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Development of a Suitable Process for the Preparation of a TNF-α Converting Enzyme Inhibitor, WAY-281418

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Abstract:

A suitable process for the preparation of kilogram quantities of a TNF-α converting enzyme (TACE) inhibitor (WAY-281418) was developed using isatin 13 as starting material and an efficient coupling step for the formation of sulfonamide 8 in a 15% overall yield. Process preparation of (+)-(1*S*,2*R*)-2-aminocyclopentane-1-carboxylic acid (7, (+)-cispentacin), a chiral component for WAY-281418, was successfully scaled up via an asymmetric hydrogenation reaction. Crystallization allowed the isolation of all intermediates and the final product 9.

Introduction

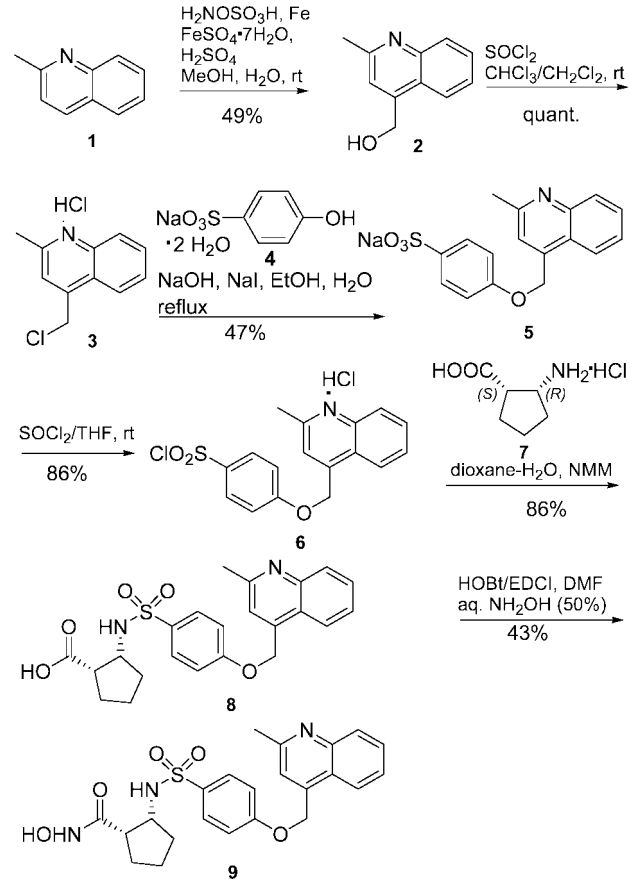
TNF-α converting enzyme (TACE)[1] is a membrane-bound metalloproteinase disintegrin that processes the membrane-associated cytokine pro-TNF-α to a biologically active soluble form. Overproduction of the TNF-α soluble form is associated with symptoms of a variety of infectious, autoimmune, and inflammatory disorders including rheumatoid arthritis (RA) and Crohn's disease.[2] Inhibition of TACE to block TNF-α overproduction is currently an important therapeutic target.[3]

In screening TACE inhibitors at Wyeth, WAY-281418 (**9**)[4] was identified as a potent lead candidate with an IC_{50} of 0.6 nM and excellent TACE selectivity. We describe our efforts to develop a scalable process towards the large-scale preparation of **9** for toxicological and clinical studies.

Results and Discussion

The original MedChem route is outlined in Scheme 1. Due to time constraints, the synthetic strategy for the preparation of **9** was not substantially changed, but the critical scale-up and safety issues were addressed. Because the MedChem synthesis of **7**, a key chiral component for **9**, was not suitable for scale-up (Scheme 2), an asymmetric hydrogenation process was developed instead.[5]

Scheme 1. **MedChem synthesis of 9**



Development Synthesis of Sulfonylchloride Hydrochloride Salt 6. Starting from quinaldine (**1**) in the MedChem route (Scheme 1), hydroxymethylation gave alcohol **2** in 49% yield. This $FeSO_4$/Fe-mediated radical reaction[6] resulted in a deep-

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(1) Black, R. A.; Rauch, C. T.; Kozlosky, C. J.; Peschon, J. J.; Slack, J. L.; Wolfson, M. F.; Castner, B. J.; Stocking, K. L.; Reddy, P.; Srinivasan, S.; Nelson, N.; Boiani, N.; Schooley, K. A.; Gerhart, M.; Davis, R.; Fitzner, J. N.; Johnson, R. S.; Paxton, R. J.; March, C. J.; Cerretti, D. P. *Nature* **1997**, *385*, 729–733.

(2) Eigler, A.; Sinha, B.; Hartmann, G.; Endres, S. *Immunol.Today* **1997**, *18*, 487–492.

(3) (a) Nelson, F. C.; Zask, A. *Expert Opin. Invest. Drugs* **1999**, *8*, 383–392. (b) Levin, J. *Curr. Top. Med. Chem.* **2004**, *4*, 1289–1310.

(4) Levin, J.; Li, Z.; Diamantidis, G.; Lovering, F. E.; Wang, W.; Condon, J. S.; Lin, Y.; Skotnicki, J. S.; Park, K. *β-Sulfonamide Hydroxamic Acid Inhibitors of TACE/Matrix Metalloproteinase*. U.S. Patent Appl. Pub. 0211730, 2006.

(5) (a) Tang, W.; Wu, S.; Zhang, X. *J. Am. Soc. Chem.* **2003**, *125*, 9570–9571. (b) Zhang, X.; Tang, W. *Preparation of Chiral Cyclic Amino Acids and Derivatives.* U.S. Patent Appl. Pub. 0242889, 2004.

(6) Citterio, A.; Gentile, A.; Minisci, F.; Serravalle, M.; Ventura, S. *Tetrahedron* **1985**, *41*, 617–620.

