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Communication

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Identification of an Unexpected Impurity in a New Improved Synthesis of Lesinurad.

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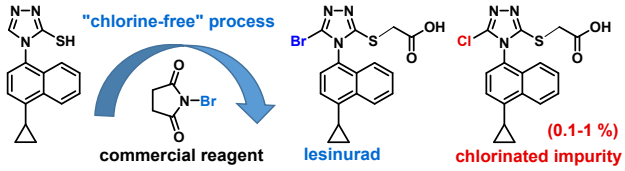
TOC


"chlorine-free" process
commercial reagent
lesinurad
(0.1-1 %)
chlorinated impurity

ABSTRACT: An unexpected phenomenon concerning otherwise common impurity of lesinurad **1** has been observed in the context of a synthetic process development. New industrial process was designed as a chlorine-free process but critical chlorinated impurity **10** was surprisingly detected in the isolated product. Due to structural similarity of the impurity and the product, no efficient separation of the impurity **10** by conventional methods, e.g. a crystallization, was discovered. Formation of the impurity was explained by chlorine impurity in commercial brominating agent. The communication also describes control of the critical impurity.

KEYWORDS: *Lesinurad, bromination, brominating agent, protection of carboxylic acids, synthetic process development*

INTRODUCTION

Lesinurad **1** (**Fig. 1**) is an active pharmaceutical substance which inhibits the activity of uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4).[1] URAT1 is a major transporter enzyme responsible for reuptake of uric acid from the renal tubules; inhibition of URAT1 function thereby increases excretion of uric acid. Lesinurad (marketed by AstraZeneca as *Zurampic*) is used in an oral therapy for the treatment of hyperuricemia associated with gout. Lesinurad should not be used as a monotherapy but in combination with a xanthine oxidase inhibitor (**Fig. 1**), e.g. allopurinol (*Zyloprim*).[1] For that reason it was also approved for the treatment of gout as a fixed-dose combination with allopurinol (trade name *Duzallo*).[2]

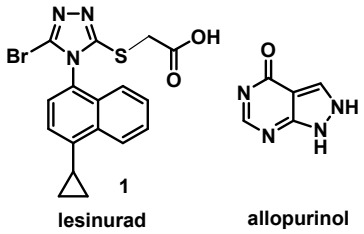
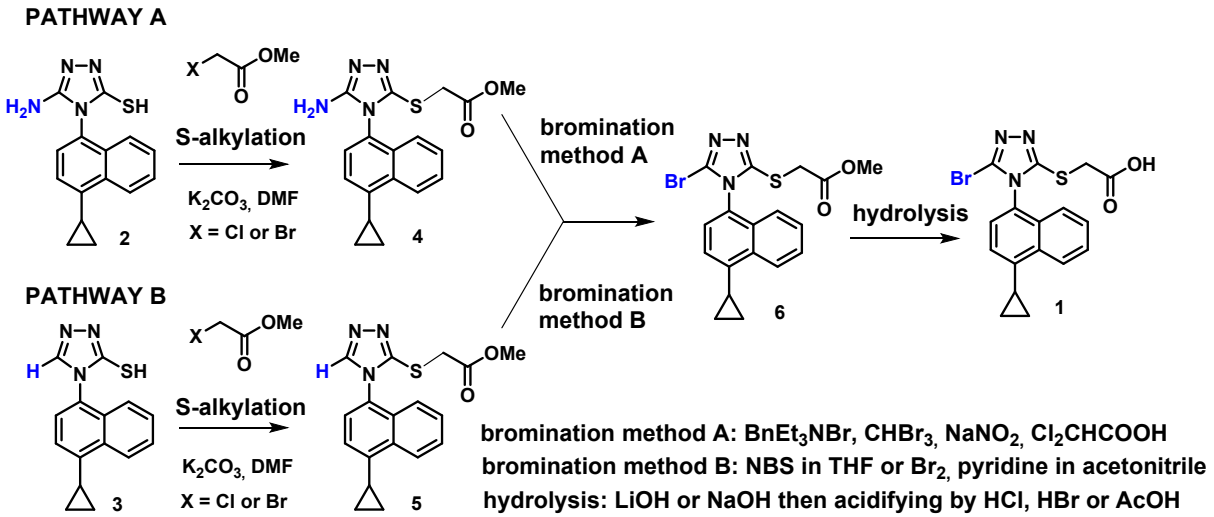


Fig. 1 Molecular structures of lesinurad **1** and allopurinol.

Chemical syntheses of lesinurad usually consist of three steps starting from two commercially available 1,2,4-triazoles (**2** and **3**). Processes may proceed by two different pathways (Scheme 1) but always do include sulfur alkylation, bromination and final conversion, most often a hydrolysis, leading to the target molecule.[3-7] Derivatives of bromo or chloro acetic acids were generally used as alkylating agents in the sulfur alkylation, namely relevant esters, amides or nitrile, the most often methyl ester. The crucial transformation in both pathways is the introduction of bromine into the structure of the advanced intermediates.

