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Process Development for the Synthesis of Monocyclic β-Lactam Core 17

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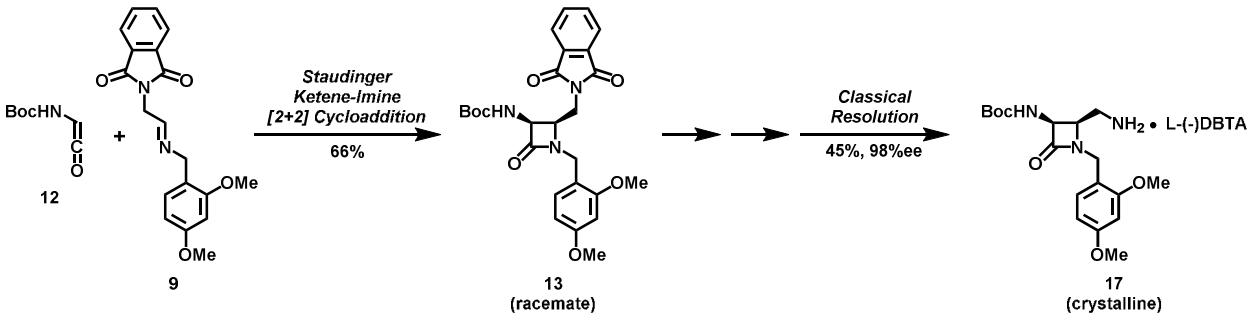


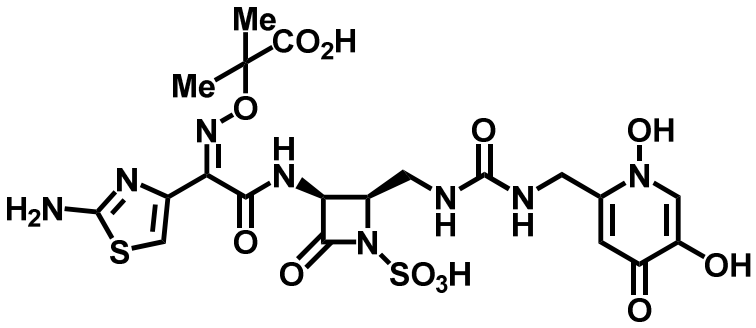
Table of Contents Graphic

ABSTRACT: Process development and multikilogram synthesis of monocyclic β-lactam core **17** is described for the novel pyridone-conjugated monobactam antibiotic (**1**). Starting with commercially available 2-(2,2-diethoxyethyl)isoindoline-1,3-dione **7**, the five step synthesis features several telescoped operations and direct isolations to provide significant improvement in throughput and reduced solvent usage over initial scale-up campaigns. A particular highlight in this effort includes the development of an efficient Staudinger ketene-imine [2+2] cycloaddition reaction of *N*-Boc-glycine ketene **12** and imine **9** to form racemic β-lactam **13** in good isolated yield (66%) and purity (97%). Another key feature in the synthesis involves a classical resolution of racemic amine **15**, to afford single enantiomer salt **17** in excellent isolated yield (45%) and high enantiomeric excess (98%).

Keywords: monocyclic β-lactam, Staudinger ketene-imine, [2+2] cycloaddition, classical resolution, antibacterial agent, multidrug-resistant strains

INTRODUCTION

Monobactam **1** (Figure 1),[1] is a synthetic pyridone-conjugated monocyclic β-lactam with potent *in vitro* antibacterial activity against clinically relevant Gram-negative species including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*. The discovery and development of new antibiotics has drawn considerable attention in recent years due to the alarming rise of resistant bacteria.[2] The growing epidemic of infections caused by multidrug resistant (MDR) Gram-negative bacteria and lack of new antibacterial agents are of considerable concern to the medical community.[3] Fortunately, iron is an essential nutrient of microbial life and plays a critical role in the virulence of microbes. Bacteria have evolved efficient iron acquisition systems to assimilate iron from their environment. One approach to the design of antibacterial agents capable of eradiating Gram-negative pathogens involves a "Trojan Horse" strategy, where the bacterial iron acquisition system is hijacked to deliver a drug to the periplasmic space, resulting in cell death.[4] Efforts in our antibacterial research program led to the discovery of monobactam **1** as a promising candidate for treatment of life threating infections caused by Gram-negative pathogens including some multidrug-resistant strains.[1]



