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Journal of Chemical and Pharmaceutical Research, 2016, 8(8):518-538

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of fesoterodine: An enantiopure active pharmaceutical ingredient (API)

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ABSTRACT

Fesoterodine is in a class of medicines called anti muscarinics. It is used to treat overactive bladder condition. Several generic drug manufactures have reported alternate approaches to this drug molecule, through an intermediate of 5-hydroxy methyl tolterodine. This compound was reacted with isobutyryl chloride to react with phenolic group followed by fumaric acid salt formation to produce the drug. Very few deviated this route. Different strategies followed by different groups are discussed in detail.

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Keywords: Fesoterodine, 5-hydroxy methyl tolterodine, Cinnamic acid, Heck reaction, Oxidation, Resolution, Friedel-Crafts alkylation, Reductive amination

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INTRODUCTION

Fesoterodine (**1**) is used to treat overactive bladder (a common problem with old age, a condition in which the bladder muscles contract unconcontrollably and cause frequent urination, urgent need to urinate, and inability to control urination). Fesoterodine is in a class of medicines called antimuscarinics. It works by relaxing the bladder muscles to prevent urgent, frequent or uncontrolled urination. Fesoterodine was developed by Schwarz pharma AG to treat overactive bladder syndrome (OAB).It was approved by European Medicines agency in April 2007, then USFDA in 2008, and Health Canada on Feb9, 2012. Fesoterodine is a prodrug. It is broken down into its active metabolite, 5-hydroxy methyl tolterodine (**2**) by plasma esterages. Pfizer Inc. acquired the worldwide rights on fesoterodine during April 2006.

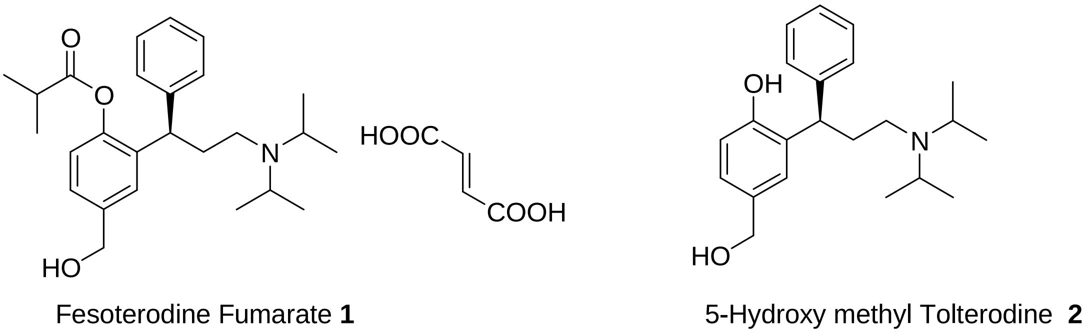


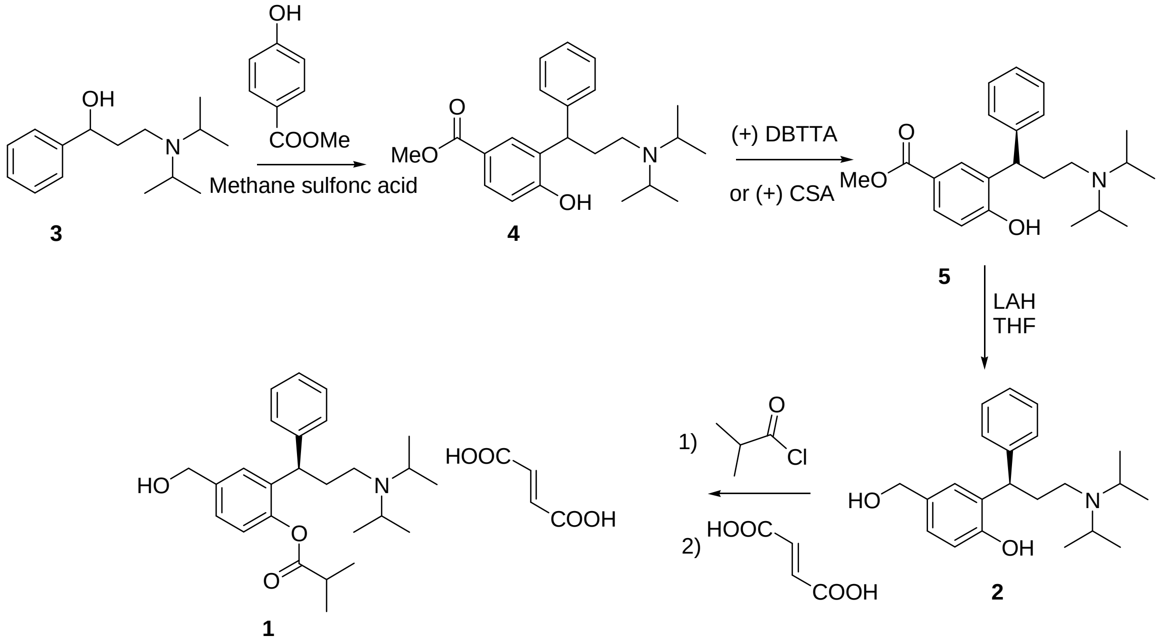
Figure 1: Structure of fesoterodine Fumarate (1) and 5-Hydroxy methyl Tolterodine (2)

By 2014 Toviaz (brand of fesoterodine) reached $236 million. Currently tablets are formulated in strengths of 4, 8 mg of fesoterodine as the freebase equivalent. Fesoterodine fumarate is a white crystalline solid and is soluble in methanol, 95% ethanol and slightly soluble in water. It has one chiral center, having an (R)-absolute configuration. Its chemical name is [2-[(1R)-3-(di(propan-2yl)amino)-1-phenyl propyl]-4-(hydroxyl methyl)phenyl]-2-methyl propionate.

Given the importance of fesoterodine as a drug. several academic groups and generic drug manufactures have searched for alternative synthetic processes. Almost all syntheses were used 5-hydroxy methyl tolterodine (**2**) as a precursor. The synthesis of compound 2 was either from tolterodine direct oxidation or conversion of methyl to methyl alcohol by different methods was used as strategy by different teams. In some cases it was started with hydroxyl methyl compound. The various synthetic strategies are discussed in detail.

Synthetic approaches involving Friedel-Crafts alkylation.

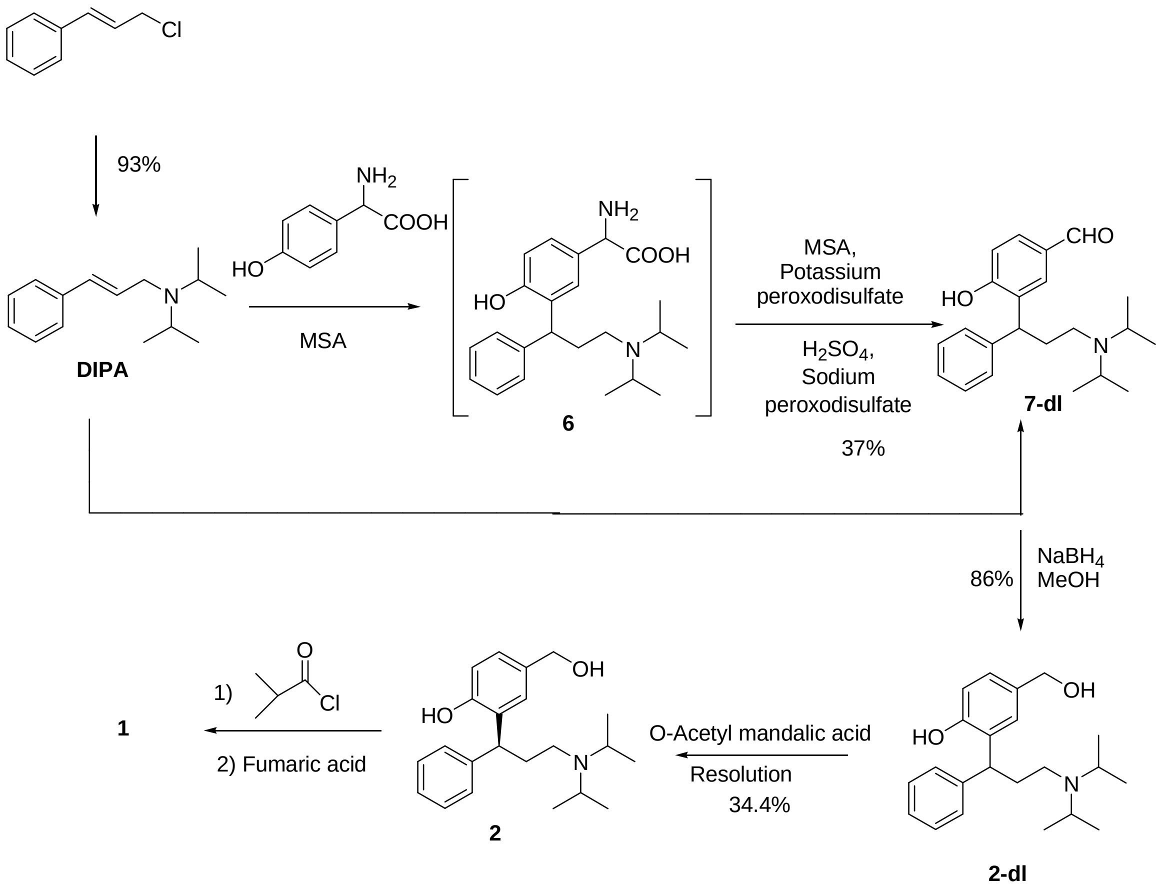
Process scientists from Dipharma Mantegazza, S [1] reacted Methyl-4-Hydroxy benzoate with 3-diispropylamino-1-phenyl propanol (**3**) in the presence of methane sulfonic acid at 50-55°C to give 3-(3-diisopropyl amino-1-phenyl-propyl)-4-hydroxy benzoate (**4**) in 92% of yield. Further the product **4** on resolution with (+) 2,3-dibenzoyl –D-tartaric acid in ethanol gave (+)2,3-dibenzoyl –D-tartaric acid of 3-(3-diisopropyl amino-1-phenyl-propyl)-4-hydroxy benzoate (**5**). Compound **5** was reduced with lithium aluminium hydride to give R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxy methyl-phenol (**2**) in 95% of yield, compound **2** was reacted with isobutyryl chloride followed by salt formation with fumaric acid to give **1**.



Scheme 1: Benzylation of phenol derivative from benzyl alcohols 3

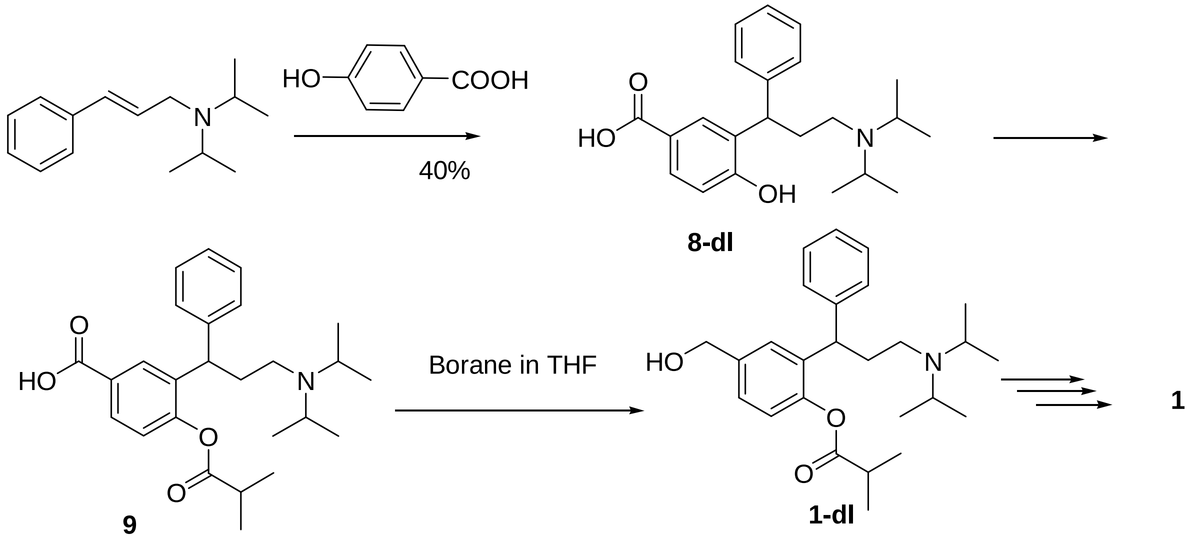
Reaction with β, γ-unsaturated Amines.

Sterk. D [2] disclosed a method that involves the coupling of (R)-2-amino-2-(4-hydroxy phenyl)acetic acid [(R)-para hydroxyl phenyl glycine] with N,N-Diisopropyl-3-phenyl prop-2-en-1-amine (DIPA) in the presence of methanesulfonic acid/ sulfuric acid at 130°C to give 2-amino-2-(3-(3-diisopropyl amino)-1-phenyl propyl)-4-hydroxy phenyl)acetic acid (**6**) in 96% yield. Further reaction of **6** with potassium or sodium per--oxodisulfate in water gave 3-(3-(diisopropylamino)-1-phenylpropyl)-4-hydroxy benzaldehyde intermediate (**7-dl**) in 37 % yield. The reaction of **7-dl** with sodium borohydride gave **2-dl** in 86 %yield. It was resolved with O-acetyl mandelic acid to give **2** in 34.3% yield.