In the first case, the amino group is replaced by bromine by a modification of the Sandmeyer reaction using a complex mixture of $BnEt_3NBr$, $CHBr_3$, $NaNO_2$, and $Cl_2CHCOOH$.[3], Conversion of 5-amino-1,2,4-triazole **4** to methyl ester **6,** according to this procedure, is carried out with large excess of $NaNO_2$ in the presence of dichloroacetic acid and benzyltriethylamonium chloride, where toxic and potentially carcinogenic bromoform is used as the source of bromine. In the latter cases, the hydrogen atom is replaced in compound **5** by the action of suitable brominating agents, e.g. NBS or bromine-pyridine complex.[4,6] The final step according to Scheme 1 is hydrolysis of appropriate lesinurad derivative; advantageously of its methyl ester **6** but other alternatives, such as the corresponding nitrile or amide were also mentioned.[3-5]

Scheme1. Reported synthetic routes of lesinurad **1**[3-6]



Knowledge of impurities and methods of reducing their content in the desired product has an important relevance for each manufacturing process of a pharmaceutical substance. According to assessment report for *Zurampic* made by EMA, lesinurad may commonly contain four known significant organic impurities (**Fig. 2**), namely amino impurity **7**, hydroxy impurity **8**, desbromo impurity **9**, and chloro impurity **10**.[8] The same impurities are also described in two recent patent applications.[4,7] The content of these impurities in the final substance depends on synthetic method and can be reduced in the final steps of the synthetic process, when e.g. isolated crude sodium salt of lesinurad is purified by crystallization from water and free acid **1** is isolated after acidification by acetic, hydrobromic or hydrochloric acids. Unfortunately the purification procedure leading to lesinurad **1** in pharmaceutical quality is rather complex process which usually requires repeated operations, see Scheme 2.[4,9]

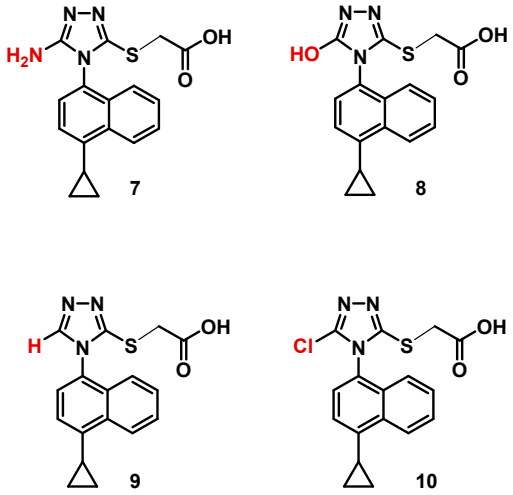
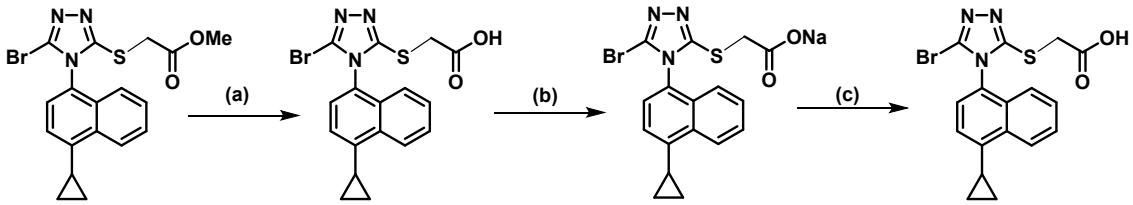


Fig. 2 Molecular structures of known organic impurities of lesinurad **1**.[4,7,8]

Scheme 2. Reported process of purification of lesinurad[4,9]



(a) 1. NaOH / H_2O 2. AcOH, (b) NaOH / H_2O (c) 1. HBr 2. EtOAc / n-heptane

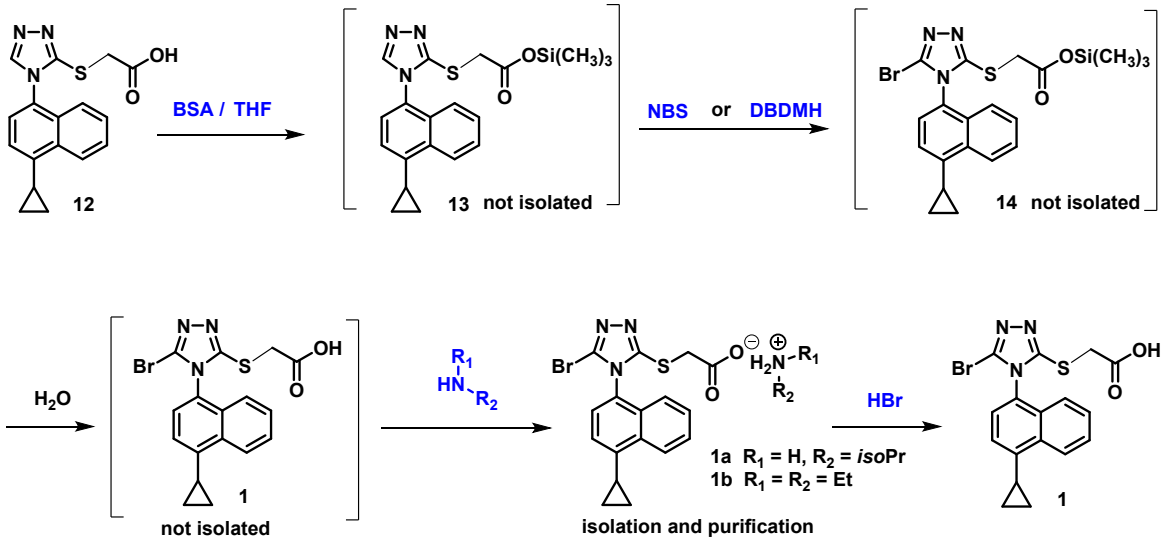
In spite of the fact that many synthetic processes have been described already, there is still a need for new and improved processes for the production of lesinurad characterized by easier work up, more cost-effective syntheses, utilisation of less toxic reagents, higher overall yield and, last but not least, by obtaining the product with a high level of chemical purity. The bromination is generally considered as the crucial synthetic step in lesinurad syntheses because it affects both yield and product quality. In order to develop a practical commercial process for lesinurad production, we have recently designed, developed and patented a new synthetic procedure, complying with all of the above mentioned requirements.[7]

