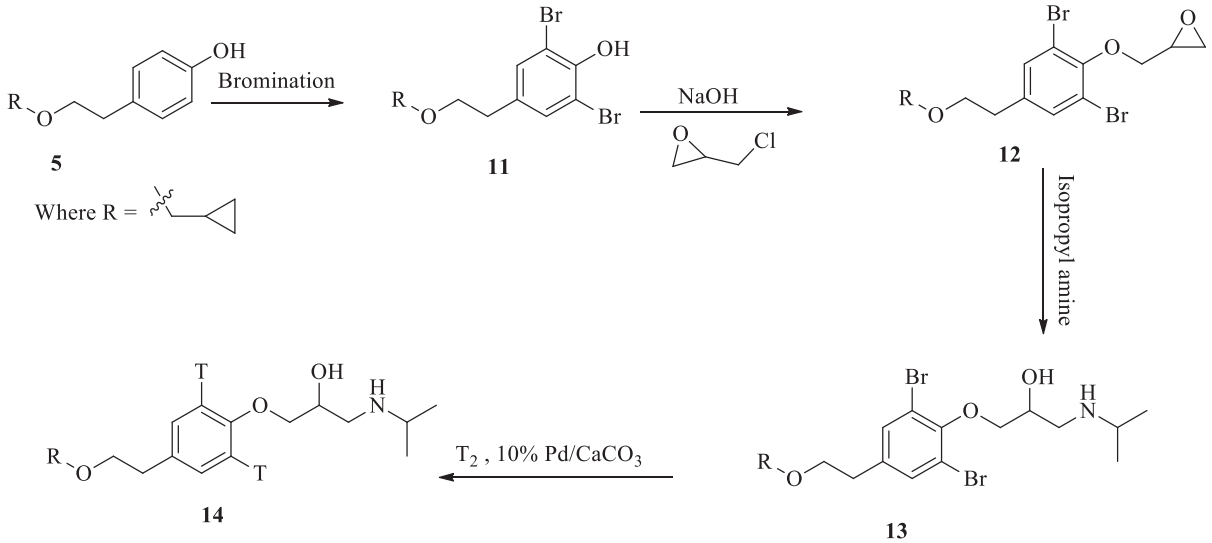
In continuation of their previous work, Manoury et al.[30] prepared pharmacologically active betaxolol. (S)-(-)-2-phenyl-3-isopropyl-5-(hydroxylmethyl)oxazolidinyl tosylate (**6**) was used for the alkylation of phenol **5**.[31] The resulting product **7** after acid-catalyzed hydrolysis afforded the (S) enantiomer of **1**. Compound **5** was also allowed to react with (2R)-3-(tosyloxy)-1,2-propanediol acetonide **8**[32] followed by hydrolysis. The resulting diol **9** was tosylated and converted to epoxide **10**. Treatment of epoxide **10** with isopropylamine furnished the (R) enantiomer of **1** (Scheme 1).

In order to check the drug metabolism, protein binding ability, and pharmacokinetics, Allen and Tizot[33] incorporated tritium in betaxolol, which exhibited high specific activity. Synthesis was initiated from the bromination of 4-[2-(cyclopropylmethoxy)ethyl]phenol, an intermediate employed for the preparation of betaxolol.[29,30] The product 2,6-dibromo phenol (**11**) was alkylated using excess epichlorohydrin under basic conditions to afford epoxypropane (**12**). Treatment of epoxypropane **12** with excess of isopropylamine at 100 °C in a bomb



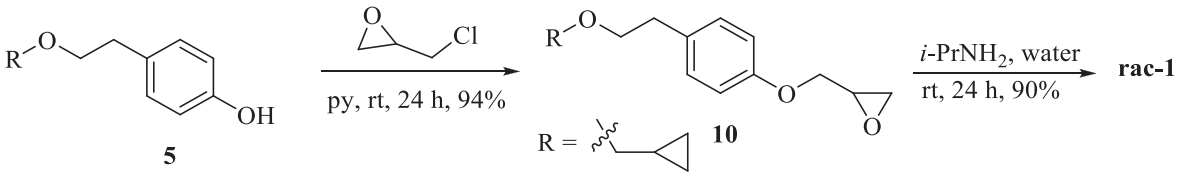
Scheme 1. Synthesis of betaxolol enantiomers.

provided 2,6-dibromobetaxolol (**13**). Debromination of **13** yielded betaxolol, which was purified and identified by instrumental techniques. Exercising the same procedure with deuterium and tritium in the presence of catalyst yielded [$^2H_2$]-betaxolol and [^{3}H]-betaxolol, respectively. The specific radioactivity of [^{3}H]-betaxolol was 49C1/mmol and 98% radiochemical purity determined by thin layer radio chromatography (Scheme 2).

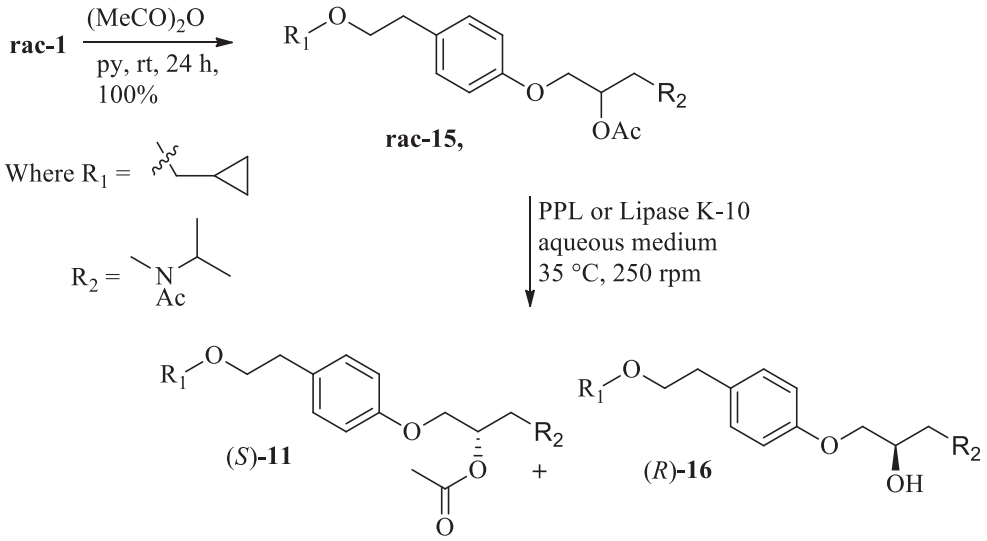


Scheme 2. Synthesis of tritium-labelled betaxolol.

The provoking attention to pure enantiomers of beta-blockers encouraged researchers to follow the cheap biotransformations. In this context, Bono and Scilimati[34] illustrated a chemoenzymatic pathway for the preparation of both (*R*) and (*S*) enantiomers of betaxolol. Lipase catalyzed kinetic resolution of the intermediate (-)-**17** and racemic betaxolol was carried out. Corresponding phenol **5** was treated with epichlorohydrin to achieve the requisite epoxide **10.** Ring opening of epoxide **10** with *i*-PrNH$_2$ afforded racemic betaxolol (Scheme 3). The purified betaxolol was *N*,*O*-bisacetylated and subjected to enzymatic hydrolysis. Proteases, subtilisin, α-chymotrypsin, lipases, and porcine pancreatic lipase were employed in this screening, monitored by GC. HPLC utilizing a CHIRALCEL OD column provided enantiomeric excesses of **16** and unreacted **15** (Scheme 4). The racemic **17** obtained from the acid treatment of **10** was also subjected to transesterification reaction with vinyl acetate (acyl donor). The optically active (–)-**17** and (+)-**18** were converted to (–)-betaxolol (82% *ee*, 76% yield) and (+)-betaxolol (60% *ee*, 76% yield), respectively (Scheme 5).[35–38] The recrystallization of the hydrochlorides of the products was also carried out using diethyl ether to afford (–)-betaxolol and (+)-betaxolol with 91% and 75% *ee*, respectively.



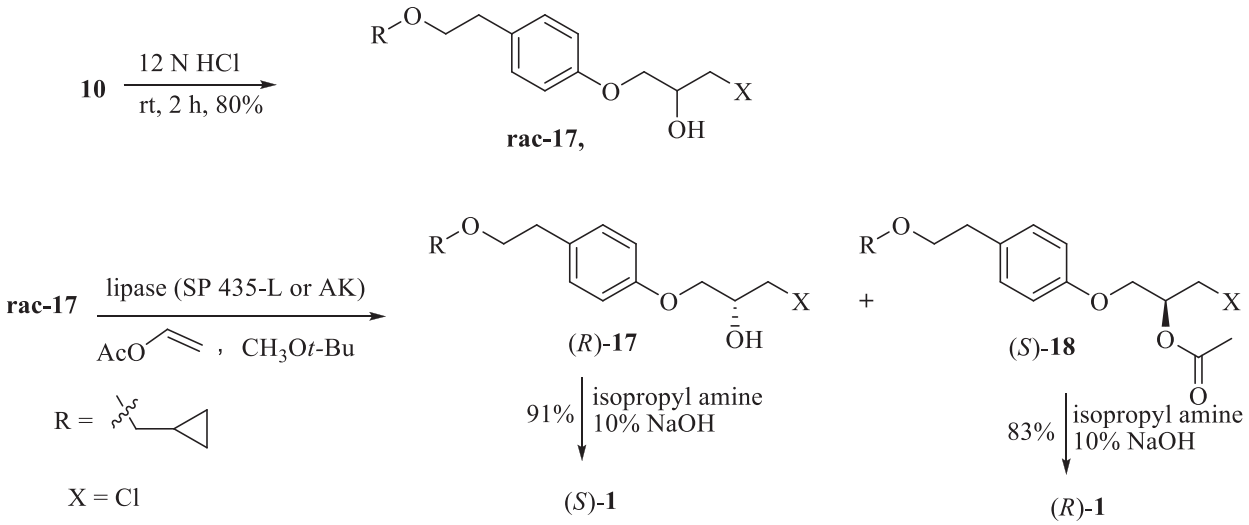
Scheme 3. Synthesis of racemic betaxolol.



Scheme 4. Enzymatic hydrolysis of *N*, *O*-bisacetylated betaxolol.

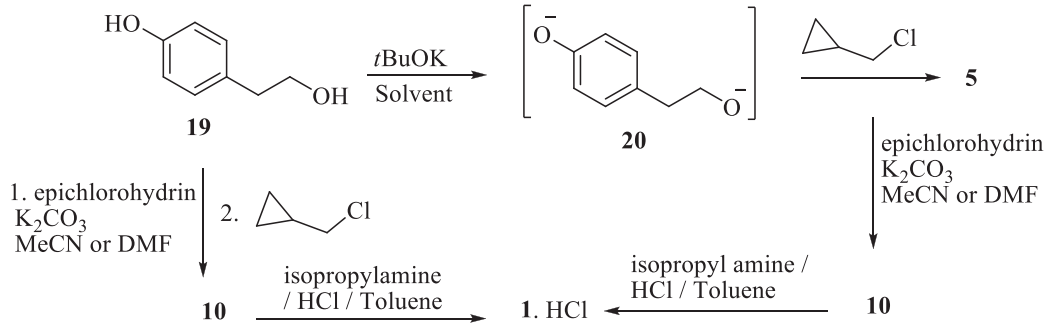
In view of the advancements in synthetic methodologies for beta-blockers, Ippolito and Vigmond[39–41] described a number of protection/deprotection syntheses of betaxolol. 4-Hydroxyphenethanol (**19**) was converted to phenoxide anion using a base followed by reaction with epichlorohydrin. The yielded product 1-[4-(2-hydroxyethyl)phenoxy]2,3-epoxypropane was treated with primary amine to provide the betaxolol intermediate. To obtain the product, protection and deprotection were the necessary steps.

Protection and deprotection increase the synthetic steps, which lowers the yield. Wang et al.[42] elaborated the protection free synthesis of betaxolol via selective alkylation. Treatment of **19** with a base provided



Scheme 5. Synthesis of betaxolol from **10**.

an oxygen dianion **20**. Formation of oxygen dianion **20** removed the need for phenolic hydroxyl protection. Reaction of oxygen dianion **20** with cyclopropylmethyl chloride afforded 4-[(2-cyclopropylmethoxy)-ethyl]phenol (**5**). Treatment of intermediate **5** with epichlorohydrin yielded an epoxide, 1-{4-[2-(cyclopropylmethoxy)-ethyl]-phenoxy} -2,3-epoxypropane (**10**) (Scheme 6). In another method[43] compound **19** was treated with epichlorohydrin followed by treatment with (chloromethyl)cyclopropane to afford **10**. Betaxolol hydrochloride was obtained when compound **10** was reacted with isopropylamine followed by the addition of HCl (Scheme 6).



Scheme 6. Synthesis of betaxolol hydrochloride from **19**.

Hydrolytic kinetic resolution (HKR), the simplest approach for enantioselective preparation of stereoisomers, has attracted considerable attention from researchers. Joshi et al.[44] utilized the said approach to synthesize (*S*)-betaxolol in enantiomerically pure form. Benzylation of 2-(4-hydroxy phenyl) ethanol (**19**) in the presence of phase transfer catalyst at ambient temperature resulted in 90% yield of regioselective product *O*-alkylated 2-(4-benzyloxyphenyl)ethanol (**21**). Condensation of **21** with allyl bromide resulted in 1-(2-allyloxy-ethyl)-4-benzyloxy benzene (**22**) (98% yield). Furukawa modification of the Simmon–Smith reaction was utilized for the cyclopropanation of the olefinic part of compound **22** to afford compound **23** (95% yield). Debenzylation of compound **23** followed by allylation provided compound **24** via **5**, which on further treatment with *m*CPBA in DCM under ambient conditions afforded epoxide **10**. Due to the fluidity of epoxide **10**, it was incorporated in the HKR approach. Using Jacobsen catalyst (Figure 3) and water at room temperature, HKR was performed

for racemic epoxide **10** for 16 h, monitored by HPLC. Upon completion, the selective separation of (*S*)-epoxide **10** (43% yield, 99% *ee*) and (*R*)-diol **9** (47% yield, 92% *ee*) was carried out over silica gel. HPLC using chiral column CHIRALCEL OD was used to determine enantiomeric excess (*ee*). The epoxide **10** was allowed to react with $i-PrNH_2$ at ambient temperature, which furnished crude (*S*)-betaxolol. Pure (*S*)-betaxolol in 99% *ee* was obtained after silica gel column chromatography (Scheme 7). Alternatively,[45] $O-$alkylation of **5** with (*R*)-(–)-epichlorohydrin using a base afforded a mixture of **10** and **17**, which upon treatment with *i*-$PrNH_2$ and HCl furnished **1**.HCl (Scheme 7).

