ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Full Paper

Metal-free Synthesis of the Methanol Solvate of S-Omeprazole Potassium Salt Using 1R-(-)-10-camphorsulfonyloxaziridine: Oxidation Process Development and Optical Purity Enhancement Strategy.

Christine Delsarte, Romuald Santraine, Baptiste Fours, and Laurent Petit

Org. Process Res. Dev., **Just Accepted Manuscript** • Publication Date (Web): 02 Mar 2018

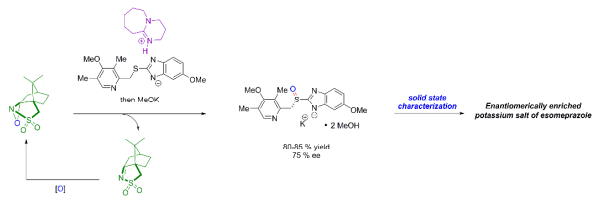
ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Metal-free Synthesis of the Methanol Solvate of *S*-Omeprazole Potassium Salt Using 1*R*-(-)-10-camphorsulfonyloxaziridine: Oxidation Process Development and Optical Purity Enhancement Strategy.

Christine Delsarte, Romuald Santraine, Baptiste Fours* and Laurent Petit*

Minakem Recherche, 145 chemin des lilas, 59310 Beuvry la forêt, France.



For Table of Contents Only

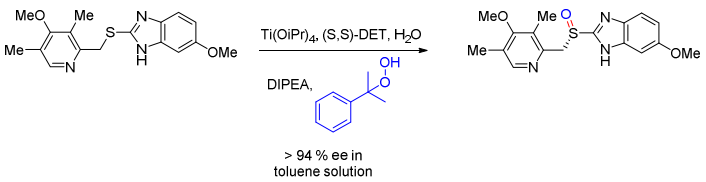
ABSTRACT

The results of our process development studies to synthesize the methanol solvate of *S*-omeprazole potassium salt **1** through the enantioselective oxidation of pyrmetazole **2** using 1*R*-(-)-10-camphorsulfonyloxaziridine **3** are reported. Optical purity enhancement was achieved by means of a reslurry from methanol, the rationale and development details of which are also described.

Keywords: Esomeprazole; Davis oxaziridine; scalable; conglomerate; resolution

INTRODUCTION

Camphorsulfonyloxaziridine is a particular member of the very versatile oxaziridine family. These linchpin chemical entities can participate in many transformations such as the transfer of either an oxygen atom or a nitrogen atom to various nucleophiles, metal-catalyzed rearrangements and dipolar additions.[1,2] It is most notably used in oxygen atom transfers such as the hydroxylation of metal enolates or the oxidation of sulfides. An industrial process for the preparation of this chiral oxidant has been developed within Minakem and the *S*-enantiomer of this reagent has been used on large scale at Minakem (to convert a densely functionalized α-β-unsaturated ester into the corresponding α-hydroxy-β-aminoester through a conjugate addition / electrophilic trapping sequence). A literature survey pointed a report by Emcure Pharmaceuticals scientists detailing the use of the *R*-enantiomer of camphorsulfonyloxaziridine in the oxidation of prochiral sulfides en route to a group of proton pump inhibitors.[3] Esomeprazole, the *S*-enantiomer of omeprazole is a prominent member of this class of molecules and is routinely produced on industrial scale in our Dunkirk facilities. We sought to develop a metal-free straightforward process towards esomeprazole as an alternative to the current process. The current best industrial route to synthesize esomeprazole is the application of the Kagan and Modena modification of the Sharpless enantioselective epoxidation protocol to pyrmetazole **2**. The most efficient esomeprazole syntheses include direct enantioselective oxidation of prochiral sulphides using tailor-made ligands[4,5]. The resolution of omeprazole *via* preferential crystallization of conglomerates[6] or diastereomeric salts formation is also a known strategy.[7] A recent patent also describes the selective precipitation of racemic omeprazole from partially enriched mixtures of racemic and *S*-omeprazole.[8] Extensive experimentation was set within our company around the Kagan and Modena procedure, but this work did not end up in the implementation of an efficient process (**Scheme 1**).[9]



Scheme 1

However, turning our attention to a metal-free approach using Davis oxaziridine proved much more rewarding. While the paper published by Emcure Pharmaceuticals lays the basis of the methodology, process optimization was mandatory before any actual scale up could be envisioned. Indeed, the strict application of the protocols described in this publication

led to somewhat disappointing results (extremely tedious work-up, low yield and enantiomeric excess and inefficient optical purity enhancement).

DISCUSSION AND RESULTS

The 2010 report by Emcure Pharmaceuticals established that the best solvent for this reaction was isopropanol and that an added base has a strong effect on both the conversion and the enantioselectivity of the oxidation. Bicyclic amidine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was selected as the best candidate from a list of nine commonly encountered bases. This protocol described the generation of *S*-omeprazole sodium salt in 67 % yield and 99.0 % e.e. after optical purity enhancement by means of a reslurry from toluene / acetone. The oxidation protocol involved the addition of solid 1*R*-(-)-10-camphorsulfonyloxaziridine **3** (0.95 equiv.) to a pyrmetazole **2** (1.0 equiv.) and DBU (1.05 equiv.) solution in isopropanol at 10-15 °C. The heterogeneous mixture was then stirred at 25-30 °C for 18 h. Camphorsulfonylimine was filtered (its reoxidation into the corresponding oxaziridine was not described in their publication) and the filtrate was concentrated to dryness. The residue was dissolved in water and the pH was adjusted to 8.2 with dilute aqueous acetic acid. Extraction into ethyl acetate was followed by a wash with brine and by a concentrated to dryness, an unsuitable operation on scale. The residue was treated with dilute sodium hydroxide to generate the water-soluble esomeprazole sodium salt and the aqueous layer was washed with dichloromethane before being concentrated to dryness. The residue was suspended in a 1:2 acetone / toluene mixture to obtain, after filtration and drying, *S*-omeprazole sodium salt in 99.0 % e.e. and 67 % yield. The preparation of crude esomeprazole sodium salt according to the Emcure Pharmaceuticals process is shown in the form of a process diagram flow below (**figure 1**).

