Organic Process Research & Development

Article

pubs.acs.org/OPRD

Practical Asymmetric Synthesis of a Chiral Piperazinone Derivative

Mark McLaughlin,* Kevin Belyk, Cheng-yi Chen, Xin Linghu, Jun Pan, Gang Qian, Robert A. Reamer, and Yingju Xu

Department of Process Research, Merck Research Laboratories, Merck & Co., Inc., Rahway, New Jersey 07065, United States

Supporting Information

ABSTRACT: A practical asymmetric route to a chiral piperazinone derivative, a fragment of MK-3207, is reported. The amine-bearing benzylic stereocenter is introduced via an asymmetric Pd-catalyzed hydrogenation of a cyclic sulfimidate in the presence of a chiral phosphine ligand. An efficient synthesis of the hydrogenation substrate is described, together with process development of the hydrogenation step and elaboration of the resulting cyclic sulfamate product to the desired piperazinone.

INTRODUCTION

The calcitonin gene-related peptide (CGRP) has been implicated in the pathogenesis of migraine headaches.[1] The development of small molecule CGRP-receptor antagonists offers potential for new treatments for this debilitating condition, which affects an estimated 13% of the general population.[2] As part of a drug development program at Merck, practical access to multikilogram quantities of clinical candidate MK-3207 was required.[3] This paper describes a second generation catalytic asymmetric approach to the key piperazinone intermediate **1**.

Clinical candidate MK-3207 comprises two main molecular fragments; piperazinone-acid **1** and aniline **2** (Figure 1). These two fragments are united via a late-stage amide formation. The focus of this report is synthesis design and process development of a commercially viable approach to the piperazinone acid **1**.

First Generation Synthesis. Early GMP deliveries of MK-3207 utilized the synthesis of the piperazinone acid **1** shown in Scheme 1. Although this route ably supported initial animal toxicology and clinical studies, it was recognized that an alternative approach would be required in the long term. The first generation route to piperazinone acid **1** comprises 10 steps in the longest linear sequence. There are several key issues with respect to process robustness/efficiency and economics. Despite extensive study, the asymmetric hydrogenation to set the benzylic stereocenter is only moderately effective and typically delivers material with enantiomeric excess in the range 60−70%. This lack of stereocontrol necessitates an upgrade via the dibenzoyltartaric acid salt in the downstream chemistry, compromising the overall process efficiency. Additionally, both the aminoketone **6** and ethyl glycine intermediates have limited chemical stability and create issues with process robustness. Furthermore, cost analysis of this route to piperazinone acid **1** identifies the synthetic amino acid "cycloleucine" as a major contributor. Since this reagent constitutes an integral part of the molecular structure of MK-3207, its use is essentially mandatory in any synthesis. Consequently, introduction of this component at such an early stage in a 10-step sequence is not the ideal strategy from an economic standpoint. Taking all of these factors into account, we set out to design a new approach to the piperazinone acid **1** that would provide higher synthetic efficiency, better stereocontrol, and greater overall economy.

Second Generation Synthesis. Retrosynthetic analysis for the proposed new route to the piperazinone acid **1** intermediate is shown in Scheme 2. The first disconnection reveals the core piperazinone heterocycle **13**, and it was anticipated that selective alkylation of the amide NH would be achievable under appropriate conditions. A benefit of this disconnection is that the source of the acid sidechain is now a readily available α-haloacetate reagent. This obviates a process robustness issue in the first generation synthesis, in which the unstable ethyl glycine free base is used as the source of this molecular fragment. To access the core piperazinone **13**, it was recognized that a cyclic sulfamate intermediate, **14**, with regiochemistry "reversed" from the first generation synthesis could significantly shorten the synthetic sequence and confer several additional advantages. In addition, cyclic sulfamates participate in ring-opening/ring-closing reaction sequences with bifunctional reagents (e.g., amino acids) to afford piperazinones in a single step.[4]

Because of steric encumbrance, cycloleucine appeared to be a challenging reaction partner for this process, but in light of the overall synthetic advantage conferred by this disconnection, it was worthy of investigation. Having identified the key chiral intermediate, a solution to the problem of the benzylic stereocenter was required. Asymmetric hydrogenation of unsaturated compounds represents one of the most attractive and practical options for control of functionalized stereocenters.[5] Consequently, we targeted cyclic sulfimidate **15** as a likely precursor of the chiral sulfamate and sought to derive this cyclic imine from a hydroxyacetophenone starting material (**16**).

Hydroxyacetophenone Synthesis. α-Hydroxyacetophenones are useful synthetic intermediates amenable to various asymmetric transformations capable of generating valuable chiral compounds.[6] Although α-hydroxyacetophenones have been featured many times in the chemical literature, there are only a limited number of reports directly focused on general procedures for their preparation, which is perhaps indicative of

