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The Lactol Route to Fesoterodine: An Amine-Promoted Friedel–Crafts Alkylation on Commercial Scale

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ABSTRACT: We report the discovery and optimization of an amine-promoted Friedel–Crafts alkylation of cinnamaldehyde with 4-hydroxymethyl phenol. This reaction has been used successfully on commercial scale (200 kg) in the context of the manufacture of fesoterodine, a muscarinic antagonist used for the treatment of overactive bladder. Reductive aminations of diisopropylamine and lactol **4** are also discussed, as well as the resolution of the racemic amine ***rac*-2** into its enantiomerically pure form.

INTRODUCTION

Fesoterodine **1** is a muscarinic antagonist used for the treatment of overactive bladder[1] and is commercialized under the name Toviaz. Fesoterodine is a pro-drug of 5-hydroxymethyl tolterodine **2**, which is the active metabolite of tolterodine **3**, a muscarinic antagonist commercialized under the name Detrol (Figure 1). Despite the close structural resemblance, fesoterodine has been shown to display superior efficacy and tolerability over tolterodine.[2]

The existing process for the commercial manufacture of fesoterodine was linear (11 steps) and utilized difficult to handle reagents (e.g., $LiAlH_4$) on commercial production scale.[3] For these reasons, a more efficient and plant-friendly process was sought.

RESULTS AND DISCUSSION

All previous synthetic approaches to fesoterodine involved multiple chemical transformations in order to install the hydroxymethyl functionality (use of protecting groups, redox chemistry, or functional group manipulations). These long synthetic routes were designed because the hydroxymethyl group is unusually prone to dehydration to form quinone methide **20** due to a synergistic effect of the phenol substituent in the para-position.[4] The resulting activated electrophile readily reacts with a wide range of nucleophiles to form impurities. As we aimed to achieve a more concise synthesis of fesoterodine, we focused our efforts on approaches avoiding the use of protecting groups, redox chemistry, or functional group manipulations. In order to achieve this goal, the hydroxymethyl group needs to be present from the start of the synthesis in the unprotected form, thus limiting the types of reaction conditions compatible with this reactive group (e.g., avoid the use of Brønsted or Lewis acids). Accordingly, we envisioned that fesoterodine could be prepared from the advanced intermediate **2**, common with the existing process. Intermediate **2** would be prepared from lactol **4** *via* reductive amination. Finally, we envisioned that the most direct and atom economical way to synthesize **4** would be *via* a

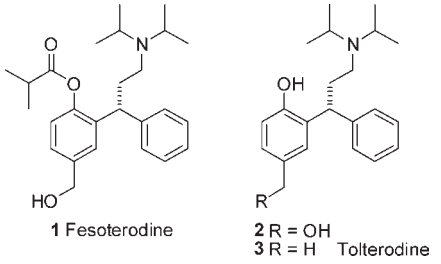

Figure 1. Structure of fesoterodine and tolterodine.

Friedel–Crafts alkylation of cinnamaldehyde **6** with the unprotected phenol **5** (Figure 2).

Amine-Catalyzed Friedel–Crafts Alkylation. Due to the facile dehydration of **5**, Lewis or Brønsted acids could not be used to activate **6** towards Friedel–Crafts alkylation with **5**, so we turned our attention to alternative ways to facilitate the reaction. We were encouraged by recent reports of iminium activation of α,β-unsaturated ketones and aldehydes towards enantioselective Friedel–Crafts alkylation reactions with electon-rich arenes.[5] Accordingly, we tested up to stoichiometric amounts of commercially available proline- and imidazolidinone- based chiral organocatalysts but failed to observe any desired product even under refluxing THF conditions. We reasoned that this was probably due to the lack of reactivity of **5**, and the steric hindrance of the chiral amines used. Achiral aminocatalysis was pioneered by Knoevenagel in 1896 and has since been mostly used for aldol reactions.[6] Although we were unaware of examples of amine-catalyzed Friedel–Crafts alkylations, we wondered whether this approach (Scheme 1) could be useful for the synthesis of fesoterodine.

We were delighted to observe good to excellent yields with stoichiometric amounts of a range of cyclic secondary amines when cinnamaldehyde **6** and phenol **5** were heated to reflux in

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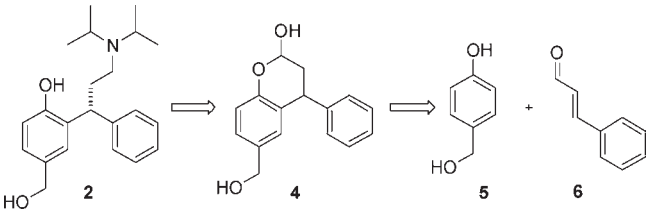


Figure 2. Retrosynthetic analysis of fesoterodine.

