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Route Development and Bulk Synthesis of CP-865,569

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Abstract:

The synthesis of zwitterionic CP-865,569 by three different synthetic routes is described. The first two routes differ in the method of introducing the sulfonic acid at the penultimate step: by sulfite displacement of a benzylic chloride and by oxidation of a benzylic thioacetate. The third route is a convergent route to the drug candidate. The synthesis strategy was primarily driven by the need to introduce the sulfonic acid functionality at the final stage of the synthesis due to the high water solubility and low organic solubility of the desired product.

Introduction

CP-865,569 (**8**) is a CCR1 antagonist.[1] The candidate contains a tertiary amine and unusual benzylic sulfonic acid functionalities and exists as a zwitterion as its neutral species. The synthesis of this candidate involved a number of synthetic and processing challenges due to the interesting functionality present and the physical properties thereof. Herein is described four iterations of bulk synthesis of the candidate, utilizing successively improved and optimized modifications of the discovery synthesis, the development and scaling of a new synthetic process for the introduction of the sulfonic acid functionality, and the development of a convergent synthesis. Process safety studies and impurity identification efforts are described in the following paper.[2]

Discovery Synthesis

The original route employed by discovery to identify the candidate[1] started with amidation of **2** with chloroacetyl chloride followed by alkylation with 5-chlorosalicylaldehyde to provide **5** as a low-melting solid (Scheme 1). Aldehyde **5** was reduced with $NaBH_4$ in THF to provide alcohol **6** which was chlorinated with excess $SOCl_2$ and sulfonylated with sodium sulfite in aqueous EtOH to give the sodium salt of CP-865569 (**8-Na**) along with ~10% ethyl ether and ~10% alcohol **6** from competitive solvolysis of the chloride during the reaction. Purification of **8-Na** away from the nonionic impurities was accomplished by ion-exchange chromatography,[3] resulting in isolation of the zwitterion (**8**), which was converted to the salt (**8-Arg**) by treatment with arginine. The only crystalline intermediate in this sequence other than the drug substance is salt **2**, and chromatographic purification of intermediates was required after two steps (**5** and **8-Na**).

First Bulk Campaign. For preparation of the first 500 g of **8-Arg**, an enabled discovery route was employed with changes in the chemistry at the beginning and end of the route. The reaction of *trans*-2,5-dimethylpiperzine with *p*-fluorobenzyl chloride[4] was uneventful and produced the desired monoalkylated product (**2**) in 89% in situ yield (as measured by HPLC) in addition to 10% of the dibenzylated product and unreacted starting material. The mixture could be separated cleanly by extraction. Unreacted piperazine was primarily purged in the basic aqueous layer discarded after the reaction. The desired product (**2**) could be separated from bis-benzylated product and excess alkylating agent by extracting **2** into water in the range of pH 4−5. Following basification to above pH 12, the desired product could be recovered cleanly, contaminated only with traces of unreacted starting piperazine. Resolution with tartaric acid using 2 equiv of acid (the salt is a 2:1 acid/product ratio) provides the resolved amine in 41% yield and >99:1 er, provided the filter-cake is washed thoroughly prior to drying and isolation. On large scale, filtration on an unstirred Nutsche filter provided variable results, whereas filtration on a filter/dryer with a stirred wash provided consistent results between runs. Following a salt break, resolved amine **2** was amidated with chloroacetic anhydride, and the resulting chloride was displaced with 5-chlorosalicylaldehyde. A solvent change from DCM to toluene allowed us to avoid formation of an undesired bis(salicylaldehyde) methylene acetal resulting from salicylaldehyde anion and residual dichloromethane in the second step, and obviated the need to isolate and handle chloride **3**, which had proven to be only moderately stable on storage. After aqueous workup, the toluene solution of chloride **3** was azeotropically dried and taken directly into the alkylation, which proceeded uneventfully when 10% v/v DMAc was added to the reaction. After a basic aqueous workup to remove unreacted chlorosalicylaldehyde, aldehyde **5** was isolated as a low-melting amorphous solid by precipitation from a DCM/IPE solution in 94% yield over the two steps. Sodium borohydride reduction of the aldehyde proceeded more efficiently in an EtOH/THF mixture than in THF alone, allowing for a reduction of the $NaBH_4$ charge and a simplified workup. Conversion of the alcohol to chloride **7** with thionyl chloride was followed by sulfonic acid introduction, which was conducted with Na_2SO_3 in

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(1) Hayward, M. M. U.S. Patent 2003/0083335 A1, 2003.

(2) Ripin, D. H. B.; Weisenburger, G. A.; am Ende, D. J.; Bill, D. R.; Clifford, P. J.; Meltz, C. N.; Phillips, J. E. *Org. Process Res. Dev.* **2007**, *11*, 762−765.

(3) Waters MCX resin, 10g/g loading, MeOH elution.

(4) Maw, G. N. WO 98/52929, 1998.