RESULTS AND DISCUSSION

Introduction to the chlorine-free synthetic process. Our primary aim has been a new industrial process for lesinurad **1** characterized by easy implementation, advantageous management and control of impurities, in particular of the chlorinated impurity **10**. Initial finding, based on our preliminary effort in direct bromination of acid **12**, proved low stability of the carboxylic group, including sulfur-containing side chain, and confirmed the necessity of its protection in the course of bromination.[7] For that reason, a modified chlorine-free process has recently been proposed and developed, see Scheme 3.[7] The key feature of the new process is *in situ* protection of the carboxylic acid group in **12** prior to the bromination, e.g. by the trimethylsilyl group (TMS).[7] Other key features in the process involve utilisation of readily available brominating agents and new lesinurad salts for efficient isolation, e.g. **1a** and **1b**. In spite of the fact, that the process was designed as a chlorine-free, chlorinated impurity **10** was surprisingly still detected in the product. Results related to this issue as well as the solution of the problem are presented in this communication.

TMS group replaces hydrogen in the carboxylic functional group to form an intermediate which is already resistant to undesirable reactions. Because of moisture sensitivity, cleavage of TMS derivatives can be achieved simply by hydrolysis under mild conditions. For that reason lesinurad, or better its crystalline salt, can be conveniently isolated in the course of the reaction mixture work up without the need for a further manufacturing step. And what is essential, many well-known TMS-agents have been described as efficient for the protection of carboxylic acids and some of them are readily commercially available, e.g. *N,O*-bis(trimethylsilyl)acetamide (**BSA**), *N,O*-bis(trimethylsilyl)carbamate (**BSC**), *N,N'*-bis(trimethylsilyl)urea (**BSU**) and 3-trimethylsilyl-2-oxazolidinone (**TMSO**), see **Fig. 3**.[10] The specific advantage of these TMS-reagents is, in particular, the fact that they do not require addition of a base or a catalyst for successful trimethylsilylation.

Scheme 3. Improved process for lesinurad synthesis[7]



BSA is one of the most potent and commonly used silylating reagents.[10] It is characterized by high silylation potential, neutral silylating conditions, simple handling (**BSA** is a stable liquid) and relatively low price. **BSA** is commercially easily available, it does not require addition of a supplementary base for successful protection and its by-products (*N*-TMS-acetamide and acetamide) are generally acceptable. Due to these facts we have chosen **BSA** as all-round advantageous TMS-agent for protecting intermediate **12** before bromination.

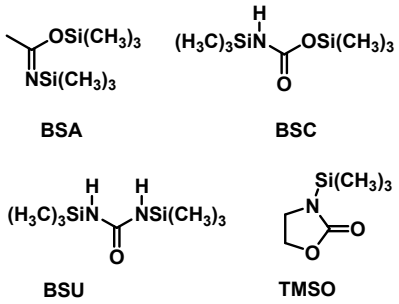


Fig.3 TMS-agents suitable for protecting of carboxylic acids.[10]

In line with our consideration we found out that an *in situ* TMS-protected intermediate **13** can be selectively brominated using readily available brominating agents. We have considered and screened several bromination agents (**Fig. 4**), e.g. *N*-bromosuccinimide (**NBS**), 1,3-dibromo-5,5-dimethylhydantoin (**DBDMH**), dibromoisocyanuric acid (**DBICA**) and pyridinium tribromide (**PTB**).[11] With regard to commercial availability and easy handling we selected two cheapest (**NBS** and **DBDMH**) as suitable agents to optimize the bromination method.

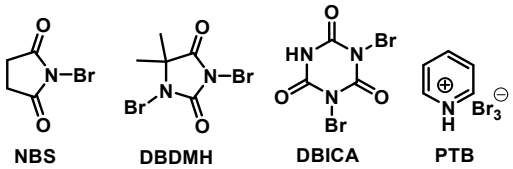
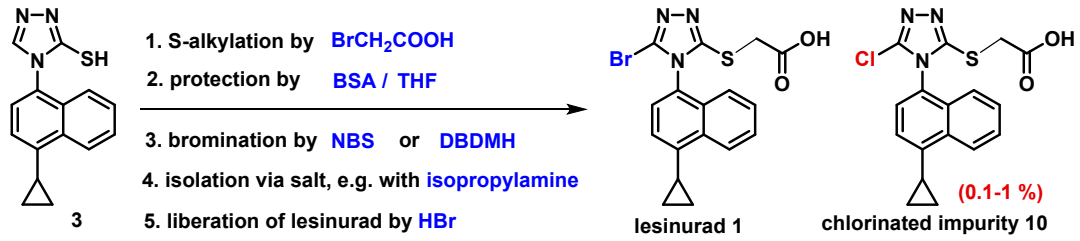


Fig. 4 Suitable brominating agents.[11]

Other typical feature of the process is isolation and purification of lesinurad *via* well crystallizing ammonium salts with suitable bases such as isopropyl amine or diethyl amine. Isopropyl amine salt **1a** is preferred with respect to the achieved yields and efficient purification effect. The salt **1a** was found efficient for removing most impurities formed during the synthesis with the exception of the chlorinated impurity **10**. Isolated crude crystalline salt **1a** usually had HPLC purity over 99.4%.

