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Improved Process for the Preparation of 1-Benzhydrylazetidin-3-ol: Development of an Efficient Synthesis and Identification of Process-related Impurities and/or Intermediates

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Abstract:

An improved, one-pot, and multikilogram-scale synthesis of 1-benzhydrylazetidin-3-ol, the pharmaceutically important moiety, has been developed. The improved process for the preparation of 1-benzhydrylazetidin-3-ol was able to minimize a content of impurities and allows the effective production of 1-benzhydrylazetidin-3-ol and its scale-up. The process was high yielding (80%) and chromatography-free with purity 99.3 area %.

1. Introduction

Azetidines[1,2] are an interesting class of four-membered nitrogen-containing heterocycle which have been receiving much attention from the chemical community recently. Some of the reasons for this increasing interest are the applications of azetidines in biological chemistry and in the field of chiral ligands.[3,4] Drugs comprising azetidine derivatives have been thoroughly investigated for their pharmacological and biological effects.[5] The number of recent research articles provides the evidence of the large use of azetidine ring system in medicinally important molecules.[5] Among the various derivatives of azetidines, 3-substitutedazetidine is most important constituent in various therapeutic potential moieties.[5] Especially, 1-benzhydrylazetidin-3-ol (*N*-(diphenylmethyl)-3-azetidinol), **1** is a useful pharmaceutical intermediate which has been widely used in the synthesis of Dezinamide (antiepileptic drug),[6] Azelnidipine (antihypertensive drug),[7] D83-7676 (an oncolytic drug),[8] azetidinyloxy analogues (antimicrobial agents),[9] oral carbapenem antibiotics such as tebipenem (LJC-11,036),[10] tebipenem pivoxil (L-084),[11] and various 3-substituted azetidine derivatives (Figure 1).

Chatterjee and Triggle[12] had first reported the preparation of the hydrochloride salt of 1-benzhydrylazetidin-3-o1, **1**, by the reaction of diphenylmethanamine (benzhydrylamine) **2** with 2-(chloromethyl)oxirane (epichlorohydrin) **3** that gave 3-chloro-1-diphenylmethylamino-2-hydroxypropane **4a** and was cyclized to 1-benzhydrylazetidin-3-o1 **1**, but experimental details or yields were not reported. Anderson and Lok[13] synthesized the salt of **1** by applying the procedure described by Gaertner[14] to this reaction, giving 60−65% yield (Scheme 1). Later, numerous procedures were reported including minor process modifications with varying yields ranging from 13 to 75%.[15] Furthermore, Oh et al[16] reported the synthesis of **1** by the reaction of benzhydrylamine **2** with epichlorohydrin **3** via *N*-((oxiran-2-yl)methyl)diphenylmethanamine, **5a**. None of the reported procedures gave purity and/or quality details of the prepared 1-benzhydrylazetidin-3-o1 **1**.

2. Results and Discussion

Our need for large quantity of 1-benzhydrylazetidin-3-ol with high quality (Purity by HPLC: not less than (NLT) 99.0% and single maximum impurity (SMI) not more than (NMT) 0.5%), led us to develop an efficient and improved process for the

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(1) D'hooghe, M.; De Kimpe, N. In *Comprehensive Heterocyclic Chemistry III*; Stevens, C. V., Ed.; Elsevier: Oxford, U.K., 2008; Vol. 2, Chapter 2.01, p 1.

(2) (a) De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Elsevier: Oxford, U.K., 1996; Vol. 1B, Chapter 1.18, p 507. (b) Kurteva, V. In *Modern Approaches to the Synthesis of O- and N-Heterocycles*; Kaufman, T., Larghi, E., Eds.; 2007; Vol. 3, p 45.

(3) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Elsevier Science: Amsterdam, 2000.

(4) Couty, F.; Evano, G.; Prim, D. *Mini-Rev. Org. Chem*. **2004**, *1*, 133–148, and references therein.

