Organic Process Research & Development **2008,** *12,* 196–201

Debottlenecking the Synthesis Route of Asenapine

Marco van der Linden, Theo Roeters, Ramon Harting, Edwin Stokkingreef, Arjan Sollewijn Gelpke, and Gerjan Kemperman*

Department of Process Chemistry, Organon NV, P.O. Box 20, 5340 NH Oss, The Netherlands

Abstract:

The discovery synthesis of asenapine that was used for the manufacture of drug substance batches up to 10 kg contained two chemical steps that were major bottlenecks for scale-up. One of these steps involved a magnesium/methanol reduction of an enamide moiety that was severely hampered by safety and efficiency problems. The other step was a laborious chromatography and isomerization cycle that was marked by a poor yield and extremely low throughput. The safety issues of the magnesium/methanol reduction could be solved by adding portions of magnesium to a solution of the enamide. In addition, an alternative process for the conversion of the mixture of *cis*- and *trans*-lactam into the desired *trans*-isomer was developed, circumventing the chromatographic separation.

1. Introduction

Asenapine is a novel psychopharmacologic agent being developed for the treatment of schizophrenia and bipolar disorder. The pharmacologic profile, kinetics, metabolism, and safety and efficacy studies in human volunteers and schizophrenic patients of asenapine have been comprehensively reviewed.[1] Asenapine has a unique in vitro receptor affinity profile, with the highest affinity in its class for an array of serotonin (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{5A}, 5-HT_6, 5-HT_7), dopamine (D_1, D_3, D_4), α-adrenergic receptors (α_{1A}, α_{2A}, α_{2B}, α_{2C}), and histamine (H_1, H_2) receptors but with minimal affinity for muscarinic receptors.[2] In a recently published phase III clinical trial, asenapine was efficacious and well-tolerated in the treatment of patients with acute exacerbation of schizophrenia.[1]

The original synthesis of asenapine has been published.[3,4] This synthesis, which is outlined in Scheme 1, starts from 5-chloro-2-phenoxyphenylacetic acid **1**, which can be prepared via several different routes, such as the route described by Harris et al.[5] The synthesis of asenapine as shown in Scheme 1 has been used for the supply of active pharmaceutical ingredient (API) required for preclinical and clinical development. To prepare adequate amounts of API, the original laboratory synthesis was scaled up to about 10 kg. Scaling up this process to commercial production was deemed impossible for at least part of the synthesis route (see the box in Scheme 1). The synthesis of unsaturated lactam **4** from 5-chloro-2-phenoxyphenylacetic acid **1** was considered to be well scalable, although optimization of the yields and reaction volumes was needed. The conversion of *trans*-lactam **5** into asenapine maleate proceeded well, but the need to decrease the reaction volumes and to improve the yield of the final recrystallization was recognized. However, the true bottleneck for scale-up of this synthesis was found to be the conversion of unsaturated lactam **4** into *trans*-lactam **5**. This report discusses the development and scale-up of alternative processes for this conversion.

2. Results and Discussion

Identification of Bottlenecks in the Conversion of 4 into 5. The conversion of unsaturated lactam **4** into *trans*-lactam **5** comprises two steps. The first step involves magnesium/methanol reduction of the double bond, which gives rise to the formation of the desired *trans*-lactam **5** and its *cis*-isomer **6** in an unfavorable ratio of approximately 1:4. In addition, a significant amount of side products are formed because the combined amount of **5** and **6** is only 60−80% of the reaction product.