Received: June 6, 2013
Published: July 11, 2013

dx.doi.org/10.1021/op400150w | Org. Process Res. Dev. 2013, 17, 1052−1060

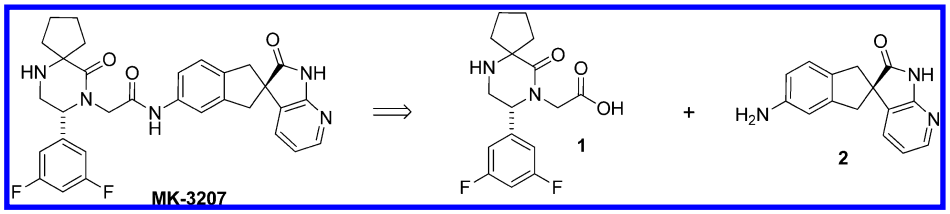
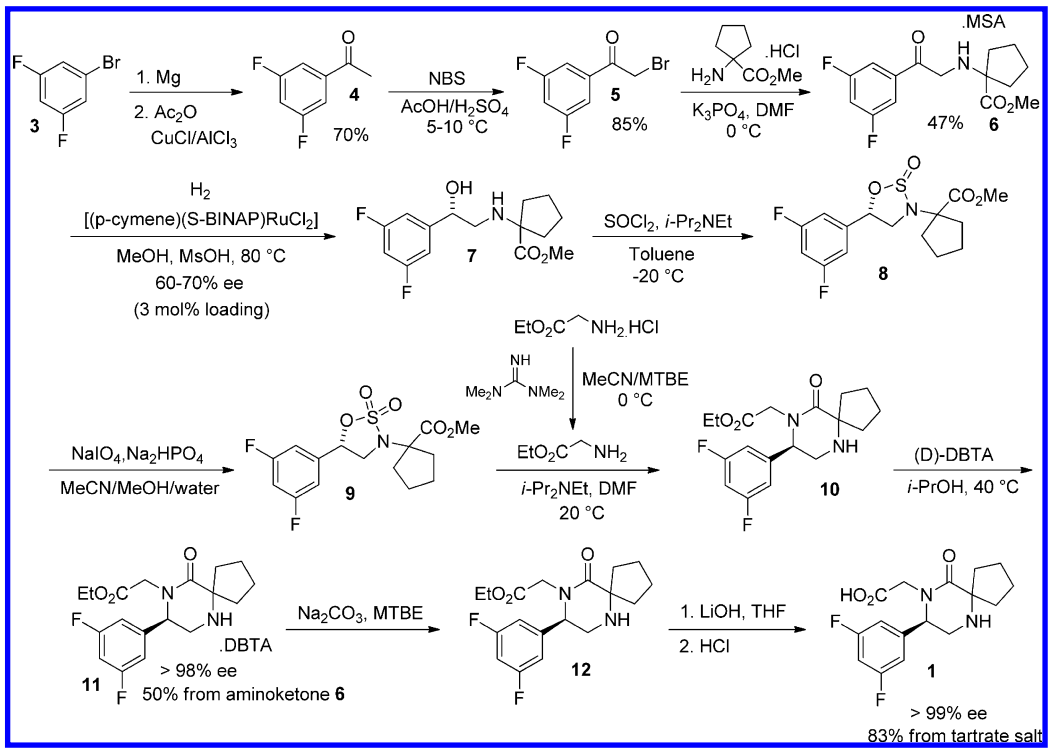
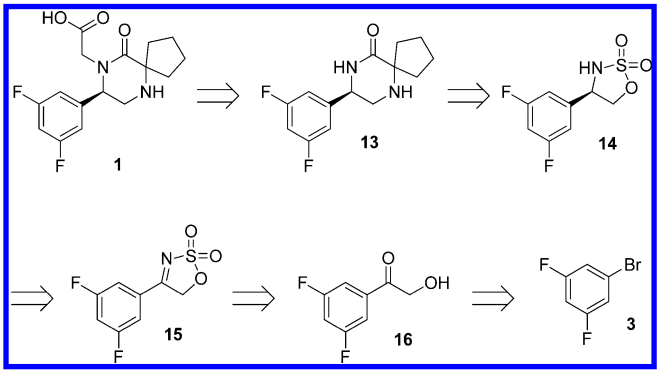


Figure 1. Amide bond disconnection of MK-3207 revealing the two key molecular fragments, piperazinone acid **1** and aniline **2**.

Scheme 1. First generation synthesis of piperazinone acid 1



Scheme 2. Retrosynthesis of piperazinone acid 1

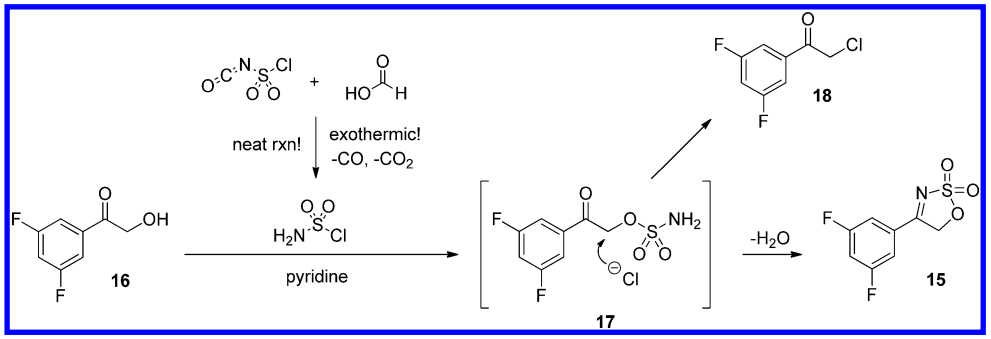


underlying stability issues associated with these intermediates.[7] Indeed, we encountered significant stability problems during our early attempts to work with our particular intermediate (**16**). These difficulties were eventually resolved when an understanding of the compound's instability to both oxygen and neutral-to-basic pH was obtained. The details of this chemistry have been described in a separate report.[8] In summary, following process development, we were ultimately able to access the desired hydroxyacetophenone in practical fashion, and this enabled study of the subsequent steps in our proposed synthesis.

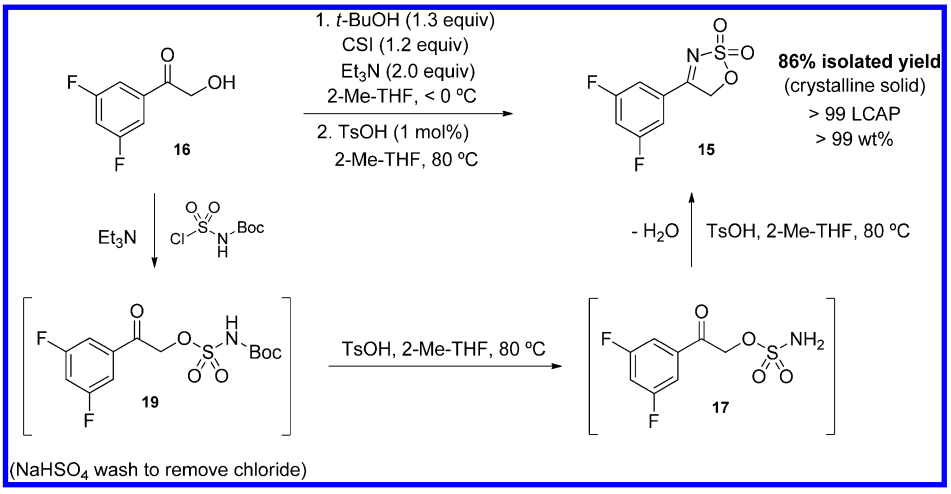
Cyclic Sulfimidate Synthesis. Cyclic sulfimidates similar to **15** have been described previously in the literature. Initial laboratory investigations quickly revealed the known methods of preparation to be entirely unsuitable for large-scale operation.[9] The literature method (Scheme 3) relies on an in situ preparation of sulfamoyl chloride, an unstable compound that is not readily commercially available on-scale. Reported procedures involve a neat reaction between *N*-chlorosulfonyl-isocyanate (CSI) and formic acid (95% aqueous), which is relatively hazardous. This reaction is highly exothermic and releases 2 mol of gas (carbon monoxide and carbon dioxide), and the mixture solidifies as conversion proceeds, affecting agitation and making control of the exotherm even more problematic. In the next stage, sulfamoyl chloride is combined with the α-hydroxyacetophenone **16** in the presence of pyridine to yield the *O*-sulfamoyl intermediate **17**, which is cyclized/dehydrated to the cyclic sulfimidate via thermal treatment during workup. A significant side-reaction here is nucleophilic attack by chloride ion on the uncyclized *O*-sulfamoyl intermediate to yield the α-chloroacetophenone **18**. Pyridine is a poor choice of base in this regard because pyridinium hydrochloride has reasonable solubility in the reaction medium and facilitates side-product formation (vide infra). In addition to having a detrimental effect on yield, the α-chloroacetophenone **18** is a severe lachrymator, creating handling/industrial hygiene issues during workup.

