Organic Process Research & Development **2009**, *13*, 900–906

Development of a Practical Large-Scale Synthesis of Denagliptin Tosylate

Daniel E. Patterson,* Jeremiah D. Powers, Michael LeBlanc, Tyler Sharkey, Emily Boehler, Erwin Irdam, and Martin H. Osterhout

Chemical Development, GlaxoSmithKline, Five Moore Drive, P.O. Box 13398, Research Triangle Park, North Carolina 27709-3398, U.S.A.

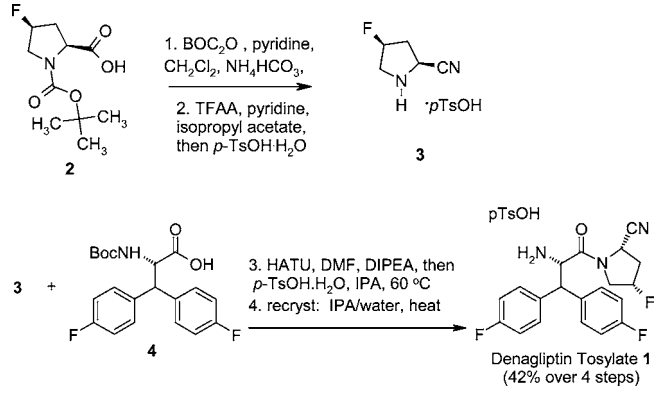
Abstract:

A large-scale synthesis of denagliptin tosylate has been developed. The efficiency of the synthesis has been improved from the initially scaled route by changing the order of steps (performing a dehydration at a late stage). The key step of the synthesis is a single-step peptide coupling/dehydration, mediated by *n*-propanephosphonic acid cyclic anhydride. The challenges of developing this synthesis into a robust and practical manufacturing route are described.

Introduction

Denagliptin tosylate[1] **1** is a dipeptidyl peptidase IV (DPP-IV) inhibitor[2] in development for the treatment of type II diabetes. For the final supply route to this compound, it was imperative to develop a synthesis that was efficient and cost effective. The initial supply route to this compound starting from *N*-Boc-(4*S*)-fluoro-L-proline **2** and (*S*)-difluorophenyl amino acid **4** is shown in Scheme 1. These starting materials were initially synthesized in-house[3] but were purchased externally as part of the final supply strategy. The initial supply route was fairly straightforward, starting with conversion of **2** to its primary amide, followed by dehydration to the nitrile and removal of the Boc-protecting group.[1a] The resulting proline nitrile **3** was coupled to acid **4** catalyzed by *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), and deprotected in the same pot. A final recrystallization gave the active pharmaceutical ingredient (API) in 42% overall yield from **2** in >97% purity. This route was successful in providing the early supplies of the compound, but several challenges had to be solved in order to develop a cost-effective and robust route. The redevelopment of the route to meet these challenges is the subject of this article.

Scheme 1. **Initial route to denagliptin tosylate**



The initial route was undesirable as a manufacturing process in part because of the cost of the peptide coupling agent HATU which was a major contributor to the overall cost of goods. In addition, there has been increasing safety concern related to the use of triazole-based coupling agents (i.e., HATU, *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU), etc.)[4] for peptide coupling on large scale due to the explosive nature of the reagents and their byproduct (>1500 J/g; maximum operating temperature approximately 50 °C).[5] For these reasons, it was a priority to find an alternate coupling agent for use in the synthesis. This was challenging because the amine **3** has low reactivity, and in initial screens only HATU was identified to give complete conversion to the desired product. A number of common coupling reagents were screened including 1,1′-carbonyl diimidazole (CDI), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PYBOP), HBTU, and cyanuric chloride. In all cases, these coupling agents gave either poor conversion, lower yields, and/or an increased level of impurities in final API **1**. A second screen of less common coupling agents identified two possible replacements; chlorodimethoxytriazine (CDMT)[6] and *n*-propanephosphonic acid cyclic anhydride (T3P)[7,8] **5** were effective for the coupling reaction, going to completion in <4 h. The CDMT reaction,

* Corresponding author. E-mail: daniel.e.patterson@gsk.com. Telephone: (919) 483-1266. Fax: (919) 483-3706.

(1) (a) Haffner, C. D.; McDougald, D. L.; Randhawa, A. S.; Reister, S. M.; Lenhard, J. M. PCT Int. Appl. WO 2003/002531 A, 2003; CAN 138: 900712003. (b) Thomas, J. M.; von Geldern, T. W. *Drug Dev. Res.* **2006**, *67*, 627.

(2) (a) For recent reports, see: Hanson, R. L.; Goldberg, S. L.; Brzozowski, D. B.; Tully, T. P.; Cazzulino, D.; Parker, W. L.; Lyngberg, O. K.; Vu, T. C.; Wong, M. K.; Patel, R. N. *Adv. Synth. Catal.* **2007**, *349*, 1369. (b) Feng, J.; Zhang, Z.; Wallace, M. B.; Stafford, J. A.; Kaldor, S. W.; Kassel, D. B.; Navre, M.; Shi, L.; Skene, R. J.; Asakawa, T.; Takeuchi, K.; Xu, R.; Webb, D. R.; Gwaltney, S. L. *J. Med. Chem.* **2007**, *50*, 2297. (c) Pei, Z.; Li, X.; von Geldern, T. W.; Longnecker, K.; Pireh, D.; Stewart, K. D.; Bakes, B. J.; Lai, C.; Lubben, T. H.; Ballaron, S. J.; Beno, D. W. A.; Kempf-Grote, A. J.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2007**, *50*, 1983.