Scheme 2: p-hydroxy phenyl glycine benzylation with DIPA

Similarly crystal pharma team [3] started from 4-hydroxy benzoic acid and reacted with N,N-Diisopropyl-3-phenyl prop-2-en-1-amine in presence of AcOH and H_2SO_4 at 85°C to give 3-(3-diisopropyl amino-1-phenyl-propyl)4-hydroxy benzoic acid (**8-dl**). Further **8-dl** was reacted with isobutyryl chloride in presence of TEA to give 2-(3-diisopropyl amino-1-phenyl-propyl)-4-carboxy phenol isobutyrate (**9**). Compound **9** was reacted with borane in THF to give dl-Fesoterodine in 96% of yield. Which was resolved with O-acetyl mandelic acid to give drug **1**.

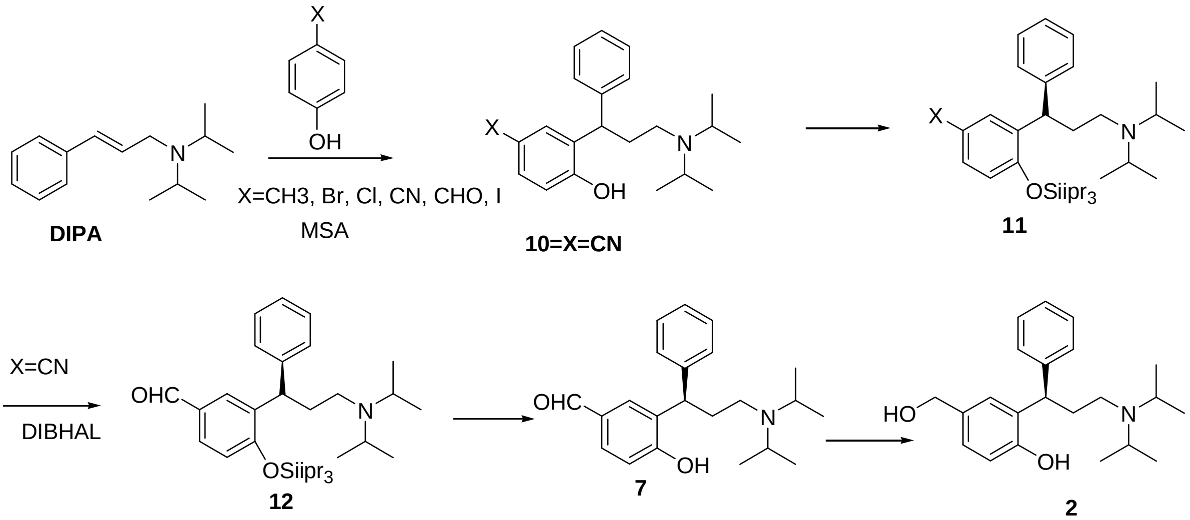


Scheme 3: 4-Hydroxy benzoic acid benzylation with DIPA

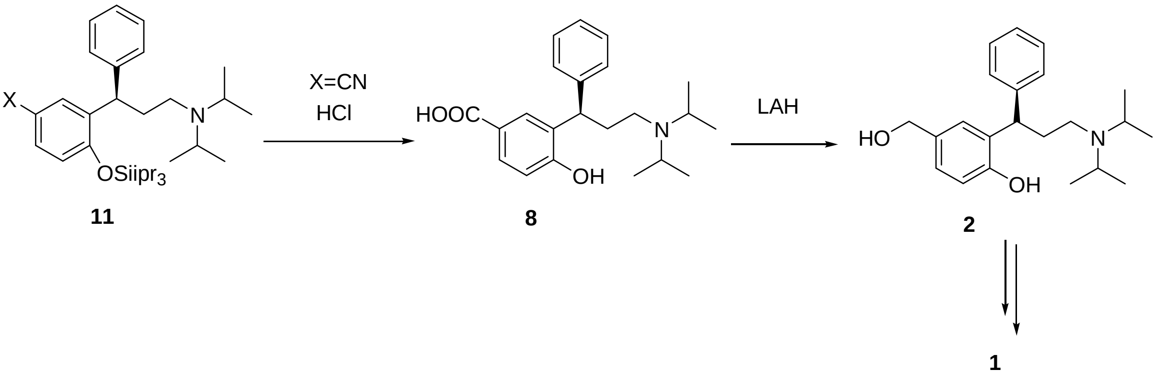
Fusher [4] from Lek group started with N,N-diisopropyl -3-phenyl prop-2-en-1-amine and reacted with 4-cyano phenol in presence of ethane sulfonic acid at 130°C to give 3-(5-cyano-2-hydroxy phenyl)-N,N-diisopropyl-3-phenyl propylamine (**10**),Which on resolution with tartaric acid in ethanol gave (R)- 3-(5-cyano-2-hydroxy phenyl)-

N,N-diisopropyl-3-phenyl propylamine. Further it was reacted with triisopropyl silyl chloride in presence of imidazole to give (R)-N,N-diisopropyl-3-phenyl- (5-formyl- 2- triisopropyl silyloxy phenyl) -prop-2-en-1 amine (**11**). Compound **11** on DIBAL reduction gave compound **12** which on hydrolysis gave **7**, and **7** on further transformations gave **2** in good yields.

In another methodology (R)-N,N-diisopropyl-3-phenyl- (5-cyano- 2- triisopropyl silyloxy phenyl) -prop-2-en-1 amine (**11)** was reacted with aq. HCl to give R-3-(3--(diisopropylamino)-1-phenyl propyl)-4-hydroxy benzoic acid (**8**). Further it was reacted with LAH in THF to give 2-(3-diisopropylamino-1-phenyl)-4-hydroxy methyl phenol **2**.



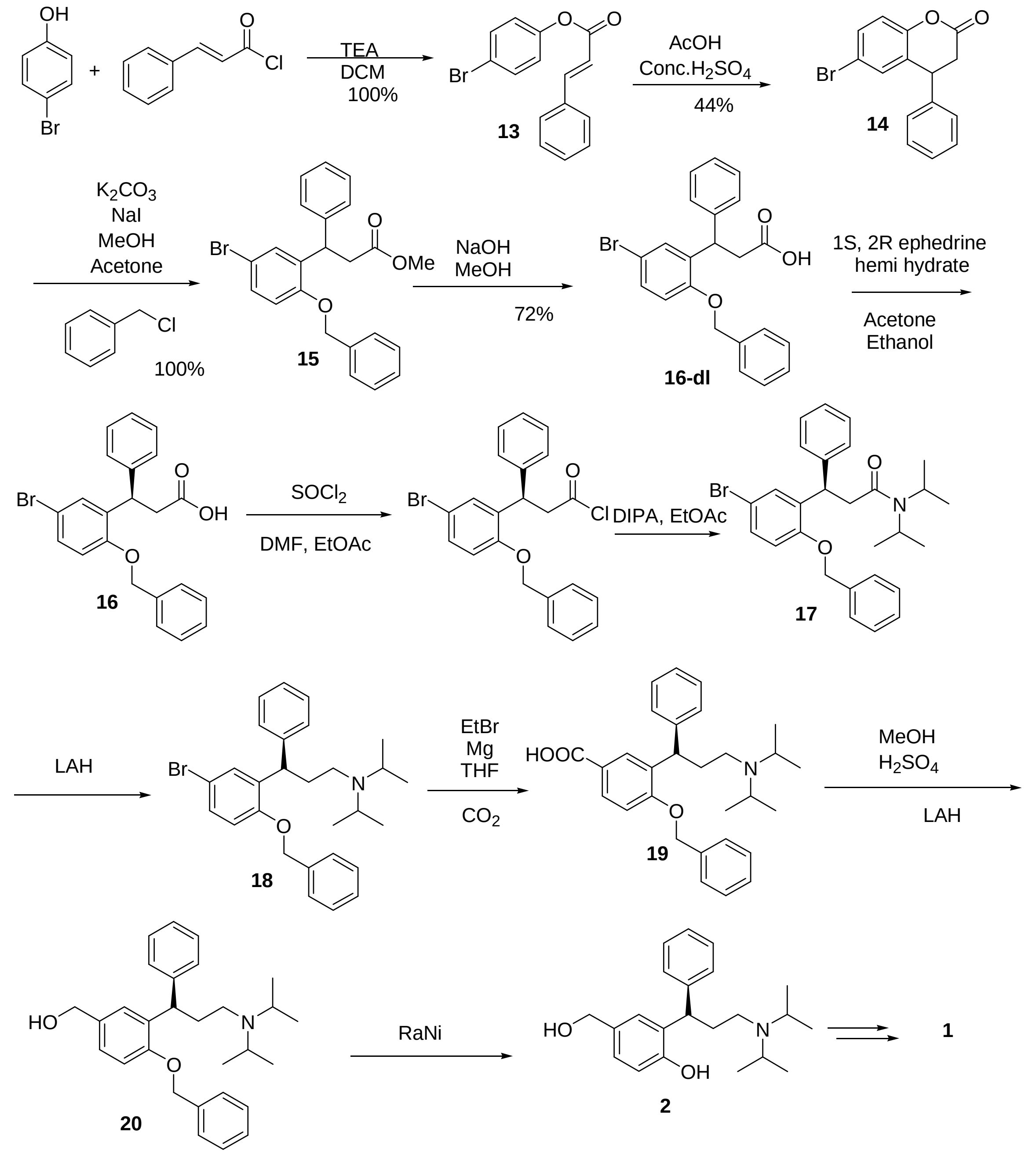
Scheme 4: 4-substituted phenol benzylation with DIPA



Scheme 5: Conversion of Aromatic –CN group to –CH$_2$OH

Reaction with unsatured acid derivatives

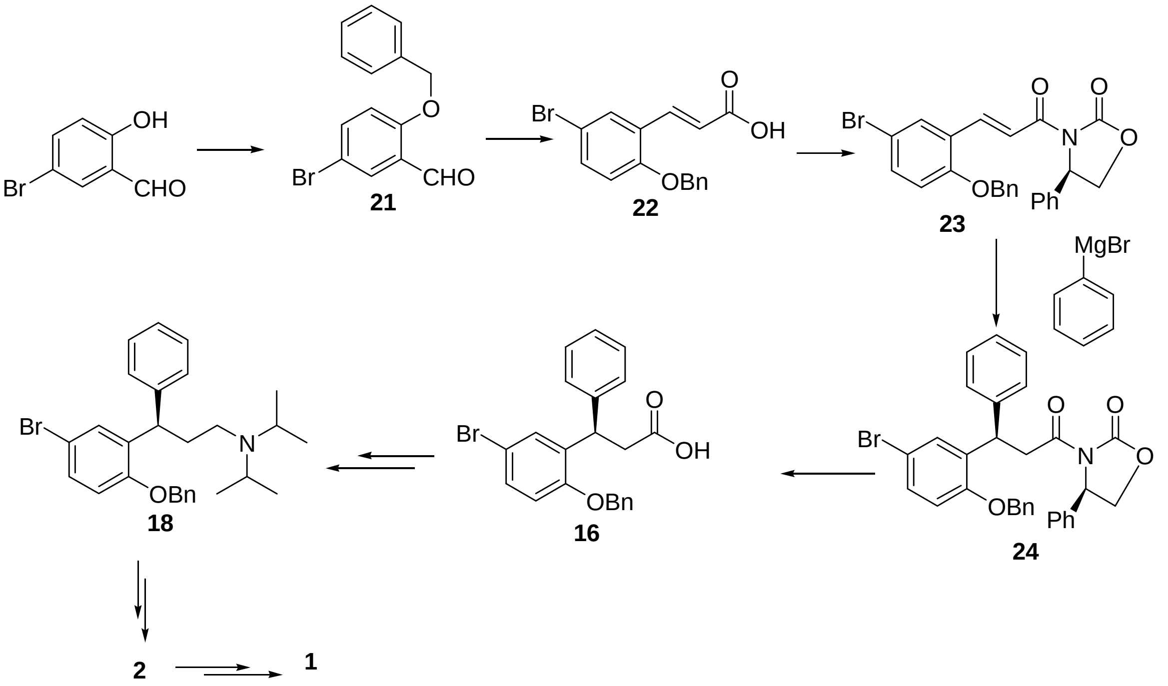
Meese and Sparf [5] from Schwarz pharma originally followed this process the 4-bromo phenol was reacted with cinnamoyl chloride in presence of TEA to give 3-phenyl acrylic acid-4-bromo phenyl ester (**13)** in 99% of yield. Which was reacted with AcOH and H_2SO_4 to give 6-bromo-4-phenyl,3,4-dihydro-coumarane -2-one (**14)**, which was further reacted with benzyl chloride in presence of K_2CO_3 to give methyl-3-(2-benzyloxy-5-bromo phenyl)-3-phenyl propionate (**15)**. Compound 15 was hydrolyzed with NaOH to give 3-(2-benzyloxy-5-bromo phenyl)-3-phenyl propionic acid (**16-dl)**. The dl acid 16 on resolution with 1S, 2R ephedrine hemi hydrate gave R-(-)3-(2-benzyloxy-5-bromo phenyl)-3-phenyl propionic acid (**16)**. Later **16** was converted to its acid chloride and was reacted with diisopropylamine to give (R)-N,N-diisopropyl-3-(2-benzyloxy-5-bromo phenyl)-3-phenyl propionamide (**17)**. Amide **17** was reacted with LAH to give R-N, N-diisopropyl-3-(2-benzyloxy-5-bromo phenyl)-3-phenyl propanamine (**18**). Further the bromo compound 18 was converted to acid 19 with ethyl magnesium



Scheme 6: Friedel-Craft alkylation of phenolic esters 13 to 14

bromide and CO_2 , the acid **19** was converted to ester, (R)-[4-benzyloxy -3-(3-diisopropylamino-1-phenylpropyl) benzoate and then it was reduced with LAH to give (R)-[4-benzyloxy -3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol (**20**). Finally **20** was debenzylated with Raney Ni to give (R)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy methyl phenol (**2**).