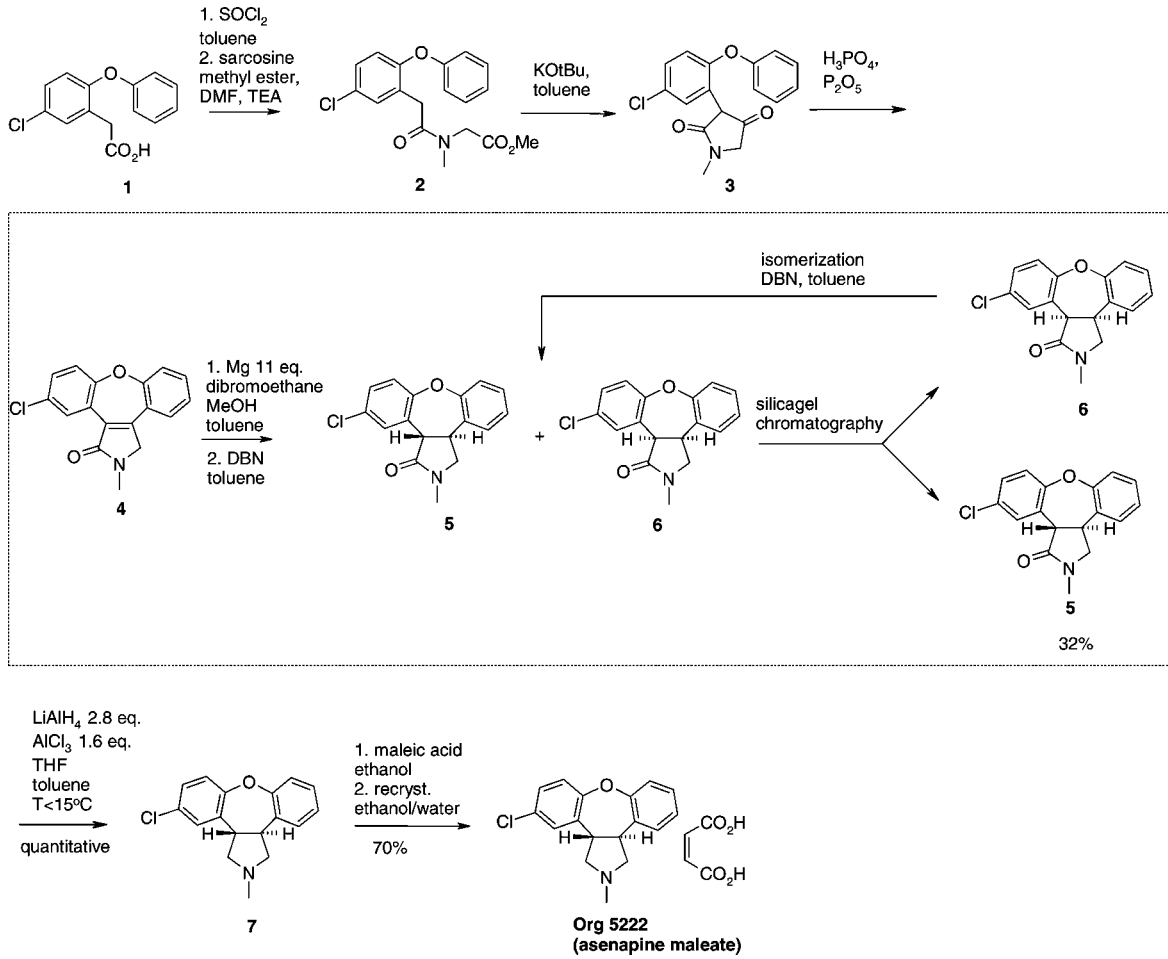
The process involves addition of unsaturated lactam **4** in toluene solution to a suspension of magnesium in a mixture of toluene and methanol. The magnesium was activated by using the carcinogenic dibromoethane before addition of the unsaturated lactam. During this process, large amounts of hydrogen gas are formed because of the inevitable exothermic side reaction of magnesium with methanol. An additional drawback of such a process is that all of the potential energy of the magnesium, in contact with methanol, is present in the reactor, resulting in a large accumulation of heat. Because there is no control over the rate in which the heterogeneous reaction between magnesium and methanol takes place, the maximum scale at which one can safely operate such a process is limited and is determined by the cooling and venting capacity of the reactor. Figure 1 shows the result of a reaction calorimetry experiment of this reaction. Clearly, the reaction is not dose-controlled. Because of the potential danger of the accumulated heat, the maximum scale was estimated to be 10−15 kg. In addition, the reaction of starting material **4**, which is dissolved in a mixture of methanol and toluene, with the reducing mixture of magnesium and methanol is highly exothermic. This restricts the rate of addition of the solution of starting material **4** to the magnesium suspension as well. The longer the addition time, the more magnesium is lost in reaction with methanol, resulting in the formation of hydrogen gas. As a consequence, an excess of magnesium (i.e., 11 equiv) is required to achieve complete

* To whom correspondence should be addressed. Ph: +31-(0)-412669375. Fax: +31-(0)-412663513. E-mail: gerjan.kemperman@organon.com.