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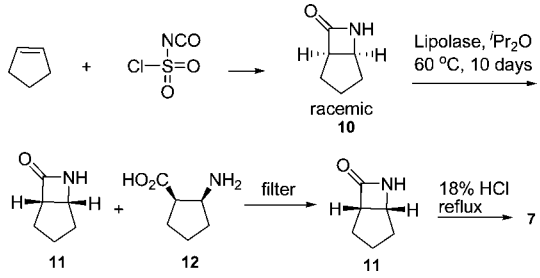
Scheme 2. **MedChem synthesis of 7**



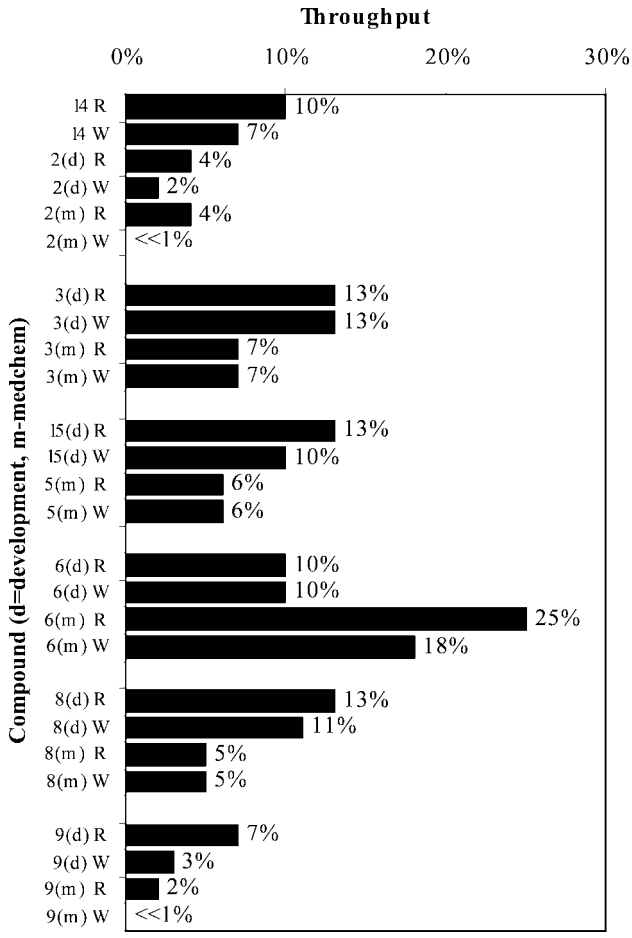


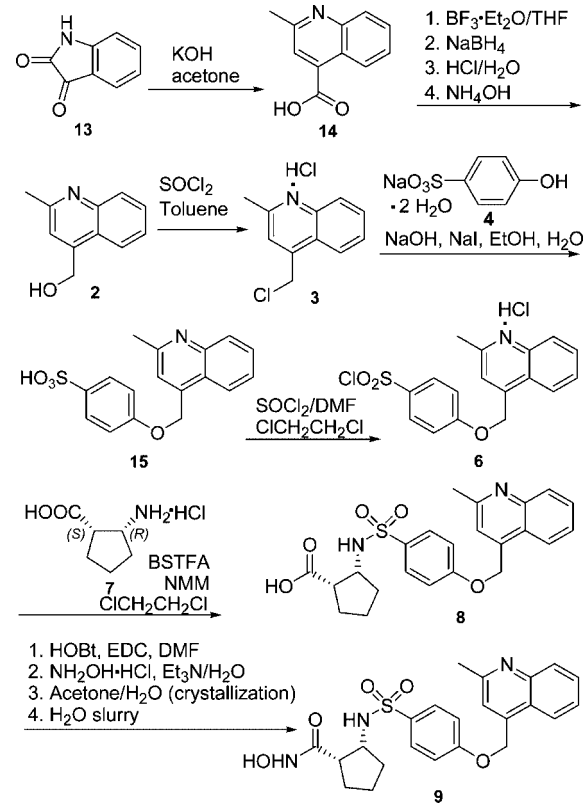
Figure 1. **Throughput comparison between MedChem and development syntheses.**

black solution with significant tar formation, which adversely affected the phase separation. Moreover, a tedious workup using large volumes of $CHCl_3$ followed by column chromatography was required to isolate **2**. Both reaction and workup throughputs[7] were low (<1.0%) for which further development was warranted (Figure 1). In order to provide a sufficient quantity of **2** for the downstream process development, this reaction was not suitable.

A two-step transformation for the preparation of **2** was designed and successfully run on a 4-kg scale in 29% yield (two steps) (Scheme 3). No further process optimization was done. Treating isatin **13** with KOH/water at 50 °C followed by the addition of acetone and pH adjustment (a Pfitzinger

(7) Throughput for reaction (*R*)/workup (*W*) is defined as kg of product from 100 L of reaction/workup mixture at maximum volume expressed as a percentage.

Scheme 3. **Development synthesis of 9**



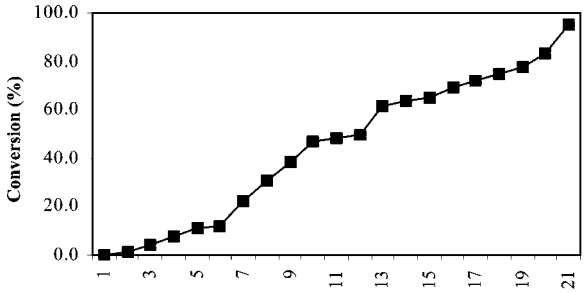
reaction)[8] afforded 2-methylquinoline-4-carboxylic acid (**14**), which was then reduced to **2** with BH_3/THF[9] (generated in situ from BF_3/Et_2O and $NaBH_4$ in THF). The low yield for the BH_3 reduction step was due to the solubility of **2** in water and significant reduction of the quinoline ring under these isolation conditions. The in situ generation of BH_3/THF was found to be more reliable and safer to control at scale relative to purchased material. The yield from this two-step process was less than that of the MedChem route; however, the requisite column chromatography and tedious workup were eliminated, the cost of goods was reduced as isatin **13** was cheaper than quinaldine (**1**), and throughputs were substantially increased. These attributes ameliorated the low yield.

Conversion of **2** to chloromethylquinoline hydrochloride salt **3** went smoothly. A suspension of **2** in toluene at room temperature (20−25 °C) was treated with $SOCl_2$ (2.0 equiv) for 2 h to afford **3** after filtration of the slurry. A higher reaction temperature (50 °C) was required if the reaction was not complete (<1.0% of starting material). Toluene replaced the solvent mixture of chloroform and dichloromethane used in the MedChem route.