(3) (a) Patterson, D. E.; Xie, S.; Jones, L. A.; Osterhout, M. H.; Henry, C. G.; Roper, T. D. *Org. Process Res. Dev.* **2007**, *11*, 624. For another approach to **4**, see: Deng, G.; Ye, D.; Li, Y.; He, L.; Zhou, Y.; Wang, J.; Li, J.; Jiang, H.; Liu, H. *Tetrahedron* **2008**, *64*, 10512. (c) For a synthesis of **2** see: Doi, M.; Nishi, Y.; Kiritoshi, N.; Iwata, T.; Nago, M.; Nakano, H.; Uchiyama, S.; Nakazawa, T.; Wakamiya, T.; Kobayashi, Y. *Tetrahedron* **2002**, *58*, 8453.

(4) Dunn, P. J.; Hoffman, W.; Kang, Y.; Mitchell, J. C.; Snowden, M. J. *Org. Process Res. Dev.* **2005**, *9*, 956.

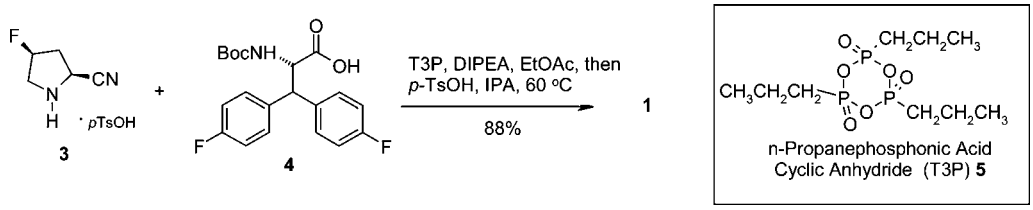
(5) Data from GSK Process Safety group. Energy of decomposition determined by DSC testing at 2 K/min. Maximum operating temperature determined by ARC testing.

(6) (a) Garrett, C. E.; Jiang, X.; Prasad, K.; Repic, O. *Tetrahedron Lett.* **2002**, *43*, 4161. (b) Kaminski, Z. *Synthesis* **1987**, *10*, 917.

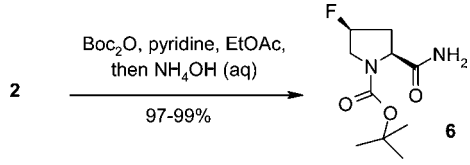
(7) T3P is a registered trademark of Clariant.

Published on Web 08/20/2009
10.1021/op900178d CCC: $40.75

Scheme 2. **Coupling using T3P**



Scheme 3. **Stage 1 using aqueous ammonium hydroxide**



however, was not as clean as that with T3P, giving higher levels of impurities and dark color in both the reaction solution and the product. The T3P-mediated reaction proceeded cleanly in 4 h at room temperature in ethyl acetate to give, after deprotection with *p*-toluenesulfonic acid, 88% yield of denagliptin tosylate in >98% purity (Scheme 2). No epimerization of the α-chiral center was observed in the coupling reaction. Diisopropylethylamine was used as base, and a slight excess (1.05 equiv) of amine **3** and T3P (1.2−1.4 equiv) were necessary for a robust and a reproducible process. The order of addition was very important for the coupling reaction, with the best results obtained when T3P was added last. The reaction did not work well if the acid was first activated with T3P and the amine subsequently added. This was due to activation of the acid followed by reaction with a second equivalent of the acid to form an anhydride (identified by LC−MS) which was less reactive. In addition, the reaction worked better if the tosylate salt was stirred for 30 min after the addition of base to ensure complete freebasing before the T3P was added. T3P had several advantages over HATU in the reaction. The cost of T3P was significantly lower (>10 times), and there were lower safety hazards associated with T3P (compared to those with HATU). In addition, the workup of the T3P reaction was very simple, requiring just two water washes to remove the byproducts and give a clean solution of the desired product. This was in contrast with many common coupling agents that require multiple washes and/or the use of base, etc. to remove the byproducts of the coupling agent.

A second major problem with the initial route involved the two-step synthesis of the nitrile **3**. The yield for this simple transformation was typically only 60−65%, which severely impacted the cost of goods and throughput of the synthesis. When we initially developed the conversion of **2** to **6** (Scheme 3) we, recognized that an aqueous workup had to be avoided because of the aqueous solubility of the product. This precluded most of the typical conditions for amidation that go through the acid chloride. Initially, the acid was activated with Boc-anhydride and pyridine in dichloromethane (DCM) and then treated with ammonium bicarbonate as the ammonia source.[9] The use of dichloromethane as a solvent was key to keeping the product in solution while allowing the excess ammonium bicarbonate to be filtered off. This procedure worked well, giving a 90% yield, but the filtration to remove the ammonium bicarbonate was undesirable on large scale. The reaction time was also long, and the process was not especially robust; one run in the pilot plant resulted in a low yield (<80%), presumably due to crystallization of the product during the filtration of the excess ammonium bicarbonate.