Scheme 4. New "chlorine-free" process



New synthetic process has been designed as chlorine-free process and it, in brief description, consists of five consecutive steps as follows: alkylation of commercially available 1,2,4-triazole **3** by bromoacetic acid, protection of acid **12**, bromination, lesinurad salt isolation and final liberation of lesinurad **1**, see Scheme 4. The protection of carboxylic acid **12** by TMS group is performed by action of **BSA** (2 eq) in THF, the following bromination is carried out by addition of **NBS** (2 eq) or **DBDMH** (1 eq). Mixing brominating agents directly with THF at ambient temperature should be avoided for the sake of safety due to limited stability and possible exothermic decomposition.[12] From that reason it is necessary to add a brominating agent as the last component to the solution acid **12**, BSA and THF. A brominating agent can be added either in a solid state optionally in the form of a cooled solution of brominating agent in THF. The solution of brominating agent in THF should be constantly kept below 10 °C.

The reaction mixture is then stirred at approx. 55 °C to achieve complete conversion of the carboxylic acid **12** (at least 99.9%). The conversion of the starting material can be advantageously monitored by HPLC analyses of the reaction mixture during bromination, see **Fig. 5**. Approx. 3h are needed for full conversion under the above described reaction conditions. THF used as reaction medium is then changed by 4-methyl-2-pentanone; resulting organic solution is washed by water, solution of sodium thiosulfate and saturated solution of sodium bromide. Isopropyl amine (alternatively diethyl amine) is added to the washed and dried solution of lesinurad; crude lesinurad isopropyl amine salt is then isolated and purified by re-crystallization. Finally free acid is liberated after addition of hydrobromic acid and crude lesinurad **1** is purified by re-crystallization to obtain final product in pharmaceutical quality.

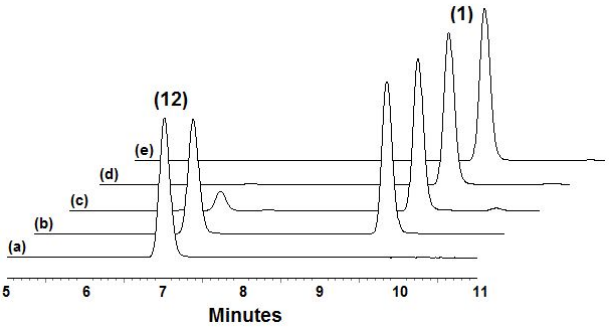


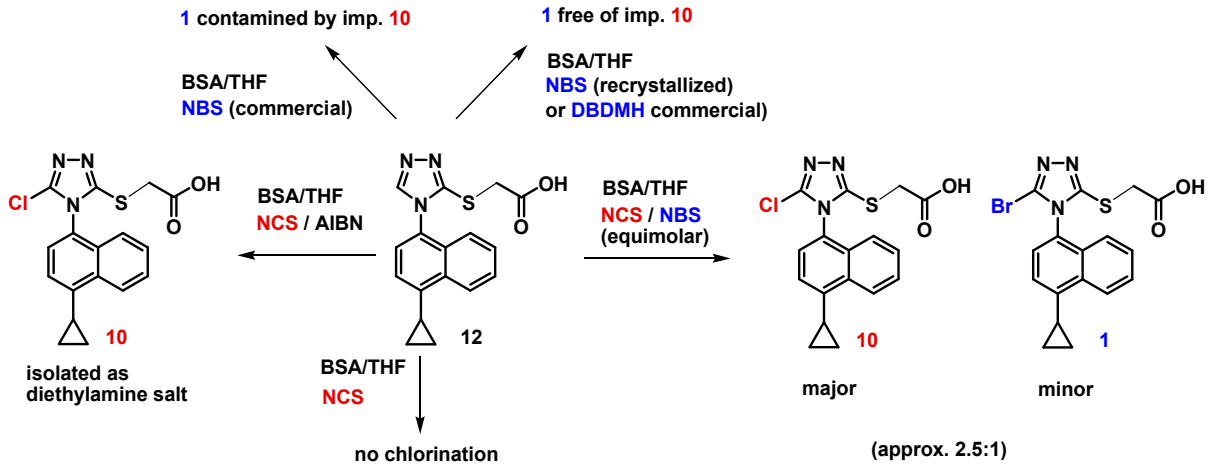
Fig. 5 HPLC analyses of the reaction mixture in the course of bromination of acid **12** to lesinurad **1** at 55 °C and at different times (a) 0min, (b) 20min, (c) 1h, (d) 2h, (e) 3h.

Unexpected occurrence of the chlorinated impurity in chlorine-free process. New synthetic process, as was mentioned above, has been designed as a chlorine-free process. That means that all chlorinated agents used in former processes (such as hydrochloric acid, chloroacetic acid, dichloroacetic

acid, benzyltriethylamonium chloride and sodium chloride) as well as chlorinated solvents to prevent any chlorine source for production chlorine impurity **10** were strictly avoided. In spite of this precaution, we just recognized the serious issue in the case of chlorinated impurity **10** which has been occasionally observed in the product in amounts significantly over limit (0.15%), sometimes even over 1%. We were able to purify crude lesinurad in the form of its salt **1a** from many minor impurities by means of crystallization. Unfortunately these crystallizations do not have any positive effect regarding the content of chlorinated impurity **10**. The same issue was observed in case of isolation of lesinurad **1** and its purification by crystallization.