Scheme 1. Amino-Catalyzed Friedel−Crafts Alkylation

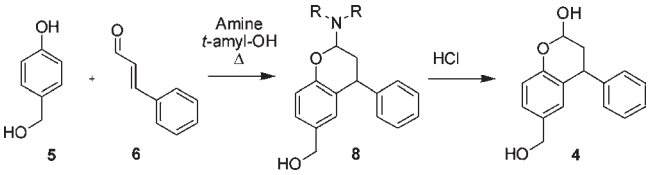


Table 1. Amine Screen for Fridel−Crafts Alkylation in Refluxing *tert*-Amyl Alcohol

Entry	Amine	Yield[a]
1	Diisopropylamine	0%[b]
2	Dibenzylamine	10%[c]
3	Di-*n*-butylamine	34%[c]
4	Piperidine	73%
5	Piperazine	69%
6	Morpholine	55%
7	*N*-methyl piperazine	80%
8	*N*-acetyl piperazine	36%[d]
9	Thiopiperazine	53%
10	*N*-isopropyl piperazine	20%[c]

[a] Yield determined by quantitative HPLC after hydrolysis. [b] No conversion observed. [c] Low conversion. [d] Multiple products observed.

tert-amyl alcohol (Table 1). Substoichiometric amounts of amine led to stalling of the reaction in direct proportion with the amount of amine used. The reaction did not proceed to any significant extent at temperatures below 80 °C, and the preferred solvents were found to be toluene, *tert*-amyl alcohol, and chlorobenzene. Results from Table 1 show that this reaction is quite sensitive to both electronic and steric factors on the amine. Acyclic amines (entries 1−3) provided no or low conversions. We were particularly interested in diisopropylamine, since if this transformation had worked, reduction of the resultant aminal would have yielded directly ***rac*-2** without the need to perform a separate reductive amination. Unfortunately this amine is too hindered to be an effective promoter and no conversion was observed. Cyclic amines (entries 4−10) showed the best conversions, with *N*-methyl piperazine (entry 7) and piperidine (entry 4) being the most efficient. Due to the presence of the unprotected phenol, the amine is incorporated in the aminal intermediate **8** hence requiring the use of at least 1 equiv of amine. Further optimization revealed that a 2:1 ratio of amine to cinnamaldehyde provided higher yields. The probable explanation of this fact was found when the reaction was performed in deuterated toluene and followed by ^{1}H NMR as it revealed the immediate formation of a 2:1 adduct **9**, which then slowly converted to the desired aminal **8** over the course of 3 h (Scheme 2). The formation of this 2:1 adduct may prevent cinnamaldehyde from degrading under the reaction conditions hence explaining the optimal results obtained with this stoichiometry. The formation of this adduct also generates water, which can react with the iminium species **10** to provide β-hydroxyaldehyde **11**. This side product is not stable under the reaction conditions and undergoes a retro-aldol reaction to produce benzaldehyde **12** (observed) and presumably acetaldehyde. About 20 mol % of benzaldehyde **12** was typically generated during the reaction, but this undesired pathway can be almost completely suppressed by the use of Dean−Stark conditions to remove water as it is generated.

The condensation of cinnamaldehyde and 4-hydroxymethyl phenol is not completely regioselective, and about 10% of regioisomer **13** was formed. Aminal **8** was not isolated but was readily hydrolysed using 2 M HCl, and lactol **4** was isolated as a cream solid by crystallization from a mixture of ethyl acetate and toluene.[7] This crystallization was pivotal to obtaining the required quality of **4** as the ingoing process stream contained large amounts of excess reagents, impurities, and polymeric materials. The solvent composition (toluene/ethyl acetate 4:1) of this crystallization results from balancing product recovery and impurity purge with toluene acting as antisolvent and ethyl acetate as solvent. These conditions resulted in an excellent purge of reagents, impurities, and polymeric materials and produced very pure lactol **4** with about 20% product lost to the liquor. This process has been repeated successfully on 200 kg scale in 57% yield on many occasions.

Reductive Amination. Reductive amination was now required in order to install the diisopropylamine moiety of fesoterodine. Four products were typically observed during the development of this transformation: the desired product ***rac*-2**, racemic tolterodine ***rac*-3**, triol **14**, and unreacted lactol **4** (Table 2). Following the reductive amination step, the reaction mixture is combined with a chiral acid to effect the resolution of the enantiomers of **2**. Consequently, the molecules that do not contain basic nitrogen (triol **14** and lactol **4**) would be expected to be purged to the mother liquor during the isolation. The challenges of the reductive amination are several fold: (*i*) conversion; (*ii*) selectivity between direct reduction of lactol **4** into triol **14** and desired reductive amination; and (*iii*) the control of over-reduction of ***rac*-2** into ***rac*-3** as this impurity is poorly purged downstream due to the close structural similarity. Results from Table 2 show that heterogeneous hydrogenation using Pd/C as catalyst was the most selective way found to reductively aminate diisopropylamine with lactol **4** (entry 1). Pt/C gave poor selectivity for over-reduction to racemic tolterodine ***rac*-3** and direct reduction of lactol to give triol **14**, even at partial conversion (entry 2). Ru/C was selective towards undesired direct reduction of lactol **4** (entry 3). Homogenous transfer hydrogenation provided selectively **14** with no pretreatment with $Ti(OiPr)_4$, and significant amounts of over-reduction with pretreatment even at low conversion (entries 4−5). Pretreatment with $MgSO_4$ was ineffective at facilitating the condensation of diisopropylamine with **4** (entry 6), and $NaBH_4$ produced large amounts of over-reduction (entry 7). Finally, $NaBH_3(CN)$ with pretreatment with $Ti(OiPr)_4$ selectively gave the over-reduced product at 70 °C but produced mostly the desired product at room temperature (entries 8−9).