In developing a new process for the amidation, Boc-anhydride was still used to activate the acid, but alternative ammonia sources such as ammonia in alcohol solvents were screened. These reactions worked well, but these reagents introduced a large amount of excess alcohol as solvent. This caused problems in the workup, since the product has relatively high solubility in alcoholic solvents and therefore required removal of a large amount of solvent to achieve a good yield in the crystallization. Aqueous ammonium hydroxide was examined as an ammonia source since it is available in high concentration and is inexpensive and readily available. Initial concerns regarding water addition to the system were not realized, and the reaction worked exceedingly well. The acid was treated with Boc-anhydride and pyridine in ethyl acetate for 2−3 h, and then 28% aqueous ammonium hydroxide was added slowly (Scheme 3). Upon addition, the product crashed out of solution, and the reaction was complete within 1 h. The product was isolated by partial solvent exchange to heptane followed by filtration to afford the amide **6** in 97−99% yield. The new procedure proceeded in higher yield and shorter reaction time, avoided the use of DCM, and was more robust since it avoided the need to filter off excess reagent.

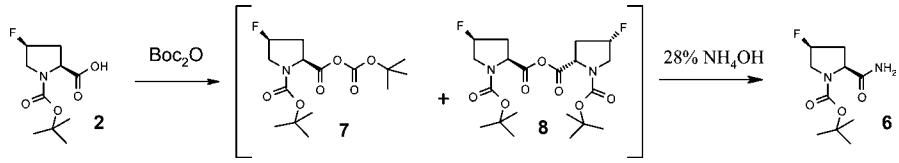
Careful analysis of the amidation gave some interesting mechanistic insight into the reaction. The initial reaction of **2** with Boc-anhydride gave the activated acid **7** as expected, but it also formed an almost equal amount of the dimeric anhydride **8** (Scheme 4).[10] Upon addition of aqueous ammonium hydroxide, the two intermediates reacted very quickly to give amide **6**. The reaction of **8** with ammonium hydroxide formed one equivalent of the desired amide but also regenerated one equivalent of the starting acid **2**. In order for the reaction to proceed to completion, the reaction of the regenerated **2** with Boc-anhydride and subsequent conversion to **6** must be faster than the reaction of ammonia with Boc-anhydride. The fact that the reaction did proceed to >99% conversion under these conditions suggests that the rates are significantly different. Further evidence for this rate difference comes from an

(8) (a) Wissmann, H.; Kleiner, H. J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 133. (b) Boggs, S. D.; Cobb, J. D.; Gudmundsson, K. S.; Jones, L. J.; Matsuoka, R. T.; Millar, A.; Patterson, D. E.; Samano, V.; Trone, M. D.; Xie, S.; Zhou, X.-M. *Org. Process Res. Dev.* **2007**, *11*, 539. (c) Helal, C. J.; Kang, Z.; Lucas, J. C.; Bohall, B. R. *Org. Lett.* **2004**, *6*, 1853.

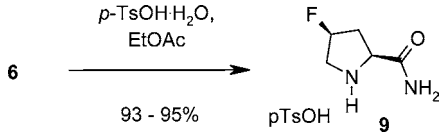
(9) Pozdnev, V. F. *Tetrahedron Lett.* **1995**, *36*, 7115.

(10) The identity of the intermediates **7** and **8** are based on LC−MS analysis.

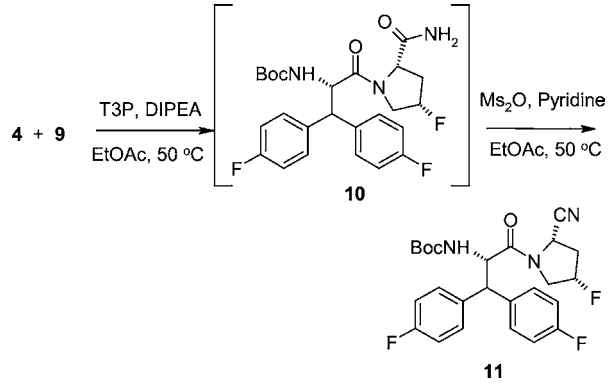
Scheme 4. **Mechanism of stage 1**



Scheme 5. **Synthesis of 9**



Scheme 6. **Synthesis of 11 by one-pot coupling/dehydration**



experiment where the aqueous ammonium hydroxide was present prior to the Boc-anhydride addition. Under these conditions, the reaction went to >80% completion, indicating that the formation of the reactive intermediate **7** was faster than decomposition of Boc-anhydride by reaction with ammonia.

The conversion of **6** to **3** (stage 2) by treatment with trifluoroacetic anhydride to effect dehydration followed by deprotection with *p*- toluenesulfonic acid was problematic due to its low yield. The low yield was due to the difficulty in crystallizing the final product which led to a large yield loss in the mother liquors. Some acid-catalyzed decomposition to unknown byproduct was also observed during the deprotection step. A large effort was made to optimize this reaction by looking at alternate reagents, solvents, and crystallization conditions, but in our hands, it was not possible to improve the yield above 70%.