The impurity **10** was specifically observed when commercial **NBS** was used as a brominating agent. On the other hand, when commercial **DBDMH** was used, chlorinated impurity in the product was either not detectable or not exceeding the limit, see Scheme 5. It is apparent that impurity **10** comes from brominating agent which is contaminated by its chloro analogue (e.g. by **NCS** in case of **NBS**). It is known that bromine may be contaminated by chlorine depending on the method of its industrial production. The manufacture of bromine involves direct reaction of chlorine with brine rich in bromine ions.[13] This contamination can be transmitted to brominating agents. Unfortunately, the level of chloro analogues' content in brominating agents is not commonly reported in commercially available sources. Undefined contamination then poses significant risk to both development and production of pharmaceutical substances prepared from commercially available brominating agents.

Scheme 5. Halogenation reaction of carboxylic acid **12** under different conditions



Several halogenation experiments of carboxylic acid **12** under different conditions have been carried out. Practically no chlorination product was detected when halogenation by **NCS** was done under identical conditions used for bromination by **NBS**. If a radical initiator, e.g. **AIBN,** was added, chlorination took place but a little bit slowly in comparison with bromination. Standard of impurity **10** in the form of its salt with diethyl amine was prepared using this procedure. If equimolar mixture of chlorinating (**NCS**) and brominating (**NBS**) agents was used, chlorination takes place preferentially, approx. 2.5 times faster than bromination (**Fig. 6**). If commercial **NBS** was used, product contaminated by impurity **10** was isolated (usually 0.1-1%). On the other hand, if commercial **DBDMH** or re-crystallized **NBS** was used, obtained product was free of impurity **10**. It has been experimentally shown that chlorination is more than twice preferred in competition with bromination what is resulting in much higher content of chlorinated impurity in desired product than it would correspond to the original contamination of the commercial brominating agent, see Scheme 5. Experimental results show that brominating agents easily generate the bromine radical without the need for a special initiation. On the other hand, the chlorine radical reacts faster in the sense of halogenation, but a special initiation is needed to generate it in the reaction mixture. I is obvious that the conventional reagents (e.g. **AIBN**) as well as the bromine radicals generated *in situ* in the reaction mixture can play role as chlorine radical activator.

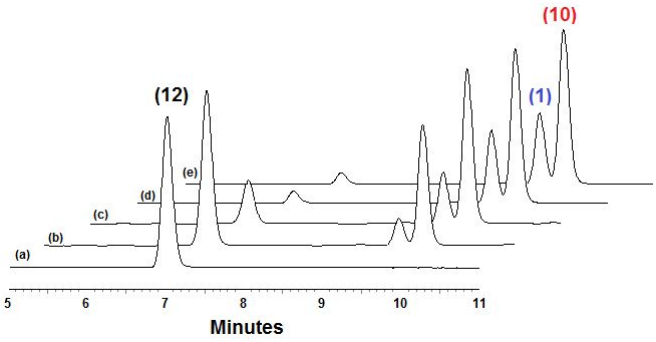


Fig. 6 HPLC analyses of the reaction mixture in the course of halogenation of acid **12** to lesinurad **1** and chlorinated impurity **10** in THF at 55 °C by mixture NBS (1 eq) and NCS (1 eq) at different times (a) 0min, (b) 20min, (c) 1h, (d) 2h, (e) 3h.

CONCLUSION

Presented new process is designed as a chlorine-free process based on unconventional bromination of carboxylic acid **12** protected *in situ* with TMS-group. Serious issue concerned with a surprising occurrence of chlorinated impurity **10** has been successfully solved. This impurity results from utilization of commercially available brominating agent, especially **NBS**, which has been slightly contaminated by its chlorine analogue. Lesinurad **1** has finally been obtained in high chemical purity (HPLC>99.8%) which conforms to the regulatory requirements. New process has been optimized for the future scale up and full production. Potential contamination of brominating agents with their chlorine analogues is not easily detectable and for that reason may have a general adverse impact on the development of bromine-containing pharmaceutical products.

EXPERIMENTAL SECTION

Analytical Methods. ^{1}H and ^{13}C NMR spectra were measured with a Bruker Avance 500 spectrometer with the measuring frequencies of 500.131 MHz and 125.762 MHz respectively. The spectra were measured in DMSO-d_6. ^{1}H chemical shifts were related to TMS (δ = 0.00 ppm) and ^{13}C chemical shifts to DMSO-d_6 (δ = 39.5 ppm). Melting points were measured on a Kofler block with the sample heating speed of 10 °C (to 70 °C) and 4 °C (over 70 °C) per minute and are uncorrected. HPLC 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 (A) and a 0.02 M aqueous solution of KH_2PO_4 (B) adjusted to pH 2.7 with aqueous H_3PO_4 (50%) were used. A gradient mode with the flow rate of the mobile phase was 1.0 mL/min. Composition on the start was 40% of A and 60% of B, this composition was held for 1 min., than changed to 80% of A and 20% of B over 14 minutes, this composition was held for 15 min., then changed to 40% of A and 60% of B over 3 min. and this composition was held to the end (overall time 36 min.). Detection at the wavelength of 230 nm was used. Methanol was used as the solvent for preparation of samples; 10-20 μL of the solution was used for the injection. The HPLC method was used for checking the compositions of the reaction mixtures as well as purity of isolated compounds.