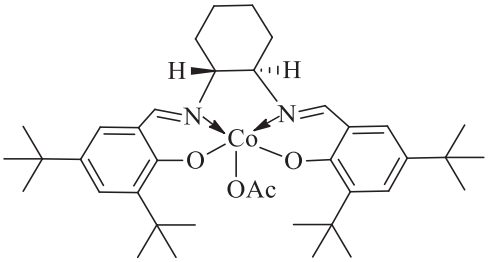
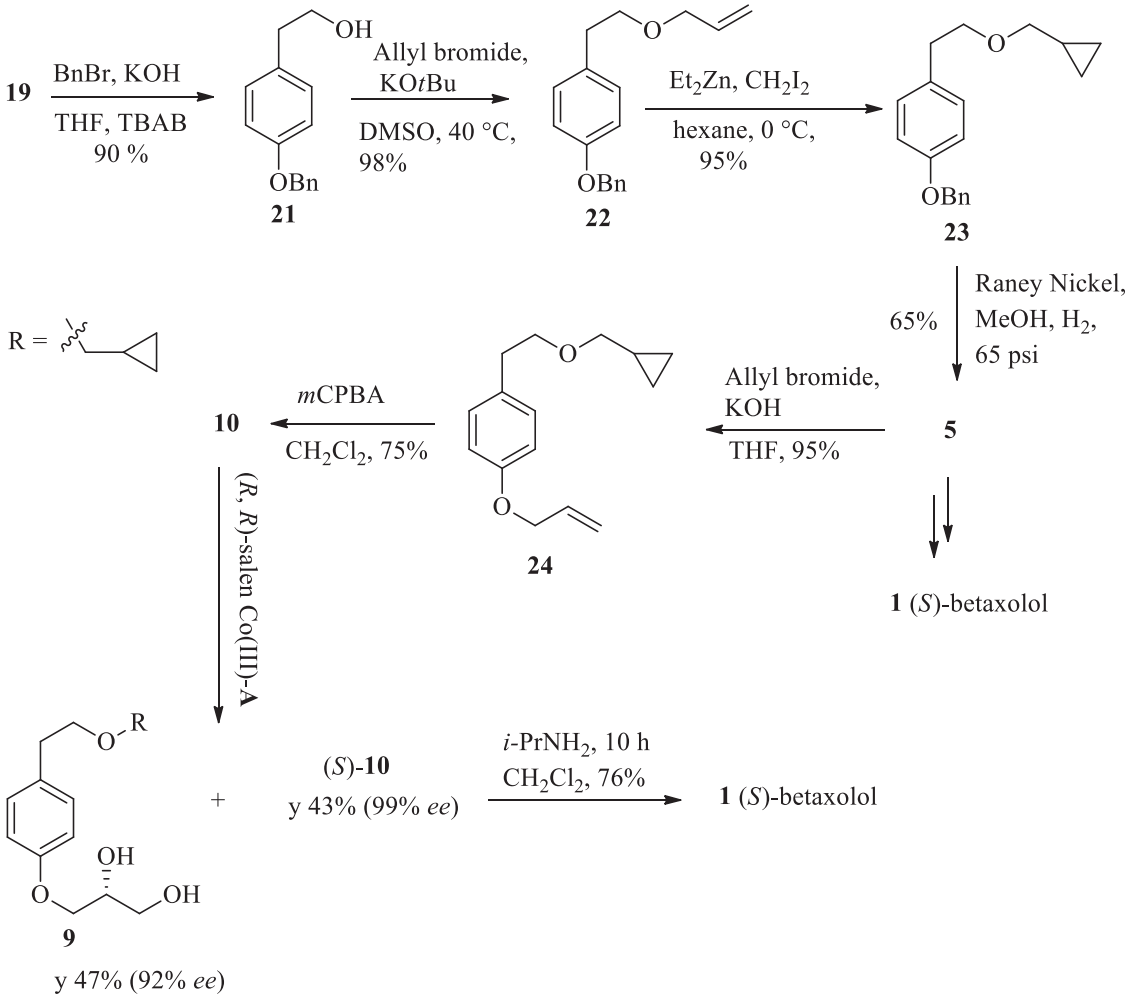
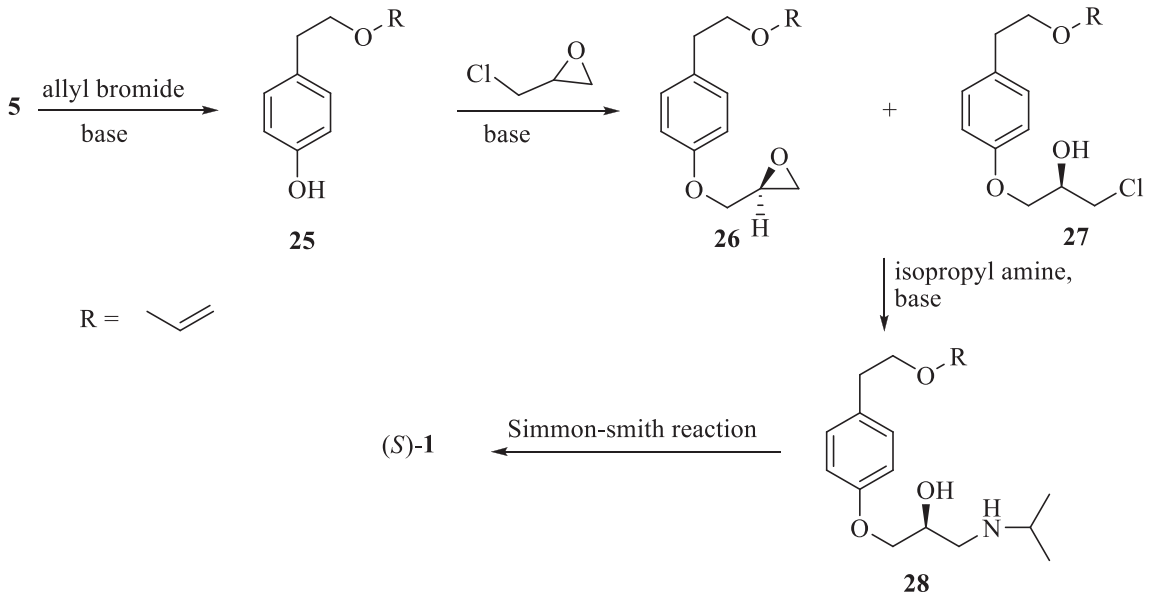


Figure 3. Structure of (R,R) salen Co(III) catalyst-A (Jacobsen catalyst).



Scheme 7. Preparation of (*S*)-betaxolol (**1**).

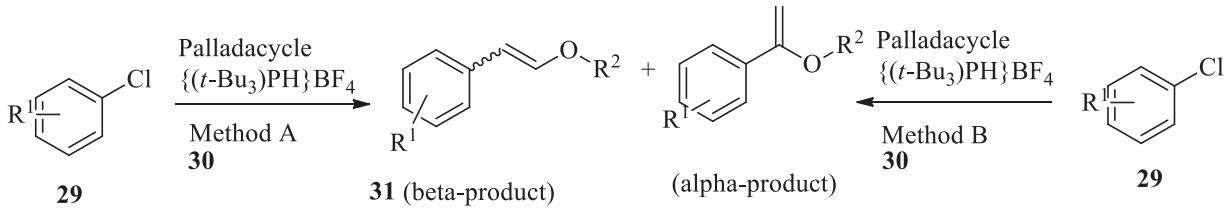
In another methodology, Joshi et al.[46] selectively allylated the alcoholic group of **5** to afford 4-(2-allyloxy-ethyl)phenol (**25**) followed by the reaction of (*R*)-(-)-epichlorohydrin with phenol **25**. The afforded intermediates **26** and **27** were then subjected to ring opening reactions with $i-PrNH_2$ in the presence of a base to furnish (*S*)-(-)-1-{4-[2-(allyloxy)-ethyl]phenoxy} -3-isopropylamino propan-2-ol (**28**). The Simmon–Smith reaction converted the amino alcohol **28** to the requisite betaxolol (**1**) (Scheme 8).



Scheme 8. Synthesis of (*S*)-betaxolol from compound **5**.

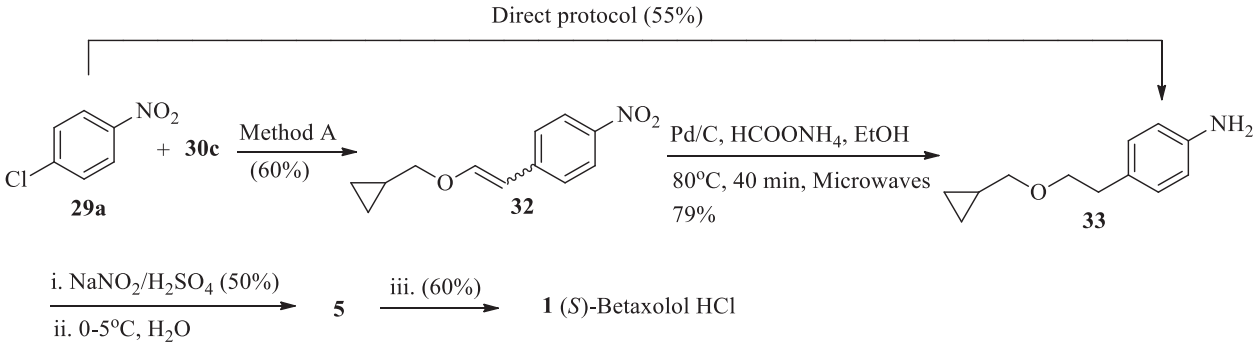
Datta et al.[47] synthesized betaxolol via Heck arylation of vinyl ethers (Scheme 9). Synthesis was started from a cheaper reagent. *p*-chloronitrobenzene (**29a**). Palladium-catalyzed transvinylation of cyclopropyl-methanol and ethyl vinyl ether using 2,2$^{'}$-bipyridyl ligand resulted in the formation of cyclopropylmethylvinyl ether (**30c**). Compound **32** (60% yield) in highly regioselective coupling was prepared using Heck arylation in aqueous DMF (Method A). The hydrogenation of the olefinic bond and nitro group of **32** furnished compound **33** (79% yield). Aryl chloride **29a** was also converted directly in one step to **33** in greater yield. Treatment of **33** with sodium nitrite (diazotization) and water resulted in phenol **5** (50% yield). Reaction of (*R*)-3-isopropylamine 1,2-epoxypropane and then refluxing in ethanol for 8 h provided active (*S*)-betaxolol. Treatment with dry HCl (gas) in dry ether and crystallization afforded (*S*)-**1**.HCl (Scheme 10).

The envisioned efficacy of HKR encouraged Muthukrishnan et al.[48] to employ this approach for the concise synthesis of (*S*)-betaxolol. Reaction of 2-(4-hydroxyphenyl)ethanol (**19**) with (±) epichlorohydrin in anhydrous 2-butanone, K_2CO_3 base, and a phase transfer catalyst for 15 h under refluxing temperature resulted in the racemate epoxide **34** (86% yield). HPLC-monitored HKR was performed for racemic epoxide **34** for 30 h at ambient temperature using Jacobsen catalyst and water in isopropanol. (*S*)-epoxide **34** (42% yield, 99% *ee*) and (*R*)-diol **35** (47% yield, 92% *ee*) were obtained over silica gel column chromatography. (*S*)-epoxide **10** (47% yield, 92% *ee*) was achieved when hydroxyl group of (*S*)-epoxide **34** was selectively *O*−alkylated using chloromethylcyclopropane in the presence of KO*t*-Bu. Treatment of (*S*)-epoxide **10** with excess *N*-isopropyl amine and refluxing for 2–10 h provided (*S*)-betaxolol. Silica gel column chromatography was then performed to purify the crude (*S*)-betaxolol (**1**) (96% yield, 99% *ee*) (Scheme 11).



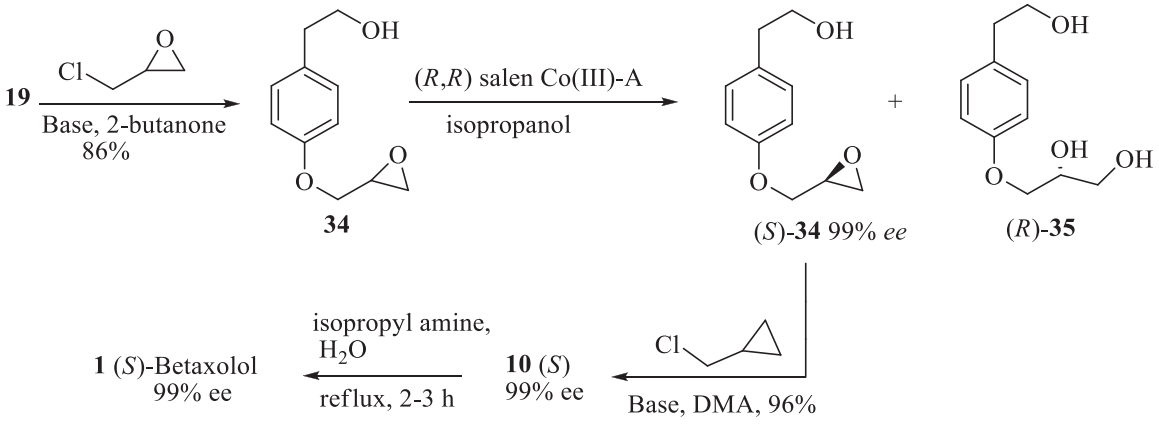
Method A: 1.0 mmol of **29**, 3.0 mmol of **30**, 0.05 mmol of palladacycle, 0.10 mmol of $[(t\text{-}Bu_3)PH]BF_4$, 3.0 mmol of Cy_2NMe, 200 mL of H_2O, and 2mL of DMF in sealed vessels. Microwave heating, 160 °C for 60 min.
Method B: 1.0 mmol of **29**, 3.0 mmol of **30**, 0.05 mmol of palladacycle, 0.10 mmol of $[(t\text{-}Bu_3)PH]BF_4$, 5.0 mmol of PMP and 2 mL of PEG-200 in sealed vessels. Microwave heating, 160 °C for 60 min.

Scheme 9. Heck arylation of vinyl ethers **30**.



(iii) a. (*R*)-3-isopropylamino-1,2-epoxypropane; NaOH; Reflux; 8 h, b. Dry HCl gas in Et_2O medium.

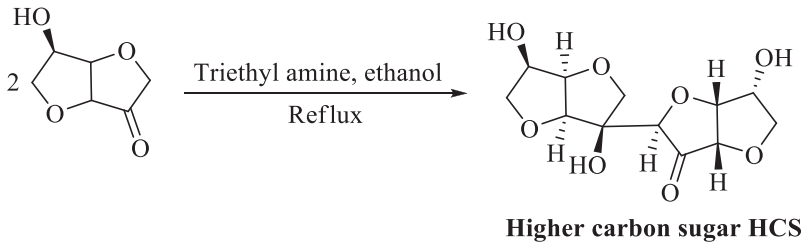
Scheme 10. Synthesis of betaxolol.HCl (**1**).



