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# Improved Process for the Preparation of Montelukast: Development of an Efficient Synthesis, Identification of Critical Impurities and Degradants

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**Abstract:**

**An improved and scalable process for the production of montelukast (Singulair, drug for asthma) based on a new and advantageous method of carrying out the key substitution reaction has been developed. The present procedure is distinguished from the previous solutions in the use of linear or cyclic polyethers, which ensures higher selectivity of the key step. The improved process for the preparation of montelukast is able to minimize a content of impurities and allows the effective production of montelukast and its scale-up.**

## Introduction

Montelukast **1** is a well-known drug indicated for the prophylaxis and chronic treatment of asthma.[1−4] It acts as a selective antagonist of the leukotriene D4 receptor which leads to the reduction of bronchoconstriction and results in less inflammation. Montelukast is administered orally once daily which yields a benefit in comparison with a majority of drugs for pulmonary disorders such as asthma.[1−4] The sodium salt of montelukast described with formula **1**, see Figure 1, is used for asthma therapy.

Several synthetic methods were reported for the preparation of montelukast **1**.[1,5−15] From the point of view of chemical synthesis the crucial step is formation of the chemical bond between carbon and sulfur atoms (thiolation step). In principle, there are two basic methods of carrying out the key step, which are described in Scheme 1. The first method is indicated as method A,[1,5–13] the second one as method B.[14,15] Both the basic methods can be further extended with a number of variants that are mainly based on alternating the order of the reaction steps. Only a few synthetic procedures were carried out in a different way than is described in Scheme 1.[16−18] The first and conventional process for production of montelukast exploits commercially available alcohol **2** and carboxylic acid **3** as starting materials.[6] This method is characterized by the use of a methanesulfonyl derivate of **2** and the dilithium salt of **3** in the key synthetic step. This solution also comprises a method of purification of crude montelukast via its salt with dicyclohexylamine and also a method of obtaining the amorphous sodium salt of montelukast **1**.

There are a number of functional groups in the montelukast structure that impair the chemical stability of this substance, see Figure 1. Montelukast **1** is known to be prone to several types of degradation.[19−26] It is mainly the case of the following chemical transformation: oxidation of the mercapto group to the sulfoxide,[20–23] photoisomerisation at the location of the double bond from geometry (*E*) to (*Z*),[23,24] dehydration at the *tert*-alcohol group, producing the corresponding olefin[25] and dehalogenation reaction.[26] The chemical impurities are usually removed by means of crystallization in the phase of montelukast salts with amines[6,9,25] or in the phase of montelukast acid.[27]

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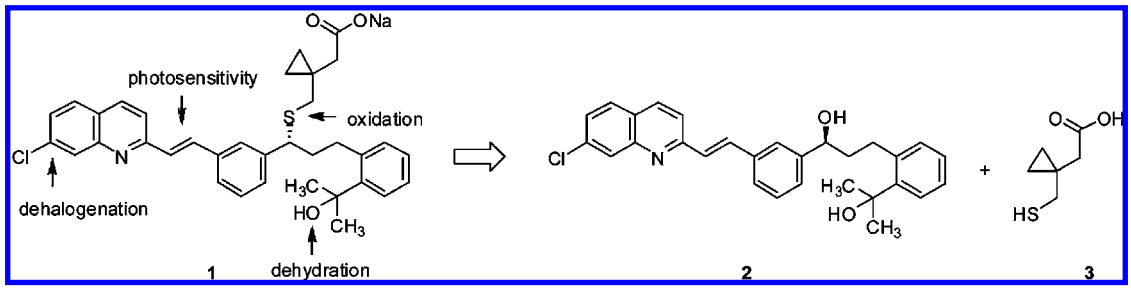
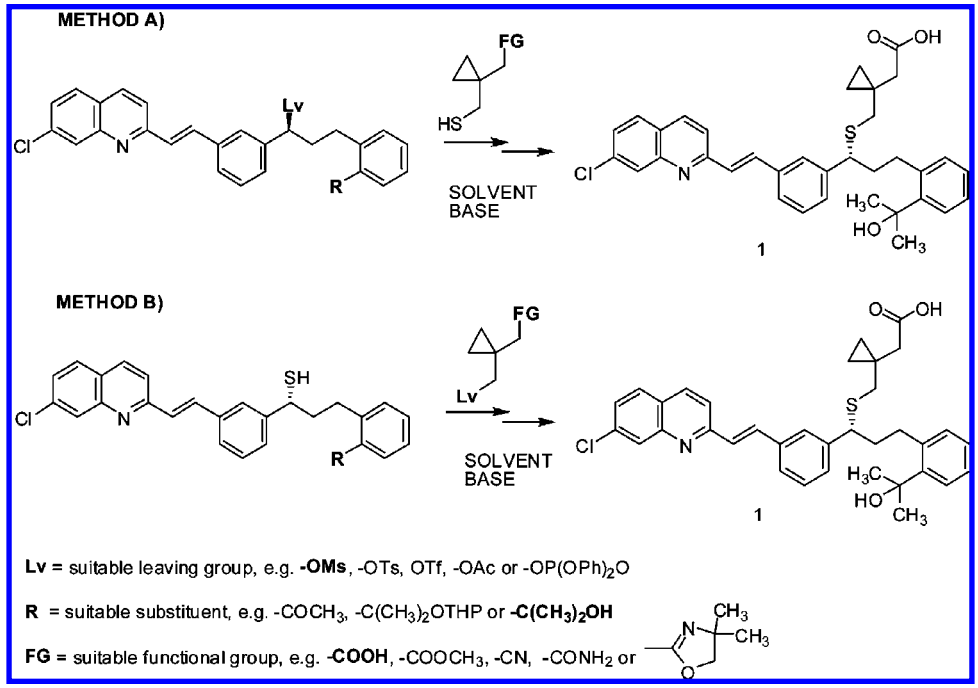



