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Process Development and Scale-up for (±)-Reboxetine Mesylate

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Abstract:

Redevelopment of the commercial process for the synthesis of (±)-reboxetine methanesulfonate is described. An optimized and efficient process for the synthesis of (±)-reboxetine starting from cinnamyl alcohol was developed. The redeveloped process minimizes impurity formation and utilizes simplified processing to substantially improve process yield and throughput, and is suitable for the efficient synthesis of multiton quantities of reboxetine.

Introduction

Reboxetine mesylate (**1**) is a selective norepinephrine reuptake inhibitor, currently approved in over 60 countries as an antidepressant, and is marketed under the trade names Edronax, Norebox, Prolift, Vestra, and Integrex in Europe and Latin America. The original commercial process closely followed the originally published synthesis of reboxetine, and is shown in Scheme 1.[1,2] Cinnamyl alcohol **2** was epoxidized with monoperoxyphthalic acid to give racemic phenylglycidol **3**, and the epoxide was reacted with 2-ethoxyphenol to give the diol **4**. The primary alcohol of the diol was protected as the *p*-nitrobenzoate ester **5**, and then the secondary alcohol was mesylated in situ, yielding **6**. Base treatment of **6** hydrolyzed the *p*-nitrobenzoate and formed the epoxide **7**. Reaction of the epoxide with ammonia yielded the amino alcohol **8**, isolated as the methanesulfonate salt. Conversion of the amino alcohol to reboxetine was done by chloroacetylation to form **9** followed by base treatment to give the lactam **10**, and finally reduction with Vitride and salt formation yielded (±)-reboxetine methanesulfonate.

This process suffers from poor yields and complicated processing which leads to low process throughput. Key areas for process improvement were as follows: (1) an improved oxidation procedure for the conversion of cinnamyl alcohol **2** to the epoxide **3**; (2) more controlled conditions for the opening of the epoxide to form diol **4** and an improved crystallization procedure for **4**; (3) a more selective protection protocol since acylation of the secondary alcohol produces about 13% of the wrong diastereomer of **8**, resulting in diminished yields and a complicated isolation procedure for **8**; and (4) minimizing formation of a dimeric impurity in the final Vitride reduction of **10**. This impurity was hard to remove and substantially reduced the overall yield.

Process redevelopment was initiated, anticipating U.S. approval of reboxetine and the need for a more efficient process to prepare multiton amounts of reboxetine per year. Since a commercial process for reboxetine had already been registered, there were significant constraints on the extent of process changes that were acceptable.

Results and Discussion

Epoxidation of cinnamyl alcohol[3] was originally done with monoperoxyphthalic acid. This reaction proceeded well, but preparation of the reagent from phthalic anhydride and hydrogen peroxide was time-consuming, and a large amount of phthalic acid was formed as a byproduct, creating a disposal issue. A variety of alternate reagents were examined for this conversion, and ultimately it was found that epoxidation with commercially available 40% peracetic acid proceeded smoothly in methylene chloride in the presence of sodium carbonate. The epoxide **3** is highly sensitive to water and acidic conditions. The sulfuric acid stabilizer in commercial peracetic acid was initially neutralized by pretreatment with sodium carbonate, but later experiments showed that this was unnecessary. An excess of solid sodium carbonate was used as a base to neutralize the acetic acid and also served to remove water from the reaction. The main impurity formed in the reaction was phenylglycerol, formed by hydrolysis of the epoxide. At the end of the reaction the inorganic salts, a mixture of sodium carbonate, sodium bicarbonate, and sodium acetate, were removed by filtration; since these byproducts were water soluble and innocuous, they were easily disposed of.

In the original process, the phenylglycidol solution was concentrated to an oil and then reacted with 2-ethoxyphenol in aqueous NaOH at 70 °C without solvent. After an aqueous workup, the product was isolated by crystallization from toluene. This process provided **4** in good purity, but the epoxide-opening reaction was run under poorly controlled conditions. The recovery of product from toluene was low due to the high solubility of **4** in toluene, and the product slurry filtered poorly. DSC experiments showed a low onset temperature for the isolated phenylglycidol made with peracetic acid, and accordingly the process was modified to eliminate concentration to an oil. After filtration to remove the inorganic salts, the solution of **3** in methylene chloride was reacted with 2-ethoxyphenol and NaOH. Heating was required to give a reasonable reaction rate, and even at 40 °C the reaction takes many hours to go to completion. To shorten the cycle time methylene chloride was distilled as

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(1) Melloni, P.; Della Torre, A.; Lazzari, E.; Mazzini, G.; Meroni, M. *Tetrahedron* **1985**, *41,* 1393−1399.
(2) All compounds in this process are strictly racemic. For clarity, only a single enantiomer is shown.
(3) Commercial cinnamyl alcohol was typically >99.5% *trans* stereoisomer. The epoxidation proceeds with complete stereospecificity.