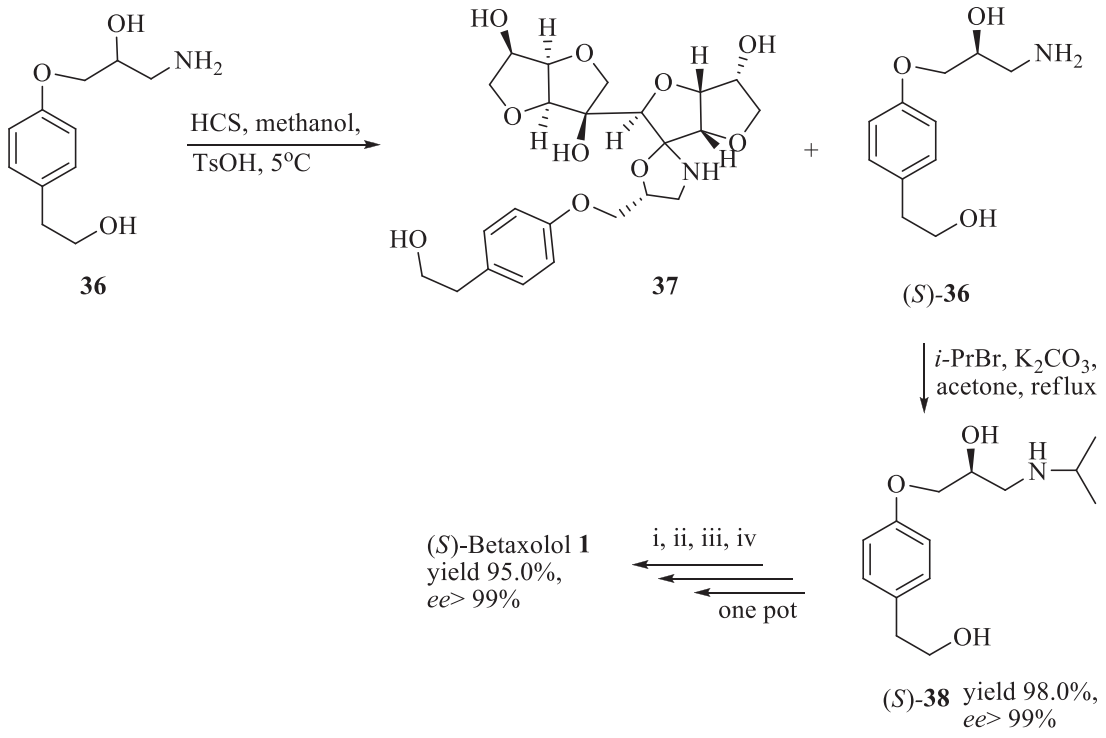
Scheme 11. Synthesis of betaxolol by Muthukrishnan et al.

Working for developing short synthetic protocols for the synthesis of drugs, Zhang et al.[49] developed a new synthetic approach for the synthesis of (*S*)-betaxolol administrating the kinetic resolution via chiral auxiliary HCS (Scheme 12). The starting compound **19** was treated with epichlorohydrin and K_2CO_3 in dry acetone to achieve the racemic epoxypropane **5**. Mixing of racemic epoxypropane **5** with 25-28% NH_3 yielded

racemic β-amino alcohols **36**. Manipulation of **36** with C12-higher carbon sugar (HCS) in methanol and traces of $p-$TsOH yielded **37** and $(S)-$**36**.Refluxing of (S)-**36** with isopropyl bromide and K_2CO_3 in dry acetone provided (S)-**38** (98% yield, $>$99% *ee*). After protection of the amino group of (S)-**38** with benzaldehyde, it was treated with bromomethyl cyclopropane to give a pale yellow oil, which was mixed with 10% HCl and then extracted with EtOAc to afford the **1**.HCl. Treatment with 10% NaOH followed by recrystallization from ether provided concerned (S)-**1** (yield 95%, *ee* $>$ 99%) (Scheme 13).



Scheme 12. Synthesis of C-12 higher carbon sugar.

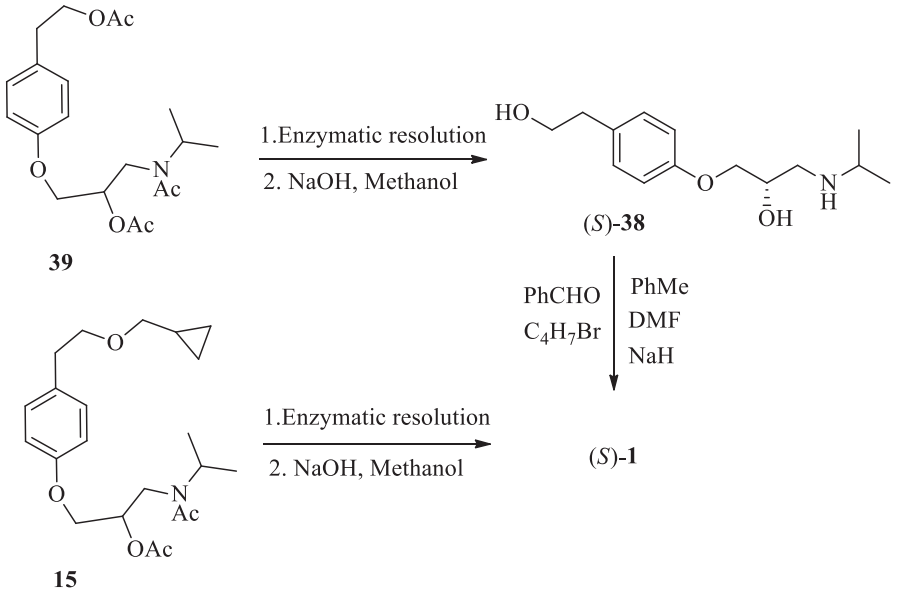


i). Toluene, phenyl aldehyde, TsOH; ii). DMF, NaH, cyclopropylmethyl bromide;
iii). 10% HCl, isopropanol; iv). 10% NaOH, H_2O, toluene.

Scheme 13. Synthesis of betaxolol from compound **36**.

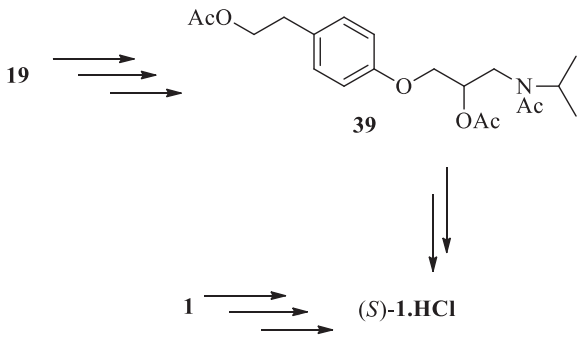
Due to the efficiency of the enzymatic kinetic resolution approach, Li et al.[50] developed a novel approach that was more economical and stereoselective, for the direct resolution of betaxolol enantiomers and its analogues. De-acetylation by enzyme catalyst was employed for kinetic resolution to afford (S)-betaxolol. A biocatalyst, the strain *Rhodotorula mucilaginosa* obtained from soil, was used for kinetic resolution of substrates **39** and **15** (acetylated intermediates). The lipase in the strain was highly selective for (R)-enantiomers.

(*S*)-betaxolol was obtained directly by chemical methods from the corresponding intermediates. This method proved to be economical and highly stereoselective (Scheme 14).



Scheme 14. Chemoenzymatic synthesis of (*S*)−betaxolol.

In connection with their previous work, Li et al.[51] synthesized (*S*)−betaxolol by chemoenzymatic approach. Betaxolol after *N*,*O*-bisacetylation was also subjected to hydrolysis by different strains. Two out of 52 strains catalyzed the hydrolysis significantly but exhibited low selectivity. Alternatively compound **39** was prepared from **19**. The complete kinetic resolution of **39** was performed to get the desired intermediates. *Phodotorula mucilaginosa* DQ832198 showed better *ee* and enantioselectivity factor. To get better yield and high yield, (*S*)-**1**, after *N*,*O*-bisacetylation, was subjected twice to kinetic resolution for 12 h. Intermediates were converted to **(*S*)-1**.HCl (98% yield, 95% *ee*).[52] Recrystallization using Et_2O enhanced the *ee* to 99% (Scheme 15).

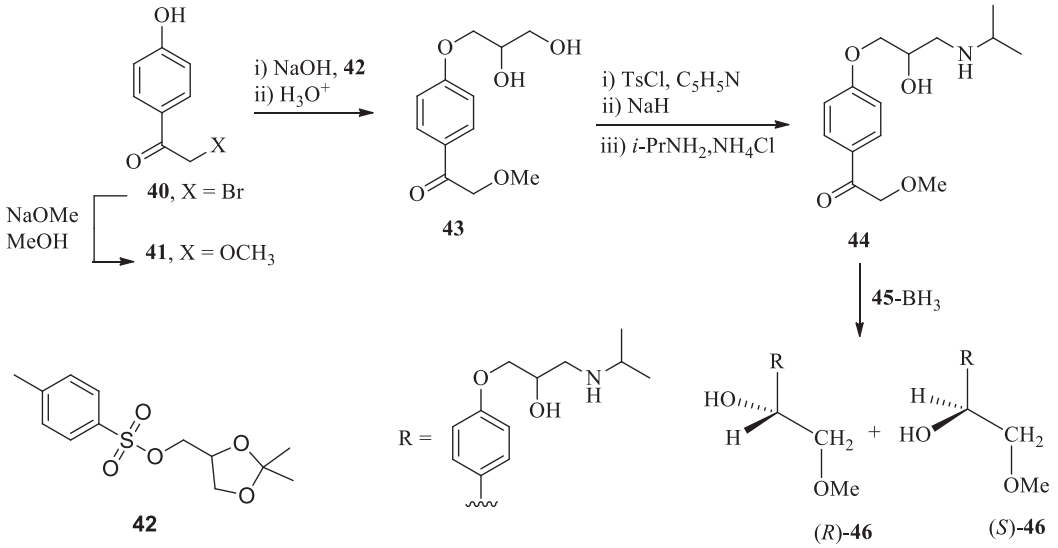


Scheme 15. Cont.

Synthesis and characterization of hydrochloride of betaxolol were carried out by Xu and Fang.[53] Selective Williamson etherification between epichlorohydrin and *p*-hydroxy phenylethyl alcohol using 18% K_2CO_3-acetone alkalescent solution was carried out to synthesize (1-[4-(2-Hydroxyethyl)phenoxy]-2,3-epoxypropane], a betaxolol hydrochloride intermediate.

2.2. Synthesis of metoprolol

The metabolism of metoprolol takes place through oxidative pathways. Shetty and Nelson[54] explained the chemical behavior of metoprolol. The asymmetric synthesis was also carried out along with the determination of absolute configuration of benzylic hydroxylated metoprolol metabolites **46**. Phenolic α-methoxyacetophenone (**41**)[55] was obtained from 2-bromo-4'-hydroxy acetophenone (**40**).[56] Compound **41** on reaction with NaOH and (*RS*) 2,2-dimethyl-4-[(tosyloxy) methyl]-1,3-dioxolane (**42**) followed by hydrolysis provided diol **43**. Tosylation and epoxidation of **43** followed by epoxide ring opening using isopropylamine and NH_4Cl in catalytic amount presented *d*-methoxyacetophenone (**44**). Chiral complex of borane and (2*S*)-(–)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**45**), synthesized from PhMgBr and (2*S*)-valine methyl ester hydrochloride, successfully reduced the ketone **44** at room temperature as compared to modified lithium aluminum hydride reagent-1,1'-bi-2-naphthol. Chromatographic separation of diastereomerically enriched and optically active compound **46** was carried out from (2*S*)-(–)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**45**). Reduction of ketone **44** with $NaBH_4$ yielded an equimolar mixture of two diastereomers of **46**. The diastereomeric compositions and configurations were also determined (Scheme 16).

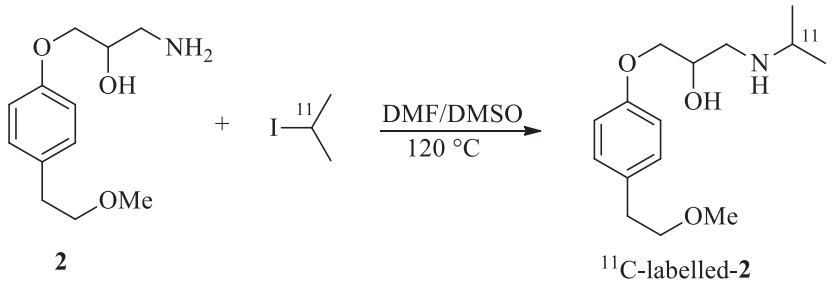


Scheme 16. Synthesis of betaxolol derivatives **46**.

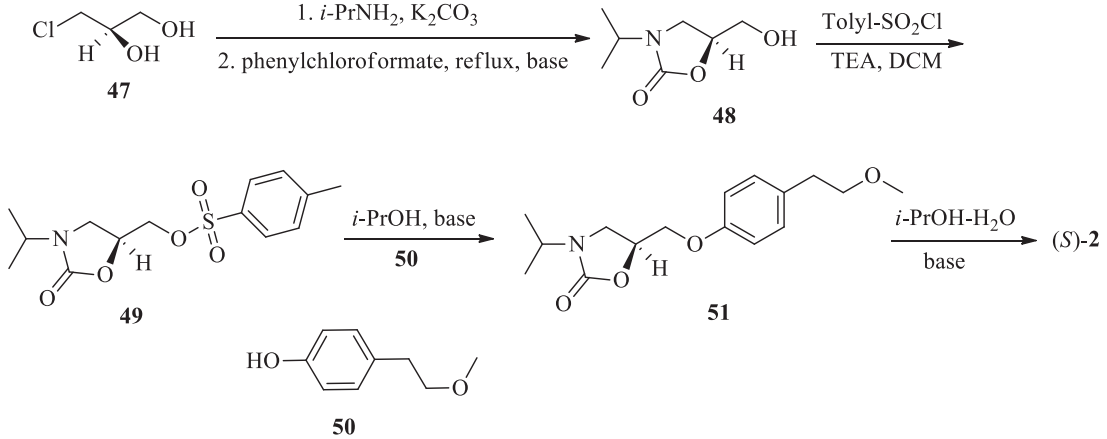
Exploring the importance of radioactive labelled drugs, Shetty et al.[57] synthesized the deuterium labelled enantiomers of metoprolol. Chiral synthons 2,2-dimethyl-1,3-dioxolane-4-methanols were employed. [D_6]-isopropyl amine and 4-(2-methoxyethyl)-2,6-[D_2]-phenol synthesized by DCl/D_2O exchange and (4*S*)-2,2-dimethyl-1,3-dioxolane-4-[D_2]-4-methanol prepared by reducing (4*S*)-methyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate with $LiAlD_4$ were the key sources of deuterium. High enantiomeric excesses were obtained for all the synthesized enantiomers.

In order to study the distribution and receptor binding studies of metoprolol, Antoni et al.[58] carried out the synthesis of metoprolol incorporating the ^{11}C-labelled technique. β-adrenergic ligand was synthesized from *N*-alkylation of [2-^{11}C] isopropyl iodide. Treatment of [2-^{11}C] isopropyl iodide[59] with metoprolol furnished the ^{11}C-labelled metoprolol (1-isopropylamino)-3-(4-(2-methoxy ethyl) phenoxy)-2-propanol (Scheme 17).

Keding et al. [60] carried out a facile synthesis of metoprolol. Treatment of (*R*)-3-chloro-1,2-propanediol (**47**) with *i*-PrNH$_2$ using a base followed by the reaction with phenylchloroformate afforded (*S*)-5-hydroxymethyl-3-isopropyloxazolidin-2-one (**48**). Compound **49** was obtained when **48** was reacted with tolylsulfonyl chloride. Treatment of **49** with **50** in the presence of a base and *i*−PrOH afforded **51**. The requisite compound (*S*)-**2** was achieved by the hydrolysis of **51** (Scheme 18).



Scheme 17. Synthesis of isopropyl - ^{11}C-labelled metoprolol.