Reductive amination using heterogeneous hydrogenation with Pd/C was optimized further. Methanol was the only solvent that

Scheme 2. Proposed Mechanism

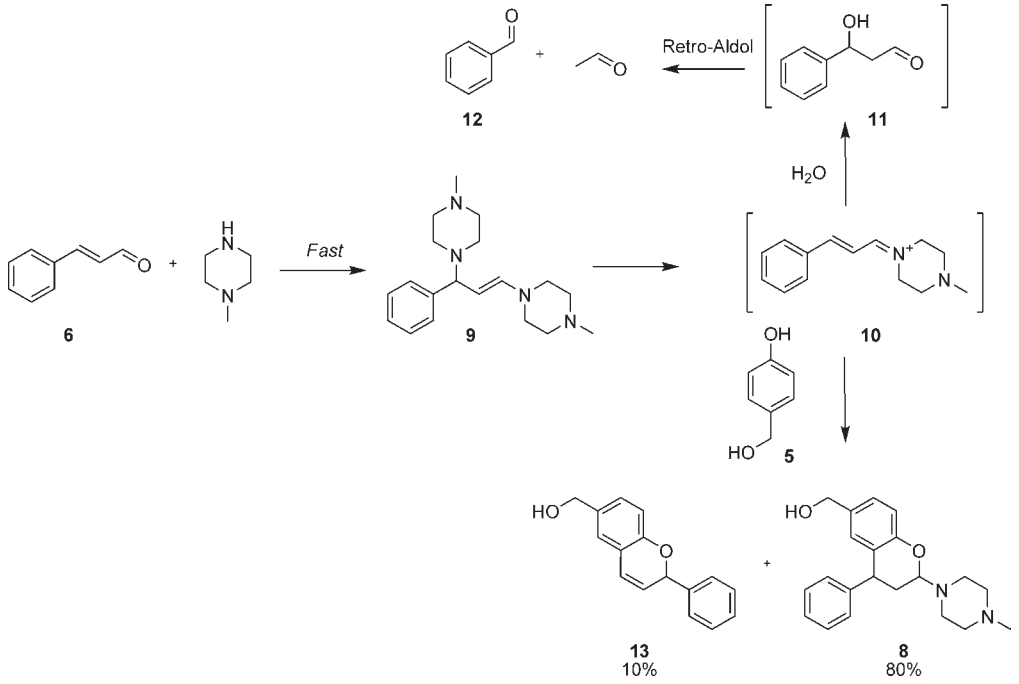
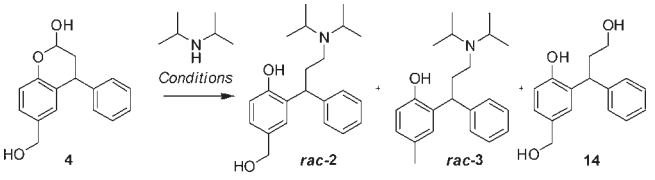


Table 2. Reductive Amination of Diisopropylamine and 4



Entry	Conditions	*rac*-2	*rac*-3	14	4
1	Pd/C, MeOH, 115 psi, 40 °C	93	1	1	5
2	Pt/C, *t*-Amyl-OH, 100 psi, 80 °C	50	5	10	35
3	Ru/C, *t*-Amyl-OH, 100 psi, 80 °C	5	1	96	0
4	$[RuCl_2p\text{-Cymene}]_2$, Diamine, THF, HCOOH, rt	1	0	99	0
5[a]	$[RuCl_2p\text{-Cymene}]_2$, Diamine, THF, HCOOH, rt	46	8	0	46
6[b]	$NaBH_4$, rt	0	0	100	0
7[a]	$NaBH_4$, rt	70	30	0	0
8[a]	$NaBH_3CN$, 70 °C	1	99	0	0
9[a]	$NaBH_3CN$, rt	88	4	0	8

[a] Pretreatment with $Ti(OiPr)_4$, THF, reflux, 1 h. [b] Pretreatment with $Mg(SO)_4$, THF, rt, 1 h.

provided good conversion and selectivity over formation of ***rac*-3**. In order to gain insights into the mechanism of the reaction and to assess the scale-up risks, some kinetic studies were performed (Figure 3). First we studied the initial rate of reaction as a function of the concentration of lactol **4** and diisopropylamine (Figure 3A and B). The initial rate of reaction is influenced by the concentration of both of these starting materials, hence suggesting that they are both involved in the rate-limiting step of this reaction. The initial rate was then studied as a function of the catalyst loading (Figure 3C). The results suggest that catalyst is involved also in the rate-limiting step and that, beyond 10% w/w of catalyst charge, extra catalyst would not significantly increase the overall rate of reaction. Finally, we studied the initial rate of reaction as a function of hydrogen pressure (Scheme 3D) and found that hydrogen pressure did not have a significant effect on the reaction rates. This result could be the consequence of two possible causes: (*i*) the overall rate of reaction is limited by the formation of the hydrogenation substrate and not by the hydrogenation event, or (*ii*) that the hydrogenation event is the rate-limiting step but does not depend on hydrogen pressure, which can be the result of a Langmuir−Hinshelwood type kinetics.[8] These kinetic studies therefore suggest that the overall reaction rate is a function of the concentrations of lactol **4**, diisopropylamine, and the Pd catalyst. Since the reaction time is long (20 h), it is unlikely that the hydrogenation event is limited by the efficiency of mass transfer within the three-phase system and therefore changes in the parameters affecting mass transfer (e.g., mixing) during scale-up should not impact the overall rate of reaction, so long as mass transfer is high enough to allow the reaction to proceed under kinetic control. This was proven to be the case across a wide range of scales, from 1 g to 200 kg.