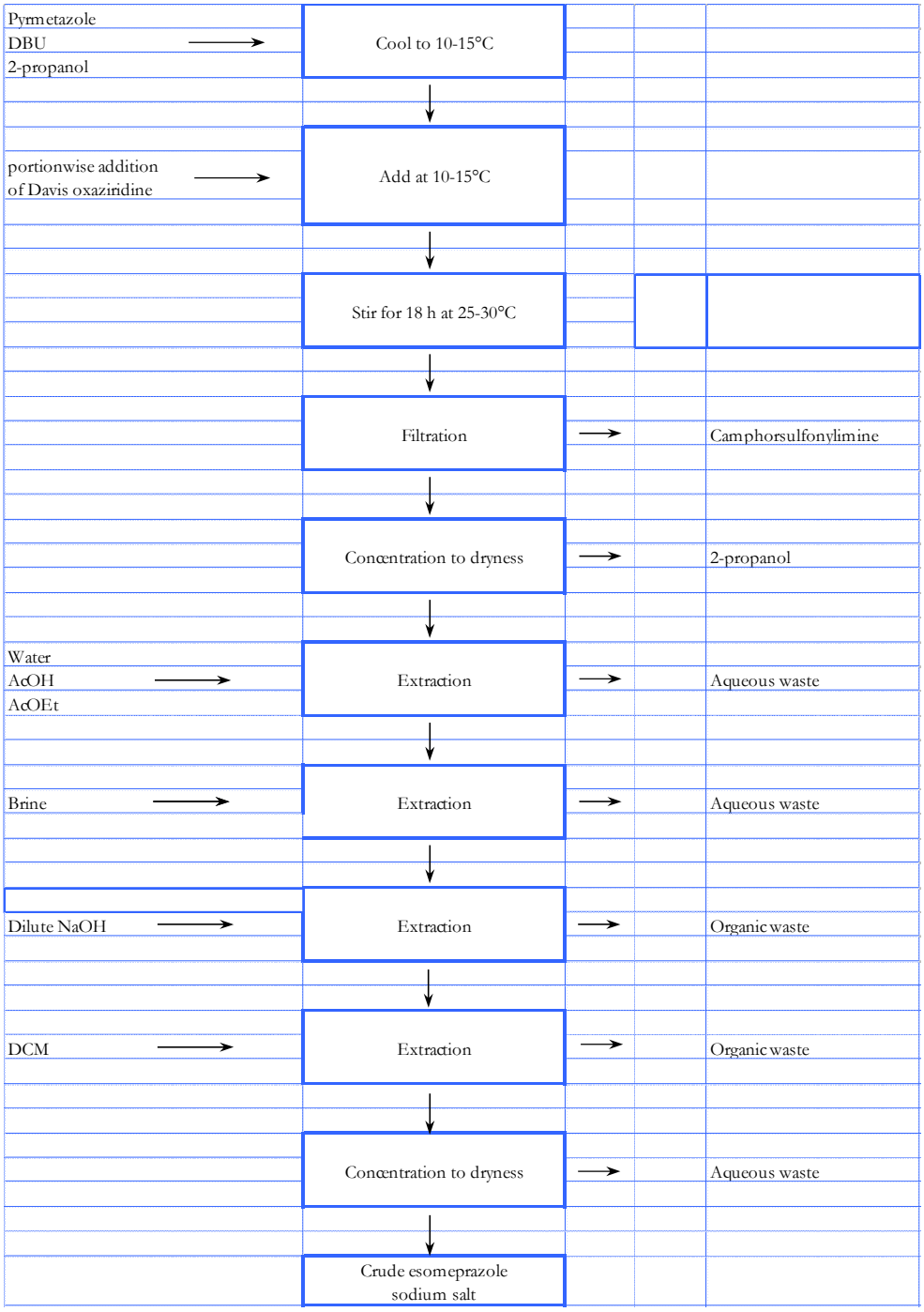
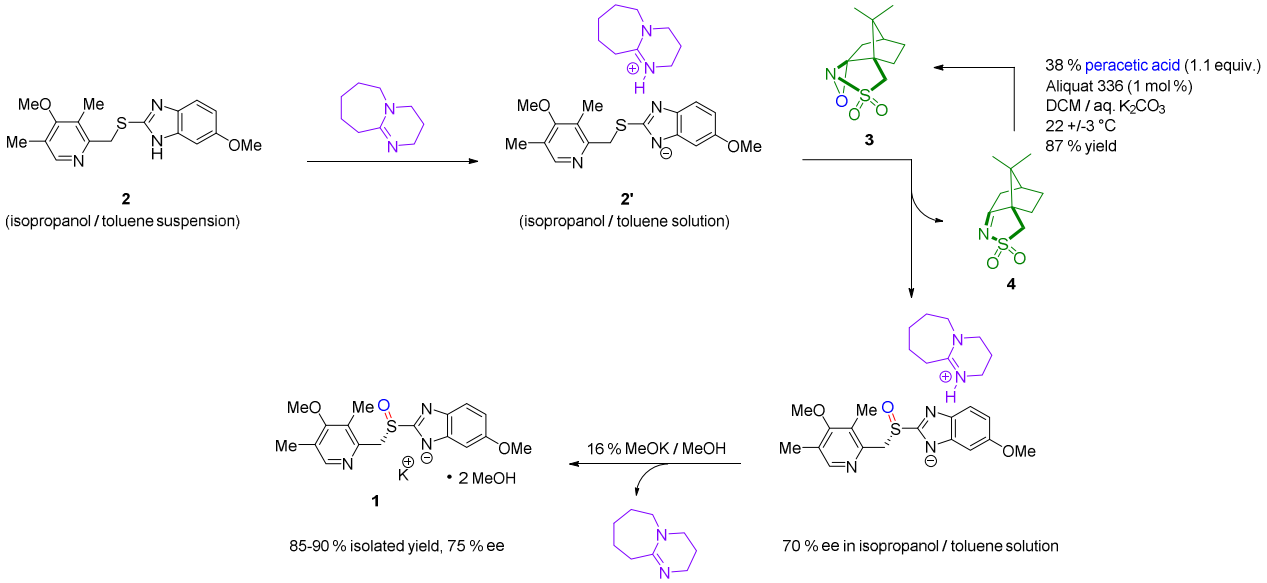