dx.doi.org/10.1021/op400150w | Org. Process Res. Dev. 2013, 17, 1052−1060

Scheme 3. Literature conditions applied to synthesis of cyclic sulfimidate 15



Scheme 4. Improved synthesis of cyclic sulfimidate 15



This procedure was deemed unsuitable for large-scale synthesis, and we developed a new process that is both safer and higher yielding (Scheme 4). The reaction of *tert*-butyl alcohol with CSI is essentially quantitative and cleanly generates *N*-Boc-sulfamoyl chloride. Since this process is a simple addition reaction, there are no gaseous byproducts. In addition, the reaction is conveniently run using an appropriate solvent (e.g., THF, 2-Me-THF), allowing for good control of the exotherm via rate of addition of reagent. Range-finding experiments indicate that over-reaction of excess *tert*-butyl alcohol with the initially formed *N*-Boc-sulfamoyl chloride is not an issue under the reaction conditions.[10] The resulting solution of *N*-Boc-sulfamoyl chloride has good stability, affording an acceptable operating window for large-scale processing.[11] Combination with the hydroxyacetophenone **16** generates negligible exotherm because there is no reaction until the subsequent addition of triethylamine; the O-sulfamoylation exotherm is controlled via addition rate of the base. O-Sulfamoylation generates intermediates (**17** and **19**) that are activated toward nucleophilic displacement by the chloride ion. The reaction temperature and age time also has a significant impact on the amount of the α-chloroacetophenone impurity formed, with >90% conversion after 24 h age at room temperature using pyridine as the base.

To mitigate these issues, we selected triethylamine as the base and 2-Me-THF as the solvent and defined the operating temperature range as −5 to 0 °C. Triethylamine hydrochloride precipitates from solution, which suppresses α-chloroacetophenone formation because of a reduced concentration of dissolved chloride ion. Cooling to <−10 °C decreases the substrate solubility and rate of reaction significantly. Above 0 °C, the solubility of triethylamine hydrochloride becomes greater, and the α-chloroacetophenone can accumulate over time. Under the optimal conditions, the O-sulfamoylation reaction is typically complete within 30 min, and the reaction is then quenched by the addition of 0.5 M $NaHSO_4$, maintaining the batch temperature around 0 °C. At this stage, the use of 2-Me-THF as solvent allows for a direct phase separation and rejection of triethylamine hydrochloride into the lower aqueous phase. A second polishing wash with additional 0.5 M $NaHSO_4$ ensures a negligible concentration of chloride ion in the organic phase and renders the intermediate *O*-sulfamoyl compound stable for continued processing at elevated temperatures.[12]

Although it is possible to isolate the *N*-Boc-protected *O*-sulfamoyl intermediate **19** via crystallization, the opportunity to through-process to the desired cyclic sulfimidate **15** was attractive. Accordingly, the wet 2-Me-THF solution of uncyclized intermediate **19** is treated with a catalytic quantity of $TsOH{\cdot}H_2O$ (1 mol %) and heated to reflux to effect sequential *N*-Boc deprotection and cyclization/dehydration to the cyclic sulfimidate **15**. The *N*-Boc group remains largely intact until the batch temperature reaches >60 °C and then undergoes smooth cleavage under the action of catalytic acid. Over the course of several hours, the conversion to cyclic sulfimidate **15** reaches >95%, and then close to complete conversion can be attained via azeotropic distillation of the 2-Me-THF.[13] The final isolation involves cooling and washing with water to remove residual inorganics ($NaHSO_4$) from the organic phase, followed by crystallization of **15** from a mixture

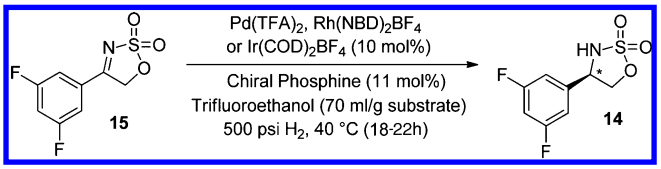
dx.doi.org/10.1021/op400150w | *Org. Process Res. Dev.* 2013, 17, 1052−1060

of 2-Me-THF/heptanes. The overall assay yield from hydroxyketone is 94% and the isolated yield is 86%.

Cyclic Imine Asymmetric Hydrogenation. Concurrent with our process development work, a literature report appeared on the asymmetric hydrogenation of cyclic sulfimidates.[9] In this report, the levels of conversion and enantiocontrol were excellent across a variety of substrates, so we were highly optimistic regarding our particular compound **15**. However, the optimal conditions described by Zhou have several potential drawbacks with respect to large-scale operation. From an economic perspective, the use of trifluoroethanol as solvent, $Pd(TFA)_2$ as a catalyst precursor, and (S,S)-Binaphane as the chiral ligand would all contribute to a high cost for the key asymmetric transformation in the new route. Furthermore, in practical terms, the requirement for relatively high pressures of hydrogen gas (500 psi) could limit options for implementing this chemistry at vendors lacking appropriate plant capabilities. To this end, we embarked upon a systematic study of the reaction conditions for this key transformation in the hope of finding an improved process.

For our initial screening of reaction conditions (Scheme 5, Figure 2), we elected to retain certain aspects of the published

Scheme 5. Conditions for initial evaluation of metal/ligand for asymmetric hydrogenation



procedure (such as the solvent (TFE) and hydrogen pressure of 500 psi) and vary the parameters of catalyst precursor and ligand. We also ran the control experiment in which the exact literature conditions were used. A summary of results is shown in Table 1.

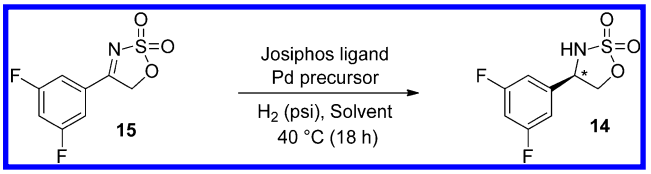
The control experiment using $Pd(TFA)_2$ and the binaphane ligand gave a result similar to that published. Complete conversion was reached in all cases, and excellent enantiomeric excess was also observed using Rh, Ir, and Pd catalyst precursors in conjunction with several alternative commercially available phosphine ligands. We selected the Josiphos ligand for further study because this was already available to us on production scale for support of another Merck marketed drug (Januvia).[14]

Examining the other reaction parameters (Table 2), we were pleased to quickly establish that $Pd(OAc)_2$ can replace $Pd(TFA)_2$ with similar performance. More significantly, in contrast to the literature report, replacement of TFE with MeOH as the reaction solvent was equally effective and confers