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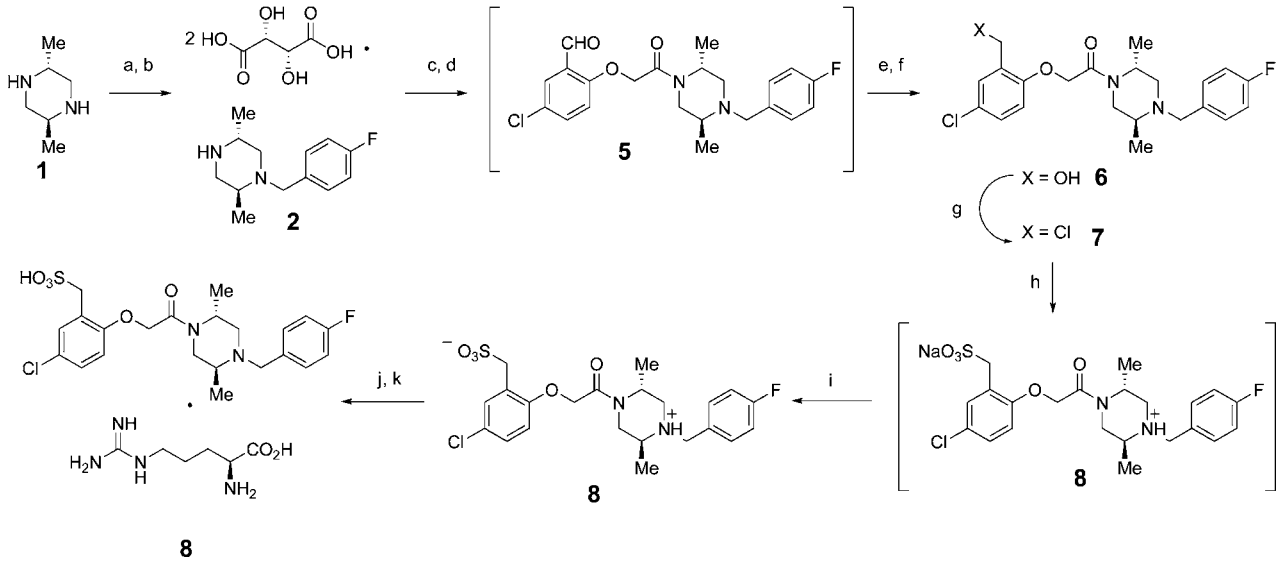
Scheme 1. **Discovery synthesis of CP-865,569 used in the preparation of the first bulk**[a,b]



[a] Reagents and conditions originally used: c) $ClCH_2COCl$, Et_3N, DCM; d) 5-chlorosalicylaldehyde, K_2CO_3, DMF, reflux; e) 2 equiv of $NaBH_4$, THF; g) 2 equiv of $Socl_2$, Dcm; h) Na_2SO_3, $EtOH/H_2O$, reflux 16 h; i) ion-exchange chromatography; j) arginine, MeOH; k) *n*-PrOH. [b]Optimized reagents and conditions: a) *p*-$FPhCH_2Cl$, NaOH, 5 mol % Bu_4NCl, cyclohexane/H_2O, 40 °C, 18 h; b) L-tartaric acid, MeOH; c) chloroacetyl chloride, Et_3N, PhMe; d) 5-chlorosalicylaldehyde, K_2CO_3, PhMe, DMAC; e) $NaBH_4$, PhMe, EtOH; f) HCl; g) $SOCl_2$, CH_2Cl_2; h) Na_2SO_3, MeCN; i) HCl, MeCN, iPrOH; j) L-arginine, EtOH; k) EtOH.

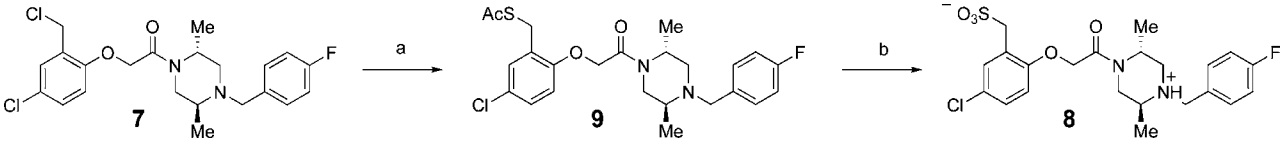
acetonitrile/water to eliminate formation of ethereal byproducts that consisted of 10−20% of the crude reaction mixture under the original conditions. The resulting 9:1 mixture of **8-Na** and **6** was separated by IPE extraction of the acetonitrile solution of the mixture, and the purified sodium salt was acidified with HCl in acetonitrile. The choice of ACN as solvent for this neutralization was driven by the low solubility of NaCl in acetonitrile across a wide range of temperatures, but it turned out to be fortuitous as the presence of acetonitrile was required to prevent gumming of the sparingly soluble zwitterion during the neutralization reaction. Zwitterion prepared in this manner contained approximately 2000 ppm sodium and was directly taken into the salt formation. After a repulp (hot slurry) to reach full crystallinity, low-sodium arginine salt **8-Arg** was isolated as a white, crystalline solid. Attempts to isolate crystalline forms of **8-Na** or the zwitterion (**8**) were unsuccessful; high-melting amorphous solids were obtained under all conditions. Interestingly, during preparation of the racemate for purposes of establishing a chiral assay, it was discovered that racemic **8-Na** is a highly crystalline solid.

Second Bulk Campaign. The next campaign resulted in the preparation of 8 kg of **8-Arg** and required modification of the neutralization/salt formation step for **8** to accommodate for limitations imposed by conducting the campaign in our kilo-lab facility. Conversion of **1** to **8-Na** proceeded as described above with little change. After synthesizing **8-Na** and extractive removal of **6** with IPE washes, the acetonitrile layer containing **8** was diluted with isopropanol and dried by azeotropic distillation. Hydrogen chloride gas was introduced to the ACN/IPA solution of **8-Na** to pH 3, and the resulting solution was added slowly to IPE to precipitate the zwitterion (**8**), which was isolated by filtration and dried under nitrogen sweep. Gumming of the zwitterion had been observed during development of this process and was a persistent concern during these operations. It was found through empirical observations that the presence of acetonitrile, the absence of water, and the addition rate were critical to prevent gumming, but the failure limits of this process are still not well understood. Solid zwitterion was then taken back into a mixture of ACN and ethanol, filtered through a 0.5 μm, and then a filtered water solution of arginine was added. Removal of water and acetonitrile was accomplished by repeated distillation and displacement with ethanol. The resulting partially crystalline **8-Arg** was then rendered completely crystalline by a reslurry in hot ethanol. In this way high-quality drug substance was delivered at the expense of a very risky and laborious endgame process that was impractical to repeat for any further large-scale campaigns.

Development of a New Method for the Introduction of the Sulfonic Acid. After encountering the difficulty in removing the sodium ion from the API, a number of other synthetic methods to install the sulfonic acid moiety were investigated. Due to the high water solubility of the zwitterionic intermediate and working under the assumption that intermediates in the synthesis also containing the sulfonic acid functionality would possess similar properties, the focus of research was to introduce the acid as the final step of the synthesis or to introduce it in a protected state. Ideas investigated included other sulfite displacements of the chloride in the absence of metal counterions, utilizing the sodium sulfite displacement followed by reaction of the sulfonic acid to form an organic soluble derivative which could be hydrolyzed following ash removal, or introducing the sulfonic acid via an entirely different method which involves no metal ions.