Figure 1

While this work showed the power of Davis oxaziridine in the generation of the desired product in good yield and useful level of enantioselectivity, there were critical issues that needed to be adressed before this method could be implemented on larger scale. Numerous solvent concentrations to dryness and tedious washes lowered the overall productivity. The enantioselectivity level reached by this method was also lower than the targeted e.e. ≥ 99.6 %. The latter value ensures the synthesis of esomeprazole magnesium trihydrate (the final API) with the quality requested by the European and American pharmacopeia. Furthermore, the strict application of this protocol to a 10 g scale reaction gave

only 89 % conversion and 68 % e.e. (in the in-process control). Isolation of the crude product yielded a compound exhibiting 69 % e.e (no improvement of the optical purity) along with 1 % of remaining pyrmetazole **2**. The toluene / acetone reslurry procedure did not improve the optical purity and two additional reslurries from acetone at 50 °C were necessary to obtain esomeprazole sodium salt in 50 % yield and 99.2 % e.e. Based on these preliminary observations, we sought a more robust process for the synthesis of enantiomerically enriched esomeprazole *potassium* salt (**Scheme 2**).



Scheme 2

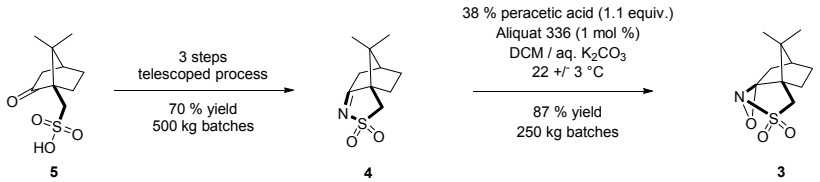
The methanol solvate of the potassium salt of esomeprazole is an isolated intermediate in the industrial process performed in our Dunkirk plant. This chemical entity appears to be a conglomerate (*vide infra*) and this feature places us in a most-favourable position for the enantiomeric excess improvement by either a reslurry or a recrystallization. This innate solid-state property was perhaps overlooked initially because the current industrial process provides Eso-K.2MeOH with a very high enantiomeric excess. The pyrmetazole **2** used for our study was available as a *ca.* 16 wt % solution in toluene from our production plant in Dunkirk. As described by Emcure Pharmaceuticals, isopropanol was the solvent of choice for both conversion and enantiomeric excess. It gave far better results than toluene alone however it was demonstrated that the presence of up to 10 % of toluene in isopropanol (V / V) in the reaction medium had no impact on the reactivity and the selectivity. Initially, DBU was added to the suspension of pyrmetazole **2** in isopropanol at 10-15 °C to give the isopropanol soluble DBU salt of pyrmetazole **2'**. In some experiments, the salt was not completely soluble at this temperature and this was addressed by adding DBU at 20-25 °C with no impact on yield and quality (other factors being equals). Using less than 0.8 equiv. of DBU gave incomplete conversion while using 1.3 equiv. of DBU did not change the impurity profile. Therefore, the use of 1.1 equiv. of DBU was recommended; Conducting the reaction in the absence of a base gives a very low conversion (< 15 %) and enantiomeric excess (< 10 %). As described by Emcure Pharmaceuticals other bases (hexamine, NaOH, dicyclohexylamine, tetraméthylguanidine, DABCO) proved much inferior. In the original

protocol, solid camphorsulfonyloxaziridine was added portionwise to the isopropanol solution of esomeprazole DBU salt **2'** but we deemed this procedure unpractical for large scale application. A reverse addition protocol was developed where the isopropanol solution of esomeprazole DBU salt was added in a controlled fashion to an isopropanol suspension of camphorsulfonyloxaziridine **3**. This process modification consistently gave higher conversions (≥ 95 % vs. 89 % using the formerly described addition mode) without generating overoxidation products (sulfone, *N*-oxide). This is a remarkable testimony of the mild oxidizing power of Davis oxaziridine. Addition time was also examined in the range 1-10 hours and was shown to have no impact on the conversion and selectivity. Thermal conversion after the addition was complete was estimated to be around 25 % only but this does constitute a safety hurdle under the reaction conditions (very slow and only slightly exothermic reaction). Sampling the reaction mixture every 90 min for chiral HPLC monitoring demonstrated that the reaction was complete within 10 h as opposed to 18 h as initially reported (see supporting information). Interestingly, most of the *R*-enantiomer (12 +/- 2 %) was formed at the beginning of the reaction and remained unchanged; the subsequent stirring time mainly served to convert residual pyrmetazole **2** into the corresponding *S*-enantiomer. The enantiomeric excess observed in solution is *ca.* 70 %. This HPLC monitoring also showed that the reaction was not dose-controlled as only a 52 % chemical conversion was observed at the end of the isopropanol pyrmetazole DBU solution addition. After complete conversion, the reaction medium was proven to be stable at 20-25 °C over a period of 24 h; similarly, after filtration of the sulfonylimine by-product, the filtrate was stable at 20-25 °C over a period of 24 h. Calorimetric study gave sufficiently precise data to prove that the reaction could be conducted safely at 10-15 °C under the optimized conditions (see supporting information). After the reaction completion (typical conversion is ≥ 95%) the camphorsulfonylimine **4** by-product was filtered-off and rinsed with isopropanol. The effect of varying reaction parameters are described summarized in the table below (**Table 1**).