In order to probe the structure of the hydrogenation substrate(s), the reaction was performed using deuterium instead of hydrogen, and the result (mass spectrometry) showed that only one deuterium atom was incorporated in the product. This suggests that the hydrogenation substrate was iminium ion **15** or aminal **17** or **24**, as opposed to enamine **16** (Scheme 3). NMR studies of the reaction mixture in deuterated methanol prior to adding the Pd/C catalyst and applying hydrogen showed that

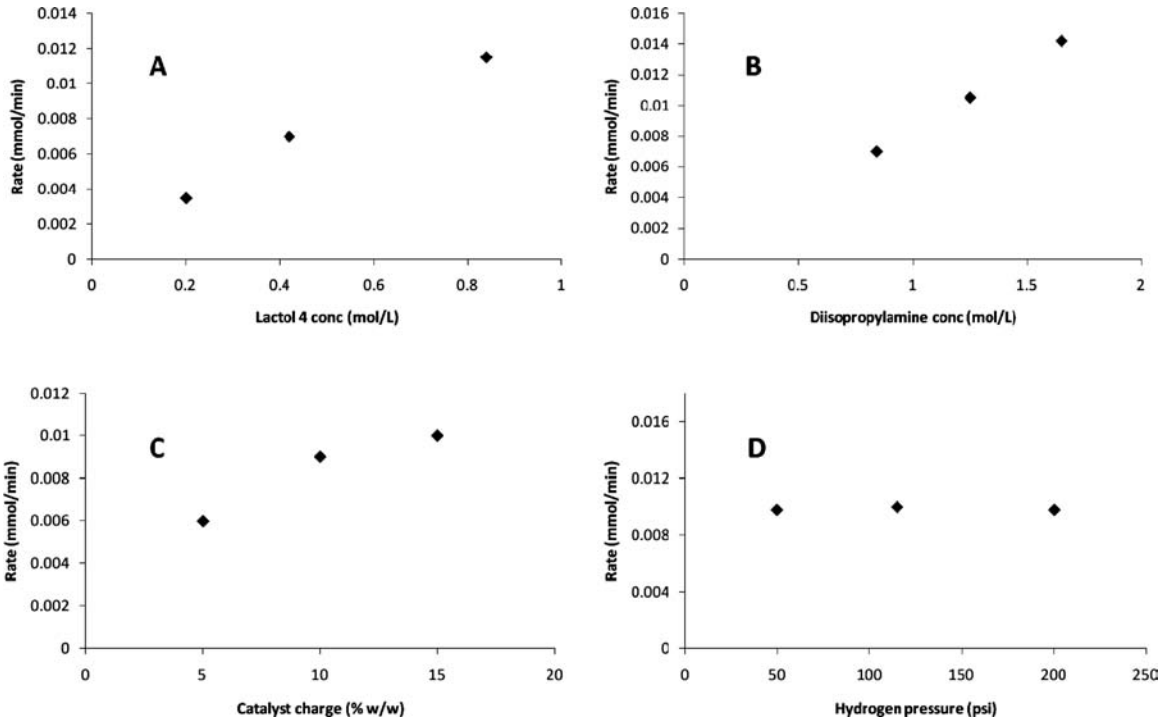
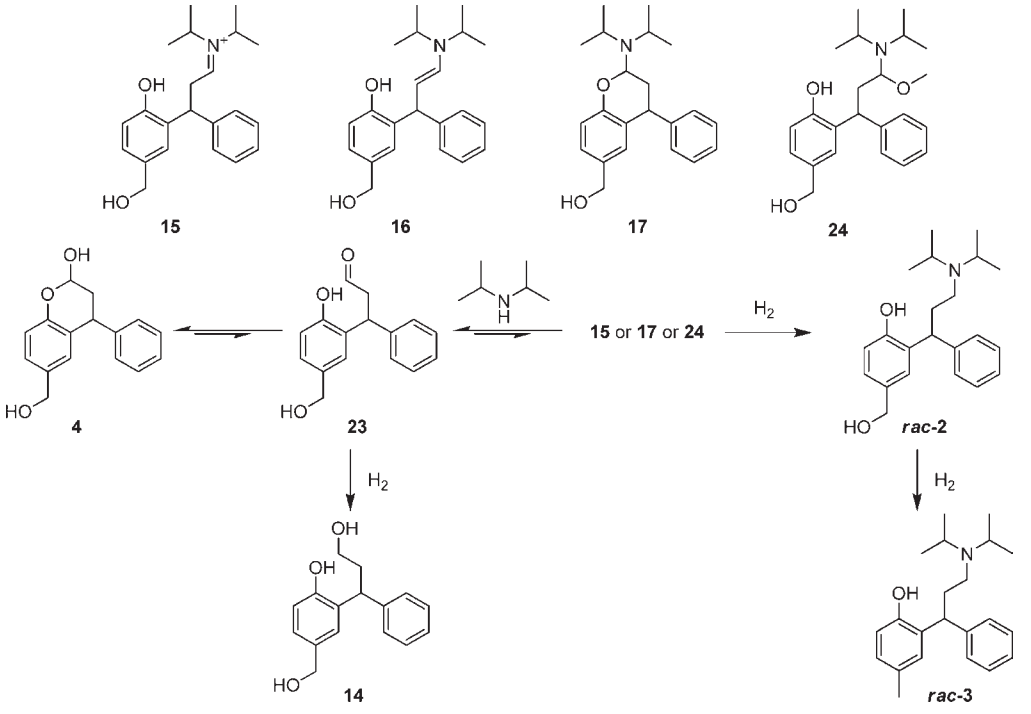


Figure 3. Kinetic studies: plots of initial rate of reaction vs. reaction parameters. (A) Initial rate (mmol/min) as a function of lactol **4** concentration (mol/L). (B) Initial rate (mmol/min) as a function of diisopropylamine concentration (mol/L). (C) Initial rate (mmol/min) as a function of catalyst loading (w/w %). (D) Initial rate (mmol/min) as a function of hydrogen pressure (psi).

