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Development of a Dynamic Kinetic Resolution for the Isolation of an Intermediate in the Synthesis of Casopitant Mesylate: Application of QbD Principles in the Definition of the Parameter Ranges, Issues in the Scale-Up and Mitigation Strategies

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Abstract:

Process development towards the improvement of the manufacturing process of casopitant mesylate (a drug developed by GlaxoSmithKline with activity on the central nervous system) identified a dynamic kinetic resolution opportunity for the improvement of the yield. In this paper, the application of quality by design principles to the DKR is presented together with the issues that were faced during different scale-ups and the at-scale solutions that were implemented.

1. Introduction

For the pharmaceutical industry, the isolation of solid intermediates is used as a means to purify compounds.[1] When a racemic mixture is obtained, precipitation of one of the enantiomers via kinetic resolution (KR) may be preferred over other resolution techniques because good enantioselectivities may be achieved from relatively simple solvent and resolving agent screening. The KR approach is more general than substrate-specific asymmetric synthesis *via* chiral catalysis, *via* the use of biological methods (e.g., enzymes), or *via* chiral auxiliary-driven synthesis, and the cost and environmental impact related to this technique are contained compared to, for example, preparative chiral chromatography.[2]

KR, however, is burdened by the fact that a maximum of 50% yield may be achieved, and the other half of the material is lost, or under the best hypothesis, isolated separately to be recycled. In this sense, the one-pot interconversion of the undesired enantiomer into the desired one by epimerization of the stereogenic center under certain reaction conditions is a much desired objective. This approach is known as dynamic kinetic resolution (DKR),[3] and it is of particular appeal to the pharmaceutical industry when the driving force for the interconversion of enantiomers is pulled by the precipitation of only one of the enantiomers from the reaction medium. In this paper, an example of such a process of DKR, and the issues faced in different scale-ups (up to manufacturing scale, 250 kg input), will be described in detail.

2. Discussion

2.1. Initial Synthetic Route. The commercial process to synthesize casopitant mesylate (**1**) is a multistage convergent process. The original synthesis from which we started to work in Chemical Development at GlaxoSmithKline is summarized in Scheme 1. The mesylate salt **1** is obtained after nine stages, including two intermediate isolations.

Crude racemic **4** is purified by crystallization from the reaction mixture as the racemate camphorsulfonate salt **3**, which is thereafter resolved by KR using L-(*S*)-mandelic acid (∼0.5 mol equiv) in 2-propanol. The total yield of these two transformations is in the range of 35−40%. Initial process studies successfully obtained intermediate **2** without isolation of the intermediate **3**, demonstrating that the isolation of the racemic salt **3** was not necessary, *i.e.* stages 3 and 4 can be telescoped into one single stage, furnishing **2** directly from **4** without detriment to the overall yield. So it was decided to focus the process studies on this approach.

2.2. Screening of a Suitable Reagent for Epimerization of the Stereogenic Center. The epimerization of the stereogenic center in (*R*)-**4** was tested with several different reagents. The mechanism that operates in the racemization attempts can be classified as the following.

2.2.1. Redox Processes. (i.e., oxidation to form the cyclic imine followed by reduction to the amine, as depicted in Scheme 2).[4] Different metal-based catalysts (PtO_2, $[Rh(COD)Cl]_2$, $[Ir(COD)Cl]_2$, $Ru(PPh_3)_3Cl_2$, catASium D(R) Rh) were screened in the presence of a reducing atmosphere. Typical reaction conditions were 10% molar ratio of catalyst, 2 bar hydrogen of pressure, at 25 or 50 °C temperature and using ethyl acetate or

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† Chemical Development.
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(1) Bamforth, A. W. *Industrial Crystallization*; Leonard Hill: London (UK), 1965.
(2) Collins, A. N., Sheldrake, G. N., Crosby, J., Eds. *Chirality in Industry II: Developments in the Manufacture and Applications of Optically Active Compounds*; John Wiley & Sons Ltd.: Chichester (UK), 1997.
(3) Reviews on racemization methods and on DKR: (a) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563–1601. (b) Brands, K. M. J.; Davies, A. J. *Chem. Rev.* **2006**, *106*, 2711–2733. (c) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734–2793. (d) Fogassy, E.; Nógrádi, M.; Kozma, D.; Egri, G.; Pálovics, E.; Kiss, V. *Org. Biomol. Chem.* **2006**, *4*, 3011–3030. (e) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291–8327. (f) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321–331. (g) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417–9476. (h) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447–456. (i) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490.
(4) Some selected examples: (a) Paetzold, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620–17621. (b) Blacker, A. J.; Stirling, M. J.; Page, M. I. *Org. Process Res. Dev.* **2007**, *11*, 642–648.