Item	Value	Comment
Solvent composition	Toluene – IPA 100 : 0 to 10 : 90 (V / V)	No impact on conversion or selectivity
DBU temperature addition	10-15°C	Incomplete solubilization of Pyrmetazole-DBU salt
	20-25°C	Improved solubility of Pyrmetazole-DBU salt
DBU amount	0.8 to 1.3 equiv.	No impact on yield or selectivity
Order of addition	Portionwise addition of Davis oxaziridine onto reaction mixture	Incomplete conversion (≤ 90 %)
	Dropwise addition of reaction mixture onto Davis oxaziridine in IPA	Higher conversion (≥ 95 %)
Addition time	1 to 10 h	No impact on yield or selectivity

Table 1

It was also demonstrated that the camphorsulfonylimine **4** recovered by filtration could be re-oxidized in 87 % yield following the exact same protocol as the one designed during our internal development program towards Davis oxaziridine (**Scheme 3**).



Scheme 3

The oxidation procedure comes from a thorough process optimization of the work published in 1992 by Schering Plough Research and Werthenstein Chemie AG.[10] This is a very important feature of this process as it lowers the global cost of goods associated with this chiral reagent. The envisioned isolation was executed by a salt-exchange reaction upon addition of potassium methoxide (16 wt % solution in methanol). The lower solubility of the potassium salt of esomeprazole drives the equilibrium towards the formation of the product. Concomitantly, the enantiomeric excess increases from *ca*. 70 % (in solution) to *ca.* 75 % upon isolation. This salt exchange reaction works well in toluene and in isopropanol.[11] The former procedure has been applied on 20 kg scale and it was later demonstrated that this exchange could also be performed in isopropanol only, thus saving a solvent switch from isopropanol to toluene. The partially enriched methanol solvate of esomeprazole potassium salt was typically obtained in 85-90 % yield from pyrmetazole and with 75 % e.e. This development study set the stage for the fit-for-purpose optical purity enhancement strategy detailed in the following section.

STUDY OF THE TERNARY SYSTEM: *R* AND *S* OMEPRAZOLE POTASSIUM SALTS IN METHANOL

Suitable crystallisation processes for the resolution of partially enriched enantiomeric mixtures involving conglomerates or racemic compounds can be designed *via* the identification of regions in the solubility diagrams, inside which the enantiomeric enrichment can be achieved. The concentration and enantiomeric ratio of the eutectic (point E) is the main parameter governing the efficiency and maximum optical enhancement achievable.[12] A physicochemical characterization was therefore initiated for the racemic potassium salt of omeprazole crystallized in methanol. This preliminary work aimed at unravelling the solid-state nature of the potassium salt system (racemic compound, conglomerate or solid solution) for the determination of the ternary phase sections, in methanol at 25 °C and 50 °C. For ternary mixtures consisting of two enantiomers and one solvent, the construction of a ternary phase section requires (at a given temperature) the determination of the solubility curve. The latter illustrates the composition of the saturated solution as a function of the total composition of the system. The number and nature of the solid phases in equilibrium with the solution must also be determined. For each working temperature, the topology of the phase diagram was determined by 1) Measuring the solubility of the enantiopure esomeprazole potassium salt in the selected solvent (by gravimetric method) and 2) Studying the composition of the polysaturated solution (eutectic point) by preparing a

suspension of potassium salt mixtures in methanol. The composition of the liquid phase (polysaturated in the potassium salts involved) was determined by gravimetric method and chiral HPLC of the dry residue (when necessary). This study was conducted using one sample of enantiopure dry esomeprazole potassium salt (Eso-K) containing less than 0.2 % of *R* enantiomer and one sample of racemic potassium salt (made from the corresponding free-acid).[13] The two samples of racemic and enantiopure potassium salts were characterised by X-Ray Powder Diffraction (XRPD) and showed superimposable profiles suggesting the system could well be a conglomerate (**Figure 2**).

