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Kilogram Synthesis of a LFA-1/ICAM Inhibitor

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Abstract:

The process development and the kilogram-scale synthesis of BMS-587101 (1) are described. The synthesis features a [3 + 2] azomethine ylide cycloaddition to efficiently build the spirocyclic core in a diastereoselective fashion followed by a classical resolution which affords the desired enantiomer in >98% enantiomeric excess. The target was prepared in four steps in an overall yield of 22%.

Introduction

Interaction between leukocyte function-associated antigen-1 (LFA-1), expressed on the surface of cytokine-stimulated cells, and intercellular adhesion molecule (I-CAM), found on the surface of both leukocytes and endothelium, plays a key function in the intercellular immune response, causing T-cell adhesion and subsequent migration through the blood vessel wall to the inflamed area.[1] Small molecules which inhibit the LFA-1/I-CAM interaction are targeted as potential drugs for the treatment of a variety of autoimmune and inflammatory diseases such as rheumatoid arthritis and psoriasis.[2,3] The LFA-1 receptor antagonist, BMS-587101, **1**,[4,5] was selected for clinical development, and we required a synthesis that would reliably generate kilogram quantities of API. This paper details the identification and development of a synthesis which enabled the realization of this goal.

Results and Discussion

The original synthesis of **1** by our Discovery colleagues provided the multigram quantities required for preclinical development studies (Scheme 1).[4,5] This route featured a stereospecific [3 + 2] cycloaddition of olefin **3** with *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine to afford a single diastereomer of the spirocyclic core in a racemic fashion, with the olefin geometry establishing the relative stereochemistry of **4**. Deprotection of the resulting *N*-benzyl pyrrolidine afforded the racemic secondary amine **5**.[6] The desired single enantiomer was obtained by a chiral chromatographic separation using supercritical fluid chromatography (SFC). The final step in the synthesis was reductive amination with 5-formyl-3-thiophenecarboxylic acid.

In order to support the synthesis of kilogram quantities of API for clinical development, a shorter and more efficient route to **1** was desired. As shown in the retrosynthetic analysis (Figure 1) our strategy centered on retaining the powerful [3 + 2] cycloaddition approach to assemble the spirocyclic core and, at the same time, eliminating or minimizing the employment of protecting groups and chromatography. Ideally, the unprotected spirocyclic hydantoin **5** would be directly obtained by a

* Author for correspondence.

(1) For a discussion on the inhibition of LFA-1/ICAM-1as an approach to treating autoimmune diseases see: Yusuf-Makagiansar, H.; Anderson, M. E.; Yakovleva, T. V.; Murray, J. S.; Siahaan, T. *J. Medicinal Research Reviews* **2002**, *22*, 146.

(2) For a discussion of therapeutic options for treatment of psoriasis, see: Gottlieb, A. B. *J. Acad. Dermatol* **2005**, *53*, S3. Larson, R. S.; Davis, T.; Bologa, C.; Semenuk, G.; Vijayan, S.; Li, Y.; Oprea, T.; Chigaev, A.; Buranda, T.; Wagner, C. R.; Sklar, L. A.

(3) For other small molecule LFA-1/ICAM-1 antagonists as potential drugs please see: (a) Pei, Z.; Xin, Z.; Liu, G.; Li, Y.; Reilly, E. B.; Lubbers, N. L.; Huth, J. R.; Link, J. T.; von Geldern, T. W.; Cox, B. F.; Leitza, S.; Gao, Y.; Marsh, K. C.; DeVries, P.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 2913. (b) Liu, G.; Huth, J. R.; Olejniczak, E. T.; Mendoza, R.; DeVries, P.; Leitza, S.; Reilly, E. B.; Olasinski, G. F.; Fesik, S. W.; von Geldern, T. W. *J. Med. Chem.* **2001**, *44*, 1202. (c) Wu, J.-P.; Emeigh, J.; Gao, D. A.; Goldberg, D. R.; Kuzmich, D.; Miao, C.; Potocki, I.; Qian, K. C.; Sorcek, R. J.; Jeanfavre, D. D.; Kishimoto, K.; Mainolfi, E. A.; Nabozny, G.; Peng, C.; Reilly, P.; Rothlein, R.; Sellati, R. H.; Woska, J. R.; Chen, S.; Gunn, J. A.; O'Brien, D.; Norris, S. H.; Kelly, T. A. *J. Med. Chem.* **2004**, *47*, 5356. (d) Last-Barney, K.; Davidson, W.; Cardozo, M.; Frye, L. L.; Grygon, C. a.; Hopkins, J. L.; Jeanfavre, D. D.; Pav, S.; Qian, C.; Stevenson, J. M.; Tong, L.; Zindell, R.; Kelly, T. A. *J. Am. Chem. Soc.* **2001**, *123*, 5643. (e) Wang, G. T.; Wang, S.; Gentles, R.; Sowin, T.; Leitza, S.; Reilly, E. B.; von Geldern, T. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 195. (f) Wattanasin, S.; Albert, R.; Ehrhardt, C.; Roche, D.; Savio, M.; Hommel, U.; Welzenbach, K.; Weitz-Schmidt, G. *Bioorg. Med. Chem. Lett.* **2003**, *12*, 499.

(4) The Discovery work towards this target compound BMS-587101 is described in: Potin, D.; Launay, M.; Monatlik, F.; Malabre, P.; Fabreguettes, M.; Fouquet, A.; Maillet, M.; Nicolai, E.; Dorgeret, L.; Chevallier, F.; Besse, D.; Dufort, M.; Caussade, F.; Ahmad, S. Z.; Stetsko, D. K.; Skala, S.; Davis, P. M.; Balimane, P.; Patel, K.; Yang, Z.; Marathe, P.; Postelneck, J.; Townsend, R. M.; Goldfarb, V.; Sheriff, S.; Einspahr, H.; Kish, K.; Malley, M. F.; DiMarco, J. D.; Gougoutas, J. Z.; Kadiyala, P.; Cheney, D. L.; Tejwani, R. W.; Murphy, D. K.; Mcintyre, K. W.; Yang, X.; Chao, S.; Leith, L.; Xiao, Z.; Mathur, A.; Chen, B.-C.; Wu, D.-R.; Traeger, S. C.; McKinnon, M.; Barrish, J. C.; Robl, J. A.; Iwanowicz, E. J.; Suchard, S. J.; Dhar, M. T. G. *J. Med. Chem.* **2006**, *49*, 6946.

(5) For additional information related to this compound see: (a) Chen, B.-C.; DelMonte, A. J.; Dhar, T. G. M.; Fan, Y.; Gougoutas, J. Z.; Malley, M. F.; McLeod, D. D.; Waltermire, R.; Wei, C. Crystalline Forms and Process for Preparing Spiro-Hydantoin Compounds. (Bristol-Myers Squibb). U.S. Patent 7,381,737 B2 . (b) Dhar, T. G. M.; Potin, D.; Maillet, M.; Launay, M.; Nicolai, E.; Iwanowicz, E. Spirocyclic compounds useful as anti-inflammatory agents. Bristol-Myers Squibb and Cerep). U.S. Patent 7,199,125 B2. (c) Launay, M.; Potin, D.; Maillet, M.; Nicolai, E.; Dhar, T. G. M.; Iwanowicz, E. Hydantoin compounds useful as anti-inflammatory agents. (Bristol-Myers Squibb). U.S. Patent 6,710,064 B2. For the radiolabelled synthesis of BMS-587101 see: Tran, S. B.; Maxwell, B. D.; Chen, S.-Y.; Bonacorsi, S. J.; Leith, L.; Ogan, M.; Rinehart, J. K.; Balasubramanian, B. *J. Labelled Compd. Radiopharm.* **2009**, *52*, 236.