In the alkylation reaction of sodium 4-hydroxybenzenesulfonate dihydrate, **4**, with **3**, the MedChem group had mixed all the reactants and reagents together in ethanol and 3.0 M NaOH (2.2 equiv) and heated the mixture to reflux for 20 h. After workup, **5** was obtained as its sodium salt but was contaminated with ~19% unreacted **4**, ~20% of NaCl, and

(8) Zemtsova, M. N.; Trakhtenberg, P. L.; Galkina, M. V. *Russ. J. Org. Chem.* **2003**, *39*, 1803–1803.

(9) Burkhardt, E. R.; Matos, K. *Chem. Rev* **2006**, *106*, 2617–2650, Use of other boron-reducing reagents was not investigated, and no further optimization studies were performed for this step.



1. NMP 2. Tetramethylsulfone 3. Acetone 4. MEK 5. BuCN 6. dichloromethane 7. DME 8. iPrOAc 9. Anisole 10. MeOAc 11. THF 12. Dioxane 13. Chlrobenzene 14. EtOAc 15. MeCN 16. DEE 17. TBME 18. Toluene 19. MeTHF 20. Trifluorotoluene 21. 1,2-dichloroethane

Figure 2. **Solvent screen for the preparation of 6.**

other unidentified minor impurities. Although NaCl can be removed in subsequent steps, excess **4** led to undesirable impurities.[10] To drive the reaction to consume **4** and prevent side reactions in the later steps, we modified the process such that reactants and reagents were charged in sequence. **4** (1.1 equiv) was combined with aq NaOH (2.0 equiv) to generate the phenoxide and was heated to 55−60 °C. To the resulting mixture was added **3** (1.0 equiv) in one portion. The reaction was stirred for 24 h in the presence of substoichiometric amount of NaI (0.5 equiv) and deemed complete while **3** was <1.0% by HPLC. The reaction was quenched with concentrated aq HCl at 55−60 °C, adjusting the pH to ∼3. The sulfonic acid **15** was isolated by filtration free from NaCl. The slight excess of **4** remaining was easily removed into the mother liquors. It was necessary to quench the reaction at higher temperatures to increase the filtration rate of the product. Acidification at room temperature (20−25 °C) produced **15** as fine crystals that caused a slow filtration.

In the MedChem route, **5** was treated with $SOCl_2$ (7 equiv) in THF at room temperature (21 °C) to afford sulfonyl chloride hydrochloride salt **6** with 94% conversion in 86% yield. However, due to contamination with NaCl and 4-hydroxybenzenesulfonyl chloride derived from **4**, the actual yield for **6** was <50%. Interestingly, when the sulfonic acid **15** was treated under the same reaction conditions, almost no conversion was observed by HPLC, possibly because HCl was a byproduct that retarded the reaction. When the sodium salt **5** was used, the byproduct NaCl precipitated out to drive the reaction. Through a design of experiments (DoE) approach, screening of solvents and the quantities of $SOCl_2$ and DMF by our group, Integrated Parallel Automation and Chemistry Technologies (InPACT), showed the optimized conditions were 2.54 equiv of $SOCl_2$ and 1.0 equiv of DMF in 1,2-dichloroethane at 75 °C. We were able to conduct this transformation on a 1.67-kg scale giving 98% conversion of **15** to **6** but contaminated with ∼3.9% of starting material as the major impurity.[11] Although the reaction in 1,2-dichloroethane performed the best in terms of conversion (Figure 2), the hazardous nature of this solvent necessitated an alternative. Acetonitrile and THF were chosen for further screening in order to replace 1,2-dichloroethane. Results revealed that MeCN could replace 1,2-dichloroethane by increasing the amount of $SOCl_2$ to 3.0 equiv and DMF to 1.5 equiv and that THF may be used but with 5.0 equiv. of $SOCl_2$ and 1.5 equiv of DMF. Further development work on MeCN or THF would be needed to optimize the reaction conditions.

Due to gas (SO_2) evolution during the reaction, controlled addition of $SOCl_2$ was required to allow the reaction to run more safely. After $SOCl_2$ addition, a sample of the reaction mixture showed an exotherm from between 60 to 110 °C from the thermal screening unit followed by an endotherm and minor exothermic decomposition at 135 °C.

Development Synthesis of (+)-(1*S*,2*R*)-2-Aminocyclopentane-1-carboxylic Acid (7). (+)-(1*S*,2*R*)-2-Aminocyclopentane-1-carboxylic acid (cispentacin) HCl salt (**7**) was not readily available in the quantities and timelines that we needed. The MedChem group prepared **7** on gram scale via an enzyme-catalyzed enantioselective ring-opening of unactivated alicyclic β-lactam[12] in less than 20% overall yield and 98% ee after repeated recrystallizations (Scheme 2). However, this approach was not scalable considering the large loading of lipolase, the long reaction time required, and the low yield obtained. Other alternative approaches[13,14] were evaluated, but these routes required either low temperatures (−95 °C) or column chromatography purifications, which were not amenable for scale-up to produce kilo quantities.

A route initially explored by our group was a kinetic chemical resolution of (±)-*cis*-2-benzyloxycarbonylaminocyclopentane carboxylic acid using commercially available dehydroabiethylamine (DAA).[15] The DAA salt was obtained by filtration in 83% yield, but resolution was not successful even after repeated recrystallizations.

Chiral hydrogenation technology (CHT) is widely used in the pharmaceutical industry to access chiral building blocks and chiral molecules on industrial scale.[16] Our CHT group within Chemical Development initiated a chiral hydrogenation screen based on Zhang's methodology,[5] and we developed a suitable process for scale-up.