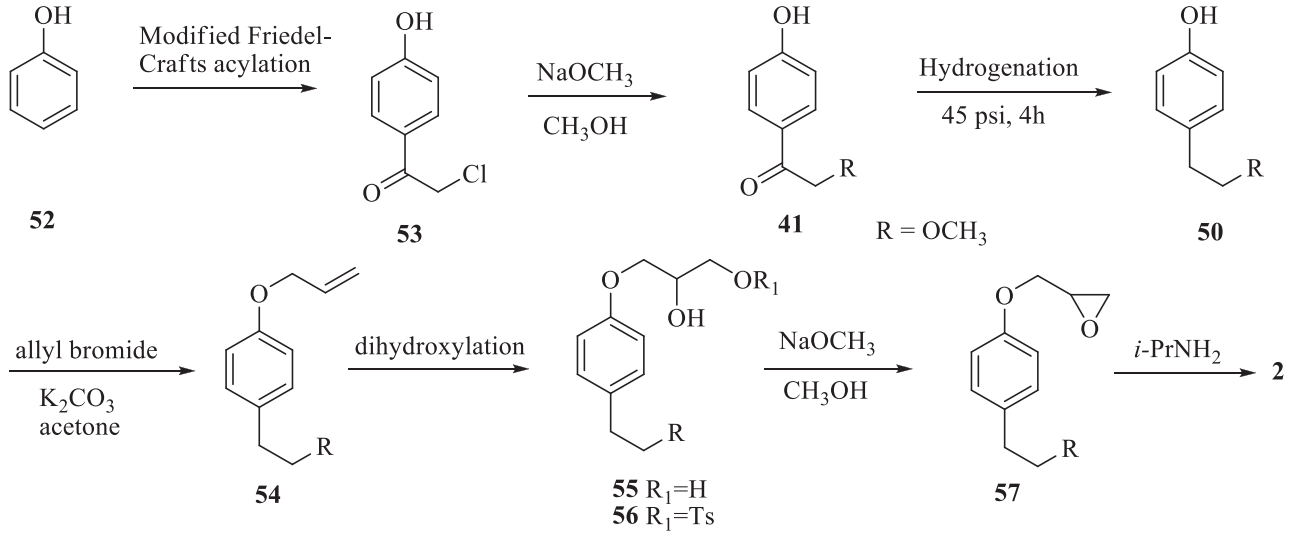
Scheme 18. Synthesis of metoprolol from compound **47**.

Gurjar et al.[61] presented an efficient and novel synthetic approach for the preparation of racemic metoprolol. Phenol **52** was subjected to modified Friedel–Crafts acylation[62] using chloroacetylchloride to achieve 2-chloro-1-(4-hydroxyphenyl) ethanone (**53**) (50% yield). Treatment of **53** with a mixture of MeOH/NaOMe at room temperature yielded **41** (90% yield). Hydrogenation of **41** employing 10% Pd-C, 45 psi for 4 h afforded **50** (96% yield). Intermediate **50** was converted to **54** (85% yield) by reacting with allyl bromide and K_2CO_3 in acetone. To get the diol **55** (80% yield) dihydroxylation reaction[63] of **54** was performed using OsO_4-NMO (*N*-methyl morpholine-*N*−Oxide) in the presence of 1:2 acetone/water mixture at room temperature. Selective mono-tosylation of **55** afforded compound **56**, which on treatment with methanolic sodium methoxide yielded epoxide **57**. Conversion of **57** into (±) metoprolol was carried out as reported previously (Scheme 19).[64]

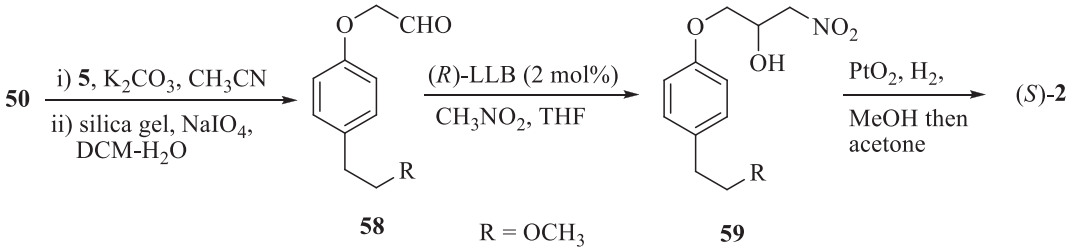
A more concise synthetic way was elaborated by Keding et al.[65,66] for the synthesis of *S*-metoprolol via an intermediate prepared by reacting 4-[2-methoxyethyl]phenol with (*S*)-5-hydroxymethyl-3-isopropyloxazolidin-2-one sulfonic acid ester.

Sasai et al.[67] synthesized metoprolol in an asymmetric way employing La-Li-BINOL (LLB) complex as catalyst. Two-step synthesis of aldehyde **58** was carried out using 4-(2-methoxyethyl)phenol (**50**). Treatment

of **58** with nitromethane using (*R*)-LLB (2 mol%) furnished nitroaldol **59** (99% *ee*, 88% yield). (*R*)-LLB was synthesized from $LaCl_3.7H_2O$.[68] Nitroaldol **59** (94% *ee*, 90% yield) was also obtained when **58** was treated with (*R*)-LLB (5 mol%), synthesized from La(O-*i*-Pr)$_3$.[69] Use of Pr-Li-BINOL catalyst (3 mol%) afforded **59** (91% *ee*, 82% yield).[70] (*S*)-metoprolol (**2**) was thus obtained from **59** using the mentioned conditions (Scheme 20).



Scheme 19. Synthesis of compound **2**.

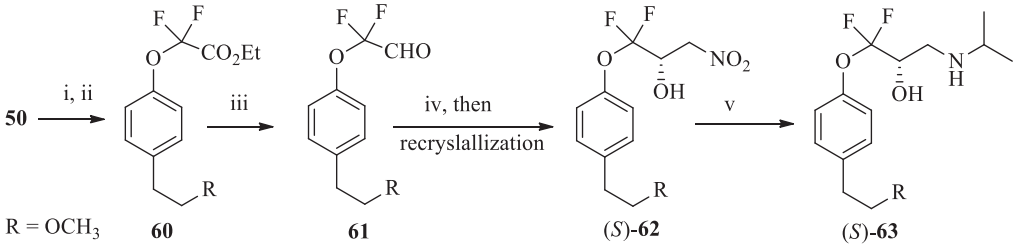


Scheme 20. Synthesis of (*S*)-metoprolol from compound **50**.

Iseki et al.[71] explained the synthesis of fluoro-substituted derivatives of metoprolol and checked their biological effectiveness. The synthetic process was started from the reaction of Na with phenol **50** and chlorodifluoroacetic acid in refluxing dioxane;[72] then subsequent esterification provided α,α-difluoro ester (**60**). Ester **60** was reduced to α,α-difluoro aldehyde (**61**) using diisobutylaluminum hydride in ether at –78 °C.[73] When aldehyde **61** was reacted with nitromethane at –40 °C using samarium-lithium-(*R*)-BINOL catalyst (8 mol%), (*S*)-1,1-difluoro-1-[4-(2-methoxyethyl)phenyloxy]-3-nitropropan-2-ol (**62**)[74] was obtained. Enantiomerically pure nitroaldol adduct **62** was achieved from the mother liquor (65%, >99% *ee*) after recrystallization from ether/hexane. PtO_2-catalyzed hydrogenation using acetone and methanol[67] executed the reductive alkylation of homochiral (*S*)-nitroaldol **62** to (*S*)-**63**. Similarly, when nitroaldol reaction of **61** was carried out in the presence of samarium-lithium-(*S*)-BINOL catalyst, the adduct (*R*)-**62** was achieved, from which metoprolol analog (*R*)-**63** was obtained in enantiomerically pure form (Scheme 21).

In connection to their previous work, Gurjar et al.[75] improved the synthetic methodology for (*S*)-metoprolol via (±)-aryl glycidyl ethers that were kinetically resolved. (*R*,*R*)-salen Co(III)OAc and water

were used for the kinetic resolution of (±)aryl glycidyl ethers. This technique provided high enantiomeric excess of aryl glycidyl ether and 1-arylglycerol derivatives. This efficient approach was employed to afford (*S*)−metoprolol.

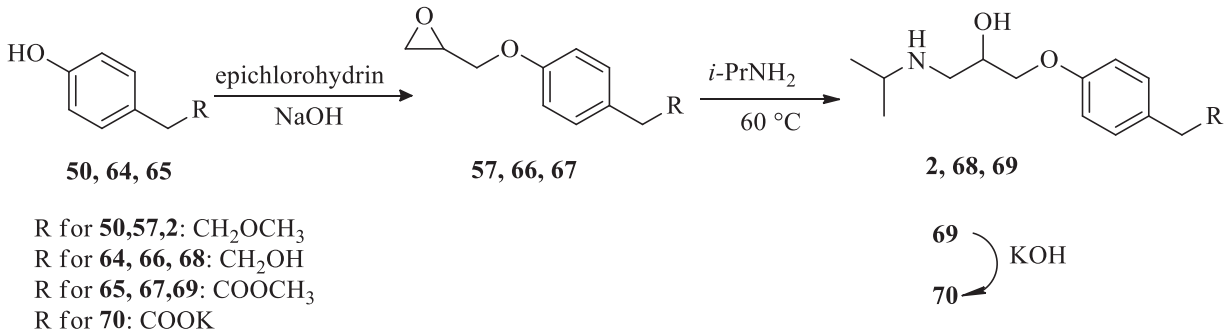


(i) Na, ClF_2CCO_2H, dioxane, reflux, 6 h; (ii) K_2CO_3, EtI, acetone, reflux, 12 h (73% over two steps);
(iii) DIBAL-H, ether, -78 °C, 1 h (80%); (iv) Sm-Li-(R)-BINOL, CH_3NO_2, THF, -40 °C, 168 h (52%, 75% ee);
(v) PtO_2, H_2, MeOH, rt, 2 h, then acetone, 50 °C, 24 h (89%, $>_{99}$% ee).

Scheme 21. Synthesis of metoprolol analogues **63**.

The use of novel and rapid instruments in the synthetic approach is always encouraged. Svensson et al.[76] employed modern techniques, Raman spectroscopy, and chemometrics to monitor the metoprolol synthesis. Epoxide **57** was heated with isopropylamine in the presence of isopropanol. The reaction mixture was heated applying a temperature gradient to produce **2**.

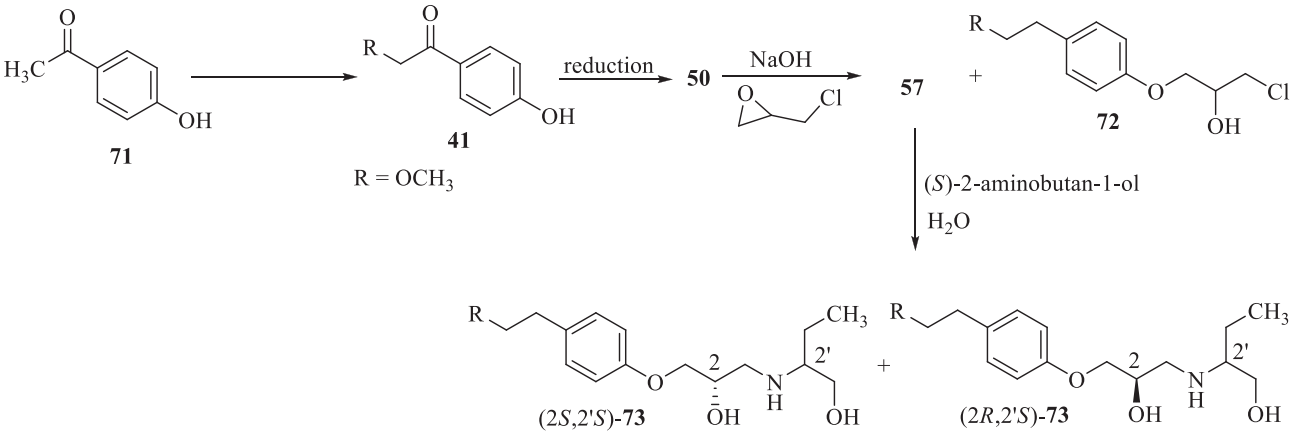
Enantioselectivity and the facile availability of materials is always a major requirement of the pharmaceutical industries. Jung et al.[52] described the asymmetric synthesis of metoprolol and related metabolites. Treatment of phenolic compounds **50**, **64**, and **65** with methanolic sodium hydroxide followed by the addition of (*R*) and (*S*)-epichlorohydrin provided the 2,3-epoxypropoxy (*R*) and (*S*) enantiomers **57**, **66**, and **67**, respectively, which were further converted to the target compounds **2**, **68**, and **69**. Hydrolysis of **69** using KOH and methanol (1:1) afforded the compound **70**. Compound **70** was isolated and characterized as potassium salt after neutralization. The enantiomers of **70** were also prepared by reacting **65** with epichlorohydrin enantiomers using excess triethylamine instead of NaOH. Optical purities of all enantiomers were determined by HPLC (Scheme 22).



Scheme 22. Synthesis of metoprolol and its metabolites.

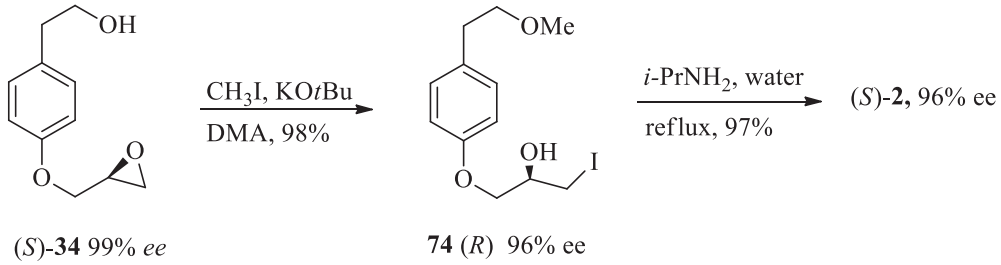
The cardiovascular activity of metoprolol derivatives inspired Melgar-Fernandez et al.[77] for the synthesis of metoprolol analogues. Four novel stereoisomeric metoprolol derivatives carrying two stereogenic centers were synthesized. The two diastereotopic methyl groups in metoprolol were converted into an alkyl group and alkyl hydroxyl group. The synthetic route was started from the preparation of 4-(2-methoxyethyl) phenol (**50**) using

Smith and co-workers' methodology.[78] Reaction of racemic epichlorohydrin and aqueous NaOH solution with phenol derivative **50** provided 2-[4-(2′-methoxyethyl)-phenoxymethyl]-oxirane (**57**) (90% yield). Side product **72** (10% yield) was separated over silica gel in column chromatography. The required diastereomeric derivatives (2*S*,2'*S*)-**73** and (2*R*,2'*S*)-**73** were achieved when racemic epoxide **57** was treated with excessive amount of (*S*)-2-amino-1-butanol in aqueous solution. The *like*[79] and pure diastereomers were crystallized out from the aqueous phase. When (*S*)-2-amino-1-butanol was distilled off from the mother liquor, the diastereomeric products (2*S*,2'*S*)-**73** and (2*R*,2'*S*)-**73** were obtained. A similar route was adopted using (*R*)-2-amino-1-butanol to afford the (2*R*,2'*R*)-**73** and (2*S*,2'*R*)-**73** (Scheme 23).



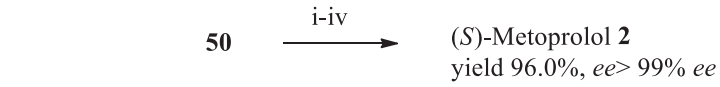
Scheme 23. Synthesis of analogues **73** of metoprolol.