(6) While effective at removing the benzyl group, avoiding the use of 1-chloroethyl chloroformate in dichloroethane was highly desirable since use of these reagents would raise concerns about genotoxic impurity formation.

(7) Throughout this paper when the molecule is a racemic mixture of a single diastereomer, solid and dashed rectangular bonds are used to convey relative stereochemistry. When the compound is a single enantiomer, solid and dashed wedged bonds are used to convey absolute stereochemistry.

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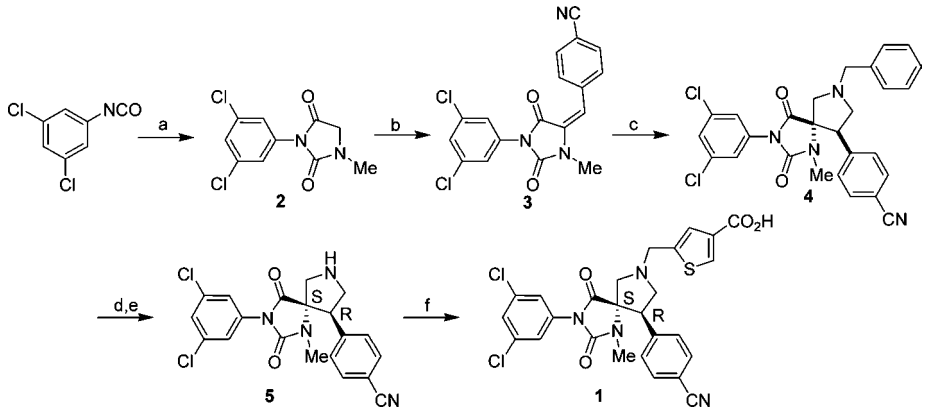
Scheme 1. **Discovery synthesis of 1**[a]



[a] Reagents and conditions: (a) Sarcosine ethyl ester, NaOH, THF/H_2O, 96%; (b) 4-cyanobenzaldehyde, β-alanine, AcOH, reflux, 35% or 4-cyanobenzaldehyde, pyrrolidine/EtOH, 78 °C 18 h, 85%; (c) *N*-(methoxymethyl)-*N*(trimethylsilylmethyl)benzylamine, THF, TFA, 0 °C to RT, 18 h, MeOH, reflux, 2 h, 50−85%;[7] (d) 1,2-dichloroethane, 1-chloroethyl chloroformate, 5 °C, to rt, 18 h, MeOH, reflux, 3 h, 50−85%; (e) Chiralpak-AD column, CO_2/MeOH, ∼100% desired enantiomer; (f) 5-formyl-3-thiophenecarboxylic acid, $Na(OAc)_3BH$, Na_2SO_4, 1,2-dichloroethane, 75−90%.

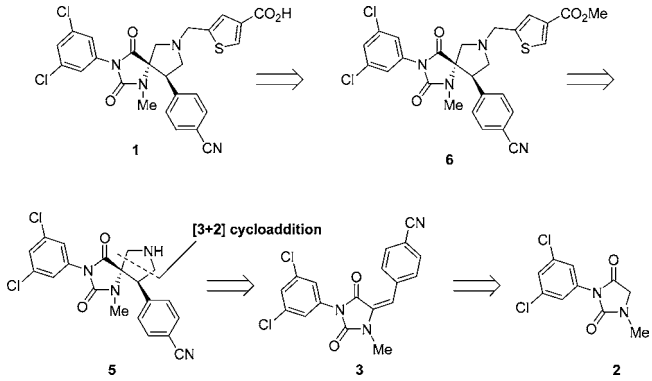
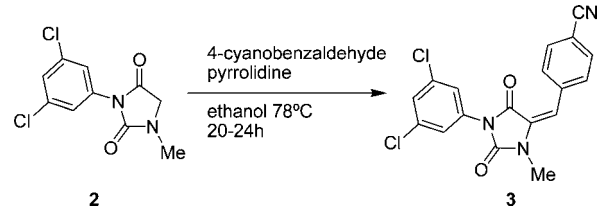


Figure 1. **Retrosynthetic analysis of 1.**

[3 + 2] cycloaddition of olefin **3** with a simple azomethine ylide derived from glycine.[8] The identification and development of an efficient chemical resolution of **5** using a chiral acid was critical to the success of this approach. We also felt it would be advantageous to introduce the thiophene intermediate at the penultimate step of the synthesis as this would provide an additional opportunity to remove structurally related thiophene-derived impurities.[9] Having a simple saponification as the final step was also an attractive feature of this synthetic approach from an impurity control perspective.

Preparation of Olefin (3). Generation of **3** with high stereoisomeric purity was an important objective during the development of this reaction as only the *E*-stereoisomer affords the desired diastereomer in the subsequent cycloaddition. Our Discovery colleagues had previously demonstrated that the

Scheme 2. **Synthesis of olefin 3**



choice of base and solvent had a strong influence on the *E*:*Z* preference and had selected pyrrolidine as the base and ethanol as the solvent.[4] We conducted a solvent screen and the results confirmed ethanol was the optimal solvent as the *E*-stereoisomer was extremely insoluble producing isolated **3** in high recovery and stereoselectivity (>100:1 *E*:*Z*).[10] The condensation of 4-cyanobenzaldehyde with the commercially available hydantoin **2** (Scheme 2) was initially conducted at 13 mL/g[11] in ethanol; however, a very thick paste typically formed and adequate mixing was not consistently achieved. By diluting to 17 mL/g and controlling the onset of crystallization with a timely addition of seeds,[12] mixing was improved dramatically. This procedure was demonstrated multiple times at kilogram scale and gave excellent yield, reproducibility and purity (84.6 kg of **3**, 83.9% average yield and >99.9 HPLC area % purity).

Azomethine Ylide Cycloaddition To Afford Spirocyclic Hydantoin 5. As mentioned above, we felt it important to develop a [3 + 2] cycloaddition process that directly generated spirocycle **5**, without the need for a deprotection step as performed in the original synthesis. In this vein, examples of direct [3 + 2] azomethine ylide cycloadditions utilizing glycine

(8) An asymmetric cycloaddition would have presented a preferred approach, and we carefully considered this option. Unfortunately, in reviewing the known systems, we found none that were easily adaptable to our system as they would all form a pyrrolidine product with a substitution pattern that would require substantial functional group transformations to afford our target molecule. For a review of asymmetric azomethine ylide [3 + 2] cycloadditions, please see: Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231.

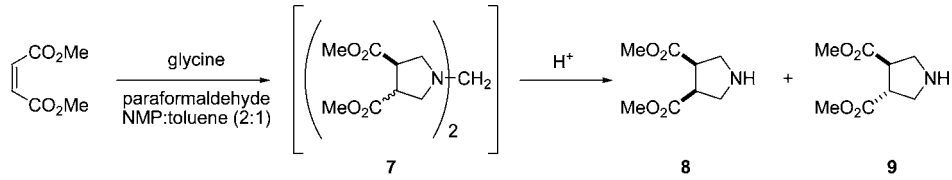
(9) There were no specific thiophene derived impurities of concern. Incorporation of the thiophene as an ester was implemented proactively as a conservative approach to minimize the potential for an impurity to be introduced into the API step.

(10) Solvents and bases screened included IPAC, EtOAc, MTBE, 1-BuOH, IPA, THF, *t*-BuOH, MeOH, EtOH, toluene, DMSO, NMP, acetone and Et_3N, 2,6-lutidine. Of these, EtOH was deemed superior as the alternative conditions suffered from either poor reaction conversion, high levels of impurities, or stirring issues.