(1) Potkin, S. G.; Cohen, M.; Panagides, J. *J. Clin. Psychiatry.* **2007**, *68*, 1492–1500.
(2) Shahid, M.; Walker, G. B.; Zorn, S. H.; Wong, E. H. F. *J. Psychopharmacol.* **2007**, in press.
(3) Vader, J.; Kaspersen, F.; Sperling, E.; Schlachter, I.; Terpstra, A.; Hilberink, P.; Wagenaars, G. *J. Labelled Compd. Radiopharm.* **1994**, *34*, 845–869.
(4) van der Burg, W. J. Tetracyclic derivatives and pharmaceutical compositions of matter. U.S. patent 4,145,434, 1979.
(5) Harris, T. W.; Smith, H. E.; Mobley, P. L.; Manier, D. H.; Sulser, F. *J. Med. Chem.* **1982**, *25*, 855–858.

10.1021/op700240c CCC: $40.75
Published on Web 02/12/2008

Scheme 1. **Synthesis of asenapine**



conversion of starting material **4**. Finally, the poor control causes an extremely vigorous reaction, leading to a significant amount of side products.

The second issue is the conversion of a 1:4 mixture of the desired *trans*-lactam **5** and the unwanted *cis*-lactam **6** into pure *trans*-lactam **5**. This step involves an isomerization and chromatography loop. First, partial isomerization of the unwanted *cis*-isomer **6** into the *trans*-isomer **5** by using DBN leads to a *trans*:*cis* ratio of 1:3, which is the thermodynamic equilibrium.

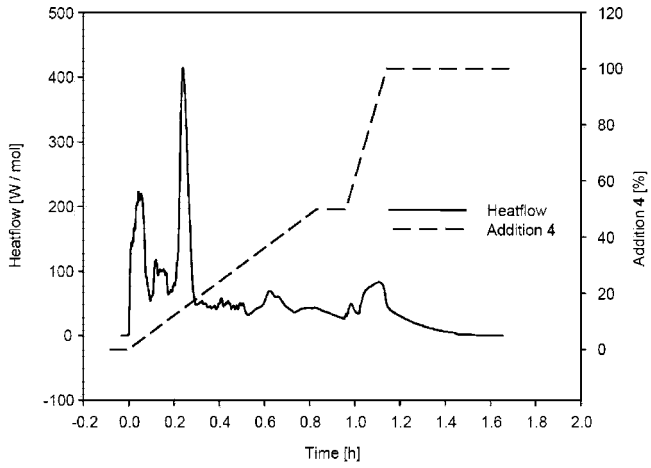


Figure 1. **Output of a reaction calorimetry experiment on the Mg/MeOH reduction. The solid line presents the heat flow, and the dotted line depicts the addition of unsaturated lactam 4.**

The *trans*-lactam **5** and *cis*-lactam **6** are then separated by chromatography over silica gel. This provides one fraction with the desired *trans*-lactam **5** and a fraction of the unwanted isomer *cis*-lactam **6**. The *cis*-isomer **6** is isomerized again using DBN, after which the chromatographic separation is repeated. After this cycle has been repeated three times, the three fractions of *trans*-lactam **5** are collected and crystallized, furnishing one batch of *trans*-lactam **5**. The overall yield of this procedure is 32%. Clearly the isomerization/chromatography loop is extremely elaborate and low yielding, which results in high cost and low throughput.