Attempted displacement of chloride **7** with ammonium sulfite resulted in a new material tentatively assigned as the benzylic amine with no desired product observed. The chloride could be very cleanly displaced by tritylmercaptan or potassium thioacetate (Scheme 2). Either product could

Scheme 2. **Installation of the sulfonic acid functionality of CP-865,569 via oxidation of thioacetate 9[a]**



[a] Reagents and conditions: a) KSAc, PhMe; b) HCO_2H, 30% H_2O_2 in H_2O or 30% AcOOH in AcOH.

then be oxidized under a variety of conditions,[5] including some metal-ion-free conditions such as performic or peracetic acid in formic or acetic acid. Under the acidic conditions, no *N*-oxide formation was observed. The crystallinity of the thioacetate derivative in conjunction with the higher atom efficiency and lower cost of the acetate as compared with that of the trityl protecting group led us to focus our attention on the thioacetate route.

Third Bulk Campaign: Demonstration of the Thioacetate Oxidation To Introduce the Sulfonic Acid. In this campaign amine **2** was prepared with less than a full equivalent of *p*-fluorobenzyl chloride to reduce the quantity of bis-alkylated byproduct formed in the reaction,[6] and the amount of tetrabutylammonium chloride was minimized from 5 mol % to 3.5 mol %. A biphasic Schotten−Baumann amide formation using chloroacetyl chloride and aqueous sodium hydroxide as base in place of triethylamine in 2-methyltetrahydrofuran (MTHF)[7] proved superior to the original conditions. The presence of chloroacetate anion (in the chloroacetyl chloride), particularly under the single-phase reaction conditions, resulted in formation of an alcoholic impurity resulting when an acetate displaces the α-chloride of the desired product and is hydrolyzed on workup. While perhaps counterintuitive to add water to a reaction plagued by hydrolysis, it seems that any acetate present in the reaction mixture is sequestered in the water layer and is unavailable to react with the product. The hydrolysis impurity is difficult to purge, and its control using the modified reaction conditions obviates significant processing needed to achieve that purification. The α-chloroamide intermediate is not indefinitely stable, and the elevated temperatures necessary for azeotropic drying on scale result in decomposition. As a result, a magnesium sulfate drying step was necessary.

The displacement of the chloride with 5-chlorosalicylaldehyde proceeds cleanly in MTHF in the presence of potassium carbonate and potassium iodide. The α-chloroamide intermediate is not a solid, and as the reaction solvents are the same, the dried reaction mixture from the previous step is used directly in this reaction. Powdered potassium carbonate is necessary to achieve reaction times of less than 12 h. Following reaction completion, the excess dark-yellow phenolate can be washed down to <1% with two sodium hydroxide washes.[8] Following layer separation, the solution can be azeotropically dried prior to the sodium borohydride reduction. Aldehyde **5** is a low-melting solid, however attempts to isolate the product by crystallization did not meet with success. As the material produced by the two-step process described above is high in purity (>94% by HPLC), **5** was carried directly into the next step.

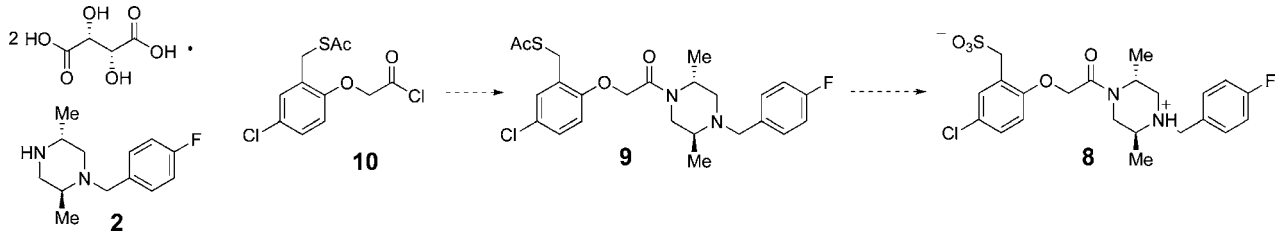
The sodium borohydride reduction was carried out in MTHF with 5.0 equiv of methanol added. When run entirely in methanol, a borane−amine complex was isolated along with the desired product in ∼10% yield. Further, the reaction in methanol, ethanol, and/or THF required removal of the reaction solvent prior to aqueous workup. In the MTHF case the reaction was quenched with aqueous sodium citrate followed by layer separation. Following workup, the alcohol can be precipitated as the amorphous HCl salt, following addition of anhydrous HCl. This procedure has the disadvantage that the benzylic alcohol, which is not very acid stable, decomposes during the precipitation, and material of only 86% purity is isolated from material that starts out at >96% purity prior to introduction of the HCl. Once in the solid state, the material does not appear to decompose, even over a period of 6 months or more. Due to the decomposition during salt formation and the high purity of the unisolated material, the decision was made to telescope alcohol **6** into the next reaction in lieu of isolation. This decision was enabled by the discovery of the solid HCl salt of chloride **7** and crystalline thioacetate **9** (vide infra).

Chloride formation using thionyl chloride proceeds without event in a number of solvents, and ethyl acetate was chosen because the purity of the material out of the reaction appeared highest. Following reaction completion, the unquenched ethyl acetate solution can be added to hexanes, and the HCl salt of chloride **7** precipitates from the reaction mixture. Little or no upgrade of purity is observed during this isolation. As a consequence, the chloride was instead telescoped one additional step prior to its isolation. In order to telescope the material into the thioacetate displacement, the reaction was quenched with base, and the free-base of chloride **7** was carried forward in solution.