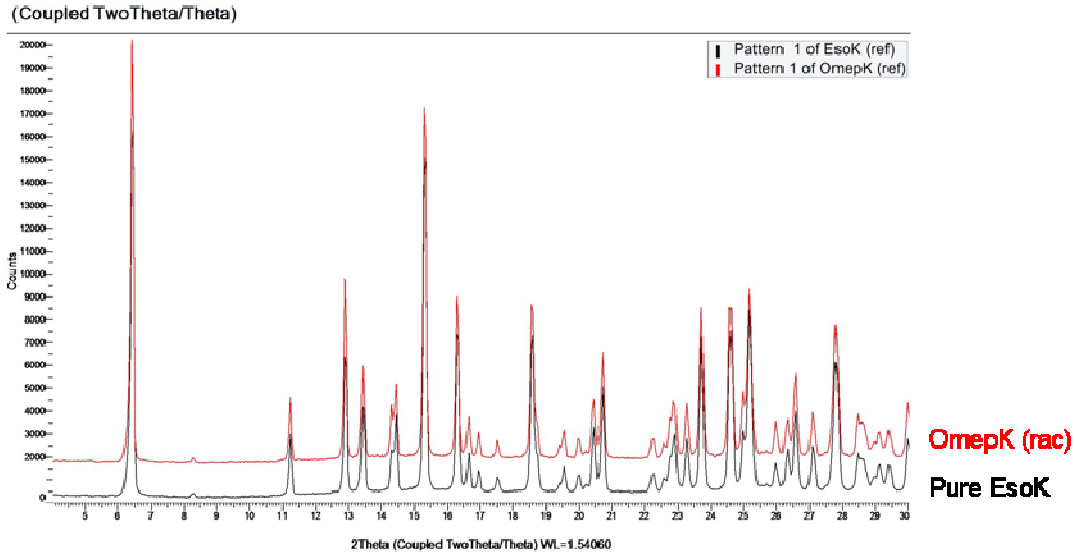


Figure 2

A thermogravimetric analysis (TGA) was carried out from a sample of enantiopure potassium salt between 25-300 °C at a heating rate of 10 °C / min (see supporting information). A weight loss of 13.9 % of the initial weight was observed which is consistent with the loss of two molecules of methanol (theoretical weight loss of 14.3 %); the sample of esomeprazole potassium salt would therefore be a methanol solvate with one molecule of esomeprazole potassium salt for two molecules of methanol. The thermogram obtained by differential scanning calorimetry (DSC), performed in an open pan, on the sample of enantiopure potassium salt (20 °C to 300 °C at a heating rate of 10 °C / min) exhibits two overlapping endothermic events followed by an exothermic event. The first onset ($T_{onset\ 1}$ = 114 °C) can be explained by the loss of solvent molecules, followed by the melt ($T_{onset\ 2}$ = 131 °C) and the degradation of the sample. The melt of the esomeprazole potassium salt recorded at *ca.* 150 - 151˚C, (onset) is higher than the melt of its corresponding racemate recorded at *ca.* 138 - 139˚C (onset). This could be consistent with the existence of a conglomerate. The solubility of the racemic and enantiopure potassium salts in methanol was determined at 25 °C and 50 °C by gravimetry. The enantiopure *S*-potassium salt has a solubility of 2.3 wt % at 25 °C and 5.2 wt % at 50 °C while the racemic potassium salt has a solubility of 3.7 wt % at 25°C and 8.7 wt % at 50 °C. These numbers were used to construct two ternary phase sections at 25 °C and 50 ˚C assuming the system is a conglomerate (see supporting information). From the experimental

ternary phase diagram constructed at 25 °C the minimum quantities of methanol needed to isolate enantiopure potassium salt were calculated for partially enriched mixtures from 80 % to 98 % of esomeprazole. The results are summarised in **Table 2** and the ternary diagram constructed at 25°C is shown in **Figures 3 and 4** (close-up). This data shows that the amount of methanol needed to purify a given S / R mixture of omeprazole potassium salts is almost linear to the enantiomeric excess of the said mixture.

Isoplethal section investigated (enantiomeric excess)	**Minimum quantity of methanol needed**		**Efficiency = theoretical expected yield**
	Wt %	**Volumes**	
60 %	91-92	12-15	75 %
80 %	84-85	6-7	89 %
90 %	73-74	3-4	95 %
96 %	54-55	1-2	98 %