(5) (a) Evans, G. B.; Furneaux, R. H.; Greatrex, B.; Murkin, A. S.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem*. **2008**, *51*, 948–956. (b) Honcharenko, D.; Barman, J.; Varghese, O. P.; Chattopadhyaya, J. *Biochemistry* **2007**, *46*, 5635–5646. (c) Slade, J.; Bajwa, J.; Liu, H.; Parker, D.; Vivelo, J.; Chen, G. P.; Calienni, J.; Villhauer, E.; Prasad, K.; Repic, O.; Blacklock, T. *J. Org. Process Res. Dev*. **2007**, *11*, 825–835.

(6) (a) Abou-Gharbia, M.; Moyer, J. A. *Drugs Future* **1991**, *16*, 3–201. (b) Johnson, D. N.; Osman, M.; Cheng, L.; Swinyard, E. *Epilepsy Res*. **1990**, *5*, 185–191.

(7) Yagil, Y.; Miyamoto, M.; Frasier, L.; Oizumi, K.; Koike, H. *Am. J. Hypertens*. **1994**, *7*, 637–646.

(8) Naito, H.; Ohsuki, S.; Ejima, A.; Makino, C.; Ohki, H. Pyrazole derivatives and salts thereof. PCT Int. Appl. WO/2000/005230, 2000.

(9) Wells, M. A. W.; Boggs, C. M.; Foleno, B. D.; Wira, E.; Bush, K.; Goldschmidt, R. M.; Hlasta, D. *J. Bioorg. Med. Chem. Lett*. **2001**, *11*, 1829–1832.

(10) Isoda, T.; Yamamura, I.; Tamai, S.; Kumagai, T.; Nagao, Y. *Chem. Pharm. Bull*. **2006**, *54*, 1408–1411.

(11) Isoda, T.; Ushirogochi, H.; Satoh, K.; Takasaki, T.; Yamamura, I.; Sato, C.; Mihira, A.; Abe, T.; Tamai, S.; Yamamoto, S.; Kumagai, T.; Nagao, Y. *J. Antibiot*. **2006**, *59*, 241–247.

(12) Chatterjee, S. S.; Triggle, D. J. *Chem. Commun*. **1968**, 93.

(13) Anderson, A. G.; Lok, R. *J. Org. Chem*. **1972**, *37*, 3953–3955.

(14) Gaertner, V. R. *Tetrahedron Lett*. **1966**, *39*, 4691–4694.

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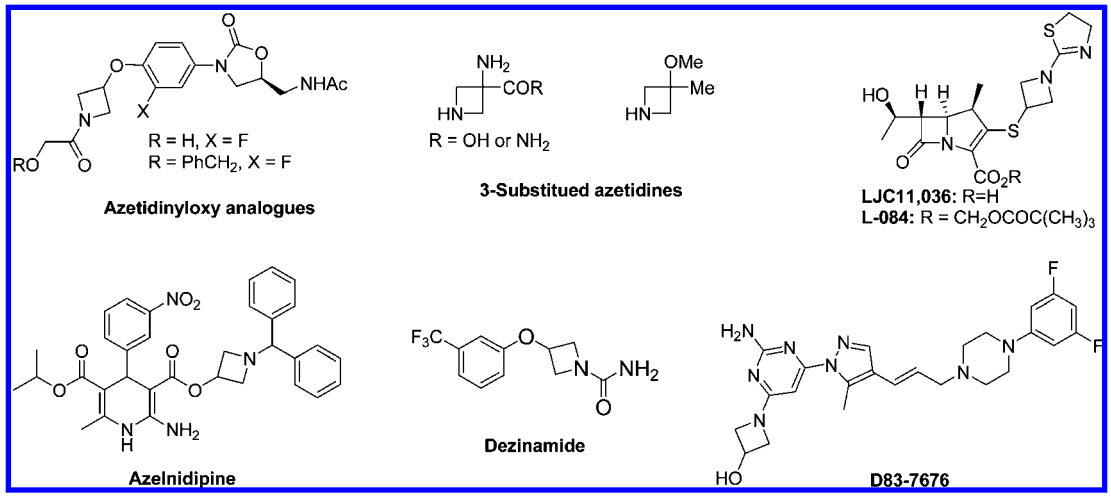