In summary, the magnesium/methanol reduction of lactam **4** is hampered by safety problems and by poor product selectivity. The conversion of the resulting mixture of **5** and **6** into the desired *trans*-lactam **5** suffers from low throughput and low yield and accordingly limited capacity and high cost.

Development of an Alternative Process for the Magnesium/Methanol Reduction. Initial attempts to develop an alternative process for magnesium/methanol reduction involved catalytic hydrogenation. A variety of palladium, platinum, rhodium, ruthenium, and iridium catalysts were tested using different ligands and solvents at pressures varying between 1 and 5 bar. Under most conditions no reaction was observed. With several palladium catalysts, only dechlorination took place.

It was also investigated whether zinc or lithium could be used to reduce unsaturated lactam **4**. In addition, the use of

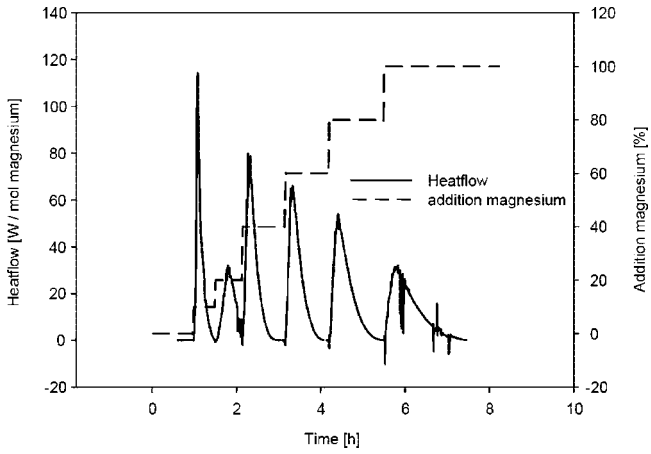


Figure 2. **Output of a reaction calorimetry experiment on the reversed addition magnesium/methanol reduction. The solid line represents heat flow; the dotted line shows the addition of the magnesium portions.**

magnesium in combination with less acidic alcohols was explored with the intention of suppressing hydrogen gas formation. It appeared that the reducing power of zinc was insufficient; no reaction was observed. However, a Birch reduction, using lithium in ammonia, was found to be too strong because a complex mixture of products was obtained using this procedure. Lactam **4** also could not be reduced with magnesium in ethanol or propanol.

Since it had been found that only magnesium in combination with methanol was able to reduce the double bond of lactam **4**, it was investigated how this reaction could be transformed into a safer and more efficient procedure. To this end, the reaction was investigated by dosing the magnesium in portions to a solution of unsaturated lactam **4** instead of dosing the lactam to the magnesium. In principle, portionwise addition of magnesium should allow for better heat control because the amount of energy introduced in the reactor is directly related to the portion size. It would be challenging to see whether the reaction would proceed with portionwise addition, given that the activation of a successive portion of magnesium could not be controlled.

The reversed addition process evolved into a procedure in which part of the magnesium turnings (i.e., approximately 0.6 equiv) was first suspended in toluene. The magnesium was activated with iodine instead of dibromoethane, which was followed by addition of a solution of the unsaturated lactam **4** in a toluene/methanol mixture. Subsequently, the required amount of magnesium was added in several portions. In this way, the reaction rate and the reaction temperature were perfectly controlled because the maximum amount of heat that can be generated was related to the size of the portions of magnesium. This should overcome the problem of accumulation encountered in the original procedure. Figure 2 illustrates a reaction calorimetry experiment of the reversed addition magnesium/methanol reduction of lactam **4**. It is evident from Figure 2 that the process was dose controlled and thus, in principle, scalable.

Another advantage of the reversed addition process was that the magnesium is only reacting with methanol in the presence of starting material. As a result, little magnesium was lost in a reaction with methanol to form hydrogen gas. Consequently, much less magnesium was required for a complete conversion of the starting material (i.e., only 3 equiv). This was beneficial to the safety of the process because only 2 mol instead of 10 mol of hydrogen gas was being formed over a controlled period of time. Another advantage was found in a better control of the temperature, resulting in a less vigorous reaction and formation of significantly fewer side products. The reversed addition process led to a product containing more than 93% of *trans*-lactam **5** and *cis*-lactam **6** together, compared with 60−80% with the original process.