The key building block **18** for asymmetric hydrogenation was prepared by telescoping the amination and *N*-acylation reactions starting from inexpensive and commercially available ethyl-2-oxocyclopentane carboxylate (**16**) (Scheme 4). The amount of NH_4OAc was reduced from 5.0 to 2.0 equiv for the amination step, and the nonenvironmentally friendly dichloromethane workup was replaced with toluene. Nonisolated **17** was directly acylated with acetic anhydride (1.5 equiv) to afford **18**. The number of equivalents of Ac_2O was reduced 4-fold, and the reaction was run in the absence of base. The compound **18** was isolated by swapping toluene with water. A comparison of the throughputs between Zhang's method and our method showed a significant increase in the reaction and workup

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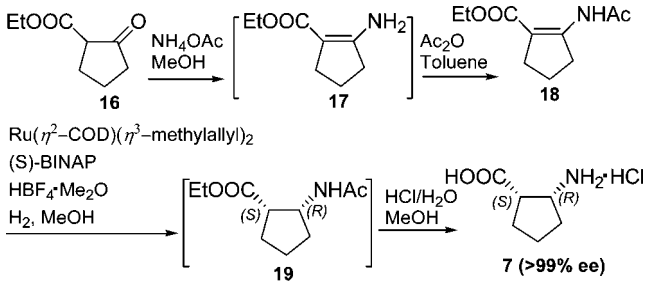
(16) Blaser, H. U.; Schmidt, E. *Asymmetric Catalysis on Industrial Scale, Challenges, Approaches and Solutions*; Wiley-VCH: Weinheim, 2004.
(17) HOBt is known to be potentially explosive in the anhydrous form. Use of the hydrated form is recommended.
(18) Transportation and storage of aqueous hydroxylamine are risky. For details, see: am Ende, D.; Vogt, P. *Org. Process Res. Dev.* **2003**, *7*, 1029–1033.
(19) ICH Harmonised Tripartite Guideline for residual solvents Q3C(M).

Scheme 4. **Development synthesis of 7**



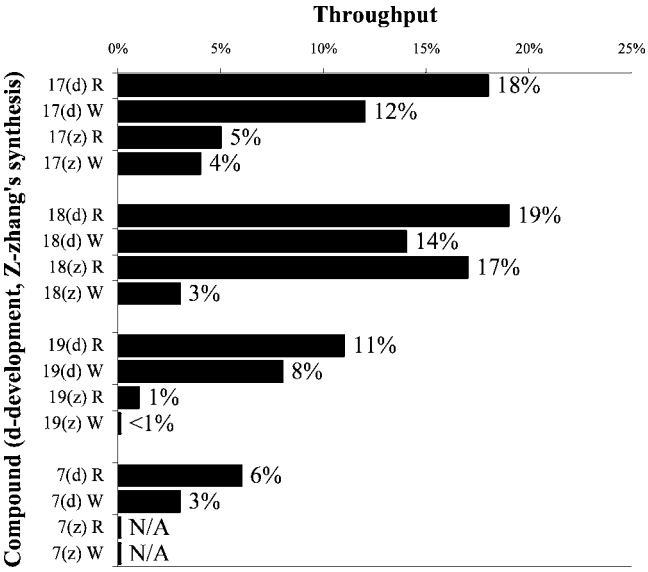


Figure 3. **Throughput comparison between Zhang's and development syntheses.**

throughputs (Figure 3). We were able to successfully produce kilogram quantities with high purity using this process.

Asymmetric hydrogenation of **18** using a modified Zhang's procedure successfully afforded **19** in quantitative yield and >99% ee on multigram to 100-g scales. These conditions were nonoptimized but were sufficient for producing enough of the chiral building block to manufacture the preclinical development API supply. The amount of the catalyst used was a cost concern. Significant cost reduction was achieved by reducing the amount of expensive Ru(η^2-COD)(η^3-methylallyl)$_2$ catalyst from 5 to 2 mol % and lowering the (*S*)-BINAP ligand from 5 to 2 mol % and $HBF_4 \cdot Me_2O$ from 10 to 4 mol %. Further reductions were possible but not explored. The volume of methanol used at small scale was reduced from 300 to 8 mL per gram of **18**. Consequently, throughputs were dramatically increased for this step. Preparation of the "active catalyst" [adding $HBF_4 \cdot Me_2O$ to a mixture of Ru(η^2-COD)(η^3-methylallyl)$_2$ and (*S*)-(−)-BINAP] was performed in methanol, forming a heterogeneous mixture which was used as is.

One key factor that ensured the success of the asymmetric hydrogenation was conducting the reduction under oxygen-free conditions, preferably using a high quality of argon (purity >99.998%). Experiments in which nitrogen was used failed, possibly due to a higher content of oxygen and moisture which deteriorated the catalyst and caused the reaction to stall, yielding a low ee of **19**.

The effect of residual solvents in **18** on reaction conversion was investigated (Figure 4). Water had a minor impact. With

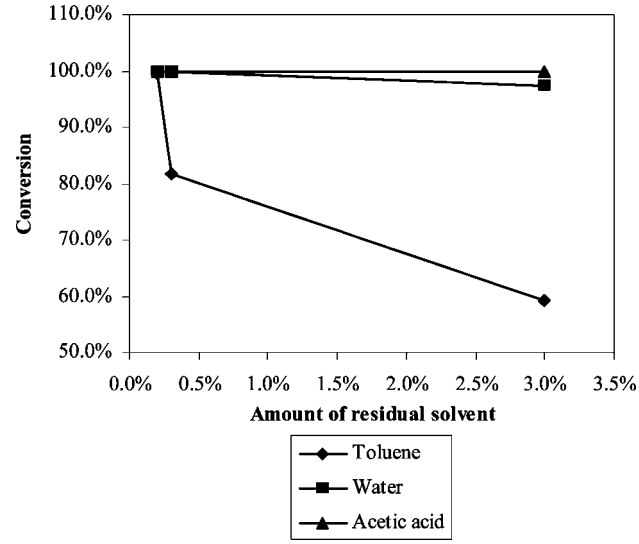


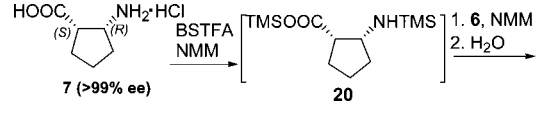
Figure 4. **Residual solvents in 18 vs reaction conversion for 19.**

up to 3% (w/w, by KF) water present, a >99% conversion was achieved. Similarly, acetic acid could be tolerated as high as 3.0% (w/w, by GC). Toluene was found to be more detrimental to the reaction conversion. The amount of residual toluene had to be controlled to less than 0.2% (w/w, by GC) to enable >99% conversion. Residual solvents present in **18** were found to have no effect on ee. Through these process development findings, the reaction ran smoothly several times on a 600-g scale to obtain **19** as a concentrated solution in methanol in quantitative yield (by HPLC assay) and >99% ee. This concentrate was telescoped into the hydrolysis step.