2-[[4-(4-Cyclopropyl-1-naphthalenyl)-4*H*-1,2,4-triazol-3-yl]thio]acetic acid (12). Triazole **3** (54.0 g, 0.202 mol) and ethanol (300 ml) were mixed at room temperature (25 °C). Then a solution of sodium bicarbonate (22 g) and water (300 ml) was added. The mixture was intensively stirred and heated to 45 °C. The neutralized solution of bromoacetic acid in water was gradually and carefully added to the mixture of starting material, water and sodium bicarbonate. This partially neutralized solution has formerly been prepared by gradual addition of sodium bicarbonate (27.0 g) to a stirred solution of bromoacetic acid (32.0 g, 0.232 mol) in water (200 ml) at room temperature. The reaction mixture was intensively stirred at 55 °C for a one hour. The resulting solution was acidified by addition of acetic acid

(200 ml) at 45-50 °C and stirred at room temperature overnight. Resulting precipitated solid was collected by filtration. The cake was washed with water (3x50 ml) and ethyl acetate (2x50 ml). Isolated solid was dried in the open air at room temperature for several hours at first and then in a vacuum dryer at 60 °C for 4 hours to give product as a white powder. Yield 60.4 g, 91.9%, HPLC 99.94%. ^{1}H NMR (DMSO-Dd$_6$), δ(ppm): 0.84 (m, 2H); 1.15 (m, 2H); 2.54 (m, 1H) ; 4.01 (s, 2H) ; 7.21 (d, *J* = 8.5 Hz, 1H); 7.41 (d, *J* = 7.63, 1H); 7.55 (d, *J* = 7.63 Hz, 1H); 7.64 (t, *J* = 7.3 Hz, 1H); 7.74 (t, *J* = 7.3 Hz, 1H); 8.57 (d, *J* = 8.5 Hz, 1H); 8.89 (s, 1H) ; 12.94 (bs, 1H). ^{13}C NMR (DMSO-d$_6$), δ(ppm): 7.0; 7.3; 34.4; 122.1; 122.6; 125.0; 125.5; 127.2; 127.4; 127.8; 128.8; 133.4; 142.3; 146.5; 150.5; 169.3.

2-[[5-Bromo-4-(4-cyclopropyl-1-naphthalenyl)-4*H*-1,2,4-triazol-3-yl]thio]acetic acid isopropyl amine salt (1a). Acid **12** (65.0 g, 0.200 mol) and tetrahydrofuran (300 ml) were mixed at room temperature (20-25 °C), and then *N*,*O*-bis(trimethylsilyl)acetamide (74 ml, 0.303 mol, 1.5 eq) was added. The mixture was stirred to obtain a clear solution and then brominating agent (2 eq. of re-crystallized NBS, 72.0 g) and THF (30 ml) were added. The reddish-brown reaction mixture was stirred at 55 °C for 3 hours and then gradually cooled to room temperature. 4-Methyl-2-pentanone (350 ml) was added to the reaction mixture and diluted reaction mixture was concentrated by vacuum distillation (55-60°C / 200 to 100 mbar). THF was distilled off during this operation (approx. 350 ml). Remaining dark brown-red solution was washed with water (250 ml), 10 % solution of sodium thiosulfate pentahydrate ($Na_2S_2O_3.5H_2O$) in water (250 ml), water again (250 ml), saturated solution of sodium bromide in water (250 ml, ca 237 g NaBr) and dried over sodium sulfate (25 g). Drying agent was filtered off and washed with acetone (250 ml). Isopropyl amine (17 ml, 0.198 mol, 1 eq) dissolved in acetone (100 ml) was added to the filtered solution at room temperature (20-25 °C). The mixture was stirred at 22-23 °C for 16 hours. Precipitated product was isolated by vacuum filtration. The cake was washed with warm acetone (twice 40 ml, approx. 45 °C), 2-butanol (once 40 ml, approx. 50 °C) and dried in the open air at room temperature for several hours to give the product as a creamy to pale ochre powder. Yield 74.0 g, 79.9%, HPLC 96.31% (no impurity**10** observed). **Re-crystallization of 1a.** The crude salt **1a** (73.0 g) was dissolved in methanol (200 ml) at 55 °C and then 2-butanol (200 ml) was added. The mixture was concentrated by vacuum distillation (60-70°C / 400 to 300 mbar). Methanol was distilled off during this operation (approx. 200 ml). The suspension was stirred at 65-70 °C for 15 min. Resulting thick suspension was filtered while hot by means of vacuum. The cake was washed with hot 2-butanol (50 ml, approx. 50 °C). Isolated crystalline solid was dried in the open air at room temperature overnight at first and then in a vacuum dryer at 60 °C for 2 hours to give product as an off white powder. Yield 47.7 g, 65.3%, HPLC 99.40% (no impurity**10** observed). ^{1}H NMR (DMSO-d$_6$), δ(ppm): 0.88 (m, 2H); 1.12 (d, *J* = 6.4 Hz, 2H); 1.14 (m, 2H); 2.54 (m, 1H); 3.20 (sept, 1H); 3.68 (m, 2H); 7.12 (d, *J* = 8.5 Hz, 1H); 7.43 (d, *J* = 7.6 Hz, 1H); 7.64 (t, *J* = 7.3 Hz, 1H); 7.73 (t, *J* = 7.3 Hz, 1H); 7.89 (bs, NH3$^+$); 8.57 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (DMSO-d$_6$), δ(ppm): 7.1; 7.3; 13.0; 20.6; 42.7; 121.8; 122.8; 125.1; 127.1; 127.2; 128.0; 128.8; 130.3; 133.5; 142.8; 155.9; 167.9. ***Note (1)*** Alternatively, 3-dibromo-5,5-dimethylhydantoin **DBDMH** (1eq, 57.5 g) was used instead of NBS to perform the bromination. Other reaction conditions remain the same. The yield was 49.3 g (67.6%, HPLC 99.39%). ***Note (2)*** When commercial NBS was used, a product **1a** contaminated with 0.5-1.0% of chlorinated impurity **10** was obtained.