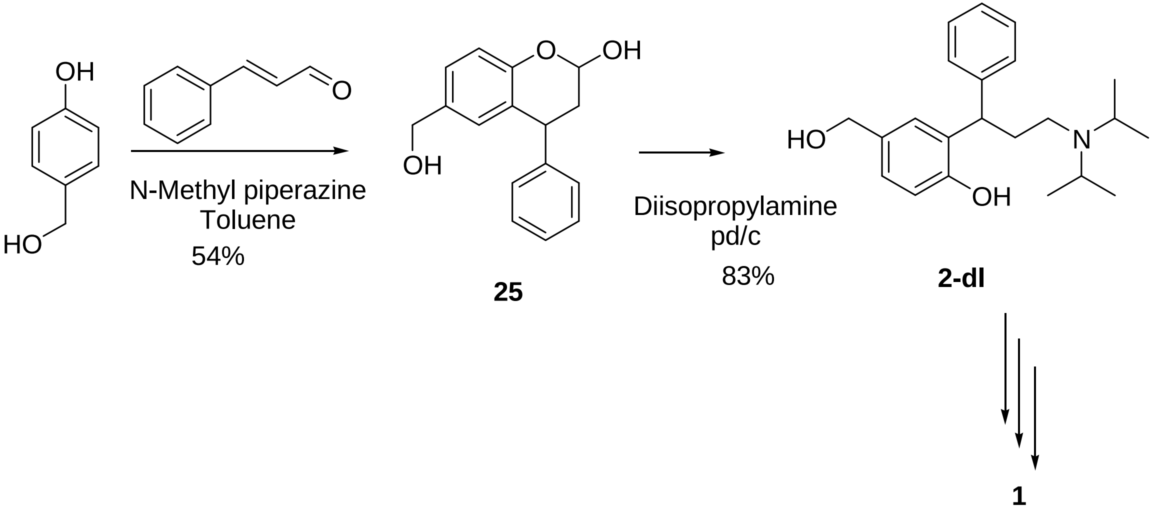
The same team [5] followed different strategy to prepare compound **2**. The 5-bromo-2-hydroxy-benzaldehyde was reacted with benzyl chloride to give 2-benzyloxy-5-bromo-benzaldehyde (**21)**. Further **21** was converted to cinnamic acid derivative 22 with malonic acid. The acid 24 was reacted with pivaloyl chloride and on condensation with (R)-2-phenyloxazolidin-2-one (chiral auxiliary) in presence of lithium chloride gave 3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one (**23)**. Further **23** was reacted with phenyl magnesium bromide in presence of dimethyl sulfide and copper(I) chloride gave 3-[-(2-benzyloxy-5-bromophenyl]-(3S)-3-phenyl propionyl]-(4R)-4-phenyloxazolidin-2-one (**24)**. Chiral auxiliary was cleaved with hydrogen peroxide and lithium hydroxide to give S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl propionic acid (**16)**. Further it was converted to S-(+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromo phenyl)-3-phenyl propionamide. And final the amide on reduction with LAH gave S-(+)-[3-(2-benzyloxy-5-bromo-phenyl)-3-phenyl]-diisopropyl amine (**18).** Compound **18** was converted **2** and then **1**.



Scheme 7: Preparation of Chiral 16 via chiral auxiliary (R)-2-phenyl oxazolidine-2-one

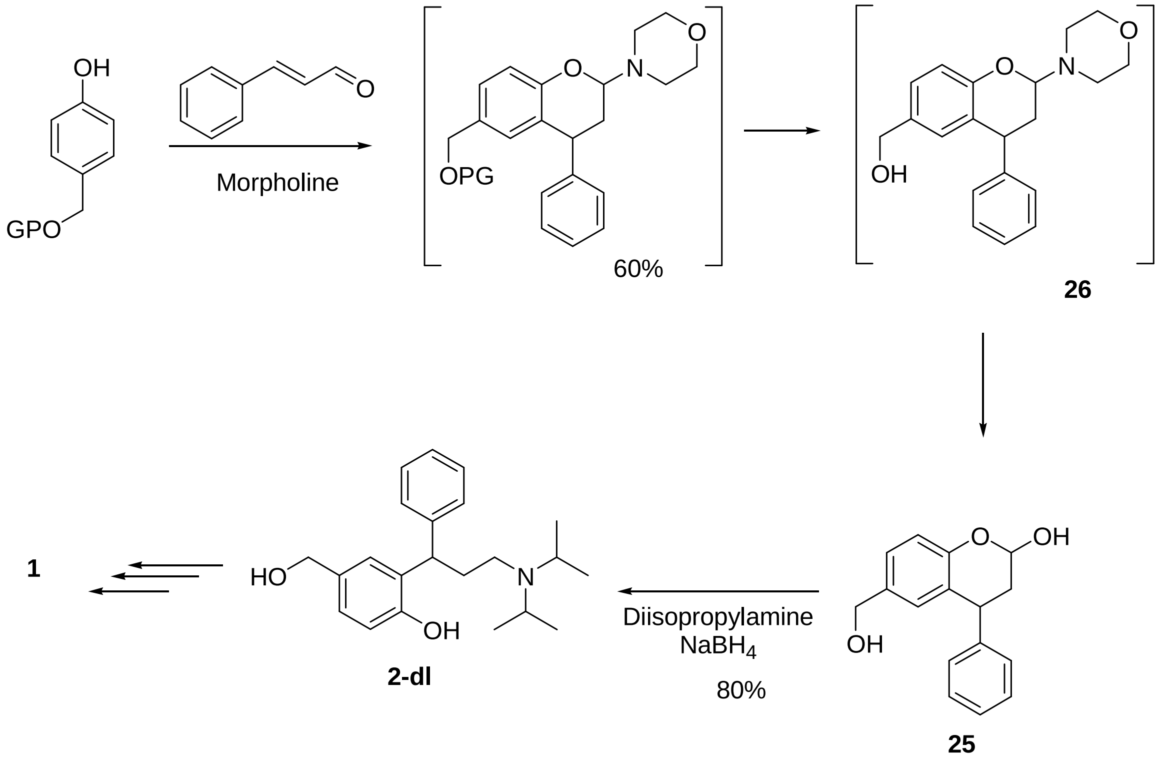
Synthesis approaches involving a reductive amination

Process chemists from Pfizer [6] reported a safe, practical and highly efficient approach to fesoterodine. The procedure for dl-2 involves only three synthetic steps with an overall yield of 44.8 %. They first studied the reaction of 4-(hydroxyl methyl) phenol with trans-Cinnamaldehyde in the presence of N-methylpiperrazine at 100-115°C. The water formed was removed by azeotropic distillation to give (2-hydroxy-4-phenyl-3,4-dihydro-2H-chromen-6-yl)methanol (**25)** in 54% yield. Further it was reacted with diisopropyl amine and hydrogen in presence of 5% Pd/C to give 2-[3-(diisopropylamino)-1-phenyl propyl]-4-(hydroxyl methyl) phenol (**2-dl)** in 83% of yield. **2-dl** was resolved with acetyl-d-mandelic acid to **2** and was converted to **1** in good yields.



Scheme 8: Benzylation of 4-hydroxy methyl phenol with cinnamaldehyde

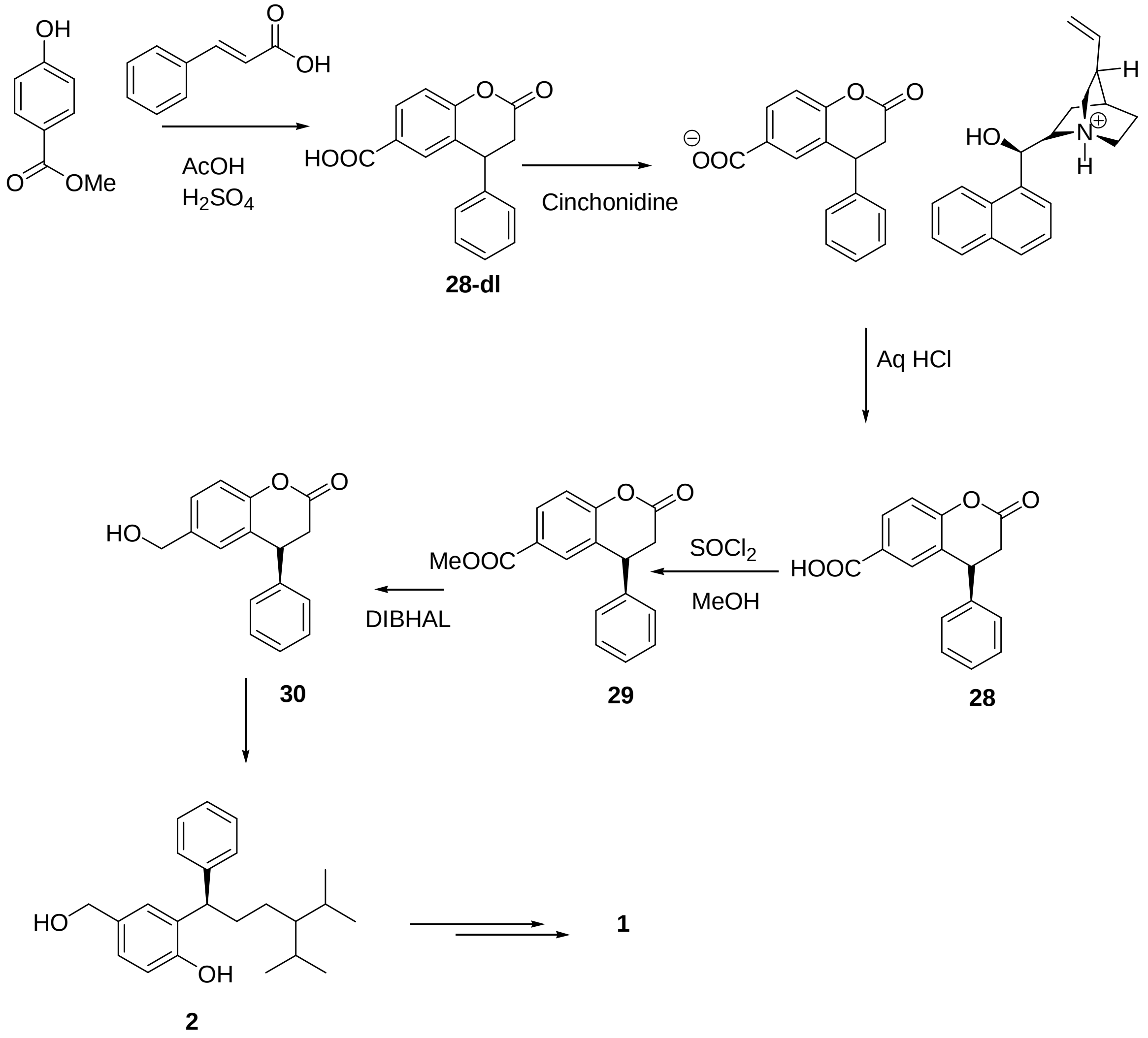
Cinambecchini [7] of Chemi group started with 4-trimethyl silyloxy methyl phenol and is reacted with cinnamaldehyde in presence of morpholine at 110-115° during azeotropic distillation gave (2-hydroxy-4-phenyl-3,4-dihydro-2H-chromen-6-yl) methanol (**26)** in 60%yield. Next it was reacted with diisopropylamine followed by reduction with sodium borohydride gave 2-[3-(diisopropylamino)-1-phenyl propyl]-4-(hydroxyl methyl) phenol (**2-dl)** in 80% yield.



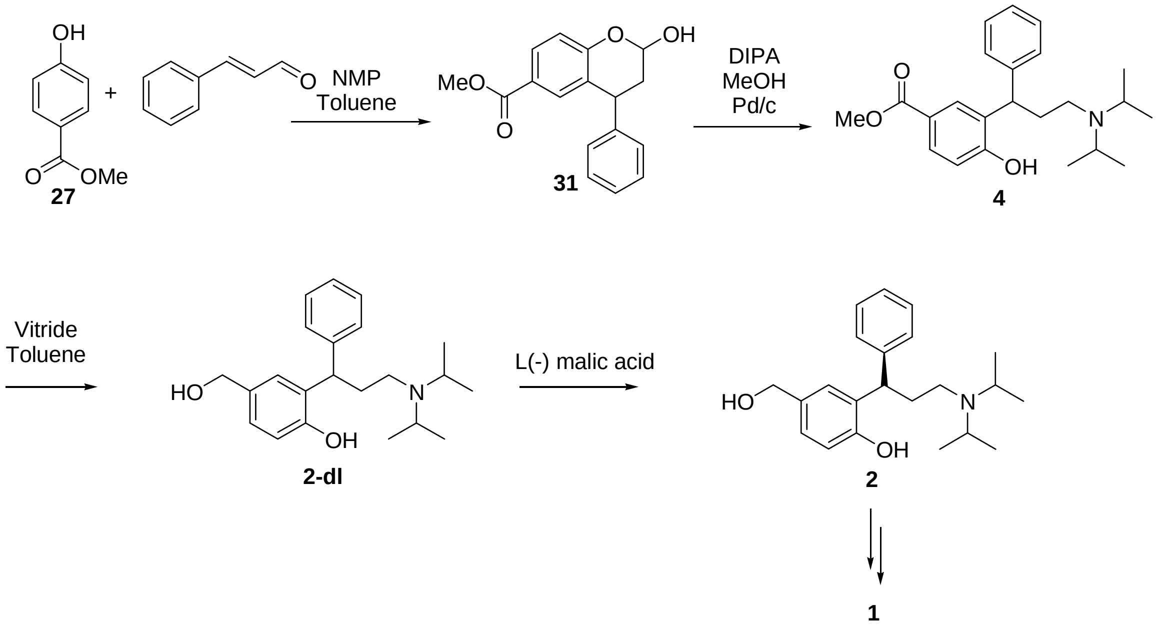
Scheme 9 : Benzylation of protected 4-hydroxy methyl phenol with cinnamaldehyde

Meese.C [8] of Schwarz pharma started with 4-Hydroxy methyl benzoate and reacted with cinnamic acid in presence of acetic acid and sulfuric acid at 100°C to give (R,S)-4-phenyl-2-chromanone-6-carboxylic acid (**28-dl)** in 78% yield. further it was resolved with cinchonidine in 2-butanone to give (R)-4-phenyl-2-chromanone-6-carboxylic acid cinchonidine salt in 90% of yield. Salt was reacted with aq HCl to give free chiral acid **28**, which was reacted with thionyl chloride and methanol in presence of pyridine to give (R)-2-oxo-4-phenyl chroman-6-carboxylic acid methyl ester (**29)** in 65%of yield. The ester **29** was reacted with DIBAL to give R-(6)-hydroxy methyl-4-phenyl chroman-2-(R,S)-ol (**30)** in 65% yield. Next **30** was reacted with diisopropylamine in presence of Pd/C under hydrogenation conditions to give (R)-4-hydroxy methyl-2-(3-diisopropylamino-1-phenyl propyl)-phenol **2**.