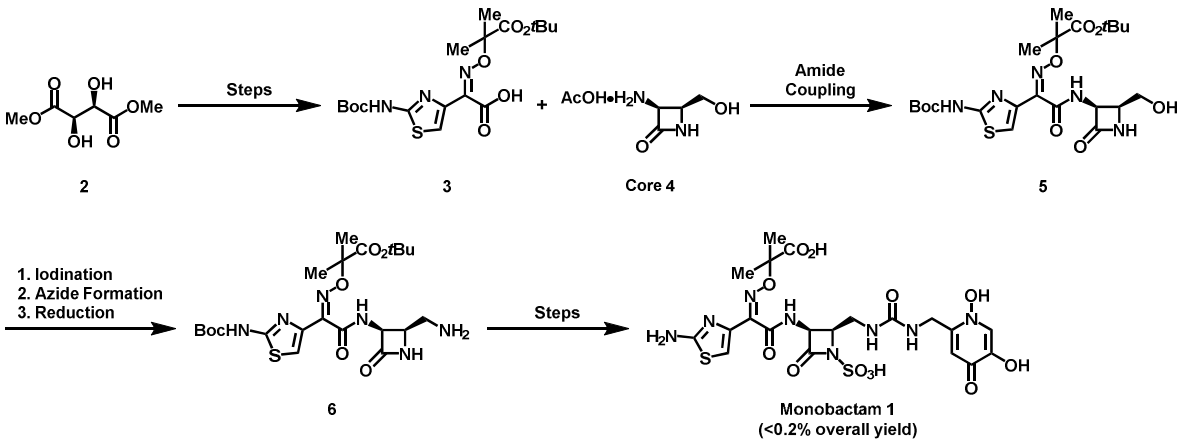
Monobactam 1

Figure 1. Chemical structure of monobactam **1**.

DISCUSSION AND RESULTS

1. **Original Synthetic Route to Monobactam (1).** In our original synthesis of monobactam **1**, 1,3-thiazole side chain **3** and aminoalcohol β-lactam core **4** were sequentially installed in a seventeen-step linear sequence from L-(+)-dimethyl tartrate **2** (Scheme 1).[1] There were several issues in this original synthesis: (1) The overall yield was less than 0.2%, most notably alcohol **5** required a three step conversion to the amine functionality utilizing hazardous reagents including tetrabutylammonium azide; (2) Several steps in the synthesis required extensive chromatography (four normal phase, one reverse phase and one chiral phase); (3) All advanced intermediates lacked crystallinity; and (4) The final form of the active pharmaceutical ingredient (API) was amorphous. The initial synthesis was further hampered by unstable intermediates and inconsistent yields in many steps and was therefore deemed unscalable. With so many issues encountered in the original synthetic approach, our efforts turned to an improved synthetic route.

