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Commercial Synthesis of (*S*,*S*)-Reboxetine Succinate: A Journey To Find the Cheapest Commercial Chemistry for Manufacture

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ABSTRACT: The development of a synthetic process for (*S*,*S*)-reboxetine succinate, a candidate for the treatment of fibromylagia, is disclosed from initial scale-up to deliver material for registrational stability testing through to commercial route evaluation and subsequent nomination. This entailed evaluation of several alternative routes to result in what would have been a commercially attractive process for launch of the compound.

A commercial synthetic route to an active pharmaceutical ingredient (API) needs to meet many criteria in terms of safety, the environment, legality, control, and throughput.[1] Cost is also an important factor, and a commercial route to an API that addresses the cost of goods is no longer sufficient to compete in the long term with patent exclusivity and generic competition. It is therefore important to develop the cheapest commercial route as early as possible in the lifecycle of a compound, where even modest cost improvements can result in large savings in the cost of manufacturing a drug substance.[2] Savings can also be realized in the short term through cheaper raw material costs, higher utilization factors of input materials, and shorter manufacturing times, which all unite to produce a simpler supply chain in both the short and long term.

Reboxetine mesylate (**1**), a selective norepinephrine reuptake inhibitor (NRI), is an antidepressant currently approved and marketed in over 60 countries with the trade name Edronax. The (*S*,*S*)-enantiomer is significantly more active than the racemate in a number of biological assays,[3] and (*S*,*S*)-reboxetine succinate (**2**) has been under late stage development at Pfizer for the treatment of fibromyalgia (Figure 1).

There are several published syntheses of the reboxetine structure in both racemic and enantioenriched forms, and many of these share the same common bond disconnections with a three-step process to build up the morpholine ring in **7** from the prerequisite amino alcohol (**3** or **4**) (Scheme 1).[4] The majority of the published routes also introduce the 2-ethoxyphenol fragment as the penultimate step,[5] requiring the use of the stoichiometric aryl-tricarbonylchromium reagent **8**. These syntheses are 8 or 9 linear steps from raw materials (not including preparation of **8**) and deliver the free base **7** in overall low yields ranging from 6% to 30%.

The first formal synthesis of **2** was published in 1985, utilizing the same bond-forming chemistry as used for the racemate (Scheme 2), with introduction of the chirality through the chiral epoxide **14**, which was accessed from the known *trans*-[(2*R*,3*R*)-3-phenyloxiran-2-yl]methanol (**10**).[6] An improved approach was published in 2007 from Pfizer,[7] with selective introduction of the requisite chiral epoxide **10** utilizing the Sharpless oxidation protocol (Scheme 2). This delivered (*S*,*S*)-reboxetine succinate (**2**) in 19% overall yield over three telescoped steps (33% from the advanced chiral diol **11**) in gram quantities using the standard three-step morpholine synthesis.

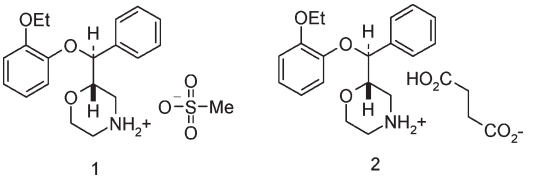

Figure 1. Reboxetine mesylate (**1**) and succinate (**2**).

As (*S*,*S*)-reboxetine succinate (**2**) progressed through late stage development, we had to balance meeting the short-term clinical demand against the long-term goal of identifying and developing the cheapest commercial synthesis. Herein this paper describes our recent efforts towards achieving this.

To support the phase 2 clinical demand, the first three batches of (*S*,*S*)-reboxetine succinate (**2**) were prepared via a classical resolution of the racemic commercial product, Edronax (**1**), using (*S*)-mandelic acid (Scheme 3). The mesylate salt (**1**) was broken to generate the requisite free amine, and this was resolved to the crystalline (*S*,*S*)-reboxetine-(*S*)-mandelate (**18**) in ~40% recovery and 92−95% ee. The material was recrystallised to upgrade the enantiomeric purity to >99.7% followed by a further salt switch to succinate to deliver the desired product **2** in an overall yield of 31%. Whilst this route was able to deliver more than 100 kg of (*S*,*S*)-reboxetine succinate (**2**) using relatively simple unit operations, it suffered from the high cost and supply issues of using an established drug substance as a starting material. In order to prepare 1 kg of **2**, 3 kg of Edronax (**1**) was used, and with the nontrivial route required to synthesize **1**, this impacted process throughput and resulted in high waste generation.

Early investigations examined a direct resolution of reboxetine free base **19** without the need to form or break the mesylate salt (Scheme 4). This approach was used to deliver 40 kg of material, and whilst several improvements were made to the early steps to improve robustness and decrease waste (e.g., replacing excess Vitride with stoichiometric $LiAlH_4$), the route suffered the same

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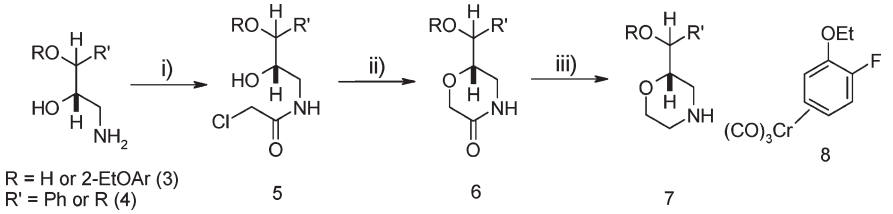
Scheme 1. Common 3-Step Morpholine Syntheses[a]



[a] (i) chloroacetyl chloride, NEt_3; (ii) KO*t*Bu, ROH; (iii) Vitride.

disadvantages, yielding API in 19−21% yield from the amino alcohol *rac*-**15**. The key disadvantages are

- Approximately 5 kg of amino alcohol *rac*-**15** was required to deliver 1 kg of API.
- High dilutions were required in the first step equating to 110 L of solvent per kg of API.
- High waste generation
- Low throughput

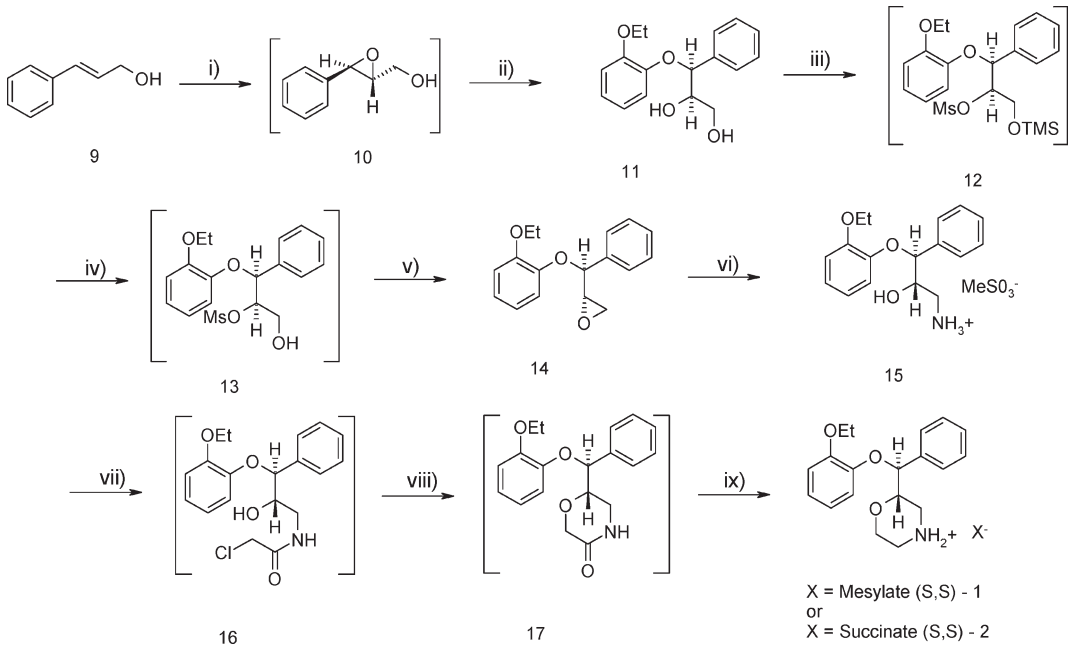
It was clear that in order to meet the demand for material moving into phase 3 and beyond, a more efficient synthesis would be required. As detailed in Scheme 2, Edronax is synthesized from a late stage racemic amino alcohol intermediate *rac*-**15** through the standard morpholine ring formation chemistry. Significant quantities *rac*-**15** were available compared to Edronax (**1**), and this provided us with a more amenable point from which to prepare (*S*,*S*)-reboxetine succinate (**2**) to support further clinical demands.