Chloride **7** is cleanly displaced in the presence of potassium thioacetate in toluene. Following reaction completion and water washes, the toluene is distilled to a low volume (∼2−4 L/kg), and hexanes are added to precipitate the product. The product is isolated as a crystalline solid with a good impurity purge. Typical purity of the material isolated is >96%. The five step sequence (amide formation, phenol displacement, borohydride reduction, chloride formation, and thioacetate displacement) proceeds in an average of 66% overall yield on 50-kg scale, and all five of the reactions proceed rapidly enough that the five steps can be executed in one week in a pilot plant.

(5) Oxidation of thioacetates to sulfonic acids: Koenig, N. H.; Swern, D. *J. Am. Chem. Soc.* **1957**, *79*, 4235−4237.
(6) It was later determined that unreacted starting material can carry through the synthesis, reacting at both amine termini and forming a pseudodimeric impurity that was observed at low levels in the finished product.
(7) Ripin, D. H. B.; Vetelino, M. *Synlett* **2003**, 2353.
(8) The remainder of this material is reduced in the next step and washed away in the aqueous workup of that step.

Scheme 3. **Potential convergent route to CP-865,569**



The success of the new route hinged upon the ability to cleanly oxidize[9] thioacetate **9** and quench the reaction in the absence of any metal-ion-containing salts. This could be accomplished using a performic acid or peracetic acid oxidation followed by quenching of the excess peroxide with activated carbon (Darco G-60). This quench, which generates oxygen, is proposed to be catalyzed by the residual metals in the activated carbon. No lot-to-lot variability was observed in the effectiveness of the quench, either between different lots of the same grade of carbon, or other types of carbon (KBB was also tried). Each lot was use-tested prior to use on scale. A significant amount of safety testing and engineering was undertaken in order to run this chemistry on a large scale. The oxidation reaction was run at 15 °C with slow addition of the oxidant to the substrate in order to control heat generation and prevent a runaway reaction. To generate the reagent in situ, 30% hydrogen peroxide was added slowly to a solution of **9** in formic acid. The oxidant was subdivided into nine separate charges to prevent accidental addition of too much oxidant at once. The reaction was monitored by in situ IR to determine reaction completion and halt oxidant charging in order to minimize the amount of peroxide requiring quenching. The completed reaction mixture was added slowly to slurried activated carbon (5 wt % as compared to the weight of **9** added) in formic or acetic acid with generation of oxygen. A nitrogen purge was maintained throughout the quench in order to keep the oxygen concentration inside the reactor to a minimum. Increasing the amount of carbon used in the quench led to more vigorous gas generation and a significant decrease in isolated yield of product. Quench completion was monitored with semi-quantitative peroxide test strips, which indicated a final peroxide concentration of less than 1 ppm. Following quench and ARC[10] testing, azeotropic drying with methanol and precipitation with isopropanol or IPE provided solid zwitterion isolated by filtration.

We chose to investigate alternative conditions for the formation of the arginine cocrystal (X-ray analysis indicates a hydrogen-bonded complex) that did not involve the use of acetonitrile or other solvents that are considered class 1 or 2 solvents by the FDA. Arginine is only soluble in water and acetic acid, and therefore unless water was employed in the cocrystallization, a solid-to-solid conversion would be necessary. To complicate matters, alcoholic solvents proved to react with the amide in the API at prolonged times at elevated temperatures to provide the ester and piperazine **2** in high amounts (over 10% after 3 days at 95 °C). Initial observations indicated that the cocrystal would not precipitate in wet solvent, and when a solution of the mixture was azeotroped dry, significant quantities of oil deposited on the sides of the flask in addition to cocrystal precipitation. These issues were resolved by dissolving the API and arginine in wet 1-propanol and treating the mixture with 7.5% w/w G-60 Darco followed by room-temperature filtration. The carbon treatment effectively removed the oils that later precipitate during the azeotropic drying and also served to remove a significant amount of color from the solution. The wet 1-propanol solution could then be azeotropically displaced with dry 1-propanol under vacuum with the pot temperature remaining well below 50 °C, thus suppressing the solvolysis reaction previously observed. The cocrystal thus obtained could be recrystallized in methanol if necessary to upgrade purity. The product precipitated from methanol as an amorphous solid and had to be repulped in refluxing 2B ethanol (toluene denatured ethanol, 99.5% EtOH, 0.5% toluene) to re-establish crystallinity. For the oxidation, cocrystal formation, and repulp, a 67−69% isolated yield of clinically suitable material was obtained.

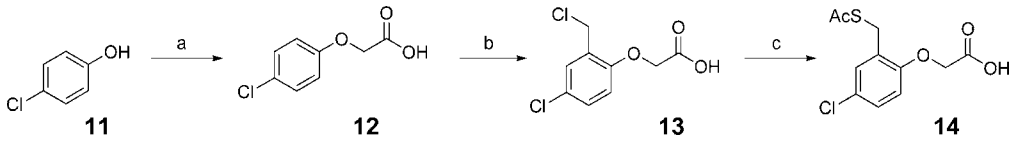
Convergent Route Development. An obvious retrosynthetic disconnection to make to achieve a more convergent synthesis would be the amide bond (Scheme 3). If amide formation could be achieved on a fully elaborated carboxylic acid precursor, the nine-step linear synthesis above could be shortened to a synthesis with a longest linear route of four to five steps. We made the decision not to pursue the most convergent route possible, wherein the sulfonic acid functionality would already be installed on the carboxylic acid precursor prior to amide formation. This decision was based on a number of reasons: the sulfonic acid would likely participate in amide formation, there was difficulty in handling the sulfonic acid functionality for more than one isolated step, the final step of the synthesis would remain the same as that for previous campaigns, and the number of linear steps would remain the same. Additionally, the route depicted in Scheme 3 has a reasonable regulatory synthesis and starting materials associated with it: amide formation, sulfonic acid formation, and salt formation.