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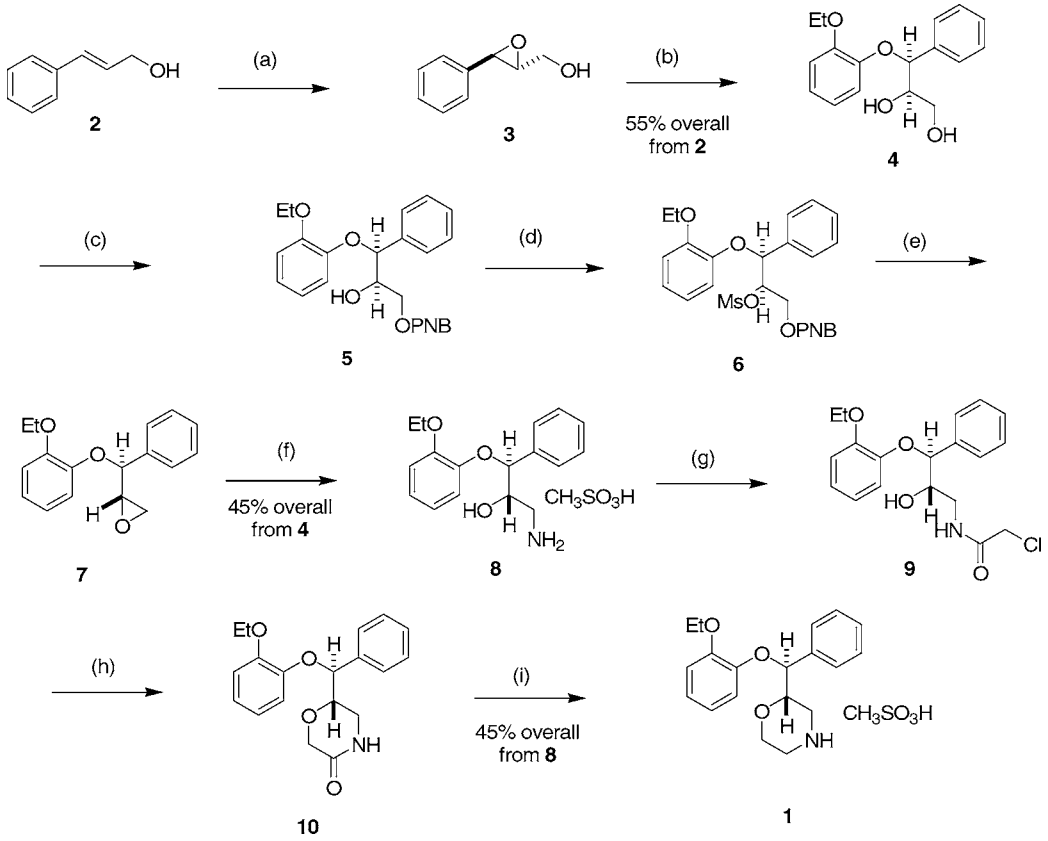
Scheme 1[a]



[a] Reagents and conditions: (a) monoperoxyphthalic acid, EtOAc; (b) 2-ethoxyphenol, NaOH; (c) *p*-nitrobenzoyl choloride, pyrdine; (d) MsCl, Et_3N; (e) NaOH, dioxane; (f) i. NH_3; ii. CH_3SO_3H; (g) $ClCH_2COCl$, Et_3N; (h) *t*-BuOK; (i) i. Vitride; ii. CH_3SO_3H.

the reaction proceeds, and the reaction was driven to completion by heating at 60 °C.

Optimization experiments showed no difference in reaction rate or impurity levels for KOH and NaOH. A survey of phase transfer catalysts showed that Bu_4NCl, $BnMe_3NCl$, Bu_3MeNCl, Aliquat 336, and $BnNMe_3OH$ gave comparable rates of reaction and amounts of impurities present. Bu_3-MeNCl solution was chosen for convenience. Temperature effects were studied in reactions at 50 °C, 60 °C, and 70 °C. The reaction proceeds faster at higher temperatures, but more impurities form, and thus, 60 °C was chosen as a compromise between reaction time and impurity levels.

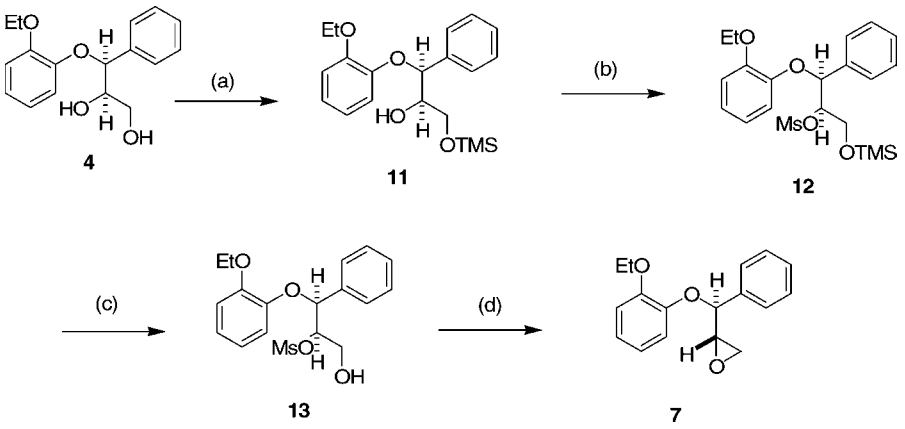
MTBE was found to be superior to toluene for the crystallization, with better product recovery and better filtering solids. Low water content was critical for high recovery from MTBE. Operationally, it was found to be more efficient to extract the product into toluene and then exchange the solvent to MTBE for the crystallization than to extract with MTBE, due to the lower water solubility and more favorable water azeotrope in toluene vs that in MTBE. Compound **4** was isolated in about 65% overall yield from cinnamyl alcohol.[4]

Selective protection of the primary alcohol in compound **4** is essential to generate the correct diastereomer of compound **8** since formation of the primary monomesylate results in the formation of the diastereomer of **8**. In the original process, *p*-nitrobenzoate was used to protect the primary alcohol of **3**. Selectivity for this protection was poor, and up to 13% of the secondary monobenzoate formed, leading to the diastereomer, which complicated purification and resulted in yield loss. In addition, a 20% excess of the *p*-nitrobenzoyl chloride was used to drive the reaction to completion which later formed about 20% of the bis-*p*-nitrobenzoate ester, compounding the yield loss.

Attempts were made to improve the selectivity of the nitrobenzoylation. The intrinsic selectivity of the *p*-nitrobenzoylation is almost irrelevant since the primary and secondary esters rapidly equilibrate under the reaction conditions. Lowering the reaction temperature did not alter the selectivity. A variety of bases were examined including triethylamine, *N*-methylpiperdine, diethylaniline, *N*-methylmorpholine, pyridine, dimethylbenzylamine, and quinoline. Use of weaker bases merely slowed the reaction rate but did not improve selectivity. Some variation was observed in the amount of bis-*p*-nitrobenzoate formed, but no remarkable improvements were seen. Mesylation and cleavage of the *p*-nitrobenzoate were facile. The monomesylate was then converted to the epoxide **7** using aqueous sodium hydroxide in dioxane. This reaction was very slow (18 h), and due to the high boiling and high freezing points of dioxane (100−102 °C and 10−12 °C, respectively), removal of the solvent was both time-consuming and a safety concern since the dioxane can freeze and damage the condenser if the jacket temperature is too cold. On a production scale the distillation of the dioxane took as much as 36 h per batch.