Scheme 1. Original synthesis of monobactam 1

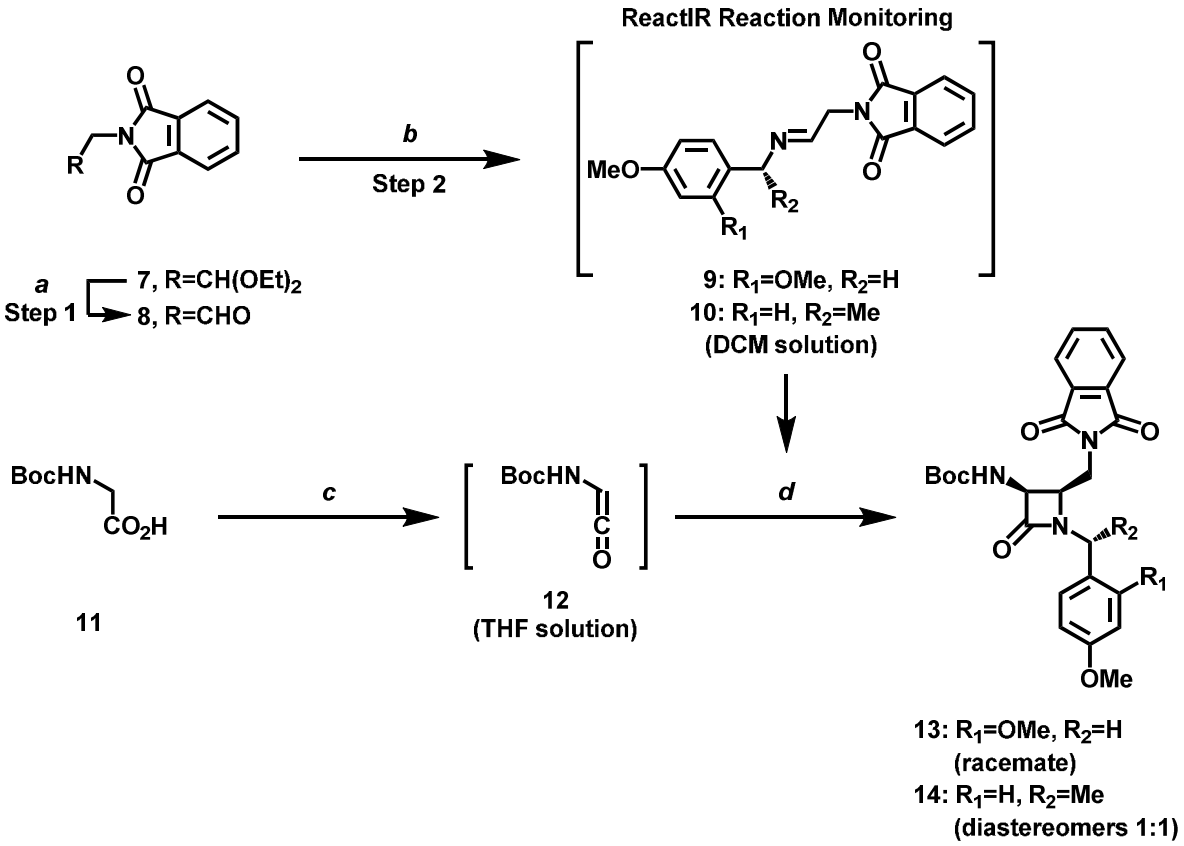


2. **Route Optimization to Amine 18.** In order to generate sufficient quantities of **1** for preclinical toxicology studies, the synthetic route to **6** required an extensive overhaul. Our primary focus was to design a streamlined and robust route to confidently ensure an initial delivery of approximately 0.5 kg of API. In addition, the route needed to be amenable to subsequent process development improvements for future multikilogram campaigns to support clinical trials. An additional challenge was to identify a stable crystalline final form of the API to enable purification and formulation development.

2.1. Preparation of Monocyclic β-Lactam Core. The initial synthesis of **1** featured a three-step sequence to convert a hydroxyl group (**5**) to an amine functional group (**6**).[1] Route efficiency could be greatly improved by early introduction of the 4-aminomethyl group. With this approach in mind, we envisioned a Staudinger ketene-imine reaction to prepare the β-lactam core through a [2+2] cycloaddition process with a suitable ketene and imine to deliver the required 4-aminomethyl group. The Staudinger ketene-imine reaction is often employed for the construction of azetidin-2-one ring systems.[5] This method provides a particularly useful and economical entry to β-lactams due to straightforward access to both ketene and imine starting materials.[6,7]

2.2. Staudinger Ketene-Imine Reaction. In the first step (Scheme 2), commercially available diethyl acetal **7** was treated with TFA under anhydrous conditions in dichloromethane to afford aldehyde **8**. Solvent swap to toluene and heptane (1:3) gave **8** in good yield (94%) as a crystalline product.

Scheme 2. Synthesis of β-lactam core 13 and 14[a]



[a]Reagents and conditions: a) TFA, DCM (94%); b) 2,4-DMB or *(R)*-α-methyl-PMB, 3Å molecular sieves, DCM; c) **11**, TEA, EtOCOCl, THF, -50 °C; d) **9**, TEA, -50 to 16 °C (66%, **13** racemate); **10**, TEA, -55 to 22 °C (70%, **14** diastereomers 1:1).