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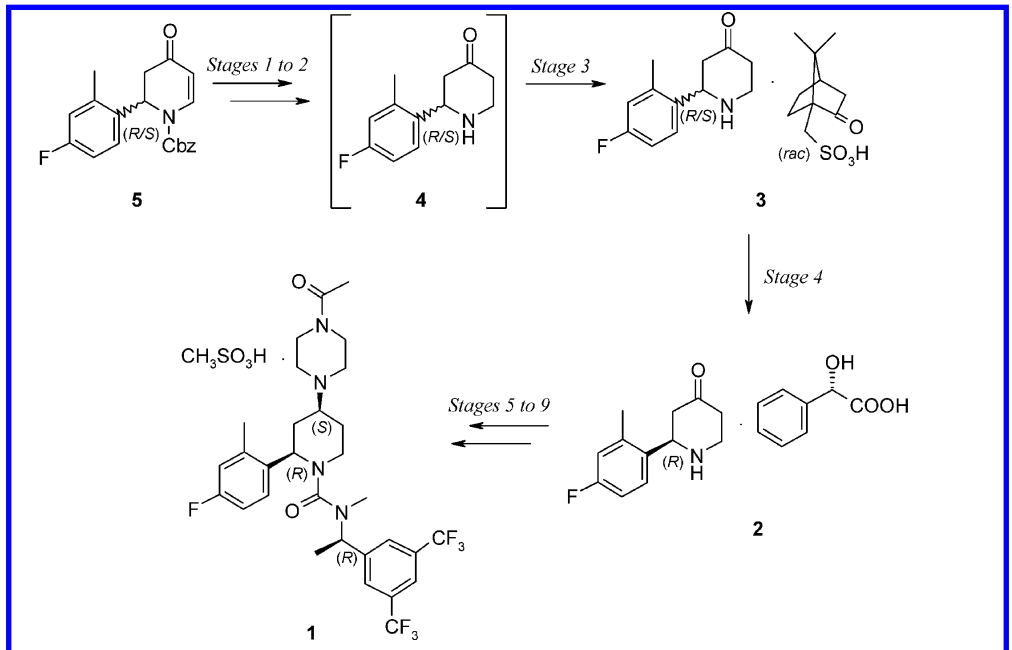
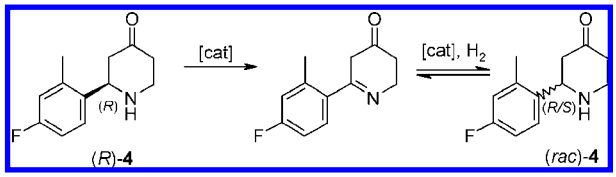
Scheme 1. **Some details of the original synthesis for the preparation of casopitant mesylate (1)**

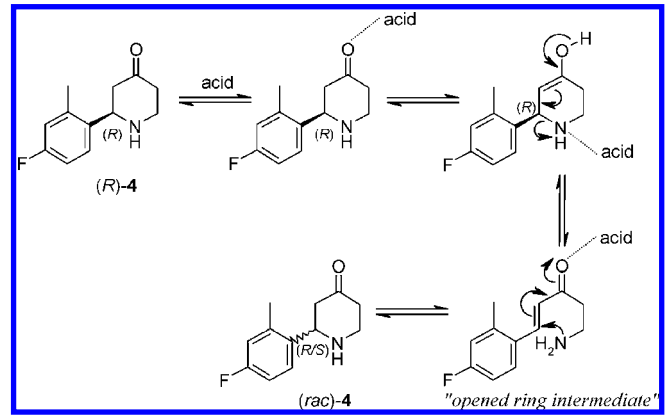


Stage 1:	ethyl acetate, Rh/C, hydrogen
Stage 2:	ethyl acetate, Pd/C, hydrogen
Stage 3:	toluene, rac-camphorsulfonic acid
Stage 4:	i) water, dichloromethane, $NaHCO_3$ (aq); ii) 2-propanol, water, L-mandelic acid
Stage 5:	i) {(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}methylamine, ethyl acetate, carbon dioxide, triethylamine; ii) chloro(trimethyl)silane; iii) pyridine; iv) thionyl chloride
Stage 6:	**2**, ethyl acetate, Na_2CO_3 (aq)
Stage 7:	triethylamine
Stage 8:	acetonitrile, 1-acetylpiperazine, $NaBH(OAc)_3$/HCOOH
Stage 9:	i) ethyl acetate; ii) acetone; iii) methanesulfonic acid; iv) casopitant mesylate seed; v) isooctane; vi) ethyl acetate

Scheme 2. **Mechanism of epimerization of (*R*)-4 by cyclic imine formation**



Scheme 3. **Epimerization of (*R*)-4 by Michael/retro-Michael mechanism**



2-propanol (10 vols) as solvent. Limited racemization was observed; the reduction product (alcohol) was always obtained in significant amount. Only $[Rh(COD)Cl]_2$ in ethyl acetate at 50 °C was successful (the racemization was obtained after 24 h), and only a small amount of alcohol was formed by reduction of the ketone.

In the absence of hydrogen, the epimerization did not proceed.

2.2.2. Epimerization by Michael/Retro-Michael Mechanism. The chemical features of the molecule, containing an amino group β to the ketone, allows the Michael/retro-Michael mechanism to operate (see Scheme 3). Three approaches were investigated.

2.2.2.1. Basic Conditions. This strategy has been referenced in the literature to effect racemization by a different mechanism, that is by abstraction of an acidic α proton to the amine.[5] The effect of different strong bases on the racemization of (*R*)-**4** were explored [sodium *tert*-butoxide, sodium ethoxide and 1,4-diazabicyclo[2.2.2]octane (DABCO)]. The bases were used at 10% mol (with respect to compound (*R*)-**4**), each reaction was performed both in ethyl acetate and 2-propanol (10 vols) at two different temperatures (25 and 50 °C). All the experiments gave no racemization, except that with DABCO and sodium ethoxide in 2-propanol at 50 °C extensive decomposition of compound (*R*)-**4** was observed.