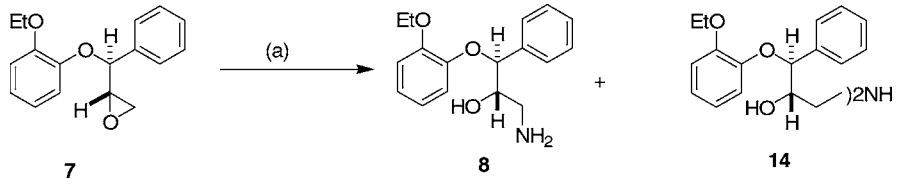
(4) The isolated diol was a single diastereomer (diastereomer <0.1%), and there was no detectable regioisomer derived from reaction of 2-ethoxyphenol at C-2 of the phenylglycidol.

Scheme 2[a]



[a] Reagents and conditions: (a) $(CH_3)_3SiCl$, Et_3N; (b) CH_3SO_2Cl, Et_3N; (c) HCl; (d) NaOH, PTC.

Scheme 3[a]



[a] Reagents and conditions: (a) NH_3, CH_3OH.

Alternatives to the use of *p*-nitrobenzoate for protection of the primary alcohol were considered. Trialkylsilyl ethers such as TBDMS or TIPS should accomplish high primary vs secondary selectivity but are too expensive for use in this application. Trimethylsilyl (TMS) protecting groups were examined, although there is little precedent for high selectivity by TMS for primary over secondary alcohols. Typically, trimethylsilylating reagents are used where the intent is exhaustive hydroxy silylation. Selectivity has been seen for reactions of secondary alcohols in different environments.[5,6] Unexpectedly, it was found that the primary alcohol of the compound **4** could be protected in very high regioselectivity using trimethylsilyl chloride and triethylamine at low temperatures.

Reaction of **4** with trimethylsilyl chloride (TMSCl) and triethylamine was very rapid even at −20 °C and was essentially complete in <10 min at this temperature to give **11** (Scheme 2). Some silyl migration occurred with extended processing times, and the selectivity deteriorated at higher temperature or in contact with excess base. Accordingly, the silylation was run as rapidly as possible while staying within the temperature range, and the solution was not held before proceeding with the mesylation. To further minimize silyl migration, the contact time with triethylamine was minimized; methanesulfonyl chloride was added first and then the second portion of triethylamine. Hydrolysis of the TMS−mesylate **12** yielded the monomesylate **13**. The monosilyl ether **11** and the silyl ether−mesylate **12** were isolated for characterization but in normal processing were reacted in situ. The selectivity of the silylation was conclusively determined by conversion to the epoxide **7**, where <0.5% of the diastereomer was found by HPLC analysis.

Table 1

equiv of NH_3	**8**:**14** (area %)
25	76:24
50	88:12
50 + saturated with NH_3 gas	91:9

Ethyl acetate was chosen as the solvent for the reaction since this was solvent used in the original registered process. Ethyl acetate was inert to the silylation and mesylation reactions, and control experiments showed that transesterification of **4** to yield the monoacetate was a slow process, even under conditions of extended distillation. Some transesterification can occur on production scale during distillation to remove water before start of the TMSCl addition.

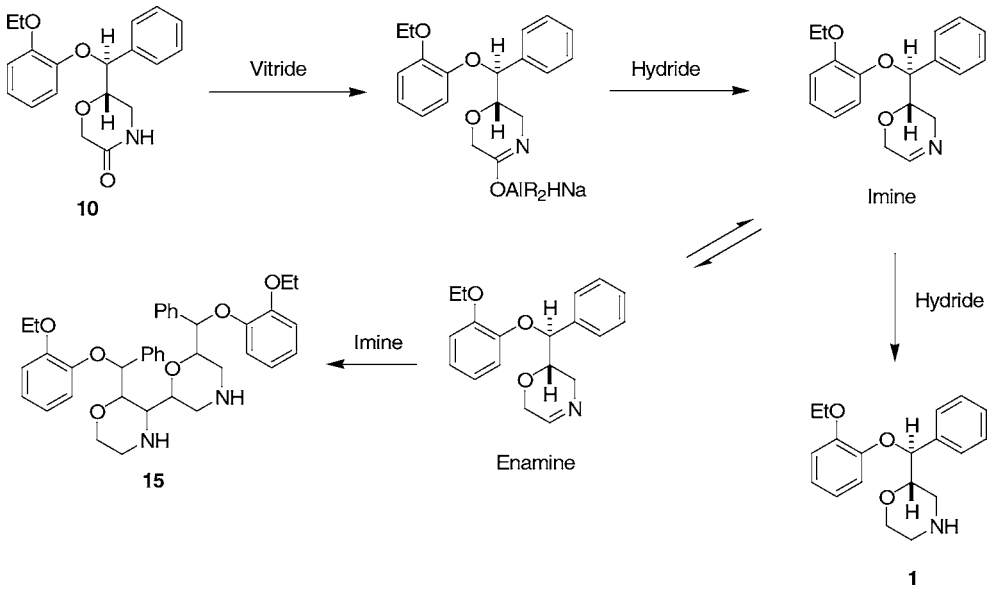
The mixture was quenched with hydrochloric acid. Hydrolysis of the TMS ether was not instantaneous and required about 30 min. When the TMS ether cleavage was complete, the solution was washed with sodium bicarbonate and sodium chloride solutions. The ethyl acetate was distilled and replaced with toluene since ethyl acetate will react in the next step.