***Figure 1.*** **Structure of montelukast sodium, 1; arrows indicates critical parts of the structure for chemical degradations; compounds 2 and 3 represent common intermediates.**

***Scheme 1.*** **Two general methods of the key step for preparation of montelukast 1**




The complicated synthesis and low stability of montelukast **1** present many problems for its large-scale production. We developed a new process that obviates many previous problems and limitations. Furthermore, we report critical impurities and a procedure for achieving the pharmaceutical quality. The improved process, whose details are presented in this paper, is suitable for large-scale production of the active pharmaceutical ingredient (API) with many advantages.

## Results and Discussion

A procedure of synthesis as well as isolation and purification of montelukast **1** has a significant influence on the economy of process. Our need for large quantities of montelukast led us to develop a scalable synthesis for this compound in pharmaceutical quality. Hence, we tried the earlier synthesis, and we distinguished three serious troubles: low selectivity of the key synthetic step, a suitable form of montelukast for efficient isolation and specific impurities formation.

**Key Synthetic Step and Its Selectivity.** The present process for synthesis of montelukast **1** relates to a new method of carrying out the substitution reaction that represents the key step in the process. This reaction is described in the Scheme 2. The compound **4** containing the methanesulfonic group as the good leaving group was used as the first starting material. The compound **4** was achieved using alcohol **2** by treating with methanesulfonyl chloride under basic catalysis. Another starting material of the present process is [1-(mercaptomethyl)cyclopropyl]acetic acid **3**, which is converted to the corresponding salt by the action of a base (2 equiv). Various substances can be used as the base, e.g. organometallic compounds such as butyl lithium.[6] Suitable bases to ensure acceptable solubility are alkoxides of alkali metals, e.g. *tert*-butoxides and *tert*-amylates. The *in situ* obtained salt of acid **3** is the active form of the reagent. In the literature was described a process for preparation of alkali metal salts of **3** by saponification of corresponding esters without isolation and characterization of these salts.[28] Several of our attempts to isolate the salts **3** with alkali metals were carried out, but they failed due to very low stability of these salts to oxygen. The properties of these salts differ; mainly their solubility depends on the kind of metal ion. The corresponding decrease of the active agent concentration reduces selectivity of the substitution reaction, see Figure 2. Low conversion of **4** to montelukast **1** in the course of the key step relates to both competitive reactions of starting material **4** and consecutive degradations of montelukast **1**, see Scheme 2.

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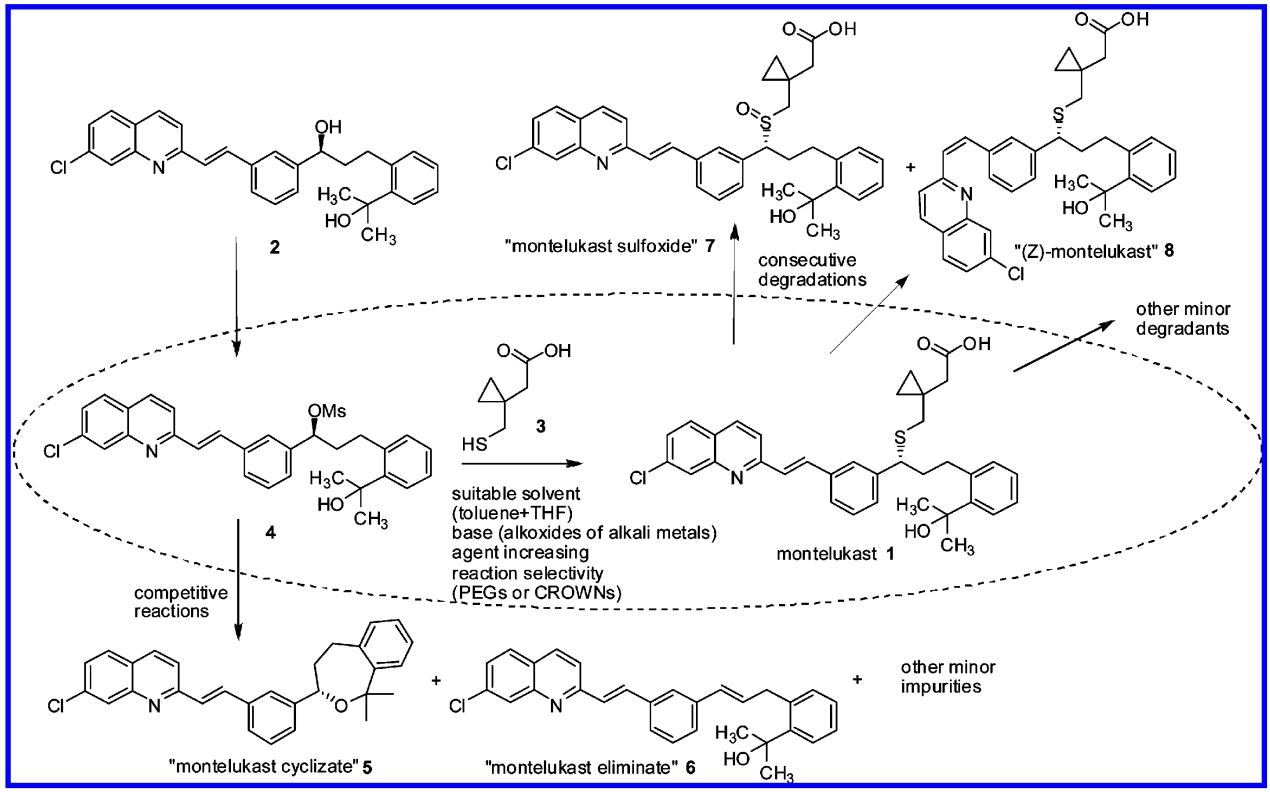
***Scheme 2.*** **Present process for the key step (inside the ellipse); unwanted reactions lead to impurities (out of the ellipse)**