2.2.2.2. Intermediacy of an Imonium Salt.[6] For this approach 3,5-dichlorosalicylaldehyde and pyridoxal hydrochloride (10% mol with respect to compound (*R*)-**4**) were tried in the presence

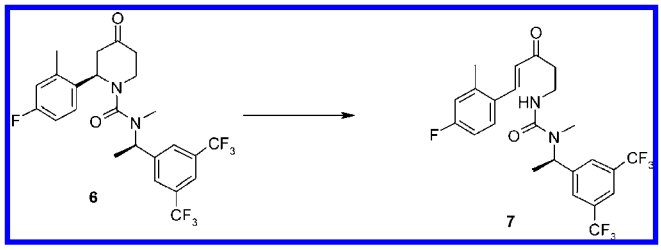
of acetic acid (50% mol with respect to compound (*R*)-**4**) in 2-propanol or ethyl acetate (10 vols) at 25 or 50 °C. In all the experiments racemization was observed at 25 °C, but at 50 °C degradation occurred.

2.2.2.3. Acidic Conditions.[7] A number of Lewis acids were screened for this approach: $ZnCl_2$, $BF_3 \cdot Et_2O$, $AlBr_3$, $SnCl_4$, $MgBr_2$, $MnCl_2$, $SnCl_2$; all of them were used at 10 mol % (with respect to compound (*R*)-**4**) in 2-propanol or ethyl acetate (10 vols) at 25 or 50 °C. The experiments resulted in epimerization of the stereogenic center. In addition, Brønsted acids such as acetic acid (50% mol with respect to compound (*R*)-**4**) in 2-propanol at 25 °C also promoted the epimerization via the Michael/retro-Michael mechanism. In all cases, an extended reaction time (more than 15 h) was necessary to reach an equilibration of the enantiomers, which resulted in the formation of decomposition byproduct in virtually all of the tests.

A plausible mechanism for this transformation is depicted in Scheme 3, although direct evidence of the formation of the opened ring intermediate was not obtained, possibly due to its transient nature.

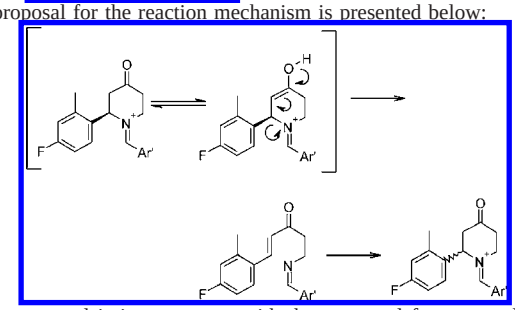
Indirect evidence of the intermediacy of an opened intermediate can be deduced from the formation of the impurity **7** (Scheme 4); this compound is obtained when one of the intermediates of the synthetic route described in Scheme 1, the piperidone-urea **6**, is treated with strong acids.[8]

Scheme 4. **Piperidone-urea 6 decomposition**



(5) There are examples in the literature of this approach, and in particular aminoacids esters can be racemized in this way. A successful example of a DKR process using this strategy can be found in Wegman, M. A.; Hacking, M. A. P. J.; Rops, J.; Pereira, P.; van Rantwijk, F.; Sheldon, R. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1739–1750.

(6) A proposal for the reaction mechanism is presented below:



This proposal is in agreement with the structural features and with the mechanism depicted in Scheme 3. In the literature, however, a different mechanism in presented: this strategy has been generally adopted to increase the acidity of the α proton to the amine by adding an aldehyde and forming the corresponding Schiff base. See (a) Guercio, G.; Bacchi, S.; Goodyear, M.; Carangio, A.; Tinazzi, F.; Curti, S. *Org. Process Res. Dev.* **2008**, *12*, 1188–1194. (b) Yamada, S.; Hongo, C.; Yoshioka, R.; Chibata, I. *J. Org. Chem.* **1983**, *48*, 843–846.

(7) Some examples from the literature: (a) Pesti, J. A.; Yin, J.; Zhang, L.-H.; Anzalone, L. *J. Am. Chem. Soc.* **2001**, *123*, 11075–11076. (b) McCague, R. *Chem. Abstr.* **1998**, *129*, 289924. U.S. Patent 5,821,369, 1998.

A further confirmation of the participation of an opened ring intermediate in the DKR mechanism is deduced from the formation of impurities **8**, **9**, and **10** shown in Scheme 5, whose formation is further detailed in section 2.3 below.

The preliminary results above suggested that epimerization of the undesired (*S*)-enantiomer of **4** is possible, although the reaction may suffer from byproduct formation. At about the same time, it was serendipitously discovered that the mother liquors from the typical KR conditions with L-(*S*)-mandelic acid contained both enantiomers of **4** in approximately 1:1 ratio, when an enrichment in the undesired (*S*)-enantiomer would be expected. We reasoned that this would be an opportunity to introduce a DKR in which the driving force would be the crystallization (as compound **2**) of the desired (*R*)-**4** from the solution.

2.3. Optimization of the DKR. It was reasoned that by increasing the reaction time and equivalents of L-(*S*)-mandelic acid (at least 1 mol equiv), the driving force of the crystallization should provide an opportunity to increase the yield. On the contrary, the yield of the reaction decreased dramatically with increasing time, which later could be ascribed to an inhibition of the precipitation of **2** caused by the formation of the autocondensation impurities **8**, **9**, and **10**. The likely mechanism for the formation of these impurities is detailed in Scheme 5 and starts with the imine formation between **4** and the opened ring intermediate that would allow for a facile autocondensation of the imine/enamine to yield the dihydropyridine **8**. This, in turn, may disproportionate to give the mixture of **9** and **10**, or oxidize with oxygen in air to the pyridine **9**.