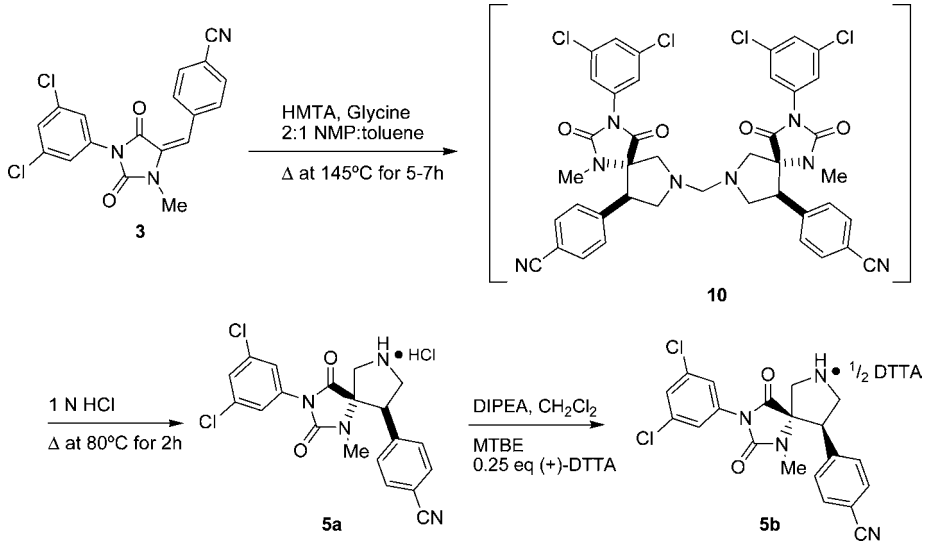
(11) mL/g refers to mL of solvent/g of substrate.

(12) The optimal seeding point was determined via lab experiments. Seeding prior to the reaction was unsuccessful as the initial mixture was not yet saturated with product and the seeds simply dissolved.

Scheme 3. **[3 + 2] cycloaddition under modified Tsuge conditions**



Scheme 4. **Synthesis of resolved spirocyclic hydantoin 5b**

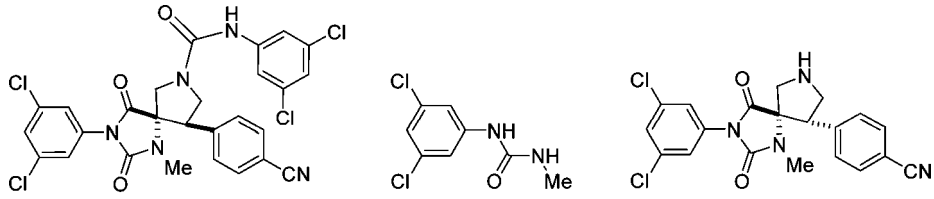


and paraformaldehyde are known.[13] Our initial investigations of this cycloaddition with a model substrate, dimethyl maleate, were conducted in toluene following the experimental procedures of Tsuge.[9] While the Tsuge conditions afforded the desired *cis*-disubstituted pyrrolidine product **8**, it quickly became apparent that this chemistry was very challenging. Obtaining consistent conversions was problematic, and we attributed this to the heterogeneous nature of the reaction in toluene or xylenes. Upon further evaluation of the reported Tsuge reaction conditions, we found it interesting that almost all examples were performed in toluene with the sole exception being a reaction that was conducted in DMF. We were intrigued as to why the heterogeneous toluene conditions were chosen over the homogeneous DMF conditions for the majority of the substrates. We repeated the cycloaddition in a mixture of 2:1 *N*-methylpyrrolidinone (NMP)/toluene which, similarly to DMF, afforded a nearly homogeneous reaction. While we were pleased to discover the NMP/toluene conditions did provide consistent reaction conversions, this modified system afforded primarily the undesired *trans*-pyrrolidine **9** (Scheme 3). It was apparent that lack of stereospecificity could make this homogeneous system impractical for systems with olefin substrates susceptible to isomerization or pyrrolidine products susceptible to epimerization. These potential liabilities would have to be considered when investigating our substrate. It should also be noted that, regardless of the solvent system utilized, the initial products afforded were *N*-methylene-bridged dimers **7** which required cleavage.[14] In order to apply this direct [3 + 2] azomethine ylide cycloaddition chemistry to the substrate of interest, control of olefin isomerization and product epimerization as well as an efficient cleavage of the *N*-methylene-bridged dimer would be required.

Initial azomethine ylide cycloadditions of **3** in toluene were heterogeneous and, as predicted from our experience with the dimethyl maleate substrate, suffered from inconsistent reaction conversions and thus poor yields. However, cycloadditions of **3** which were conducted in 2:1 mixtures of NMP/toluene with paraformaldehyde did provide consistent reaction conversion. Isomerisation of the olefin **3** or epimerization of the [3 + 2] cycloaddition adduct would have negated this synthetic approach; thus, we were very pleased to observe that after acidic hydrolysis of the initial *N*-methylene-bridged dimer **10**[15] (Scheme 4) we found almost exclusively the desired diastereomer.[16] We evaluated other formaldehyde sources and replaced paraformaldehyde with the more soluble hexamethylenetetramine (HMTA).[17] The reaction could be performed at temperatures as low as 100 °C, but much cleaner purity profiles and faster rates were obtained at higher temperatures (140−145 °C). It was also imperative to cool the reaction mixture once full conversion to product was attained since prolonged heating dramatically increased impurity levels.[18] Impurities that were identified (Figure 2) include 3,5-dichloroaniline, the mixed ureas **11**, and minor amounts of the diastereomer **13** which results

(13) (a) Mortier, J.; Joucla, M. *J. Chem. Soc., Chem. Commun.* **1985**, *22*, 1566. (b) Borsato, G.; Della Negra, F.; Gasparrini, F.; Misiti, D.; Lucchini, V.; Possamai, G.; Villani, C.; Zambon, A. *J. Org. Chem.* **2004**, *69*, 5785. (c) Joucla, M.; Mortier, J. *Bull. Soc. Chim. Fr.* **1988**, *3*, 579. (d) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Chem. Soc. Jpn.* **1987**, *60*, 4079. (e) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Chem. Lett.* **1986**, *6*, 973. (f) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, S.; Takenaka, S.; Ueno, K. *Chem. Lett.* **1987**, *60*, 4067.

(14) The currently accepted mechanism suggests the azomethine ylide precursor is the methylene-bridged dimer 3,3′-methylenedioxazolidin-5-one.



11 **12** **13**

Figure 2. **Impurities formed in the [3 + 2] cycloaddition reaction.**

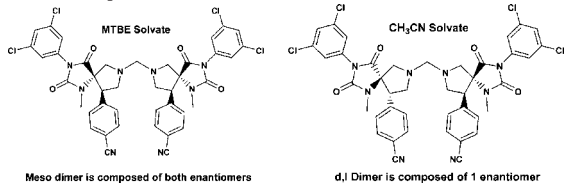
from epimerization of the desired compound **5** during prolonged aging under the basic reaction conditions.[19]