Scheme 3. Possible Hydrogenation Substrates and Proposed Mechanism



protons in the beta position from the nitrogen (around 2 ppm) in lactol **4** were exchanged by deuterium, thus indicating that enamine **16** was indeed formed in the reaction mixture (Figure 4). These studies however failed to observe **15**, **16**, **17**, or **24**, presumably due to their low concentration. Finally, we searched for a set of conditions that would provide the widest window for reaching high conversion with low amounts of over-reduction. DoE experimentation showed that the best compromise was

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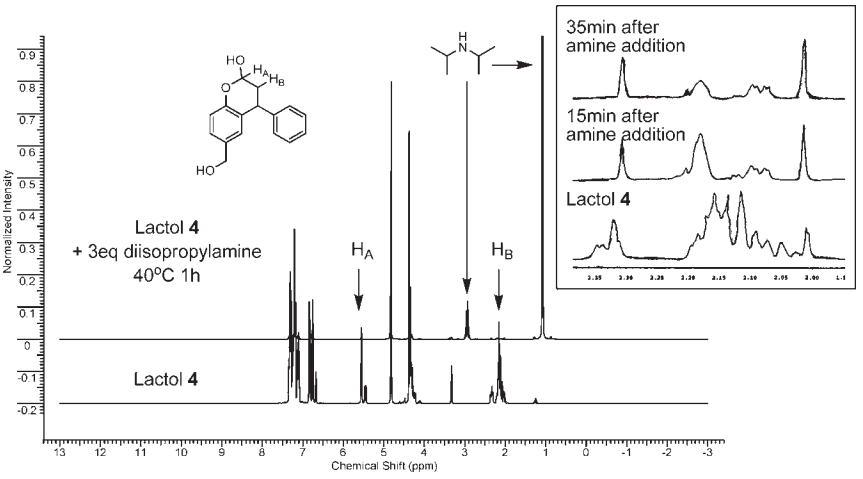
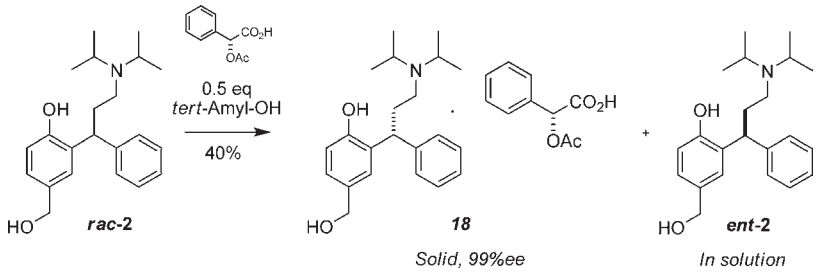


Figure 4. ^{1}H NMR in MeOH-d_4 of Lactol **4** with and without diisopropylamine.

Scheme 4. Resolution of *rac*-2

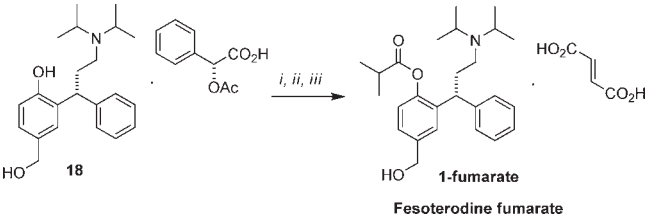


found using 10% w/w of catalyst at low temperatures (40 °C) and high stoichiometry of diisopropylamine (3 equiv), presumably in order to shift the pre-equilibrium towards **15**, **17**, or **24**. After filtration to remove the catalyst, the hydrogenation reaction stream was not isolated but telescoped directly into the next step (resolution) after a solvent switch into *tert*-amyl alcohol *via* distillation under reduced pressure.

Resolution of the Enantiomers of 2. In order to resolve the enantiomers of **2**, chiral acids were screened in order to identify those that would allow a selective crystallization of the desired diastereomeric salt. (*R*)-Acetyl mandelic acid was identified as a promising lead and provided on optimization an efficient crystallization of the desired salt **18** when no more than 0.5 equiv of chiral acid in *tert*-amyl alcohol was used (Scheme 4). Methanol and diisopropylamine present in the ingoing solution of ***rac*-2** from the previous step had to be removed to low levels since the presence of methanol leads to the formation of the methyl ether impurity **19**,[9] and diisopropylamine selectively forms a salt with acetyl mandelic acid, thereby reducing the available acid stoichiometry for the desired salt formation. Accordingly, a distillation under reduced pressure was performed at the end of the hydrogenation reaction. Under those conditions, the resolution step afforded 38% yield (80% of theoretical yield) of a salt containing **2** with >99% *ee* and complete purge of lactol **4** and triol **14**.

Completion of the Synthesis. The synthesis of fesoterodine was completed by a salt break of **18** in a biphasic mixture of toluene and aqueous potassium carbonate, yielding the advanced

Scheme 5. Completion of the Synthesis of Fesoterodine[a]



[a] Reagents and conditions: (*i*) K_2CO_3, water, toluene, 50 °C, 80%; (*ii*) isobutyryl chloride, DCM, −10 °C, 90%; (*iii*) fumaric acid, MEK, 82%.

common intermediate **2** after a seeded crystallization from toluene in 85% yield. Acylation of the phenol using isobutyryl chloride was accomplished in dichloromethane at −10 °C (Scheme 5). The selectivity of the acylation (mono (**1** and **21**) vs diacylation (**22**) and acylation of phenol (**1**) vs primary alcohol (**21**)) is influenced by solvent, temperature, and stoichiometry of isobutyryl chloride (Figure 5). The internal nitrogen acts as a base in this reaction, and the addition of an extra equivalent of base leads to poorer selectivities. The free base of **1** is not isolated, and the organic stream is telescoped into the next step. The synthesis is completed by a fumarate salt formation in methyl ethyl ketone to afford the commercial salt of fesoterodine in 82% yield.