Unlike the previous solutions, the present process uses the linear or cyclic polyethers as agents to increase reaction selectivity. These compounds play the role of phase transfer catalyst, which can solvate metal ions and thus increase the solubility and reactivity of the nucleophilic reagent. The increased reactivity of the nucleophilic reagent (dialkali metal salt of **3**) resulted in higher selectivity of the process, and unwanted competitive reactions were suppressed. As suitable linear polyethers various polyethylene glycols (PEG) can be used. CROWN ethers with different cycle sizes can serve as suitable cyclic polyethers. When the key step was carried out without addition of any polyethers, compound **5** was found as a main product (typical final content of reaction mixture by HPLC: 53.9% of **5**, 20.6% of **1**, 8.1% of **6**, 4.6% of **2**, other minor impurities making up the rest of 100%).

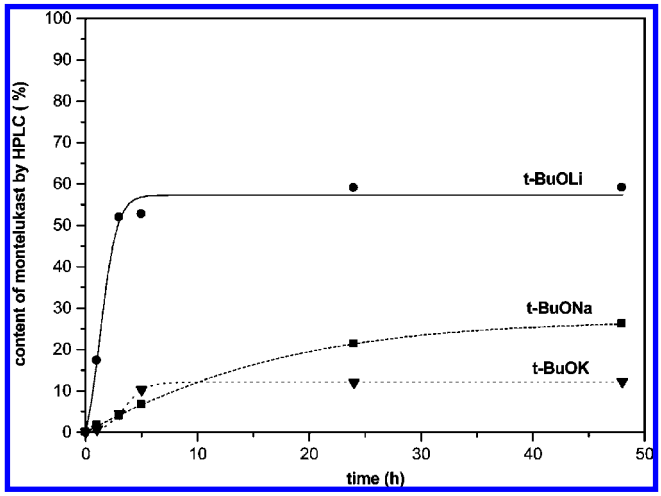



***Figure 2.*** **Time dependence of the contents of montelukast in the reaction mixture of substitution reactions carried out with various *tert*-butoxides of alkali metals and without addition of agents increasing selectivity.**

The set up of rough conditions for the key step procedure was made by means of a series of preliminary experiments. Their results and experimental conditions are described in Table 1. The experiment based on the use sodium *tert*-butoxide and PEG-600 was chosen as a ground for the scale-up procedure. For instance, the final montelukast content in the reaction mixture is usually about only 20% when the mixture of toluene and tetrahydrofuran is used as a solvent and sodium *tert*-

***Table 1.*** **Conversions of 4 and contents of montelukast 1 after 24 h from mixing of the reaction components in different modifications of the key synthetic step[a]**

| base (2 equiv) | component increasing selectivity (1 equiv) | conversion of starting material **4** (%) | content of montelukast **1** (%) |
|---|---|---|---|
| *tert*-BuOLi | — | 97.9 | 60.8 |
| *tert*-BuOLi | 12-CROWN-4 | 97.3 | 59.6 |
| *tert*-BuONa | — | 82.3 | 21.4 |
| *tert*-BuONa | 18-CROWN-6 | 96.1 | 75.9 |
| *tert*-BuONa | 15-CROWN-5 | 94.6 | 73.3 |
| ***tert*-BuONa** | **PEG-600** | **93.2** | **81.0** |
| *tert*-BuONa | PEG-1500 | 81.4 | 68.2 |
| *tert*-BuOK | dibenzo-18-CROWN-6 | 94.8 | 65.6 |
| *tert*-BuOK | PEG-600 | 96.2 | 72.7 |
| *tert*-BuOK | — | 89.5 | 12.0 |
| *tert*-AmylOK | — | 95.0 | 9.6 |
| *tert*-AmylOK | 18-CROWN-6 | 92.7 | 51.5 |

[a] Twenty milliliters of toluene, 0.28 g of acid **3**, a base (2 equiv to acid) and a polyether (1 equiv) were mixed under argon atmosphere and cooled to ~−10 °C. The solution of **4** (1 g) in 5 mL of THF was then added to obtain the slurry, and the mixture was gradually allowed to warm from −10 °C up to room temperature in 1 h and stirred at room temperature for several hours. Conversion of **4** and montelukast content was checked by HPLC (isocratic mode).