Interestingly, during the course of the reaction a water-soluble, white solid slowly collected in the condenser. This was a concern as a potential safety liability should the condenser become completely occluded.[20] Analysis indicated this solid was not paraformaldehyde as we first postulated but rather ammonium carbamate, resulting from condensation between the liberated CO_2 and ammonia. We rationalized that incorporation of a nitrogen sweep would aid in dilution of these gases, thus minimizing accumulation of the solid. We were pleased to observe this modification not only substantially decreased the amount of ammonium carbamate collected but also favorably impacted the reproducibility of the reaction rate. Early in our development efforts, reaction times were highly variable and ranged from 7 to 20 h. However, after incorporation of a vigorous nitrogen sweep, the reaction was consistently complete in 4−6 h.[21] As expected, the initial product from the [3 + 2] cycloaddition is the *N*-methylene-bridged dimer **10**. Because the [3 + 2] cycloaddition is achiral and both enantiomers of the spirocycle are produced, **10** can, in principle, be generated as either a single enantiomer (DL, not shown) or *meso*-compound.[15] Monitoring levels of this intermediate was challenging as **10** was not directly detectable by reverse phase HPLC due to hydrolytic instability and was observed as a broad peak under normal phase HPLC conditions. However, we found that levels of **10** could be monitored indirectly by treating a sample of the crude reaction mixture with sodium triacetoxyborohydride (STAB) which converts **10** to a mixture of the desired, spirocyclic hydantoin **5** and the corresponding N-methylated spirocyclic hydantoin, both detectable by reverse phase HPLC. React-IR was ultimately demonstrated to be an effective approach for monitoring the presence and consumption of the N-methylene bridged dimer.[22]

The procedure initially developed and implemented on multikilogram scale employed an acidic workup to break the *N*-methylene-bridged dimer which enabled isolation of **5** as a racemic HCl salt **5a**. Although effective, one unappealing feature of this approach, which we needed to address for subsequent campaigns, was the slow rates of filtration and washing of the resulting HCl salt (12 h on 42 kg scale). The successful implementation of this process was demonstrated on three batches at kilogram scale and afforded good yields and purities (41.8 kg of **3**, 77.1% average yield, and 98.6−99.4 HPLC area % purity).

Diastereomeric Salt Resolution of 5. A key objective in the design of the synthetic process was to identify a diastereomeric salt resolution to avoid the need for large scale

(15) Although the [3 + 2] cycloaddition product is primarily a single diastereomer, the initial product is a mixture of D,L- and *meso*-methylene-bridged dimer as shown below. Each was isolated as a single crystal solvate form, and X-ray structures were determined. Full crystallographic data sets have been deposited to the Cambridge Crystallographic Data Center (CCDC reference numbers 756962 and 756963). Copies of the data can be obtained free of charge via the internet at http://www.ccdc.cam.ac.uk.



(16) During the course of the development work a full set of control experiments were run prior to scale-up. No isomerization of the starting material **3** was observed under the reaction conditions. The product **5a**, however, was found to be susceptable to base-catalyzed epimerization and equilibrium between **5a** and **13** could be readily achieved by treatment with DBU. Additional evidence of base-catalyzed epimerization of the benzylic center was obtained during stress tests of the hydrolysis reaction in which diastereomer was formed at pH ∼14 in THF/alcohol mixtures.

(17) During the development of the [3 + 2] cyclopropanation, both the HMTA and glycine equivalents were optimized with the highest in-process yield resulting from 2.0 equiv of glycine and 0.7 equiv of HMTA. However, in an attempt to minimize build-up of ammonium carbonate in the condenser and epimerization of product (see ref 16) as well as increase the ease in developing a telescoped reaction, ultimately 1.9 equiv of glycine and 0.33 equiv of HMTA were utilized. Our initial attempts at scaling up paraformaldehyde conditions indicated that a portionwise addition was required on ∼10−100 g scale to achieve a reasonable yield. The same protocol when implemented on a 1−5 kg scale afforded substantially decreased yields. The yield significantly improved when HMTA was utilized and there was no requirement to add in small portions to achieve reproducibility on small or large scale.

(18) When the isolated spirocyclic hydantoin **5a** was resubjected to the reaction conditions for 8h at 140 °C, only 62% of **5a** was recovered. Diastereomer **13** was present in 12%, 3,5-dichloroaniline in 4% and mixed urea **11** in 2%. Under the same conditions without HMTA present, 92% of **5a** was recovered.

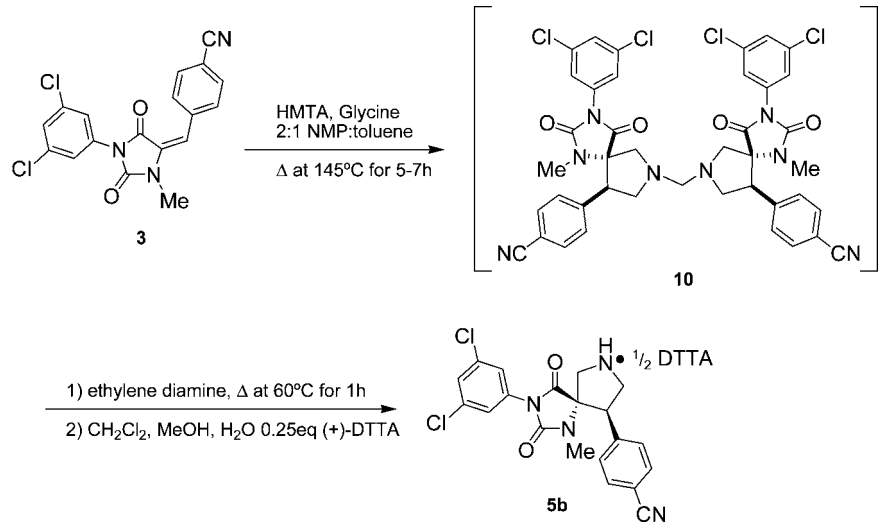
(19) All impurities were identified by either NMR or MS and were either isolated from the reaction mixture or synthesized independently.

(20) Prior to scale-up, a full safety evaluation was performed including reaction calorimetry, measurement of off-gassing and dust-explosivity testing. Although CO_2 and ammonia are released during the reaction conditions, no foaming or frothing was observed. However, a control experiment in which a large excess of ammonium carbamate (2 g) was initially added to the reaction mixture (10 g of starting material **3**) did result in vigorous off-gassing as the reaction temperature reached 90−100 °C during the heat-up to 130 °C, further emphasizing the need to avoid the accumulation of this solid in the condenser. The excess ammonium carbamate had no effect on the reaction conversion.

(21) We postulate that incorporation of a nitrogen sweep reduces the concentration of ammonia in the reaction mixture. This has a positive impact on the reaction rate because high levels of ammonia lead to reformation of HMTA as opposed to the desired formation of the azomethine ylide precursor (3,3′-methylenedioxazolidin-5-one). While one could easily envision a loss of solvent under refluxing conditions with a nitrogen sweep, we found that a properly functioning condenser kept losses to a minimum.

(22) For React-IR data please see the Supporting Information.

Scheme 5. **Telescoped cyclization/resolution for the direct preparation of 5b**



chromatographic separation of the enantiomers. Our initial salt screens were conducted utilizing free base generated *in situ* by addition of diisopropylethylamine (DIPEA) to **5a**. Our first salt screen identified (*S*)-(+)-camphorsulfonic acid (CSA) as a promising candidate for resolution in methylethyl ketone (MEK). In initial laboratory experiments, effective resolution was observed with ee >95%. However, when slurries of the CSA salt were held for extended periods, the enantiomeric excess (ee) eroded and it became obvious that the CSA salt was not suitable for kilogram-scale synthesis. Fortunately, studies with a second lead from our screening efforts, (+)-di-*p*-toluyl-D-tartaric acid ((+)-DTTA) in CH_2Cl_2 were more successful. We found that resolution of **5** as its hemi-(+)-DTTA salt **5b** also afforded enantiomeric excess of >95%. Fortunately, **5b** was found to be thermodynamically stable and not subject to the same deterioration of ee as observed with the CSA salt upon aging of the crystallization slurry. The successful implementation of this process was demonstrated in two batches on kilogram scale and gave excellent yields and purities (48.1 kg of **5b**, 30.6% average yield, 98.1−99.2% ee and 98.5−98.6 HPLC area % purity). The overall yield from **3** was 23.6%.