An effective solution was quickly identified starting with the amino alcohol *rac*-**15** used in the late resolution approach. By shifting the resolution from the end to the beginning of the synthesis, a significant improvement in throughput and yield should be realized and with minimal development as the same morpholine ring construction could be employed (Scheme 5).

A screen of a wide range of resolving agents and solvent systems for the amino alcohol *rac*-**15** identified several hits (Table 1), and upon verification only (*R*)-camphanic acid proved to be robust and scalable (entry 3).

Because of its manufacture from camphor, camphanic acid proved difficult to access as both enantiomers, and unfortunately the widely available (*S*)-configuration led to precipitation of the *undesired* enantiomer of **15** as the requisite salt. A work around was duly developed utilising 0.55 equiv of the resolving agent, where the undesired enantiomer could be removed by filtration as the corresponding salt (at 97.8% ee). The filtrate contained the desired enantiomer as the free base (∼88% ee), and this could be successfully precipitated as the corresponding benzoate salt **20** with concomitant upgrade of the ee to >99% (Scheme 5). This process robustly scaled to 150 kg starting material input and delivered material in exceptional yields for a resolution step (average of 47%). The introduction of the new resolution resulted in a 3-fold increase in throughput due to carrying this out early in the synthetic route versus late in the route as previously conducted.

Scheme 2. First Synthesis of (*S*,*S*) Reboxetine Succinate (2)[a]



[a] (i) L-DIPT, Ti(*i*-PrO)$_4$, TBHP, EtOAc; (ii) 2-ethoxyphenol, NaOH [58% over 2 steps]; (iii) TMSCl, NEt_3 then $MeSO_3Cl$, NEt_3; (iv) H_2O, HCl, EtOAc; (v) NaOH, Bu_3MeNCl, PhMe [60% over 4 steps]; (vi) NH_3, then $MeSO_3H$; (vii) chloroacetyl chloride, NEt_3; (viii) *t*-AmONa; (ix) Vitride, PhMe then succinic acid or $MeSO_3H$, solvent, [55% over 4 steps].

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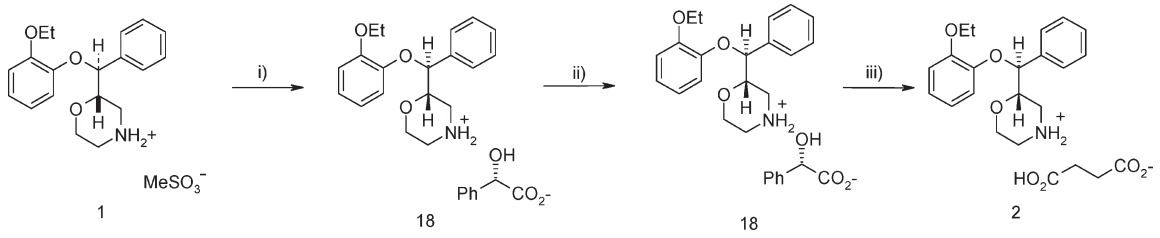
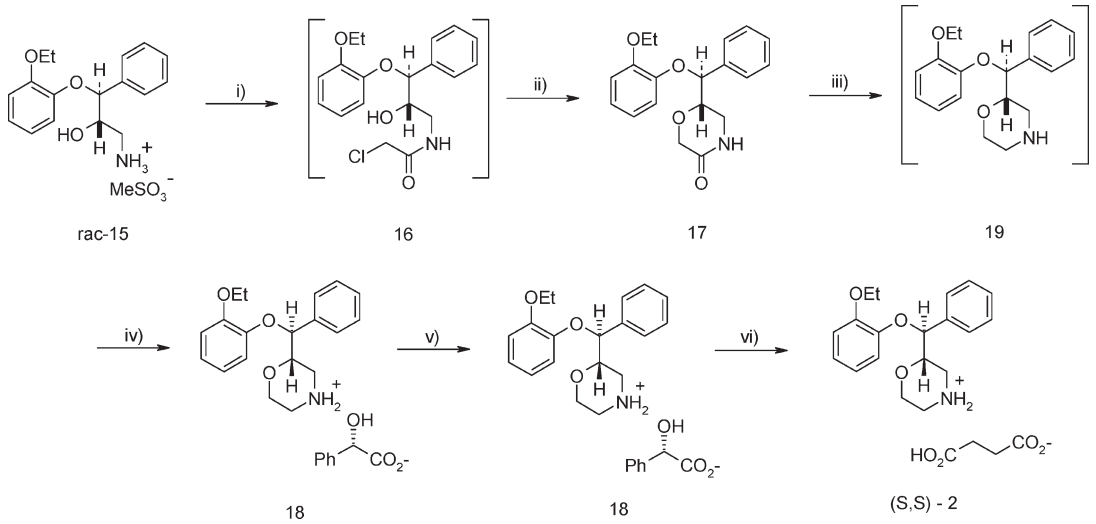
Scheme 3. Resolution of Edronax (1)[a]



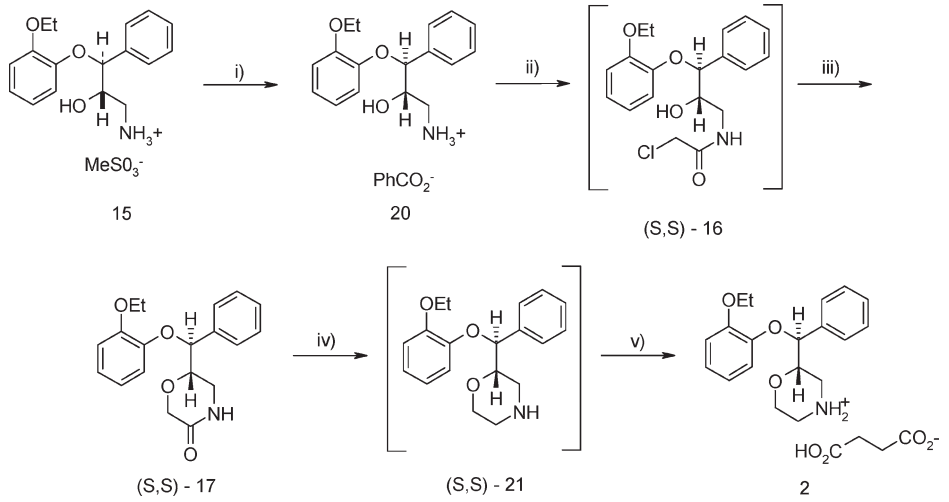
[a] (i) aq NaOH, DCM then (*S*)-Mandelic acid, EtOH, [43%]; (ii) EtOH recrystallisation, [92%]; (iii) aq NaOH, DCM then succinic acid, EtOH, [88%].