Table 2

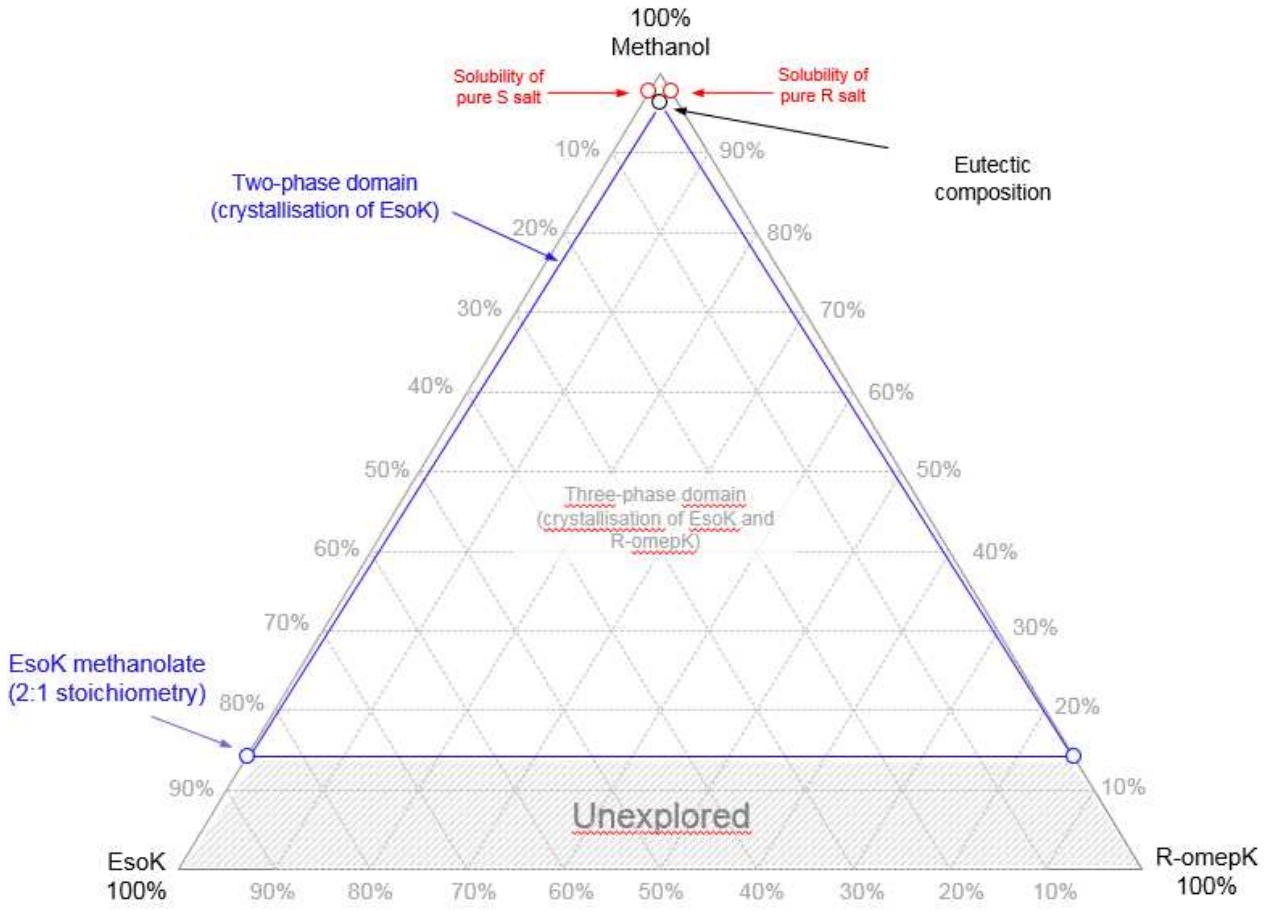

100%
Methanol
Solubility of
pure S salt
Solubility of
pure R salt
Eutectic
composition
Two-phase domain
(crystallisation of EsoK)
10%
90%
20%
80%
30%
70%
40%
60%
50%
50%
60%
40%
70%
30%
80%
20%
90%
10%
Three-phase domain
(crystallisation of EsoK and
R-omepK)
EsoK methanolate
(2:1 stoichiometry)
Unexplored
EsoK
100%
R-omepK
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%

Figure 3

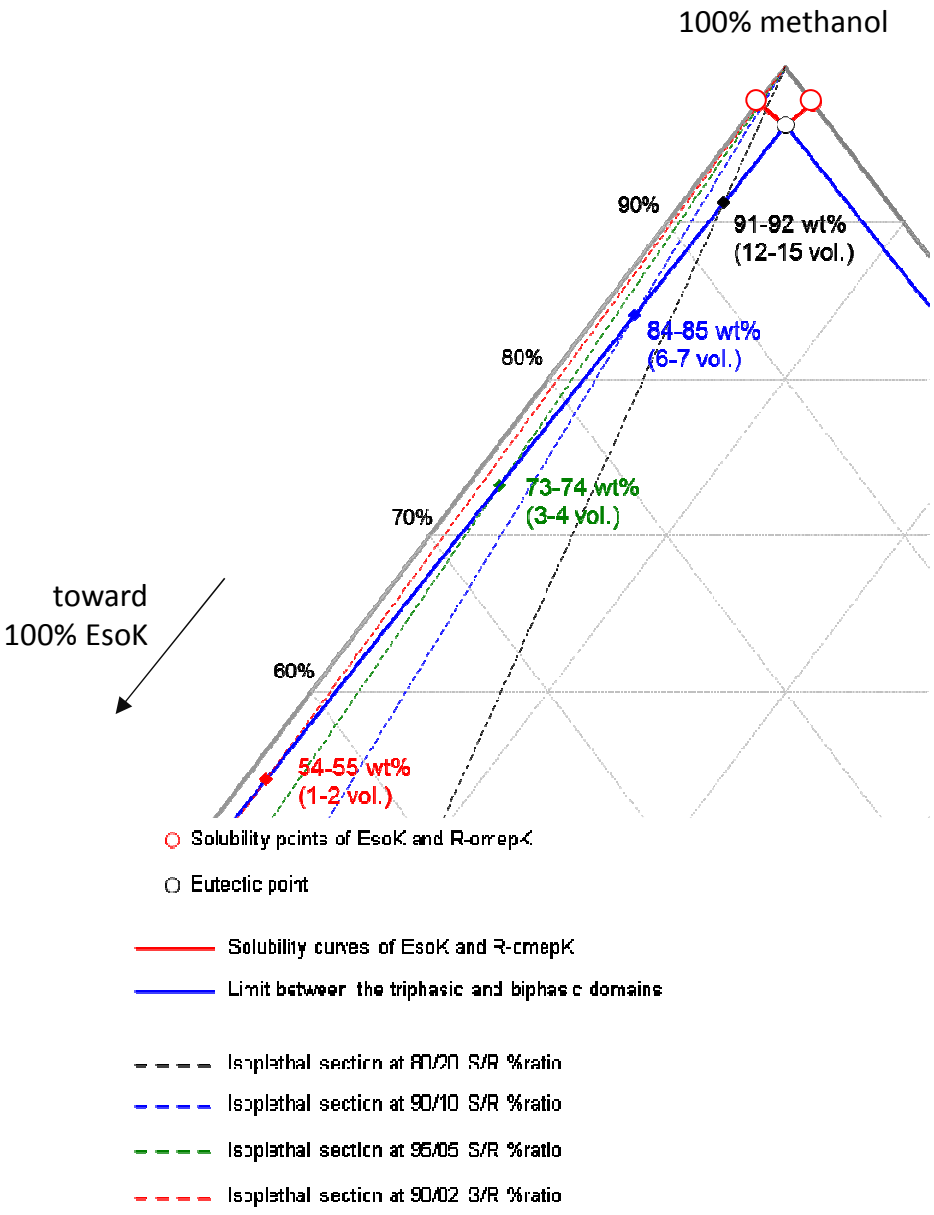

100% methanol
90%
91-92 wt%
(12-15 vol.)
80%
84-85 wt%
(6-7 vol.)
70%
73-74 wt%
(3-4 vol.)
60%
54-55 wt%
(1-2 vol.)
toward
100% EsoK
Solubility points of EsoK and R-crepK
Eutectic point
Solubility curves of EsoK and R-crepK
Limit between the triphasic and biphasic domains
Isoplethal section at 80/20 S/R %ratio
Isoplethal section at 90/10 S/R %ratio
Isoplethal section at 95/05 S/R %ratio
Isoplethal section at 90/02 S/R %ratio

Figure 4

During the pilot scale production, the final reslurry was initially performed in the filter-dryer used for the crude product isolation. The optical purification results were below the expectations (98.4 % e.e.) and this was attributed to the somewhat inefficient stirring inherent to such equipment (*ca.* 30 rpm when performing a reslurry). Indeed, much better results (99.6 % e.e.) were obtained when the reslurry was performed in a standard reactor (110 rpm). We do not believe this is a scale dependent result. The geometry and design of the equipment along with the low stirring speed has a clear influence on the mixing efficiency and consequently on the dissolution / dispersion of the unwanted enantiomer.