Table 1. Preliminary screening of catalyst/ligand combinations for asymmetric hydrogenation of cyclic sulfimidate 15

entry	ligand	metal	% ee
1	A	Pd	96
2	B	Pd	98
3	B	Rh	99
4	B	Ir	99
5	C	Pd	97

Table 2. Optimization of catalyst precursor and loading, solvent, hydrogen pressure, and reaction temperature



entry	metal precursor	solvent	H_2 (psi)	S/C	% conv	% ee
1	$Pd(TFA)_2$	TFE	500	200	>99.5	96
2	$Pd(TFA)_2$	MeOH	80	200	>99.5	96
3	$Pd(OAc)_2$	MeOH	80	200	>99.5	96
4	$Pd(OAc)_2$	MeOH	40	330	>99.5	96
5	$Pd(OAc)_2$	MeOH	20	330	>99.5	96
6	$Pd(OAc)_2$	MeOH	40	500	>99.5	96
7	$Pd(OAc)_2$	MeOH	20	500	84	96
8	$Pd(OAc)_2$	MeOH	40	1000	52	96
9	$Pd(OAc)_2$	MeOH	20	1000	14	96

several process advantages, such as cost reduction, alleviation of industrial hygiene concerns around TFE, and the opportunity for a simple product isolation (vide infra). Also notable is the option to conduct the hydrogenation using significantly lower hydrogen pressures and still obtain good reaction performance.

In the final process, the cyclic sulfimidate is dissolved in 5 vol of MeOH and subject to 0.3 mol % catalyst loading (0.33 mol % ligand) under 40 psi hydrogen at 40 °C (Scheme 6). After complete conversion, the batch is treated with carbon and filtered, and the desired product is isolated via crystallization following addition of water. The isolated yield is 94%, and the white solid is typically >99 wt % pure. The measured enantiomeric excess of the isolated material matches the in-process-control assay, indicating no upgrade is available via this crystallization. Subsequent crystallization of a downstream intermediate affords the necessary upgrade in stereochemical purity.

Piperazinone Formation. Cyclic sulfamates are known to undergo reactions with amino esters that ultimately cascade to piperazinones.[4] For the target piperazinone **13**, the amino ester required is the unnatural but commercially available "cyclo-

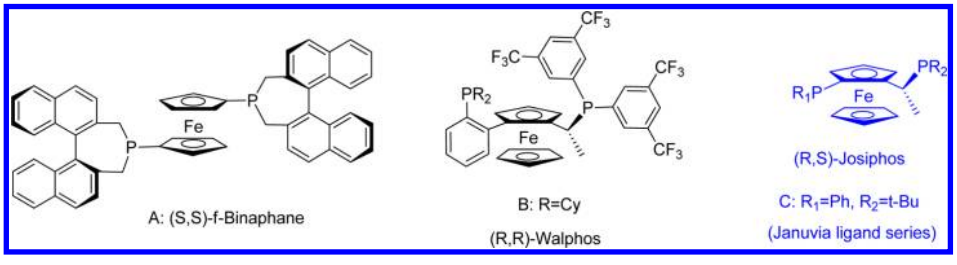
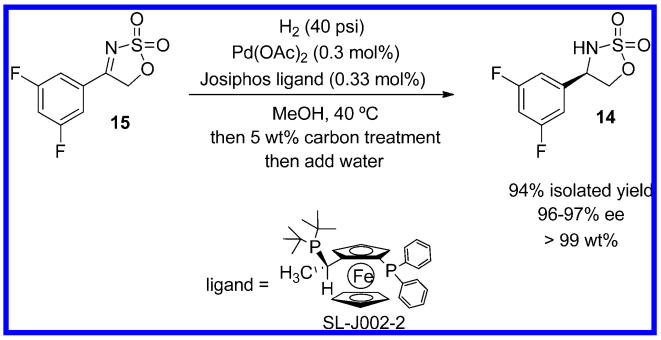


Figure 2. Ligands used for initial evaluation of the asymmetric hydrogenation.

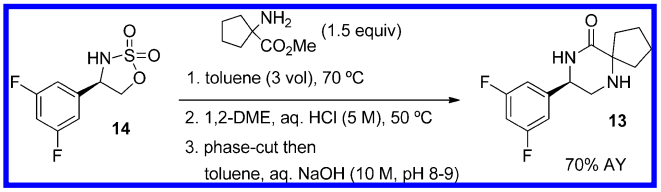
dx.doi.org/10.1021/op400150w | Org. Process Res. Dev. 2013, 17, 1052−1060

Scheme 6. Optimized conditions for asymmetric hydrogenation of 15



leucine". Because of the steric hindrance around the quaternary center, cycloleucine is an extremely poor nucleophile. In fact, in contrast to more typical amino esters, cycloleucine free-base is relatively stable for extended periods and does not polymerize to any significant extent.[15] This lack of reactivity necessitated significant process development to achieve an acceptable rate of reaction with cyclic sulfamate **14** and eventual yield of the desired piperazinone **13**. The reaction conditions used to gain proof-of-concept for this particular piperazinone formation are shown in Scheme 7.

Scheme 7. Initial conditions used to prepare piperazinone 13



Cycloleucine is available commercially as a hydrochloride salt that needs to be converted to free-base before reaction with cyclic sulfamate **14**. In our initial studies, cycloleucine free-base was extracted into toluene from aqueous potassium phosphate tribasic. Concentration of the organic phase allowed for azeotropic drying prior to reaction with the cyclic sulfamate.[16] Heating the dry toluene solution of cycloleucine and cyclic sulfamate **14** at 70 °C led to ring-opening, and then 5 M aqueous HCl was used to effect cleavage of the *N*-sulfate; however, the two-phase nature of the toluene/water system made the hydrolysis very slow. Addition of an acid-stable cosolvent (in this case, 1,2-DME) was necessary to make the phases partially miscible and increase the rate of hydrolysis to a practical level. After hydrolysis, the majority of substrate was present in the acidic aqueous phase (as determined by HPLC assay), whereas the organic phase contained some dark polymerized material, which was separated via a phase cut at this stage. Adjustment of the pH via treatment with 10 M aqueous NaOH caused lactam formation and partitioning into the freshly replaced organic phase. After phase cut and solvent switch, the desired lactam was isolated via crystallization.