The improvements to the peptide coupling and amidation steps detailed above represented major improvements from the initial synthesis. The overall yield was improved from 42% to 55%, but more importantly, the cost of goods and robustness of the process were greatly improved. This route was used to supply phase II and to make the initial phase III clinical supplies (>1 t of API). It was still a goal of the project team to improve the overall yield of the synthesis, which led us to investigate a new route. Because the project was at a late stage of development, the new synthesis would have to provide material that matched or had an improved impurity profile compared to that of the current route. It was preferred that the route use the same starting materials, since reliable suppliers of both starting materials had already been established. Therefore, it was decided to change the order of steps to perform the coupling before the dehydration in hopes of avoiding the issues related to dehydration at an early stage. It was hoped that the amino-amide intermediate **9** (Scheme 5) would be easier to isolate and could be synthesized in higher yield than the amino-nitrile **3**. The risk of this approach, based on previous experience, was that the dehydration to the nitrile would be done late in the synthesis. Since the conditions for dehydration are often harsh, there was a risk of decomposition or formation of new impurities during this late stage dehydration.

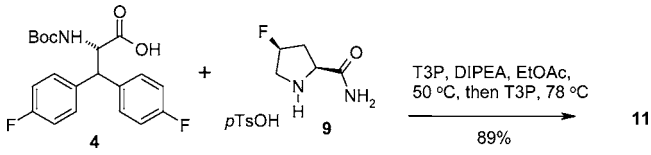
Stage 1 of the new route was identical to stage 1 of the initial route and was not changed. Stage 2 was a simple deprotection of Boc-amide **6** to give fluoroprolinamide **9**. Multiple acids and solvents were screened, but the best conditions were *p*-toluenesulfonic acid in ethyl acetate. These conditions gave amino-amide **9** which precipitated as its tosylate salt and could be filtered directly in high yield (Scheme 5).

The conditions used for the coupling in the initial route translated nicely to the coupling of amino amide **9** with Boc-protected amino acid **4**. Treatment with T3P and diisopropylethylamine in ethyl acetate led to complete conversion to the desired coupled product **10** with no epimerization. The development of the dehydration proved to be more challenging. We screened a number of common dehydrating agents including phosphorous oxychloride, trifluoroacetic anhydride, tosyl chloride, oxalyl chloride, thionyl chloride, and cyanuric chloride, but all formed impurities or did not go to completion. T3P and diisopropylethylamine were examined for the dehydration, but even at 50 °C with a large excess of reagent, the reaction did not go to completion.[11] *p*-Toluenesulfonic anhydride appeared to be a viable way forward, but our inability to find a large-scale supplier of this reagent precluded its use. We finally had success with methanesulfonic anhydride as the dehydrating agent. The transformation proceeded very cleanly with pyridine as the base at 50 °C, giving **11** in 90% yield (see Scheme 6). This material was taken on to give API with an improved impurity profile. A process was developed for the coupling /dehydration whereby after the T3P coupling, the reaction was washed with water twice, and dried by atmospheric distillation to <0.1 wt %/vol water. Pyridine and methanesulfonic anhydride were added, and the reaction was heated to 55 °C for 1 h. After workup and three washes, the product was crystallized from isopropanol/water to give **11** in 90% yield. This process was successfully demonstrated on 150 kg scale, giving material of acceptable purity.

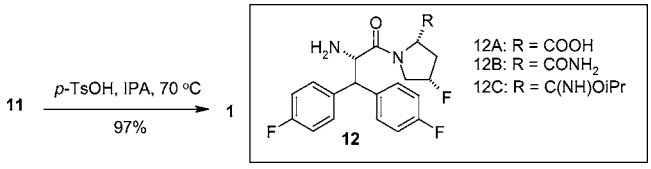
During development, it was observed that if the T3P coupling was run at high temperature, a significant amount of dehydration of the product to form **11** was also observed. This led us to reexamine T3P for the dehydration step. To our surprise, by raising the temperature and lowering the amount

(11) (a) Meudt, A.; Wisdom, R. *Chim. Oggi.* **2008**, *26*, 28. (b) Garcia, A. L. L. *Synlett* **2007**, *8*, 1328. (c) Meudt, A.; Scherer, S.; Nerdinger, S. PCT Int. Appl. WO 2005/070879 A1; CAN 143:172649, 2005.

Scheme 7. **Coupling/dehydration mediated by T3P**



Scheme 8. **Synthesis of denagliptin tosylate (intermediate grade)**



of base, it was possible to do both the coupling and the dehydration in one pot with T3P as the reagent (Scheme 7). In practice, the coupling was run as previously, and after the reaction was complete, a second portion of T3P was added, and the reaction was heated to 78 °C. This led to complete conversion to the desired product in 2 h, and crystallization gave the desired product in 89% yield (>99% purity). This process had an advantage in cycle time over the methanesulfonic anhydride process in that it did not require aqueous washes or an azeotropic drying distillation before the dehydration step. In addition, the removal of methanesulfonic anhydride from the process was advantageous from a genotoxic impurity perspective since, when using methanesulfonic anhydride, there is the possibility of forming alkyl methanesulfonate esters, especially since alcoholic solvents are used in subsequent steps. Switching to the T3P process removed the potential to form these genotoxic impurities.