Conclusion. This process illustrates the discovery and use on commercial scale (200 kg batch size) of an amine-promoted Friedel−Crafts alkylation and offers a significantly shorter

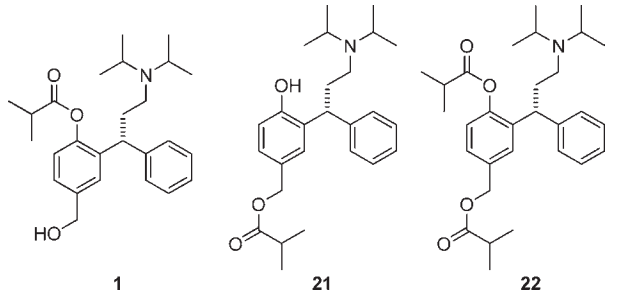


Figure 5. Potential acylation products.

synthesis of fesoterodine. Because this route does not require the use of protecting groups, redox chemistry. or functional group manipulations, it is significantly more efficient than the existing process (6 vs 11 steps and only 4 isolations), thus allowing significant environmental savings (green chemistry E factor (298 vs 711) and solvent usage (280 kg/kg vs 644 kg/kg) improved by 60%) .

EXPERIMENTAL SECTION

General. Melting points were determined by closed cell DSC. All reagents and solvents were used as received without further purification.

(2-Hydroxy-4-phenyl-3,4-dihydro-2*H*-chromen-6-yl)methanol (4). 4-(Hydroxymethyl)phenol **5** (100 g, 0.81 mol, 1.0 equiv) was stirred with *N*-methylpiperazine (202 g, 2.01 mol, 2.5 equiv) in toluene (900 mL, 9 mL/g) and then heated to reflux. Upon reaching reflux, cinnamaldehyde **6** (133 g, 1.01 mol, 1.25 equiv) was then added over 3 h maintaining the reaction mixture at reflux with azeotropic removal of water. Once the addition was complete the reaction mixture was heated at reflux with removal of water for 2 h, and then some toluene was removed by distilling under reduced pressure, reducing the volume to approximately 600 mL. The mixture was then allowed to cool to room temperature, and ethyl acetate (1.8 L, 18 mL/g) was added. The product solution was then sequentially washed with 2 M aqueous hydrochloric acid (1.8 L, 18 mL/g), 1 M aqueous hydrochloric acid (700 mL, 7 mL/g), 0.25 M aqueous sodium hydrogen carbonate solution (700 mL, 7 mL/g), and water (1 L, 10 mL/g). The organic phase was then diluted with toluene (650 mL, 6.5 mL/g), and the mixture was distilled down to approximately 600 mL volume. The mixture was cooled to 22 °C and stirred for 6 h. The suspension was cooled to 2 °C and stirred for a further 2 h. The slurry was filtered, and the cake was washed twice with toluene (300 mL, followed by 100 mL). The resulting pale tan solid was dried in vacuum for 24 h at up to 60 °C, to give (2-hydroxy-4-phenyl-3,4-dihydro-2*H*-chromen-6-yl)methanol **4** (118.6 g, 57% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.35 (m, 2 H); 7.23 (m, 4 H); 7.06 (m, 1 H); 6.78 (m, 1 H); 6.64 (bs, 0.76 H); 6.56 (bs, 0.24 H); 5.54 (m, 0.76 H); 5.44 (m, 0.24 H); 4.93 (m, 1 H); 4.28 (m, 3 H); 2.08 (m, 2 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm Major diastereoisomer 151.3, 144.6, 134.0, 128.6, 128.5, 127.4, 126.5, 126.2, 124.9, 116.3, 90.4, 62.6, 36.7, 36.5. Minor diastereoisomer 152.7, 144.3, 134.1, 128.6, 128.5, 127.1, 126.6, 126.2, 125.2, 116.1, 94.1, 62.6, 36.7, 36.5. HRMS (ES) Calcd for $C_{16}H_{16}O_3Na$ (MNa+) 279.0992, found 279.0994.

2-[3-(Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol (*rac*-2). (2-Hydroxy-4-phenyl-3,4-dihydro-2*H*-chromen-6-yl)methanol **4** (200 g, 0.78 mol, 1.0 equiv) was stirred in methanol (1.5 L, 7.5 mL/g). Diisopropylamine (237 g, 2.34 mol, 3.0 equiv) was then added over 15 min maintaining the temperature below 40 °C. The resulting solution was then stirred for 1 h under nitrogen. The catalyst Pd-ESCAT 142 (Supplier Engelhard) [(5% w/w Pd/C paste, ca. 50% water wet) 20 g, 10% w/w] was added, and the system was purged with nitrogen. The mixture was hydrogenated at 793 kPa (115 psi, 7.92 bar) at a temperature of 40 °C for 20 h. The mixture was cooled and purged with nitrogen and then filtered using filter aid, and the residue pad was washed with methanol (2 × 400 mL, 2 × 2 mL/g). The combined filtrate and washings were transferred to a distillation vessel where the product solution was concentrated to a 330 mL (1.65 mL/g) volume under reduced pressure. *tert*-Amyl alcohol (670 mL, 3.35 mL/g) was added, and the mixture was reconcentrated to 330 mL (1.65 mL/g) volume. Six further additions of *tert*-amyl alcohol (each of 670 mL, 3.35 mL/g), each followed by a distillation under reduced pressure to a 330 mL (1.65 mL/g) volume, were performed to remove the excess diisopropylamine and methanol. The mixture was diluted with *tert*-amyl alcohol (1270 mL, 6.35 mL/g) to give a *tert*-amyl alcohol solution of the product 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol ***rac*-2** for use in the next step. Quantitative HPLC analysis indicated the crude solution contained 221 g of product (83% yield). This intermediate is not isolated and carried through to the next step with no further purification.