Scheme 4. Late Resolution Approach[a]



[a] (i) Chloroacetyl chloride, THF, aq NaOH; (ii) KO*t*Bu, THF [81.0% 50 kg batch size]; (iii) $LiAlH_4$, THF then aq sodium tartrate, PhMe, EtOH; (iv) (*S*)-mandelic acid, EtOH [34.5%]; (v) EtOH recrystallisation [91.5% 50 kg batch size]; (vi) TBME, EtOH, aq NaOH then succinic acid, EtOH [79.9% 40 kg batch size].

Scheme 5. Optimised Early Resolution Approach to (*S,S*)-Reboxetine Succinate (2)[a]



[a] (i) aq NaOH, toluene, (*S*)-camphanic acid then aq NaOH, toluene, benzoic acid [47.4% over 3 steps, 75 kg batch size]; (ii) chloroacetyl chloride, THF, aq NaOH; (iii) KO*t*Bu, *t*BuOH, cyclohexane [75.8% over 2 steps, 60 kg batch size]; (iv) $LiAlH_4$, THF then $N(CH_2CH_2OH)_3$, cyclohexane, EtOH; z(v) succinic acid, EtOH, [71.8% over 2 steps, 50 kg batch size].

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Table 1. Resolution Screen for the Amino Alcohol *rac*-15

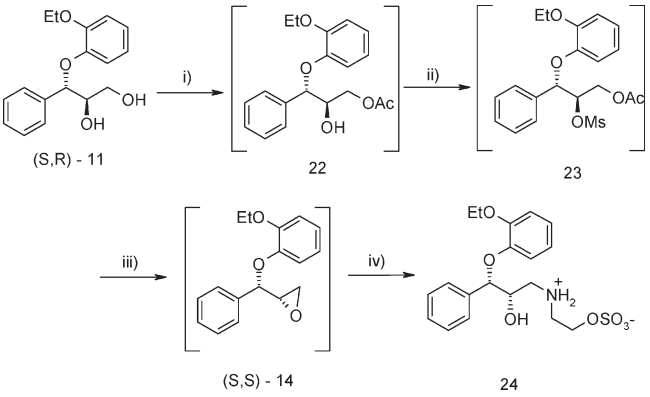
entry	optically active acid	solvent	% ee of liquors
1	(*S*)-(−)-4-(2-chlorophenyl)-2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide	IPA	59
2	(*S*)-(+)-2-hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinane	IPA	57
3	(1*R*)-(+)-camphanic acid	toluene	89
		THF	90
		EtOAc	97
		acetone	75
		IPA	96
		MeCN	100
		MeTHF	100
4	*N*-acetylhydroxy-L-proline	IPA	69
		THF	94
		EtOAc	92
5	*N*-(carbobenzyloxy)-L-phenylalanine	Acetone	61
		THF	81
		MeTHF	77
		5% water/THF	79
6	*N*-acetyl-L-aspartic acid	EtOAc	76
		IPA	72
7	(*Z*)-L-serine	EtOAc	57
		IPA	55
8	0.9 equiv di-*P*-toluoyl-L-tartaric acid 0.1 equiv L-tartaric acid	EtOAc	88
9	0.9 equiv di-*P*-toluoyl-L-tartaric acid 0.1 equiv dipivoyl-L-tartaric acid	EtOAc	87

The second major change in the early resolution approach was to telescope the reduction step directly into the salt formation, which placed significant challenges on the use of $LiAlH_4$ and the removal of the aluminum and lithium waste. To address these an efficient and scalable workup need to be developed. Initially an aqueous disodium tartrate wash was developed; however, this suffered from mass transfer issues upon scaleup, and hence an alternative was quickly developed utilizing triethanolamine as a fully soluble quench procedure to completely eliminate the previously observed issues. Although development of the route shown in Scheme 5 gave an efficient process that was capable of delivering several hundreds of kilograms of clinical grade material, ultimately this process was still far from ideal in a manufacturing setting in the long term.

The key areas to address with a commercial route for (*S,S*)-reboxetine succinate are

- Control of the stereochemistry. The best methodology for introducing the chirality proved to be that already supported in the literature, via Sharpless asymmetric epoxidation of cinnamyl alcohol (Scheme 2).
- Introduction of the 2-ethoxy phenol subunit. The best methodology for introducing the 2-ethoxyphenol subunit proved to be via a nucleophilic based approach to glycidyl epoxide (**10**, Scheme 2).
- Best methodology to build the morpholine ring. The standard three-step morpholine synthesis was substituted for by a streamlined two step procedure from the prerequisite epoxide via the use of 2-amino ethyl hydrogen sulfate (2-AEHS), as a two carbon subunit at the correct oxidation state. Using a nucleophile such as 2-AEHS eliminates the necessity for subsequent redox operations to achieve the desired oxidation state of the eventual morpholine.

Scheme 6. Step 1 of the Commercial Route to (*S,S*)-Reboxetine Succinate[a]



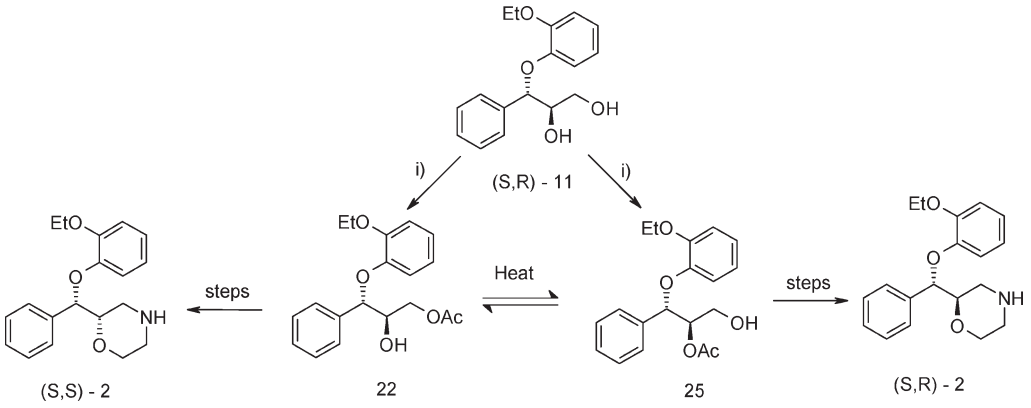
[a] (i) Novozym 435 (*Candida antarctica* lipase B), isopropenyl acetate, PhMe; (ii) MsCl, NEt_3, PhMe; (iii) aq NaOH, PhMe, $MeN(n\text{-}Bu)_3Cl$, PhMe; (iv) $H_2NCH_2CH_2OSO_3H$, DBU, PhMe, EtOH, [86% over 4 steps].