The role of impurities **8**, **9**, and **10** in inhibiting the precipitation of **2** was confirmed by spiking experiments, which are summarized in Table 1.

Table 1. **Effect of impurities 8, 9, and 10 in the yield of the precipitation of 2**

amount of **8**, **9**, and **10** in solution of **4** in 2-propanol (% a/a)[a]	yield of isolated **2** (%)
12	40
16	19
19	0

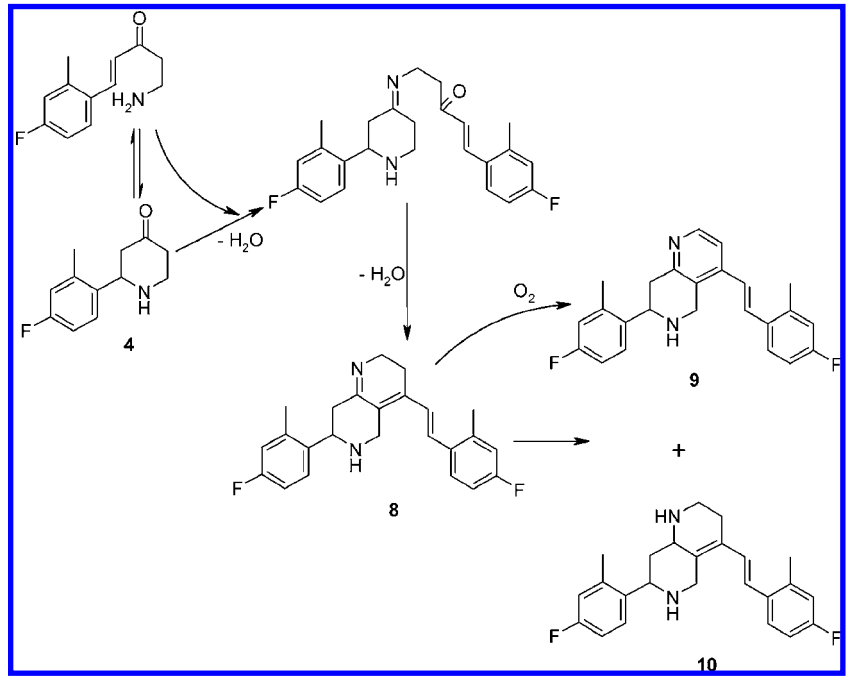
[a] Total of **8**, **9**, and **10**.

At this point it was deduced that, as the imine formation is the first step of the decomposition pathway, the addition of water into the reaction mixture could minimise this byproduct formation and hence improve the yield. Indeed, the addition of ∼1 equiv of water to the mixture increased the yield of the reaction and minimised the presence of **8**, **9**, and **10**, at the expense of a longer reaction time. Table 2 summarises the yields obtained versus DKR reaction time.

Table 2. **Effect of DKR reaction time on yield of isolated 2**

DKR reaction time (h)	yield of isolated **2** (%)	enantiomeric excess (%)
6	43	99
12	50	99
18	56	99
24	60	99.2
48	68	99.2

Scheme 5. **Likely pathway for the formation of impurities 8, 9, and 10**



From the data of Table 2, it is evident that the DKR requires a long reaction time to reach a maximum yield. From a practical point of view, it was decided to limit the reaction time to 24 h.

Subsequently, we proceeded to optimize the different reaction parameters, namely, reaction time, volume, temperature, equivalents of L-(*S*)-mandelic acid and equivalents of water. To control reaction parameters, within GlaxoSmithKline a multivariate approach was taken (design of experiments - DoE). The advantage of this approach is that not only will parameters that have an impact on yield be ascertained, but also which parameters have an impact on quality and the interactions among them. Our approach to quality control is based on the quality by design (QbD) principles,[9] and we have recently published a number of articles on the practical application of this novel concept.[8,10] The use of QbD principles and its specific terminology is extensively collected in the above-mentioned articles, and they will not be a subject of further discussion here; only the conclusions of the studies are presented in the next paragraphs.

The quality of the final drug substance (this is, impact on the drug substance critical quality attributes) may be impacted by operations, parameters, specifications, on/off line monitoring testing and procedural adherence for every single stage. In the case of the DKR stage, the quality of the final drug substance is only impacted by the (*S*)-enantiomer content in isolated **2**. A suitable level of (*S*)-enantiomer in **2** was determined by spiking experiments and applying the QbD principles,[8] and was set to no more than (NMT) 1.5% a/a.[11] Among the parameters explored, equivalents of L-(*S*)-mandelic acid, equivalents of water, and reaction volume were found to have an impact on the level of (*S*)-enantiomer present in **2** and should be controlled to ensure quality (*i.e.* these are critical process parameters - CPPs). The yield was also one of the responses of the DOE, and yields obtained were in the range 47−63%. The amount of mandelic acid, reaction time, and reaction temperature have an effect on the yield (shorter reaction time, higher temperature, and lower amount of mandelic acid gave lower recovery). Figure 1 graphically represents the impact of water, L-(*S*)-mandelic acid, and reaction volume on the enantiomer content, obtained with the commercially available software *Design Expert Version 7.0.3*.