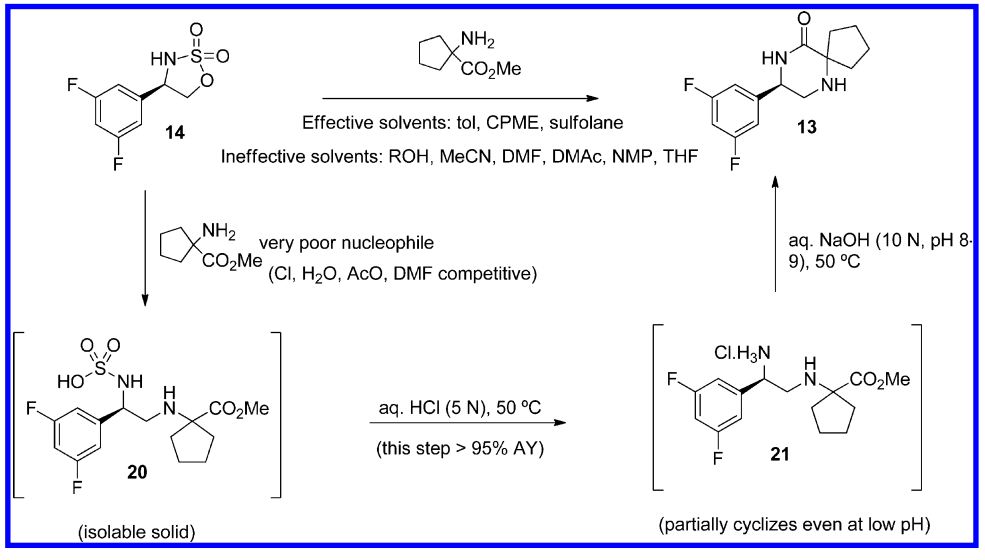
Although the overall yield was reasonable, a close examination of the various operations revealed several opportunities for process improvements. The overall piperazinone process involves four distinct stages: free-base of cycloleucine, ring-opening of cyclic sulfamate **14**, *N*-sulfate cleavage, and pH adjustment/ring closure to the piperazinone **13**.

In developing this overall process, the following parameters received close attention (Scheme 8):

(a) volatility of cycloleucine during free-base process
(b) dipolar aprotic solvent to enhance nucleophilic displacement
(c) absence of extraneous nucleophiles (including water and certain solvents)
(d) water miscibility/pH stability across a wide range for *N*-sulfate cleavage and lactamization

To address the sluggish nature of the ring-opening step, an evaluation of solvents was made, with particular focus on those likely to facilitate formation of the initially formed highly polar reaction intermediate (*N*-sulfate **20**). Protic solvents, such as MeOH and EtOH, were excluded after experiments confirmed partial solvolysis of the cyclic sulfamate substrate **14**. More surprising and discouraging, however, were observations that typical dipolar aprotic solvents, such as THF, MeCN, DMF, DMAc, and NMP, did not provide improved results. In fact, in the case of DMF and DMAc, these solvents are sufficiently nucleophilic to be competitive with cycloleucine and

Scheme 8. Reaction sequence for piperazinone formation



dx.doi.org/10.1021/op400150w | Org. Process Res. Dev. 2013, 17, 1052−1060

consequently lead to unwanted side-reactions and poor reaction profiles.

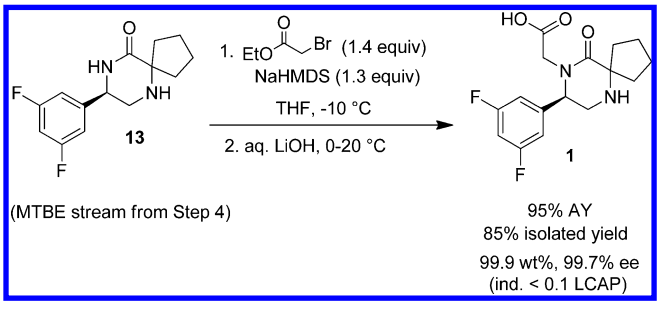
Following these observations, we turned our attention to sulfolane, a solvent that has been gaining in popularity for a variety of reactions and appeared to be a good candidate for our particular process.[17] Sulfolane has one of the highest dielectric constants of any solvent and was expected to promote the initial desired ring-opening to yield *N*-sulfate **20**. In addition and in contrast to other common dipolar aprotic solvents, sulfolane is nonnucleophilic, which virtually eliminates nonproductive solvolytic process, such as those encountered with DMF. Last, sulfolane is aqueous miscible and stable at low pH, which helps streamline the overall piperazinone-forming process.

The finalized process for piperazinone formation is as follows: Cycloleucine free-base is generated via partition of the hydrochloride salt between aqueous K_3PO_4 and MTBE followed by azeotropic drying of the MTBE layer.[18] The relative volatility of MTBE ensures minimal loss of the cycloleucine free-base during this distillation process. Upon reaching the desired water content specification (<100 ppm), the MTBE solution is concentrated and transferred into a solution of the cyclic sulfamate in sulfolane. Further distillation under reduced pressure removes MTBE from the system, and the resulting sulfolane solution of reactants is heated to 70 °C to promote the desired ring-opening.[19] Typical conversion is >95% after heating for 10 h. Addition of 5 M aqueous HCl and continued heating leads to hydrolysis of the *N*-sulfate; the aqueous miscibility of sulfolane renders the reaction system single phase and facilitates this hydrolysis.

Next, the system is adjusted to pH 10 using aqueous NaOH and heated to ensure complete lactamization. At the end of reaction, the mixture is extracted with MTBE, and after washing with brine, the majority of the sulfolane is rejected to the aqueous phase. The MTBE layer is decolorized with carbon, and the product piperazinone **13** can ultimately be isolated (vide infra) via crystallization following solvent switch into heptane. The typical corrected isolated yield is 70% (96% ee unchanged from input stream).[20] Given the lack of stereochemical upgrade achieved via the isolation of **13**, it appeared more attractive to through-process this intermediate into the final N-alkylation step. To our satisfaction, the crystallization after the N-alkylation step proved highly robust and consistently afforded good overall purity and sufficient stereochemical upgrade (vide infra).

Piperazinone Amide N-Alkylation. Alkylation of the piperazinone amide NH is accomplished via deprotonation using NaHMDS in THF followed by treatment with ethyl bromoacetate (Scheme 9).[21,22] The resulting ester is hydrolyzed in situ during workup with aqueous LiOH, and adjustment to pH 1 with aqueous HCl leads to precipitation of the crude intermediate HCl salt. Reslurry of this HCl salt in water followed by treatment with 1 equiv of NaOAc and heating to 80 °C allows for neutralization of the HCl and crystallization of the product **1** as the neutral form. This crystallization also affords the necessary upgrade in enantiopurity to deliver material that matches the previously established purity specifications for this regulated API starting material (>99 LCAP, 99.9 LC wt % purity, 99.7% ee). In addition, using piperazinone acid **1** (from the new chemistry) for the final amide bond formation to generate MK-3207 API was also shown to provide material matching the established specification.