A commercial route was hence selected and developed that incorporated six chemical transformations in a total of two synthetic steps with one isolated intermediate, Scheme 6. With the enantioenriched diol (*S,R*)-**11** in hand, the next step involved regioselective protection of the primary alcohol. Our initial attempts utilized a trimethylsilyl protecting group (Scheme 2); unfortunately, these suffered from moderate yields and moderate regiocontrol and were found to be nonrobust when processing larger batch sizes. An alternative protecting group was sought, and after investigation of several alternatives, an acetyl group was identified as a suitable alternative.

Classical chemical acetylation conditions suffered from significant levels of di-acetylation and poor regiocontrol, and hence a biocatalytic acylation was investigated and met with great success. A highly active and commercially available immobilized enzyme preparation, Novozym 435 (*Candida antartica* lipase B), was identified along with conditions that were amenable to telescoping, allowing the selective mono-acetylation of the primary alcohol as the corresponding acetate **22** with >98% regioselectivity in >99% in situ yield. The regioselectivity of this transformation could further be improved to 99% whilst maintaining the excellent in situ yield by the incorporation of 10% THF in the solvent system on a laboratory scale. Simple filtration removed the biocatalyst, and the solution was successfully progressed onto the next transformation. It was also noted that on laboratory scale the recovered enzyme catalyst could be recycled and reused successfully with no loss in regioselectivity or in situ yield over several cycles.

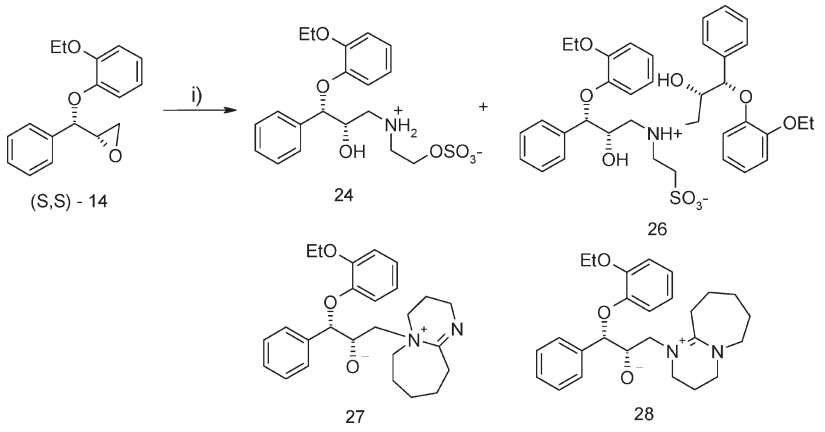
The major process impurity observed in this transformation was the acetylated secondary alcohol **25**. This impurity was of some concern as the formation of the secondary acetylated product **25** would ultimately result in producing the diastereoisomer of the API (*S,R*)-**2**. There are two proposed mechanisms for the formation of this impurity: via isomerisation of the

Scheme 7. Formation of (*S,R*)-Reboxetine through Uncontrolled Diol Acetylation Regioselectivity[a]



[a] (i) Novozym 435 (*Candida antarctica* lipase B), isopropenyl acetate, PhMe [quant].

Scheme 8. Formation of the Zwitterion 24 via Opening of the Epoxide (*S,S*)-14[a]



[a] (i) $H_2NCH_2CH_2OSO_3H$, DBU, PhMe, EtOH [86%].

acetylated primary alcohol **22** or via the imperfect regioselectivity of the enzyme (Scheme 7). Closer investigation of the formation of **25** suggested both pathways were playing a role. Optimal control of the regioisomer formation could be achieved through low reaction temperature and short reaction times whereby carrying out the acetylation below 25 °C and for less than 16 h proved highly beneficial. This process gave a solution of **22** in toluene for progression into the later stages of the synthesis.

With **22** in hand the next transformation involved activation of the secondary alcohol for S_N2 displacement with the primary alcohol upon acetyl deprotection. The methanesulfonyl leaving group was utilized resulting in a quantitative yield of **23**. After a standard workup procedure the toluene solution containing the product was telescoped into the next transformation.

The terminal epoxide (*S,S*)-**14** was delivered in a highly concise manner by treatment of the toluene solution containing **23** with 12 M sodium hydroxide solution in the presence of a catalytic phase transfer catalyst. The combination of base and catalyst were extensively investigated, and the best combination of reaction time (less than 6 h) and ambient reaction temperatures along with the low cost of reagents delivered a highly efficient and economical chemical transformation. Methyltributylammonum chloride was chosen as this was the cheapest phase transfer catalyst on scale and could also be sourced as an aqueous solution for ease of charging in a manufacturing environment.

Because of concerns over the stability of the terminal epoxide (*S,S*)-**14** and the difficulties involved in isolating an oil in a manufacturing environment, it was decided to telescope this intermediate as a solution in toluene into the next step, ring opening with 2-aminoethyl hydrogen sulphate (2-AEHS) (Scheme 8). As 2-AEHS exists as a zwitterion, treatment with a base was required to liberate the amine functionality for the reaction. After extensive screening of suitable bases the optimum proved to be 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU).[8] The use of DBU maximised product formation whilst simultaneously minimising the formation of the zwitterionic amine adducts such as **27** and **28** when employing DBU. The major impurity, dimer **26**, forms during this transformation as a result of the desired product **24** reacting with additional epoxide (*S,S*)-**14**. The key parameters that were important to controlling the formation of **26** were found to be charge of DBU, charge of 2-AEHS, mode of addition of the reagents, cumulative addition time, and reaction temperature. A quick and efficient isolation of **24** was developed by pH adjustment of a basic solution containing the zwitterion **24** with hydrochloric acid to the isoelectric point of **24** of 5.1, and then

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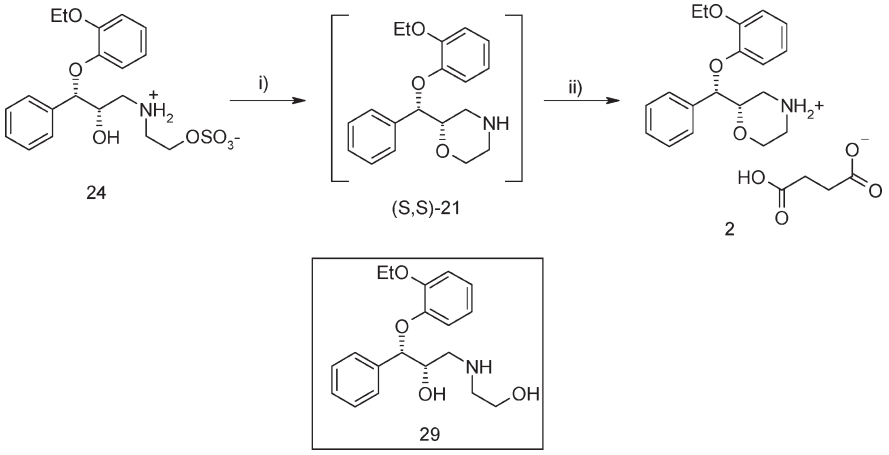
Scheme 9. Morpholine Formation in the Commercial Route of (*S,S*)-Reboxetine Succinate (2)[a]



[a] (i) NaOH, THF, EtOH; (ii) succinic acid, EtOH [78−80%].

simple filtration and washing with water yielded the desired product containing the dimer **26**.