From the DoE, it could be concluded that L-(*S*)-mandelic acid and water need to be controlled between suitable ranges, whilst the reaction volume would be limited by a minimum value. The ranges were deduced from a robustness experiment (DoE), followed by verification experiments (a set of four experiments part of a workpackage called scoping experiment: one experiment run at forcing condition, one at mild conditions, and two at central point conditions) run at 2-L scale in equipment configured to mimic full-scale plant equipment. This was achieved through maintaining geometric similarity and

(8) Cimarosti, Z.; Bravo, F.; Castoldi, D.; Tinazzi, F.; Provera, S.; Perboni, A.; Westerduin, P. *Org. Process Res. Dev.* DOI: 10.1021/op1000622.

(9) (a) *Pharmaceutical cGMPs for the 21st Century - A risk based approach (initiative launched in 2002)*; U.S. Department of Health and Human Services, Food and Drug Administration: Rockville, MD, 2004. (b) *ICH Q8 Pharmaceutical Development*, (R2); U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, Aug 2009. (c) *ICH Q9 Quality Risk Management*; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, June 2006. (d) *ICH Q10 Pharmaceutical Quality System*; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, April 2009.

(10) (a) Cimarosti, Z.; Bravo, F.; Stonestreet, P.; Tinazzi, F.; Vecchi, O.; Camurri, G. *Org. Process Res. Dev.* DOI: 10.1021/op900242x. (b) Bravo, F.; Cimarosti, Z.; Tinazzi, F.; Castoldi, C.; Stonestreet, P.; Galgano, A.; Westerduin, P. *Org. Process Res. Dev.* DOI: 10.1021/op1000836.

(11) The other attributes included in the specification of the intermediate **2** were: compound **9** (NMT 0.5% a/a), over-reduction byproducts of **2**: alcohol (NMT 1.5% a/a), defluorinated analogue (NMT 0.15% a/a). All these limits were defined based on purging/spiking experiments. No solvents were specified with a limit as the drying was the step where these solvents were controlled, and moreover they were not critical for the next process steps.

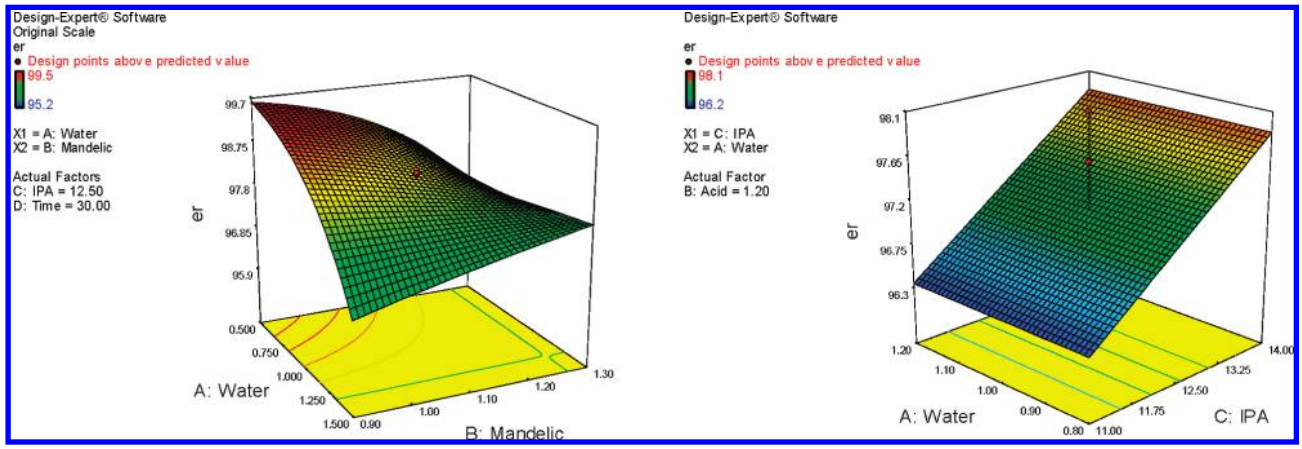


Figure 1. **Impact of amount of water, L-(*S*)-mandelic acid and reaction volume on the (*S*)-enantiomer content in 2.**

Table 3. **Proven acceptable ranges for the quality process parameters of the DKR**

QPP	PAR	target value[b]
amount of water	0.8−1.2 equiv	1.0 equiv
amount of L-mandelic acid	1.10−1.26 equiv	1.15 equiv
reaction volume	NLT[a] 12.0 vols	14.0 vols

[a] NLT = not less than. No impact on quality from use of higher volume. [b] The forcing experiment gave the following results: yield 54%, ee 99.6% (99.8/0.2 was the relative ratio between (*R*)-**4** and (*S*)-**4** in isolated **2**, while the mild experiment gave: yield 45%, ee 99.4% (99.7/0.3 was the relative ratio between (*R*)-**4** and (*S*)-**4** in isolated **2**.

operating under conditions scaled according to accepted chemical engineering principles, e.g., using the constant power-per-unit volume (*P*/*V*) principle for scaling agitation speed to also take into consideration mass transfer and heat transfer limitations. From these experiments, verifying that intermediate **2** contained the (*S*)-enantiomer in not more than 1.5% a/a by chiral HPLC (97% ee), the operating ranges (Proven Acceptable Ranges - PARs) for the parameters that have an impact on quality (Quality Process Parameters - QPPs) presented in Table 3 were obtained.