Rajesh [9] et al from panacea started with 4-Hydroxy methyl benzoate (**27**) and reacted with cinnamaldehyde in presence of N-methyl piperazine in toluene at 110-115°C during which the water formed in reaction was removed azeotropically to give methyl-2-hydroxy-4-phenyl chromane-6-carboxylic acid (**31)** in 75% yield. Further reaction with DIPA and 10% Pd/C in methanol under hydrogenation gave 3-(3-diisopropylamino-1-phenyl propyl)4-hydroxy benzoic acid methyl ester (**4)** in 72% of yield. Further **4** was reacted with vitride in toluene at 10°C to give 2-(3-diisopropylamino-1-phenyl propyl)-4-hydroxy methyl phenol (**2-dl).** Compound **2-dl** was resolved with L(-) malic acid to giver R (+) 2-(3-diisopropylamino-1-phenyl propyl)-4-hydroxy methyl phenol **2.**

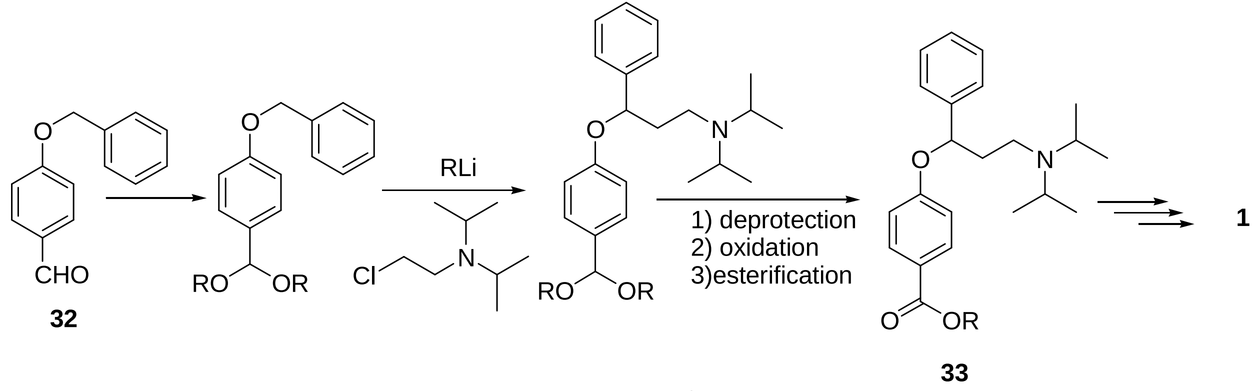


Scheme 10: Resolution of 28-dl with cinchonidine to 28



Scheme11: 4-hydroxy benzoic acid methyl ester alkylation with cinnamaldehyde

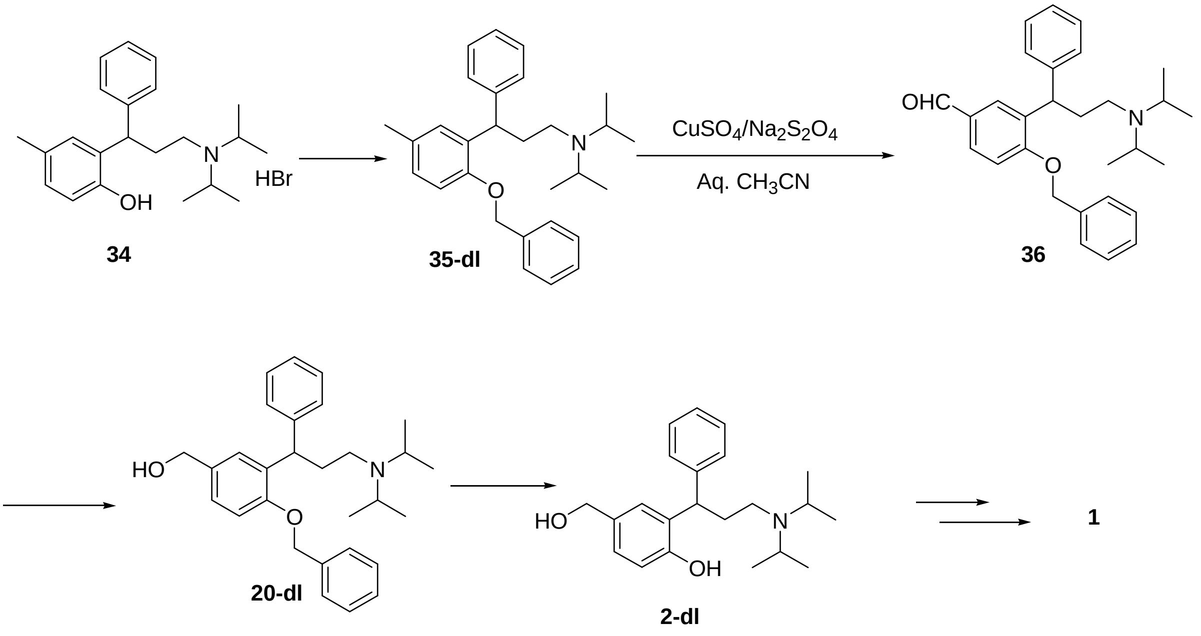
Reddy R.B.[10] et al started with 4-benzyloxy benzaldehyde (**32)** and protected the aldehyde and under alkyl lithium conditions it was phenylated, deprotected, oxidized and etherified to give **33-dl** and was resolved to get **33** chiral, which was converted **2** in a regular way.



Scheme 12: Phenylation of benzyl ethers

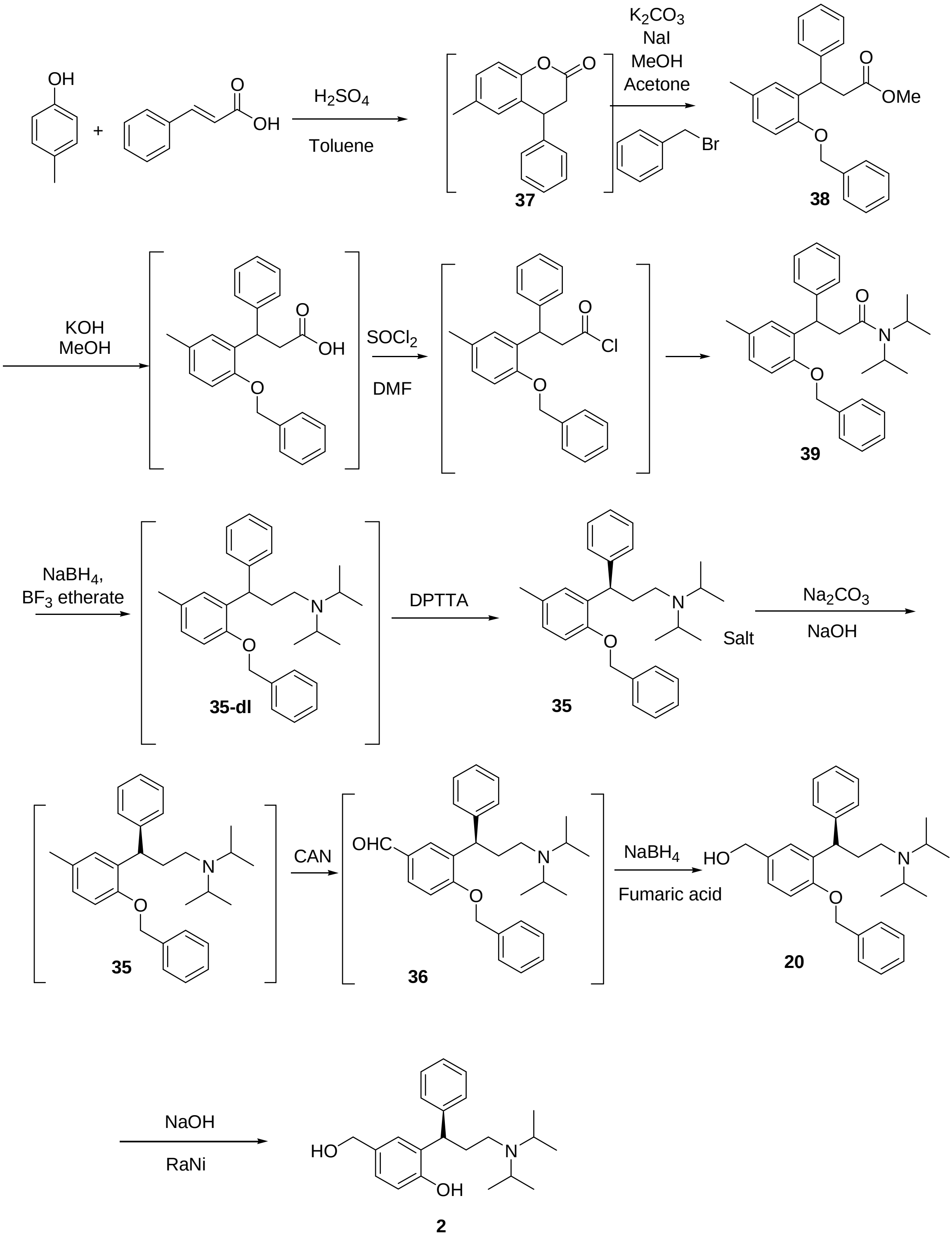
Synthetic approaches from tolterodine.

Kumar. Y [11] etal from ranbaxy (India) group started from dl-tolterodine **(34)** Phenolic group of tolterodine was protected with benzyl chloride to give 3-(2-bezyloxy-5-methyl-phenyl)3-phenyl-propyl)-diisopropylamine **(35-dl).** Further **35-dl** was reacted with copper sulfate and sodium persulfate in acetonitrile to give 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzaldehyde (**36**). Compound **36** on reduction with sodium borohydride gave [4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl] methanol (**20-dl**), compound **20-dl** on debenzylation with 10% Pd/C gave 2-(3-diisopropyl amino-1-phenyl-propyl)-4-hydroxy methyl –phenol (**2-dl**).



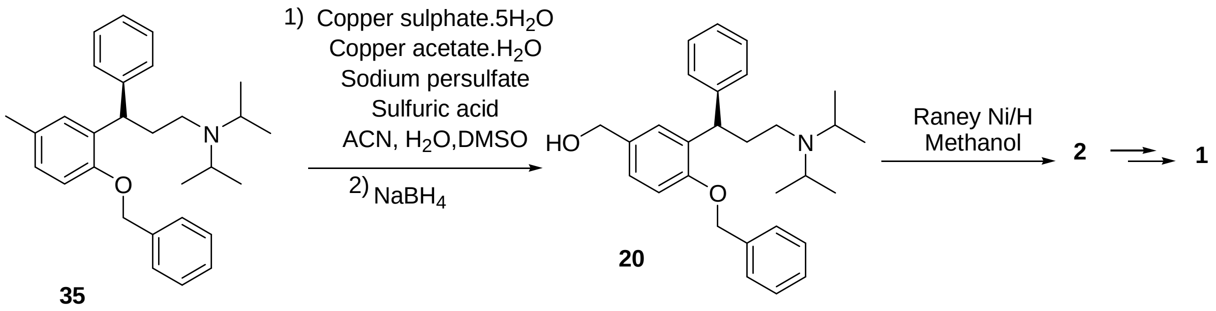
Scheme 13: Oxidation of 35-dl with sodium persulfate and copper sulfate to 36

Raman J.V [12] et al started from p-cresol and was reacted with cinnamic acid in acidic conditions to give 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-one (**37**). Further **37** was benzylated to give methyl-3-(2-benzyloxy-5-methyl-phenyl)-3-phenyl-propionate (**38**). Compound **38** was hydrolyzed with KOH to give 3-(2-Benzyloxy-5-methyl-phenyl)-3-phenyl-propionic acid, the acid was reacted with thionyl chloride and later with DIPA to give 3-(2-Benzyloxy-5-methyl-phenyl)-N,N-diisopropyl-3-phenyl-propionamide (**39**). Compound **39** was reduced with $NaBH_4$ and BF_3 etherate to give [3-(2-Benzyloxy-5-methyl-phenyl)-3-phenyl-propyl]-diisopropyl-amine (**35-dl).** compound **35-dl** on resolution with DPTTA gave R-[3-(2-Benzyloxy-5-methyl-phenyl)-3-phenyl-propyl]-diisopropyl-amine (**35**). The aromatic methyl group of chiral **35** was converted with ceric ammonium nitrate(CAN) to aldehyde **(36**), compound **36** was reduced with $NaBH_4$ to give R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl] methanol **(20)** and was debenzylated with raney Ni to give R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxy methyl phenol(**2**).