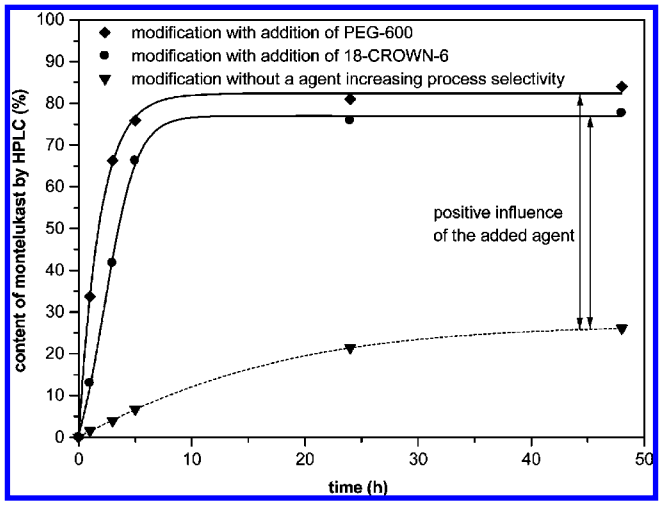



***Figure 3.*** **Dependencies of montelukast content on reaction time for the key substitution carried out under various conditions; sodium *tert*-butoxide was used as a base and the mixture of toluene and tetrahydrofuran as a solvent in all cases**

butoxide as a base. The addition of an agent to increase selectivity, for example PEG-600 (1 equiv) or 18-CROWN-6 (1 equiv), to this reaction mixture in the beginning increases the final montelukast content to 80%, and the final content of competitive products is reduced. Figure 3 compares the composition of reaction mixtures with or without the use of a polyether and demonstrates the positive influence of the agent added.

**Isolation and Purification Process.** The output of the key synthetic step is a reaction mixture that contains a salt of montelukast **1** with an alkali metal and several undesired impurities dissolved together in organic solvents used. It was impossible to isolate and purify sodium montelukast directly due to its good solubility in numerous solvents from polar ones (e.g., water, ethanol) to nonpolar ones (e.g., diethyl ether, toluene). The product was isolated from the reaction mixture by means of conversion of the crude substance to well-crystallizing salts with amines, followed by recrystallization of these salts with simultaneous removal of chemical impurities. A very important aspect in the method of isolation of montelukast ammonium salts is the use of acetonitrile as a cosolvent. Acetonitrile specifically prevents the adhesion of separated crystals to the crystallization vessel or to the agitator. This finding can be applied in production scale with substantial advantages without the risk of excessive losses of the product that would otherwise remain stuck on the production equipment.[29] Pure amine salts were used for direct transformation to the pharmaceutically useful amorphous sodium salt of **1**. The setup of conditions for the isolation and purification procedure was made by means of a series of preliminary experiments with many alkylamines, see Table 2. Better results were observed for *primary* amines in comparison with *secondary* as well as *tertiary* amines. The results for *n*-propylamine and isopropylamine obtained at the stage of preliminary experiments were almost the same. However, repeated experiments with isopropylamine on real reaction mixtures show slightly better reproducibility, yields and product quality (isolated yields from reaction mixture were 70−75%, and purity was around 94% by HPLC) in comparison with *n*-propylamine (isolated yields 65−70%, purity around 93% by HPLC). The experiment based on the use of isopropylamine was chosen as a ground for the scale-up procedure.

**Critical Impurities and Degradants.** Montelukast **1** and its intermediates show extremely low chemical stability which has great influence on its industrial production.[19–26] One of the sources of chemical contamination of montelukast **1** is low stability of the normally used starting material **4**. In parallel to the key thiolation reaction, compound **4** is subjected to undesired reactions, namely cyclization and elimination that lead to compounds **5** and **6**,[30] see Scheme 2. Impurities of this type are not critical and can be easily removed by crystallization of montelukast salts with amines, especially from nonpolar solvents, e.g., toluene.

The impurities generated by degradation of the target substance are structurally very similar to the source substance, and therefore, it is very difficult to reduce their content in the API by common methods (e.g., crystallization). It has been found that the transformation of montelukast **1** to (*Z*)-isomer **8** was unexpectedly fast under sunlight and air. Already within minutes the concentration of (*Z*)-isomer **8** may grow to a level of percent units.[31] Simultaneously, but more slowly, the mercapto group was oxidized, producing (*E*)-montelukast sulfoxide **7**, see Scheme 2.[20–24,31]

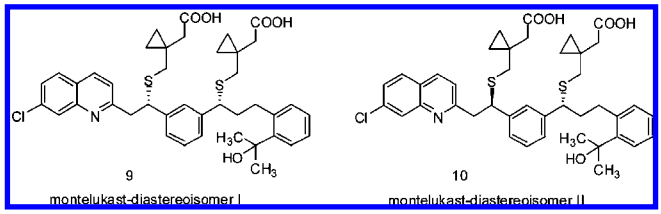
A mixture of diastereoisomers **9** and **10** has been found as a specific and so far unknown impurity in crude montelukast sodium **1**. These compounds are generated through the reaction of alkali metal salts of **3** with primarily obtained montelukast