The key [2+2] cycloaddition reaction was achieved through a series of telescoped operations. Aldehyde **8** was treated with 1.0 equivalent of 2,4-dimethoxybenzylamine (2,4-DMB) in dichloromethane from 0 to 20 °C. The solution was charged with Type 3Å molecular sieves to scavenge deleterious water and drive Schiff base formation.[8a] Imine formation was monitored by *in situ* ReactIR (Figure 2). Trend analysis shows imine (1677 cm^{-1}, C=N vibration stretch) formation is rapid, occurring upon addition of the

amine to the aldehyde (1727 cm^{-1}, C=O vibration stretch) indicating fast and complete consumption of starting materials to form Schiff base adduct **9**. Off-line proton NMR could also be used to monitor the Schiff base formation. After filtration, the imine solution in dichloromethane was directly telescoped into the next operation. Concurrently, *N*-Boc-glycine **11** (2.0 equivalent) in THF was treated with TEA (2.2 equivalent), followed by ethyl chloroformate (2.6 equivalent) at -55 ^{o}C. The reaction mixture was held at -50 ^{o}C for 3 hours to ensure complete formation of the mixed anhydride. Furthermore, using ReactIR we were able to detect the formation of the mixed anhydride (1820 cm^{-1}) but not the proposed ketene (2100 cm^{-1}).[8b] A stress test analysis indicated the reaction mixture could be held at -50 ^{o}C for up to 6 hours with minimum profile change. The imine solution in dichloromethane was then added to the mixed anhydride solution in THF at -50 ^{o}C, followed by additional TEA (1.1 equivalent), which presumably initiates ketene (**12**) formation thereby facilitating the [2+2] cycloaddition. The temperature of the reaction mixture was gradually increased to 16 ^{o}C and held for 12 hours, resulted in a relatively clean β-lactam product profile. The mixture was quenched with water and the organic solvents were removed under vacuum. The solution was treated with MTBE which gave **13** as a crystalline solid from the biphasic solvent system. Racemic β-lactam **13** was isolated is good yield (66%) and HPLC purity (97%).