Conversion of **13** to the epoxide **7** was found to proceed smoothly under phase transfer conditions. As before, $BnMe_3NCl$ was used as the catalyst, and the reaction was run in toluene with aqueous NaOH as the base. The reaction was rapid and essentially quantitative. These conditions eliminate dioxane from the process.

The main side reaction in the ammonolysis was formation of the secondary amine dimer **14** (Scheme 3). The amount of dimer **14** formed was directly related to the amount of ammonia used in the reaction, as shown in Table 1. Reaction

(5) Schneider, H. J.; Horning, R. *Leibigs Ann. Chem.* **1974**, 1864−1871.
(6) Yankee E. W.; Axen, U.; Bundy, G. L. *J. Am. Chem. Soc.* **1974**, 5865−5876.

Scheme 4



temperature did not have an effect on dimer formation; however, at elevated temperatures the rate of reaction was faster. The final optimized conditions use 45 equiv of ammonium hydroxide to produce about 14% of dimer **14** with none detected after workup and isolation. **8** was isolated as the methanesulfonate salt by crystallization from IPA. It was also possible to isolate **8** as the free base, but isolation as the mesylate was more reliable and gave better-handling solids. Unexpectedly, **8** mesylate was found to be the monohydrate.

No significant changes were made to the conversion of **8** to **9** to minimize the regulatory impact of the proposed process changes. The reaction was done in dimethyl carbonate, which had been previously implemented as a replacement for methylene chloride due to emission concerns. These conditions were far from ideal because of the reactivity of dimethyl carbonate and its high mp (2−4 °C), which severely constrains reaction temperature. Conditions for this reaction were optimized in the synthesis of (*S*,*S*)-reboxetine (subsequent article) to eliminate the formation of colored material and impurities derived from reaction of **8** with dimethylcarbonate.

Lactamization to give **10** was done with potassium *tert*-butoxide in IPA. This reaction was originally run at low temperature ostensibly to avoid impurity formation. The main impurities formed were the trivial product arising from isopropoxide displacement of the chloride and a number of cyclic and acyclic dimers. A detailed study of the reaction showed that virtually anything that slows the reaction led to elevated impurity formation and that, in fact, the reaction ran best at high temperatures. The preferred conditions call for very rapid addition of the *tert*-butoxide−IPA solution to the amide, which caused very rapid cyclization to the lactam.

The primary issue in the final Vitride[7] reduction was the formation of the RRT 3.25 impurity **15**. This was isolated, and the structure was determined to have the dimeric structure shown, as an indeterminate mixture of diastereomers, by NMR and mass spectral data. This dimer is an unqualified impurity with a specification of NMT 0.1%. Amounts typically produced in the processing were about 0.5%, and this was removed from the process stream by controlled pH extractions, causing loss of substantial amounts of the reboxetine that could not readily be recovered. The reduction was normally run with 2.4 equiv of Vitride; although less should be required in theory, in practice this was about the minimal amount required for complete reduction. The reduction was initially rapid and then slowed substantially, requiring several hours to go to completion even though there was still a substantial amount of active hydride present as evidenced by hydrogen evolution during the quench.

Table 2

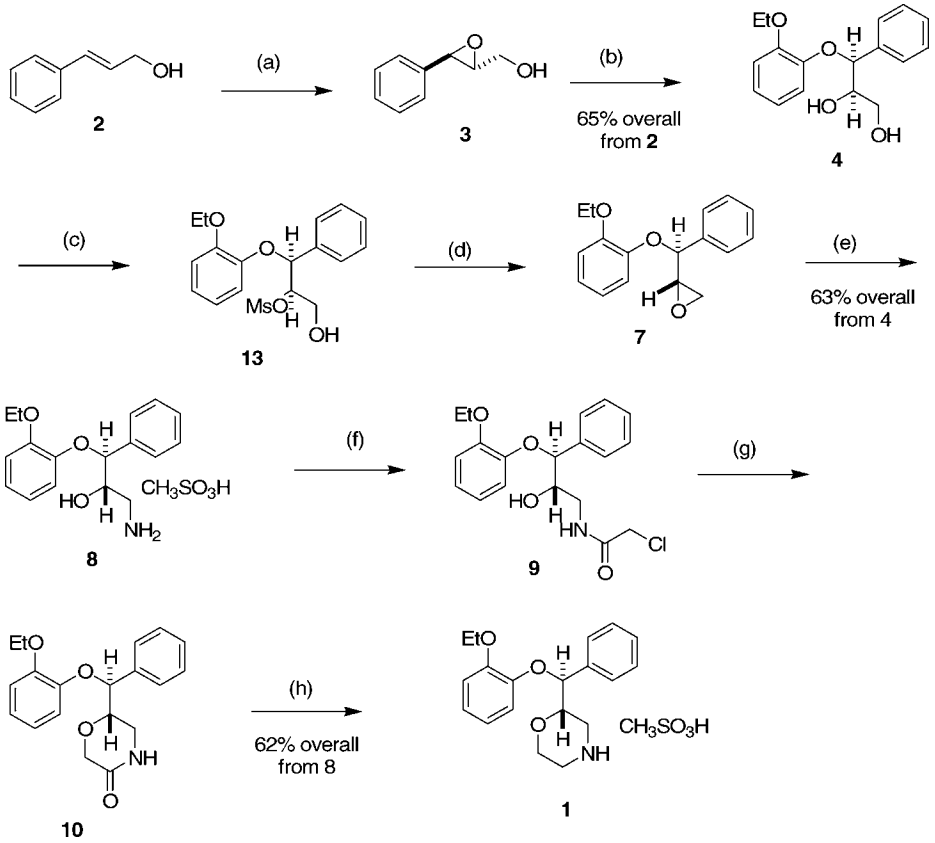
mode of addition	equiv Vitride	area % **15**
inverse	2.5	1.02
inverse	3	0.63
inverse	3.5	0.64
inverse	4	0.48
inverse	4.5	0.28
inverse	5	0.06
normal	5	0.43

A plausible mechanism for the formation of the dimer is shown in Scheme 4. Key observations were that adding Vitride to **10** gave dimer **15** regardless of Vitride equivalents and that inverse addition of Vitride (2.4 equiv) also gave high dimer. We felt that if the imine could be intercepted by hydride before it could tautomerize to the enamine, then dimer formation could be suppressed. In the key experiment, inverse addition to 5 equiv of Vitride gave very low dimer formation. The results from a definitive set of experiments are shown in Table 2.