Scheme 9. Piperazinone amide N-alkylation



CONCLUSION

In summary, we have developed a practical asymmetric synthesis of **1**, the chiral piperazinone acid fragment of CGRP clinical development candidate MK-3207 (Scheme 10). A scalable process for preparation of the prochiral cyclic sulfimidate **15** was defined, and an efficient asymmetric hydrogenation of this intermediate was used to set the key benzylic stereocenter. Significant improvements to the hydrogenation procedure were realized. The final process is conducted at mild temperature (40 °C) under relatively low pressure of hydrogen (40 psi) with low catalyst loading (0.3 mol %) and affords the desired product **14** in 96−97% ee. Further, the use of MeOH solvent allows for simple product isolation via addition of water and crystallization at the end of the reaction. Elaboration of the chiral cyclic sulfamate **14** into piperazinone **13** was achieved via a cascade reaction sequence with cycloleucine. The low reactivity of cycloleucine necessitated careful control of reaction conditions, and sulfolane was identified as a uniquely effective solvent for this process. Last, selective N-alkylation of the piperazinone amide with ethyl bromoacetate followed by in situ ester hydrolysis generated the target piperazinone acid **1** in high yield. Final crystallization of the piperazinone acid **1** results in consistent upgrade of stereochemical purity to afford material that matches the established specification for material prepared via the first-generation chemistry. In addition, comparison of both routes indicates the second-generation approach comprises fewer steps; has greater overall yield; and, as a result, is significantly more economical. Consequently, the new piperazinone acid chemistry based on cyclic sulfimidate asymmetric hydrogenation was chosen as the long-term synthesis for this fragment of clinical development candidate MK-3207.[23]

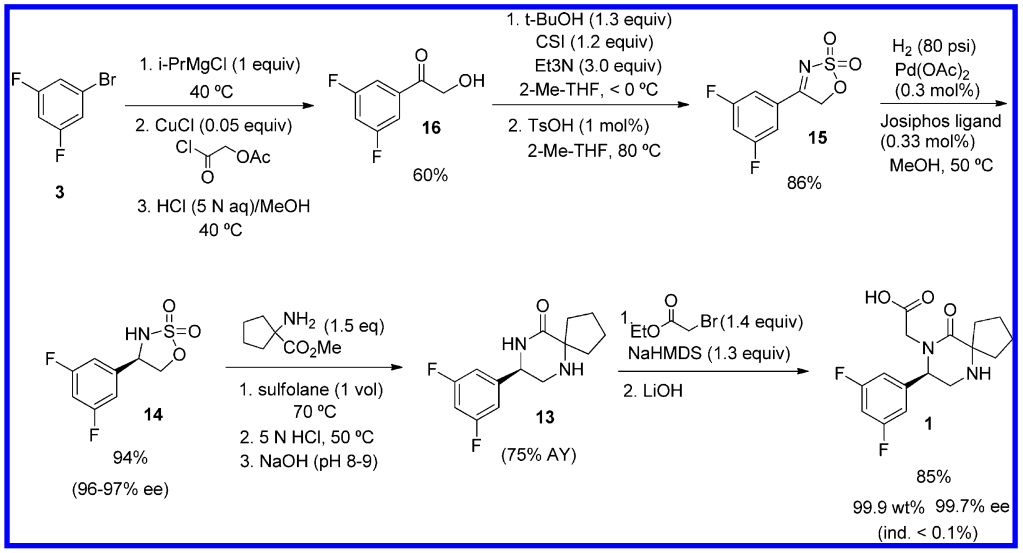
EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers. All reagents and solvents were used as supplied by manufacturers. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker 500 MHz spectrometer in the solvents indicated. HPLC was performed using an Agilent 1100 series instrument. HPLC method details for both reaction monitoring and % ee determination can be found in the Supporting Information, together with all relevant NMR spectra.

Preparation of 4-(3,5-Difluorophenyl)-5*H*-1,2,3-oxathiazole 2,2-Dioxide (15). A solution of 2-Me-THF (600 mL, 20 ppm water content by KF titration) and *t*-BuOH (73 mL, 762 mmol, 1.3 equiv, 570 ppm water content by KF titration) was cooled to between −10 and 0 °C. Neat *N*-chlorosulfonylisocyanate (CSI) (61 mL, 702 mmol, 1.2 equiv)

dx.doi.org/10.1021/op400150w | Org. Process Res. Dev. 2013, 17, 1052−1060

Scheme 10. The second generation synthesis of piperazinone acid 1



was charged at −5 to 0 C°. This solution of *N*-Boc-sulfamoyl chloride was aged for 30 min. A solution of hydroxyketone **16** (102 g, 580 mmol, 1 equiv) in 2-Me-THF (600 mL) was prepared (water content of solution was 322 ppm by KF titration). The solution of hydroxyketone **16** was transferred into the cooled (<0 °C) solution of *N*-Boc-sulfamoyl chloride with negligible exotherm. Neat Et_3N (114 mL, 818 mmol, 1.4 equiv) was charged at −10 to 0 C°. A precipitate of Et_3N·HCl formed. Temperature control at this stage and throughout workup of this step is critical to minimize formation of undesired side-product (*α*-chloroacetophenone derivative). After 1 h age between −10 and 0 C°, the reaction was quenched with 0.5 M $NaHSO_4$ (552 mL, 0.5 equiv) at 0−5 °C. Additional water (300 mL) was added. The lower aqueous phase was cut, and the pale yellow organic phase was washed with 0.5 M $NaHSO_4$ (552 mL, 0.5 equiv). After cutting the lower aqueous phase, catalytic TsOH·H_2O (1.1 g, 5.8 mmol, 0.01 equiv) was added, and the mixture was heated to 75 °C (reflux condition). After 14 h under standard reflux, the reaction was driven to completion via azeotropic water removal. The solution was cooled to 25 °C, and water (1 L) was added. The lower aqueous phase was cut, and the orange organic phase was dried via azeotropic distillation (KF < 500 ppm) and then concentrated to ∼0.2 L, during which time the product crystallized. Heptanes (0.4 L) were slowly added (at 20 °C) as antisolvent until a final ratio of 1:2 2-Me-THF/heptane was achieved. The resultant slurry of product **15** was cooled to 0 °C and aged for 1 h before filtration. The cake was washed with 2 bed volumes of 1:2 mixture of 2-Me-THF/heptanes mixture then, finally, with 2 bed volumes of heptanes. After drying, 116 g of **15** was obtained in >99 LCAP and >99 wt % purity by ^{1}H NMR vs 1,3,5-trimethoxybenzene as standard. The corrected isolated yield was 86% from **16**.

^{1}H NMR (500 MHz, DMSO): δ 6.09 (s, 2 H), 7.78−7.76 (m, 3 H). ^{13}C NMR (126 MHz, DMSO): δ 77.6, 111.3 (t, J_{CF} = 26 Hz), 113.2 (m), 130.8 (t, J_{CF} = 10 Hz), 163.9 (dd, J_{CF} = 250 and 13 Hz), 177.6 (t, J_{CF} = 3 Hz). HRMS calcd. for $C_8H_5SO_3NF_2$ (M + Na), 255.9856; found, 255.9857.