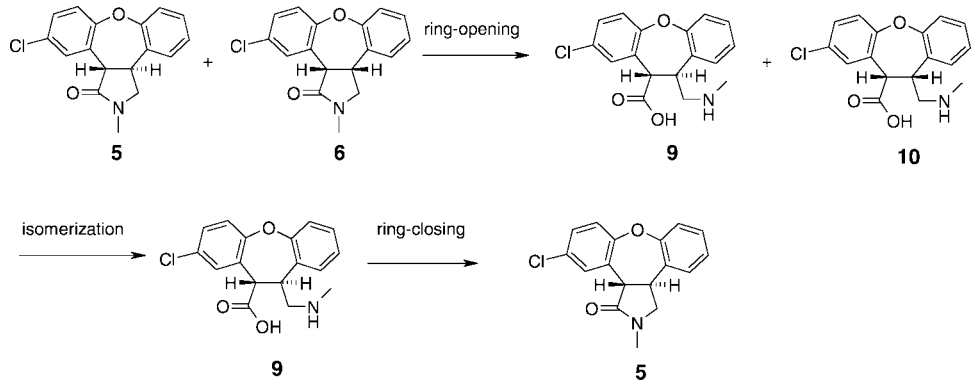
Development of an Alternative Process for the Isomerization and Chromatography Loop. A complicating factor in the preparation of *trans*-lactam from the *cis*/*trans* mixture was that the thermodynamic equilibrium between the *cis*- and *trans*-lactam was in favor of the unwanted *cis* compound **6**. It was found that the *cis*-isomer could be selectively crystallized from toluene, leading to a mother liquor that consisted of **5** and **6** in a more favorable 1:1 ratio. Nevertheless, the batchwise chromatography process was not amenable to scale-up because of the low throughput. Because the aim of the chromatography step was the separation of two components, application of simulating moving bed chromatography (SMB) was a potential alternative. Separation of *cis*- and *trans*-lactam by SMB appeared to be potentially scalable against acceptable cost. However, prepurification would be required; with SMB, it is important to start with a relatively pure mixture of two components. Therefore, alternative solutions were sought.

A solubility study of *cis*- and *trans*-lactam in various solvents pointed out that the *cis*-lactam was 10 times less soluble in toluene, whereas the *trans*-lactam was 2 times less soluble in methanol. This finding suggested that a preferred crystallization process might be possible. In the laboratory, preferred crystallization worked reasonably well with pure mixtures of *cis*- and *trans*-lactam, but the yield of the crystallizations was too low when the reaction mixtures contained other impurities.