The methanolic solution of **19** was hydrolysed with 12.0 equiv of HCl in MeOH/water. The workup required the concentration of the reaction mixture to <5% methanol to ensure the efficient removal of the catalyst when the aqueous concentrate was filtered. The aqueous filtrate was then concentrated to replace water and excess HCl with acetonitrile, and **7** was isolated by filtration as a white crystalline solid in 85% yield and >99% ee. Residual ruthenium was found to be <11 ppm.

Coupling of 6 with 7. In the MedChem route, sulfonamide **8** was obtained by combining **6** with **7** in the presence of *N*-methylmorpholine (NMM) in a mixture of dioxane and water followed by extractive workup. However, the product was isolated with up to 20% of **15** as the major impurity, which was produced via hydrolysis of **6** during the reaction. In the absence of water, both **6** and **7** had low solubility in dioxane as well as other polar solvents, such as acetonitrile and DMF. To circumvent issues associated with low solubility of **7** and **8** in a nonaqueous solvent system and to minimize the sulfonic acid **15**, we pretreated **7** with *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) in the presence of NMM, which provided a very soluble *N,O*-bis-silylated intermediate **20** (Scheme 5).

Scheme 5. **Development synthesis of 8**



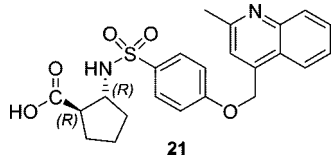


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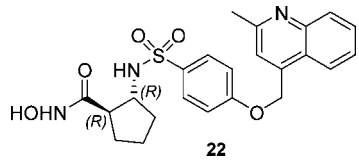
Figure 5. **1*R*,2*R* Diastereomer.**

This intermediate was coupled with **6** in the presence of NMM to afford the desired sulfonamide **8** after removal of the TMS protecting group during aqueous workup. *N*,*O*-bis(trimethylsilyl)acetamide (BSA), which was less expensive than BSTFA, could also be used for this reaction, but TMSCl did not work. With these process improvements, the major impurity **15** in the product was controlled to less than 2%. LC−MS analysis further identified the 1*R*,2*R* diastereomer **21** at up to 1.5% (Figure 5). However, this impurity was effectively removed in the next step.

Hydroxyamidation of **8** in the MedChem route using 1-hydroxybenzotriazole hydrate (HOBt,[17] 3.0 equiv), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC, 3.0 equiv) and 50% aq. NH_2OH (8.0 equiv) in DMF at 0∼5 °C for 18 h led to **9** in 43% yield and 85% purity. Low yield and purity were found that was associated with excess HOBt and EDC and this created a tedious workup. Minor process changes (amount of reagents) made from the MedChem route for this step increased the API yield. We did not explore other coupling reagents. However, attempts to convert **8** to its acid chloride by using $(COCl)_2$/DMF/THF followed by quenching the reaction mixture with aq NH_2OH led to an unstirrable mixture and an incomplete reaction (>20% of starting material by HPLC). Reaction of **8** with the lesser amounts of HOBt (1.2 equiv) and EDC (1.2 equiv) worked well in DMF at 20−25 °C followed by quenching the reaction mixture in aq NH_2OH, which was generated in situ from solid hydroxylamine hydrochloride salt and Et_3N in water.[18] The resulting slurry was filtered after dilution with water to provide **9** as crude API. Minor impurities identified in the API included the 1*R*,2*R* diastereomer **22** (Figure 6) and the pyrazolone **24** which was only identified by LC−MS. A proposed pathway of formation of **24** is activation of the hydroxyl group in **9** by EDC, rendering it as a leaving group followed by nucleophilic attack by the nitrogen of the sulfonamide group in the presence of Et_3N (Scheme 6).

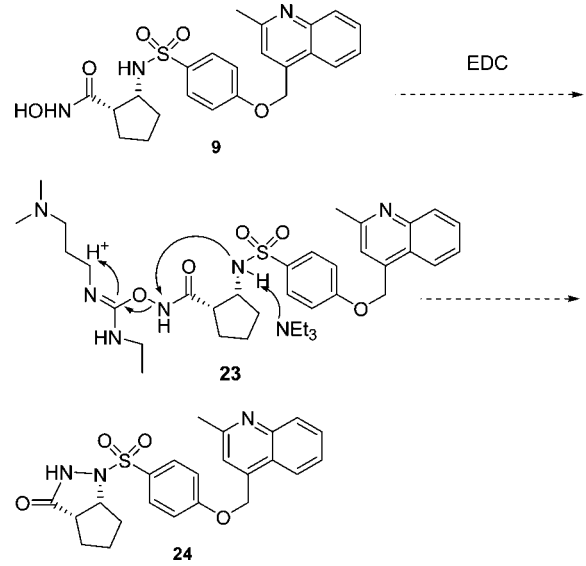


22

Figure 6. **1*R*,2*R* API diastereomer 22.**

Recrystallization and purification of crude API **9** was achieved from an acetone/water solvent system after an extensive solvent screening. Purification was also effective from ethanol/water or THF/water combinations. However, in ethanol/water, the undesirable ethanol solvate polymorph was formed and using THF/water in the last step of the synthesis was not the preferred option due to the low specification limit of THF

Scheme 6. **Possible formation pathway to 24**



(720 ppm) in the final API.[19] The most stable polymorph and the desired purity profile was obtained in acetone/water (10:1). High residual acetone in the API was removed by a hot water reslurry, albeit there was no impurity rejection and the purity profile in **9** did not change. The quality of the API produced was adequate to conduct preclinical studies.

Conclusion

In conclusion, we developed a suitable process for the preparation of WAY-281418 (**9**), which consisted of seven reaction steps and one crystallization step. The process was used for the preparation of multikilograms of API for both early-stage toxicological and clinical studies. The reaction and workup throughputs for every step were significantly increased. Scale-up issues for the synthesis of **2** were addressed using the inexpensive isatin **13** as starting material. The coupling reaction to prepare **8** was improved effectively. An asymmetric hydrogenation approach for the scale-up of **7** was developed for the successful preparation of API.