2.4. Drying of the Solid. The reported PARs for the parameters are derived when control on filtration (see section 2.5 for a detailed discussion on issues experienced during filtration) and drying is optimal, that is to say that enantiomeric excess of **2** is not negatively impacted by these unit operations. In the case of drying, it was observed that **2** exhibited a level of thermal instability and tended to epimerize at high temperatures (see Figure 2). The stability graph presented in Figure 2 establishes that **2** has negligible racemisation at 30 °C for 72 h, a much longer drying time than required at full manufacturing scale. At 40 °C, however, the epimerization is unacceptable, presenting an issue for the quality.

Based on the data presented in Figure 2, the drying temperature was also considered a QPP, and its PAR set to NMT 30 °C, with an operating target value of 25 °C.

2.5. Isolation and Filtration of 2: Issues on Scale Up. The first isolation tests carried out in the laboratory and scale-up laboratory (up to 500-g scale) were performed by employing three washes each of one cake volume (wet cake), following the standard washing conditions of using reaction solvent (2-propanol) as the wash solvent. Up to this scale, intermediate **2** quality was found to be acceptable, albeit it was appreciated that the filtration could be time-consuming (∼5 h total filtration time at the maximum scale).

Indeed, during the first scale-up in pilot plant (∼160 kg scale) the filtration required around 30 h to be completed. Quite disappointingly, the (*S*)-enantiomer content in isolated **2** was about 10% a/a, far beyond the acceptable limit. From the relative solubility of **2** in 2-propanol (0.014 g/mL),[12] it was proposed, as a plausible explanation, that the solid **2** of good enantiomeric purity was partly dissolving in the 2-propanol remaining in the wet cake. As the DKR occurs at room temperature and there is mandelic acid present, this would promote the same Michael/retro-Michael mechanism that operates during the DKR, thus racemizing part of the material (see Scheme 3), which then precipitates back out, lowering the enantiomeric purity. This possibility of racemization of **2** under the conditions present in the wet cake in 2-propanol was demonstrated in the laboratory, and it was also confirmed that fast removal of the solvent, even without any washing applied, gave intermediate **2** with suitable content of the (*S*)-enantiomer.

This unexpected behavior suggested alternative strategies should be considered; however, a change in the route was not possible as this was the only scalable route.

In the hypothesis of keeping this process and accepting that intermediate **2** would be of poor quality, it was clear that any attempt to achieve the right quality of the compound by a recrystallization would have resulted in a failure as the racemization of **2** occurred also in the filtration and not only in the crystallization.

Replacing the DKR step with an alternative purification step based on chromatography, such as SMB,[13] would have given the same result, as, even if the purification would have been successful, the next steps of crystallization and filtration would have suffered from the same drawbacks described above.

The alternative approach not to isolate intermediate **2** after the SMB step was also considered. This approach was discarded as this would have wasted the enantiomer (*S*)-**4**, only giving 50% potential yield. Further attempts to racemize the enantiomer (*S*)-**4** would have resulted in complex racemisation/purification cycles, not compatible with manufacturing timings. An additional hurdle to be considered would have been the low stability of intermediate **2** in solution recently described.[8]

(12) The solubility of the (*S*)-**4** as L-mandelate salt is 0.025 g/mL.
(13) Simulating Moving Bed.

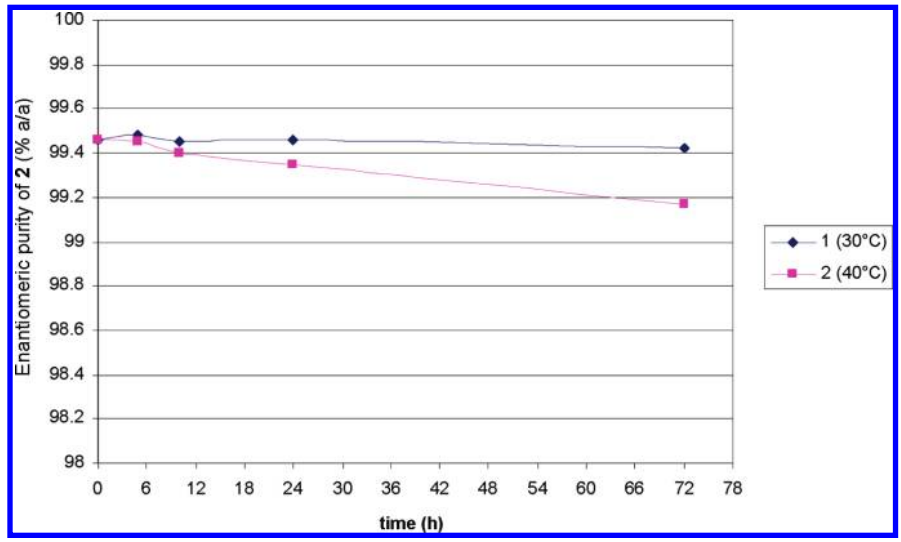


Figure 2. **Thermal stability of 2.**

Therefore, it was considered that a complete displacement of 2-propanol was required, in order to avoid the partial dissolution of **2**. A solvent in which **2** was not soluble at all was sought out, and cyclohexane was selected because of its relatively high viscosity compared to other low polar hydrocarbon solvents, which would favor the displacement of 2-propanol ($\mu_{2\text{-propanol}} = 2.04$ cP at 25 °C; $\mu_{\text{cyclohexane}} = 0.98$ cP at 25 °C).[14] In order to avoid precipitation of the undesired (*S*)-enantiomer as a consequence of a sudden change of polarity, a gradient displacement was selected. Given the difficulties faced in predicting at laboratory scale the performance of the washing, the final gradient was fine-tuned in the pilot plant and consisted of the following washes:

first 1 vol of 2-propanol
second 2 vol of 2-propanol/cyclohexane, 1:1
third 2 vol of 2-propanol/cyclohexane, 1:3
fourth 3 vol of cyclohexane.