***Table 2.*** **Preparation and yields of salts of various amines with montelukast[a]**

| amine | separated form | yield (%) | melting point (°C) | start of crystallization (min) |
|---|---|---|---|---|
| *n*-propylamine | solid state | 95 | 97−100 | 10 |
| isopropylamine | solid state | 94 | 97−100 | 10 |
| *tert*-butylamine | solid state | 92 | 98−101 | 45 |
| benzylamine | solid state | 85 | 93−96 | 120 |
| α-methylbenzylamine | solid state | 92 | 98−102 | 5 |
| 2-methylaminoethanol | oil | — | — | — |
| di-*n*-propylamine | not separated | — | — | — |
| di-isopropylamine | not separated | — | — | — |
| dicyclohexylamine | solid state | 82 | 118−121 | 120 |
| triethylamine | oil | — | — | — |
| di-isopropylethylamine | solid state | 52 | 152−154 | 180 |

[a] Ten milliliters of toluene, 2.5 mL of acetonitrile and 1.05 equiv of the amine were added to 1 g of montelukast acid; 10 mL of *n*-heptane was gradually added to the solution under stirring. In case of solid separation the montelukast salt was filtered, washed with 5 mL of heptanes and dried.

**1**. This unwanted reaction is probably allowed due to increased reactivity of nucleophilic reagent. This also is only one negative side effect of added polyether which was observed. Stereochemical differentiation of compounds **9** and **10** was made after assignment of their $^{1}H$ and $^{13}C$ NMR signals in NMR spectra measured in deuteriochloroform solution. This stereochemical differentiation comes from the premise that both impurities **9** and **10** come into existence from the montelukast which has one chiral centre with configuration R, and this configuration remains unchanged. Stereochemistry of the second chiral carbon was determined on the basis of NOE interactions in NMR spectra and thus distances of protons in the surrounding area of both chiral centers of the molecule. The contents of diastereoisomers **9** and **10**, shortly referred to as montelukast diastereoisomer I and diastereoisomer II, respectively, were successfully removed by means of crystallization of salts of montelukast with amines in polar solvents, e.g., isopropyl alcohol. During the montelukast sodium process development, four critical impurities were observed, namely (*Z*)-montelukast **8**, (*E*)-montelukast sulfoxide **7**, and diastereoisomers **9** and **10**. The preparation of critical montelukast impurities, including the methods of their separation and isolation, are described in the Experimental Section.




**Scalable Process.** The process for preparation of montelukast sodium **1** used in the scale-up experiment consists of five separate operations. In the first step alcohol **2** was converted to the intermediate **4** by action of methanesulfonyl chloride in acetonitrile medium and with the addition of DIPEA as a base. Compound **4** of low stability was isolated in the paste form, and it was used immediately in the next synthetic step. In the second step was mixed acid **3** with sodium *tert*-butoxide and PEG-600 in toluene. The obtained mixture was cooled below −5 °C, and then a solution of **4** in THF was added dropwise. Further, the reaction mixture was maintained under the inert atmosphere and stirred for several hours. This solution usually contained 80−85% of montelukast **1** according to HPLC analyses. In the third step crude montelukast sodium was converted to a solution of montelukast acid and further isolated in the form of a crystalline salt of montelukast with isopropylamine. In the fourth step the salt of montelukast with isopropylamine was purified by crystallizations in isopropyl alcohol and toluene. The final removal of the impurities occurs in this step of the scale-up process. The target amorphous form of montelukast sodium was obtained in the last step by direct conversion of the montelukast isopropylammonium salt by

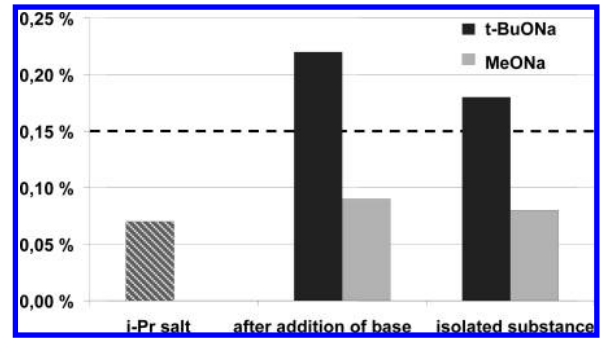



***Figure 4.*** **Contents of montelukast sulfoxide 7 (by HPLC) in montelukast 1 during final step, depending on base used.**

action of sodium methylate as a suitable source of sodium ions. Previously selected sodium *tert*-butoxide has been changed due to its mild oxidation effect, see Figure 4. The overall yield of montelukast sodium **1** comprising five whole separate operations was approximately 28%; the achieved chemical purity was higher than 99.5% with the contents of individual impurities below 0.1%. Analytical data obtained by means of XRPD unambiguously characterize the amorphous features of montelukast sodium **1**.

## Conclusions

The improved process represents a new and advantageous method of carrying out the key substitution reaction that leads to montelukast **1**. In carrying out the key step in accordance with the present process, the resulting composition of the reaction mixture is conveniently controlled without the necessity of long-term cooling or the use of protective groups. Isolation and purification lead to the product which conforms to all the regulatory requirements.