(*R*)-2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol (*R*)-acetoxy(phenyl)acetate (18). A solution of 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)-phenol in *tert*-amyl alcohol (44.2 L, equivalent to 2.95 kg of ***rac*-2**, 8.64 mol, 1 equiv) was heated to 70 °C. (*R*)-(−)-*O*-Acetylmandelic acid (0.84 kg, 4.32 mol, 0.5 equiv) was dissolved in *tert*-amyl alcohol (14.8 L), and the resulting solution was added to the solution of ***rac*-2** in *tert*-amyl alcohol keeping the internal temperature at 70 °C. The solution was seeded with **18** (0.03 kg, 1 wt %). The resulting slurry was cooled to 60 °C over 2 h and then to 25 °C over another 3 h. The mixture was stirred at 25 °C for an additional 12 h. The slurry was filtered, and the cake was deliquored well. The cake was slurry washed with *tert*-amyl alcohol (2 × 29.5 L, 2 × 10 mL/g) and deliquored well. The white solid was dried under reduced pressure at 40 °C for 12 h. (*R*)-2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)-phenol (*R*)-acetoxy(phenyl)acetate **18** (2.04 kg, 3.81 mol) was isolated in 37.8% yield (corrected for 14.3% w/w *tert*-amyl alcohol) and 99% *ee*. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.42−7.46 (m, 2 H); 7.23−7.35 (m, 7 H); 7.13−7.19 (m, 2 H); 6.95 (dd, J = 8.21, 2.15 Hz, 1 H); 6.76 (d, J = 8.21 Hz, 1 H); 5.64 (s, 1 H); 4.29−4.38 (m, 3 H); 3.32 (br. s., 2 H); 2.54−2.76 (m, 2 H); 2.29 (br. s., 2 H); 2.06 (s, 3 H); 1.37 (d, J = 7.62 Hz, 1 H); 1.01−1.09 (m, 13 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm 170.1, 169.6, 153.6, 144.3, 137.1, 132.8, 129.6, 128.1, 128.0, 127.8, 127.7, 127.5, 26.1, 125.8, 125.6, 114.8, 76.3, 68.8, 63.0, 44.6, 40.9, 35.9, 28.7, 20.8, 8.6. Diacel Chiralpak IC 250 mm × 4.6mm, 5 μm; isochratic 96:4 heptane/ethanol + 0.5% diethylamine, flow 1.0 mL/min, 210 nm, R_t (min) 12 (undesired), 13 (desired). Enantiomeric excess 99%. HRMS (ES) Calcd for $C_{22}H_{32}NO_2$ (MH+) 342.2428, found 342.2435.

(*R*)-2-[3-(Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol (2). (*R*)-2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol (*R*)-acetoxy(phenyl)acetate **18** (30 g, 0.056 mol, 1.0 equiv) was slurried in toluene (180 mL, 6 mL/g) and warmed to 50 °C. A 10 wt %/vol aqueous

solution of potassium carbonate (180 mL, 6 mL/g) was charged maintaining the temperature at 50 °C. The mixture was stirred vigorously at 50 °C for 6 h. The two solution phases were allowed to settle and were separated at 50 °C. The organic phase was washed with water (120 mL, 4 mL/g) at 50 °C. The phases were separated at 50 °C, and the toluene volume was reduced to 120 mL (4 mL/g) by distillation under reduced pressure. The temperature was adjusted to 60 °C and then cooled to 40 °C over 1 h. The batch was held at 40 °C and then seeded with **2** (150 mg). The mixture was granulated for 90 min at 40 °C and then cooled to 20 °C over 4 h. The batch was granulated at 20 °C for 4 h. The slurry was then cooled to 2 °C over 2 h and granulated at 2 °C for 4 h. The suspension was filtered, the cake was washed with cold toluene (30 mL, 1 mL/g), and the resulting white solid was dried at 35 °C for 12 h to give (*R*)-2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol **2** (16.43 g) in 85.9% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (br. s., 1 H); 7.21−7.32 (m, 4 H); 7.17 (d, J = 1.95 Hz, 1 H); 7.09−7.15 (m, 1 H); 6.94 (dd, J = 8.11, 2.05 Hz, 1 H); 6.72 (d, J = 8.21 Hz, 1 H); 4.93 (br. s., 1 H); 4.32−4.41 (m, 3 H); 2.95 (dt, J = 13.09, 6.55 Hz, 2 H); 2.27−2.37 (m, 2 H); 2.06 (q, J = 7.23 Hz, 2 H); 0.89 (dd, J = 6.45, 1.37 Hz, 12 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm 153.4, 145.3, 132.7, 130.8, 128.1, 127.9, 127.6, 126.1, 125.7, 125.5, 125.2, 114.6, 63.0, 47.8, 43.0, 40.6, 36.1, 20.7, 20.5. IR (KBr pellets) cm^{-1} 3142, 3082, 3025, 2975, 2936, 2868, 1610, 1491, 1452, 1438, 1388, 1366, 1269, 1242, 1110, 1011, 904, 767, 744, 698. HRMS (ES) Calcd for $C_{22}H_{32}NO_2$ (MH+) 342.2428, found 342.2435.