Addition of a solution containing 1.2 equiv of aqueous NaOH and allowing the exotherm from the quench to heat the mixture to as high as 45−55 °C was sufficient to dissolve

(7) Vitride is sodium bis(2-methoxyethoxy)aluminum dihydride. $NaAlH_2(OCH_2CH_2OCH_3)_2$, also known as Red-Al, and was purchased as a 65 wt % solution in toluene.

Scheme 5[a]



[a] Reagents and conditions: (a) CH_2CO_3H, Na_2CO_3 CH_2Cl_2; (b) 2-ethoxyphenol NaOH; (c) i. TMSCl, Et_3N. ii. MsCl, Et_3N. iii. HCl; (d) NaOH, PTC, CH_2Cl_2; (e) i. NH_3. ii CH_3SO_3H; (f) $ClClH_2COCl$, Et_3n; (g) *t*-BuOK; (h) i. Vitride. ii. CH_3SO_3H.

all aluminum solids or gels and produced a clean phase break in the subsequent extractions. Rewarming the mixture also produced clean phase breaks if solids or gels formed upon cooling. The toluene solution after the Vitride quench was concentrated and the solvent exchanged to acetone. The calculated amount of methanesulfonic acid was added, causing precipitation of the final product, which was filtered and dried.

Conclusion

An efficient process was developed for the large-scale synthesis of reboxetine methanesulfonate. Key improvements eliminated impurity formation, leading to more efficient processing and higher yields relative to the original registered process. Overall chemical yield was increased from about 11% yield in the original process to about 25% in the modified process, substantially increasing process throughput. The optimized scheme for the final process is shown in Scheme 5.

Experimental Section

Materials were obtained from commercial suppliers and used without purification. Production-scale procedures were run in 4000-L or 8000-L nominal volume, glass-lined reactors equipped with typical utilities. Products were isolated on agitated stainless steel pressure nutsches and dried with positive pressure nitrogen. Melting points were run in open tube capillaries and are uncorrected. IPA refers to 2-propanol; MTBE refers to methyl-*tert*-butyl ether. NMR spectra were run on Varian INOVA operating at 400 MHz for ^1H and 100 MHz for ^{13}C. Mass spectra were recorded on a Micromass Platform LC mass spectrometer.

(2*RS*,3*SR*)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenyl-1-propanol (4). Sodium carbonate (420 kg, 3962 mol), cinnamyl alcohol (375 kg, 2794 mol), and methylene chloride (3700 L) were charged to an 8000 L reactor. The internal temperature was adjusted to 15−20 °C. A solution of peracetic acid (40% in acetic acid−water, 717 kg, 3773 mol) was added over about 3 h, maintaining the temperature between 20 and 25 °C. The mixture was stirred for 3 h, and then a solution of sodium sulfite (300 kg dissolved in 2250 L water) was added, maintaining the temperature <30 °C. At the end of the quench the temperature was adjusted to 30−35 °C. The phases were separated, and the aqueous phase was extracted with 375 L of methylene chloride. The organic phases were combined and added to a mixture of water (1530 L), 50% NaOH (240 kg, 3000 mol), tributylmethylammonium chloride (50 kg), and 2-ethoxyphenol (575 kg, 4166 mol). The mixture was agitated and heated to 60 °C and the methylene chloride distilled. The mixture was held at 60 °C until reaction was complete (about 4 h) and then was cooled to 25 °C. Toluene (2350 L) was added, and the phases were separated. The aqueous phase was extracted with 1500 L of toluene. The organic phases were combined and washed with aqueous NaOH (2 × 60 kg 50% NaOH in 750 L of water) and then with 750 L of water. The toluene solution was distilled to an oil, and then MTBE (1425 L) was added, and

the mixture was seeded and cooled to 0 °C to crystallize. The solids were filtered and washed with 0 °C MTBE (2 × 375 L) and then dried at 30 °C with nitrogen. Yield: 525 kg of **4** as a white solid (65% overall yield from cinnamyl alcohol).

A sample of material from a smaller-scale run was characterized: mp 71−74 °C. ^{1}H NMR (399.76 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.50 (t, J = 7.0 Hz, 3H), 3.25−3.29 (m, 1H), 3.39 (d, J = 8 Hz, 1H), 3.63−3.70 (m, 1H), 3.87−3.99 (m, 2H), 4.1 (q, J = 7.0 Hz, 2H), 5.25 (d, J = 4.1 Hz, 2H), 6.61−6.4 (m, 1H); 6.68−6.74 (m, 1H), 6.86−6.92 (m, 2H), 7.27−7.42 (m, 5H).^{13}C NMR (100.53 MHz, $CDCl_3$) δ 15.0. 62.5, 64.4, 86.3, 99.9, 112.8, 116.54, 121.0, 122.5, 126.6, 128.3, 128.9, 138.2, 147.3, 149.3. LRMS-APCI *m/z* calcd for $C_{17}H_{21}O_4$ $(M + H)^+$: 289. Found: *m/z* = 289 $[M + 1]^+$. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.85; H, 7.07.