## Experimental Section

**Analytical Methods.** The standards of critical impurities **7**, **8**, **9** and **10** were obtained by separations with the use of the Waters autopurification system, and their structures were checked by NMR and MS. The Waters autopurification system with SQ detector, XBridge Prep OBC C18 column, 100 mm × 19 mm, and mixture of two mobile phases was used. The Waters autopurification system is a combination of various instruments integrated in a specific configuration that enables automated separation and isolation of particular substances from a sample on the basis of a signal from UV and MS detectors. **$^{1}H$ and $^{13}C$ NMR** spectra were measured with the Bruker Avance 500 spectrometer with the measuring frequency of 500.131 and 125.762 MHz, respectively. The spectra were measured in DMSO-$d_6$ or in $CDCl_3$ solutions. $^{1}H$ chemical shifts were related to TMS ($\delta = 0.00$ ppm) and $^{13}C$ chemical shifts to DMSO-$d_6$ ($\delta = 39.6$ ppm) or $CDCl_3$ ($\delta = 77.6$ ppm). **The mass spectra** were measured using a Sciex API 3000 Mass Spectrometer (Sciex, Canada) with positive atmospheric pressure ionization (TurboIonspray) or using LTQ Orbitrap Hybrid Mass Spectrometer (Thermo Finnigan, U.S.A.) with direct injection into APCI source in positive mode. **X-ray diffraction patterns** (XRPD) of amorphous montelukast sodium were measured with the X'PERT PRO MPD PAN analytical diffractometer: radiation Cu Kα ($\lambda = 1.54178$ Å), graphite

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monochromator, 45 kV excitation voltage, 40 mA anode current, measurement range 2−40° 2$\theta$, increment 0.01 2$\theta$. **Melting points** of the salts of montelukast with amines obtained in the solid state were measured on the Kofler block with the sample heating speed of 10 °C (to 70 °C) and 4 °C (over 70 °C) per minute. The measured values of melting points are summarized in Table 2. **HPLC (isocratic mode)** chromatograms were measured with the EliteLachrom device made by the Hitachi Company. Stationary phase: RP-18e was used for the analyses; column temperature was 20 °C. Mobile phase: Acetonitrile (80%) and a 0.1 M aqueous solution of ammonium formate adjusted to pH 3.6 with formic acid (20%) were used. The flow rate of the mobile phase was 1.5 mL/min. Detection at the wavelength of 234 nm was used. Methanol was used as the solvent for preparation of samples; 10−20 $\mu$L of the solution was used for the injection. The isocratic HPLC method was used for checking the compositions of the reaction mixtures. **HPLC (gradient mode)** chromatograms were measured with the Alliance HPLC device with PDA detector. Stationary phase: STAR RP-8e, 250 mm × 4 mm, 5 $\mu$m was used for the analyses; column temperature was 15 °C. Mobile phase: Acetonitrile (A) and 0.01 M aqueous solution of $KH_2PO_4$ adjusted to pH 2.2 with phosphoric acid (B) were used. Gradient mode with the flow rate of mobile phase 0.8 mL/min was used. Composition on the start was 60% of A and 40% of B, then changed to 15% of A and 85% of B over 20 min; this composition was held for 5 min, then changed to 60% of A and 40% of B over 5 min, and this composition was held to the end (overall time 35 min.). Detection at the wavelength of 234 nm was used. Methanol was used as the solvent for the preparation of the samples; 10−20 $\mu$L of the solution was used for the injection. The gradient HPLC method was used for checking the quality of the target substance including its salts with amines and of isolated standards of impurities. **HPLC (determination of (*S*)-enantiomer by HPLC)** chromatograms were measured with the Alliance HPLC device with PDA detector. Stationary phase: Chiralpak IA (5 $\mu$m), size 0.25 m, internal diameter 4.6 mm (manufactured by Daicel) was used for the analyses, column temperature 10 °C. Mobile phase: hexane/ethanol/1,4-dioxan/trifluoroacetic acid (77:3:20:0,1 v/v/v) was used. The flow rate of the mobile phase was 1.0 mL/min. Detection at the wavelength of 285 nm was used. Methanol was used as the solvent for preparation of samples; 10 $\mu$L of the solution was used for the injection. The isocratic elution was used for checking the optical purity of target montelukast. Typical retention times: montelukast: 9.3 min, (*S*)-montelukast: 12.9 min.

**Preparation of 2-(3-(*S*)-(3-(2-(7-Chlorquinolinyl)ethenyl)phenyl)-3-methanesulfonyloxypropyl)phenyl-2-propanol 4 (Scale-Up Process).** A mixture of 2-(2-(3(*S*)-(3-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-hydroxypropyl)phenyl-2-propanol **2** (4 kg), acetonitrile (21 L) and toluene (8,4 L) was stirred under inert atmosphere and cooled to −15 °C. Then diisopropylethylamine (1.89 L in 0.5 L acetonitrile) was added gradually. A solution of methanesulfonylchloride (0.79 L) in toluene (1.1 L) was added in portions over 20 min, maintaining the temperature at −13 to −15 °C. The reaction mixture was stirred for 3.5 h at −15 °C, and the separated solid was filtered under an inert atmosphere. The cake was washed with cooled acetonitrile (2 × 4 L, −15 °C). The yield of the crude product in a paste form was 6.4 kg which corresponds to 3.33 kg of **4** recalculated to dry product (yield **71** %). Obtained crude product was used immediately in the next step.