Alkylation of *p*-chlorophenol with methyl chloroacetate followed by in situ hydrolysis resulted in a high yield of acid **12** (Scheme 4). Potassium phosphate was preferred over potassium carbonate due to a large increase in reaction volume and gas output during acidification with potassium carbonate. The actual isolated yield was not determined as the solids contained a high amount of inorganic salts and

(9) For a review of large-scale oxidation reactions, see: Caron, C.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Ripin, D. H. B. R. *Chem. Rev.* **2006**, *106*, 2943−2989. Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Process Res. Dev.* **2005**, *9*, 253−258.

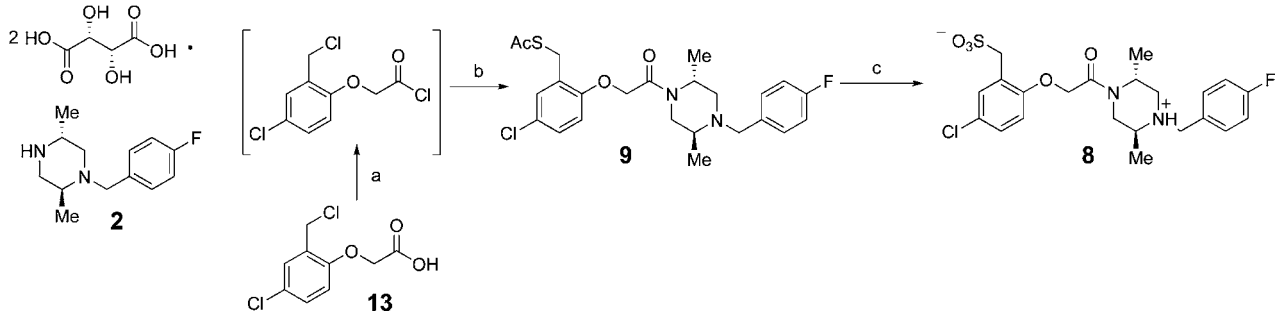
(10) Accelerated Rate Calorimetry.

Scheme 4. **Synthesis of functionalized acetic acid coupling partners**[a]



[a] Reagents and conditions: a) i) K_3PO_4, $ClCH_2CO_2Me$, acetone, 50 °C; ii) H_2O, distill acetone to 85 °C; iii) concn HCl to pH 1. b) $(HCOH)_n$, AcOH, HCl, H_3PO_4, 90 °C, 60%, 2 steps. c) KSAc, DMSO, 50 °C.

Scheme 5. **Convergent synthesis of CP-865,569**[a]



[a] Reagents and conditions: a) $SOCl_2$ (or $(COCl)_2$, DMF, PhMe. b) i) PhMe, Et_3N; ii) KSAc, EtOAc, 55 °C, 89%, 2 steps. c) i) HCO_2H, H_2O_2; ii) G-60 Darco, 75−90%.

was carried directly into the next reaction. This carboxylic acid could then be converted to benzylic chloride **13** directly in a reaction wherein **12** and paraformaldehyde were suspended in concn HCl, H_3PO_4, and HOAc and heated for 18 h. Despite our fears to the contrary, the deposition of paraformaldehyde polymer on the reaction vessel setup was not observed. After reaction completion, the product could either be precipitated with the addition of water or taken through an extractive workup with EtOAc. The extractive workup was the preferred method as it purged some low-level impurities that the precipitation did not.

At this stage in the synthesis, we were faced with a choice of either taking acid **13** into an amide formation to reconverge with the linear synthesis at chloride **7** or displacing the chloride with thioacetate prior to amide formation to reconverge at thioacetate **9**. Both sequences were investigated, and the preferred method actually turned out to be a blend of the two (Scheme 5). We found that chloride **13** was easier to handle than **14**, and thus proceeded with the coupling of **13** and **2**. Following completion of the amide formation, EtOAc and KSAc were added, and the thioacetate was installed prior to isolation of the product. This procedure provided 89% of the desired thioacetate **9** in high purity after crystallization. Oxidation as previously described completed the synthesis of CP-865,569. This route was demonstrated on lab scale but has not been run on kilogram scale.

Conclusions

CP-865,569 has been synthesized on large-scale using three different methods. Due to the water solubility of the final product, the performic acid oxidation approach, which produces the desired material in the absence of metal counterions, proved to be superior to a sulfite displacement approach to the sulfonic acid. The performic acid oxidation proved safe and reliable to run on 30-kg scale. Using the oxidation route, 96.2 kg of material was produced with an overall campaign yield of 45% from amine **2**. CP-865,569 was synthesized via a convergent route in 80% yield (from **2**) and a longest linear route of four steps from *p*-chlorophenol. A comparison of this route to the other routes previously scaled is shown in Table 1.

Table 1. **Comparison of three routes to CP-865,569 from 2**

	convergent oxidation route	linear oxidation route	discovery route
% overall yield (from **2**)	80	45	30
no. of bulk operations	6	5	8
safety	oxidation reaction	oxidation reaction	no issues
total waste/ L/kg	123	188	455
organic waste/ L/kg	118	144	301
solid intermediates	6/6	5/9	5/9

Experimental Section

General. All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. All reactors were glass-lined steel vessels with the exception of those used for catalytic hydrogenations, which were Hastelloy. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by TLC, GC, or HPLC. HPLC analyses were performed using one of the following systems: Chiralpak AD 4.6 mm × 250 mm Sn column *n*-heptane/DEA (99.8/0.2 v/v) mobile phase or a Zorbax SB-CN 4.6 mm × 150 mm column, and a mobile phase consisting of acetonitrile and either 0.5% perchloric acid or 0.2% phosphoric acid. GC analyses were performed on a DBWaxEtr (15 m × 0.25 mm i.d. × 0.25 μm film). Proton and carbon NMR spectroscopy was performed on a Bruker-Spectrospin Avance 400 MHz instrument. Karl Fischer

measurements were obtained on a Mettler Toledo DL38 Volumetric Karl Fischer apparatus. Melting points were determined on a Büchi B-545 melting point apparatus. Elemental analyses were performed by Quantitative Technologies Inc. of Whitehouse, NJ.