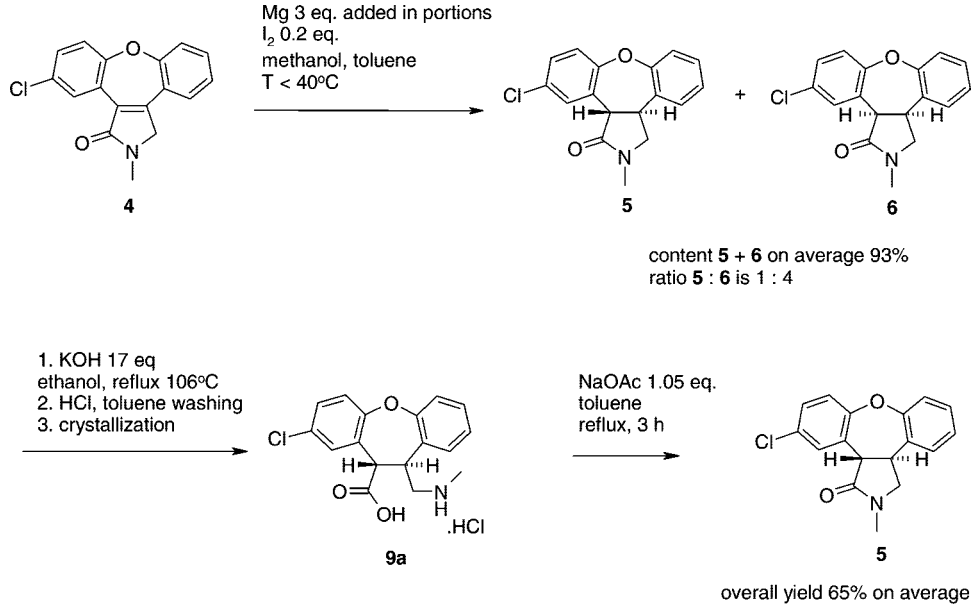
For both chromatography and preferred crystallization, the yield was affected heavily by the unfavorable *cis*/*trans* ratio at thermodynamic equilibrium and by the need to perform a prepurification on the crude *cis*/*trans* mixture. Therefore, we attempted to convert the *cis*- and *trans*-lactam into derivatives that have a more favorable *trans*/*cis* ratio at thermodynamic equilibrium. Conceptually, the idea was to open the five-membered lactam ring of compounds **5** and **6**, whereby the corresponding amino acid derivatives **9** and **10** would be formed as shown in Scheme 2. It is plausible that the *trans*-amino acid **9** was more thermodynamically stable than the *cis*-isomer **10**, such that after equilibration the preferred *trans*-isomer **9** should predominate. When the ring closure of *trans*-amino acid **9** is accomplished, *trans*-lactam **5** was selectively provided.

It was found that ring-opening of *trans*-lactam **5** and *cis*-lactam **6** could be achieved by treating a reaction mixture with potassium hydroxide in refluxing ethanol (Scheme 3). Under these conditions, the boiling temperature of the solvent exceeded 100 °C, resulting in a fast reaction. The ring-opening reaction was completed in about 4 h. The reaction mixture comprised *trans*-amino acid **9** and *cis*-amino acid **10** in a ratio of approximately

Scheme 2. **Concept of ring-opening and -closing toward *trans*-lactam 5**



Scheme 3. **Developed processes for the conversion of unsaturated lactam 4 into *trans*-lactam 5**



10:1, suggesting an isomerization concomitant to the ring-opening process. By using deuterium labeling, it was demonstrated that the isomerization of the amino acid isomers proceeds via deprotonation of the α-hydrogen. It was found that the *trans*-amino acid could be crystallized as a zwitterion, but the hydrochloride salt could be crystallized in a higher yield. After crystallization, the *trans*-amino acid contained less than 1% of the *cis*-isomer. The reaction could also be conducted in *n*-butanol or *n*-propanol. The higher boiling point of *n*-butanol led to a shorter reaction time for the ring opening, but the workup was found to be more difficult as a result of the polarity of *n*-butanol and its partial immiscibility with water. The relatively high solubility of the amino acid in *n*-butanol, even at high or low pH, caused loss of product during the acid/base extractions.

Next, it was investigated how to effect ring closure of the *trans*-amino acid to obtain the desired *trans*-lactam **5**. It was found that ring closure could be achieved in several ways. First, the hydrochloride salt of the *trans*-amino acid (compound **9a** in Scheme 3) could be converted into the acid chloride derivative by treatment with thionyl chloride. When the acid chloride was reacted with a base such as triethylamine, the *trans*-lactam was obtained in a yield of 75%. A second method involves heating a suspension of the hydrochloride salt **9a** in toluene in the presence of silica gel for 24 h. In this way the *trans*-lactam could be obtained in yields varying from 80% to 86%. The reaction could also be accomplished without the use of silica gel albeit at a higher temperature. Thus, heating **9a** in xylene for 24 h led to *trans*-lactam in similar yields. A third option was to use the zwitterion **9**, which upon heating in toluene, showed a fast and clean ring-closing reaction, providing the *trans*-lactam in a yield of 90%. Although the third option is preferable for scale-up, because of the neutral and relatively mild conditions, the isolation of the zwitterion **9** led overall to lower yields. We therefore attempted to find a basic additive that could be used to generate the zwitterion **9** in situ from the amino acid hydrochloride salt **9a**. This would have the advantage of carrying out the reaction in a stainless-steel reactor instead of a glass-lined reactor, avoiding the risk of electrical discharge. A series of salts was investigated (e.g., sodium hydrogen carbonate, sodium carbonate, sodium hydroxide, ammonium hydroxide, and sodium acetate), and all worked nearly equally well. Sodium acetate was selected for scale-up because it was found to result in the fastest reaction. Also NaOH and NH_4OH have been