Experimental Section

General. NMR spectra were recorded at 300 MHz (^1H and ^{13}C) in DMSO-d_6. HPLC analyses were determined on a Waters Alliance 2690 HPLC instrument equipped with a PDA (model 2996) detector, and the results are described as area % (AP). HPLC conditions for chiral purity: Column: CHIRALPAK AD-H 250 mm × 4.6 mm, no. ADHOCE FC033. Mobile phase: heptanes/ethanol = 150:850 mL. Flow rate: 1.0 mL/min. UV detector: 235 nm. Inj vol: 5 μL. Instrumentation: Detector - WATERS PDA 996. Pump - Alliance 2690 System G. Isocratic - time from 0 to 30 min. Residual solvent levels were measured on a Perkin-Elmer Autosystem XL serial no. 610N0092213 GC with FID and using the following conditions: Gamma-Dex-225, 30 m, 0.25 mm i.d. 0.25 μm at 150 °C for 40 min, inlet 200 °C, detector 220 °C. Flow rate: helium 1.0 mL/min, split 150 mL/min. Chloride content analyses were

determined using a column IONPAC AG17 50 mm × 4 mm no. 001596 @ 30 °C, Dionex ED50 as detector and NaCl as reference. Residual Ru was measured using a Perkin-Elmer Optima 4200DV ICP. Methanol used in the preparation of **7** was bubbled (degassed) with argon prior to use.

(2-Methylquinolin-4-yl)methanol (2). To a 50-L jacketed cylindrical reactor equipped with an impeller-style agitator, condenser, thermocouple, and nitrogen inlet were charged isatin (**13**, 4.00 kg, 27.19 mol), 85% aqueous potassium hydroxide (12.43 kg, 188.27 mol), and potable water (24.9 kg). The reaction mixture was heated to 50 °C for 40 min. Acetone (3.16 kg, 54.37 mol) was then added over a minimum of 4 h, maintaining the temperature at 50 °C. After being stirred for 1 h, the reaction mixture was cooled to room temperature and acidified to pH 7 by addition of concentrated HCl (17.04 kg, 170.4 mol). The resulting KCl was filtered, and the pH of the mother liquor was further adjusted to 3 by adding concentrated HCl (2.52 kg) to obtain a heavy slurry which was filtered and dried at 75 °C under vacuum to afford 2-methylquinoline-4-carboxylic acid (**14**, 4.386 kg, 86% yield, 99.6 AP).

To a 30-L jacketed cylindrical reactor equipped with an impeller-style agitator, condenser, thermocouple, and nitrogen inlet were charged **14** (3.3 kg, 17.63 mol), THF (21.3 kg), and boron trifluoride etherate (7.5 kg, 52.89 mol). The resulting mixture was stirred at 20−25 °C for 15 h. To the mixture was added $NaBH_4$ (1.0 kg, 26.42 mol) portionwise over a minimum of 2 h, maintaining the temperature in the range of 20 to 35 °C. After being stirred for 1 h at 32−38 °C, the reaction mixture was added to aqueous HCl (2.5 M, 17.8 L) over a minimum of 30 min, maintaining the temperature in the range (5−30 °C). Removal of THF by atmospheric distillation and pH adjustment of the aqueous mixture to 10 by addition of ammonium hydroxide (28%, v/v, 6.5 kg) over a minimum of 1 h, maintaining the temperature in the range of 20−30 °C gave rise to a precipitate, which was collected by filtration, washed with toluene (3.03 kg) and water (3.5 kg), and dried at 70 °C under vacuum for 15 h to obtain (2-methylquinolin-4-yl)methanol (**2**, 1.055 kg, 34% yield, 97 AP). ^{1}H NMR δ 7.91−8.00 (m, 2H), 7.66−7.71 (m, 1H), 7.49−7.55 (m, 1H), 7.46 (s, 1H), 5.51 (t, J = 5.7 Hz, OH, 1H), 5.00 (d, J = 5.7 Hz, 2H), 3.31 (s, 3H). MS: 174 $[M + 1]^+$.

4-Chloromethyl-2-Methylquinoline HCl Salt (3). To a 30-L jacketed cylindrical reactor (internal diameter 300 mm) equipped with a 250 mm diameter impeller-style agitator, condenser, thermocouple, baffle, and nitrogen inlet were charged (2-methylquinolin-4-yl)methanol (**2**, 1.1 kg, 6.35 mol) and toluene (9.52 kg). Thionyl chloride (1.51 kg, 12.7 mol) was then slowly added over 1 h while maintaining temperature below 25 °C. After being stirred for 2 h, the reaction was filtered and washed with toluene (500 mL × 2) to provide 4-chloromethyl-2-methylquinoline as the HCl salt (**3**, 1.40 kg, 97% yield, 94 AP) after drying in oven under vacuum at 75 °C for 15 h. ^{1}H NMR δ 8.40−8.43 (m, 2H), 8.05−8.11 (m, 1H), 8.01 (s, 1H), 7.89−7.94 (m, 1H), 5.45 (s, 2H), 2.96 (s, 3H). MS: 229 $[M + 1]^+$. Cl^- content: found 15.8% (calcd 15.6%).

4-(2-Methylquinolin-4-ylmethoxy)benzenesulfonic Acid (15). To a 20-L jacketed cylindrical reactor equipped with an impeller-style agitator, condenser, thermocouple, baffle, and nitrogen inlet were charged NaOH (0.471 kg, 11.78 mol), potable water (6.56 kg), and sodium 4-hydroxybenzenesulfonate dihydrate (**4**, 1.437 kg, 6.19 mol). The mixture was stirred for 10 min to obtain a solution. To the solution was then charged ethanol (4.62 kg), NaI (76.9 g, 0.513 mol), and 4-chloromethyl-2-methylquinoline hydrochloride salt (**3**, 1.30 kg, 5.70 mol). The reaction mixture was heated to 55−60 °C over 15 min and monitored by HPLC. After being stirred for 24 h, the reaction mixture was quenched by adding concentrated HCl (0.586 kg) over 30 min at 55−60 °C and adjusted pH to 3−3.3. The resulting thick slurry was stirred for 30 min, cooled to 20 to 25 °C, and filtered, and the cake was washed with water (1 L × 3) and ethanol (1 L × 3) to give 4-(2-methylquinolin-4-ylmethoxy)benzenesulfonic acid (**15**, 1.824 kg, 97% yield, 99 AP) as an off-white solid after drying in an oven under vacuum at 70 °C for 24 h. Mp 227.2 °C. ^{1}H NMR δ 8.44 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.07−8.12 (m, 1H), 8.03 (s, 1H), 7.90−7.94 (m, 1H), 7.58 (d, J = 6.6 Hz, 2H), 7.14 (d, J = 6.6 Hz, 2H), 5.90 (s, 2H), 2.94 (s, 3H). MS: 330 $[M + 1]^+$.