Figure 1. **Various azetidine derivatives synthesized from 1-benzhydrylazetidin-3-ol.**

synthesis of targeted compound in multikilogram (multikilo) scale. Development of an improved process for the synthesis of 1-benzhydrylazetidin-3-ol involved three main steps: (1) generation of standards i.e., intermediates 3-chloro-1-diphenylmethylamino-2-hydroxypropane **4a**,[14] *N*-((oxiran-2-yl)methyl-)diphenylmethanamine **5a**[16] along with the final targeted molecule **1**; (2) development of HPLC method with the prepared standards to monitor the completion of starting material (benzhydrylamine) in addition to intermediate **4a** or **5a** followed by identification and/or preparation of process-related impurities; (3) performing optimization of the reaction conditions to maximize throughput and minimize impurities.

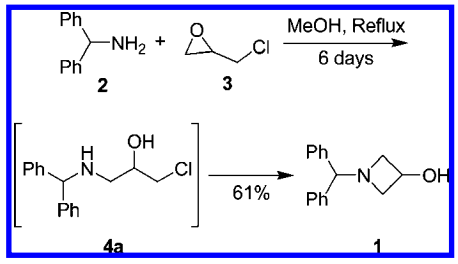
2.1. Generation of Standards. As a part of the generation of standards i.e., for the preparation of compound **4a**, **5a** and **1**, we repeated the reported procedure[16] and isolated the intermediate as well as final compound. The intermediate was identified as 3-chloro-1-diphenylmethylamino-2-hydroxypropane, **4a** by ^{1}H and ^{13}C NMR. As expected, the reaction was proceeding through intermediate **4a** not via **5a**. However, compound **5a** was prepared from **4a** by the reaction with sodium hydroxide in methanol at 0 °C (Scheme 2). For the comparison, the same reaction sequence was also performed with benzylamine instead of benzhydrylamine and also prepared 1-benzylazetidin-3-ol.

2.2. Development of the HPLC Method Followed by Identification and/or Preparation of Process-Related Impurities. Nonchiral RP-HPLC method for the analysis of compounds **1**, **2, 4a**, and **5a**: A Waters model Alliance 2690-separation module equipped with a Waters 996-photodiode array UV detector was used. Inertsil ODS 5 μ, 4.6 mm × 150 mm, 35 °C, injection volume 10 μL, Solvent A: 20 mM NH_4HCO_3, pH 7.0,;Solvent B: acetonitrile, gradient 10−90% B in 25 min, then 10% B for 10 min, at 1.0 mL/min and detection at 210 nm using an ultraviolet visible detector. Samples were dissolved in acetonitrile. The approximate retention time (RT) and relative retention time (RRT) of compounds **1**, **2**, **4a**, and **5a** are given in Table 1. RRTs of each compound are specified relative to compound **1**.

While monitoring the progress of the reaction by HPLC, through injecting the reaction mass of both the reactions (reaction of epichlorohydrin with benzhydrylamine or benzylamine), we observed the formation of one impurity in about 7−9% as a peak during benzhydrylamine reaction, and the analysis of this peak by LC−MS revealed its identity as **6a** (bis impurity), whereas there was about 20−22% of **6b** in the benzylamine reaction (Figure 2). The formation of bis impurity **6** is obvious while opening of oxiranes using primary amines, and it could not be avoided but nevertheless can be reduced with the usage of excess amine. The bis impurity **6b** was prepared by the reaction of benzhydrylamine with excess moles of epichlorohydrin. However, the benzhydrylamine reaction was taken up for further optimization to produce the targeted compound **1**.

2.3. Optimization. First, to establish the appropriate reaction conditions, the reaction was studied as a two-step synthesis. To evaluate the solvent effect in the first step (reaction of epichlorohydrin with benzhydrylamine), the reaction was performed using methanol or isopropanol in two independent experiments under identical conditions. In both the cases, the formation of bis impurity **6a** was about 7−9%, while no formation of *N*-((oxiran-2-yl)methyl)diphenylmethanamine **5a**