(2*RS*,3*SR*)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenyl-1-(trimethylsilyloxy)propane (11). 3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenylpropanol (1.44 g, 5 mmol) and triethylamine (0.77 mL, 5.5 mmol) were dissolved in ethyl acetate (15 mL) and cooled to −17 °C. Trimethylsilyl chloride (0.64 mL, 5.0 mmol) dissolved in 5 mL of ethyl acetate was added over 10 min, keeping the temperature below −15 °C. A white precipitate formed during this addition. The mixture was stirred below −15 °C for 15 min, and the 20 mL of pentane was added. The solids were removed by filtration, and the filtrate was concentrated under vacuum to yield a cloudy oil. The oil was chromatographed on silica (230−400 mesh), eluting with 4:1 heptane−ethyl acetate. The product-containing fractions were combined and evaporated to yield 1.80 g (88.5%) of the product as a clear, colorless oil. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.47 (t, J = 6.8 Hz, 3H), 2.82 (d, J = 5.2 Hz, 1H), 3.80 (m, 3H), 4.0−4.11 (m, 4H), 5.08 (d, J = 6.0 Hz, 1H), 6.76 (m, 2H), 7.2−7.45 (m, 5H).. ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 0.0, 15.54, 63.34, 65.06, 75.22, 83.71, 114.28, 118.60, 121.51, 122.95, 127.84, 128.49, 128.84, 138.93, 148.34, 150.40. LRMS-APCI *m/z* calcd for $C_{20}H_{29}O_4Si$ $(M + H)^+$: 361. Found: *m/z* = 361 $[M + 1]^+$.

(2*RS*,3*SR*)-3-(2-Ethoxyphenoxy)-2-mesyloxy-3-phenyl-1-(trimethylsilyloxy)propane (12). 3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenylpropanol (1.44 g, 5 mmol) and triethylamine (0.77 mL, 5.5 mmol) were dissolved in ethyl acetate (15 mL) and cooled to −17 °C. Trimethylsilyl chloride (0.64 mL, 5.0 mmol) dissolved in 5 mL of ethyl acetate was added over 10 min, keeping the temperature below −15 °C. A white precipitate formed during this addition. The mixture was stirred below −15 °C for 15 min. Triethylamine (0.8 mL, 5.7 mmol) was added, followed by methanesulfonyl chloride (0.46 mL, 6.0 mmol) dissolved in 5 mL of ethyl acetate, keeping the temperature below −15 °C. The mixture was stirred below −15 °C for 15 min, and the 20 mL of pentane was added. The solids were removed by filtration, and the filtrate was concentrated under vacuum to yield a cloudy oil. The oil was chromatographed on silica (230−400 mesh), eluting with 4:1 heptane−ethyl acetate. The product-containing fractions were combined and evaporated to yield 2.00 g (91.2%) of the product as an oil that solidified on standing; mp 80−82.5 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.17 (s, 9H), 1.50 (t, J = 6.8 Hz, 3H), 3.06 (s, 3H), 3.77 (dd, J = 11, 6 Hz, 1H), 4.00 (dd, J = 11, 6 Hz, 1H), 4.10 (q, J = 6.8 Hz, 2H), 5.07 (m, 1H), 5.51 (d, J = 4.4 Hz, 1H), 6.75 (m, 2H), 6.91 (m, 2H), 7.2−7.49 (m, 5H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 0.1, 15.66, 38.87, 61.57, 64.88, 79.90, 85.20, 113.97, 116.99, 121.32, 122.79, 128.26, 129.09, 129.14, 147.72, 149.95. LRMS-APCI *m/z* calcd for $C_{21}H_{31}O_6SSi$ $(M + H)^+$: 439. Found: *m/z* = 439 $[M + 1]^+$.

(2*RS*,3*SR*)-3-(2-Ethoxyphenoxy)-2-mesyloxy-3-phenyl-1-propanol (13). 3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenylpropanol (0.288 g, 1 mmol) and triethylamine (0.15 mL, 1.1 mmol) were dissolved in ethyl acetate (5 mL) and cooled to −17 °C. Trimethylsilyl chloride (0.13 mL, 1.0 mmol) dissolved in 2 mL of ethyl acetate was added over 10 min, keeping the temperature below −15 °C. A white precipitate formed during this addition. The mixture was stirred below −15 °C for 15 min. Triethylamine (0.15 mL, 1.1 mmol) was added, followed by methanesulfonyl chloride (0.085 mL, 1.1 mmol) dissolved in 2 mL of ethyl acetate, keeping the temperature below −15 °C. The mixture was stirred below −15 °C for 15 min. Hydrochloric acid (2M, 2 mL) was added, and the mixture was allowed to warm to 20−25 °C and stirred for 30 min. The phases were separated, and the organic phase was washed with aqueous sodium chloride solution (5 mL) and dried over sodium sulfate. The solution was evaporated to yield 0.377 g of an oil. The oil was chromatographed on silica (230−400 mesh), eluting with 1:1 hexane−ethyl acetate. The product-containing fractions were concentrated to yield 0.33 g (91%) of the product as an oil that solidified on standing; mp 83−86 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.66 (t, J = 8.2 Hz, 3H), 2.85 (s, 3H), 4.14−4.35 (m, 4H), 5.12 (m, 1H), 5.52 (d, J = 6.1 Hz, 1H), 6.8−7.15 (m, 4H), 7.5−7.7 (m, 5H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 14.73, 37.80, 62.19, 64.27, 81.40, 84.04, 112.88, 117.19, 120.67, 122.86, 127.40, 128.77, 128.86, 146.40, 149.30. LRMS-APCI *m/z* calcd for $C_{18}H_{23}O_6S$ $(M + H)^+$: 367. Found: *m/z* = 367 $[M + 1]^+$.