The final two steps of the synthesis were similar to the initial route. Deprotection of **11** by treatment with *p*-toluenesulfonic acid in isopropanol proceeded smoothly to give **1** in 97% yield (Scheme 8). In order to control the gas evolution, a solution of *p*-toluenesulfonic acid was added to a solution of **11** in isopropanol at 70 °C over 1 h. The reaction was stirred for an additional 6 h at 70 °C until completion. In some plant-scale batches, three impurities (**12A**−**C**, Scheme 8) were observed in the isolated product, that were not present in typical lab-scale batches. In addition, some of these batches had different levels of these three impurities in different spins of the same batch (batches where the reaction was run in a single batch, but were filtered in a centrifuge and dried in portions).

Studies of the Boc-deprotection showed that none of these impurities were formed during the reaction, but were formed in the dryer. Spiking studies showed that these impurities only formed if there was excess *p*-toluenesulfonic acid in the filter cake during drying (Table 1). Interestingly, these impurities only form in the solid phase, and heating **1** in solution with *p*-toluenesulfonic acid failed to give these impurities under a variety of conditions.

The instability of **1** to drying in the presence of excess *p*-toluenesulfonic acid highlighted the need for efficient washing of the filter cake prior to drying. In practice, washing the cake twice in a filter dryer with two volumes of isopropanol was sufficient to remove the free toluenesulfonic acid from the cake and avoid impurity formation.

Table 1. **Degradation of 1 under drying conditions (16 h 55 °C)**

conditions	**12A** (%)	**12B** (%)	**12C** (%)
1 washed wet cake	–	–	–
1 unwashed wet cake	3.7	–	–
1 + IPA (20 wt %)	0.02	–	–
1 + H_2O (10 wt %)	0.05	–	–
1 + TsOH (5 wt %)	3.4	–	–
1 + TsOH (5 wt %), IPA (20 wt %)	1.2	1.2	0.3

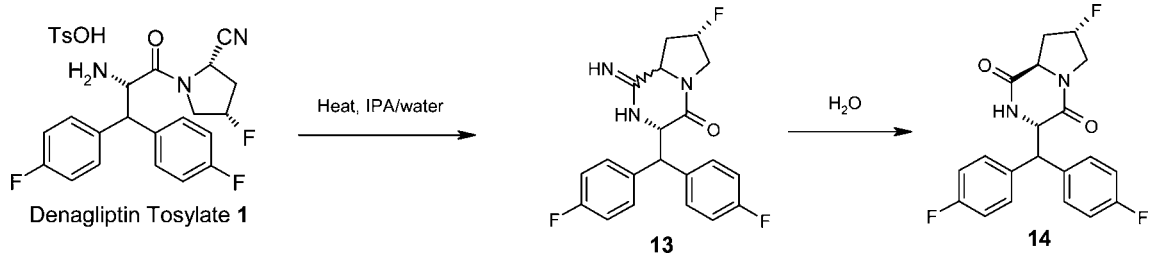
The final step of the synthesis was a recrystallization from isopropanol and water. A recrystallization was performed for two main reasons. First, the use of a separate, final-stage crystallization led to a more reproducible impurity profile and consistent physical properties of the final API. In addition, a separate crystallization was needed to control the level of isopropyl tosylate, a potential genotoxic impurity, in the API. Isopropyl tosylate was formed in the Boc-deprotection step when *p*-toluenesulfonic acid was heated in isopropanol. The levels in the reaction solution could be as high as 5000 ppm, and the isolated crude API typically contained 20−60 ppm. This was not an issue, as any isopropyl tosylate was readily decomposed in isopropanol/water mixtures in the final crystallization. The final crystallization was a straightforward cooling crystallization. One issue with this process was that at high temperature, in isopropanol/water mixtures, the API decomposes by cyclization of the amine onto the nitrile to give amidine **13** (and/or) diketopiperazine **14** impurities (Scheme 9).

The initial recrystallization process was run by dissolving the API in 10 volumes of a 2:3 IPA/water mixture and heating to 80 °C to dissolve. However, in stability studies of the reaction mixture, it was observed that at 80 °C the decomposition to the amidine impurities was rapid. As the process was scaled up, it was recognized that the batch would be held at high temperature for extended periods of time as the reaction was heated, filtered while hot, and then cooled back down. The stability of **1** at various temperatures is shown in Figure 1. The data indicate that decomposition was significantly slower at 70 °C and negligible at temperatures under 60 °C. On the basis of these data, a lower temperature recrystallization was desired.

Solubility studies of denagliptin tosylate in varying ratios of isopropanol and water showed that by lowering the initial concentration of water in the solvent system it was possible to dissolve the material at 70 °C without increasing the total volumes above 10 (Figure 2). In practice, the crystallization was run in 10 volumes of 1:1 isopropanol/water. The slurry was heated to 70−72 °C to dissolve, filtered while hot, and then cooled to 5 °C. At 5 °C an additional 3 volumes of water was added to push more material out of solution, giving an isolated yield of 92%. By changing to a lower temperature process, the risk of degradation was mitigated.

The final manufacturing route to denagliptin tosylate is shown in Scheme 10. This route is notable for its high yield (>70% over five steps), and excellent scalability and operability. The new route changed the order of steps to effect dehydration at a late stage, which solved the major problems associated with the original route. This route overcame the low yield and stability issues related to the synthesis of nitrile **3**. In addition, T3P was identified as a cost-effective, safe alternative to HATU, greatly improving the overall cost of goods of the process. By

Scheme 9. **High temperature decomposition of denagliptin tosylate**



using T3P for both the coupling and the dehydration, it was possible to perform these two operations very cleanly in a single stage. This transformation underscores the utility of T3P for use on large scale. The development of the new route also removed dichloromethane from the synthesis and removed two salt filtrations from the process, improving the safety and operability of the process. This route proved to be very robust on scale and was used to produce more than a metric ton of API.