CONCLUSION

An optimized process for the oxidation of pyrmetazole **2** using camphosulfonyloxaziridine **3** has been developed. The mild oxidation power of the Davis oxaziridine was pivotal to the implementation of a counter-intuitive reverse addition protocol that was successfully applied on 20 kg scale. The optical purity of the crude product was increased by means of a reslurry from methanol. This procedure can be repeated if needed without hampering the yield as the amount of methanol used (and therefore the expected yield) depends on the level of *R*-enantiomer to be removed. This was applied to the preparation of > 1 kg of enantiomerically and chemically pure methanol solvate of esomeprazole potassium salt in our kilolab facility.

EXPERIMENTAL SECTION

Materials and methods.

The chemical conversion and enantiomeric excess achieved during the oxidation of pyrmetazole was monitored using a chiral HPLC method (Chiralpak column AD-H 250 x 4.6 mm x 5 μm; 0.8 mL / min rate; Temperature: 30°C; UV detection wavelength : λ = 302 nm; Eluent (Isocratic) : Hexane 10 / Ethanol 10 /Isopropanol 2 /acetic acid 1). The enantiomeric excess of isolated esomeprazole potassium salt was determined using a different chiral HPLC method (Chiral AGP column 150 x 4.0 mm x 5 μm; 0.6 mL / min rate; Temperature: 25°C; UV detection wavelength: λ = 302 nm; Eluent (Isocratic) : acetonitrile 75 / 0.025 M phosphate buffer 425). X-Ray Powder Diffraction patterns were collected on a Bruker D8 diffractometer using Cu Ka radiation (40kV, 40mA), θ-2θ goniometer, a Ge monochromator and a Lynxeye detector. The instrument is performance checked using a certified Corundum standard. The software used for data collection was Diffrac. SUITE and the data analysed and presented using Diffrac.EVA. Samples were run under ambient conditions as flat plate specimens using powder as received without grinding. Approximately 50-100 mg of the sample was lightly pressed on a glass slide to obtain a flat surface. The sample was rotated in its own plane during analysis. The details of the data collection are: Angular range: 3 to 32 °2θ; Step size: 0.05 °2θ; Collection time: 0.5 s/step. DSC data were collected on a Perkin Pyris Diamond DSC. The instrument was calibrated for energy and temperature using certified indium. Typically, 2-5 mg of each sample, in a pin-holed aluminium pan, was heated at 10 °C/min from 25 °C to 200 °C. A nitrogen purge at 50 ml/min was maintained over the sample. The instrument control and data analysis software was PYRIS Software version 7.0.0.011. TGA data were collected on a Perkin Pyris Diamond TGA. 5-10 mg of each sample was loaded onto a pre-weighed aluminium crucible and was heated at 10 °C.min-1 from ambient temperature to 400°C. A nitrogen purge at 50 ml.min-1 was maintained over the sample.The instrument control and data analysis software was PYRIS Software version 7.0.0.011.

Enantioselective oxidation: To a 600 L stainless-steel reactor was added 122 kg of a 16.4 wt % solution of pyrmetazole (20.0 kg, 60.7 mol, 1.0 equiv.) in toluene (obtained from the Minakem production site at Dunkirk). The solution was concentrated to low volume (110 L collected) at 40-45 °C under vacuum (150 to 24 mbars). Isopropanol (60 L) was added and the distillation was carried out under the same conditions (60 L collected). Isopropanol (130 L) was added to the residue and the temperature was adjusted to 22 +/- 3 °C. DBU (10.2 kg, 66.9 mol, 1.1 equiv.) was then charged in 40 min at max. 25 °C and the addition funnel was rinsed with isopropanol (5 L). In a separate 600 L reactor were charged isopropanol (60 L) and 1*R*-(-)-10-camphorsulfonyloxaziridine (14.7 kg, 64.1 mol, 1.05 equiv.) and the temperature of the suspension was adjusted to 12 +/- 3 °C. The pyrmetazole solution in isopropanol was added to the oxaziridine suspension in *ca.* 60 min at 12 +/- 3 °C *via* an addition funnel. The latter was then rinsed with isopropanol (5 L). The reaction mixture was stirred for 10 h at 12 +/- 3 °C and was sampled for conversion check by HPLC. The suspension was transferred to a 160 L filter-dryer and the mother liquors containing the product were collected. The cake was washed twice with isopropanol (2 x 20 L). The camphorsulfonylimine cake was dried and collected (12.2 kg, 57.2 mol, 89 % recovery yield). The mother liquors and the cake washes were combined and charged into a 600 L stainless steel reactor and the solvent was distilled off under vacuum at 40 +/- 5 °C (260 L collected). Toluene (40 L) was added and the distillation was carried forward (43 L collected). Toluene was added (80 L) and the temperature was adjusted to 33 +/- 2 °C. The 16 wt % potassium methoxide solution in methanol (31.6 kg, 72.1 mol, 1.2 equiv.) was added at this temperature in *ca*. 4 h and the resulting suspension was stirred at 20 +/- 3 °C for 60 min. The mixture was transferred into a 160 L filter-dryer and the mother liquors were collected. The cake was washed twice with a cold (2 +/- 3 °C) 1 : 1 mixture of toluene and methanol (20 L) and then with cold (2 +/- 3 °C) methanol (40 L). The solid was partially dried under vacuum at 30 °C to obtain 34.1 kg of wet product containing *ca.* 32 wt % of methanol (corresponding to 23.2 kg of dry methanol solvate of esomeprazole potassium salt, 51.8 mol, 85 % yield, 76 % e.e.).