(*1RS, 2SR*) 3-Amino-1-(2-ethoxy-phenoxy)-1-phenyl-propan-2-ol (8). 4 (250 kg, 868 mol), triethylamine (105 kg, 1037 mol), and ethyl acetate (2500 L) were charged to an 8000 L reactor. The mixture was agitated and cooled to −15 to −20 °C. Trimethylsilyl chloride (98 kg, 903 mol) was added, maintaining the temperature between −15 and −20 °C. The mixture was stirred for 15 min after completion of the trimethylsilyl chloride addition. Methanesulfonyl chloride (119 kg, 1039 mol) was added, and then triethylamine (105 kg, 1037 mol) was added, maintaining the temperature at −15 to −20 °C. The mixture was stirred for 15 min after completion of the triethylamine addition, and then a solution of HCl (85 kg of concd HCl in 799 L of water) was added. The mixture was heated to between 15 and 35 °C for 45 min, and then the phases were separated. Sodium bicarbonate solution (43 kg of $NaHCO_3$ in 434 L of water) was added to the organic phase. The mixture was agitated, and then the phases were separated. The organic phase was washed with a solution of NaCl (108 kg in 334 L

water). The organic phase was concentrated, and toluene (2 × 1506 kg) was added and distilled to a final volume of 1700 L. Water (470 L), 50% NaOH (312 kg), and tributylmethylammonium chloride (21.7 kg) were added, and the mixture was stirred at 20−25 °C for about 2 h. The phases were separated, and the aqueous phase was extracted with 376 kg of toluene. The toluene solutions were combined and washed with NaCl solution (108 kg of NaCl in 334 L of water). The organic phase was concentrated to a volume of 520 L. Methanol (2 × 2604 L) was added and distilled to a final volume of 520 L.

A sample of epoxide prepared from a smaller scale run was characterized. **(2*RS*,*SR*)-[(2-Ethoxyphenoxy)phenylmethyl]oxirane (7):** ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.44 (t, J = 7.0 Hz, 3H), 2.73 (dd, J = 2.6, 5.0 Hz, 1H), 2.81 (dd, J = 4.2, 5.0 Hz, 1H), 3.48 (m, 1H), 4.1 (q, J = 7.0 Hz, 2H), 4.92 (d, J = 6.0 Hz, 1H), 6.75−6.93 (m, 4H), 7.29−7.48 (m, 5 H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 15.22, 44.84, 55.31, 64.97, 76.99, 83.56, 114.65, 118.64, 121.18, 122.87, 127.05, 128.51, 128.77, 137.98, 138.00, 148.05, 150.22. LRMS-APCI *m*/*z* calcd for $C_{17}H_{19}O_3$ $(M + H)^+$: 271. Found: $m/z = 2$ $[M + 1]^+$. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.32; H, 6.77.

The epoxide solution was diluted with 2344 L of methanol, and 2347 kg of 28% aqueous ammonia was added. The mixture was heated to 40 °C for 3 h. The mixture was cooled to 15−25 °C, and 1938 L of methylene chloride was added. The aqueous phase was extracted with methylene chloride (2 × 868 L). The combined methylene chloride phases were distilled to a volume of about 2600 L. Methylene chloride (1562 L) was added and the mixture again distilled to 2600 L. Methylene chloride (868 L) and water (2170 L) were added. The mixture was agitated, and the aqueous phase was separated and discarded. A solution of 103 kg of concd HCl in 2170 L of water was added. The aqueous phase was separated, and the organic phase was extracted with 2170 L of water. The combined aqueous phases were extracted with 400 L of methylene chloride. Methylene chloride (1250 L) and 86.7 kg of 50% NaOH were added to the aqueous phase. The phases were separated, and the aqueous phase was extracted with 625 L of methylene chloride. The methylene chloride solutions were combined and distilled under vacuum. IPA (2 × 1736 L) was added and distilled to a volume of 1736 L. Methanesulfonic acid (68.6 kg, 599 mol) was added, and the mixture was stirred for about 4 h, then cooled to 0 °C, and stirred for 1 h. The solids were filtered and washed with 868 L of IPA cooled to 0 °C. The solids were dried with 60 °C nitrogen to yield 229 kg of **8** methanesulfonate monohydrate (63% overall from **4**) mp 122−125 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.67−2.83 (m, 2H), 3.26 (br s, 2H), 4.00−4.08 (m, 3H), 5.25 (d, J = 5.1 Hz, 1H), 5.82 (br s, 1H), 6.68−6.94 (m, 4H) 7.29−7.48 (m, 5 H), 7.74 (br s, 3H). ^{13}C NMR (100.62 MHz, CD_3OD) δ 14.03, 38.27, 42.08, 64.50, 70.46, 84.15, 113.46, 117.02, 120.79, 122.43, 127.24, 128.31, 128.40, 137.48, 147.18, 149.34. LRMS-APCI *m*/*z* calcd for $C_{17}H_{22}NO_3$ $(M + H)^+$: 364. Found: $m/z = 364$ $[M + 1]^+$. KF calcd for $C_{17}H_{21}NO_3-CH_3SO_3H-H_2O$: 4.49 wt % H_2O; found: 4.48 wt % H_2O. Anal. calcd for $C_{17}H_{21}NO_3-CH_3SO_3H-H_2O$: C, 53.85; H, 6.68; N, 3.49. Found: C, 53.81; H, 6.59; N, 3.42.

Free base: mp 107−110 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.49 (t, J = 7.0 Hz, 3H), 2.56 (dd, J = 13.0, 6.4 Hz, 1H), 2.66 (dd, J = 13.0, 3.5 Hz, 1H), 3.94 (m, 1H), 4.1 (t, J = 7.0 Hz, 2H), 4.75 (d, J = 7.99 Hz, 1H), 4.58 (d, J = 8.2 Hz, 1H), 6.60−6.93 (m, 4H), 7.31−7.39 (m, 5H). ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 15.07, 43.45, 64.49, 76.60, 87.84, 113.20, 119.73, 121.07, 123.48, 127.50,128.54, 128.81, 138.99, 148.34, 150.25. LRMS-APCI *m*/*z* calcd for $C_{17}H_{21}NO_3$ $(M + H)^+$: 364. Found: $m/z = 364$ $[M + 1]^+$. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.95; H, 7.47; N, 4.81.

Reboxetine Methanesulfonate (1). 8 methanesulfonate monohydrate (125 kg, 298 mol) and 1534 L of dimethyl carbonate were charged to a 4000 L reactor. Triethylamine (103 kg, 1018 mol) was added, and the contents were cooled to 4−10 °C. A solution of chloroacetyl chloride (30 kg, 265.5 mol) in 44 L of dimethyl carbonate was added, maintaining the temp between 4 and 10 °C. After this addition was completed, chloroacetyl chloride (30 kg, 265.5 mol) in 47 L of dimethylcarbonate was added, maintaining the temperature between 4 and 10 °C. After 30 min, 1250 L of water was added, and the mixture was stirred for 15 min and then allowed to settle. The aqueous phase was removed, and the organic phase was washed with an aqueous solution of NaCl (2 × (25 kg of NaCl dissolved in 1225 L of water)). The organic phase was concentrated under vacuum to a volume of 500 L.