The envisioned efficacy of hydrolytic kinetic resolution method (KHR) encouraged Muthukrishnan et al.[48] to utilize it for the concise synthesis of (*S*)-metoprolol incorporating 2-(4-hydroxy-phenyl) ethanol (**19**) as the starting reagent. Treatment of intermediate (*S*)-epoxide **34** with methyl iodide followed by the addition of *i*-propylamine afforded the crude (*S*)-metoprolol hydroiodide salt **74**. Moreover, 6% ammonia solution was used to free the crude (*S*)-metoprolol hydroiodide salt. Silica gel column chromatography was performed to purify the crude (*S*)-metoprolol **2** (97% yield, 96% *ee*) (Scheme 24).



Scheme 24. Synthesis of metoprolol from (*S*)-**34**.

Use of chiral auxiliary HCS for the kinetic resolution by Zhang et al.[49] was developed for the synthesis of (*S*)-metoprolol. The starting reagent **50** was converted to metoprolol as described earlier (Scheme 25).[49]

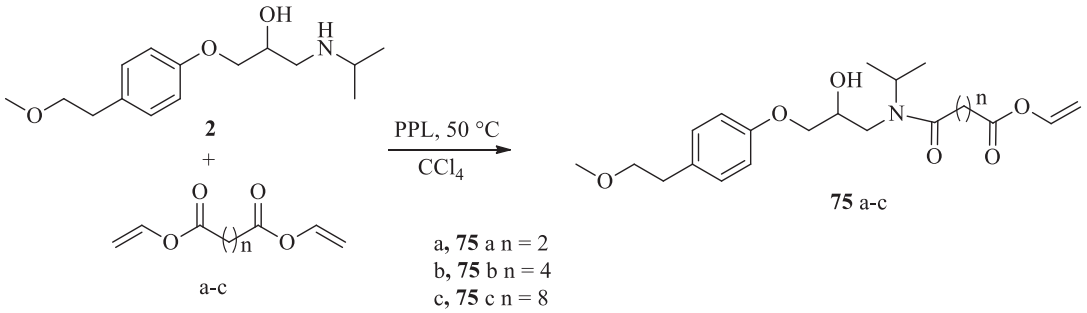


(i) (±) epichlorohydrin, K_2CO_3, acetone (ii) ammonia (25-28%), 0-10 °C (iii) HCS, methanol, TsOH, 5 °C (iv) isopropyl bromide; k_2CO_3, acetone, reflux.

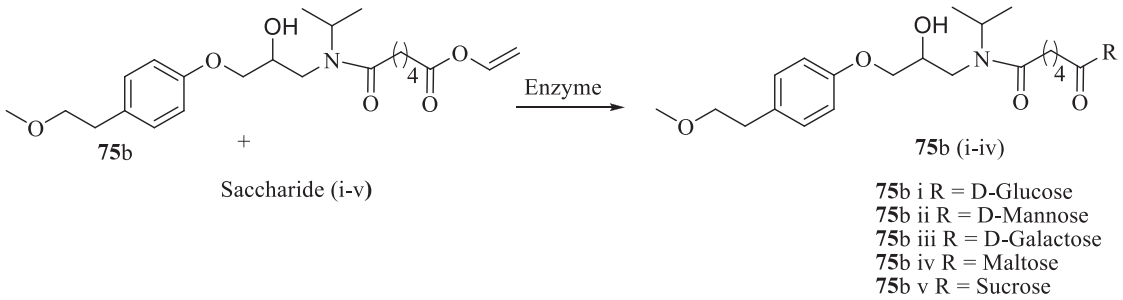
Scheme 25. Synthesis of (*S*)-metoprolol from compound **50**.

A novel synthetic method for metoprolol was elaborated by Gaung-Wei et al.;[80] benzyl protection, Darzen condensation, and rearrangement reaction converted the 4-hydroxy benzaldehyde to 4-benzyloxyphenylacetaldehyde. Addition reaction between sodium bisulfite and 4-benzyloxyphenylacetaldehyde followed by KBH_4 reduction, methylation, deprotection, etherification, and amination afforded metoprolol (**2**).

Zheng et al.[81] synthesized the conjugates of metoprolol and saccharides by selective enzymatic approach. The effect of organic solvents on the preparation of conjugates was also evaluated. Initially *N*-(vinyloxycarbonyl)metoprolol derivatives (**75** a–c) were synthesized by reacting metoprolol **2** and divinyl dicarboxylates in the presence of porcine pancreas lipase (PPL) and anhydrous carbon tetrachloride at 50 °C (Scheme 26). Pure products were obtained by silica gel column chromatography. Highly regioselective reactions of these derivatives with different saccharides were carried out in the presence of alkaline protease from *Bacillus subtilis* and pyridine at 50 °C to afford metoprolol-saccharide conjugates (**75b** i–v). All products were purified by silica gel column chromatography (Scheme 27).



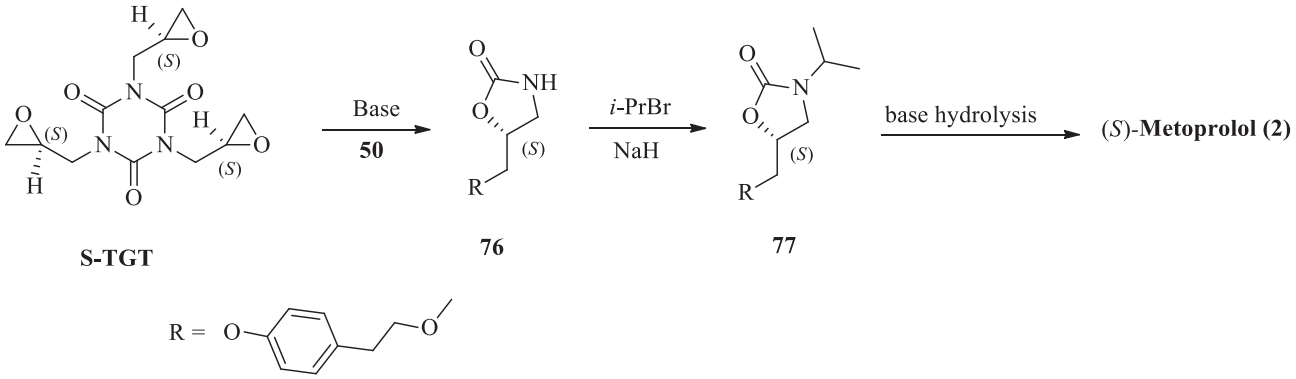
Scheme 26. Enzymatic synthesis of *N*-(vinyloxycarbonyl) metoprolol.



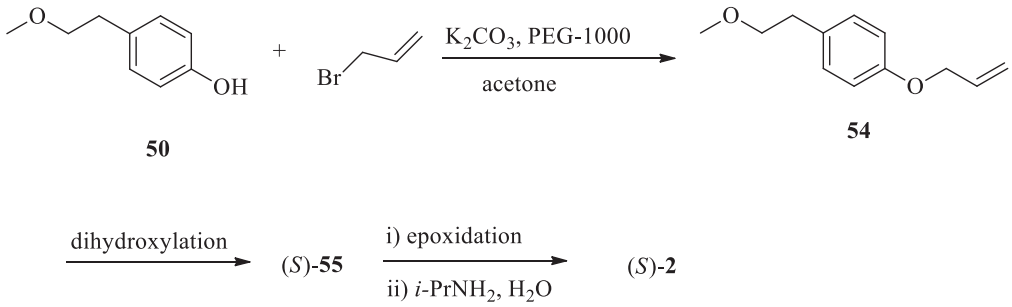
Scheme 27. Synthesis of metoprolol-saccharide conjugates.

The use of the chiral building blocks inspired Sonawane et al.[82] to report a short synthetic strategy for the asymmetric synthesis of (*S*)-metoprolol manipulating chiral building block (2*S*,2′*S*,2" *S*)-Tris-(2,3-epoxypropyl)-isocyanurate (S-TGT).[83] Treatment of S-TGT with phenol **50** afforded pure oxazolidine **76**. (*S*)-*N*-alkylated oxazolidine (**77**) was achieved by reacting **76** with isopropyl bromide in NaH. Base hydrolysis of **77** afforded the desired (*S*)-metoprolol in quantitative yield (Scheme 28).

Cheng et al.[84] reported the enantioselective synthesis of metoprolol under Sharpless asymmetric dihydroxylation. The process was performed using polymer ligand QN-AQN-gmnnOPEG-OMe, which could easily be recovered. The synthesis started from the base catalyzed nucleophilic attack of phenol **50** on the allyl bromide in dry acetone. The obtained compound **54** (87% yield) was subjected to asymmetric dihydroxylation with the help of $K_2OsO_2(OH)_4$, QN-AQN-OPEG-OMe using co-oxidants $K_3Fe(CN)_6$ and K_2CO_3 in a t-BuOH/H_2O system. Extraction with DCM, diethyl ether incorporation, and filtration afforded the QN-AQN-OPEG-OMe (95%). The obtained diol (S)-**55** (96% *ee*) was subjected to epoxidation using trimethylorthoacetate, PPTS, and AcBr in the presence of K_2CO_3. The synthesized epoxide on treatment with isopropylamine was converted to (S)-metoprolol (**2**) (62% yield, 91% *ee*) (Scheme 29).



Scheme 28. Synthesis of (S)-metoprolol using S-TGT.

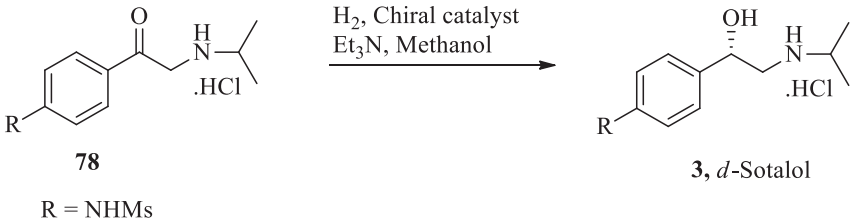


Scheme 29. Synthetic route of (S)-metoprolol **2**.

2.3. Synthesis of sotalol

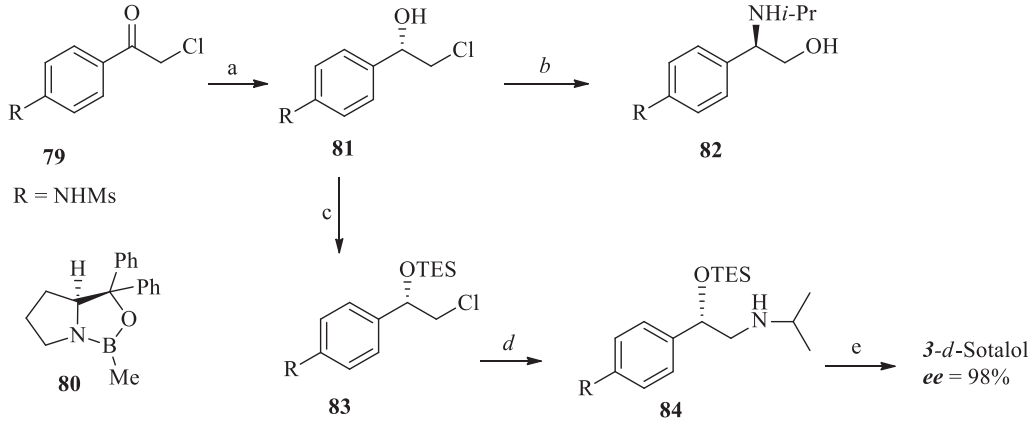
The concise synthesis of d-sotalol was presented by Smith et al.[85] employing homogeneous chiral hydrogenation[86–88] of (4-isopropylaminoacetyl)methanesulfonanilide hydrochloride (**78**) over chiral BINAP[89,90] catalyst. Rh complexed with (R)-BINAP or (S)-BINAP provided the required $d-$sotalol (**3**) in the presence of a base and methanol (Scheme 30).

Brodfuehrer et al.[91] performed the chiral synthesis of $d-$sotalol and evaluated it as an antiarrhythmia agent. CBS reduction (Corey–Bakshi–Shibata reduction) of the carbonyl group of commercially available 4-(chloroacetyl) methanesulfonanilide (**79**) using (S)-MeCBSOB (**80**) in 1 M BH_3-THF and t-BuOMe provided the chiral chloroalcohol **81**[92] (87.2% yield, 95% optical activity). The reaction of chiral chloroalcohol **81** with isopropylamine at 130 °C in a steel bomb provided **82**, instead of $d-$sotalol. To avoid this problem, the



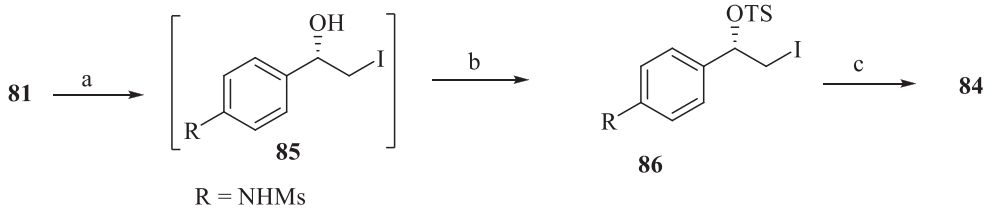
Scheme 30. Catalytic asymmetric hydrogenation of **78**.

hydroxyl group of **81** was first protected using triethylsilyl chloride (TESCl). Reaction of **83** with i-PrNH$_2$ at 130 °C for 16.5 h in a steel bomb provided TES-protected $d-$sotalol (**84**) (30.1% yield). For good yield (98% *ee*) d-sotalol **3** was slurried in 2-propanol with 3.9 N HCl in MeOH. $d-$Sotalol (58.3% yield) as a free base was achieved by desilylation of **84** (Scheme 31). To eliminate the synthesis of TES-protected $d-$sotalol (**84**) and the use of a steel bomb, compound **81** was reacted with saturated NaI in acetone for 9 h (Finkelstein conditions)[93] and subsequently protection of the hydroxyl group using TESCl afforded iodosilyl ether (**86**) (77.3%) having 7%–9% of its chloro analogue **83**. Treatment of **86** with i-PrNH$_2$ resulted in the formation of TES-protected $d-$sotalol (**84**) (49.2% yield) (Scheme 32).



a). (*S*)-MeCBSOB (**80**), 1M BH$_3$-THF, *t*BuOMe; 92.2%, *ee* = 96% b) *i*-PrNH$_2$ 130 °C, 2 h, steel bomb
c) Et$_3$SiCl, Imidazole, DMF, rt, 18 h; 79.8% d) *i*-PrNH$_2$, 130 °C, 16.5 h, steel bomb; 30.1% e) i). TBAF, THF, Reflux, 3 h; 58.3%
ii). 3.9 N HCl in MeOH, isopropylamine; 100%.

Scheme 31. Synthesis of sotalol **3**.