Experimental Section

General Methods. HPLC purity was determined on a Hewlett-Packard series 1100 system using Phenomenex Luna C18 (2) columns (50 mm × 2 mm, 3 μm), and a mixture of water and acetonitrile with trifluoroacetic acid as mobile phase (gradient at a flow rate of 1.0 mL/min and UV detector at 220 nm).

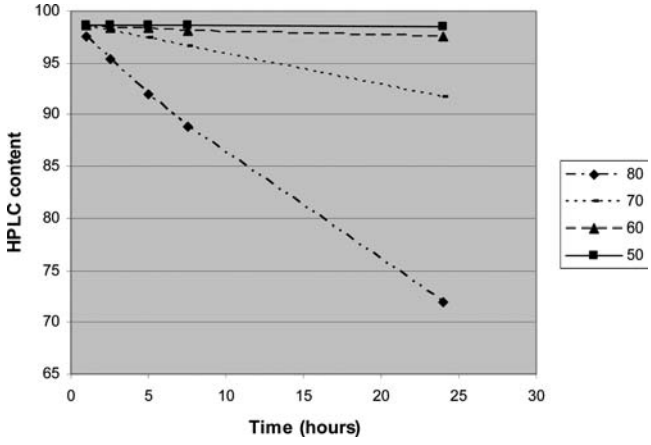


Figure 1. **Stability of denagliptin tosylate in isopropanol/water.**

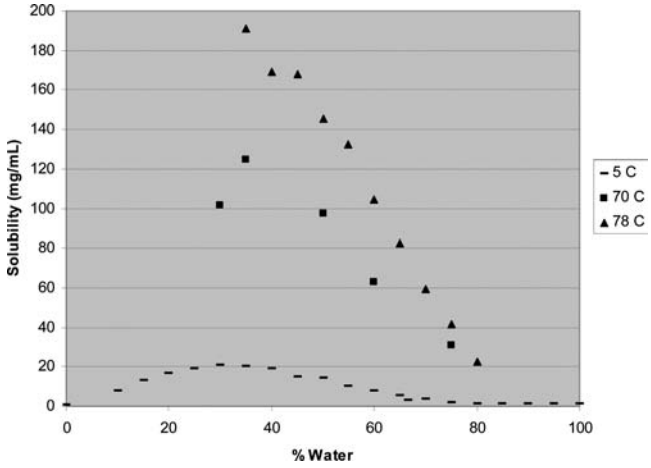


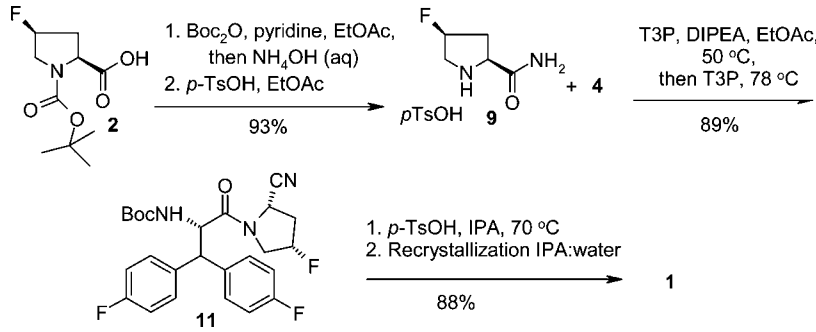
Figure 2. **Solubility of denagliptin tosylate in IPA/water.**

(4*S*)-1-(*tert*-Butoxycarbonyl)-4-fluoro-L-prolinamide (6). A mixture of **2** (100 kg, 429 mol), ethyl acetate (1000 L, 10 vol), and di-*tert*-butyl dicarbonate (117 L, 511 mol) was treated with pyridine (42 L, 523 mol) and was stirred at 25 °C for 2−3 h. A solution of 28−30% w/w ammonium hydroxide (35 L, 528 mol) was charged over at least 20 min. (NOTE: Strong off-gassing observed!) The reaction was stirred at 25 °C for 3 h. The solvent was removed by vacuum distillation (50−100 mbar) to 400 L (4 vol). Heptane (900 L, 9 vol) was charged, and solvent was removed by vacuum distillation (50−100 mbar) to 800 L (8 vol). The reaction was cooled to 5 °C and held for 30 min. The batch was filtered, washed with heptane (200 L, 2 vol), and dried at 75 °C to give 95.6 kg (96%) of **6** as a white solid. Mp: 161 − 164 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.20 (m, 2H), 5.22 (d, J = 54 Hz, 1H), 4.13 (m, 1H), 3.60 (m, 2H), 2.39 (m, 1H), 2.16 (m, 1H), 1.39(s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.8, 154.1, 92.0 (d, J = 173 Hz), 79.4, 59.1, 53.6, 37.6, 28.5. Anal. Calcd For $C_{10}H_{17}FN_2O_4$: C, 51.72; H, 7.38; N, 12.06. Found: C, 51.58; H, 7.42; N, 12.08.