(*2S,5R*)-1-(4-Fluorobenzyl)-2,5-dimethylpiperazine (2). To a clean, dry, nitrogen-purged 1900-L reactor were charged *trans*-2,5-dimethylpiperazine (**1**) (25.8 kg, 226 mol), tetrabutylammonium chloride (2.22 kg, 7.91 mol, cyclohexane (258 L), process water (36.1 L), 50% sodium hydroxide solution in water (23.6 L), and 4-fluorobenzyl chloride (31.3 kg, 215 mol). The reaction was heated to 35−45 °C for a minimum of 6 h. The reaction was cooled 20−25 °C, sampled, and checked for completion by GC. The mixture was allowed to settle for at least 20 min. The phases were separated, and process water (258 L) and 37% hydrochloric acid (22.2 L) were added to the organic layer. The reaction mixture was allowed to stir for at least 20 min after which the pH of the lower aqueous layers was analyzed (pH range is between pH 4 and 5). The reaction mixture was settled for at least 25 min. The phases were separated, and to the aqueous layer were added 2-methyltetrahydrofuran (387 L) and 50% sodium hydroxide solution in water (23.6 L kg). The mixture was stirred for a minimum of 20 min. The pH of the lower aqueous layer was analyzed (pH range between pH 12 and 14 recommended), and the contents were settled for a minimum of 25 min. The phases were separated, and the 2-methyltetrahydrofuran layer was concentrated atmospherically until the pot temperature reached 82 °C and then was vacuum stripped to a final volume of 75−90 L. The solution was cooled to 20−30 °C, and methanol (129 L) was added to the reaction. The reaction solution was concentrated atmospherically to a final volume of 75−90 L. The previous step was repeated one more time. To the concentrated mixture was added 1800 L of methanol and L-tartaric acid (68.2 kg, 452 mol). The reaction mixture was heated 60−70 °C and held for a minimum of an hour. The solution was cooled to 10−20 °C until a white precipitate came out of solution. The white slurry was heated to 45−50° and held for a minimum of 12 h. The reaction was cooled to 20−25 °C and then filtered on an adequately sized filter and washed with methanol (52 L). After drying under vacuum at 40−50 °C for at least 12 h with a slight nitrogen bleed, 45 kg (86 mol) of (*2S,5R*)-1-(4-fluorobenzyl)-2,5-dimethylpiperazine (**2**) was isolated in 38% yield (based on a maximum resolution yield of 50%) mp: 96−97 °C. ^{1}H NMR (400 MHz, methanol): δ 7.36 (m, 2H), 7.06 (m, 2H), 4.47 (s, 4H), 4.19 (d, 1H), 3.30 (m, 4H), 2.85 (m, 2H) 2.70 (m, 1H), 2.14 (m,1H) 1.26 (d, 3H) 1.20 (d, 3H). ^{13}C NMR (DMSO): δ 174.8, 72.6, 51.4, 49.2, 48.5, 48.3, 48.0, 47.8, 47.74, 47.72, 47.6, 47.4, 47.2, 15.9, 15.2. Anal. calcd for $C_{21}H_{31}FN_2O_{12}$: C, 48.27; H, 5.98; N, 5.36. Found: C, 45.55; H, 5.97; N, 4.78.

1-((*2R,5S*)-4-(4-Fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-(4-chloro-2-(hydroxymethyl)phenoxy)ethanone (6). To a clean, dry, nitrogen-purged 1900-L reactor were charged (*2S,5R*)-1-(4-fluorobenzyl)-2,5-dimethylpiperazine (**2**) (79.6 kg, 152 mol), 2-methyltetrahydrofuran (1651 L), process water (238 L), and 50% sodium hydroxide solution in water (55 L). The reaction was stirred for 30 min for complete dissolution. Chloroacetyl chloride (19.3 kg, 168 mol) was added to the reaction mixture, while keeping the pot temperature between 15 and 30 °C during the addition. The reaction was held at 20−25 °C for 25 min. The reaction was sampled and checked for completion. The reaction mixture was settled for 20 min. The phases were separated, and magnesium sulfate (19.9 kg) was added to the 2-methyltetrahydrofuran layer. The reaction was stirred for 20 min. The reaction slurry was filtered and concentrated to 567 L using vacuum distillation. Potassium carbonate (32.2 kg, 229 mol), potassium iodide (27.8 kg, 168 mol), and 5-chlorosalicyladehyde (25.0 kg, 160 mol) were added to the reaction mixture. The reaction mixture was heated to 66−70 °C for a minimum of 10 h. The reaction was cooled to 20−30 °C and sampled for completion by HPLC. To the reaction was added process water (159 L) and 50% sodium hydroxide solution in water (6.35 L). The reaction was stirred for a minimum of 15 min, settled for a minimum of 15 min, and the phases were separated. This organic layer wash was completed two more times. On the final wash the phases were separated, and magnesium sulfate (19.9 kg) was added to the 2-methyltetrahydrofuran layer. The reaction slurry was filtered and concentrated to 114 L using vacuum distillation. To the reaction mixture were added methanol (208 L) and 2-methyltetrahydrofuran (416 L). To the reaction mixture was added sodium borohydride (1.12 kg, 28.9 mol) in four equal portions while keeping the pot temperature 20−30 °C. The reaction was stirred for 30 min at 20−30 °C. The reaction was sampled for completion by HPLC. To the reaction mixture was added ethyl acetate (1000 L), process water (160 L), 50% sodium hydroxide solution in water (18 L), and citric acid (32.5 kg). The mixture was stirred for 20 min, settled for 15 min, and the phases were split. To the organic layer was added magnesium sulfate (2.8 kg), and the mixture was stirred for 20 min, and the insolubles were filtered off. The reaction mixture was concentrated and used as a solution in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 3H), 7.18 (dd, 1H), 7.06 (t, 2H), 6.78 (m, 1H), 4.75 (m, 2H), 4.68 (s, 2H), 3.6 (d, 1H) 3.4 (d, 1H), 3.2 (s,-1H) 3.04 (s, 1H) 2.70 (s, 1H) 2.2 (dd,1H) 1.75 (s,1H), 1.3 (dd,3H), 0.98 (dd,3H). ^{13}C NMR ($CDCl_3$): δ 128.65, 113.71, 77.58, 77.26, 76.95, 66.87, 61.54, 58.15.