Reslurry from methanol in a filter dryer: Methanol (128 L) and 29.5 kg of partially dried methanol solvate of esomeprazole potassium salt (corresponding to 20.1 kg of dried material, 44.8 mol) were charged in a 160 L filter dryer. The agitation speed was set to 40 rpm and the temperature was adjusted to 42 +/- 3 °C. The slurry was stirred under these conditions for 3 h and it was cooled to 20 +/- 3 °C and stirred for 60 min. The mother liquors were collected and the cake was washed with 20 L of methanol at 20 +/- 3 °C. The product was dried at 30 °C under vacuum (14.4 kg, 72 % yield, 98.4 % e.e.).

Reslurry from methanol in a reactor: Methanol (13.5 L) and 1.75 kg of partially enriched dried methanol solvate of esomeprazole potassium salt were charged in a 25 L reactor. The agitation speed was set to 100 rpm and the temperature was adjusted to 42 +/- 3 °C. The slurry was stirred under these conditions for 5 h and it was cooled to 20 +/- 3 °C and stirred for 60 min. The suspension was transferred onto a sintered funnel and the cake was washed with methanol (3 x 1.8 L) at 20 +/- 3°C. The product was dried at 30°C under vacuum (1.04 kg of product corresponding to 60 % overall yield; 99.6 % e.e.).

Oxidation of camphorsulfonylimine into camphorsulfonyloxaziridine: Dichloromethane (115 L) was charged in a 600 L reactor followed by Aliquat®336 (0.44 kg, 1.1 mol, 0.01 equiv.). Camphorsulfonylimine (23 kg, 108 mol, 1.0 equiv.) was

added and the temperature was adjusted to 2 +/- 3°C. Aqueous potassium carbonate (73.6 kg solid K_2CO_3 in 110 L of water, 533 mol, 5.0 equiv.) was added to the reactor in *ca.* 30 min. Peracetic acid (23.6 kg of a 38 % solution is acetic acid, 119 mol, 1.1 equiv.) was added in *ca.* 60 min at 2 +/- 3°C. The biphasic mixture was stirred for 60 min and sampled for conversion check (typically ≥ 99.0 % conversion by HPLC). Sodium sulfite (0.69 kg, 5.5 mol, 0.05 equiv.) was then added at 2+/-3°C and the mixture was stirred for 30 min at this temperature. Water (69 L) was added and the temperature was allowed to reach 22+/-3°C. The layers were separated, and the organic layer was washed with water (46 L) and then with a 5 % aqueous solution of sodium bicarbonate at 22+/-3°C. The organic layer was then distilled under vacuum at max. 30°C. Isopropanol (46 L) was added and distilled under vacuum at max. 30°C. To the residue was added isopropanol (138 L) and the suspension was stirred for 30 min at 30 +/- 3°C. The temperature was then adjusted to 2+/-3°C and the suspension was stirred for 90 min. The suspension was transferred to a 160 L filter-dryer and the cake was washed twice with isopropanol at 2+/-3°C (12 L). The product was then dried under vacuum (down to 10 mmbars) at 30°C to yield 1*R*-(-)-10-camphorsulfonyloxaziridine (21.5 kg, 94 mol, 87 % yield). This protocol has been applied in our plant in Dunkirk to generate more than 3 MT of Davis oxaziridine (250 kg batches)

ASSOCIATED CONTENTS

Description of the conversion over time during the oxidation; process safety data; TGA and DSC data; Ternary phase diagrams at 25°C and 50°C.

AUTHOR INFORMATION:

Corresponding Authors

*E-mail: laurent.petit@minakem.com; baptiste.fours@minakem.com

Notes

The authors declare no competing financial interest

ACKNOWLEDGMENTS

We thank Dominique Delbrayelle for insightful discussions. We also warmly thank Dr. Olivier Jentzer and Frédéric Gauchet for supporting this work and allowing us to share these results with the chemical community.

REFERENCES

[1] Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Sheppard, A. C.; Kumar, A.; Davis, F. A. *Org. Synth.* **1990**, *69*, 158.
[2] Williamson, K. S.; Michaelis, D. J.; Yoon, T. P. *Chem. Rev.* **2014**, *114*, 8016.
[3] Mahale, R. D.; Rajput, M. R.; Maikap, G. C.; Gurjar, M. K. *Org. Proc. Res. Dev*. **2010**, *14*, 1264.
[4] Talsi, E. P.; Rybalova, T. V.; Bryliakov, K. P. *ACS Catal.* **2015**, *5*, 4673.
[5] Song, W.; Dong, L.; Zhou, Y.; Fu, Y.; Xu, W. *Synth. Commun*. **2014**, *45*, 70.
[6] Hein, J. E.; Cao, B. H.; Meijden,M. W.; Leeman, M.; Kellogg, R. M. *Org. Process Res. Dev.*, **2013**, *17*, 946.
[7] Stabile, P.; Bertolazzi, M.; Faccin, N.; Rasia, D. Efficient process for the preparation of esomeprazole (*S*)-binol complex EP2980086B1 Feb. 3, 2016.
[8] Stabile, P.; Rasia, D.; Faccin, N.; Bertolazzi, M. Improved process for the preparation of optically pure esomeprazole EP3064495B1 Sep. 7, 2016.
[9] Cotton, H.; Elebring, T.; Larsson, M.; Li, L.; Sörensen, H.; von Unge, S. *Tetrahedron Asym.* **2000**, *11*, 3819.

[10] Mergelsberg, I.; Scherer, D.; DiBenedetto, D.; Tanner, M. *Tetrahedron Lett.* **1992**, *33*, 161.
[11] Performing the salt exchange in methanol only impaired the isolated yield and did not improve the enantiomeric excess of the product.
[12] J. Jacques, A. Collet, S.H. Wilen, Enantiomers, racemates, and resolutions, N.Y, Wiley, c1981. ISBN 0-89464-876-4
[13] Both samples were obtained from the Minakem Dunkirk plant which routinely produces and sells these chemicals on a multi-ton scale.