4-(2-Methylquinolin-4-ylmethoxy)benzenesulfonyl Chloride Hydrochloride Salt (6). To a 3-L multinecked round-bottom flask quipped with mechanical stirrer, condenser, thermocouple, and nitrogen inlet were charged **15** (1.67 kg, 5.06 mol), 1,2-dichloroethane (20.7 kg), and DMF (369 g, 5.06 mol). The mixture was heated to 70−80 °C, and thionyl chloride (1.53 kg, 27.9 mol) was added over 3 h. The reaction was stirred for 1 h, and the mixture was cooled to 20−25 °C. The suspension was filtered and washed with 1,2-dichloroethane (3 × 2.0 kg) to afford 4-(2-methylquinolin-4-ylmethoxy)benzenesulfonyl chloride hydrochloride salt (**6**, 1.79 kg, 93% yield, 95 AP) as a yellow solid after drying in an oven under vacuum at 50 °C for 12 h. ^{1}H NMR δ 8.50 (m, 2H), 8.15 (m, 1H), 8.09 (s, 1H), 7.96 (m, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 5.94 (s, 3H). MS: 348 $(M + 1)^+$. Cl^- content: found 18.96% (calcd 18.49%).

Ethyl-2-acetamido-1-cyclopentene-1-carboxylate (18). To a 2-L jacketed reactor quipped with mechanical stirrer, condenser, thermocouple, and nitrogen inlet were charged 2-oxocylopentanecarboxylic aicd ethyl ester (**16**, 200 g, 1.28 mol), ammonium acetate (198 g, 2.56 mol), and methanol (700 mL). The mixture was heated to 65 °C and stirred for a minimum of 2 h until the reaction was complete (<0.5% of starting material **16** by HPLC). The reaction mixture was cooled and concentrated, and residual methanol was chased with toluene (400 mL). The resulting toluene solution (~800 mL) was washed with water (500 mL × 2) and concentrated. To the concentrated toluene solution (~400 mL) was added acetic anhydride (196 g, 1.92 mol) and the mixture heated to 75 °C and stirred for a minimum of 2 h until the reaction was complete (<0.5% of **17** by HPLC). Water (400 mL) was added to the reaction after cooling, the mixture was stirred for a minimum of 1 h, and the resulting layers were separated. The organic layer was washed with water (400 mL), saturated sodium bicarbonate (400 mL), and water (400 mL). The organic layer was concentrated, and toluene was replaced with water (300 mL). The resulting slurry was filtered and washed with water (300 mL × 3) to afford ethyl-2-acetamido-1-cyclopentene-1-carboxylate (**18**, 191 g,

76% yield, 99.7 AP) after drying at 35−40 °C, 10 mmHg, for a minimum of 3 h until KF specification (0.5%) is met.

(+)-(1*S*,2*R*)-2-Aminocyclopentane-1-carboxylic Acid (7). To a 5-L jacketed reactor equipped with mechanical stirrer, condenser, thermocouple, and argon inlet were charged Ru(η^2-COD)(η^3-methylallyl)$_2$ (19.56 g, 0.0612 mol), (*S*)-(−)-BINAP (38.16 g, 0.0612 mol), and degassed (argon) methanol (3.0 L) under an inert argon atmosphere. The mixture was cooled to 0−5 °C, and to the mixture was added dropwise tetrafluoroboric acid dimethyl ether complex (17.16 g, 15.6 mL, 0.128 mol) over a minimum of 10 min, keeping the batch temperature between 0 and 10 °C. The reaction mixture was stirred for 15 min at 0−10 °C and for 1 h at 20−25 °C. The resulting orange mixture was transferred to a 2-gal hydrogenation pressure vessel containing ethyl-2-acetamido-1-cyclopentene-1-carboxylate (**18**, 0.60 kg, 3.04 mol) and degassed methanol (1.8 L) under an inert atmosphere. The mixture was hydrogenated at 75 psi, 50 °C, and at a stirring rate of 350 rpm for a minimum of 3 h. The reaction was complete when <0.5% (GC analysis at RT: 19.5 min) of the starting material remained. The reaction mixture was filtered through a 0.2-μm cartridge, and the cartridge was washed with degassed methanol (2.0 L). The filtrate was concentrated under vacuum to a volume of 2.49 L containing **19**. To the concentrate containing **19** was added water (795 mL) followed by adding concentrated HCl (3.0 L) over a minimum of 0.5 h, maintaining the batch temperature at 20−25 °C, and the mixture was heated to 80−85 °C over a minimum of 1 h and stirred for a minimum of 24 h. The reaction was complete when <0.5% (HPLC analysis) of starting material **19** remained. The reaction mixture was concentrated to a volume of 3.50 L, which was filtered through a Celite pad, and the Celite pad was washed with water (500 mL × 3). The filtrate was concentrated under vacuum to a volume of 1.29 L. To the concentrate was added acetonitrile (1.50 L × 3), and the mixture was concentrated again to 1.29 L three times. To the concentrate was added acetonitrile (1.5 L), and the resulting slurry was stirred at 0−5 °C for 2 h. The slurry was filtered, and the cake was washed with cold acetonitrile (0.51 L × 2) and dried at 50 °C in a vacuum oven (10 mmHg) for a minimum of 24 h to yield (+)-(1*S*,2*R*)-2-aminocyclopentane-1-carboxylic acid (**7**, 0.423 kg, 85% yield) with 99.5% ee by GC at RT 24.6 min. ^{1}H NMR δ 12.8 (brs, 1H), 8.04 (brs, 3H), 3.60 (brs, 1H), 2.97 (ddd, J = 8.4, 6.6, 6.3 Hz, 1H), 1.85−2.01 (m, 3H), 1.70−1.84 (m, 2H), 1.53−1.65 (m, 1H).