(4*S*)-Fluoro-(2*S*)-cyanopyrrolidine *p*-Toluenesulfonate (3). A mixture of isopropyl acetate (250 L, 5 vol), **6** (50 kg, 215 mol) and pyridine (38.3 L, 474 mol) was treated with trifluoroacetic anhydride (33.5 L, 237 mol). The reaction was stirred at 20 °C for 1 h and filtered, and the filtercake was washed with isopropyl acetate (100 L, 2 vol). To the filtrate was added water (100 L, 2 vol), and the mixture was stirred for 15 min and allowed to settle. The layers were separated, and the aqueous layer was back-extracted with isopropyl acetate (100 L, 2 vol). The combined organic layer was concentrated under vacuum (50−100 mbar) to 150 L (3 vol), and was treated with *p*-toluenesulfonic acid monohydrate (82 kg, 430 mol). The reaction was stirred at 20 °C for 6 h, and isopropanol (150 L, 3 vol) was added. The reaction was cooled to 5 °C over 30 min, filtered, washed with isopropyl acetate (50 L, 1 vol), and dried at 50 °C to give 38.2 kg (62%) of **3** as a white solid. Mp: 156−157 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.2 (m, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 5.53 (d, J = 52 Hz, 1H), 5.02 (m, 1H), 3.59 (m, 2H), 2.62 (m, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.4, 138.6, 128.7, 126.0, 116.8, 92.3 (d, J = 175 Hz), 52.5, 45.7, 37.5, 21.3. Anal. Calcd For $C_{12}H_{15}FN_2O_3S$: C, 50.34; H, 5.28; N, 9.78. Found: C, 50.33; H, 5.29; N, 9.72.

(4*S*)-Fluoro-L-prolinamide *p*-Toluenesulfonate (9). A mixture of *p*-toluenesulfonic acid monohydrate (110.7 kg, 581 mol) and ethyl acetate (270 L, 3 vol), was heated to 35 °C until all of the solids dissolved. This solution was added over 60 min to a solution of **6** (90 kg, 387 mol) in ethyl acetate (270 L, 3 vol) at 50 °C. The reaction was stirred at 50 °C for 2−3 h. The batch was cooled to 5 °C and stirred for 30 min. The reaction

Scheme 10. **Final manufacturing route to denagliptin tosylate**



was filtered, washed with ethyl acetate (90 L, 1 vol), and dried at 50 °C to give 112 kg (95%) of **9** as a white solid. Mp: 190−193 °C. ^{1}H NMR (500 MHz, DMSO-*d*16) δ 9.10 (bs, 2H), 8.00 (s, 1H), 7.72 (s, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 5.38 (dt, J = 52.3, 3.7 Hz, 1H), 4.35 (dd, J = 10.7, 3.4 Hz, 1H), 3.58 (ddd, J = 19.5, 13.7, 2.0 Hz, 1H), 3.44 (t, J = 37.1, 13.2, 3.7 Hz, 1H), 2.62 (m, 1H), 2.31 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 145.7, 138.4, 129.3, 128.6, 126.0, 93.2, 92.4 (d, J = 174 Hz), 58.0 (d, J = 80 Hz), 52.1 (d, J = 23 Hz), 37.2, 21.3. Anal. Calcd For $C_{12}H_{17}FN_2O_4$: C, 47.36; H, 5.63; N, 9.20. Found: C, 47.39; H, 5.63; N, 9.16.

Initial Synthesis of (2*S*)-Cyano-(4*S*)-fluoro-1-pyrrolidinyl]-2-oxoethylcarbamate *p*-Toluenesulfonate (Denagliptin Tosylate) (1). A mixture of **4** (100 kg, 265 mol) and **3** (78 kg, 272 mol) in ethyl acetate (700 L, 7 vol) at 0 °C was treated with Hunig's base (153 L, 875 mol), and the reaction was stirred for 30 min at 0 °C. T3P in EtOAc (50 w/w%, 221 L, 371 mol) was added, keeping the reaction temperature below 5 °C. The reaction was stirred at 0 °C for 20 min, then heated to 20 °C and stirred for 4 h. The reactor was charged with water (600 L, 6 vol), and the mixture was stirred for 10 min. The layers were separated, and the organic layer was washed with water (600 L, 6 vol). The ethyl acetate solution of **8** was solvent exchanged under vacuum (50−100 mbar) to isopropanol (600 L final volume, 6 vol). To this slurry was added a solution of *p*-toluenesulfonic acid monohydrate (101 kg, 530 mol) in isopropanol (400 L, 4 vol). The solution was heated to 60 °C for 6 h. The reaction was cooled to 5 °C and stirred at this temperature for 30 min. The reaction was filtered, washed with isopropanol (200 L, 2 vol), and dried at 50 °C to give 127 kg (88%) of **1** as a white solid. Mp: 241−245 °C dec. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (bs, 3H), 7.73 (m, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.36 (m, 2H), 7.24 (m, 2H), 7.14 (d, J = 8.1, 2H), 7.05 (m, 2H), 5.34 (d, J = 53.0 Hz, 1H), 4.91 (m, 2H), 4.45 (d, J = 11.4 Hz, 1H), 3.84 (ddd, J = 39.2, 12.5, 3.4, 1H), 3.39 (dd, J = 24.2, 12.5, 1H), 2.62 (m, 1H), 2.34 (m, 1H), 2.30 (s, 3H), 2.24 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 162.2 (d, J = 244.5 Hz), 162.0 (d, J = 244.5 Hz), 145.7, 138.4, 134.7, 134.3, 131.6, 131.5, 130.6, 130.5, 128.6, 126.0, 117.8, 116.3, 116.1, 115.9, 92.0 (d, J = 175.1) 53.8, 53.7, 53.6, 52.5, 45.1, 35.8, 21.2. Anal. Calcd For $C_{27}H_{26}F_3N_3O_4S$: C, 59.44; H, 4.80; N, 7.70. Found: C, 59.52; H, 4.85; N, 7.70.