Preparation of 4-(3,5-Difluorophenyl)-1,2,3-oxathiazolidine 2,2-Dioxide (14). Cyclic imine **15** (116 g, 0.50 mol, 1 equiv) was charged to an autoclave vessel, followed by MeOH (1.2 L). In a separate vessel, the catalyst was prepared by mixing $Pd(OAc)_2$ (337 mg, 1.5 mmol, 0.3 mol %) and phosphine ligand (*S*)-(−)-1-[(*R*)-2-(diphenylphosphino)-ferrocenyl]ethyldi-*t*-butylphosphine (788 mg, 1.65 mmol, 0.33 mol %) in CH_2Cl_2 (40 mL) at room temperature for 15 min. The catalyst solution was then transferred to the substrate in MeOH under vacuum, and the system was placed under an atmosphere of H_2 (40 psi). The autoclave was heated to 40 °C for 16 h. After this time, sampling for HPLC analysis indicated >99% conversion and 97% assay yield. The reaction mixture was treated with carbon (Ecosorb C-941) and then filtered over Celite to afford a light brown solution. Addition of water to this MeOH solution induced crystallization of the sulfamate product **14**, which was collected by filtration and rinsed with further portions of MeOH/water. After drying at 40 °C under a nitrogen sweep, the product **14**, 110 g, was obtained as a white solid. The material was >99 LCAP, 96.4% ee and >99 wt % purity by ^{1}H NMR vs 1,3,5-trimethoxybenzene as standard. The corrected isolated yield was 94% from **15**.

^{1}H NMR (500 MHz, DMSO): δ 4.42−4.44 (m, 1 H), 4.97−4.99 (m, 1 H), 5.17−5.18 (m, 1 H), 7.20−7.22 (m, 3 H), 8.63 (d, J = 6.1 Hz, 1 H). ^{13}C NMR (126 MHz, DMSO): δ 57.8 (t, J_{CF} = 2 Hz), 75.0, 104.2 (t, J_{CF} = 26 Hz), 110.4 (m), 143.1 (t, J_{CF} = 9 Hz), 162.9 (dd, J_{CF} = 247 and 13 Hz). HRMS calcd. for $C_8H_7SO_3NF_2$ (M + Na), 258.0012; found, 258.0005.

Preparation of 8-(3,5-Difluorophenyl)-6,9-diazaspiro[4.5]decan-10-one (13). Cycloleucine hydrochloride salt (40.8 g, 0.23 mol, 1.7 equiv) was free-based via partition between MTBE (3 × 100 mL) and aqueous potassium phosphate (78.4 g, 0.37 mol, 2.7 equiv in 200 mL of water). The combined MTBE extract was distilled at constant volume under atmospheric pressure (with continuous addition of fresh 400 mL MTBE) to effect azeotropic water removal until the water content measured by KF titration was <100 ppm. Sulfolane (40 mL) was added, and the majority of MTBE was removed via continued distillation. Cyclic sulfamate **3** (32.4 g, 0.14 mol, 1 equiv) was charged, and the resultant solution was heated to 50 °C for 7 h. After this time, aqueous HCl (100 mL of 5 M, 0.50 mol, 3.7 equiv) was charged, and the mixture was heated to 60 °C for 3 h. The mixture was then pH-adjusted via addition of 10 M NaOH and heated to 60 °C for a further 2 h before cooling to room temperature. MTBE (300 mL) and 15% aq NaCl (450 mL) were charged, and the resulting two-phase

dx.doi.org/10.1021/op400150w | *Org. Process Res. Dev.* 2013, 17, 1052−1060

mixture was agitated for 10 min. The lower aqueous phase was cut, and the organic phase was washed with more 15% aq NaCl (2 × 300 mL) to remove sulfolane. The organic phase was then treated with Ecosorb C941 and filtered, and the solvent was switched to heptane to effect crystallization of the piperazinone **13**. After filtration, the product **13** was rinsed with heptane (100 mL) and dried to give a yellow solid (26.50 g, 97.5% NMR wt % for 70% corrected isolated yield).

^{1}H NMR (500 MHz, DMSO): δ 1.61−1.66 (m, 6 H), 1.93−1.96 (m, 1 H), 2.03−2.06 (m, 1 H), 2.67 (dd, J = 13.4, 6.9 Hz, 1 H), 3.12 (dd, J = 13.4, 4.6 Hz, 1 H), 4.56−4.59 (m, 1 H), 6.99−7.02 (m, 2 H), 7.12−7.13 (m, 1 H), 7.90 (s, 1 H). ^{13}C NMR (126 MHz, DMSO): δ 25.3, 25.4, 38.4, 38.5, 47.0, 56.8, 66.2, 103.0 (t, J_{CF} = 26 Hz), 110.1 (m) 147.3 (t, J_{CF} = 9 Hz), 162.8 (dd, J_{CF} = 247 and 13 Hz), 175.7. HRMS calcd. for $C_{14}H_{16}N_2OF_2$ (M + H), 267.1309; found, 267.1304.

Preparation of (*R*)-2-(8-(3,5-Difluorophenyl)-10-oxo-6,9-diazaspiro[4.5]decan-9-yl)acetic Acid (1). A solution of piperazinone **13** (4 g, 14.6 mmol, 1 equiv) in THF (16 mL) was cooled to −20 °C, and a THF solution of NaHMDS (1 M, 18.9 mL, 18.9 mmol, 1.3 equiv) was charged dropwise, maintaining the internal temperature <−10 °C. A homogeneous light brown solution was obtained. A solution of ethyl bromoacetate (2.3 mL, 20.4 mmol, 1.4 equiv) in THF (8 mL) was charged, again maintaining the internal temperature <−10 °C. A precipitate of NaBr was observed. The mixture was allowed to reach 10 °C, and then aqueous LiOH (5 wt %, 19.0 mL, 43.7 mmol, 3 equiv) was charged to effect in situ hydrolysis of the ethyl ester. After 2 h, the hydrolysis was complete, and the mixture was partitioned between water (10 mL) and heptane (35 mL). The lower, basic aqueous phase (containing the product acid **1**) was separated and cooled to 0−5 °C, then carefully acidified to a final pH of 1 using concentrated HCl. The product acid **1** crystallized (as the HCl salt) during pH adjustment and was collected via filtration. The cake was washed with 2 M aqueous HCl (20 mL) and briefly dried before being reslurried in water (40 mL). The slurry was heated to 80 °C, which dissolved the solid. Treatment of this solution with NaOAc (1.2 g, 14.6 mmol, 1 equiv) neutralized the HCl salt and caused recrystallization of the desired acid **1**. After filtration and drying, the acid **1** was obtained as a white solid (4.1 g, > 99 LCAP, > 97 wt % purity by NMR vs 1,3,5-trimethoxybenzene as standard, 99.9 LC wt % purity, 99.7% ee and corrected isolated yield of 85%). ^{1}H NMR (500 MHz, DMSO): δ 1.67−1.81 (m, 6 H), 1.93−2.01 (m, 1 H), 2.07−2.14 (m, 1 H), 2.83 (dd, *J* = 13.5, 3.8 Hz, 1 H), 3.21 (d, *J* = 17.1 Hz, 1H), 3.25−3.32 (m, 1H), 4.22 (d, *J* = 17.1 Hz, 1 H), 4.67 (s, 1 H), 7.02−7.06 (m, 2 H), 7.13−7.17 (m, 1 H). ^{13}C NMR (126 MHz, DMSO): δ 25.2, 25.5, 38.6, 39.3, 46.8, 47.9, 62.2, 67.1, 103.4 (t, J_{CF} = 26 Hz), 111.0 (m), 145.6 (t, J_{CF} = 9 Hz), 162.8 (dd, J_{CF} = 247 and 13 Hz), 170.5, 175.2. HRMS calcd. for $C_{16}H_{18}N_2O_3F_2$ (M + H), 325.1364; found, 325.1361.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of relevant NMR spectra and chromatograms are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

E-mail: mark_mclaughlin@merck.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors wish to thank T. J. Novak for the rapid acquisition of high resolution mass spectrometry data.