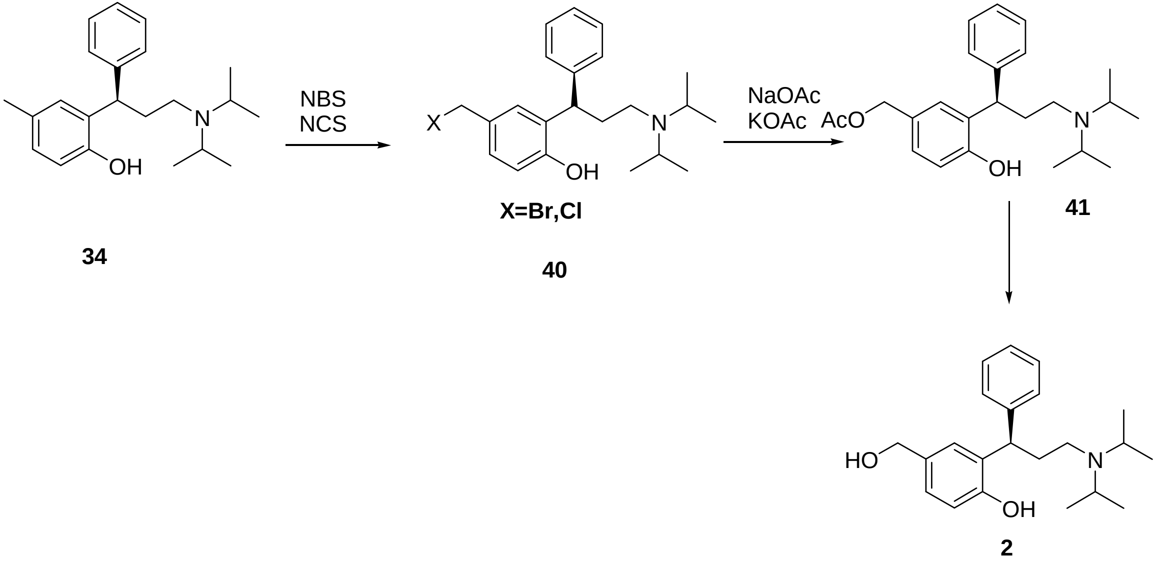
Scheme 14: Oxidation of 35 with ceric ammonium nitrate to 36

Raman, J. V [13] et al developed another oxidation method to convert the benzyl tolterodine **35** to **22** with copper sulphate, copper acetate and sodium persulfate in presence of sulfuric acid. **20** was reduced with sodium borohydride in 79% of yield, and was debenzylated with Raney Ni to give R-(+)-[4-hydroxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol(**2**).



Scheme 15: Oxidation of 35 with copper sulfate, copper acetate and sodium persulfate followed by reduction to 20

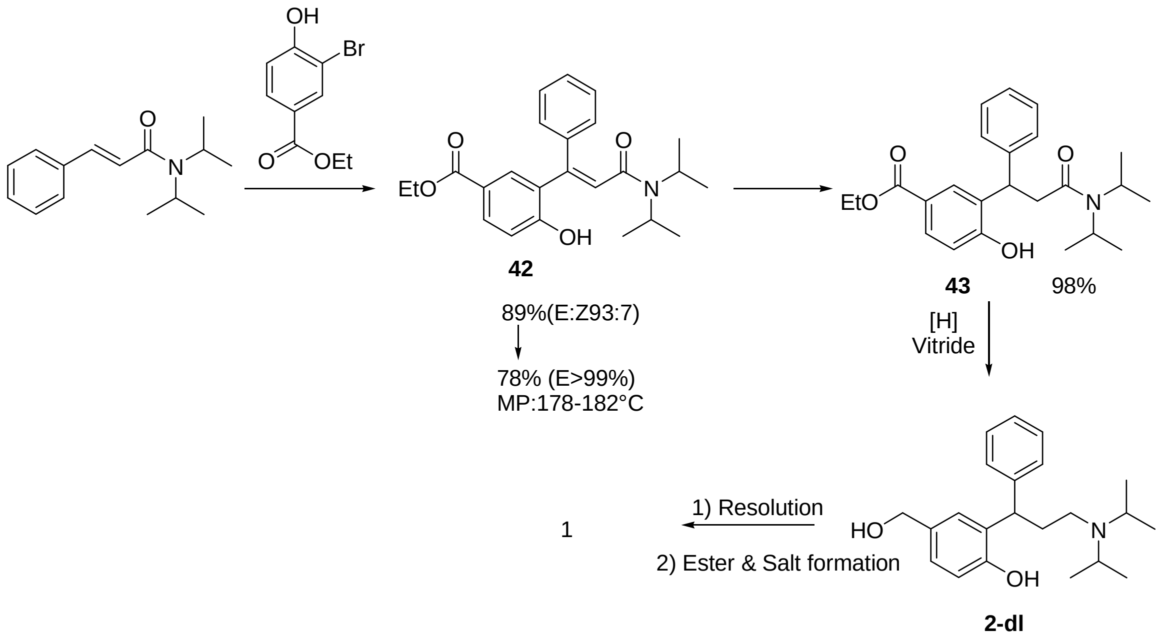
Reddy, M.S [14] et al converted tolterodine **34** to **2** via halogenation and nucleophilic substitution with acetate followed by hydrolysis. Tolterodine **(34)** was brominated with N-bromo succinimide to give (R)-4-(bromomethyl)-2-(-(diisopropylamino)-1-phenyl propyl) phenol (**40**). Further **40** was acetylated with sodium acetate in DMF to give (R)-3-(3-(diisopropylamino)-1-phenyl propyl)-4-hydroxy benzyl acetate (**41**). Compound **41** was hydrolyzed with lithium hydroxide in aq methanol to give compound **2.**



Scheme 16: Oxidation of 34 via halogenation of 34 and solvolysis of 40 to 41 and 2

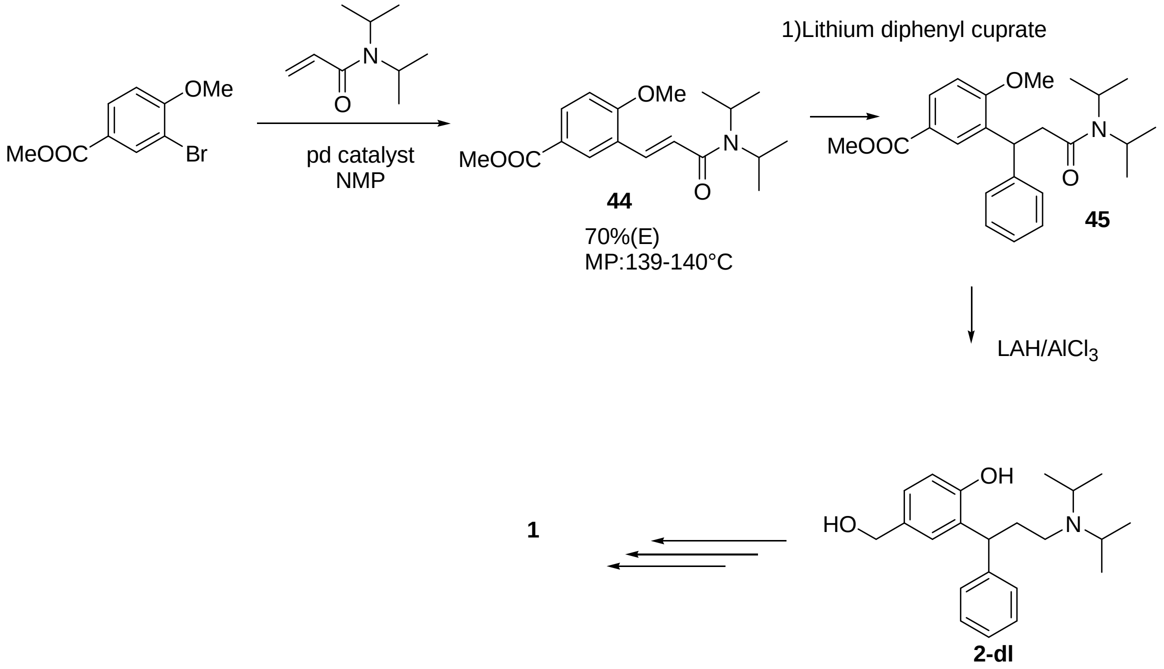
Process involving Heck reaction

Oreste. P [15] et al has disclosed a new method that involves the coupling of ethyl-3-bromo-4-hydroxy benzoate with N,N-Diisopropyl-cinnamide in presence of N,N-dicyclohexyl-methylamine and pd catalyst [Pd(pt-Bu$_3$)$_2$] to give 3-(3-N,N-diisopropyl amino)-3-oxo-1-phenyl prop-1-en-1-yl)-4-hydroxy benzoate (**42**). Compound **42** was hydrogenated in the presence of 5% pd/C and 2-Me-THF to give (R, S)-3-(3-N, N-diisopropylamino -3-oxo-1-phenyl propyl)-4-hydroxy benzoate **(43)** in 94% yield. Further reduction with vitride in toluene at 25-30°C gave a dl-2-(3-N, N-Diisopropyl amino-1-phenyl propyl)-4-hydroxy methyl-phenol.HCL (**2-dl**) in 76% yield. It was resolved and converted **1**.



Scheme 17: Heck of cinnamic derivative with 2-bromo phenol derivative to 42

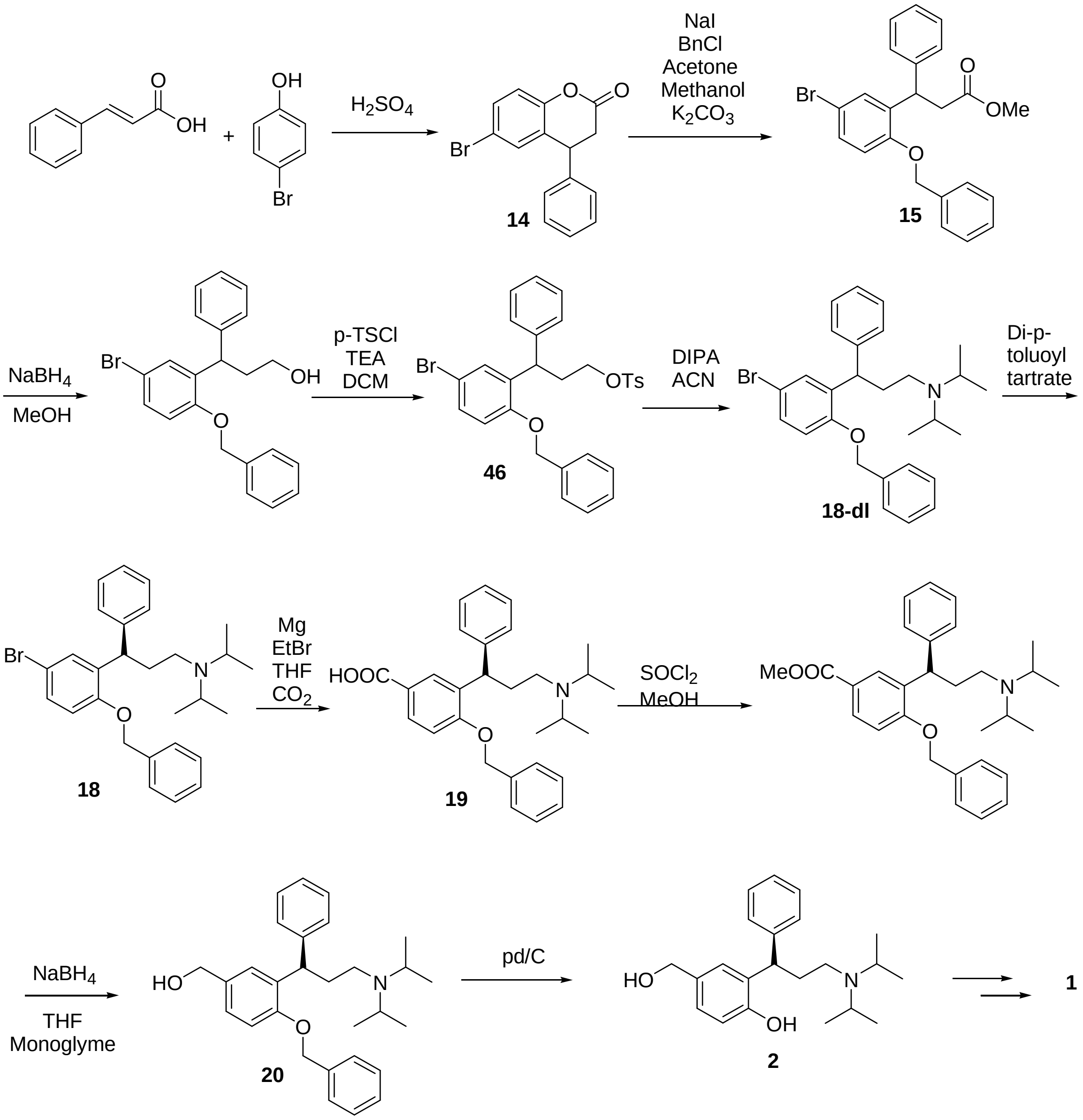
Mease. C and Sparf. B [5] described another heck reaction with N,N-Diisopropyl acrylamide and methyl-3-bromo-4-methoxy benzoate in presence of bis-(benzonitrile)-palladium-II-chloride and sodium acetate in N-methyl-2-pyrrolidinone to give N,N-diisopropyl-3-(2-methoxy-5-methoxycarboxyphenyl)acrylamide (**44**). Further **44** was reacted with lithium diphenyl cuprate in presence of trimethylchlorosilane to give N,N-diisopropyl-3-(2-methoxy-5-methoxy carboxy phenyl)-3-phenyl propionamide (**45**). Compound **45** was reduced with LAH and $AlCl_3$ to give 2-(3-diisopropylamino-1-phenyl)-4-hydroxy methyl phenol (**2-dl**), which is then resolved to give chiral **2**.