**Preparation of Crude Montelukast Sodium 1 (Scale-Up Process for the Key Synthetic Step).** In 25.6 L of toluene, [1-(mercaptomethyl)cyclopropyl]acetic acid **3** (950 g), sodium *tert*-butoxide (1.25 kg) and PEG-600 (3.6 kg in 3.8 L of toluene) were mixed together; the mixture was stirred under argon atmosphere and cooled to ∼−10 °C. Then, a solution of **4** (3.33 kg recalculated to dry product) in 14 L of tetrahydrofuran was added to the obtained slurry. The reaction mixture was gradually stirred from −10 °C up to the room temperature for 2 h. It was further stirred at room temperature (about 21 °C) for 5−6 h. The reaction mixture was monitored by means of HPLC. At the end of the monitoring, the reaction mixture contains 85.7% of montelukast.

**Isolation and Crystallization of Montelukast Salt with Isopropylamine (Scale-Up Process).** The reaction mixture from the previous step was concentrated in vacuum; 10.5 L of toluene was added to the residue and concentrated in vacuum again. The residue was diluted with toluene to the volume of 27 L. This solution was washed twice with a 0.5 M solution of tartaric acid (4 L) and once with 4 L of water, and the obtained toluene solution was dried over sodium sulfate. Then, filtration of the drying agent and addition of 3.4 L of acetonitrile, 970 mL of isopropylamine and 16.1 L of *n*-heptane followed. After one hour of stirring another 8.5 L of *n*-heptane was added to the suspension, and it was stirred for another hour. Then, filtration was performed, and the cake was washed with 2 × 2 L of toluene and 2 × 2 L of *n*-heptane. An off-white powder, 2.8 kg, was obtained after drying at room temperature in vacuum. The salt of montelukast with isopropylamine was repeatedly recrystallized from isopropyl alcohol (twice) and toluene (once). An off-white powder (1.81 kg, HPLC 99.7%) was obtained after drying at 55 °C. The yield comprising both the synthesis of the crude sodium salt of montelukast and isolation and recrystallization of the salt with isopropylamine was 45%.

$^1$H NMR (DMSO-$d_6$) $\delta$ (ppm) 0.23−0.47 (m, 4H, 2 × $CH_2$ cyclopropyl), 1.08 (d, 6H, 2 × $CH_3$ isopropyl), 1.44 (s, 6H, 2 × $CH_3$), 2.10−2.30 (m, 4H, 2 × $CH_2$), 2.51 (m, 1H, CH), 2.52 and 2.63 (m, 2H, $CH_2$), 2.77 a 3.07 (2 × m, 2H, $CH_2$), 3.06 (m, 1H, CH isopropyl), 4.01 (t, 1H, CH), 5.70 (bb, 4H, $NH^{3+}$, OH), 7.03−8.41 (m, 15H, CH═CH, and CH−arom.).

**Preparation of the Amorphous Form of Montelukast Sodium (Scale-Up Process).** Toluene (19.4 L) was added to the crystalline salt of montelukast with isopropylamine (1.3 kg). The suspension was stirred for 20 min, then sodium methylate (112.6 g) was added, and the suspension was further stirred at the temperature of approximately 68−72 °C for 45 min. Then, filtration was performed, and the clear, pale-yellow-colored filtrate was injected into 43 L of intensively stirred *n*-heptane. The obtained suspension was stirred for another hour and then was filtered. An off-white amorphous powder (1.09 kg, yield 89%, HPLC 99.7%, amorphous feature was checked by X-ray

powder diffraction) was obtained after vacuum drying under the stream of nitrogen at the temperature of 55 °C.

**Preparation of the Standard of [*R*-(*E*)]]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfinyl]methyl]cyclopropane Acetic Acid 7 (Montelukast Sulfoxide).** Montelukast sodium (6.0 g) was dissolved in 100 mL of methanol; subsequently, 30% hydrogen peroxide (30 mL) was added. After 3 h of stirring, methanol was evaporated in vacuum, and acetic acid (3 mL) was added to the residue. Water (50 mL) was added to the separated suspension, and the mixture was stirred for 30 min; then, the suspension was filtered, the cake was washed with water, with a toluene/heptane (1:1) mixture and finally with *n*-heptane. After vacuum drying at 65 °C, 5.5 g of a yellow powder was obtained with the chemical purity 93% (by HPLC). A portion of the crude material was subjected to the autopurification separation system (see Analytical Methods), while the standard (∼250 mg) was obtained.

$^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 0.34 (m, 1H); 0.48 (m, 1H); 0.63 (m, 1H); 1.42 (s, 3H); 2.22 (m, 1H); 2.26 (m, 1H); 2.44 (m, 1H); 2.46 (m, 1H); 2.61 (d, 1H, $J$ = 13.7 Hz); 2.67 (d, 1H, $J$ = 13.7 Hz); 2.76 (m, 1H); 2.97 (m, 1H); 4.05 (dd, 1H, $J$ = 11.0 and 4.1 Hz); 7.10 (m, 1H); 7.15 (m, 1H); 7.36 (d, 1H, $J$ = 7.7 Hz); 7.38 (d, 1H, $J$ = 7.6 Hz); 7.48 (t, 1H, $J$ = 7.7 Hz); 7.54 (d, 1H, $J$ = 16.4 Hz); 7.61 (dd, 1H, $J$ = 8.7 and 2.1 Hz); 7.73 (d, 1H, $J$ = 7.8 Hz); 7.76 (s, 1H); 7.91 (d, 1H, $J$ = 16.4 Hz); 7.96 (d, 1H, $J$ = 8.6 Hz); 8.03 (d, 1H, $J$ = 8.8 Hz); 8.04 (d, 1H, $J$ = 2 Hz); 8.45 (d, 2H, $J$ = 8.6 Hz). $^{13}$C NMR (DMSO-$d_6$) $\delta$ (ppm): 10.8; 12.3; 13.9; 30.9; 31.3; 31.6; 40.1; 56.9; 66.4; 71.6; 120.3; 125.3; 125.6; 126.4; 126.8; 127.0; 127.9; 128.3; 129.3; 129.4; 129.8; 131.0; 134.5; 135.2; 136.0; 136.4; 136.9; 139.6; 146.7; 147.5; 156.5; 172.6. MS: 602.2125 $(M + 1)^+$.