Scheme 1. **Synthesis of 1-benzhydrylazetidin-3-ol, 1**



Scheme 2. **Synthesis of compound 5a**

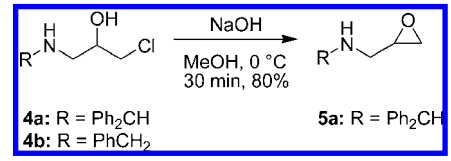


Table 1. **RT and RRT of compounds 1, 2, 4a, and 5a**

compound	RT	RRT
1	14.54	1.00
2	14.11	0.97
5a	17.92	1.23
4a	18.27	1.25

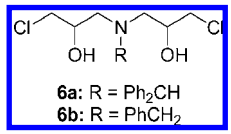


Figure 2. **Structure of bis impurity, 6.**

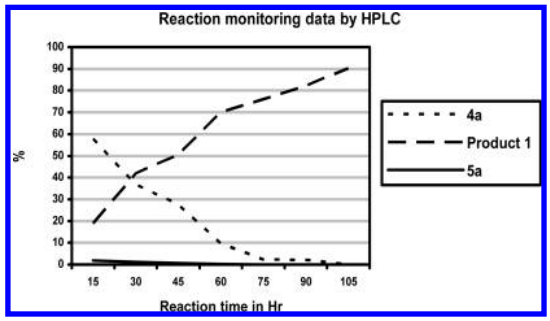


Figure 3. **Formation of 1 and decay of starting material 4a and intermediate 5a.**

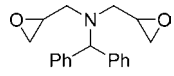


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Figure 4. **Structure of compound 7.**

was observed.[14] The analysis of the two reactions using HPLC divulged isopropanol as a better solvent than methanol with respect to the percentage of the product, 3-chloro-1-diphenylmethylamino-2-hydroxypropane, **4a**, as well as completion of the reaction. The progress of the latter step (cyclization of compound **4a**) was also studied thoroughly using different bases such as Na_2CO_3, $NaHCO_3$, K_2CO_3, $KHCO_3$, *N*,*N*-diisopropylethyl amine (DIPEA), or triethylamine (TEA) in different solvents such as methanol, isopropanol, *N*,*N*-dimethylformamide (DMF), or acetonitrile at reflux temperature. While monitoring of all the described reactions using HPLC, the identified better conditions among all of the attempts was TEA with acetonitrile as solvent in a period of 100−105 h at reflux temperature (Figure 3).

During the initial hours of the second step, the formation of intermediate **5a** was observed in about 2−4% along with conversion of intermediate **4a** to compound **1**. In order to understand the further conversion of **5a**, a reaction was performed on **5a** with TEA in acetonitrile under reflux conditions which resulted in the formation of **1**. This proves that, in addition to formation of compound **1** from **4a,** compound **5a** also converts to compound **1**.

The bis impurity **6a** observed in the first step was not traceable (by HPLC) in the second step conversion. Upon LC−MS analysis, we concluded that **6a** was converting into the new impurity, **7** (RRT 1.43 relative to **1**) under the second step conditions (Figure 4). However, compound **7** was easily removed during isolation of **1**.

Summarizing, it became important that reaction mass in the second step was maintained in reflux conditions until conversion of **4a** and **5a** (less than 1.0% by HPLC) to compound **1** (Scheme 3) and **6a** (less than 0.5% by HPLC) to compound **7**.

Once better reaction conditions were identified for two steps individually, efforts were extended to apply these reaction conditions for the one-pot sequence. Attempts to switch IPA to the second step and acetonitrile to the first step in order to keep the solvents common in both steps were not successful. Neither mixture of IPA and acetonitrile in various proportions was successful. However, the aim of using a one-pot setup was achieved by distilling the first step solvent, isopropanol, followed by introducing acetonitrile, and TEA was then added to the reaction mass to initiate cyclisation of **4a**.

For final isolation of compound **1** from the reaction mass (after evaporation of acetonitrile), various solvents and solvent ratios were screened to study both purity and yield. Finally, methanol and water with the appropriate ratio 1:3.3 was set up as a suitable solvent mixture for isolation. The ratio was significant to ensure that both process-related impurities carried over from the first step and those formed in the second step were successfully removed, which further strengthens the use of one pot.

Manufacturing cost of the target material **1** was drastically reduced over 50% by minimal solvent volumes, improved yield, and chromatography-free process by introducing a simple isolation method. All the described positives made the one-pot process robust.