A sample of the amide was characterized. **2-Chloro-*N*-[3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropyl]-acetamide (9):** mp 115−117.5 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.48 (t, J = 7.0 Hz, 3H), 3.16−3.31 (m, 2H), 3.97 (s, 2H), 4.05−4.12 (m, 3H), 4.31 (s, 1H), 4.58 (d, J = 8.2 Hz, 1H), 6.56−6.93 (m, 4H), 7.29−7.48 (m, 5 H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 15.06, 41.21, 42.83, 64.49, 73.88, 87.77, 113.16, 120.33, 121.14, 124.04, 127.55, 129.05, 129.10, 137.87, 147.90, 150.32, 166.10. LRMS-APCI *m*/*z* calcd for $C_{19}H_{23}ClNO_4$ $(M + H)^+$: 364. Found: $m/z = 364$ $[M + 1]^+$. Anal. Calcd for $C_{19}H_{22}ClNO_4$: C, 62.72; H, 6.09; Cl, 9.74; N, 3.85. Found: C, 62.66; H, 6.02; Cl, 9.56; N, 3.83.

IPA (813 L) and *tert*-butanol (48 kg) were charged to a 4000 L reactor and held at about 20 °C. Potassium isopropoxide (319.4 kg of a 20% solution) in IPA was added. The IPA solution was then transferred to the slurry of **9**, maintaining the temp >20 °C. After 1 h, an 8% solution of HCl in water was added to a pH between 4 and 7.2 (about 164 L). The mixture was then distilled under vacuum to a volume <1000 L and then cooled to <45 °C. Toluene (376 L) and water (384 L) were added. The phases were separated, and the aqueous phase was extracted with 2 × 376 L of toluene. The toluene phases were combined and washed with a solution of 5 kg of NaCl in 1105 L of water. The phases were separated, and the toluene solution was washed with 10% NaCl (2 × 419 kg). The toluene solution was then distilled under vacuum and the final volume adjusted to 600 L with toluene.

A sample of the lactam was characterized as a colorless glass. **6-[(2-Ethoxyphenoxy)phenylmethyl]-3-morpholinone (10):** ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.41 (t, J = 7.0 Hz, 3H), 3.03−3.07 (m, 1H), 3.27 (dd, J = 11.7, 11.3 Hz, 1H), 4.04 (q, J = 7.0 Hz, 2H), 4.15−4.18 (m, 1H), 4.21 (d, J = 12.9 Hz, 1H), 4.27 (d, J = 12.9 Hz, 1H), 5.22 (d, J = 6.3 Hz, 1H), 6.7−6.9 (m, 4H), 7.07 (br s, 1H), 7.26−7.39 (m, 5H).^{13}C NMR (100.62 MHz, $CDCl_3$) δ 15.19, 42.98, 64.75, 67.89, 75.82, 76.96, 82.22, 114.32, 118.96, 121.06, 123.07, 127.53, 128.69, 137.08, 147.55, 150.26, 169.37. LRMS-APCI *m/z* calcd for $C_{19}H_{22}NO_4$ $(M + H)^+$: 328. Found: *m/z* = 328 $[M + 1]^+$. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.32; H, 6.62; N, 4.22.

Two hundred liters of toluene and 450 kg of Vitride were charged. The solution was cooled to <10 °C, and the solution of **10** in toluene was added to the Vitride, maintaining the temp <10 °C with rapid agitation. The solution was stirred for 15 min after completion of the addition. A solution of NaOH (53 kg 15% solution) and 42 L of water were slowly added to the Vitride solution, maintaining the temperature <55 °C. When the quench was complete, 456 kg of 15% NaOH and 456 L of water were added. The mixture was stirred for 15 min, and then the aqueous phase was removed. The toluene solution was washed with 5% Na_2CO_3 solution (3 × 122 L), 1500 L of water was added, and the pH was adjusted to 3 to 3.5 with 8% HCl (105 kg). The aqueous phase was separated, and 1617 kg toluene was added. The pH was adjusted to 10−12 with 10% NaOH (70 L), and the toluene phase was removed and washed with 122 kg of 5% Na_2CO_3 solution. The toluene phase was washed with 440 L of water and then distilled to an oil; 250 L of acetone was added. The solution was clarified by recirculation through a carbon filter for 30 min. Methanesulfonic acid (13.03 L) was added, and the slurry was stirred at 0−5 °C for 1 h. The solids were filtered and washed with 400 L of acetone cooled to 0 °C. The solids were dried to yield 78.7 kg (62% overall from **8**) of reboxetine methanesulfonate (**1**). Mp 148.4−149.1 °C (lit. mp 145−146 °C).[1] ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.43 (t, J = 7.0 Hz, 3H), 2.71 (s, 3H), 2.9−3.1 (m, 2H), 3.29−3.35 (m, 2H), 3.89−3.95 (m, 1H), 4.02−4.08 (m, 3H), 4.24−4.28 (m, 1H), 5.13 (d, J = 4.3 Hz), 6.66−6.90 (m, 4H), 7.26−7.39 (m, 5H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 15.15, 39.50, 43.16, 44.68, 64.07, 64.56, 75.88, 82.2, 113.85, 119.0, 120.94, 123.27, 127.51, 128.62, 136.82, 147.36, 150.17. LRMS-APCI *m/z* calcd for $C_{19}H_{23}NO_3$ $(M + H)^+$: 314. Found: *m/z* = 314 $[M + 1]^+$. Anal. Calcd for $C_{19}H_{23}NO_3-CH_3SO_3H$: C, 58.66; H, 6.65; N, 3.42. Found: C, 58.83; H, 6.70; N, 3.30.

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