Despite extensive investigations the formation of the dimeric impurity **26** could not be prevented, but it could be minimized and subsequently purged further by the introduction of an ethanol reslurry of the isolated material. This resulted in minimising the levels of **26** in the isolated product from 8% to less than 3%. Such levels were well tolerated and purged in the downstream chemistry prior to API formation. It was later found that the dimeric impurity could be tolerated up to 8% in the downstream chemistry with only an impact on the yield of the isolated API (81% vs 74%). Avoiding the reslurry would ultimately make the process more streamlined and ultimately cheaper as the reslurry and subsequent drying of the zwitterion **24** is a time-consuming operation on a manufacturing scale.

With the zwitterion **24** in hand the final chemical transformation involved morpholine formation and then subsequent succinate salt formation to furnish the API **2**. A base-mediated ring closure of **24** was explored with a focus on screening a wide range of bases in solvents where salt formation could be carried out following reaction completion and workup (Scheme 9). Both solid NaOH and KOH were quickly identified as effective bases, which at high concentrations suppress the formation of the major impurity observed in such chemistry, the amino diol **29**. The use of solid sodium hydroxide in THF in combination with an additive significantly increased the rate of reaction as well as also improving the yield from 65% to 90%. Several solvent additives were identified that yielded homogeneous reaction conditions whilst maintaining the chemoselectivity, reaction rates, and high yield of this chemical transformation (water, MeOH, EtOH, *t*-BuOH, *i*-PrOH, *t*-AmylOH). It was found that alcohols offered a far greater robust operating range compared to water. The use of water required less than 1% incorporation into the solvent matrix. At these levels this proved highly beneficial, whereas at levels greater than 3% both a retardation of the reaction rate as well as an increase in the production of the amino diol **29** were observed.[9]

The new process delivered clinical grade API in 78−80% yield that equates to an overall yield of 67−69% over six chemical transformations. Compared to the previously optimized 33% for the early resolution route (Scheme 3) an almost double improvement has been realized through the identification and

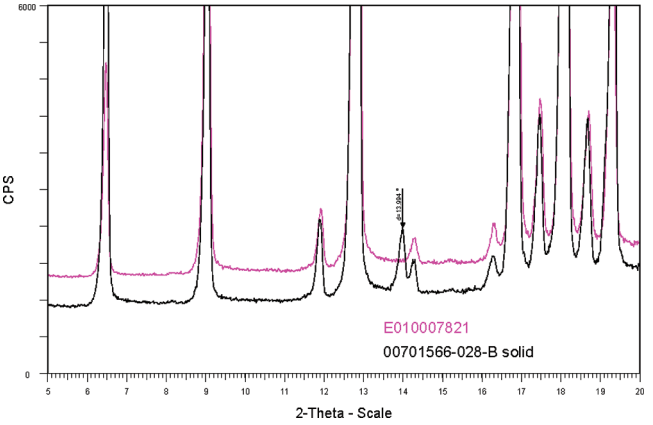


Figure 2. Powder pattern highlighting additional peak at 13.99° 2θ (black line) compared to reference standard of (*S,S*)-reboxetine succinate **2** (pink line).

development of the commercial route. When you compare the use of the diol (*S,R*)-**11** as a starting material through the previously published synthetic route[7] to the amino alcohol (*S,S*)-**15** coupled with the optimized three-step morphline formation highlighted earlier in this paper, which furnished (*S,S*)-reboxetine succinant (**2**) in an overall yield of 33%, you can see that a nearly double improvement in overall yield has also been realized by developing the commercial route.

With the change in synthetic route, several batches of API were synthesised to facilitate stability studies. The initially synthesized material prepared via the new commercial route suffered from out of specification residue on ignition (ROI) levels. Powder X-ray diffraction was used as a detection technique to identify monosodium succinate as the impurity causing the ROI issue (Figure 2). This was found to be a result of sodium hydroxide carryover from the morpholine ring closure into the succinate salt formation.

The problem was quickly rectified by the implementation of a water wash prior to salt formation. The volume of water used was crucial so as to avoid yield losses to the aqueous phase. To monitor this crucial phase separation and to ensure that all the sodium hydroxide was removed from the organic phase prior to

salt formation, an online conductivity-based process analytical technique (PAT) was developed.[10]

With the successful laboratory development of the commercial route to (*S*,*S*)-reboxetine succinate (**2**) the process was transferred to our large scale laboratory, and the chemistry was successfully scaled to a 1 kg input of the chiral diol (*S*,*R*)-**11**. No deviations were observed and clinical grade API was manufactured in 70% yield over the two steps and six chemical transformations. The first step was accomplished in 86% yield followed by ring closure and salt formation in 81% yield.

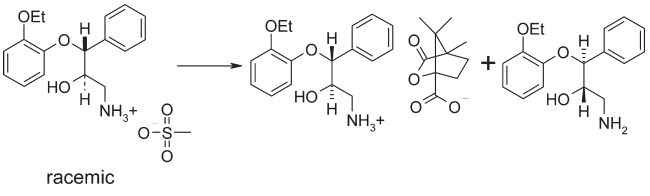
With the demonstration of the new commercial route, comparison with the previous manufacturing routes could be made. The implementation of a new commercial route had the opportunity to realize large savings for the launch campaign whilst simultaneously reducing the waste generated, with estimations showing a >500 MT reduction from just early development to product launch and >1300 MT from product launch to peak volume.

The commercial manufacture of (*S*,*S*)-reboxetine succinate has undergone several route changes to meet the clinical demands. The utilization of a late stage resolution approach enabled fast delivery of drug substance early in the project. Later the early resolution based approach allowed delivery of bulk material to fund large clinical trials. It was quickly identified that in order to meet the long-term demands of the project a new commercial route was required. Identification of the commercial route was realized after evaluating several alternatives and selecting one for further development to allow demonstration on a kilogram scale. The change to the commercial route afforded a 58% improvement in overall yield and a significant saving in API cost along with a potential to reduce the waste generated by over 1300 MT/yr at peak drug substance volumes.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus spectrometer at 400 and 100.6 MHz, respectively.

(2*R*,3*R*)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenylpropylamine (*S*)-(−)-Camphanate



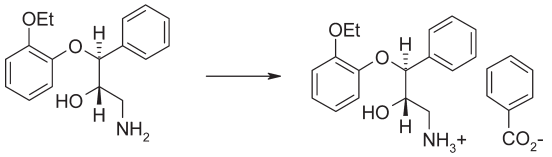
Stage 1: Mesylate Salt Break. (i) Racemic (2*RS*,3*RS*)-3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropylamine mesylate (75.0 kg, 207.0 mol, 1.0 equiv) was agitated in toluene (750 L) at 55 °C. A solution of NaOH (15.0 kg, 375.0 mol, 1.8 equiv) in water (150 L) was added. The slurry turned into a clear biphasic solution within 30 min, and the reaction mixture was agitated for an additional 1 h at 55 °C. The lower aqueous layer was removed and the upper organic layer was progressed to the next stage.