Table 1. **Batch analysis data of *trans*-lactam 5**

batch	a/a % by HPLC						
	5	**6**	RRT 0.67	RRT 0.71	RRT 0.73	RRT 0.80	others (total)
Discovery Route to *trans*-Lactam **5**							
Lot 1	95.67	<0.05	0.24	1.65	<0.05	1.99	<0.05
Lot 2	97.86	<0.05	0.16	0.66	<0.05	0.92	0.27
Lot 3	98.51	0.13	0.42	0.20	0.05	0.49	0.09
Lot 4	98.86	0.15	0.21	0.09	0.22	0.20	0.15
Lot 5	97.59	0.10	0.63	0.67	<0.05	0.80	0.13
Lot 6	98.64	0.12	0.37	0.24	0.06	0.38	0.11
Developed Route to *trans*-Lactam **5**							
Lot 7	99.82	0.08	<0.05	<0.05	<0.05	<0.05	0.10
Lot 8	99.80	0.11	<0.05	<0.05	<0.05	<0.05	0.09
Lot 9	99.90	0.06	<0.05	<0.05	<0.05	<0.05	<0.05
Lot 10	99.87	0.09	<0.05	<0.05	<0.05	<0.05	<0.05
Lot 11	99.86	0.08	<0.05	<0.05	<0.05	<0.05	0.06
Lot 12	99.88	0.09	<0.05	<0.05	<0.05	<0.05	<0.05

successfully scaled up in the plant and were used to produce 20-kg batches of *trans*-lactam **5**.

The new processes for the conversion of unsaturated lactam **4** into *trans*-lactam **5** have been outlined in Scheme 3.[6] The processes are highly telescoped. The reaction mixture from the magnesium reduction is directly used in the ring-opening process. After filtration of the hydrochloride salt **9a**, the solvent-wet crystals are immediately transferred back into the reactor for the ring-closing reaction. The overall yield of the conversion is 65%, which is significantly higher than the 32% obtained via the original procedure. In addition, the processes were found to be well scalable and are currently operated at batch sizes of 120 and 250 kg, respectively.

Table 1 shows comparisons of the impurity profile of a number of batches of *trans*-lactam **5** from the original chromatography process with that of batches from the developed processes. It appears that the quality of the *trans*-lactam made via the new processes is significantly better than that of the original processes. Although the *trans*-lactam batches made via the original route had a variable impurity profile, with some impurities being present at levels up to 2%, the *trans*-lactam from the developed process has a consistent impurity profile characterized by a purity >99.8%. This high level of control of the purity of *trans*-lactam **5** minimized the risk for introduction of new impurities into asenapine via the new manufacturing processes.

In conclusion, safe and scalable processes have been developed for the manufacture of *trans*-lactam **5**, which is the final intermediate in the synthesis of asenapine maleate. The developed processes led to an improvement of the yield for the conversion of **4** into **5** from 32% to 65%. In addition, the developed processes have resulted in a significant improvement of the impurity profile of compound **5**.