The Hazard and Operability (HAZOP) studies were also carried out for existing process and operations in order to evaluate potential hazards and operability problems before execution of the final process on the 12 kg level. However, we have not identified any possible deviations from normal operations and also placed appropriate safeguards to prevent accidents.

Frequently, researchers utilize the compound **1** through further derivatization at *C*-3 or *N*-1 sites. Transforming the alcohol functionality into a better leaving group such as methanesulfonyl (Ms) aids alkylation at *C*-3 as well as deprotection of the benzyhydryl group, facilitating derivatization at the *N*-1 site of compound **1**.

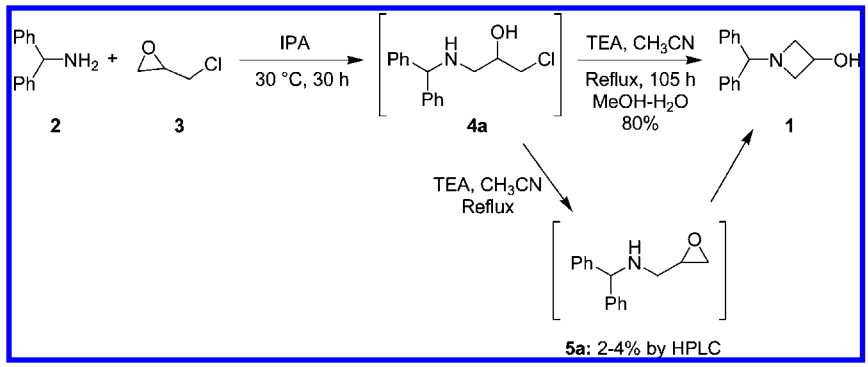
Applications of 1. As reported,[15c,d,17] compound **1**, further treated with MsCl and triethylamine in acetonitrile, yielded the corresponding *O*-mesyl derivative **8**. While, implementing purification of the compound **8** in methanol, formation of one unknown impurity was observed, and LC−MS revealed the identity as 1-benzhydryl-3-methoxy-azetidine. Purification of **8** was carried out in water instead of methanol; thus, formation of impurities was avoided. Furthermore, removal of the ben-

(15) (a) Higgins, R. H.; Cromwell, N. H.; Paudler, W. W. *J. Heterocycl. Chem.* **1971**, *8*, 961–966. (b) Kozikowski, A. P.; Fauq, A. H. *Synlett* **1991**, 783–784. (c) Jung, M. E.; Choi, Y. M. *J. Org. Chem.* **1991**, *56*, 6729–6730. (d) Frigola, J.; Pares, J.; Corbera, J.; Vano, D.; Merce, R.; Torrens, A.; Mas, J.; Valenti, E. *J. Med. Chem.* **1993**, *36*, 801–810. (e) Kobayashi, T.; Inoue, T.; Nishino, S.; Fujihara, Y.; Oizumi, K.; Kimura, T. *Chem. Pharm. Bull.* **1995**, *43*, 797–817. (f) Vuilhorgne, M.; Commercon, A.; Mignani, S. *Chem. Lett.* **1999**, *28*, 605–606. (g) MacKenzie, A. R.; Marchington, A. P.; Meadows, S. D.; Middleton, D. S. U.S. Patent 5,968,923, 1999.

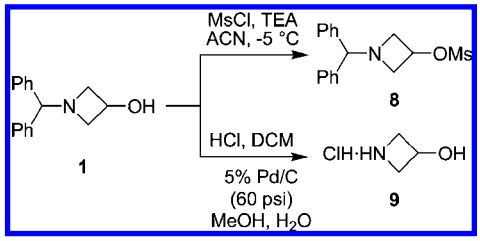
(16) Oh, C. H.; Rhim, C. Y.; You, C. H.; Cho, J. R. *Synth. Commun.* **2003**, *33*, 4297–4302.