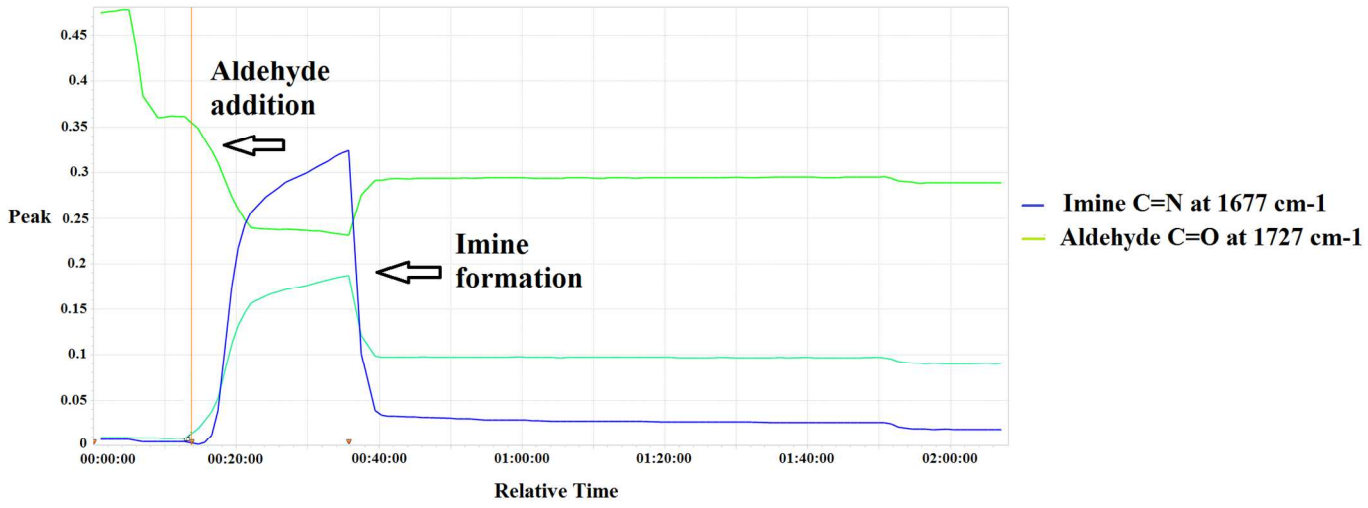


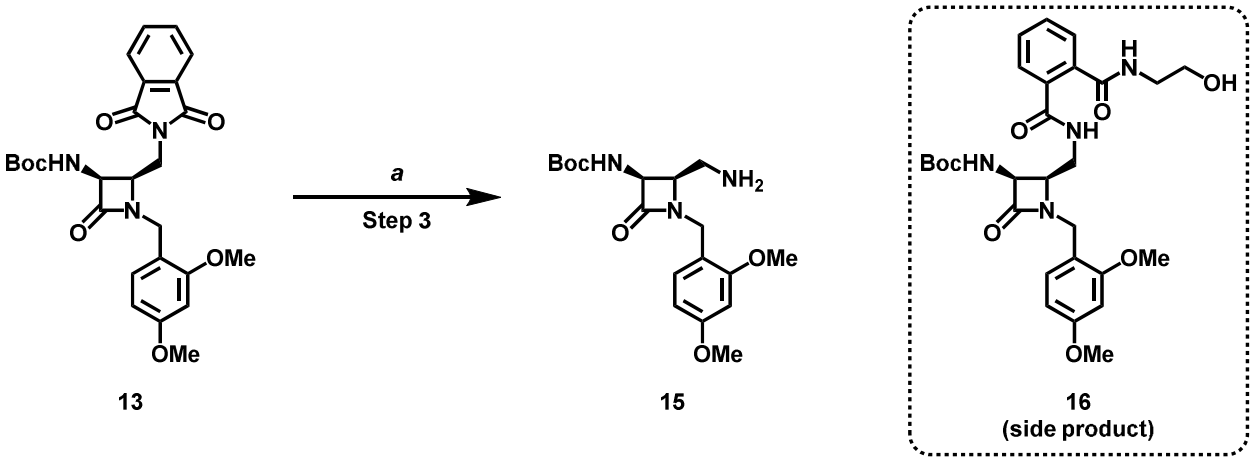
Figure 2. ReactIR trend analysis of characteristic peaks: aldehyde (1727 cm^{-1}) and imine (1677 cm^{-1}).[12]

Asymmetric Staudinger ketene-imine cycloaddition reactions have been reported in the literature previously[9] and this approach theoretically provides a stereoselective route to the β-lactam nucleus. For instance (Scheme 2), we proposed that the reaction between chiral imine **10**, prepared from achiral aldehyde **8** and chiral amine *(R)*-4-methoxy-α-methylbenzylamine and *N*-Boc-glycine derived achiral ketene **12** might proceed with useful levels of asymmetric induction. Unfortunately, chiral imine **10** gave β-lactam **14** with no observable diastereoselectivity (1:1); albeit comparable [2+2] cycloaddition conversion (70%). With no diastereomeric preference observed with the *(R)*-α-methyl-PMB auxiliary and similar isolated yields (**13**, 66% vs. **14**, 70%), we moved forward with the more cost-effective 2,4-DMB group.

To liberate the primary amine from phthalimide **13**, a milder and safer method was sought to overcome the shortcomings associated with using a hydrazinolysis approach on scale.[10] We found ethanolamine (Scheme 3) to be an exceptionally mild

phthalimide deprotecting agent which avoided epimerization and/or β-lactam ring opening observed with other reagents (i.e. $MeNH_2$, $H_2N(CH_2)_2NH_2$, $NaBH_4$). Thus, phthalimide **13** was treated with 15 equivalents of ethanolamine in ethyl acetate under reflux for 2 hours to give a mixture of amine **15** and side product bis-amide **16** (~10%). Attempts to decrease side product **16** through reaction modification were not successful. Fortunately, **16** was partially removed by recrystallization from EtOAc/heptane (1:4) to afford **15** (contaminated with 4% side product **16**) in 88% yield. Further manipulation prior to the classical resolution *(vide infra)* completely removed **16**.

Scheme 3. Phthalimide cleavage[a]



[a]Reagents and conditions: a) Ethanolamine, EtOAc (88%).