Procedure for re-crystallization of commercial NBS. A commercial NBS (100 g, e.g. Sigma-Aldrich, product number B81255) and de-ionized water (400 ml) were mixed at room temperature (20-25 °C), and then gradually heated to 90-95 °C. The result was a clear red solution and bromine vapours over the solution. The mixture was gradually cooled to room temperature for at least 2 hours. Resulting suspension was furthermore stirred at 5 °C overnight. Precipitated solid was filtered off and washed with water (3x50 ml). Wet product was then dried in the open air at room temperature for several hours at first and then in a vacuum over silica at room temperature overnight. Isolated product was stored at dark and dry place at 5-10 °C. Yield 69.2 g, 69.2%.

2-[[5-Bromo-4-(4-cyclopropyl-1-naphthalenyl)-4*H*-1,2,4-triazol-3-yl]thio]acetic acid (1). Isopropyl amine salt **1a** (34.5 g, 0.074 mol) was dissolved in water (140 ml) at 60-65°C. Acetone (170 ml) was gradually added to this still hot solution. 2M Hydrobromic acid (43 ml) was added drop-wise to the still hot solution in water-acetone mixture. The solution was stirred under gradual cooling to 20-25 °C for 4 hours. Precipitated solid was collected by suction. The cake was washed by 50 ml of a mixture of acetone and water (1:1). Isolated solid was dried in the open air at room temperature overnight at first

and then in a vacuum dryer at 55 °C for 2 hours to give product as an off white powder. Yield 24.4 g, 81.1%, HPLC 99.80% (no impurity**10** observed). **Re-crystallization of 1**. Crude lesinurad acid (24.0 g) was dissolved in acetone (150 ml) at 55 °C. Heptane (150 ml) was added to this solution and the mixture stirred at 55 °C for 5 minutes and then gradually cooled to 20-25 °C for 2 hours. Precipitated solid was collected by suction. The cake was washed by heptane (25 ml). The isolated crystalline solid was dried in the open air at room temperature overnight and then in a vacuum dryer at 55 °C for 6 hours to give product as an off white powder. Yield 19.2 g, 63.8% (for synthetic step incl. re-crystallization), HPLC 99.89% (no imp.**10** observed). ^{1}H NMR (DMSO-d_6), δ(ppm): 0.87 (m, 2H); 1.15 (m, 2H); 2.56 (m, 1H); 4.00 (m, 2H); 7.16 (d, *J* = 8.5 Hz, 1H); 7.44 (d, *J* = 7.3, 1H); 7.64 (d, *J* = 7.3 Hz, 1H); 7.66 (t, *J* = 7.6 Hz, 1H); 7.74 (t, *J* = 7.6 Hz, 1H); 8.58 (d, *J* = 8.5 Hz, 1H); 12.99 (s, COOH). ^{13}C NMR (DMSO-d_6), δ(ppm): 7.3; 7.4; 12.9; 34.1; 121.8; 122.7; 125.2; 126.6; 126.8; 127.3; 128.1; 128.6; 131.4; 133.5; 143.2; 153.5; 169.0.

2-[[5-Chloro-4-(4-cyclopropyl-1-naphthalenyl)-4*H*-1,2,4-triazol-3-yl]thio]acetic acid diethyl amine salt 10. DEA (standard of impurity 10). The Acid **12** (16.3 g, 0.050 mol) and THF (120 ml) were mixed at room temperature (20-25 °C), and then BSA (17 ml, 0.070 mol, 1.4 eq) was added. The mixture was stirred to obtain clear solution, then AIBN (1.7 g) and chlorinating agent (12.5 g NCS, 0.094 mol, 1.9 eq) were added. The reaction mixture was stirred at 55 °C for 4 hours (incomplete conversion); second portion of NCS (7.5 g, 0.056 mol, 1.1 eq) was added and stirred at 55 °C overnight. The mixture was concentrated by vacuum distillation and the rest was dissolved in dichloromethane (250 ml). The solution was washed by water (50 ml), 2M HCl (50 ml), water again (50 ml) and brine (50 ml). Organic solution was dried over sodium sulphate and filtered. The solution was concentrated by vacuum distillation. The rest was dissolved in acetone and diethyl amine is added (5 ml). The mixture was stirred at room temperature overnight. The precipitated solid was filtered off, washed with hot acetone (35 ml, 50 °C), then with acetone (15 ml) at room temperature and with diethyl ether (twice 20 ml). Isolated solid was dried at open air overnight. Yield 5.5 g, 25.3%, HPLC 95.4%, m.p. 125-128°C. ^{1}H NMR (DMSO-D_6), δ(ppm): 0.88 (m, 2H); 1.10 (t, *J* = 7.3 Hz, 6H); 1.15 (m, 2H); 2.55 (m, 1H); 2.81 (q, *J* = 7.3, 1H); 3.73 (m, 2H); 7.19 (d, *J* = 8.5 Hz, 1H); 7.45 (d, *J* = 7.6, 1H); 7.66 (m, 2H); 7.75 (t, *J* = 7.3 Hz, 1H); 7.73 (t, *J* = 7.32 Hz, 1H); 8.59 (d, *J* = 8.50 Hz, 1H); 9.15 (bs, $Et_2N\underline{H_2}^+$). ^{13}C NMR (DMSO-D_6), δ(ppm): 7.2; 7.4; 11.1; 13.0; 41.0; 121.7; 122.7; 125.2; 126.8; 126.2; 127.2; 128.1; 128.7; 133.5; 141.6; 143.0; 155.2; 168.7.