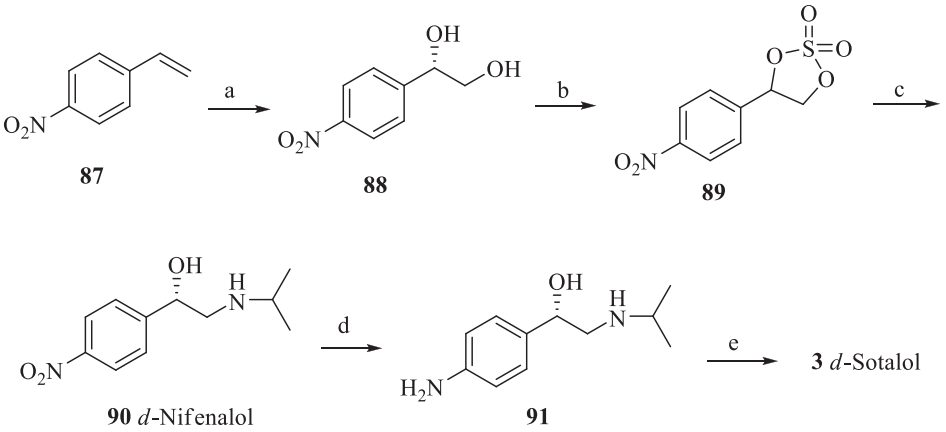


a). NaI, acetone, reflux, 69 h, 93% conversion b) Et$_3$SiCl, imidazole, DMF, rt, 16 h, 77.3 %
c) *i*-PrNH$_2$, reflux, 22 h, 49.2%.

Scheme 32. Synthesis of compound **84**.

Due to interest in enantiomerically enriched diols, Phukan et al.[94] reported a new methodology to prepare $d-$sotalol assessing Sharpless asymmetric dihydroxylation. The synthetic route was started from the synthesis

of nitrostyrene (**87**) as reported previously.[95–97] The asymmetric dihydroxylation of **87** in the presence of a chiral ligand DHQ-PHAL gave rise to the chiral diol **88**. Treatment of diol **88** with $SOCl_2$ in pyridine afforded the cyclic sulfite, which upon oxidation with $NaIO_3$ and a catalytic amount of $RuCl_3$, furnished the cyclic sulfate **89**. Refluxing of **89** with i-$PrNH_2$ in THF was carried out. Upon the completion of the reaction, the reaction mixture was treated with 20% H_2SO_4 followed by 20% NaOH to achieve nifenalol (**90**) (61% yield, enantiomeric purity 96%). Chiral β-hydroxy propylamine (**90**) was obtained in quantitative yield under S_N2 mechanism. Reduction of nifenalol (**90**) with H_2/Pd-C in the presence of ethanol at 50 psi pressure provided amino compound **91**. Treatment of **91** with methanesulfonyl chloride furnished the desired $d-$sotalol (**3**) (40% yield). A side product was also obtained due to mesylation of the hydroxyl group. Column chromatography was applied to separate the $d-$sotalol (optical purity 94%) (Scheme 33).

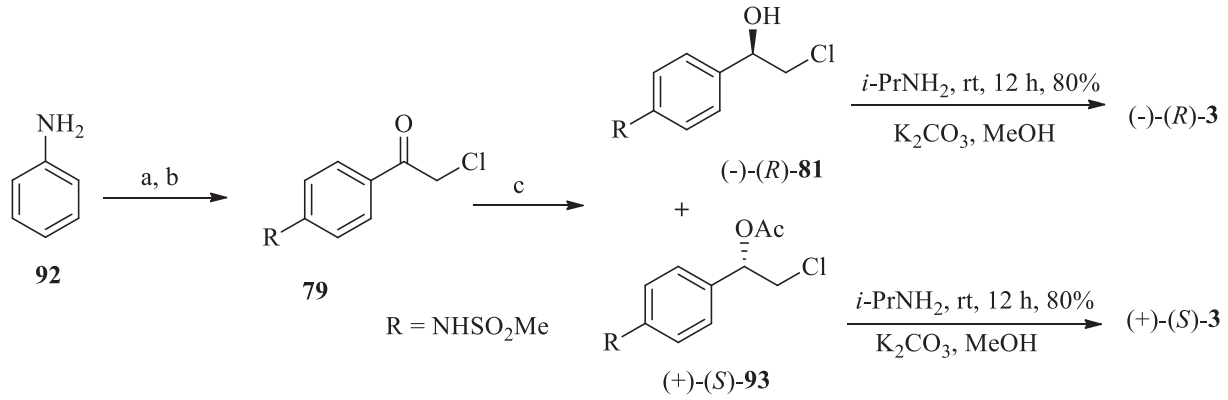


a) DHQ-PHAL, OsO_4, t-BuOH-H_2O b) i. $SOCl_2$, Pyridine, ii. $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O
c) i-$PrNH_2$ d) H_2-Pd/C e) MsCl, base.

Scheme 33. Synthesis of sotalol from compound **87**.

For the first time enzymatic resolution effort was adopted by Kamal et al.[98] for the synthesis of both enantiomers of sotalol. Reaction of aniline **92** with methane sulfonyl chloride in DCM and subsequent treatment with chloroacetyl chloride provided the ketone **79**. One pot reduction of **79** and then enzymatic resolution of racemic chlorohydrins was the main step in this protocol. Reduction was performed using $NaBH_4$ and moist neutral aluminum oxide in diisopropyl ether. Resolution of chlorohydrins was carried out in situ by transesterification using immobilized *Pseudomonas cepacia* lipase (PS-C) and isopropyl acetate (acyl donor). The resolved alcohol (–)-**81** (90% *ee*) and acetate (+)-**93** (94% *ee*) were treated with i-$PrNH_2$ to achieve the sotalol (–)-**3** (90% *ee*) and (+)-**3** (94% *ee*) (Scheme 34).

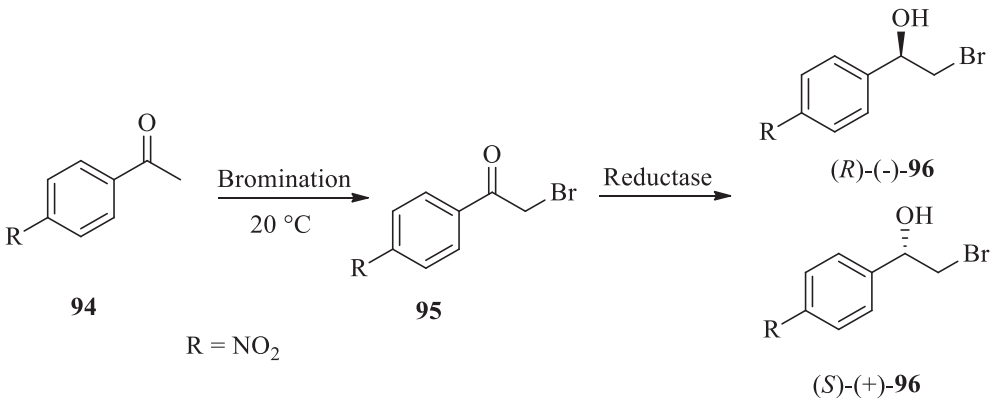
For the facile synthesis of sotalol, Kapoor et al.[99] prepared and resolved the chiral bromohydrin, a precursor to (S)-sotalol. The best strategy for the biocatalytic synthesis of (R)- and (S)-2-bromo-1-(4-nitrophenyl)ethanol (**96**) in high enantiomeric purity, was making use of three different techniques. Monobromination of 4-nitroacetophenone (**94**) afforded 4-nitrophenacyl bromide (**95**). The bioreduction of **95** using different dehydrogenases (reductase) provided 2-bromo-1-(4-nitrophenyl) ethanol (**96**) (Scheme 35). This approach did not provide convincing results. In terms of enantiopurity, *Pichia capsulate* and *S. cerevisiae* provided (S)-**96** (70%) and (R)-**96** (67.8%), respectively. The lipase-esterease catalyzed hydrolysis approach was manipulated, initiated by the reduction of **95** using $NaBH_4$/MeOH to achieve (±)-**96**. Racemic alkyl acyl esters



(a) $MeSO_2Cl$, pyridine, CH_2Cl_2, rt, 12 h, 94%; (b) chloroacetyl chloride, $AlCl_3$, CH_2Cl_2, rt, 6 h, 75%; (c) $NaBH_4$, moist Al_2O_3, diisopropyl ether, lipase PS-C, isopropyl acetate, 40 °C, 18 h.

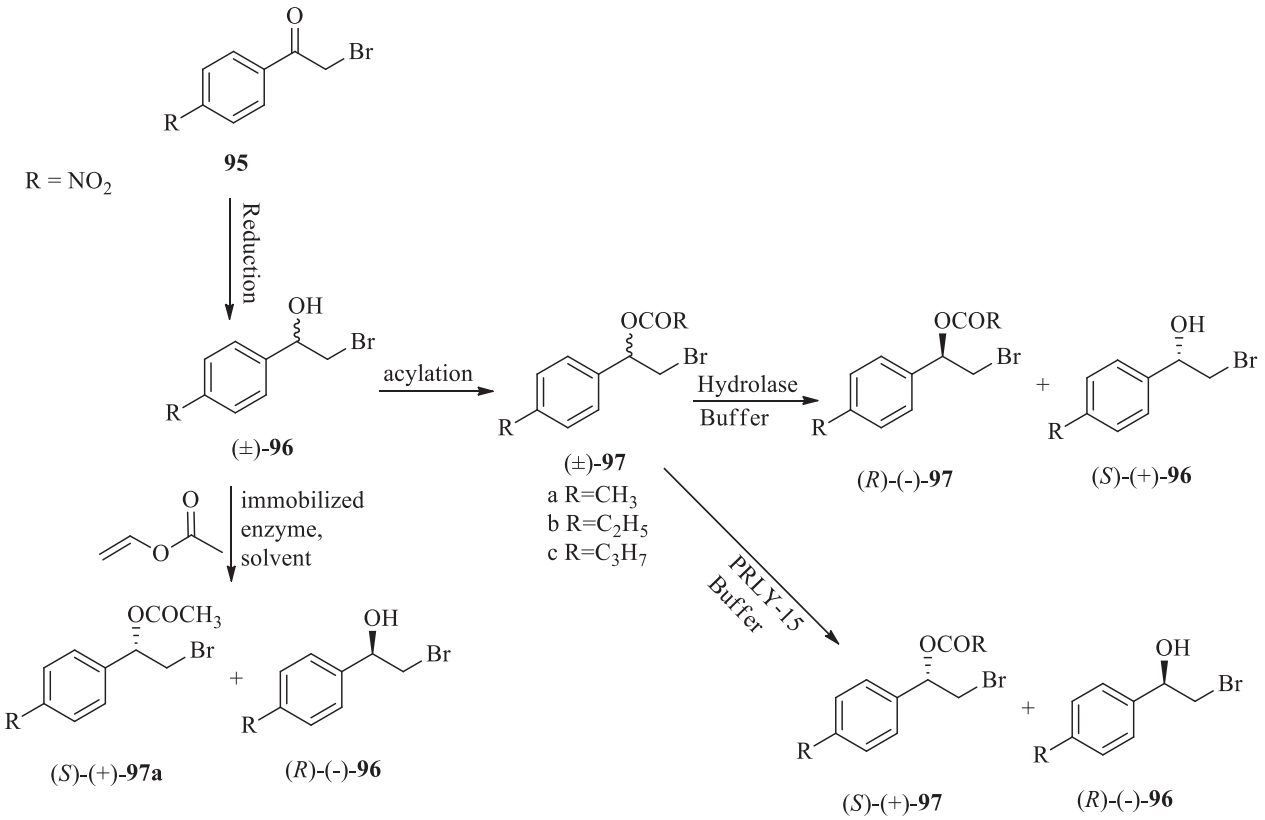
Scheme 34. Synthesis of sotalol from compound **92**.

97a–c were stereoselectively hydrolyzed by a number of lipases/estereases (Scheme 36). The enantiopurity was not improved by this approach for the hydrolyzed products. Commercial enzyme CRL hydrolyzed the butyl ester **97**c (60% *ee*, 47% conversion), while the *Arthrobecter* sp. provided better selectivity (75% *ee*) for the acetate. Effectiveness of co-solvent to improve selectivity was also checked. Transesterification was also performed using different estereases. PS-C-II as a catalyst with vinyl acetate (acyl donor) and solvent provided the best results. In order to improve the transesterification reaction by PS-C-II in a short time, various solvents were employed. Transesterification proved to be the most effective for the resolution of **96** racemic mixture under optimum conditions (PS-C-II, 200 g/L conc., toluene). Toluene improved the reaction rate, afforded the efficient resolution and complete conversion in a short time (Scheme 37).

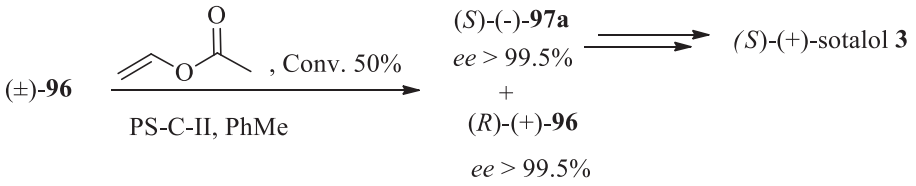


Scheme 35. Bioreduction of **95**.

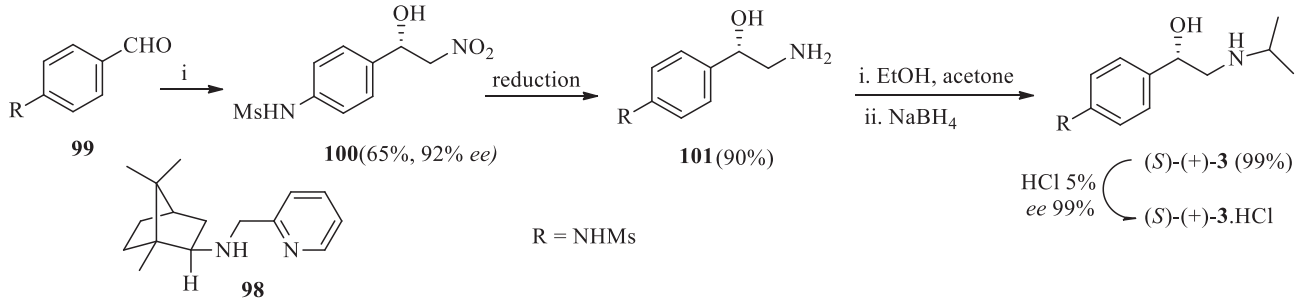
To overcome the deficiency of easily available reagents, Blay et al.[100] adopted the highly stereoselective Henry reaction to afford (*S*)-(+)-sotalol using appropriate aldehyde. The main feature of this synthesis is the Henry reaction, which produced the desired nitro alcohol in high *ee* using aminopyridine copper complex (**98**). Reaction between *p*-aminobenzaldehyde and mesyl chloride in pyridine yielded *N*−(4-formyl phenyl) methanesulfonamide **99**. Reaction of CH_3NO_2 and diisopropyl ethyl amine (DIPEA) with aldehyde **99** in the presence of 10 mol% of $Cu(OTf)_2$-**98** complex in ethanol at –30 °C afforded nitro alcohol **100** (65% yield, 92%



Scheme 36. Lipase/esterase catalyzed kinetic resolution of acyl derivatives **97**a–c.



Scheme 37. Transesterification of (±)-**96** using PS-C-II.



(i) **98**, $Cu(OAc)_2$-H_2O, diisopropyl-ethylamine (DIPEA), EtOH, CH_3NO_2, -30 °C.

Scheme 38. Enantioselective synthesis of (*S*)-(+)-sotalol.

ee). Catalytic hydrogenation[101] of compound **100** using 10% Pd/C in MeOH/EtOH (1:2) provided the amino alcohol **101** in good yield. Compound **101** was reacted with acetone-$NaBH_4$ for reductive alkylation[102] to achieve (*S*)-(+)-sotalol (92% *ee*), which on further reaction with 5% HCl was converted to (*S*)-(+)-sotalol.HCl (Scheme 38).