2-(4-Chlorophenoxy)acetic Acid (12). To a clean, dry 2000-mL three-neck flask fitted with a reflux condenser, temperature probe, and a glass stopper were added potassium phosphate tribasic (413 g, 1.94 mol), *p*-chlorophenol (**11**) (100 g, 0.778 mol), methyl chloroacetate (127 g, 1.17 mol), and acetone (300 mL). The reaction mixture was heated to 40−60 °C for 10 h. The reaction mixture was analyzed by HPLC, and process water (1000 mL) was added to the reaction mixture. The reaction mixture was concentrated at 80−90 °C until all acetone distilled off. The reaction was heated for 14 h at 80−90 °C. The reaction mixture was cooled to 25−30 °C, and concentrated hydrochloric acid (210 mL) was added. The reaction was stirred for 20 min, cooled to 10−15 °C, and the white product was filtered. The white

product was washed with 20 mL of water and dried in a vacuum oven for use in the following step. Mp: 152−153 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 7.23 (dd, 2H), 6.88 (dd, 2H), 5.21 (s, 1H), 4.62 (s, 2H). ^{13}C NMR (CD_3OD): δ 171.26, 159.95, 129.21, 126.16, 116.00, 64.86, 47.92. Anal. calcd for $C_8H_7ClO_3$: C, 51.50; H, 3.78. Found: C, 50.33; H, 3.54.

2-(4-Chloro-2-(chloromethyl)phenoxy)acetic Acid (13). To a clean, dry 2-L vessel were added 2-(4-chlorophenoxy)-acetic acid (**12**) (100 g, 0.536 mol), paraformaldehyde (72.4 g, 0.800 mol), acetic acid (400 mL, 6.98 mol), 37% concentrated hydrochloric acid (368 mL, 4.29 mol), and phosphoric acid (59.6 mL, 1.07 mol). The reaction was heated to 85−95 °C for 18 h. The reaction was cooled to 20−30 °C and then analyzed for reaction completion by HPLC. Ethyl acetate (500 mL) was added to the reaction which was then stirred for 20 min. The phases were separated, the organic layer was concentrated, and the white product was filtered off and washed with ethyl acetate (20 mL). After drying under vacuum at 40−50 °C for 12 h with a slight nitrogen bleed, 2-(4-chloro-2-(chloromethyl)phenoxy)acetic acid (**13**) was isolated. Mp: 112−113 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 7.4 (dd, 1H), 7.26 (qd, 1H), 6.9 (dd, 1H), 4.74 (s, 2H), 4.69 (s, 2H). ^{13}C NMR (CD_3OD): δ 170.87, 154.75, 130.09, 129.28, 128.72, 126.07, 113.61, 65.31, 39.98. Anal. calcd for $C_9H_8Cl_2O_3$: C, 45.99; H, 3.43. Found: C, 45.33; H, 3.32.

1-((*2R,5S*)-4-(4-Fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-(4-chloro-2-(chloromethyl)phenoxy)ethanone (7). To a concentrated solution of 1-((*2R,5S*)-4-(4-fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-(4-chloro-2-(hydroxymethyl)-phenoxy)ethanone (**6**) in 2-methyltetrahydrofuran (74.0 kg/75.9 L solution) was added ethyl acetate (214 L). The resulting solution was concentrated under atmospheric pressure to a minimum stir volume. To the concentrated solution was added ethyl acetate (214L). Again, the solution was concentrated to a minimum stir volume. The ethyl acetate charge/concentration sequence was repeated until the water content was reduced to 1.0% or less via KF analysis. Upon completion of drying, ethyl acetate (874 L) was added to the concentrated solution to create a final dried solution with a concentration of 0.50 M. To a nitrogen-purged solution of thionyl chloride (31.4 kg) in ethyl acetate (532 L) at 20 °C was added the dried ethyl acetate solution of 1-((*2R,5S*)-4-(4-fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-(4-chloro-2-(hydroxymethyl)phenoxy)ethanone (**6**) at a rate to ensure the temperature did not exceed 35 °C. The reaction mixture was stirred at 25 °C for 2 h followed by an aqueous quench (361 L). The organic layer was separated, washed with water, and added to a 1.0 N NaOH solution (381 L) at a rate to ensure the temperature did not exceed 30 °C. The resulting mixture was stirred for 30 min at 20 °C, and the organic layer was separated and dried with several atmospheric ethyl acetate azeotropic distillations. The product (**7**) was delivered to the next step as a dried ethyl acetate solution (0.30 M, calculated as 100% yield from starting benzyl alcohol).

1-((*2R,5S*)-(4-(4-Fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-(4-chloro-2-(acetoxythiomethyl)phenoxy)ethanone (9). To a nitrogen-purged ethyl acetate solution of 1-((*2R,5S*)-(4-(4-fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-(4-chloro-2-(chloromethyl)phenoxy)ethanone (**7**) (584 L/0.30 M) at 20 °C was added solid potassium thioacetate (30.1 kg/1.50 equiv.). The reaction was heated to 50 °C for 8 h, and then cooled to 25 °C and washed with water (2 × 150 L). The organic layer was separated and concentrated atmospherically to approximately 100 L (1.50 M, calculated from starting benzyl alcohol). Toluene (215 L) was added to the oil followed by reduced pressure distillation to approximately 100 L (max. pot temperature not to exceed 40 °C). The toluene dilution/concentration was twice repeated. The ethanethioate oil was again diluted with toluene (150 L) followed by hexane (230 L). Some precipitation was evident at this point. The resulting mixture was heated to 60 °C and held until a complete solution was achieved. The heated solution was cooled to 10 °C and stirred for 2 h following initial precipitation. The precipitate was filtered, rinsed with hexanes, and dried under vacuum at 50 °C. Yield: 81% (two steps). ^{1}H NMR (DMSO-d_6): δ 0.92 (d, 3H), 1.22 (d, 3H), 2.22 (d, 1H), 2.31 (s, 3H), 2.70 (dd, 1H), 2.98 (m, 1H), 3.31(bs, 1H), 3.44 (d, 1H), 3.59 (d, 1H), 3.71-(bs, 1H), 4.10 (s, 2H), 4.26 (bs, 1H), 4.76 (d, 1H), 4.86 (d, 1H), 6.95 (d, 1H), 7.09 (t, 2H), 7.22 (dd, 1H), 7.28 (d, 1H), 7.36 (t, 2H). ^{13}C NMR (DMSO-d_6): δ 7.0, 15.9, 20.1, 26.9, 29.7, 42.9, 45.9, 48.3, 51.0, 56.7, 66.9, 113.8, 114.4, 124.1, 126.4, 127.7, 128.2, 129.1, 129.6, 134.7, 154.6, 160.1, 161.7, 165.5.