■ REFERENCES

(1) (a) Ho, T. W.; Edvinsson, L.; Goadsby, P. *J. Nat. Rev. Neurol.* **2010**, *6*, 573. (b) Durham, P. L. *Headache* **2008**, *48*, 1269.

(2) Stovner, L. J.; Hagen, K.; Jensen, R.; Katsarava, Z.; Lipton, R. B.; Scher, A. I.; Steiner, T. J.; Zwart, J. A. *Cephalalgia* **2007**, *27*, 193.

(3) For the discovery of MK-3207, see: Bell, I. M.; Gallicchio, S. N.; Wood, M. R.; Quigley, A. G.; Stump, C. A.; Zartman, C. B.; Fay, J. F.; Li, C.-C.; Lynch, J. J.; Moore, E. L.; Mosser, S. M.; Prueksaritanont, T.; Regan, C. P.; Roller, S.; Salvatore, C. A.; Kane, S. A.; Vacca, J. P.; Selnick, H. G. *Med. Chem. Lett.* **2010**, *1*, 24−29.

(4) (a) Williams, A. J.; Chakthong, S.; Gray, D.; Lawrence, R. M.; Gallagher, T. *Org. Lett.* **2003**, *5*, 811. (b) Bower, J. F.; Rujirawanicha, J.; Gallagher, T. *Org. Biomol. Chem.* **2010**, *8*, 1505.

(5) (a) Chen, Q.-A.; Ye, Z.-S.; Duan, Y.; Zhou, Y.-G. *Chem. Soc. Rev.* **2013**, *42*, 497. (b) Etayo, P.; Vidal-Ferran, A. *Chem. Soc. Rev.* **2013**, *42*, 728.

(6) (a) For example, asymmetric hydrogenation affording 1,2-diols, see: Ohkuma, T.; Utsumi, N.; Watanabe, M.; Arai, N.; Murata, K. *Org. Lett.* **2007**, *9*, 2565. (b) Asymmetric Mannich-type reactions affording β-amino-alcohols, see: Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (c) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778.

(7) For acetophenone oxidation, see: (a) Moriarty, R. M.; Berglund, B. A.; Penmasta, R. *Tetrahedron Lett.* **1992**, *33*, 6065. (b) Chen, C.; Feng, X.; Zhang, G.; Zhao, Q.; Huang, G. *Synthesis* **2008**, 3205. Via the dimethyl acetal, see: (c) Moriarty, R. M.; Hou, K.-C.; Prakash, I.; Arora, S. K. *Org. Synth.* **1986**, *64*, 138. Oxidation of silyl enol ethers, see: (d) Moriarty, R. M.; Prakash, O.; Duncan, M. P. *Synthesis* **1985**, 943. (e) Le, J. C.-D.; Pagenkopf, B. L. *J. Org. Chem.* **2004**, *69*, 4177. From α-haloacetophenones, see: (f) Zhu, G.; Casalnuovo, A. L.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 8100. (g) Wong, F. F.; Chang, P.-W.; Lin, H.-C.; You, B.-J.; Huang, J.-J.; Lin, S.-K. *J. Organomet. Chem.* **2009**, *694*, 3452. For enzymatic cleavage of α-acetoxyacetophenones, see: (h) Paizs, C.; Tosa, M.; Majdik, C.; Bódai, V.; Novák, L.; Irimie, F. D.; Poppe, L. *J. Chem. Soc., Perkins Trans. 1* **2002**, 2400. For hydroxymethylation of benzaldehydes, see: (i) Demir, A. S.; Ahyan, P.; Igdir, A. C.; Duygu, A. N. *Tetrahedron* **2004**, *60*, 6509. (j) Kuhl, N.; Glorious, F. *Chem. Commun.* **2011**, *47*, 573.

(8) McLaughlin, M.; Belyk, K. M.; Qian, G.; Reamer, R. A.; Chen, C. *J. Org. Chem.* **2012**, *77*, 5144.

(9) Wang, Y.-Q.; Yu, C.-B.; Wang, D.-W.; Wang, X.-B.; Zhou, Y.-G. *Org. Lett.* **2008**, *10*, 2071.

(10) In contrast, when the system is deficient in *tert*-butyl alcohol, the excess CSI can react directly with the hydroxyacetophenone to produce a carbamate side-product that is difficult to reject.

(11) Stability of prepared *N*-Boc-sulfamoyl chloride was demonstrated via 24 h hold prior to use in subsequent reaction, and equivalent results were observed.

(12) It is important to avoid a final brine wash of the organic layer because this will leave residual chloride in the organic phase and ultimately generate the α-chloroacetophenone side-product.

(13) The cyclic imine is stable to water at the elevated temperatures required for solvent distillation.

(14) Hansen, K. B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.; Spindler, F.; Malan, C.; Grabowski, E. J. J.; Armstrong, J. D. *J. Am. Chem. Soc.* **2009**, *131*, 8798.

(15) We observed <5% degradation, even after several weeks' storage of the free-base at room temperature.

(16) Because of the volatility of cycloleucine free-base, some material is lost via codistillation during azeotropic drying with toluene.

(17) Tilstam, U. *Org. Process Res. Dev.* **2012**, *16*, 1273.
(18) A final brine is not conducted since this was shown to leave residual chloride in the MTBE layer, which reduced the percent AY for the sulfamate ring opening via competitive nucleophilic attack by chloride.
(19) Range-finding studies demonstrated up to 10 vol % MTBE can be tolerated in the reaction system.
(20) Separate studies using isolated *N*-sulfate intermediate demonstrated that hydrolysis and lactamization occur in very high yield (95%), indicating the overall yield of 70% is associated with the ring-opening step.
(21) Ethyl bromoacetate is a potential genotoxic impurity; however, the strongly basic hydrolysis step followed by two different crystallizations (HCl salt and then final neutral form) is likely to consume/reject this reagent to below default threshold of toxicological concern. Prior to implementation of this new chemistry for GMP production, the development of MK-3207 was discontinued.
(22) Other bases studied include LiHMDS, KHMDS, and KO*t*-Bu, but inferior results were observed.
(23) During initial demonstration of the new process for synthesis, development of MK-3207 was discontinued. As a result, experimental details are provided for the 100 g scale early demonstration runs.