(17) (a) Pryde, D. C.; Corless, M.; Fenwick, D. R.; Mason, H. J.; Stammen, B. C.; Stephenson, P. T.; Ellis, D.; Bachelor, D.; Gordon, D.; Barber, C. G.; Wood, A.; Middleton, D. S.; Blakemore, D. C.; Parsons, G. C.; Eastwood, R.; Platts, M. Y.; Statham, K.; Paradowski, K. A.; Burt, C.; Klute, W. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1084–1088. (b) Scribner, A.; Moore, J. A., III; Ouvry, G.; Fisher, M.; Wyvratt, M.; Biftu, T.; Leavitt, P.; Liberator, P.; Gurnett, A.; Brown, C.; Mathew, J.; Thompson, D.; Schmatz, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1517–1521. (c) Faust, M. R.; Hoesl, C. E.; Wanner, K. T. *Heterocycles* **2008**, *75*, 2981–2988. (d) Yager, K.; Chu, S.; Appelt, K.; Li, X. U.S. Patent 2005/54697, 2005.

Scheme 3. **Improved Synthesis of Compound 1**



Scheme 4. **Synthesis of compound 8 and compound 9 from compound 1**



zhydryl group of compound **1** was achieved by protonation of the heterocyclic nitrogen atom, followed by hydrogenolysis over 5% Pd on carbon in water−ethanol resulting in **9** in near quantitative yield (Scheme 4).[11,18]

Conclusion

We reported our efforts to develop relatively a high-yielding, high purity, improved and cost-effective synthesis for 1-benzhydrylazetidin-3-ol, **1**. The improved process for the preparation of **1** resulted in 80% yield and 99.3 area % purity by HPLC (any single maximum impurity: less than 0.5%) and was demonstrated at large scale.

Experimental Section

Benzhydrylamine and epichlorohydrin were obtained from commercial sources and used without further purification. All reagents and solvents employed were of commercial grade and were used as such, unless otherwise specified. Reaction flasks were oven-dried at 200 °C, flame-dried, and flushed with dry nitrogen prior to use. All moisture- and air-sensitive reactions were carried out under an atmosphere of dry nitrogen. Organic extracts were dried over anhydrous Na_2SO_4. Flash chromatography was performed using Kieselgel 60 brand silica gel (230−400 mesh). The melting points were determined in an open capillary tube using a Büchi B-540 melting point instrument and were uncorrected. The IR spectra were obtained on a Nicolet 380 FT-IR instrument (neat for liquids and as KBr pellets for solids). NMR spectra were recorded with a Varian 300 MHz Mercury Plus Spectrometer at 300 MHz (^{1}H) and at 75 MHz (^{13}C). Chemical shifts were given in ppm relative to trimethylsilane (TMS). Mass spectra were recorded on Waters quattro premier XE triple quadrupole spectrometer using either electron spray ionisation (ESI) or atmospheric pressure chemical ionization (APCI) technique.

1-Benzhydrylazetidin-3-ol (1). A 200-L glass-lined reactor was purged with nitrogen and charged with IPA (60 L) and benzhydrylamine **2** (12.0 kg, 65.5 mol). To this stirred solution, epichlorohydrin **3** (7.27 kg, 78.6 mol) was added over a period of 1 h, maintaining the batch temperature <30 °C. After the addition, the mixture was agitated for an additional 30 h at the same temperature (30 °C) and then sampled for HPLC analysis. HPLC typically indicated less than 1.0 area % of **2** remaining in the reaction mixture. At this point the majority of the IPA was removed by distillation at <45 °C under reduced pressure (80−100 Torr) to obtain the residue of 3-chloro-1-diphenylmethyl amino-2-hydroxypropane, **4a**. To this residue, acetonitrile (36 L) was added, and the suspension was cooled to 10−15 °C. Triethylamine (27.3 kg, 270 mol) was added slowly by maintaining the bath temperature <15 °C, and an exotherm to 3 °C occurred. At the end of the triethylamine addition, the reaction mixture temperature was raised to reflux, stirred for 100−105 h, and then sampled for HPLC analysis. HPLC indicated less than 1.0 area % of **4a** and **5a** followed by less than 0.5 area % of **6a** remaining in the reaction mixture. At this point the majority of the organic volatiles (acetonitrile and triethylamine) were removed by distillation at <50 °C under reduced pressure (80−100 Torr) to give crude compound **1** which was dissolved in methanol (36.0 L) at 30 °C. The product was precipitated by the addition of water (120.0 L) over 1 h while maintaining the temperature at 25−35 °C, and an exotherm to 5 °C occurred. During the water addition, the initial clear reaction mixture became cloudy and heterogeneous. After ∼2/3 of the water has been added, the product began to crystallize. The slurry was stirred for >5 h at 20−25 °C and was then filtered. The wet cake was washed with 24 L of water followed by 36 L of *n*-hexane. The wet cake was dried under vacuum at <50 °C (LOD = 0.5%). Compound **1** was obtained as a white solid in 80% yield, 12.54 kg, with an HPLC purity of 99.3 area % (SMI less than 0.5%). Mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.0 (br s, 1H), 2.8 (t, 2H), 3.5 (t,