Stage 2: R,R-Camphanate Salt Formation. (ii) To the organic solution was added (*S*)-camphanic acid (20.4 kg, 102.8 mol, 0.55 equiv) at 55 °C. A white precipitate appeared within 30 min. The temperature was increased to 75 °C, and the slurry was agitated for an additional 2 h after which the temperature was decreased to 30 °C over 3 h and maintained for 16 h. The slurry was filtered to remove the undesired enantiomer, and the filter cake was washed with toluene (150 L) and dried to yield the desired compound as a white solid (52.7 kg, 52.6%). This material assayed at 97.8% ee. Mp 194−196 °C. ^{1}H NMR (400 MHz, d_4-MeOD) δ 7.46−7.44 (m, 2H), 7.40−7.31 (m, 3H), 6.98 (dd, J = 8.2, 1.0 Hz, 1H), 6.88 (ddd, J = 8.2, 6.4, 2.7 Hz, 1H), 6.74−6.69 (m, 2H), 5.20 (d, J = 5.1 Hz, 1H), 4.21−4.11 (m, 3H), 3.08−2.98 (m, 2H), 2.48 (ddd, J = 13.2, 10.5, 4.2 Hz, 1H), 2.00−1.83 (m, 2H), 1.55 (ddd, J = 13.0, 9.0, 4.1 Hz, 1H), 1.48 (t, J = 7.0 Hz, 3H), 1.09 (s, 3H), 1.06 (s, 3H), 0.93 (s, 3H). For chiral HPLC assay details, see Table 2.

Table 2

column	Chiralpak AD-H
mobile phase	93:7 heptane/isopropy alcohol + 0.3% TFA + 0.2% DEA
flow	1.5 mL/min
detector	276 nm
run time	12.0 min
column temperature	45 °C
retention times	
(2*R*,3*R*)-3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylproylamine	6.9 min
(2*S*,3*S*)- 3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylproylamine	9.5 min

(2*S*,3*S*)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenylpropylamine Benzoate



Stage 3: (S,S)-Benzoate Salt Formation. (iii) The combined organic liquors obtained at the end of step (ii) above were heated to 45 °C and treated with a solution of NaOH (3.8 kg, 93.8 mol, 0.45 equiv) in water (1.0 L). The resulting biphasic solution was agitated at 45 °C for 3 h after which the lower aqueous phase was removed. The upper organic layer was dried by distillation under Dean−Stark conditions, cooled to ∼65 °C, and subsequently used in the next step without further purification. Alternatively, the title compound can be isolated by the addition of an anti-solvent such as cyclohexane that results in crystallization of the desired compound. This material assayed at 88% ee via chiral HPLC method as before. Mp 98−101 °C. ^{1}H NMR (400 MHz, d_4-MeOD) δ 7.44−7.41 (m, 2H), 7.38−7.26 (m, 3H), 6.94 (dd, J = 8.1, 1.5 Hz, 1H), 6.87−6.83 (m, 1H), 6.77−6.68 (m, 2H), 5.08 (d, J = 6.3 Hz, 1H), 4.15−4.08 (m, 2H), 3.94 (q, J = 6.3 Hz, 1H), 2.63 (d, J = 5.7 Hz, 2H), 1.46 (t, J = 7.03 Hz, 3H)

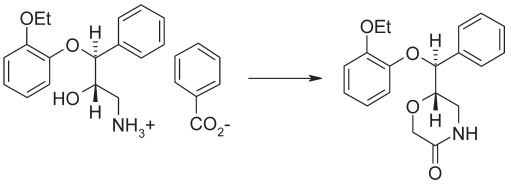
A previously prepared solution of benzoic acid (3.8 kg, 30.8 mol, 0.15 equiv) in toluene (1 L) was added to the organic solution obtained at the end of step (iii). Nucleation was initiated by seeding (1 wt %) and was ripened at 65 °C for 5 h. Further benzoic acid (7.5 kg, 61.5 mol, 0.30 equiv) in toluene (150 L) was added over ∼3 h while maintaining the temperature between 60 and 70 °C. The slurry was agitated for 16 h, cooled to 20 °C over 4 h, and agitated for a further for 4 h at 20 °C. The slurry was filtered, and the filter cake was washed with toluene (150 L) and dried to yield (2*S*,3*S*)-3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropylamine benzoate (41.0 kg, 47.4%) as a white solid. This material assayed at >99% ee. Mp 148−150 °C. ^{1}H NMR

Table 3

column	Chiralpak AD-H
mobile phase	93:7 heptane/isopropy alcohol + 0.3% TFA + 0.2% DEA
flow	1.5 mL/min
detector	276 nm
run time	12.0 min
column temperature	45 °C
retention times	
(2*R*,3*R*)-3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylproylamine	6.9 min
(2*S*,3*S*)- 3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylproylamine	9.5 min

(400 MHz, d_4-MeOD) δ 7.96−7.93 (m, 2H), 7.45−7.30 (m, 8H), 6.97 (dd, J = 8.0, 1.0 Hz, 1H), 6.88 (ddd, J = 8.3, 6.3, 2.4 Hz, 1H), 6.74−6.68 (m, 2H), 5.19 (d, J = 5.1 Hz, 1H), 4.20−4.10 (m, 3H), 3.06−2.97 (m, 2H), 1.47 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, d_4-MeOD) δ 175.4, 150.7, 146.8, 138.9, 138.7, 131.6, 130.4, 129.7, 129.6, 128.9, 128.6, 123.7, 122.1, 118.4, 114.9, 85.5, 72.2, 65.8, 43.5, 15.4. m/z $[M + H]^+$ = 288. For chiral HPLC assay details, see Table 3.

(2*S*,3*S*)-2-[α-(2-Ethoxyphenoxy)benzyl]morpholine-5-one



(2*S*,3*S*)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenylpropylamine benzoate (60.0 kg, 146.0 mol, 1.0 equiv) was dissolved in tetrahydrofuran (300 L) and water (60 L) at 20−25 °C. An aqueous solution of sodium hydroxide (17.6 kg, 440.0 mol, 3.0 equiv) in water (60 L) was added, and the biphasic mixture was agitated for 30 min. The reaction mixture was cooled to 10 °C, and a solution of chloroacetyl chloride (19.8 kg, 176.8 mol, 1.2 equiv) in tetrahydrofuran (15 L) was added over 1 h. The reaction mixture was warmed to ambient temperature, and cyclohexane (120 L) was added. The phases were separated, and the upper organic phase was washed with 15% w/v brine (30 L) and azeotropically dried by distillation to give an organic solution containing the amide **16**.

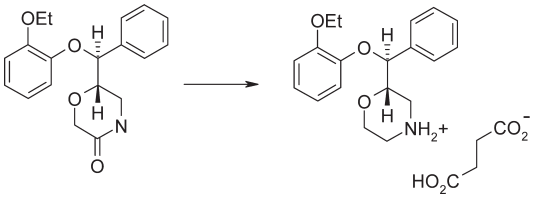
The organic solution from above was added over 30 min to a 5 °C solution of potassium *tert*-butoxide (33.0 kg, 294.6 mol, 2.0 equiv) in THF (24 L) and *tert*-butanol (240 L). The reaction was agitated for 15 min and then quenched with 10 wt % aqueous acetic acid (120 L). The reaction mixture was allowed to warm to room temperature over 1 h, cyclohexane (120 L) was added, and the phases were separated. The upper organic phase was azeotropically dried by distillation and then distilled to ∼150 L (∼2.5 L/kg). Isopropyl alcohol (144 L) was added, and the reaction mixture was distilled to 2.4 L/kg. The solution was cooled to 10 °C, and the resulting slurry was granulated for 8 h and isolated by filtration. The solid was washed with isopropyl alcohol (60 L) and dried at 50 °C to yield the title compound as a white crystalline solid (36.2 kg, 75.8%). Mp 126−127 °C. ^{1}H NMR (400 MHz, d_4-MeOD) δ 7.46−7.43 (m, 2H), 7.37−7.28 (m, 3H), 6.92 (dd, J = 8.2, 1.6 Hz, 1H), 6.88−6.82 (m, 2H),