**Preparations of the Standards of 2-[(*R*)-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)-(*S*)-1-({[1-(carboxymethyl)cyclopropyl]-methyl}thio)ethyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropane]acetic Acid 9 (Diastereoisomer I) and 2-[(*R*)-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)-(*R*)-1-({[1-(carboxymethyl)cyclopropyl]methyl}thio)ethyl]-phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropane]acetic Acid 10 (Diastereoisomer II).** A solution of 2.6 g of PEG-600 in 3 mL of toluene was added under argon atmosphere to the mixture of acid **3** (0.7 g), toluene (20 mL) and sodium *tert*-butoxide (0.85 g). Then, a solution of montelukast sodium (2.72 g) in 15 mL of tetrahydrofuran was added dropwise to the stirred mixture. The obtained mixture was stirred at the room temperature and under argon atmosphere for 30 days. Then, toluene (100 mL) was added, and 45 mL of the liquid was removed by vacuum distillation. The residue was washed with a solution of tartaric acid and water. The organic phase was dried over sodium sulfate and concentrated to the volume of 30 mL after filtration of the desiccant. To the concentrated residue were added 3 mL of acetonitrile, 0.5 mL of isopropylamine and gradually 30 mL of *n*-heptane. The separated suspension of the salt of montelukast with isopropylamine was filtered off, and the filtered mother liquor was concentrated in vacuum. An oily product (0.4 g) was obtained containing 70% of a mixture of montelukast diastereoisomers I and II (according to HPLC). The standards of both the diastereoisomers in the form of free acids were obtained in the quantities of approximately 80 mg with the use of the Waters autopurification system (see Analytical Methods).

*Montelukast Diastereoisomer II:* $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.36−0.62 (m, 8H); 1.56 (s, 3H); 1.57 (s, 3H); 1.98 (m, 1H); 2.13 (m, 1H); 2.00 (m, 1H); 2.46 (m, 1H); 2.20 (d, 1H); 2.65 (d, 1H); 2.36 (d, 1H); 2.48 (d, 1H); 2.77 (m, 1H); 2.96 (m, 1H); 3.29 (dd, 1H); 3.68 (dd, 1H); 3.95 (t, 1H); 4.36 (dd, 1H); 7.09 (m, 1H); 7.10 (m, 1H); 7.16 (dd, 1H); 7.18 (dd, 1H); 7.27 (m, 1H); 7.28 (m, 1H); 7.30 (m, 1H); 7.35 (m, 1H); 7.36 (m, 1H); 7.40 (dd, 1H); 7.61 (d, 1H); 8.02 (d, 1H); 8.09 (d, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 12.1; 12.3; 12.5; 12.8; 16.6; 17.0; 31.6; 31.7; 32.1; 38.8; 39.1; 40.0; 40.5; 45.7; 50.3; 51.0; 74.3; 123.3; 125.3; 125.4; 125.6; 125.9; 126.8; 127.1; 127.2; 127.4; 128.2; 129.1; 131.7; 135.9; 136.7; 140.4; 142.4; 142.7; 144.8; 147.3; 161.0; 175.9; 176.2. MS: 432.2591 $(M + 1)^+$.

*Montelukast Diastereoisomer I:* $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.38 (m, 2H); 0.41−0.48 (m, 4H); 0.56 (m, 2H); 1.60 (s, 3H); 1.61 (s, 3H); 2.00 (d, 1H); 2.40 (d, 1H); 2.16 (q, 2H); 2.33 (d, 1H); 2.43 (d, 1H); 2.35 (d, 1H); 2.55 (d, 1H); 2.37 (d, 1H); 2.49 (d, 1H); 2.97 (q, 2H); 3.37 (dd, 1H); 3.62 (dd, 1H); 3.93 (t, 1H); 4.29 (dd, 1H); 7.11 (m, 1H); 7.17 (m, 2H); 7.23 (m, 1H); 7.24 (m, 1H); 7.28 (m, 1H); 7.30 (m, 1H); 7.38 (d, 1H); 7.4 (dd, 1H); 7.70 (d, 1H); 8.08 (d, 1H); 8.11(d, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 12.2; 12.5; 12.6; 17.1; 17.7; 31.6; 31.8; 32.4; 38.1; 39.2; 39.3; 40.0; 41.2; 45.4; 50.7; 51.2; 123.2; 125.4; 125.5; 126.1; 126.2; 126.8; 127.3; 127.5; 128.2; 128.8; 129.4; 131.8; 135.9; 139.7; 140.7; 142.3; 142.6; 144.6; 147.2; 161.0; 175.7; 175.9. MS: 432.2586 $(M + 1)^+$.

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