(18) (a) Gobbini, M.; Armaroli, S.; Banfi, L.; Benicchio, A.; Carzana, G.; Fedrizzi, G.; Giubileo, M.; Marazzi, G.; Pozzi, M.; Scotti, P. E.; Torri, M.; Cerri, A.; Ferrari, P.; Giacalone, G.; Micheletti, R.; Moro, B. *J. Med. Chem.* **2008**, *51*, 4601–4608. (b) Falgueyret, J.-P.; Oballa, R. M.; Okamoto, O.; Wesolowski, G.; Aubin, Y.; Rydzewski, R. M.; Prasit, P.; Riendeau, D.; Rodan, S. B.; Percival, M. D. *J. Med. Chem.* **2001**, *44*, 94–104. (c) Rosenberg, S. H.; Spina, K. P.; Condon, S. L.; Polakowski, J.; Yao, Z.; Kovar, P.; Stein, H. H.; Cohen, J.; Barlow, J. L. *J. Med. Chem.* **1993**, *36*, 460–467. (d) Katritzky, A. R.; Cundy, D. J.; Chen, J. *J. Heterocycl. Chem.* **1994**, *31*, 271–276. (e) Alberto, C.; Giorgio, F.; Alessandra, B.; Giuseppe, B.; Patrizia, F.; Mauro, G.; Rosamaria, M.; Marco, P.; Enrico, S. P. PCT Int. Appl. WO/2007/118830, 2007.

2H), 4.3 (s, 2H), 4.5 (m, 1H), 7.1−7.2 (m, 2H), 7.2−7.3 (m, 4H), 7.4 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.6, 63.2, 78.3, 127.2, 127.3, 128.4, 141.5; IR (KBr): ν 701, 1050, 1168, 1161, 1348, 1450, 1491, 1595, 2850, 3087 cm^{-1}; ESI-MS: *m*/*z* 240.3 [$M^+ + 1$].

1-Benzhydrylazetidin-3-yl Methanesulfonate (8). To a stirred solution of 1-benzhydrylazetidin-3-ol **1** (100 g, 0.418 mol) in acetonitrile (300 mL), triethylamine (63.3 g, 0.626 mol) was added over 15 min, maintaining the batch temperature <30 °C. The suspension was cooled to −10 °C, and methanesulfonyl chloride (57.2 g, 0.5 mol) was added dropwise over 1 h, while maintaining the temperature at −5 °C. Reaction was stirred at −5 °C for 1 h and then sampled for HPLC analysis. HPLC indicated less than 1.0 area % of **1** remaining in the reaction mixture. Later, the product was precipitated by the addition of water (1 L), while maintaining the temperature at <5 °C. The slurry was stirred for 5 h at 20−25 °C and was then filtered. The wet cake was washed with an excess of water followed by 300 mL of IPA. The wet cake was dried under vacuum at <45 °C. Compound **8** was obtained as an off-white solid in 95% yield, 126 g, with an HPLC purity of 99.2 area %. Mp 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.9 (s, 3H), 3.2 (t, 2H), 3.6 (t, 2H), 4.4 (s, 1H), 5.1 (m, 1H), 7.1−7.2 (m, 2H), 7.2−7.3 (m, 4H), 7.4 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.9, 60.1, 67.9, 78.1, 127.2, 127.3, 128.5, 141.3; IR (KBr): ν 704, 862, 1175, 1360, 1453, 2843, 3028 cm^{-1}; ESI-MS: *m*/*z* 318.1 [$M^+ + 1$].