Scheme 18: Heck reaction of Acrylamide to bromoanisole derivative to 44

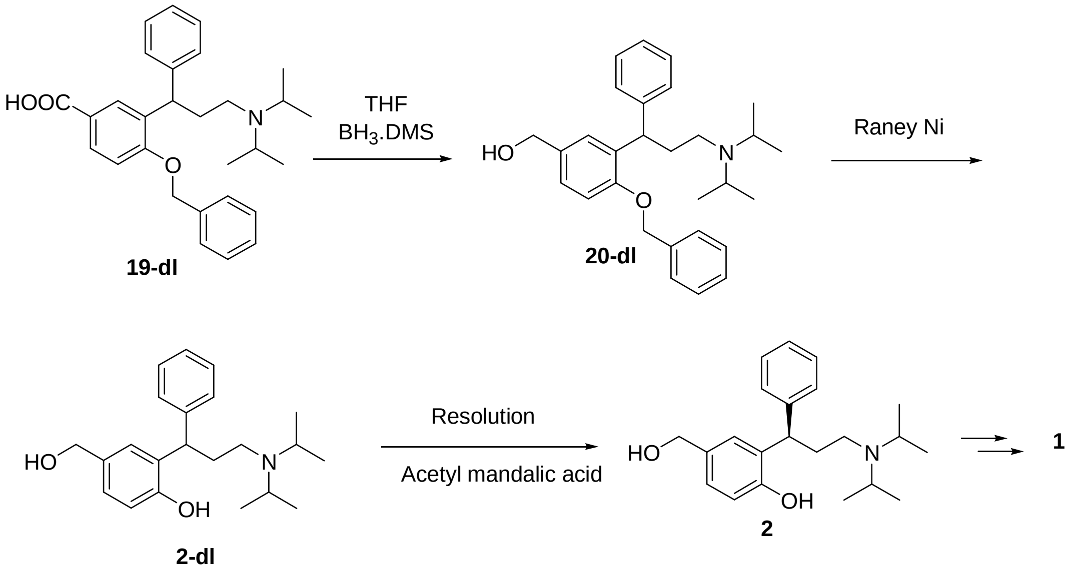
5 Synthesis approaches via chromanone derivative

Charugundla.K [16] et al started the synthesis from p-bromo phenol and reacted with cinnamic acid in presence of H_2SO_4 to give 6-bromo-4-phenyl chroman-2-one (**14**), which was reacted with benzyl chloride in presence of K_2CO_3 in acetone and methanol to give 3-(2-benzyloxy)-5-bromophenyl)-3-phenyl propionate (**15**). Compound **15** was reduced with $NaBH_4$ to give 3-(2-benzyloxy)-5-bromophenyl)-3-phenyl propan-1-ol, and the primary alcohol was converted to diisopropyl amine via tosylate to give benzyloxy amine (**18-dl**). Further **18-dl** was resolved with ptolyl –L-tartaric acid to give chiral 20. and 20 was reacted with Mg and CO_2 to give (R)-4-benzyloxy -3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride (**19**). Further **19** was converted to fesoterodine via a similar route of Meese[5] et al.



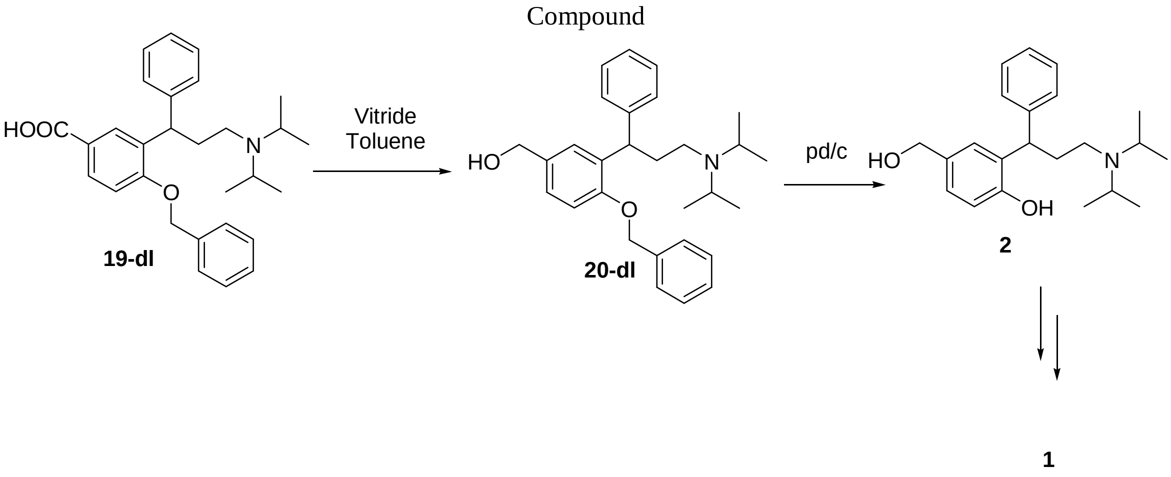
Scheme 19 : Alkylation of 4-bromo phenol with cinnamic acid to 14

Dasai, S. J [17] et al described the reduction of acid 21 with BH_3.DMS in THF to give N,N-diisopropyl-3-(2-benzyloxy-5-hydroxy methyl phenyl)-3-phenyl propylamine (**20-dl),** which on debenzylation with raney Ni to give N,N-Diisopropyl-3-(2-Hydroxy-5-hydroxy methyl phenyl)-3-phenyl propylamine **2-dl**. It was resolved and converted to drug.



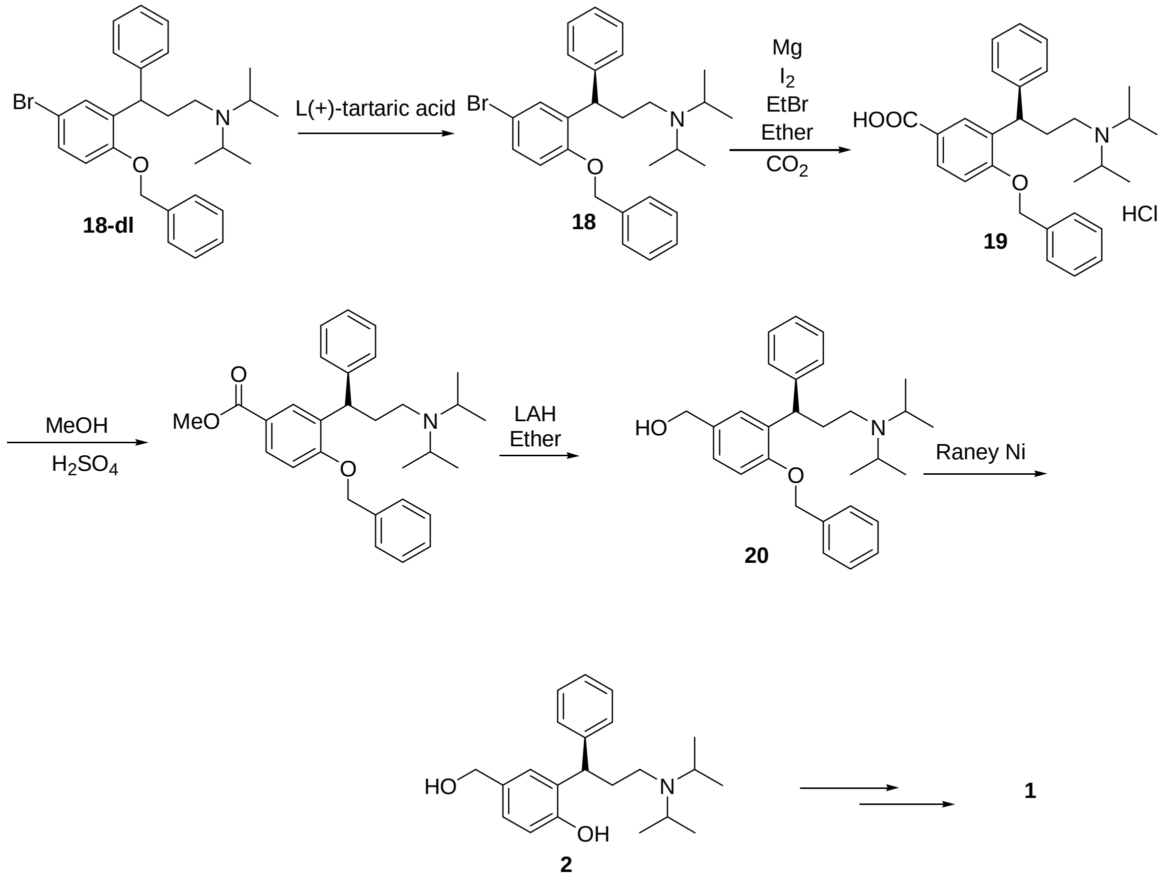
Scheme 20: Reduction of carboxyl derivative of 19-dl to 20-dl

Dwivedi, S. D. [18] et al reduced 19-dl with vitride in toluene to give (R)-[4-benzyloxy -3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol(20-dl). 20-dl on debenzylation with pd/c in methanol gave (R)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy methyl phenol (**2**).



Scheme 21 : Reduction of carboxyl group of 19-dl to give 20-dl with Vitride

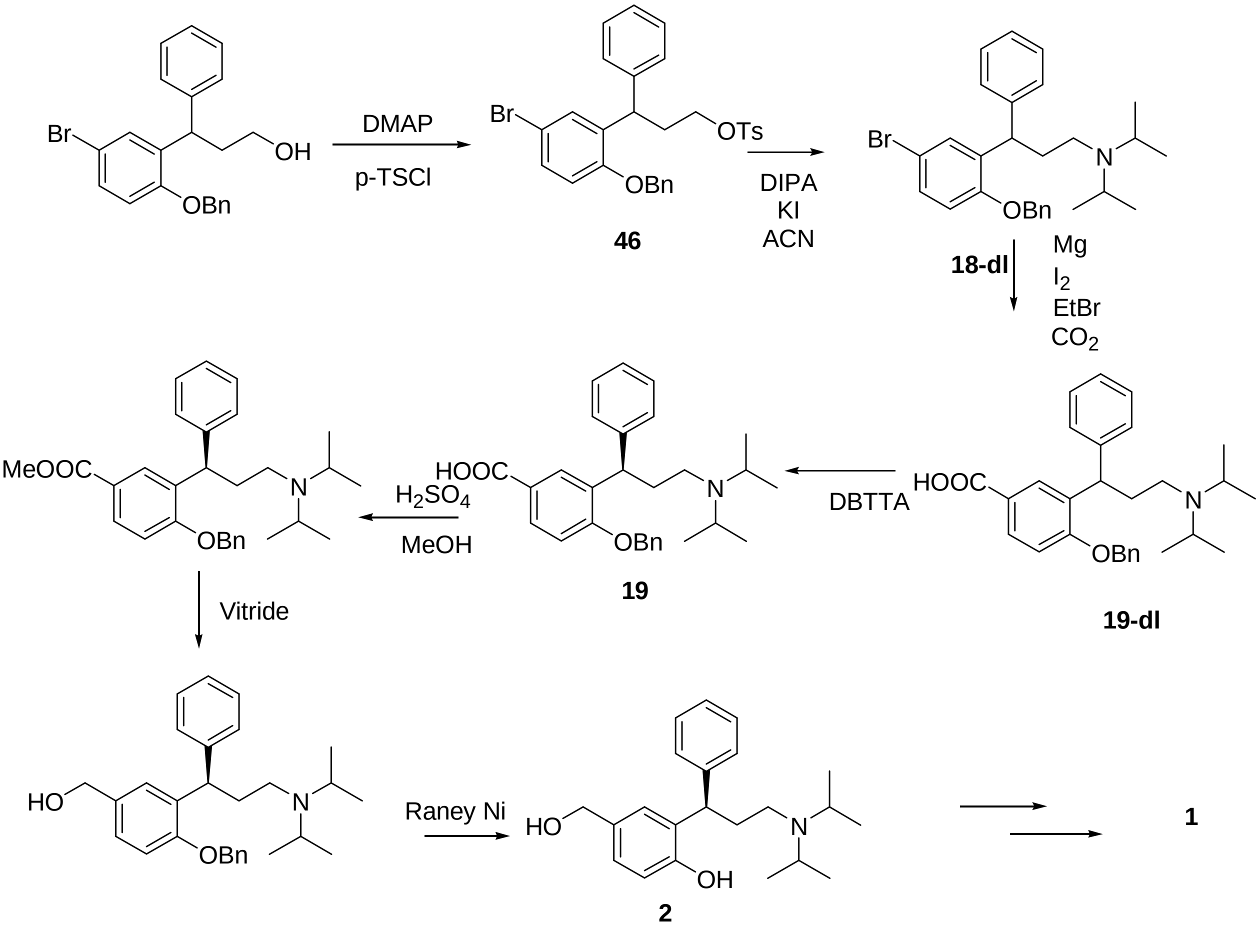
Johansson [19] et al resolved compound **18-dl** with L(+) tartaric acid to give (+)-N,N-diisopropyl-3(2-benzyloxy-5-bromophenyl)-3-phenyl propylamine (**18**). The chiral compound **18** was reacted with Mg and CO_2 in presence of ether and I_2 to give (-)N,N-Diisopropyl-3-(2-benzyloxy-5-carboxy phenyl)-3-phenyl propyl amine.HCl (**19**) in 77% of yield. Compound **19** was reacted with MeoH in presence of H_2SO_4 to give ester of **19,** which was reduced with LAH to give (+)-N,N-diisopropyl-3-(2-benzyloxy-5-hydroxy methyl phenyl)-3-phenyl propylamine (**20**). Finally debenzylation was done with Raney Ni to give compound **2**.