(2-(2-((*2R,5S*)-4-(4-Fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-oxoethoxy)-5-chlorophenyl)methanesulfonic Acid (8). To a nitrogen-purged reactor at 20 °C were added solid (2-(2-((*2R,5S*)-4-(4-fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-oxoethoxy)-5-chlorophenyl)methanesulfonic acid (**9**) (34.2 kg/71.3 mol) and 96% formic acid (7.20 L/kg ethanethioate). To the formic acid solution at 20 °C was added 30% hydrogen peroxide (3.77 L/0.467 equiv). The exotherm was noted, and the temperature rise was recorded. The reaction was stirred at 20 °C for 2 h followed by the addition of a second aliquot of 30% hydrogen peroxide (3.77 L/0.467 equiv). Again, the exotherm was noted, and the temperature rise was recorded. The reaction was stirred at 20 °C for 2 h. The reaction mixture was sampled and analyzed by HPLC to monitor starting material consumption and sulfonic acid formation. (A lack of starting material consumption and sulfonic acid formation implies a buildup of hydrogen peroxide, and subsequent additions should be discontinued.) Upon determination of safe hydrogen peroxide consumption, the reaction mixture was treated with seven further aliquots of 30% hydrogen peroxide (3.77 L/0.467 equiv) with 2-h reaction times at 20 °C. Samples for HPLC analysis were taken following aliquots 5 and 8 to reaffirm safe peroxide consumption. Upon complete addition of hydrogen peroxide, the reaction mixture was added to a suspension of 96% formic acid (39 L) and activated carbon (Darco G-60) (1.70 kg) at 20 °C under a high-volume nitrogen sweep over 2 h. A gentle gas evolution was noted and confirmed a controlled consumption of excess hydrogen peroxide. The resulting suspension was stirred at 20 °C for

12 h, and a reaction sample was analyzed by accelerated rate calorimetry to ensure complete peroxide consumption. The quenched reaction was filtered through Celite, and the filtrate was diluted with glacial acetic acid (316 L). The resulting solution was concentrated under reduced pressure to a volume of approximately 30 L with a maximum pot temperature of 50 °C. The desired (2-(2-((*2R*,*5S*)-4-(4-fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-oxoethoxy)-5-chlorophenyl)methanesulfonic acid (**8**) oil was diluted with methanol (140 L) and added to isopropyl ether (1400 L) at 20 °C over1 h. The resulting slurry was stirred at 20 °C for 2 h followed by filtering, washing with isopropyl ether (35 L), and vacuum drying at 50 °C. Yield: 91%.

(2-(2-((*2R*,*5S*)-4-(4-Fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-oxoethoxy)-5-chlorophenyl)methanesulfonic Acid L-Arginine-cocrystal (8-Arg). To a nitrogen-purged reactor at 20 °C were added solid (2-(2-((*2R*,*5S*)-4-(4-fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-oxoethoxy)-5-chlorophenyl)-methanesulfonic acid (**8**) (37.1 kg/69.6 mol), solid L-arginine (12.4 kg/69.6 mol), 1-propanol (380 L), and water (76 L). The resulting solution was stirred at 25 °C for 2 h followed by addition of activated carbon (Darco KBB) (2.8 kg) and Celite (1.9 kg). The new suspension was stirred at 25 °C for 2 h and then filtered through a pad of Celite (1.0 kg). The filter pad was washed with 1-propanol, and the collected filtrate was concentrated under reduced pressure to a volume of approximately 110 L (maximum pot temperature of 55 °C). The concentrated solution was diluted with 1-propanol (190 L) followed by distillation at reduced pressure to 110 L. The 1-propanol charge/concentration was repeated two more times, a sample was removed, and water content was determined by KF analysis. Upon completion of azeotropic removal of water (water less than 1.0%), the slurry was cooled to 20 °C and stirred for 6 h. The solids were filtered, washed with 2B ethanol, and dried on the filter under nitrogen flow. The collected solids were added to a reactor followed by 2B ethanol (380 L). The slurry was stirred at reflux for 12 h, cooled to 20 °C, and stirred for 1 h. The solids were filtered, washed with 2B ethanol (75 L), and dried under vacuum at 50 °C for 24 h. Yield: 67%. ^{1}H NMR (DMSO-d_6): δ 0.91 (d, 3H), 1.21 (d, 3H), 2.21 (d, 1H), 2.70 (d, 1H), 2.96 (s, 1H), 3.29 (bs, 1H), 3.43 (d, 1H), 3.58 (d, 1H), 3.76 (bs, 1H), 3.84 (s, 2H), 4.29 (bs, 1H), 4.69 (d, 1H), 4.75 (d, 1H), 6.92 (d, 1H), 7.09 (t, 2H), 7.15 (dd, 1H), 7.36 (t, 2H), 7.57 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 7.0, 15.9, 43.3, 45.8, 48.3, 49.4, 51.1, 56.8, 67.9, 114.3, 114.4, 124.2, 126.3, 126.7, 129.6, 130.0, 134.8, 154.8, 157.0, 160.1, 161.7, 166.0. Potency: 96.9%. HPLC purity: 97.5%. Arginine content: 27.3% (26.4% theoretical). Water: 0.4%. Ethanol 0.24%.

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