Experimental Section

General Information. Nuclear magnetic resonance spectra were recorded on a Bruker DPX 400. Chemical shifts were reported in parts per million (ppm). ^{1}H NMR chemical shifts were referenced to TMS as internal standard. Mass spectra were recorded on a PE SCIEX API 165. The synthesis of 11-chloro-2,3-dihydro-2-methyl-1*H*-dibenz[2,3;6,7]oxepino[4,5-*c*]pyrrol-1-one (**4**) was performed according to the findings of Vader et al.[3]

Reduction of 11-Chloro-2,3-dihydro-2-methyl-1*H*-dibenz-[2,3;6,7]oxepino[4,5-*c*]pyrrol-1-one (4) via the Reversed Addition Method. Under a nitrogen atmosphere magnesium turnings (2.2 kg, 90.6 mol) were added to a solution of iodine (8.5 kg, 22.0 mol) in toluene (100 L). This was followed by addition of a solution of 11-chloro-2,3-dihydro-2-methyl-1*H*-dibenz[2,3;6,7]oxepino[4,5-*c*] pyrrol-1-one (**4**) (45 kg, 151.2 mol) in a mixture of methanol (225 L) and toluene (225 L) over a period of approximately 30 min at a temperature below 40 °C. Subsequently, over a period of 5 h, 7 portions of magnesium (1.3 kg, 53.5 mol) were added. The reaction mixture was diluted with toluene (900 L) and neutralized with a mixture of 18% hydrochloric acid (220 L) and water (540 L). The layers were separated, and the water layer was extracted twice with toluene (600 L). The combined toluene layers were washed with water (450 L) and evaporated to dryness. This gave a mixture of *trans*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one (**5**) and *cis*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one (**6**) (45.3 kg, ~100%) in a ratio of 1:4 as determined by ^{1}H NMR and HPLC.

Preparation of *trans*-11-Chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one (5). Potassium hydroxide was added (144 kg, 2571 mol) to a mixture of *cis*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one (**6**) and *trans*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one (**5**) (45.3 kg,150.5 mol *cis*:*trans* ratio 4:1) dissolved in ethanol (675 L). The reaction mixture was concentrated by distillation of part of the ethanol (300 L) until a temperature of 106 °C was reached. The mixture was maintained at reflux temperature for 4 h. The reaction mixture was cooled and diluted with ethanol (180 L), water (450 L), and toluene (225 L). The pH of the solution was adjusted to 1 by using 18% hydrochloric acid (~510 L) at a temperature below 55 °C. The toluene layer was separated. The aqueous phase was partly evaporated to

(6) Kemperman, G. J.; van der Linden, J. J. M.; Reeder, M. Intermediate compounds for the preparation of *trans*-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*-dibenz[2,3;6,7]oxepino[4,5-*c*]pyrrole. Patent WO2006/106136, 2006.

remove the ethanol and subsequently cooled to ambient temperature to start crystallization of the product. The crystals of *trans*-8-chloro-10,11-dihydro-11-[(methylamino)methyl]-dibenz-[*b*,*f*]oxepin-10-carboxylic acid hydrochloride (**9a**) were filtered and washed once with water (25 L). The wet crystals were directly transferred back in the reactor containing a suspension of sodium acetate (3.2 kg, 39 mol) in toluene (350 L). The reaction mixture was heated and distilled until a temperature of 92 °C was reached while maintaining the volume by adding toluene. After the reaction mixture was cooled to 70 °C, a suspension of sodium acetate (9.5 kg, 116 mol) in toluene (50 L) was added. The reaction mixture was heated to reflux for 3 h and then cooled to 70 °C, followed by filtration to remove salts. Evaporation of the toluene followed by crystallization of the product from methanaol furnished 28.8 kg (64% overall) of *trans*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one (**5**): mp 150.6 °C; ^{1}H NMR data (measured at 399.87 MHz in $CDCl_3$ relative to TMS) δ (ppm) 3.03 (s, 3H, N-CH_3), 3.53–3.65 (m, 3H, CH_β + CH), 3.82 (m, 1H, CH), 4.03 (m, 1H, CH_α), 7.01–7.28 (m, 6H, ArH), 7.87 (dd, 1H, ArH).

Acknowledgment

Drs. Leo Letendre, Michael Reeder, and Tim Stuk (Pfizer Inc.) are acknowledged for the pleasant collaboration and for their contribution to the process development activities for asenapine.

Supporting Information Available

Additional synthetic methods. This information is available free of charge via the Internet at http://pubs.acs.org.

Received for review October 26, 2007.

OP700240C