Direct Preparation of Chiral Spirocyclic Hydantoin 5b from 3. Although the two-step process for producing **5b** was effective, the slow filtration of **5a** and the low overall yield of **5b** (23.6%) suggested a telescoped procedure, which avoided isolation of the HCl salt, could increase the overall efficiency of this process. A crucial component of a telescoped process is the efficient cleavage of the *N*-methylene-bridged dimer **10**. We were pleased to observe **10** was readily cleaved in the crude reaction mixture by treatment with ethylene diamine at 50 °C for 2 h. A one-pot process was demonstrated by subjecting the resulting solution containing monomeric racemic pyrrolidine to an extractive workup, solvent swap into methylene chloride, and treatment with (+)-DTTA. The earliest attempts to develop this process proved challenging since the ee's and yields were highly variable. However, a critical observation was made during the laboratory development studies that imparted consistency and robustness to the resolution process. Reactions which were azeotropically distilled with MeOH and contained residual methanol in the crystallization matrix consistently yielded material of very high purity and enantiopurity.[23] It was subsequently determined that MeOH (0.5−1 mL/g) was required to achieve a robust resolution that reliably produced high quality (purity and ee) **5b** with consistent yield. On scale, the MeOH content was adjusted to the desired stoichiometry immediately prior to the crystallization. In addition, the introduction of one equivalent of water was also shown to be advantageous as it also facilitated the formation of crystals with high enantiopurity **5b** (>98% ee).[24] Using these optimized conditions, the process was extremely tolerant of excess (+)-DTTA so stoichiometry adjustments were not required based on in-process yield of **5**. The successful implementation of this process (Scheme 5) was demonstrated on kilogram scale and gave excellent yield and purity (33.2 kg of **5b**, 32.2% yield, 98.7% ee and 99.9 HPLC area % purity). Interestingly, in the original process when the HCl salt **5a** was isolated, thus affording higher purity input material for the resolution, the addition of MeOH and water were not required.

Preparation of the Penultimate Intermediate 6. Reductive amination (Scheme 6) was utilized to effect the convergent coupling of **5b** and the methyl ester-protected thiophenecarboxaldehyde **14**. To obtain a homogeneous solution, a suspension of **14** and **5b** in THF was treated with triethylamine and acetic acid. The resulting solution was then treated with 4 equal portions of STAB over 2 h.[25] After addition of MTBE, three extractions, one back extraction, and a subsequent solvent swap to isopropanol, the desired product was isolated as the HCl salt, **6**. It is interesting to note that no enhancement of the enantio-

(23) During the development work, a MeOH azeotropic distillation was investigated to aid in removal of toluene. Ultimately an alternative procedure which did not involve an MeOH distillation was developed and optimized for scale-up.

(24) The expected water content for a monohydrate is 2.87%. While combustion analysis of the initial sample characterized from the non-telescoped process indicates a hemi-hydrate, when a variety of developmental samples were analyzed, the KF ranged from 1.1 to 5.5%. This may indicate that while a hemi-hydrate is achievable, it is possible to easily over-dry or under-dry the isolated solid. It may also suggest that alternative forms are available or that the isolated product is hygroscopic.

(25) It should be noted that no significant exotherm was observed; however, low levels of hydrogen off-gassing were evident during the STAB additions.

Scheme 6. **Reductive amination of 5b**

meric purity was observed during the crystallization. Further process development successfully reduced the workup protocol to only one sodium bicarbonate wash with no sacrifice to yield or purity. This process was demonstrated on eight batches at kilogram scale and gave excellent yields and purities (22.9 kg of **5b**, 89.8% average yield, 97.8−98.9% ee and 99.1−99.5 HPLC area % purity).

Two-Step Preparation of BMS-587101 (1). Our initial synthetic strategy intentionally incorporated a simple hydrolysis as the final step to facilitate impurity control. However, deprotection of **6** was more challenging than initially anticipated since impurities resulting from hydration of the nitrile (**15**) or hydrolysis of the hydantoin core (**16**) were readily formed (Figure 3). Screening a variety of reagents, solvents, and reaction conditions indicated that a low-temperature (10 °C) hydrolysis in THF with KOH effectively controlled the level of impurity formation; however, the rate of reaction was extremely slow. We were pleased to observe that the addition of 2 equiv of 1,2-propanediol accelerated the hydrolysis reaction. We postulate this rate acceleration is via transesterification with 1,2-propanediol to initially form **17** and **18** which provide intramolecular anchimeric assistance in the ester hydrolysis.[26] A concern with using this approach was the presence of residual **17** and **18**. Fortunately, these impurities were observed in very low levels and were easily removed via the crystallization process as was the methyl ester starting material.

The isolation of the active pharmaceutical ingredient (**1**) was complicated by a propensity to form solvates with a broad diversity of solvents. This property was strategically employed to better control purity levels in our initial process. Specifically, we developed a two-drop process, in which THF solvate **1a** was first isolated. Dissolution of **1a** in an 95:5 isopropyl acetate/H_2O mixture and subsequent azeotropic distillation resulted in crystallization of **1** (Scheme 7).[27] This approach afforded two opportunities to provide purity enhancement with the final crystallization used to control the crystalline form. In order to achieve the desired particle size (d_{90} < 66 μm) wet milling was performed post-distillation. This process was successfully performed on three batches at kilogram scale and provided **1a** of excellent quality (25.0 kg of **6**, 89.6% average yield and 98.7−99.2 HPLC area % purity, and 90.5−92.9 area weight % purity). The three THF solvate **1a** batches were converted to **1** in good yield and excellent quality (80.9% average yield, d_{90} < 60 μm, 99.7−99.9 HPLC area % purity, and 99.5 area weight % purity). The overall yield of **1** from **6** was 72.5%.

One-Step Preparation of BMS-587101 (1). The obvious potential efficiency gains of a one-drop process dictated exploration of alternative crystallization protocols. A key procedural step which enabled the one-step process was a heptane extraction immediately after the hydrolysis of **6** was complete. This heptane extraction proved to be effective in removing ester impurities such as **6**, **17**, and **18**. Substitution of acetic acid with citric acid, for acidification after the saponification, was also implemented to address odor concerns. A solvent swap into isopropyl acetate after the hydrolysis in THF allowed for direct crystallization of **1**. In addition to an improved yield over the two-drop process (90% versus 72%), the cycle time was significantly reduced (68 h versus 135 h). To further reduce cycle time, simultaneous wet milling during the distillative crystallization was demonstrated in the final batch with no impact to purity or particle size. This process was demonstrated on kilogram scale (six batches) and gave excellent yield and purity (232.3 kg of **1**, 90% average yield, d_{90} < 60 μm, and >99.3 HPLC area % purity).