Scheme 22: Grignard reaction of 18-dl to give 19.

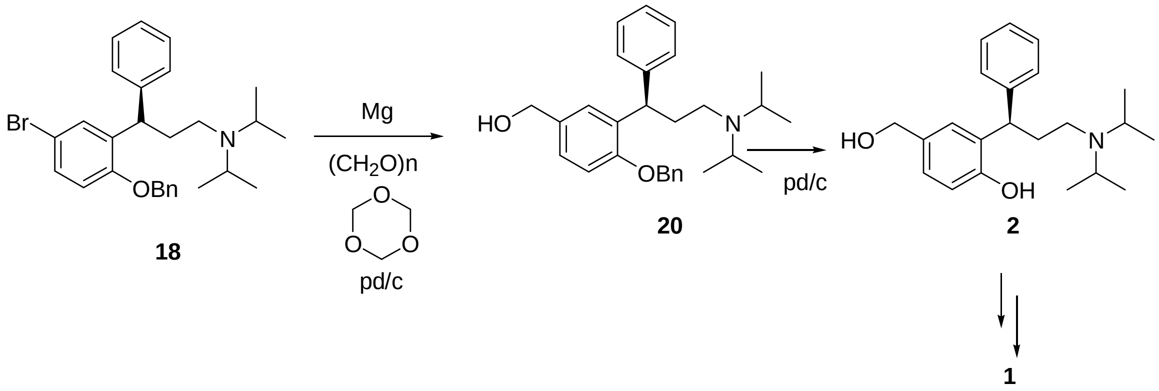
Synthetic approaches via Grignard reaction

Reddy, R.B [10] et al started from 3-(2-benzyloxy-5-bromo phenyl)-3-phenyl propane-1-ol and was converted it via its tosylate and reacted with diisopropyl amine to N,N-diispropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenyl propylamine (**46)**. further bromo derivative was converted to acid **19-dl** via Grignard reaction with solid CO_2. The acid was resolved with DBTA(dibenzoyl tartaric acid) to give (-)-N,N-diisopropyl-3-(2-benzyloxy-5-carboxy phenyl)-3-phenyl propylamine. DBTA. Which was converted to ester and was reduced with vitride to give (+) N,N-diispropyl-3-(2-benzyloxy-5-hydroxy-methyl phenyl)-3-phenyl propylamine, which was further debenzylated with raney nickel to give (+)-N,N-diispropyl-3-(2-hydroxy-5-hydroxymethyl phenyl)-3-phenyl propylamine **2**.



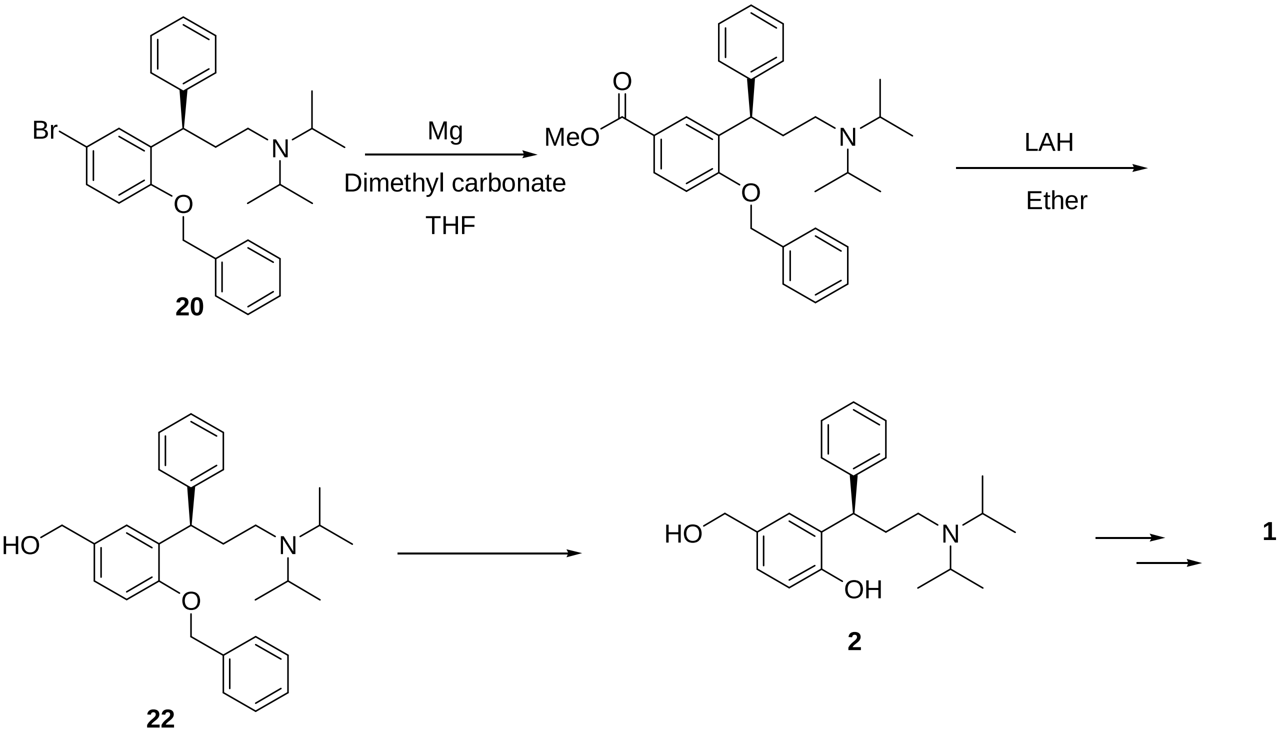
Scheme 23 : Resolutioon of 19-dl to 19 with DBTA

Ennirs, C.S [20] et al from Schwarz converted R-(-)-[3-(2-benzyloxy-5-bromo phenyl)-3-phenyl propyl]-diispropyl amine (18**)** with magnesium ethyl bromide and paraformaldehyde to R-(-)-4-benzyloxy-3-(3-diispropyl amio-1-phenyl propyl)-phenol methanol (**20)**. Compound **20** was debenzylated in presence of Pd/C to give (+)-N,N-diispropyl-3-(2-hydroxy-5-hydroxymethyl phenyl)-3-phenyl propylamine (**2**)



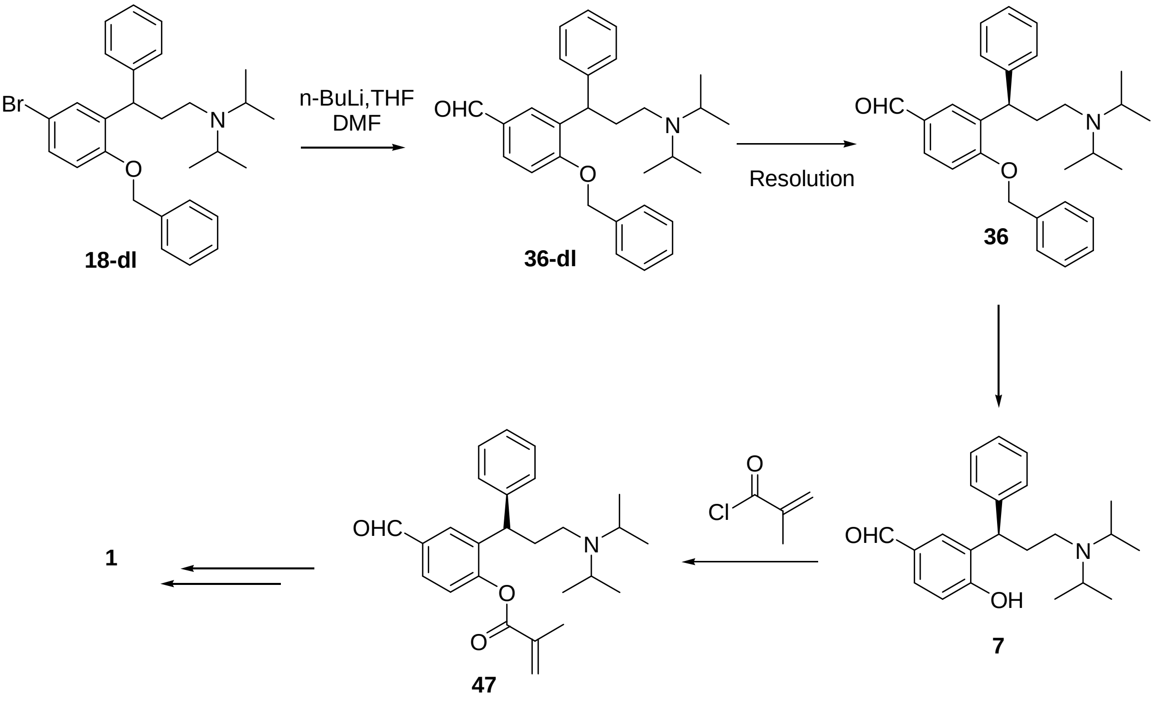
Scheme 24: Formylation of 18 with para formaldehyde to 20

Browne.R and Kilkellt, M [21] reacted (+)-N,N-Diisopropyl-3-(2-benzyloxy-5- bromo phenyl)-3-phenyl propyl amine (**28)** with Mg in presence of dimethyl carbonate in THF to give R-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl propyl)-benzoic acid methyl ester. Further the ester was reduced with LAH to give (+)-N,N-diisopropyl-3-(2-benzyloxy-5-hydroxy-methyl phenyl)-3-phenyl propylamine (**20)** in 99% of yield, which was debenzylated with Raney Ni to give **2**.



Scheme 25 : Quenching of Grignard of 18 with dimethyl carbonate followed by reduction to 20

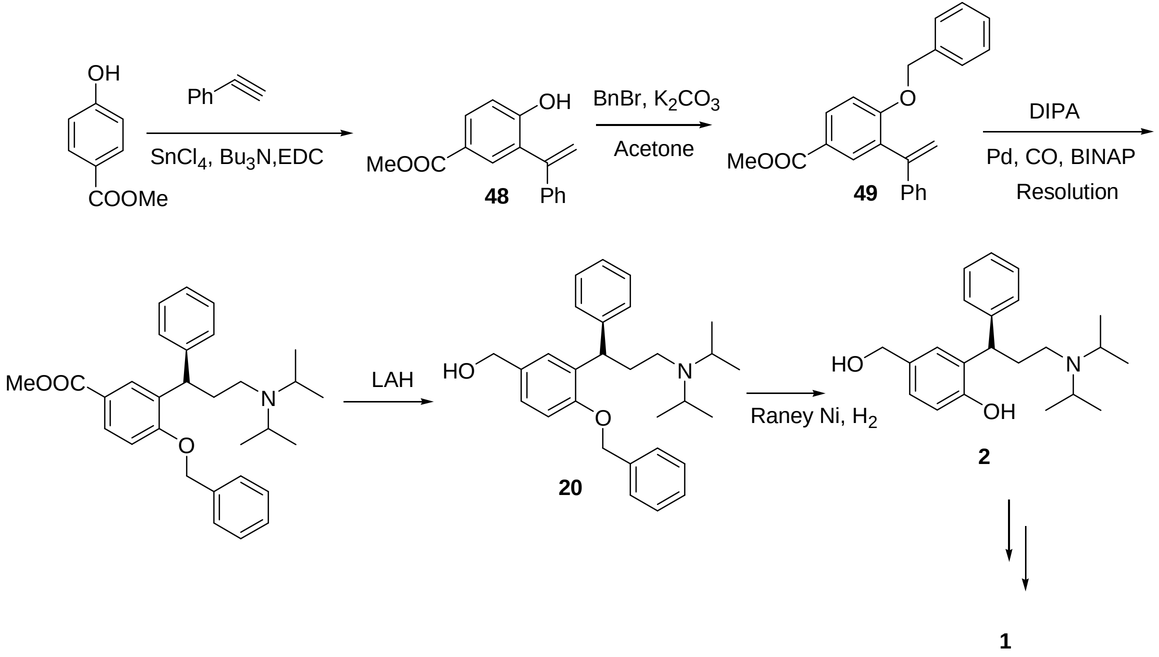
Manne, S.R [14] et al reacted the bromo compound **18-dl** with DMF in presence of n-Butyl lithium to give 4-(benzyloxy)-3-(3-(diisopropyl amino)-1-phenyl propyl) benzaldehyde **36-dl**. Further it was resolved with D-(-) tartaric acid in IPA to give R-4-(benzyloxy) - 3 - (3- (diisopropyl amino)-1-phenyl propyl) benzaldehyde **36**. The debenzylation of **36** with 5% Pd/C to give (R)-N,N-diisopropyl-3-(5-formyl-2-hydroxy phenyl)-3-phentl propanamine (**7)**. Compound **7** was reacted with methacryloyl chloride to give R-2-(3-diisopropyl amino-1-phenyl propyl)-4-formyl phenyl methacrylate (**47)**. Compound **47** was converted to **1**.