***tert*-Butyl{(1*S*)-1-[bis(4-fluorophenyl)methyl]-2-[(2*S*)-cyano-(4*S*)-fluoro-1-pyrrolidinyl]-2-oxoethylcarbamate (11).** A mixture of diisopropylethylamine (145.1 kg, 1124 mol) and **4** (106 kg, 281 mol) in ethyl acetate (424 L, 4 vol), was treated with **7** (94.3 kg, 309 mol). The reaction was stirred for 30 min at room temperature, and 50% wt T3P in EtOAc (270.2 kg, 422 mol) was added while keeping the batch temperature less than 50 °C. The reaction was stirred at 40−50 °C for 30 min, and then a second portion of 50 w/w % T3P in EtOAc (270.2 kg, 422 mol) was added. The reaction was heated to 75−80 °C and held for 6−12 h. The reaction was cooled to 25 °C. Water (530 L, 5 vol) was added, and the reaction was stirred 15 min. The stirring was stopped, the layers were allowed to separate, and the bottom layer was removed. Water (318 L, 3 vol) was added, and the reaction was stirred 15 min. The stirring was stopped, the layers were allowed to separate, and the bottom layer was removed. Solvent was removed by atmospheric distillation to approximately 3 volumes. Isopropanol (424 L, 4 vol) was added, and solvent was removed by atmospheric distillation to approximately 3 volumes. Isopropanol (424 L, 4 vol) was added, and solvent was removed by atmospheric distillation to 5 volumes. The batch was cooled to 65−75 °C, and water (265 L, 2.5 vol) was charged into the batch at a constant rate over approximately 60 min, keeping the temperature at 65−75 °C. The batch was seeded at 70 °C with 0.005 wt of **1**. The batch was held at 70 °C for at least 30 min. Water (424 L, 4 vol) was charged into the batch at a constant rate over at least 60 min, keeping the temperature at 65−75 °C. The batch was cooled to 20 at 0.5 °C/min and held for 15 min. The batch was filtered and washed with 35 v/v% isopropanol in water (318 L, 3 vol). The solids were dried at 75 °C to give 123 kg (97%) of **11** as a white solid. Mp: 205−208 °C dec. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.47 (m, 2H), 7.30 (dd, J = 8.7, 5.5 Hz, 2H), 7.13 (t, J = 8.9 Hz, 2H), 7.00 (t, J = 8.9 Hz, 2H), 5.37 (d, J = 52 Hz, 1H), 5.02 (dd, J = 11.7, 8.7 Hz, 1H), 4.87 (d, J = 9.0 Hz, 1H), 4.43 (d, J = 11.7 Hz, 1H), 3.86 (ddd, J = 39.3, 12.6, 3.4 Hz, 1H), 3.7 (dd, J = 24.2, 12.6 Hz, 1H), 2.41 (m, 1H), 2.31 (m, 1H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 162.0, 160.0, 155.3, 136.9, 136.5, 130.6, 130.0, 117.8, 115.2, 114.8, 92.6 (d, J = 140 Hz), 78.4, 54.6, 52.9, 51.2, 44.2, 35.4, 28.8. Anal. Calcd For $C_{25}H_{26}F_3N_3O_3$: C, 63.42; H, 5.53; N, 8.87. Found: C, 63.45;H, 5.62; N, 8.89.

Denagliptin Tosylate (1). To a mixture of **11** (110 kg, 232 mmol) in isopropanol (550 L, 5 vol) at 70 °C was added a solution of *p*-toluenesulfonic acid monohydrate (88.4 kg, 464 mol) in isopropanol (550 L, 5 vol) over one hour while maintaining the temperature at 70 °C. After the addition, the reaction was stirred at 70 °C for 6 h. The batch was cooled to 20 °C, held for 30 min, filtered,

and washed with isopropanol (2 × 220 L, 2 vol). The solids were dried at 55 °C to give 118 kg (89%) of **1** as a white solid.

Recrystallization of Denagliptin Tosylate (1). A mixture of denagliptin tosylate (100 kg, 183 mol) and isopropanol (500 L, 5 vol) and water (500 L, 5 vol), was heated until all the solids dissolved (approximately 72 °C). The hot solution was filtered into another vessel. The solution was cooled to approximately 5 °C, and water (300 L, 3 vol) was added. The reaction was stirred at this temperature for 30 min and was filtered. The filtercake was washed with filtered isopropanol (2 × 200 L, 2 × 2 vol), and pulled dry. The solids were dried at 55 °C to give 91.9 kg (92%) of **1** as a white solid.

Supporting Information Available

Copies of the NMR spectra of all intermediates and the final product. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review July 13, 2009.

OP900178D