Using ruthenium catalyst, Lu et al.[103] cited the preparation of chiral halohydrins in an enantioselective way, a precursor to (*S*)-sotalol. In this approach different ligands and a variety of surfactants were employed for their asymmetric transfer hydrogenation efficacy. Monobromination of *p*−nitroacetophenone incorporating bromine in acetic acid afforded the bromoketone **95**. Asymmetric transfer hydrogenation of bromoketone over **L5**-$[RuCl_2(p\text{-cymene})]_2$ catalyst (Figure 4) in $HCOONa/H_2O$ system yielded chiral bromoalcohol (*S*)-(+)-**96** (93% *ee*). Reduction with Pt/C transformed the nitro group of the intermediate into an amino group, which on further reaction with mesyl chloride in pyridine afforded sulfonamide. Sulfonamide was subjected to S_N1 substitution reaction with *i*-propylamine, providing the concerned (*S*)-sotalol (35% yield).

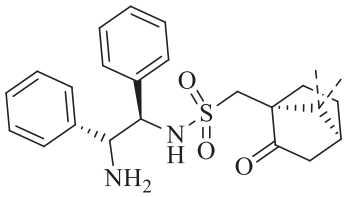
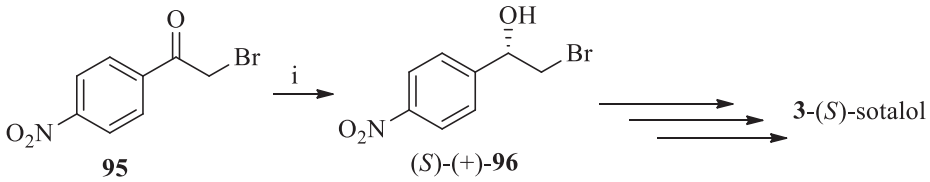


Figure 4. Structure of **L5** (R,R,R)-Cs-DPEN) or [Ru(*p*-cymene) Cl_2]$_2$ catalyst.



i) $[Ru(p\text{-cymene})Cl_2]_2$ / **L5,** $HCOONa/H_2O$

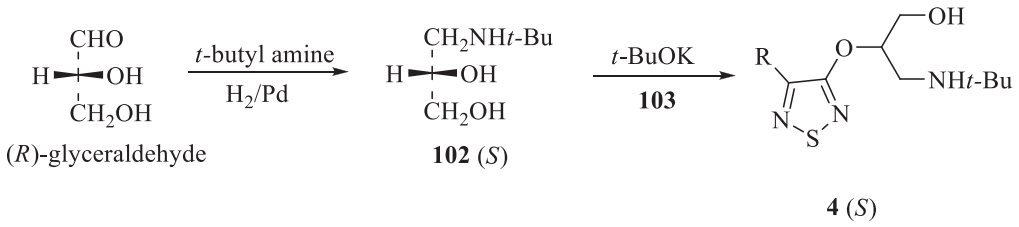
Scheme 39. Enantioselective synthesis of (*S*)-sotalol from **95**.

Shanghai-AoBo[104] presented the short synthesis of sotalol hydrochloride. Aniline was treated with mesyl chloride to achieve *N*-phenylmethanesulfonamide, which on reaction with chloroacetyl chloride furnished *N*-[4-(2-chloroacetyl)phenyl]methanesulfonamide. Addition of isopropylamine to *N*-[4-(2-chloroacetyl)phenyl]methanesulfonamide followed by reduction and saltification afforded sotalol hydrochloride (64% yield).

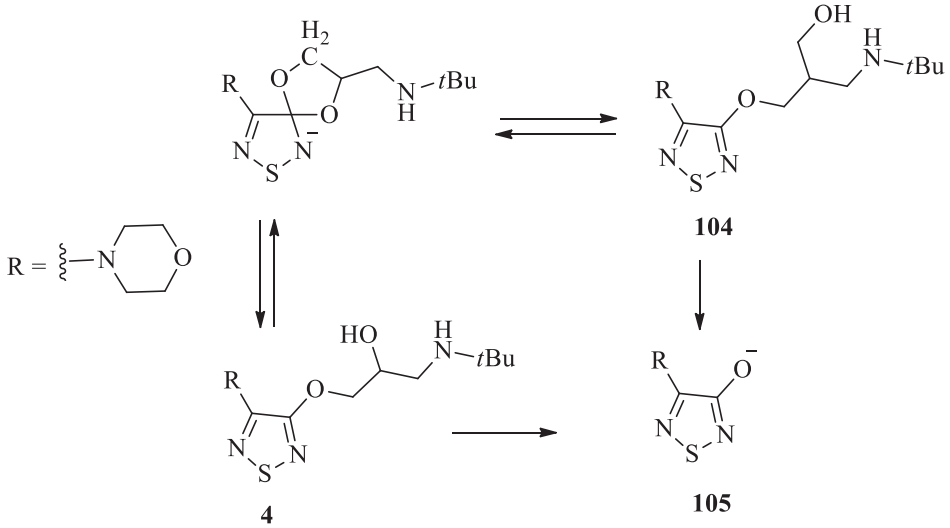
2.4. Synthesis of timolol

Utilizing optically active precursors, Weinstock et al.[31] carried out the synthesis of timolol. In the first step, (*S*)-3-*tert*-butylamino-1,2-propandiol (**102**) (54% yield) was obtained by treating (*R*)-glyceraldehyde with H_2/Pd and *tert*-butylamine. Condensation of **102** with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole (**103**) using potassium *tert*-butoxide furnished the timolol levorotatory, separated as maleate salt in low yield (Scheme 40). Due to low yield and nonavailability of glyceraldehyde this methodology is restricted to the laboratory. The base-sensitive nature of **4** (*S*) resulted in its equilibration with **104** (Smiles rearrangement), which lowers the yield. Base sensitivity also caused the loss of side chains from **4** and **104** providing 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole anion **105** (Scheme 41). The encountered shortcomings were eliminated by

protecting the secondary alcohol functionality of (*S*)-**102** by treating with benzaldehyde resulting in oxazolidine (**109**) formation. Reaction of **109** with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole (**103**) using potassium *tert*-butoxide and subsequent hydrolysis provided timolol (50% yield) (Scheme 42). Alternatively treatment of optically active epoxide **106** with sodium salt of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**105**) also introduced the side chain amino-propanediol providing compound **4** (36% yield) (Scheme 42). To compensate the need of (*R*)-glyceraldehyde, aminoglycol (**102**) was synthesized alternatively. Reaction of D-mannitol-1,2,5,6-bisacetonide (**107**)[105] with lead tetraacetate produced 2 equivalents of (*R*)-glyceraldehyde acetonide (**108**). Reductive alkylation using $t-\mathrm{BuNH_2}$ of **108** followed by hydrolysis furnished **102** (70% yield) (Scheme 43).



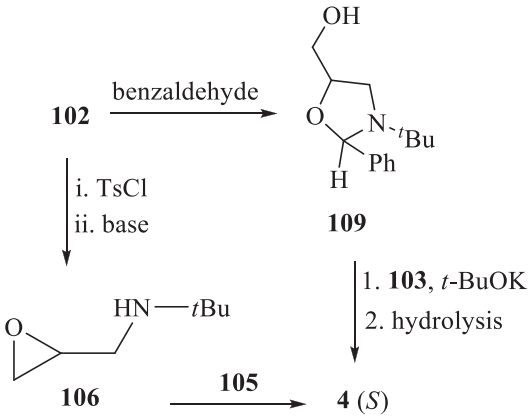
Scheme 40. Synthesis of thiadiazole **4**.



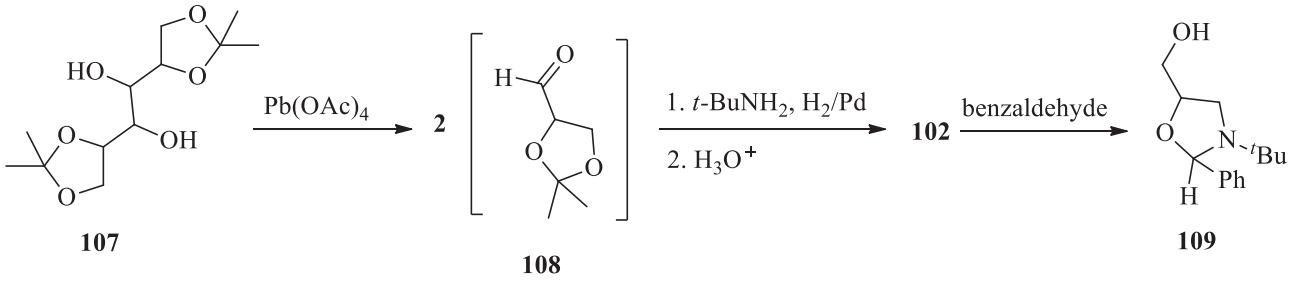
Scheme 41. Cont.

In order to enhance the ocular delivery of timolol, Bundgaard et al.[106] synthesized timolol prodrugs. Esters of timolol were also evaluated for their hydrolysis kinetics and lipophilicity. After maintaining suitable pH and extraction of timolol maleate, excess of 3 M HCl in methanol was added to get timolol hydrochloride. Slurry of timolol hydrochloride was prepared in benzene and then treated with appropriate acid chloride. Separation of timolol esters (**110**–**113**) was also carried out (Scheme 44).

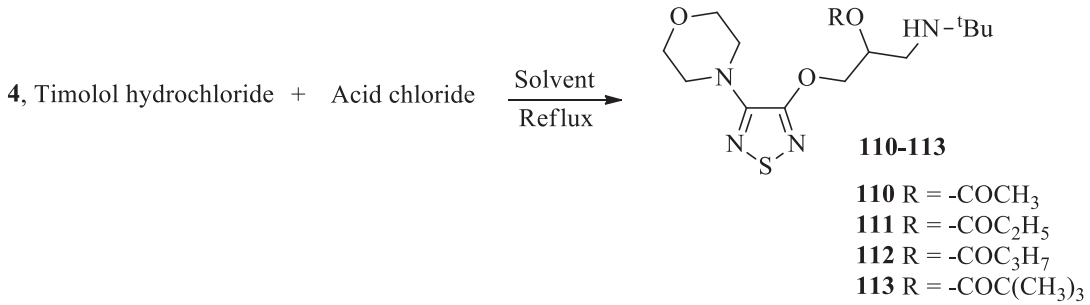
In continuation of their previous work, Bundgaard et al.[107] reported the synthesis of different substituted timolol esters and checked their stability and lipophilicity. Some timolol esters in the form of their hydrochlorides were prepared as reported earlier.[106] Using the same methodology, the hydrochloride salt of *O*-isobutyryl ester was also prepared and isolated. Reaction of timolol maleate and corresponding acid chloride in acetonitrile resulted in the formation of all other esters as fumarate salts except two. After slurry formation of timolol



Scheme 42. Cont.



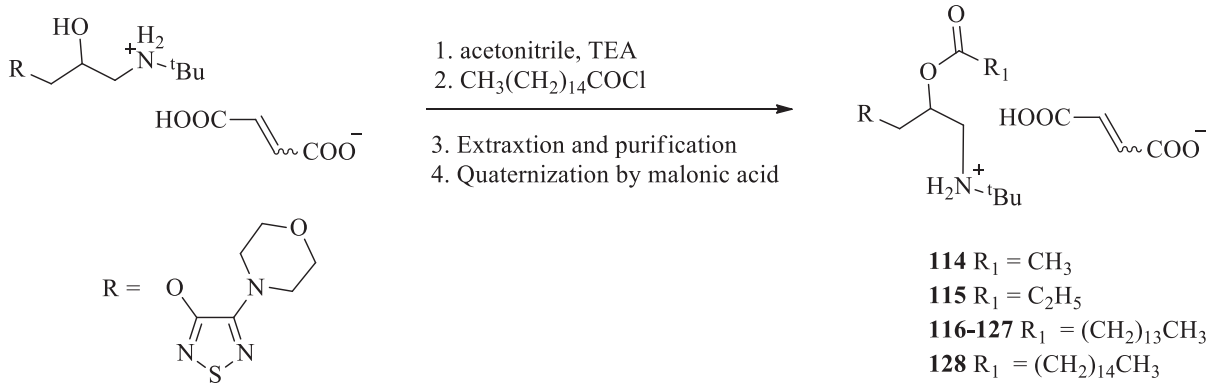
Scheme 43. Cont.



Scheme 44. Synthesis of timolol esters.

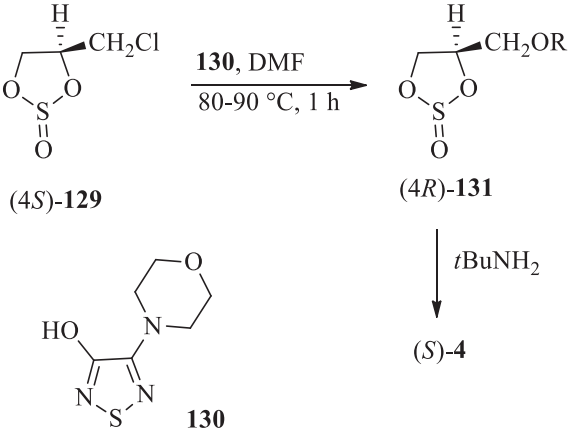
maleate in acetonitrile, it was reacted with appropriate acid chloride. HPLC analysis was also carried out after stirring for 4 h (for aliphatic esters) or 20 h (for aromatic esters) at 80 °C was carried out. Residues obtained were separated, washed, and treated with ether or mixture of ethyl acetate, ether, and a solution of fumaric acid in the presence of 2-propanol to get fumarate salts of timolol esters.

To overcome the systemic effects and to increase the bioavailability, the amphiphilic prodrugs could be effective. Following this statement, Pech et al.[108] described the synthesis of timolol prodrugs to enhance ocular delivery and also explained hydrolysis and conformational behavior of the synthesized compounds **114**–**128**. A mixture of slurried timolol maleate and palmitoyl chloride was stirred for 24 h at 80 °C. Introduction of ethylamine, extraction, and purification provided the quaternary ammonium salt. Reaction of malonic acid in 2-propanol with quaternary ammonium salt produced the desired palmitoyl timolol malonate (Scheme 45).



Scheme 45. Synthesis of palmitoyl timolol malonate.