Table 4

column	Chiracel OJ
mobile phase	25:75 ethanol/heptane + 0.05% diethylamine
flow	0.70 mL/min
detector	275 nm
run time	30 min
retention times	
(2*R*,3*R*)-2-[α-(2-ethoxyphenoxy) benzyl]morpholine	9.3 min
(2*S*,3*S*)-2-[α-(2-ethoxyphenoxy) benzyl]morpholine	12.4 min

6.74−6.70 (m, 1H), 5.33 (d, J = 6.1 Hz, 1H), 4.29−4.18 (m, 3H), 4.12−4.04 (m, 2H), 3.35 (dd, J = 12.1, 10.5 Hz, 1H), 2.99 (dd, J = 12.1, 2.9 Hz, 1H), 1.43 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, d_4-MeOD) δ171.3, 151.3, 149.0, 138.7, 129.7, 129.6, 128.8, 123.8, 122.2, 119.4, 115.8, 83.0, 77.0, 68.3, 66.0, 43.7, 15.5. m/z $[M + H]^+$ = 328.

(2*S*,3*S*)-2-[α-(2-Ethoxyphenoxy)benzyl]morpholine Succinate Salt (*S*,*S*)-Reboxetine Succinate)

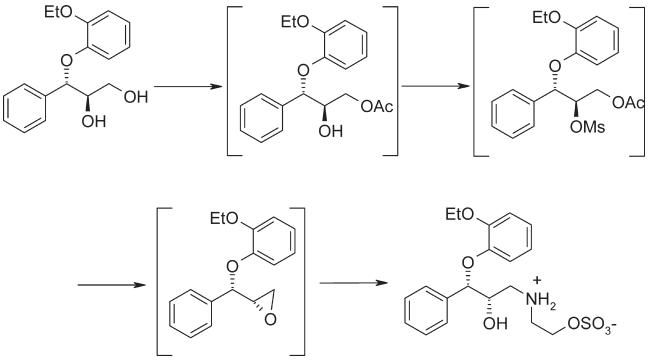


(2*S*,3*S*)-2-[α-(2-Ethoxyphenoxy)benzyl]morpholine-5-one (50.0 kg, 152.7 mol, 1 equiv) was dissolved in anhydrous THF (250 L) and added over 4 h to a 2.4 M solution of lithium aluminium hydride (63.5 L, 152.7 mol, 1 equiv) stirring at 20−25 °C. The reaction mixture was stirred for 2 h and quenched with addition of a solution of triethanolamine (53.6 kg, 360.0 mol, 2.4 equiv) in THF (100 L) over 2 h. The reaction was agitated for 30 min, and NaOH in water (25.7 kg in 250 L) was added. The reaction mixture was agitated for an additional 15 min, then cyclohexane (150 L) was added, and the phases were separated. The upper organic phase was washed twice with aqueous NaOH (2 × 12.8 kg NaOH in 125 L water) followed by water (50 L). The organic phase was azeotropically dried and distilled to ∼125 L (∼2.5 L/kg). Ethanol denatured with 3% cyclohexane (250 L) was added and distilled to ∼125 L (∼2.5 L/kg). The ethanol charge/distillation process was repeated to yield (*S*,*S*)-reboxetine free base as an ethanol solution.

Succinic acid (19.9 kg, 168.7 mol, 1.1 equiv) was dissolved in ethanol denatured with 3% cyclohexane (175 L) at 55 °C, and the solution was added to the solution of (2*S*,3*S*)-2-[α-(2-ethoxyphenoxy)benzyl]morpholine in ethanol from above. The reaction mixture was heated to reflux for 30 min and subsequently cooled to 0 at 0.3 °C/min. The reaction mixture was granulated for 1 h at 0 °C, and the solid was isolated by filtration. The solid was washed twice with ethanol denatured with cyclohexane (2 × 50 L) and dried at ∼55 °C to yield (*S*,*S*)-reboxetine succinate as a white crystalline solid (43.1 kg, 71.8%). This material assayed at greater than 99% ee. Mp 149−152 °C. $[\alpha]^{32}_D$ = (c 37, ethanol) +18.37. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.22−7.54 (m, 5H), 6.66−6.96 (m, 4H), 5.27 (d, J = 6.0 Hz, 1H), 4.01 (q, J = 7.1 Hz,

2H), 3.83 (m, 2H), 3.50 (m, 2H), 2.61−2.82 (m, 3H), 2.34 (br s, 4H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 174.4, 149.0, 147.3, 137.8, 128.2, 127.3, 120.7, 116.7, 114.4, 80.8, 77.5, 65.9, 64.1, 45.8, 44.1, 39.7, 39.5, 39.3, 39.1, 30.2, 14.9. m/z $[M + H]^+$ = 314. For chiral HPLC assay details, see Table 4.

2-{[(2*S*,3*S*)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenylpropyl]amino}ethyl Hydrogen Sulfate



Stage 1: Acetylation. Toluene (5.0 L) and isopropenyl acetate (765.0 mL, 6.9 mol, 2.0 equiv) followed by (2*R*,3*S*)-3-(2-ethoxyphenoxy)-3-phenylpropane-1,2-diol (1.0 kg, 3.5 mol, 1.0 equiv) were added to a 25 L fixed rig. The reaction mixture was agitated and heated to an internal temperature of 30 °C. Novozymes CaL B (20.0 g, 2 mol %) was added, and the mixture was agitated for 17 h. The enzyme was removed by filtration, and the filtrate was progressed to stage 2.

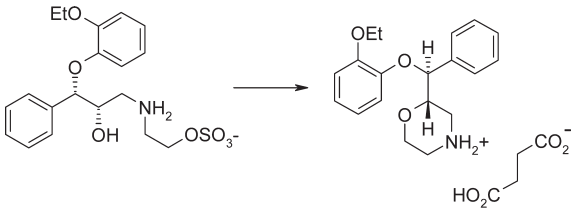
Stage 2: Mesylation. To a stirred solution from stage 1 at 20 °C was added triethylamine (822 mL, 5.9 mol, 1.7 equiv) in one portion. Methanesulfonyl chloride (362 mL, 4.7 mol, 1.4 equiv) in toluene (1.0 L) was added dropwise over ∼2 h. The reaction mixture was agitated for a further 1 h to ensure reaction completion. Aqueous hydrogen chloride (1 M, 3.0 L, 3.0 mol) was added in a single portion. The biphasic mixture was agitated for 30 min. The phases were separated, and the upper organic phase was progressed to stage 3.

Stage 3: Epoxide Formation. A solution of sodium hydroxide (1.4 kg, 36.0 mol) in water (3.0 L) and methyltributylammonium chloride (81.8 g, 347 mmol, 0.1 equiv) was added to the organic stream from stage 2. The resulting mixture was agitated for 3.5 h to ensure reaction completion. The phases were allowed to separat,e and the lower aqueous phase was discarded. The upper organic phase was washed with water (2.0 L) and progressed to stage 4.