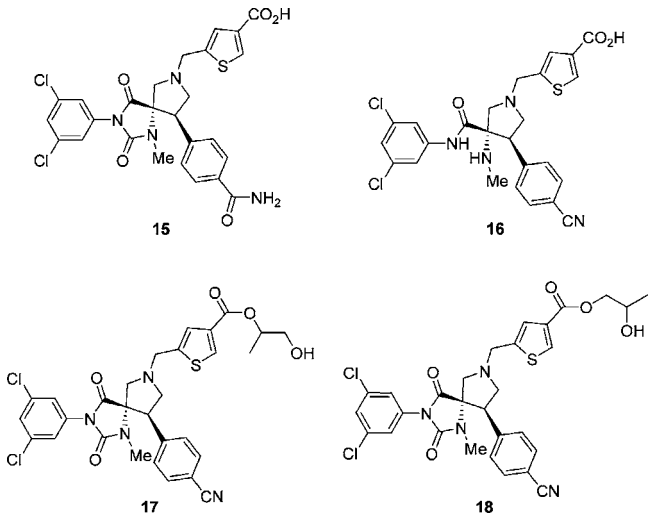


Figure 3. **Impurities formed in the API step.**

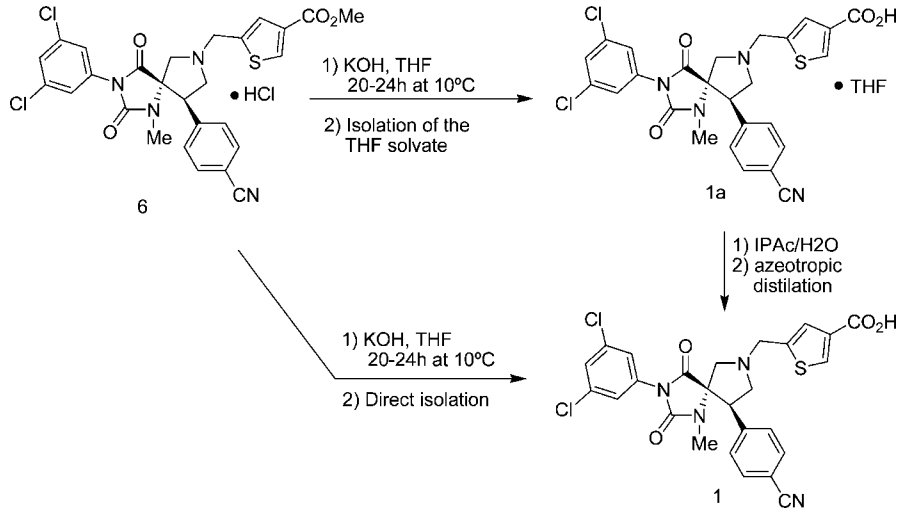
Conclusions

In summary, we have described an efficient, four-step synthesis of BMS-587101 (**1**) from commercially available hydantoin **2** as shown in Scheme 8. All key intermediates were crystalline, and no exotic processing equipment was required, providing versatility in future manufacturing site selection. The

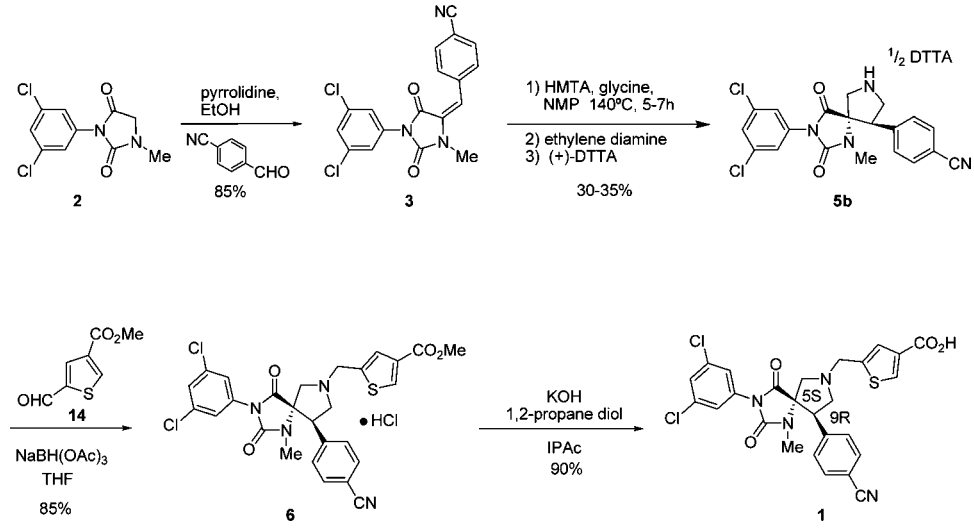
(26) For literature precedent see: (a) Balakrishnan, M.; Rao, G. V.; Venkatasubramanian, N. *Tetrahedron Lett.* **1972**, *45*, 4617. (b) In side-by-side reactions at 7 °C, in 21 h the conversions for the reactions with the 1,2-propanediol and without any additives were 84.6% and 57.2%, respectively.

(27) After a thorough screen, isopropyl acetate was identified as one of the few solvents which did not form solvates with **1**. However, in order to develop a practical procedure, the low solubility of **1a** in isopropyl acetate would need to be addressed. It was determined that low levels of water significantly increased **1a** solubility in isopropyl acetate. Solubility data: Compounds **1** and **1a** in isopropyl acetate with low water content (KF = 0.023%) have a solubility of 2.2 wt %. Compounds **1** and **1a** in isopropyl acetate with 1.2 wt % water have a solubility of 3.6 wt %.

Scheme 7. **Two-drop and one-drop preparation of 1 from 6**



Scheme 8. **Efficient four-step synthesis of 1 (BMS-587101)**



use of glycine and HMTA in the [3 + 2] azomethine ylide cycloaddition provides quick and direct access to spirocycle **5**. In addition, an efficient telescoped resolution with (+)-DTTA was developed for the direct conversion of **3** to **5b** which circumvented the isolation the racemic HCl salt **5a**, increased yields, and reduced processing time. The overall process has been demonstrated on multikilogram scale and is amenable for commercial-scale manufacture.

Experimental Section

All reactions were performed under a nitrogen atmosphere. All reagents purchased from vendors were used as received unless otherwise indicated. Chiral analysis was conducted on a Shimadzu HPLC with a Chiracel AD or AD-H column unless stated otherwise. Proton and Carbon NMR were run on a Bruker AC-300 at 300 MHz for proton and 75 MHz for carbon or on a Bruker AVANCE 400 at 400 MHz for proton and 100 MHz for carbon. The melting points were obtained with a Mettler-Toledo FP 62 melting point instrument by measurement of the change of luminous intensity during the melting process. Reported yields have not been corrected for impurity levels or moisture content.

Preparation of (*E*)-4-((1-(3,5-Dichlorophenyl)-3-methyl-2,5-dioxoimidazolidin-4-ylidene)methyl)benzonitrile (3). A mixture of **2** (69.0 kg, 266.3 mol) and 4-cyanobenzaldehyde (52.8 kg, 402.5 mol) was heated in EtOH (980 kg) to 60 °C. Pyrrolidine (19 kg, 267.2 mol) and an ethanol line rinse (4.0 kg) were charged. The mixture was held at 65 °C, and after 0.5 h seeds (259 g) were charged. The mixture was then heated at reflux for 16 h. The slurry was cooled to 55 °C and diluted with THF (305 kg) to afford a more readily stirrable solution. The mixture was then cooled to 45 °C. Ethanol was charged (50 kg), and then the slurry was cooled over 2−3 h to 20 °C and filtered. The cake was washed with ethanol (220 kg), and upon drying, **3** was obtained as a fluffy, yellowish crystalline solid (84.6 kg of **3**, 85.4% yield, and >99.9 HPLC area % impurity). Mp = 239−241 °C. ^{1}H NMR (DMSO-,d_6): 8.07 (2H, d, J = 8.3 Hz), 7.86 (2H, d, J = 8.4 Hz), 7.72 (1H, m), 7.59 (2H, m), 6.72 (1H, s), 3.35 (3H, s). ^{13}C NMR (DMSO-,d_6): (159.80, 151.48, 137.64, 133.83, 133.70, 131.80, 130.80, 130.68, 127.71, 125.51, 118.83, 114.48, 110.32, 26.72). Anal. Calcd for $C_{18}H_{11}Cl_2N_3O_2$: C, 58.08; H, 2.97; N, 11.29; Cl, 19.05. Found: C, 58.14; H, 2.72; N, 11.14; Cl, 19.15.