Scheme 26: Formylation 18-dl with BuLi and DMF to 36-dl

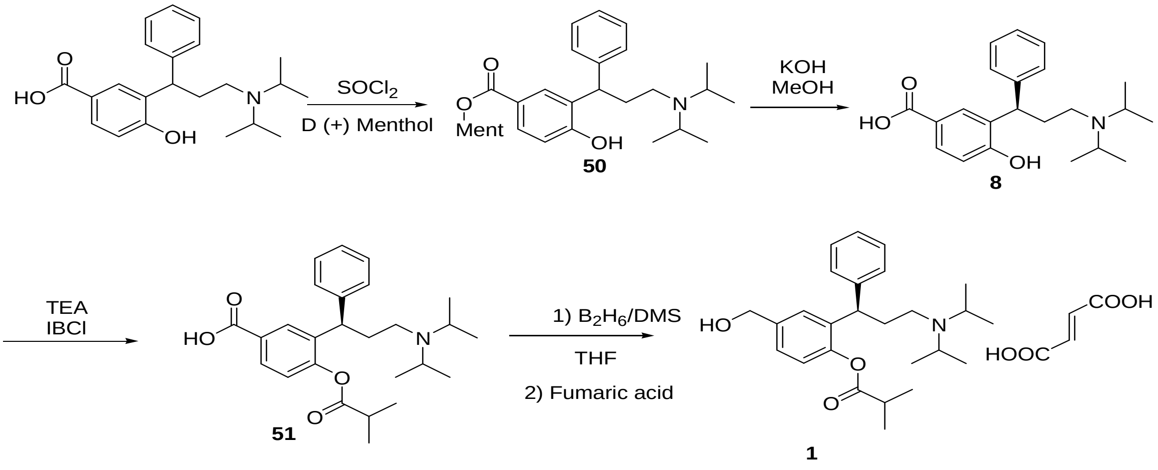
Miscellaneous Synthetic approaches

Donsbach. M [22] et al reacted p-hydroxy methyl benzoate with phenyl acetylene in presence of $SnCl_4$ and tributylamine to give 4-hydroxy-3-(1-phenyl vinyl)-methyl benzoate (**48**). Further **48** was reacted with benzylbromide in presence of K_2CO_3 to give 4-benzyloxy-3-(1-phenyl vinyl)-methyl benzoate (**49).** Compound **49** was reacted with diisopropyl amine in presence of Pd catalyst and BINAP and CO in dioxane to give 4-benzyloxy-3-(3-diispropylamine-1-phenyl-propyl)-methyl benzoate. The ester was reduced with LAH in presence of ether to give (+)-N,N-diisopropyl-3-(2-benzyloxy-5-hydroxy methyl phenyl)-3-phenyl propylamine (**20**). Finally debenzylation with Raney Ni in presence of MeOH to give (+)N,N-Diisopropyl-3-(2-Hydroxy-5-hydroxy methyl phenyl)-3-phenyl propylamine (**2**).



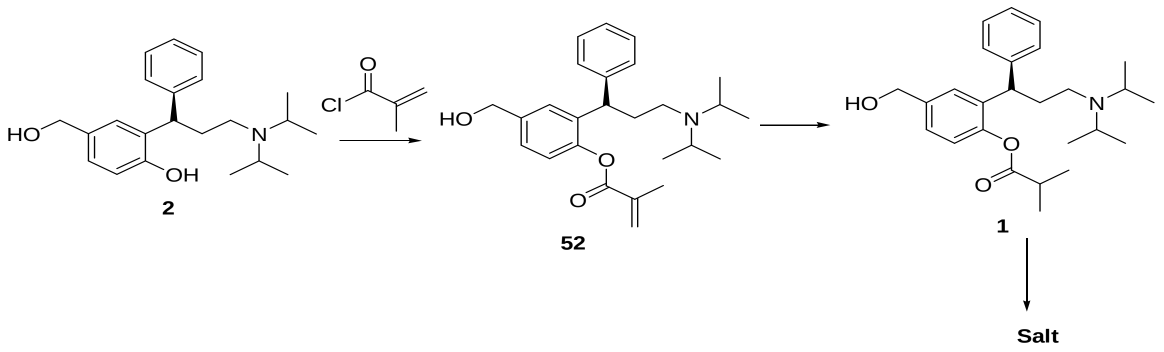
Scheme 27: Methyl-4-hydroxy benzoate reaction with phenyl acetylene to 48

Crystal pharma [23] team resolved 3-(3-N,N-diisopropylamino-1-phenyl-propyl)-4-hydroxy benzoic acid with chiral auxiliary D(+) menthol in presence of thionyl chloride to give D-(+)-methyl-3-(3-N,N-diisopropylamino-1(R)-phenyl-propyl)-4-hydroxy benzoate.HCl (**50**), which was hydrolyzed with KOH to give R(+)3-(3-N,N-diisopropylamino-1-phenyl-propyl)-4-hydroxy benzoic acid (**8**). Further it was reacted with isobutyryl chloride to give R (+)3-(3-N,N-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxy benzoic acid (**51).** Compound **51** was reacted with B_2H_6/DMS in THF to give Fesoterodine (**1**).



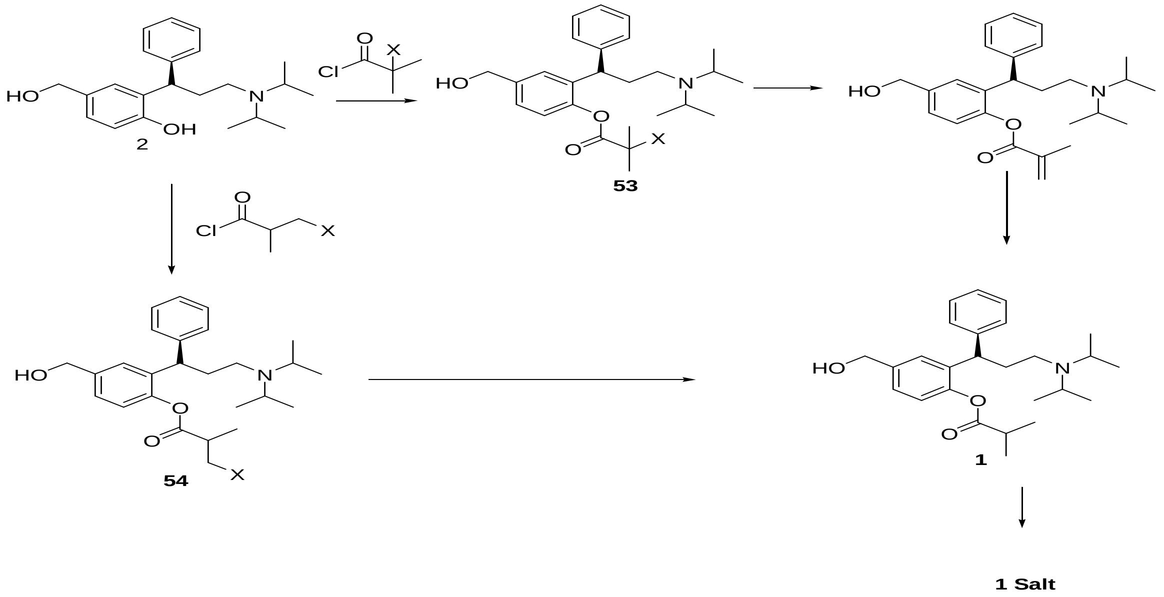
Scheme 28: Reduction with borane DMS of 51 to 1

Manne S.R [14] et al reacted compound **2** with methacryloyl chloride in chloroform to give (R)-2-(3-(diisopropylamino)-1-phenyl propyl)-4(hydroxyl methyl)- phenyl methacrylate (**52**). Further **52** was reacted with Pd/C to give isobutyric acid-2((R)-3-diisopropylammonium-1-phenyl propyl)-4-(hydroxyl methyl) phenyl ester (**1**).



Scheme 29: Reduction 50 with Pd-C/hydrogenation to 1

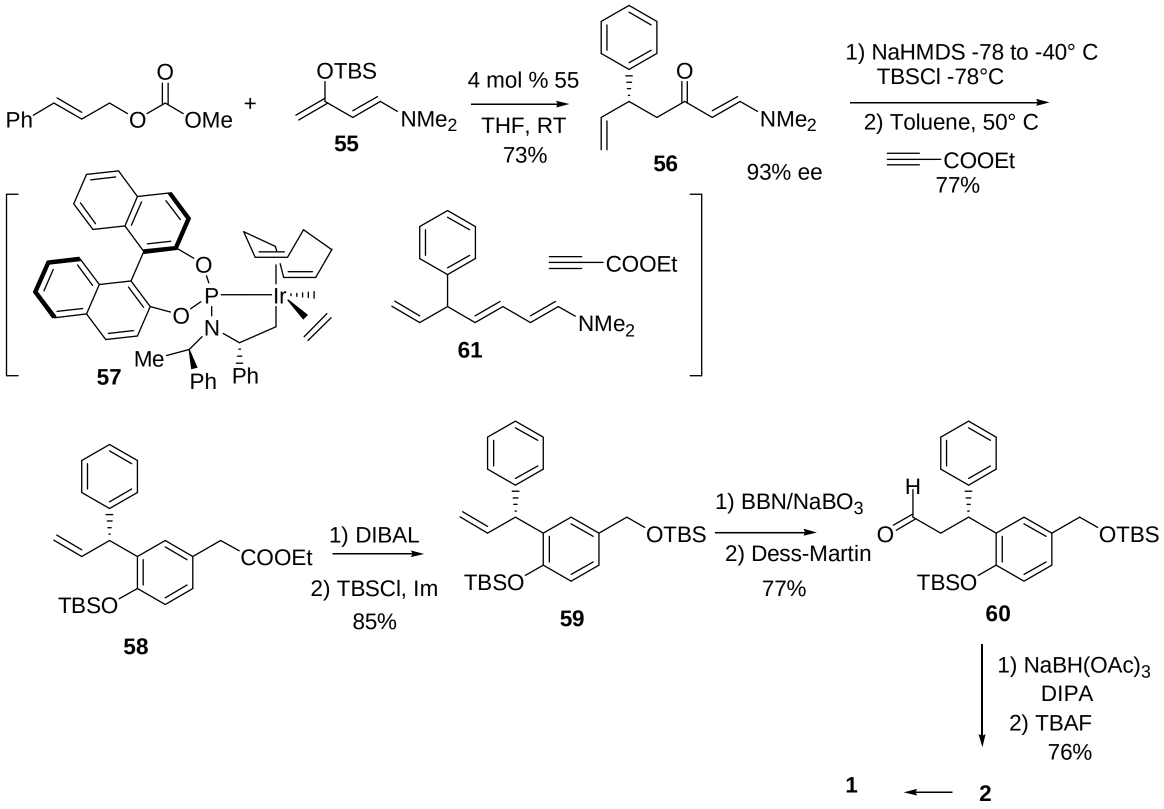
The same team reported the synthesis of fesoterodine **1**, from **2**, by reacting **2** with 2-bromo-2-methyl propanoyl chloride or 3-bromo-2-methyl propanoyl chloride in



Scheme 30: Dehydrohalogenation of 53/54 with Pd/C to 1

presence of sodium bicarbonate to give 2-((R)-3-(diisopropylamino)-1-phenyl propyl)-4-(hydroxymethyl) phenyl-2 or 3 bromo-2-methyl propanoate (**53/54)**. Further **53/54** was reacted with sodium acetate in presence 10% Pd/C under hydrogenation conditions gave isobutyric acid-2((R)-3-diisopropylammonium-1-phenyl propyl)-4-(hydroxyl methyl) phenyl ester (**1)**.

Hartwig and Chen [24] reported a novel method of fesoterodine via Iridium-catalysed enantio slective allylic substitution of enolsilanes **55** on vinologous. ester/amides Compound **56** was converted to into diene **61** with NaHMDS and TBSCl [25]. [4+2] cycloaddition of diene **61** and ethyl propiolate at 50°C in toluene provided 1,1 diarylalkene **58** in 77% yield. DIBAl reduction of the ethyl ester of **58** gave alcohol and on protection with TBSCl gave bis-TBS ether **59** in 85% yield. Hydroboration and oxidation of **59,** followed by Dess-martin oxidation of the resulting primary alcohol afforded aldehyde **60** in 77% yield. Reductive amination of aldehyde **60** with diisopropylamine and $NaBH(OAc)_3$, followed by deprotection of the two TBS groups with TBAF provided compound **2** in 76% yield.



Scheme 31: Enantioselective synthesis of fesoterodine

CONCLUSION

In this review, we have compiled an overview of the different approaches towards the synthesis of fesoterodine. Except few syntheses, most of the syntheses pass through 5-hydroxy methyl tolterodine. Although significant chemistry has been developed for fesoterodine, three main strategies have been tried by different groups. First one being oxidative method from tolterodine, second one is grignard method of halocompounds for introduction of hydroxyl methyl group(-CH2OH from Br), and the third and important one is starting from cinnamyl derivative. Commercially the cinnamaldehyde route was reported to have good yields.

The other methods are more of academic interest for example Heck reaction and palladium/CO reaction. The present review explains how generic manufacturers search for non-infringing, novel approaches to an API of interest. Hopefully more novel and imaginative ideas will provide new approaches to this drug in the coming years.

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