Stage 4: Zwitterion Formation. In a separate vessel, 2-aminoethyl hydrogen sulfate (1.2 kg, 8.7 mol, 2.5 equiv) was slurried in toluene (2.0 L) and ethanol (2.0 L). 1,8-Diazabicyclo-[5.4.0]undec-7-ene (1.3 L, 8.6 mol, 2.48 equiv) was added in a single portion, and the contents were heated to 65 °C and agitated for 1 h to ensure complete deprotonation. The organic solution from stage 3 was diluted with toluene (5.0 L) and added to the activated amine mixture over 1 h. The mixture was agitated at 70 °C for 2 h post end of addition. The reaction mixture was subsequently cooled to ambient temperature and extracted into an aqueous solution of sodium hydroxide (416 g in 8.0 L of water, 3.0 equiv NaOH) for 2 h. The upper organic phase was discarded, and the lower aqueous phase was treated with conc HCl to adjust the pH to 5.1−5.2 (1.2 L, 36% conc HCl) resulting in crystallization of the product, which was isolated by filtration, washed with water (3.0 L), and dried to yield the desired product as an off white solid (1.2 kg, 86% yield).

The zwitterion product from above (1.2 kg, 3.0 mol, 1.0 equiv) was slurried in ethanol denatured with cyclohexane (6.1 L), heated to 50 °C, and then subsequently agitated for 2 h. The slurry was then cooled to 10 °C over 2 h and granulated for 16 h after which the slurry was filtered, washing with ethanol denatured with cyclohexane (2.5 L). A second wash was performed with ethanol denatured with cyclohexane (2.5 L), and the filter cake was deliquored and then dried in vacuo at 50 °C to yield the desired product (1.1 kg, 84%) as a white solid. Mp 183−185 °C. ^{1}H NMR (400 MHz, d_4-MeOD) δ 7.42 (m, 2H), 7.34 (m, 2H), 7.28 (m, 1H), 6.93 (dd, J = 8.1, 1.6 Hz, 1H), 6.84 (ddd, J = 8.1, 7.3, 1.6, 1H), 6.74 (dd, J = 8.1, 1.6 Hz, 1H), 6.68 (ddd, J = 8.1, 7.3, 1.6 Hz, 1H), 5.14 (d, J = 5.3 Hz, 1H), 4.26 (ddd, J = 9.8, 5.3, 3.4 Hz, 1H), 4.21 (m, 2H), 4.11 (dq, J = 11.8, 7.1, 1H), 4.10 (dq, J = 11.8, 7.1, 1H), 3.32 (m, 2H), 3.18 (dd, J = 12.6, 9.8 Hz, 1H), 3.10 (dd J = 12.6, 3.4 Hz, 1H), 1.43 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 149.9, 147.6, 138.0, 128.7, 128.4, 127.9, 122.8, 121.2, 118.1, 114.8, 82.7, 69.4, 64.6, 61.8, 49.6, 47.7, 15.3. m/z $[M + H]^+$ = 412 and $[M - SO_3]^+$ = 332.

(2*S*,3*S*)-2-[α-(2-Ethoxyphenoxy)benzyl]morpholine Succinate Salt (*S*,*S*)-Reboxetine Succinate



To a 25 L fixed rig were introduced tetrahydrofuran (7.1 L) and ethanol (denatured with 3% cyclohexane) (210 mL) followed by 2-{[(2*S*,3*S*)-3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropyl]amino}ethyl hydrogen sulfate (1.1 kg, 2.6 mol, 1 equiv). The slurry was agitated at 18 °C for 1 h, and then sodium hydroxide (318 g, 7.1 mol, 3.0 equiv) was added in a single portion. The reaction mixture was subsequently heated to reflux (65 °C) for ∼5 h. The reaction mixture was cooled to room temperature and then treated with water (5.3 L). The reaction mixture was agitated for 16 h after which cyclohexane (4.2 L) was added, and the phases were separated. The upper organic phase was washed with water (2.2 L) and distilled at atmospheric pressure under Dean−Stark conditions to decrease the water levels to <0.2% (as determined by Karl Fischer analysis). The organic phase was concentrated by distillation under atmospheric pressure to a volume of ∼2.0 L. Ethanol (denatured with 3% cyclohexane) (5.1 L) was added, and a distill and replace operation was performed using ethanol (denatured with 3% cyclohexane) (3 × 5.1 L) to achieve not more than 1% tetrahydrofuran and a total volume of 2−2.5 L.

Further ethanol (denatured with 3% cyclohexane) (4.9 L) was charged to the reaction vessel followed by succinic acid (301 g, 2.60 mol, 1.0 equiv), and the contents were heated to reflux to ensure full dissolution. The temperature was lowered to ∼65 °C, and the solution was seeded with (*S*,*S*)-reboxetine succinate (5.5 g, 12.8 mol, 0.05 equiv) followed by granulation for 3 h. The slurry was cooled to 0 at 0.5 °C/min and granulated for a further 16 h. The slurry was filtered, washing with ethanol (denatured with 3% cyclohexane) (2.1 L/kg), and dried at 50 °C to yield (*S*,*S*)-reboxetine succinate (897 g, 82%) as a white solid. ^{1}H NMR

Table 5. (*S*,*S*)-Reboxetine Succinate HPLC Assay

column	Phenomenex Luna C8 (2) 150 m × 4.6 mm, 5 μm
gradient[a]	
0	75.0 MPA, 25.0 MPB
4	75.0 MPA, 25.0 MPB
26.5	30.0 MPA, 70.0 MPB
30	30.0 MPA, 70.0 MPB
31	75.0 MPA, 25.0 MPB
36	75.0 MPA, 25.0 MPB
flow	1 mL/min
temp	45 °C
injection	50 μL
detection	276 nm
sample prep	0.2 mg/mL (27.5 mg in 100 mL [25% MeCN in buffer])

[a] MPA = 0.02 M KH_2PO_4 at pH 6.8 (0.5 M KOH). MPB = acetonitrile.

Table 6. (*S*,*S*)-Reboxetine Succinate Chiral HPLC Analysis[a]

column	Diacel chiracel OJ 250 m × 4.6 mm
MP	heptane/ethanol/diethylamine 1500:500:1
flow	0.7 mL/min
temp	30 °C
injection	20 μL
detection	276 nm
run time	20 min
sample prep	1.0 mg/mL in MP

[a] (*R*,*R*)-Reboxetine enantiomer measured at not more than 0.05% (none detected).

(400 MHz, d_6-DMSO) δ 7.22−7.54 (m, 5H), 6.66−6.96 (m, 4H), 5.27 (d, J = 6.0 Hz, 1H), 4.01 (q, J = 7.1 Hz, 2H), 3.83 (m, 2H), 3.50 (m, 2H), 2.61−2.82 (m, 3H), 2.34 (br s, 4H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 174.4, 149.0, 147.3, 137.8, 128.2, 127.3, 120.7, 116.7, 114.4, 80.8, 77.5, 65.9, 64.1, 45.8, 44.1, 39.7, 39.5, 39.3, 39.1, 30.2, 14.9. m/z $[M + H]^+$ = 314. $[\alpha]^{32}_D$ = +18.37 (c 37, ethanol). HPLC assay: 72.2% as is, 99.5% salt corrected. Impurities: no impurities detected at levels of not more than 0.05%. For HPLC assay details, see Tables 5 and 6.

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(10) Conductivity measurements were taken of the aqueous phases prior to drug substance isolation and then calibrated against measured ROI levels in the drug substance. This allowed a calibration model to be developed to allow a conductivity ceiling to be set that would ultimately lead to the isolation of drug substance that met the ROI specification.