Preparation of 4-[(5S*,9R*)-3-(3,5-Dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-9-yl]-benzonitrile hydrochloride salt (5a). A mixture of **3** (41.8 kg, 112.3 mol), glycine (21.5 kg, 286.4 mol) and hexamethylenetetramine (12.0 kg, 85.6 mol) in 1-methyl-2-pyrrolidinone (222 kg) and toluene (92.0 kg) was heated at 140 °C for 10 h. Upon reaction completion (<1% **3** remaining), the mixture was cooled to 20 °C and polish filtered. The filtrate was heated to 70 °C and 1 M HCl (580 kg) was charged (to extract the basic product into the aqueous layer). The resulting biphasic mixture was stirred for 10−15 min. Agitation was halted and the phases were separated. The organic phase was washed with 1 M HCl (72 kg) at 65 °C. The aqueous phases were combined and were stirred at 80 °C for 2 h. The solution was cooled to 50 °C and seeded with **5a** (200 g) followed by slow cooling to 15 °C with gentle stirring. The resulting suspension was held at 15 °C for 4 h with no agitation and then filtered. The filter cake was washed with 1 M HCl (2 × 110 kg) and reslurried in 250 kg water at 100 °C for 0.5 h. The mixture was cooled to 85 °C and seeded with **5a** (200 g). The mixture was cooled to 5 °C over 16 h with low agitation and the slurry was filtered. The slurry was washed with water (2 × 17.5 kg) and dried under vacuum at 35 °C. Spirocyclic hydantoin **5a** was obtained as a beige crystalline solid (41.5 kg of **5a**, 82.6% yield, and 98.6 HPLC area % purity). Mp = 183−185 °C. ^{1}H NMR (DMSO-d_6): 7.87(2H, d, J = 8.1 Hz), 7.61 (1H, m), 7.40 (2H, d, J = 8.1 Hz), 6.68 (2H, m), 4.17 (1H, m), 3.85 (2H, m), 3.76 (2H, m), 3.43 (3H, s), 3.24(2H, s). ^{13}C NMR (DMSO-d_6): (170.84, 152.92, 137.35, 133.94, 132.87, 132.35, 128.01, 124.50, 118.12, 111.30, 71.42, 46.57, 45.11, 25.51). Anal. Calcd for $C_{20}H_{17}Cl_3N_4O_2$ + 1.3 H_2O: C, 50.51; H, 3.91; N, 11.79; Cl, 22.39. Found: C, 50.56; H, 3.86; N, 11.58; Cl, 21.98; KF, 5.12.

Preparation of 4-[(5*S*,9*R*)-3-(3,5-Dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-9-yl]-benzonitrile Semi (+)-DTTA Salt (5b). To a suspension of **5a** (50.0 kg, 120.4 mol) in dichloromethane (650 kg) was added diisopropylethylamine (17.4 kg, 134.6 mol). The mixture was stirred until a clear solution formed, to which (+)-Di-*p*-toluoyl-D-tartaric acid (10.5 kg, 27.2 mol) was added. The resulting solution was heated to 35 °C and seeded with **5b** (200 g). The mixture was held for 30 min and cooled to 20 °C over 2 h. MTBE (175 kg) was added over 0.5 h. The suspension was stirred at 20 °C for 5 h and filtered. The filter cake was washed with dichloromethane (27 kg)/MTBE (8 kg), followed by an MTBE wash (22 kg). The solid was dried at 40 °C. The resolved spirocyclic hydantoin **5b** was obtained as a white crystalline solid (29.7 kg of **5b**, 33.1% yield, 98.6 HPLC area % purity, and 98.1% ee). Mp = 175−177 °C. ^{1}H NMR (DMSO-d_6): 7.86 (2H, d, J = 8.1 Hz), 7.81 (2H, d, J = 8.3 Hz), 7.61 (1H, m), 7.28 (2H, d, J = 8.1 Hz), 7.22 (2H, 8.5 Hz), 6.68 (2H, m), 5.71 (1H, s), 3.81(1H, m), 3.50 (4H, m), 3.06 (3H, s), 2.34 (3H, s). ^{13}C NMR (DMSO-d_6): (171.45, 169.40, 165.04, 152.88, 143.61, 138.99, 133.88, 133.08, 132.16, 129.26, 129.20, 128.76, 127.84, 126.99, 124.51, 118.25, 110.78, 72.81, 73.38, 48.15, 47.51, 46.30, 24.90, 21.14). Anal. Calcd for $C_{30}H_{25}Cl_2N_4O_6$ + 0.5 H_2O: C, 58.40; H, 4.17; N, 9.08; Cl, 11.49. Found: C, 58.58; H, 4.06; N, 8.94; Cl, 11.38; KF, 1.59.

Preparation of 4-[(5*S*,9*R*)-3-(3,5-Dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-9-yl]-benzonitrile Semi (+)-DTTA Salt (5b) Directly from 3. A mixture of **3** (68.8 kg, 184.4 mol), glycine (26.4 kg, 351.7 mol), hexamethylenetetramine (8.5 kg, 60.6 mol) in 355 kg *N*-methylpyrrolidinone and 150 kg of toluene was heated at 144 °C under a nitrogen sweep. After 6 h the reaction was cooled to 55 °C, THF (355 kg) and a line rinse of toluene (10 kg) were charged, followed by ethylene diamine (18.6 kg, 309.5 mol) and 11.2 kg of THF. The solution was held at 55 °C for 1 h and cooled to 20 °C. To the mixture were charged 20 wt/wt % NaCl in water (1022 kg) and toluene (20 kg), maintaining temperature <20 °C. The mixture was stirred 15 min and allowed to settle for 30 min. The aqueous phase was discarded, and toluene (150 kg) was charged to the organic phase. The solution was distilled under vacuum (<50 mbar) at 55 °C. The reaction was cooled to <25 °C, and CH_2Cl_2 (840 kg) was charged. The mixture was sampled for KF (target <0.2%) and toluene (target <0.09 g/mL) content and then polish filtered. and CH_2Cl_2 (272 kg), H_2O (4.2 kg) and MeOH (26.8 kg) were charged. The mixture was stirred 15 min, seeds (175 g) were added. and (+)-DTTA (16.1 kg) was charged. The slurry was held for 20 h, cooled (0−5 °C). and held for 3.5 h. The slurry was filtered and washed three times with CH_2Cl_2 (120 kg, 270 kg, and 120 kg). The isolated solid was dried in an agitated filter dryer for 37 h. The resolved spirocyclic hydantoin **5b** was obtained as a white solid (36.2 kg of **5b**, 32.2% yield, 99.7 HPLC area % purity, and 98.5% ee).

Preparation of 5-[(5*S*,9*R*)-9-(4-Cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-9-yl-methyl]-thiophene-3-carboxylic Acid Methyl Ester Hydrochloride Salt (6). To a suspension of **5b** (23.3 kg, 38.3 mol), methyl 5-formylthiophene-3-carboxylate (6.8 kg, 40.0 mol), and 280 kg THF was added triethylamine (7.0 kg, 69.2 mol) at 20−25 °C followed by a THF rinse solution (20 kg). The mixture was stirred until a clear solution was obtained, to which acetic acid (4.1 kg, 68.3 mol) was added followed by a THF line rinse (20 kg). The resulting mixture was stirred at 20−25 °C for 1 h and then cooled to 15 °C. Solid sodium triacetoxyborohydride (4.1 kg, 19.3 mol) was added, and the reaction mixture was stirred for 1 h. The addition of sodium triacetoxyborohydride was repeated three more times. After all of the sodium triacetoxyborohydride (16.4 kg, 77.4 mol in total) was added over 3 h, the reaction mixture was stirred at 20−25 °C for an additional 4 h. Upon reaction completion (<1% **5b** remaining as monitored by HPLC), MTBE (177.6 kg) and 5% sodium hydrogen carbonate solution (340 kg) were added to the resulting mixture. The mixture was agitated for 45 min and held for 40 min. The aqueous layer was discarded, the organic layer was polish filtered, and the tank and filter were washed with 39.5 kg MTBE. The mixture was distilled to a volume of 250 L, and isopropanol (550 kg) was charged. The mixture was distilled until 220 L was collected, and the mixture was warmed to 70 °C. A 33% hydrochloric acid solution (5.2 kg) was charged followed by an isopropanol rinse (20 kg). Seed crystals (100 g) were charged, and the mixture was cooled to 20 at 15 °C/h and held for 6 h. The slurry was filtered and washed with isopropanol (50 kg). After drying the methyl ester **6** was