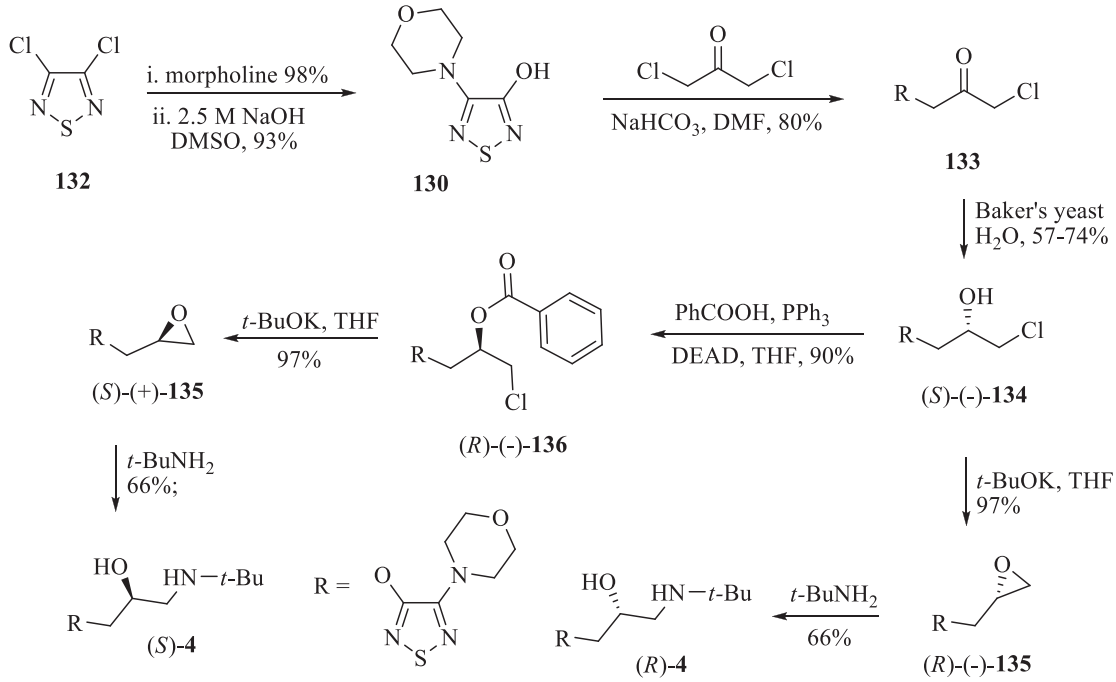
A novel synthetic approach to synthesize nonracemic (*S*)-timolol incorporating cyclic sulfites was presented by Bredikhina et al.[109] Synthesis of scalemic β-AB ((*S*)-timolol) from (*S*)-glycidol, utilizing cyclic sulfites as an important intermediate, was carried out. Treatment of a mixture of (2*RS*, *4S*)-**129** with 3-hydroxy-4-morpholino-1,2,3-thiadiazole (**130**) in the presence of DMF resulted in a mixture of isomers (2*RS*, 4*R*)-**131** (59:41, 80% yield). A double nucleophilic substituted undesirable product, 1,3-bis[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol, was isolated along with isomeric major products (2*RS, 4R*)-**131** under the applied conditions. Separation of products **131** and 1,3-bis[(4-morpholino-1,2,5-thiadiazol-3-yl)oxylpropan-2-ol was carried out by column chromatography. Partial crystallization of a mixture of sulfites (**131**) took place upon storage and resulted in crystals enriched in (2*S*, 4*R*)-**131**. Reaction of sulfites (4*R*)-**131** with *t*-BuNH$_2$ in DMF at 60–80 °C furnished (*S*)-**4** (∼80% yield). The salient feature of this synthesis is the use of chloromethyl sulfites instead of epichlorohydrin as administrated in the previous approaches. Synthesis involving epichlorohydrin always produced a racemic mixture, while use of chloromethyl sulfites provided only one enantiomer (Scheme 46).



Scheme 46. Synthesis of timolol from compound **129**.

A bioenzymatic approach was incorporated by Tosi et al.[110] for an excellent asymmetric synthesis of both the enantiomers of timolol. The synthetic route was started from the synthesis of 4-morpholin-4-yl-1,2,5-thiadiazol-3-ol (**130**). Two-step treatment of 3,4-dichloro-1,2,5-thiadiazole (**132**) resulted in the formation of **130** (91% yield). Haloketone **133** (80% yield) was obtained by the treatment of **130** with dichloroacetone in

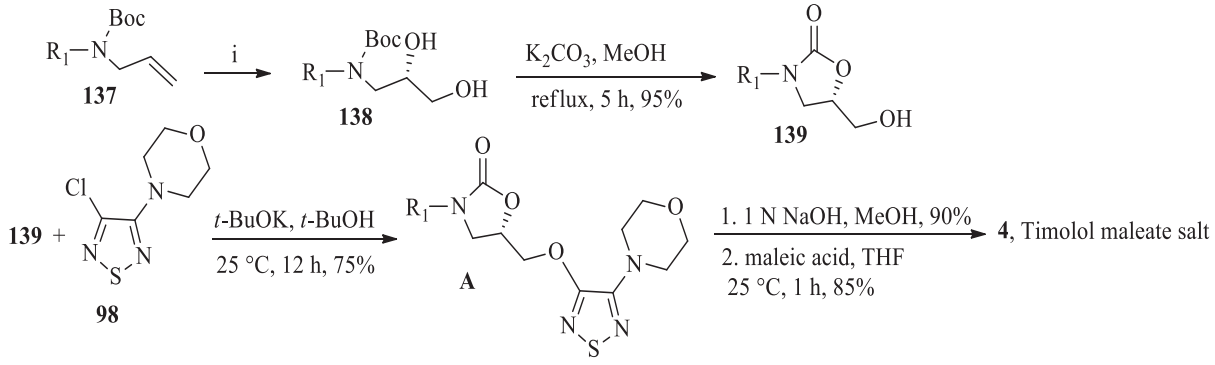
dry DMF along with $NaHCO_3$. The biocatalyst baker's yeast[111] was used for the asymmetric reduction of haloketone **133**. This step was carried out using different yeast/substrate ratios and some additives such as glucose, allyl bromide, and allyl alcohol. The function of additives herein is to act as selective inhibitors for the different oxido-reductase of the multienzymatic system.[112] Levorotatory enantiomer of (2*S*)-1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxyl]propan-2-ol (**134**) was the main product of the asymmetric reduction independent of the additives; however, variable *ee* (59% to 87%) was achieved. Configuration of (-)-**134**, i.e. (*S*), was determined by treating it with *t*-BuOK in THF at 0 °C to achieve the epoxide (*R*)-(-)-**135**[113] (97% yield). Treatment of (*R*)-(–)-**135** with *t*−$BuNH_2$ afforded the *R*-(–)-**4**, timolol. To achieve (*S*)-(–)-**4**, Mitsunobu methodology was adopted for inversion of configuration[114] and benzoate ester (*R*)-(–)-**136** (80% yield) of (–)-**134** was obtained by manipulating it with diethyl-azodicarboxylate (DEAD) and triphenyl phosphine (PPh_3). Removal of the acyl group and intramolecular alkylation of (*R*)-(–)-**136** using *t*-BuOK in THF provided the (*S*)-(+)-**135**. Reaction of intermediate (*S*)-(+)-**135** with *t*−butylamine provided the concerned (*S*)-timolol (66% yield, 87% *ee*) (Scheme 47).



Scheme 47. Synthesis of timolol from compound **132**.

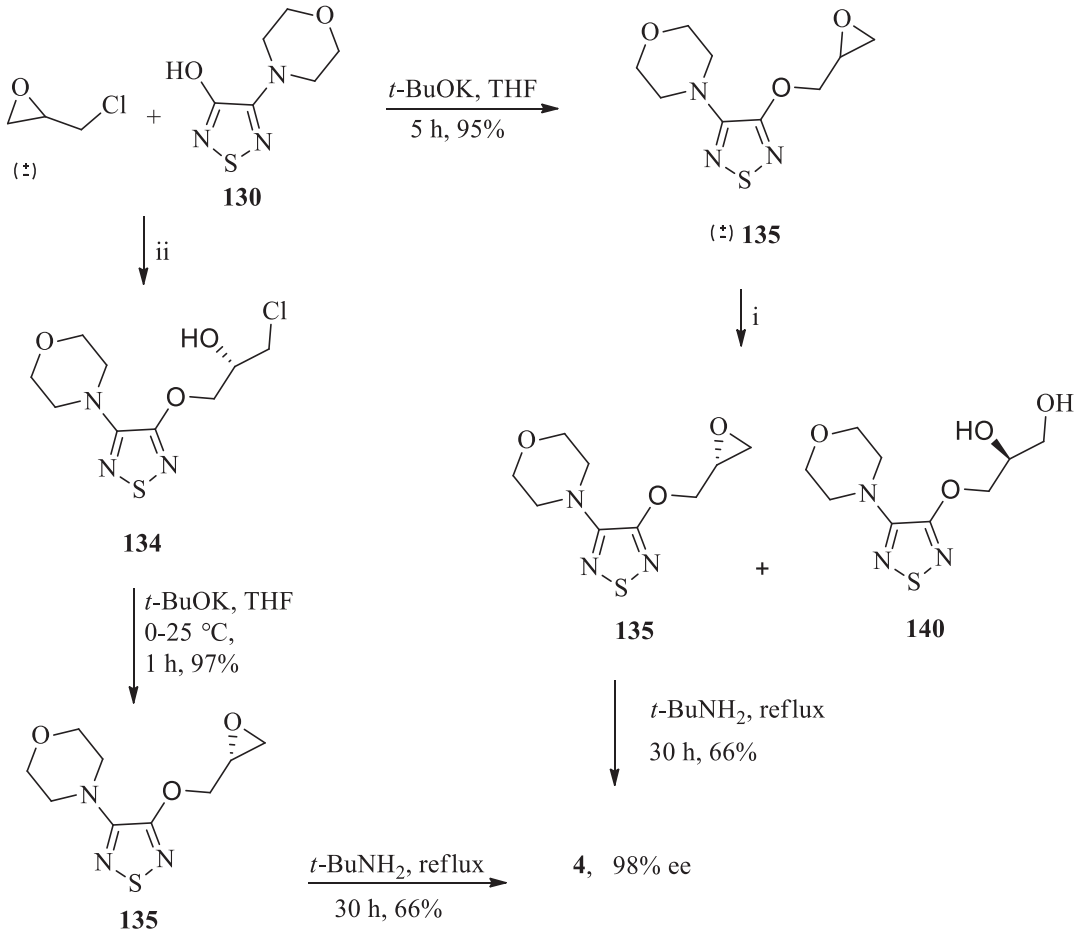
Asymmetric synthesis of (*S*)-timolol was presented by Jinhui et al.[115] D-mannitol was used as chiral synthon. Oxazolidine derivative was afforded by treating (*S*)-(–)-3-*t*-butyl-amino-1,2-propanediol with benzaldehyde. Reaction of oxazolidine derivative with 3-chloro-4-morpholino-1,2,5-thiadiazole and *t*-BuOK/*t*-BuOH followed by hydrolyzation resulted in (*S*)-timolol.

In 2007, Narina and Sodalai[116] presented an asymmetric synthesis of (*S*)-timolol from readily available reagents. The dihydroxylation of allylamine[117] and the kinetic resolution of terminal epoxides[118] are the key features of this synthesis. The Boc- protected *tert*-butyl amine was alkylated with allyl bromide using NaH to afford *N*-*tert*-butyl allylamine (**137**). The Os-catalyzed asymmetric dihydroxylation of **137** with $(DHQ)_2$-PHAL ligand afforded a chiral diol (93% yield) (**138**). Addition of K_2CO_3 and MeOH in diol



i. Cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 0-25 °C, 24 h, 93%, 56% *ee*.

Scheme 48. Asymmetric synthesis of (S)-timolol from compound **137**.

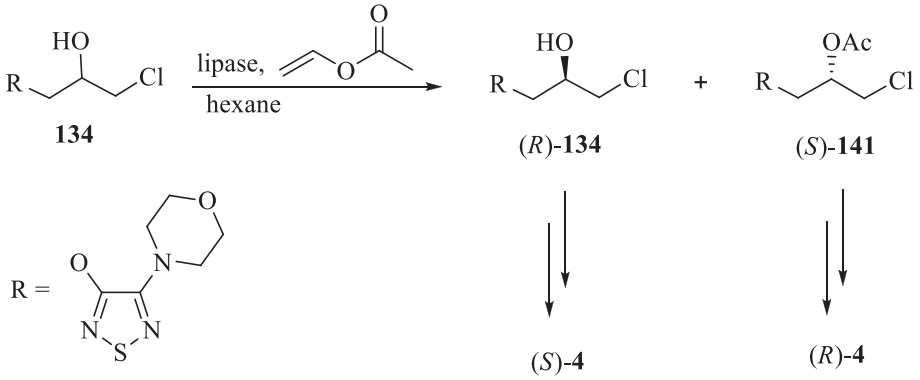


(i) (*S*,*S*)-salen-cobalt(II) (0.5 mol%), AcOH (2 mol%), THF, H_2O (0.55 equiv), 0 °C, 14 h.
(ii) (*R,R*)-(salen)-Co[$OC(CF_3)_3$] (0.044 equiv), epichlorohydrin (2.5 equiv), *tert*-butyl methyl ether, 12 h.

Scheme 49. Synthesis of timolol from compound **130**.

132 and refluxing provided 2-oxazolidinone (**139**)[119] (95% yield, 56% *ee*). *O*-alkylation of **139** using 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole (**98**)[31] resulted in oxazolidinone **A**. Timolol **4** was obtained after hydrolysis of **A** with 1 N NaOH in MeOH[120] and then maleate salt of **4**[31] (85% yield, 56% *ee*) was isolated (Scheme 48). To increase the *ee* of timolol, a new method was adopted. *O*-alkylation of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**130**) using epichlorohydrin resulted in excessive yield of racemic epoxide **135**. The hydrolytic kinetic resolution (HKR)[121,122] of **135** provided the chiral epoxide **135** (46% yield, 90% *ee*) and its diol **140** (45% yield). Column chromatography was performed to separate the compounds **135** and **140**. *tert*-Butylamine was used for ring opening of chiral epoxide **135** regiospecifically[31] and (*S*) timolol **4** was obtained. At the end, maleate salt of **4** (85% yield, 90% *ee*) was achieved (Scheme 49). HKR resulted in greater optical purity of (*S*)-timolol but half epoxide **135** was lost. Enantioselective ring opening of terminal epoxide using phenolic substrate followed by kinetic resolution approach was utilized. Alternatively chiral epoxide **135** could be obtained via (2*R*)-1-chloro-3-[(4-morpholino-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (**134**) (86% yield, 98% *ee*) when (±) epichlorohydrin was treated with 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadizole (**130**) using (*R*, *R*)-(salen)Co(OC(CF$_3$)$_3$] complex and *tert*-butylmethyl ether at 25 °C. The requisite epoxide **135** (97% yield) was prepared from chlorohydrin **134** using *t*−BuOK and THF at 0 °C. Regiospecific ring opening of chiral epoxide **135** was carried out to achieve (*S*)-timolol **4**, which was isolated in the form of maleate salt (85% yield, 98% *ee*) (Scheme 48).

Kamal et al.[123] innovated a new synthetic route for the preparation of (*R*) and (*S*)-timolol via enzyme-catalyzed resolution. 3,4-Dichloro-1,2,5-thiadiazole (**132**) was converted to **134** as previously reported.[110] Racemic alcohol **134** was treated with lipase and vinyl acetate in successive steps to obtain compound (*R*)-**134** and (*S*)-**141**, separated by column chromatography. (*R*)-**134** and (*S*)-**141** (after deprotection) were converted to (*S*)-**4** and (*R*)-**4** respectively,[110] which were purified by column chromatography (Scheme 50).



Scheme 50. Synthesis of timolol from compound **134**.

3. Conclusion

The synthetic/medicinal value of beta-blockers is well-known. The synthetic approaches attempted so far towards the synthesis of beta-blockers (betaxolol, metoprolol, sotalol, and timolol) have been summarized in this article. It is evident that the synthesis of beta-blockers can be achieved by different pathways. This article is especially useful for scientists/chemists interested in the synthesis of analogues of beta-blockers.

Acknowledgment

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