Azetidin-3-ol Hydrochloride (9). To a stirred solution of 1-benzhydrylazetidin-3-ol **1** (100 g, 0.418 mol) and dichloromethane (1 L), HCl gas was purged over a period of 30 min. The precipitated solids were filtered, and the wet cake was washed with an excess of dichloromethane. The wet solid was dried at <45 °C to give 114 g of hydrochloride salt of **1**. In a 2-L, one-neck, Parr bottle, the hydrochloride salt of **1** (114 g, 0.413 mol) was diluted with ethanol (900 mL) followed by water (100 mL) and charged with 5% Pd/C (5 g) and H_2 (50 psi). After 24 h at room temperature, the reaction was complete. The catalyst was filtered off and the filtrate concentrated to an oily solid. The crude product was slurried in ethyl acetate (250 mL) overnight and then filtered to give azetidin-3-ol hydrochloride (**9**) as a white crystalline solid in 96% yield over two steps, 43.8 g, with an HPLC purity of 99.3 area %. Mp 86−88 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.7 (m, 2H), 4.0 (m, 2H), 4.5 (m, 1H), 6.2 (br s, 1H, D_2O exchangable), 9.1 (br s, 2H, D_2O exchangable); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.0, 61.3; ESI-MS: *m*/*z* 74.1 [$M^+ + 1$].

***N*-((Oxiran-2-yl)methyl)diphenylmethanamine (5a).** To a stirred solution of 3-chloro-1-diphenylmethylamino-2-hydroxy propane, **4a** (10 g, 0.036 mol), in methanol (50 mL) was added sodium hydroxide (1.75 g, 0.044 mol) in methanol (10 mL) dropwise at <−5 °C. After the addition, the mixture was agitated for an additional 30 min at −5 to 0 °C and then sampled for TLC. Upon completion of **4a**, solvent (MeOH) was removed by distillation under reduced pressure at <40 °C. The obtained residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The phases were separated,and the aqueous phase was twice extracted with ethyl acetate (50 mL). The combined organic layers were washed with water (75 mL) and dried over anhydrous sodium sulfate; the solvent was removed by distillation under reduced pressure to give the crude **4a** which was purified by column chromatography, eluting with ethyl acetate/hexane (1:1) to give **5a** as colorless oily liquid in 75% yield, 6.5 g; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.6−2.7 (m, 2H), 2.7−2.8 (m, 1H), 2.9−3.0 (m, 1H), 3.1−3.2 (m, 1H), 4.8 (s, 1H), 7.18−7.22 (m, 2H); 7.26−7.32 (m, 4H); 7.39−7.42 (m, 4H); IR (neat): ν 701, 747, 1453, 1489, 1595, 2924 3056 cm^{-1}.

Bis Impurity (6b). To a stirred solution of benzhydrylamine (10 g, 0.055 mol) in IPA (75 mL) was added epichlorohydrin (12.63 g, 0.137 mol) at 30 °C over a period of 1 h, and then the reaction mixture temperature was raised to reflux, and the mixture was stirred for 24 h. After completion of the reaction, solvent (IPA) was removed by distillation under reduced pressure at <50 °C, and the obtained crude compound **6** was purified by column chromatography, eluting with ethyl acetate/hexane (1:1) to give **6** as a white solid in 45% yield, 9.0 g; Mp 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.7−2.9 (m, 4H), 3.3−3.5 (m, 6H), 3.7−3.8 (m, 2H), 5.0 (m, 1H), 7.2−7.4 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.4, 47.5, 55.2, 56.3, 69.0, 70.2, 71.1, 71.3, 127.3, 127.4, 127.5, 128.4, 128.5, 128.9, 129.0, 129.1, 139.8, 140.4, 141.0; IR (KBr): ν 471.5, 702.5, 744.2, 1023.9, 1069.5, 2875.5, 3355.3 cm^{-1}; ESI-MS: *m*/*z* 366 [$M^+ - 1$].

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Supporting Information Available

Characterization data of **1**, **4a**, **5a**, **8**, and **9** and HPLC chromatograms of **1, 8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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