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REFERENCES

(1) (a) Hoy, S. M. Lesinurad: First Global Approval. *Drugs* **2016**, 76 (4), 509-516. (b) Bobulescu I. A.; Moe O. W. Renal Transport of Uric Acid: Evolving Concepts and Uncertainties. *Adv. Chronic Kidney Dis.* **2012**, *19*, 358-371.

(2) The Medical Letter on Drugs and Therapeutics: Lesinurad/Allopurinol (Duzallo) for Gout-Associated Hyperuricemia *J. Am. Med. Assoc.* **2018** *319* (2), 188-189.

(3) (a) Quart, B. D.; Girardet, J. L.; Gunic, E.; Yeh, L. T. Preparation of azole carboxylates as modulators of blood uric acid levels. WO2009070740 A2, 2009. (b) Meng Q. ; Zhao T.; Kang D. ; Huang B.; Zhan P.; Liu X. The development of an effective synthetic route of lesinurad (RDEA594). *Chem. Central J.* **2017**, 11:86.

(4) Gunic, E.; Galvin, G. Manufacture of 2-[5-bromo-4-(cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio]acetic acid and related compounds. WO2014008295 A1, 2014.

(5) Chen, W.; Luo, J.; Liu, L.; Fan, Y. A process for the preparation of thiotriazole derivatives. WO2014198241 A1, 2014.

(6) Wang, P.; Li, P.; Gu, X. Method for preparing medicine Lesinurad for treating gout and lesinurad intermediate. WO2015054960 A1, 2015.

(7) (a) Stach, J.; Radl, S.; Zvatora, P.; Pisa, O.; Benediktova, K.; Halama, A. Process for preparing 2-(5-bromo-4-(1-cyclopropylnaphthalen-4-yl)-4h-1,2,4-triazol-3-ylthio)acetic acid. EP3281941 A1, 2018. (b) Zvatora, P.; Dammer, O.; Krejcik, L.; Schongut, M.; Stach, J.; Halama, A.; Kutzendoferova, P.; Benediktova, K.; Man, S.; Tkadlecova, M. Solid forms of lesinurad amine salts EP3372592 A1, 2018.

(8) For more information about EMA assessment report for *Zurampic*, see: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/003932/WC500203069.pdf.

(9) Galvin, G.; Treiber, L. R.; Zamansky, I.; Girardet, J. L. Polymorphic forms of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid and uses thereof. WO2012092395 A2, 2012.

(10) (a) Klebe, J. F.; Finkbeiner, H.; White D. M. Silylations with Bis(trimethylsilyl)acetamide, a Highly Reactive Silyl Donor. *J. Am. Chem. Soc.*, **1966**, *88* (14), 3390–3395. (b) De Koning, J. J.; Kooreman, H. J.; Tan H. S.; Verweij J. One-step, high yield conversion of penicillin sulfoxides to deacetoxycephalosporins. *J. Org. Chem.*, **1975**, *40* (9), 1346–1347. (c) Berry, P. D.; Brown, A. C.; Hanson, J. C.; Kaura, A. C.; Milner, P. H.; Moores, C. J.; Quick, J. K.; Saunders, R. N.; Southgate, R.; Whittall N. A convenient large scale synthesis of 7α-formamido cephalosporins. *Tetrahedron Lett.* **1991**, *32* (23), 2683-2686. (d) L. Birkhofer, L.; Sommer, P. Siliciumorganische verbindungen: LXI. *N*-trimethylsilyl-carbamidsäure-trimethylsilylester; ein neues silylierungsmittel. *J. Organomet. Chem.***1975**, *99* (1), C1-C4. (e) Verboom, W.; Visser, G. W.; Reinhoudt, D. N. *N*,*N*′-Bis[trimethylsilyl]-urea: A Useful Silylating Agent for Alcohols and Carboxylic Acids. *Synthesis* **1981** (10), 807-809. (f) Palomo, C. A Convenient Synthesis of Trimethylsilyl Carboxylates using *N*-Trimethylsilyl-2-oxazolidinone in the Absence of Catalysts. *Synthesis* **1981** (10), 809-811.

(11) (a) Reeves, W. P.; King, R. M. A Convenient Method for Bromination of Aromatic Amines *Synth. Commun.* **1993**, *23* (6), 855-855. (b) Baraldi, P. G.; Bazzanini, R.; Manfredini, S.; Simoni, D.; Robins, M. J. Facile access to 2′-*O*-acyl prodrugs of 1- (β-D-arabinofuranosyl)-5(*E*)-(2-bromovinyl)uracil (BVAraU) via regioselective esterase-catalyzed hydrolysis of 2′ 3′, 5′-triesters *Tetrahedron Lett.* **1993**, *34* (19), 3177-3180. (c) Cabaj, J. E.; Kairys, D.; Benson, T. R. Development of a Commercial Process to Produce Oxandrolone *Org. Process Res. Dev*. **2007**, *11* (3), 378-388.

(12) Shimizu, S.; Imamura, Y.; Ueki, T. Incompatibilities between *N*-Bromosuccinimide and Solvents *Org. Process Res. Dev.*, 2014, *18* (2), 354–358.

(13) Yalçin, H.**;** Koç, T.**;** Pamuk, V. Hydrogen and bromine production from concentrated sea-water *Int. J. Hydrogen Energy* **1997**, *22*, (10–11), 967-970.