The addition of cyclohexane resulted in a certain cake shrinkage. This phenomenon, and its impact on quality, was studied in detail using a laboratory Rosenmund filter. The experiments were designed to mimic total washing time and cake height in plant, with the aim of setting adequate pressure to apply and verify the impact of cake compression. The results of the laboratory tests did not indicate any further risk, and a filtration procedure based on displacement wash (leaving the cake wet at all times between washes and filtering to dry land, defined as filtration until the line of solvent is just above the line of the solid in the cake) following the four gradient washes detailed above was selected for full manufacturing scale. This washing procedure was verified in a pilot-plant campaign up to 160 kg of input, obtaining **2** of good quality (enantiomer content below 0.5% a/a by chiral HPLC).

The finalized washing procedure was transferred to the site of manufacturing and tested at full manufacturing scale (250 kg). At this scale, the cake shrinkage observed when cyclohexane was introduced in the washing was amplified compared to pilot-plant performance, and intermediate **2** with high content of the (*S*)-enantiomer content (about 3% a/a by chiral HPLC) was obtained.

From the explanations given before, it was assumed that inefficient displacement of 2-propanol by cyclohexane due to the shrinkage was the root cause of the increased level of (*S*)-enantiomer as the solvent would preferentially flow through the channels created. As shrinkage is an intrinsic property of this material, and it is apparently magnified as scale increases, we considered that the gradient washing procedure should be kept in place, but a better 2-propanol displacement would be achieved by fully deliquoring the cake between any two washes, followed by reslurrying the cake with the fresh wash solvent mixture. Note that the reslurry washing procedure is generally not a recommended practice,[15] but in our case it gave the intermediate **2** of identical quality to that obtained in the pilot plant using the displacement procedure (enantiomer content below 0.5% a/a by chiral HPLC in all batches produced).

3. Conclusion

The development of a DKR based on Michael/retro-Michael mechanism promoted by L-(*S*)-mandelic acid has been presented. The driving force is the crystallization at room temperature of the desired (*R*)-enantiomer from 2-propanol as the L-mandelate salt **2**. The fact of having a DKR which proceeds at room temperature forced us to develop a washing procedure that allowed the gradual substitution of 2-propanol with a solvent such as cyclohexane, in which **2** is completely insoluble. Finally, cake shrinkage was found to be scale dependent, and

(14) Other hydrocarbons were considered but not tried as their viscosity was not suitable for the intended scope: hexane is 0.294 cP at 25 °C, heptane is 0.386 cP at 25 °C, isooctane is 0.50 cP at 20 °C. So cyclohexane due to its relatively high viscosity would have minimized the risk related to poor mixing.

(15) Re-slurry washing is not a recommended practice because impurities are diluted instead of being removed by the front of the solvent. However, in the case of an extreme cake shrinkage, as is the case reported here, the re-slurry procedure may be the only option. As a matter of fact, based on the experience accumulated by us, within GlaxoSmithKline's guidelines, the re-slurring of the cake has been adopted as the recommended procedure when cake shrinkage is unavoidable. See also Anderson, N. G. *Practical Process Research and Development* Academic Press: San Diego (U.S.A.), 2000; pp 241−243.

an appropriate reslurry washing procedure was developed. Of note, all improvements in the isolation procedure (from 2-propanol washing to gradient introduction of cyclohexane, and from displacement washing to reslurry washing) were introduced directly as solutions to a particular problem at scale (either pilot plant or manufacturing plant), as the laboratory scale was not able to provide accurate predictive information in this case. The yield of this stage at full manufacturing scale ranged from 66 to 71%.

4. Experimental Procedures

4.1. Synthesis of (2*R*)-2-(4-Fluoro-2-methylphenyl)-4-piperidinone (*S*)-L-Mandelate (2). Compound **5** (250 kg, 1 wt) is hydrogenated on 5% Rh on charcoal (5.73 kg, 0.0229 wt based on the dry catalyst) in ethyl acetate (500 L, 2 vol) after purging with three cycles of N_2/vacuum, followed by five cycles of H_2/vacuum, and then pressurization to 2.5 bar of H_2. The reaction is stirred for ~1 h at 25 °C until complete consumption of the starting material. The catalyst is filtered, and the spent catalyst is washed with ethyl acetate (2 × 75 L, 2 × 0.3 vol). The reactor is purged with three cycles of N_2/vacuum, and 5% Pd on charcoal (7.55 kg, 0.0302 wt based on the dry catalyst) is added over the reaction mixture. The reactor is purged with three cycles of N_2/vacuum, followed by five cycles of H_2/vacuum, and finally pressurized at 2.5 bar of H_2. The stirring is kept at 25 °C until complete conversion into **4** (~1 h), venting the headspace with cycles of H_2/vacuum, and repressurizing the reactor with H_2 regularly throughout the reaction in order to remove the CO_2. The mixture is filtered, and the solution of **4** in EtOAc is collected. The reactor and the spent catalyst are washed with ethyl acetate (1 × 250 L − 1 × 1 vol; then 2 × 125 L − 2 × 0.5 vol). Finally, the filtered catalyst waste is disposed appropriately.[10b] The solution of **4** (yield of hydrogenations is ~80%) in ethyl acetate is concentrated under vacuum to 3 vol (750 L). 2-Propanol (1250 L, 5 vol) is added to the solution, and the resulting solution is then concentrated to 1250 L (5 vol). Further 2-propanol (1250 L, 5 vol) is added, and the resulting solution is concentrated to 1000 L (4 vol); the amount of ethyl acetate in the reaction mixture is less than 2% mol with respect to 2-propanol. Additional 2-propanol (250 L, 1 vol) is added, followed by H_2O (7.4 kg, 0.03 wt; this is enough to have water in the range of 0.034−0.051 wt with respect to **5**, considering water present in the solution of **4** in 2-propanol, water in L-(*S*)-mandelic acid, and water in 2-propanol). To the resulting mixture, a solution of L-(*S*)-mandelic acid (103 kg, 0.412 wt) in 2-propanol (460 L, 1.84 vol) is added slowly at 24 °C. The mixture is seeded with **2** (0.4 kg, 0.0016 wt) when ~12.5% of the L-(*S*)-mandelic acid solution has been added. The addition is complete in approximately 45 min, and the reaction is then aged for 24 h at 24 °C. The slurry is filtered and washed by a reslurry procedure (that is, blowing the cake to dryness, adding the fresh wash, and stirring the cake and solvent together before filtering) at 1.6 bar g of pressure. The washing regime used is:

first 2-propanol (250 L, 1 vol)
second 2-propanol/cyclohexane, 1:1 (500 L, 2 vol)
third 2-propanol/cyclohexane, 1:3 (500 L, 2 vol)
fourth cyclohexane (750 L, 3 vol).

The solid is dried under vacuum at NMT 30 °C, obtaining 140−150 kg of **2** (66−71% for the stage).

The impurity profile of this batch was the following: (*S*)-**4** as L-mandelate salt (0.52% a/a), compound **9** (0.06% a/a), over-reduction byproduct of **2**: alcohol (0.76% a/a), defluorinated analogue (0.04% a/a).

2: ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.22 (m, 1 H); 2.30 (m, 1 H); 2.31 (s, 3 H); 2.46 (dd, J = 13.61, 11.96 Hz, 1 H); 2.53 (m, 1 H); 2.90 (td, J = 12.23, 3.30 Hz, 1 H); 3.32 (ddd, J = 12.17, 6.94, 1.79 Hz, 1 H); 4.06 (dd, J = 11.69, 2.89 Hz, 1 H); 4.96 (s, 1 H); 7.03 (m, 2 H); 7.27 (m, 1 H); 7.33 (t, J = 7.56 Hz, 2 H); 7.40 (d, J = 7.42 Hz, 2 H); 7.52 (dd, J = 8.11, 6.46 Hz, 1 H). LC−MS: $[M + H]^+$ (as the free base) = 208; $[M + H + H_2O]^+$ = 226.

Compounds **8** and **10** are formed at impurity level and can be found in the isolated **2** and/or in the solution of **4** in 2-propanol and have been identified by LC−MS (compound **8**) and/or LC−NMR (compound **10**), and no further attempts for their isolation were tried. Impurity **9** is a much more stable compound, and its isolation is possible by preparative chromatography using a Phenomenex Gemini C18 as a stationary phase and a solution of acetonitrile/buffer ammonium carbonate 10 mM at pH 10 as mobile phase.

Impurity **8**: LC−MS: $[M + H]^+$ = 379. Fragmentation pattern (m/z = 242) compatible with the proposed structure.

Impurity **9**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.38 (s, 3 H); 2.43 (s, 3 H); 2.85 (dd, J = 16.48, 10.99 Hz, 1 H); 2.96 (dd, J = 16.48, 3.30 Hz, 1 H); 4.10 (m, 2 H); 4.29 (d, J = 16.48 Hz, 1 H); 7.03 (m, 2 H); 7.07 (td, J = 8.52, 2.75 Hz, 1 H); 7.11 (dd, J = 9.90, 2.70 Hz, 1 H); 7.13 (d, J = 15.66 Hz, 1 H); 7.47 (d, J = 16.21 Hz, 1 H); 7.49 (dd, J = 9.30, 6.30 Hz, 1 H); 7.54 (d, J = 5.22 Hz, 1 H); 7.81 (dd, J = 8.65, 6.18 Hz, 1 H); 8.34 (d, J = 4.94 Hz, 1 H). LC−MS: $[M + H]^+$ = 377. Fragmentation pattern (m/z = 240) compatible with the proposed structure.

Impurity **10**: ^{1}H NMR (HPLC−NMR, 600 MHz, D_2O/CH_3CN) δ 1.42 (q, J = 11.35 Hz, 1 H); 1.9−2.0 (m, 1 H); 2.31 (s, 3 H); 2.33 (s, 3 H); 2.37 (m, 2 H); 2.73 (m, 1 H); 3.10 (d, J = 12.45 Hz, 2 H); 3.56 (m, 1 H); 4.02 (d, J = 12.09 Hz, 1 H); 4.31 (d, J = 14.65 Hz, 1 H); 6.75 (d, J = 15.75 Hz, 1 H); 6.90 (m, 4 H); 7.14 (d, J = 15.75 Hz, 1 H); 7.31 (t, J = 6.96 Hz, 1 H); 7.57 (t, J = 6.96 Hz, 1 H).

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