obtained as white crystalline solid (21.8 kg of **6**, 94.0% yield, 99.3 HPLC area % purity and 98.6% ee). Mp = 204−207 °C. ^{1}H NMR ($CDCl_3$): 14.22 (1H, b), 8.18 (1H, d, J = 0.9 Hz), 7.86 (1H, m), 7.67 (2H, d, J = 8.1 Hz), 7.24 (1H, m), 7.23 (2H, d, J = 8.1 Hz), 6.67 (2H, m), 4.76 (2H, m), 4.46 (1H, m), 4.16 (1H, m), 4.02 (2H, m), 3.86 (3H, s), 3.75 (1H, m), 3.38 (3H, s). ^{13}C NMR ($CDCl_3$): (171.24, 162.32, 152.98, 136.05, 135.27, 134.03, 132.83, 131.94, 130.46, 128.85, 128.56, 123.92, 117.52, 113.43, 71.13, 52.43, 52.22, 46.73). Anal. Calcd for $C_{27}H_{23}Cl_3N_4O_4S$: C, 53.52; H, 3.83; N, 9.25; S, 5.29; Cl, 17.55. Found: C, 53.07; H, 3.69; N, 9.08; S, 5.23; Cl, 17.20.

Preparation of 5-[(5*S*,9*R*)-9-(4-Cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-9-yl-methyl]-thiophene-3-carboxylic Acid (1) with Isolation of the THF Solvate. To a solution of **6** (20.12 kg, 33.2 mol) and 1,2-propanediol (6.4 kg) in tetrahydrofuran (226 kg) and water (127.2) was added cold (0−10 °C) potassium hydroxide solution (16.0 kg KOH and 127.1 kg H_2O) at 8−12 °C over 0.5 h. The resulting biphasic mixture was stirred at 8−12 °C for 18 h until the reaction was complete. *n*-Heptane (208.7 kg) was charged to the reactor, and after stirring 1 h, agitation was stopped. After 1 h, the aqueous layer was removed, combined with isopropyl alcohol (39.9 kg), and neutralized to pH 7.5 with aqueous acetic acid (only a portion of a solution of 20 kg acetic acid and 19.1 kg H_2O was charged). Seeds (150 g in 2.1 kg H_2O) were charged to the reaction mixture, and the pH was adjusted to pH = 4.8 by addition of aqueous acetic acid. The reaction mixture was stirred for 12 h, filtered, and washed with H_2O (127.1 kg). The THF solvate **1b** was obtained as a white solid (93.1% yield and 98.8 HPLC area % purity).

The THF solvate **1b** (20.1 kg) was charged to the reactor followed by isopropyl acetate (592.6 kg) and H_2O (7.6 kg). The mixture was heated to 68 °C and after complete dissolution, polish filtered. The solution was distilled under vacuum (240 Torr) until approximately 10% of the volume was removed. Seeds (250 g in 1.1 kg isopropylacetate) were charged and the distillation was continued until only 160 L remained. The slurry was cooled to 40 °C and sampled for KF (0.032%). The slurry was cooled to 20−25 °C, passed through a wet mill for 1 h to reduce the particle size to $d_{90} < 60$ μm. The crystal slurry was stirred at 20−25 °C for ≥2 h and was then filtered. The cake was washed with (5−10 °C) isopropylacetate (22.2 kg) and dried in vacuum at 35−40 °C to a constant weight. Acid **1** (15.0 kg, 80.4% yield, 99.9 HPLC area % purity and 99.5 weight % purity) was obtained as white and sandy crystalline solid. The overall yield from **6** was 74.8%. Mp = 209−230 °C.[28] ^{1}H NMR (acetone-d_6): 8.19 (1H, d, J = 1.3 Hz), 7.76 (2H, d, J=8.4 Hz), 7.49 (2H, d, J = 8.2 Hz), 7.43 (1H, d, J = 1.0 Hz), 7.41 (1H, t, J = 1.9 Hz), 6.87 (2H, d, J = 1.9 Hz), 4.16 (1H, dd, $J1$ = 13.9 Hz $J2$ = 0.8 Hz), 4.10 (1H, dd, $J1$ = 11.7 Hz, $J2$ = 6.2 Hz), 3.99 (1H, d, J = 14.0 Hz), 3.48(1H, d, J = 10.6 Hz), 3.47 (1H, dd, $J1$ = 9.6 Hz, $J2$ = 6.2 Hz), 3.25 (3H, s), 3.24 (1H, dd, $J1$ = 9.6 Hz, $J2$ = 11.7 Hz), 3.01 (1H, d, J = 11.3 Hz). ^{13}C NMR (acetone-d_6): (172.69, 163.7, 153.98, 144.55, 142.23, 135.26, 135.09, 134.41, 133.89, 132.96, 130.33, 128.27, 126.98, 125.18, 119.07, 112.44, 74.28, 59.09, 56.45, 54.33, 50.73, 25.75). Anal. Calcd for $C_{26}H_{20}Cl_2N_4O_4S$: C, 56.22; H, 3.62; N, 10.08; S, 5.77; Cl, 12.76. Found: C, 56.27; H, 3.20; N, 9.97; S, 5.65; Cl, 12.68.

Preparation of 5-[(5*S*,9*R*)-9-(4-Cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-9-yl-methyl]-thiophene-3-carboxylic Acid (1) Directly from 6. To a solution of **6** (46.9 kg, 77.6 mol) and 1,2-propanediol (11.8 kg) in tetrahydrofuran (41.7 kg) and water (266.8 kg) was added cold (0−10 °C) potassium hydroxide solution (1 N, 244.5 kg) at 8−12 °C in 0.5 h. The resulting biphasic mixture was stirred at 8−12 °C for 18−24 h until the reaction was complete (<1% **6** remaining as monitored by HPLC). The reaction mixture was washed with *n*-heptane (385.7 kg). The pH was adjusted to 7.5 with addition of 1.5 M citric acid (22.9 kg). Isopropyl acetate (817.8 kg) was charged, and 1.5 M citric $acid_{(aq)}$ (∼22.9 kg) was added until a pH of 6.5 was attained. After agitating for 15 min and holding for 30 min, the aqueous layer was discarded, and the organic layer was washed with H_2O (470 kg). The solution was then polish filtered, and isopropylacetate (52.2 kg) was used to rinse the polish filter assembly. The solution was concentrated under reduced pressure (240 Torr) to a volume of 718 L at <45 °C. Seeds (500 g) were charged, and the distillation was continued until a volume of ∼207 L was attained. Heptane (117.8 kg) was charged, the slurry was cooled to 20 °C over 1.5 h and was subsequently wet milled until $d_{90} < 60$ μm. The slurry was held for >2 h and filtered. The cake was washed with a 1:1 isopropyl acetate/heptane solution (109.7 kg) isopropyl acetate and dried in vacuum at 35−40 °C to a constant weight. Acid **1** (39.6 kg, 91.5% yield and 99.33 HPLC area % purity) was obtained as a white and sandy crystalline solid.

Acknowledgment

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Supporting Information Available

React-IR data for the ethylenediamine cleavage of **10** and DSC of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) For a copy of the DSC, please see the Supporting Information.