(*R*)-(+)-Isobutyric Acid 2-[3-(Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl Ester 1. (*R*)-2-[3-(Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol **2** (50 g, 0.146 mol, 1.0 equiv) was dissolved in dichloromethane (400 mL, 8 mL/g) and then cooled to −12 °C. To this was added a solution of isobutyryl chloride (16.15 g, 0.155 mol, 1.04 equiv) in dichloromethane (250 mL, 5 mL/g), maintaining the reaction temperature between −15 and −10 °C, followed by a vessel and line rinse of dichloromethane (100 mL, 2 mL/g). The reaction mixture was stirred at −12 °C for 2 h. A 5 wt %/wt aqueous sodium carbonate solution (110 mL, 2.2 mL/g) was then added to the reaction, allowing the temperature to rise towards 0 °C during the addition, and the resulting pH was confirmed to be between pH 7.5 and 8.5. The two phases were allowed to settle, and the organic phase was sequentially washed with water (450 mL, 9 mL/g), 5% wt/wt aqueous sodium carbonate solution (450 mL, 9 mL/g), and twice with water (2 × 450 mL, 2 × 9 mL/g). The product solution was then concentrated under reduced pressure to a volume of 260 mL, and methyl ethyl ketone (500 mL, 10 mL/g) was added. The solution was reconcentrated under reduced pressure to a volume of 260 mL. Two further additions of methyl ethyl ketone (each of 500 mL, 10 mL/g), each followed by a distillation under reduced pressure to 260 mL, were performed to remove the dichloromethane. This provided a methyl ethyl ketone solution of the product (*R*)-(+)-isobutyric acid 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester **1** for use in the next step (fumarate salt formation). Quantitative HPLC analysis indicated the solution contained 52.85 g of product (88% yield).

(*R*)-(+)-Isobutyric Acid 2-[3-(Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl Ester Hydrogen Fumarate 1-Fumarate. Fumaric acid (14.47 g, 0.125 mol, 0.95 equiv) was slurried in methyl ethyl ketone (162 mL, 3 mL/g) at 20 °C. A solution of (*R*)-(+)-isobutyric acid 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester **1** (54.03 g, 0.131 mol, 1.0 equiv) in methyl ethyl ketone (270 mL, 5 mL/g) was then added to the slurry of fumaric acid followed by a vessel and line rinse with methyl ethyl ketone (38 mL, 0.7 mL/g). The resulting mixture was warmed to 37 °C with agitation for 30 min ensuring that all the solids fully dissolved. The solution was filtered into a crystallising vessel, rinsing the vessel and lines with methyl ethyl ketone (70 mL, 1.3 mL/g). The solution was cooled to 20 °C and seeded with **1-fumarate** (0.54 g). After holding the mixture at 20 °C for 1 h the slurry was cooled to 5 °C, and filtered cyclohexane (65 mL, 1.2 mL/g) was added over 1 h. The mixture was stirred at 5 °C for 8 h and then filtered, washing the cake with a mixture of cyclohexane (65 mL) and methyl ethyl ketone (16 mL), followed by cyclohexane (54 mL), and the product was dried under vacuum at 22 °C for 16 h to give (*R*)-(+)-isobutyric acid 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)-phenyl ester hydrogen fumarate **1-fumarate** (57.1 g, 82% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.71 (br. s., 1 H); 7.26 (m, 4 H); 7.17 (d, J = 8.3 Hz, 1 H); 7.15 (m, 1 H); 6.91 (d, J = 8.3 Hz, 1 H); 6.87 (s, 2 H); 4.84 (br. s., 1 H); 4.62 (d, J = 13.3 Hz, 2 H); 3.96 (t, J = 8.4 Hz, 1 H); 3.63 (sept, J = 6.6 Hz, 2 H); 2.96 (br. s., 1 H); 2.81 (sept, J = 7.0 Hz, 1 H); 2.73 (br. s., 1 H); 2.86−2.57 (m, 4 H); 1.33 (d, J = 7.0 Hz, 6 H); 1.27 (d, J = 6.6 Hz, 12 H). ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm 175.6, 170.3, 147.5, 142.3, 140.5, 135.6, 134.4, 128.7, 127.6, 126.8, 126.7, 126.4, 122.2, 63.7, 54.4, 45.8, 41.9, 34.1, 31.6, 19.1, 18.9, 17.7. Anal. Calcd: C (68.29%), H (7.83%), N (2.65%). Found: C (68.40%), H (7.92%), N (2.58%). IR (KBr pellets) cm^{-1} 3473, 2978, 2937, 2877, 2825, 2769, 2696, 1755, 1707, 1570, 1468, 1387, 1234, 1178, 1097, 984, 912, 868, 795, 748, 702. Mp 103.5 °C.

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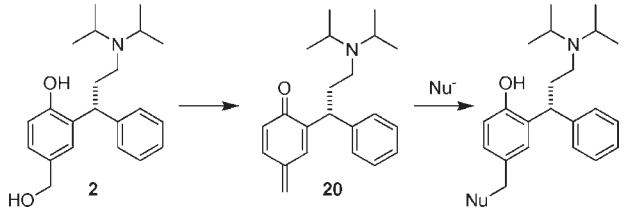

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