(1*S*,2*R*)-2-[4-(2-Methylquinolin-4-ylmethoxyl)benzenesulfonylamino]cyclopentanecarboxylic Acid (8). To a 20-L jacketed cylindrical reactor equipped with an impeller-style agitator, condenser, thermocouple, baffle, and nitrogen inlet were charged (1*S*,2*R*)-aminocyclopentane-1-carboxylic acid HCl salt (**7**, 926 g, 5.59 mol), 1,2-dichloroethane (12.3 kg), and *N*-methylmorpholine (570 g, 5.64 mol). The reaction mixture was stirred for 30 min. BSTFA (2.875 kg, 11.17 mol) was then added over 10 min. The reaction mixture was stirred at 40 °C until a solution was obtained and held for 2 h. The solution was cooled to 5−10 °C, and *N*-methylmorpholine (0.951 kg, 9.41 mol) was added over 5−10 min. **6** (1.79 kg, 4.66 mol) was added to the reaction mixture while maintaining the temperature between 5−10 °C. After 15 min of stirring, the reaction mixture was warmed to 21 °C and left overnight (>12 h). To the reaction mixture was added water (7.16 kg) over a minimum of 30 min. The resulting slurry was stirred for a minimum of 2 h, filtered, and washed with 1,2-dichloroethane (2.33 kg, 1.85 L) followed by water (1.85 kg, 1.85 L) to provide **8** (1.74 kg, 85% yield, 98.2 AP). ^{1}H NMR δ 12.1 (brs, 1H), 8.16 (m, 2H), 7.87 (m, 1H), 7.82 (d, J = 9 Hz, 2H), 7.01 (s, 1H), 7.50 (m, 1H), 7.34 (d, J = 9 Hz, 2H), 5.79 (s, 2H), 3.75 (m, 1H), 2.77 (s, 3H), 1.89−1.56 (m, 4H), 1.49−1.25 (m, 3H). MS: 441 [M + 1]$^+$.

(1*S*,2*R*)-2-[4-(2-Methylquinolin-4-ylmethoxy)benzenesulfonylamino]cyclopentanecarboxylic Acid Hydroxyamide: Crude WAY-281418 (9). To a 5-L jacketed cylindrical reactor (internal diameter 300 mm) equipped with a 250 mm diameter impeller-style agitator, condenser, thermocouple, baffle, and nitrogen inlet were charged **8** (0.350 kg, 0.79 mol), HOBt (0.128 kg, 0.950 mol), and DMF (0.991 kg, 1.05 L). To the mixture was added a slurry of EDC (0.182 kg, 0.950 mol) in DMF (0.826 kg, 0.875 L) over a minimum of 30 min with a rate of addition of 15 to 20 mL/min, maintaining the temperature in the range of 20−25 °C. After being stirred for 2 h, the reaction mixture was quenched into an aqueous solution of hydroxylamine generated from hydroxylamine HCl (0.681 kg, 9.80 mol, 12.4 equiv) in water (1.40 kg) upon addition of Et_3N (0.992 kg, 9.80 mol) while maintaining the temperature of the resulting mixture at −1 to 2 °C. This was warmed to 20−25 °C and stirred for 1 h. Water (5.25 kg) was added to the mixture over a minimum of 1 h to give a suspension. Filtration, washing with water (3 × 0.350 kg), and drying at 60 °C, 10 mmHg, for 24 h provided crude API (**9**, 0.33 kg, 91.7% yield, 97.8 AP).

Crystallization of (1*S*,2*R*)-2-[4-(2-Methylquinolin-4-ylmethoxy)-benzenesulfonylamino]cyclopentanecarboxylic Acid Hydroxyamide, WAY-281418 (9). To a 70-L jacketed reactor equipped with an impeller-style agitator, condenser, thermocouple, baffle, and nitrogen inlet were charged the crude **9** (1.24 kg), acetone (19.6 kg) and purified water (USP, 2.48 kg). The mixture was heated to reflux (59.1 °C) for 10 min, clarified at 50 °C through a 0.2 μm cartridge, and heated to reflux again for 10 min. The mixture was then cooled to 50 °C to generate crystals without seeding, held for 1 h, then further cooled to 20 °C over a minimum of 2 h, and held for 1 h again. The crystals were collected by filtration, washed with acetone (3 × 1.0 kg), and dried at 60 °C, 10 mmHg for 12 h to afford the purified API **9** (0.953 kg, 76.8% yield, 99.2 AP, >99.9% ee). The material was resuspended in purified water (USP, 9.0 kg) at 50 °C for 2 h to remove residual acetone (1.1%). Filtration and drying at 50 °C, 10 mmHg for 16 h gave the final API **9** (0.895 kg, 99% yield, 99.2 AP, >99.9% ee). Ru < 1 ppm. Mp 195.3 °C. ^{1}H NMR 10.45 (s, 1H), 8.80 (s, 1H), 8.11 (dd, J = 0.9, 8.4 Hz, 1H), 7.98 (dd, J = 0.9, 8.4 Hz, 1H), 7.80 (d, J = 9 Hz, 2H), 7.76−7.73 (m, 1H), 7.63−7.56 (m, 2H), 7.31 (d, J = 9 Hz, 2H), 5.71 (s, 2H), 3.50 (brs, 1H), 2.67 (s, 3H), 2.54−2.45 (m, 2H), 1.72−1.55 (m, 4H), 1.42−1.34 (m, 2H). ^{13}C NMR δ 170.3, 161.6, 159.3, 148.1, 142.3, 134.1, 130.1, 129.6, 126.6, 124.5, 124.4, 120.8, 115.9, 67.3, 57.1, 44.9, 32.1, 28.0, 25.7, 22.4. MS: 456.1 [M + 1]$^+$.

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Note Added after ASAP Publication: The version published on the Web September 9, 2008, has been changed. Two authors have been added, and the acknowledgment has been changed in the version published on the web September 27, 2008, and in the print version.

Supporting Information Available

HPLC conditions and retention time for intermediates **14**, **2**, **3**, **15**, **6**, **8**, **17**, **18**, **19**, and API **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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