*2.3. Classical Resolution of Racemate **15**.* Attention was then turned to the classical resolution of racemic amine **15** (Scheme 4). Amine **15** is a relatively strong base

with a calculated pKa of 9.14 (ACD labs v 9.08). Consequently, there was little concern that it would form salts with carboxylic acid resolving agents chosen for the screen.[11] Initially a broad screen was run using eight counterions *(S)*-O-acetylmandelic acid, *(1R,3S)*-camphoric acid, *(S)*-camphorsulfonic acid, dibenzoyl-L-tartaric acid, di-*p*-toluoyl-L-tartaric acid, L-malic acid, *(S)*-mandelic acid, and L-tartaric acid) and five solvents (acetone, acetonitrile, ethanol, ethyl acetate, and 2-propanol).

Table 1 summarizes the conditions and results from the resolution screen. The best resolutions were obtained using dibenzoyl-L-tartaric acid (L-(-)DBTA) in relatively non-polar solvents ethyl acetate > MIBK > 2-methyltetrahydrofuran > isopropyl acetate. The next best resolving agent was di-*p*-toluoyl-L-tartaric acid, which performed best in acetonitrile > ethyl acetate. While resolution was not very high with *(S)*-mandelate and L-tartrate salts formed from alcoholic solvents, these two resolving agents provided good removal of miscellaneous more polar impurities.

Table 1. Summary of salt resolution screen for 15[a-b]

		Acid							
		(S)-O-Acetylmandelic acid	*(1R,3S)*-Camphoric acid	*(S)*-Camphorsulfonic acid	Dibenzoyl-L-tartaric acid	Di-p-toluoyl-L-tartaric acid	L-Malic acid	*(S)*-Mandelic acid	L-Tartaric acid
Solvent	Acetone								
	Acetonitrile					47.4 (85.8)		3.8 (90.0)	5.2 (91.4)
	Butanol	N/R	N/R	N/R		N/R	N/R	N/R	N/R
	Ethanol							3.6 (97.7)	7.6 (99.5)

	Ethyl Acetate			3.2 (96.4)	**88.8 (78.1)**	(22.6) (85.3)		3.0 (87.9)	
	Isopropyl acetate	N/R	N/R	N/R	70.8 (79.7)	N/R	N/R	N/R	N/R
	2-Methyl THF	N/R	N/R	N/R	83.8 (68.7)	N/R	N/R	N/R	N/R
	MIBK	N/R	N/R	N/R	85.0 (74.3)	N/R	N/R	N/R	N/R
	2-Propanol						6.6 (90.8)	4.0 (96.5)	8.4 (90.3)

[a]Chiral SFC method used to resolve **15** enantiomers, for details see Experimental Section.

[b]**17** percent ee values (top value = % ee) and combined area percent for **15** and **17** (bottom value = (area %)) as isolated solids.

[c]ee and area % values were from chiral SFC chromatograms from samples of each solid dissolved in methanol at 1 mg/mL. The starting lot of racemate PF-05284482 showed 2.8% ee and 82.75 area% by this assay.

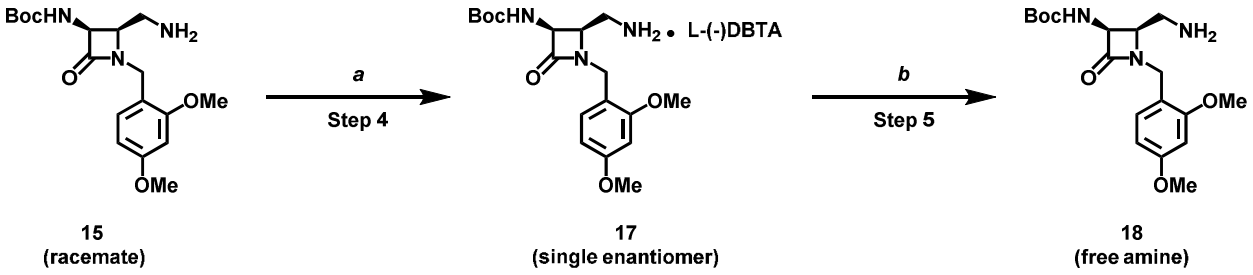
[d]Experiments that produce either solutions or oils are left blank in the table.

Experiments that were not run are noted as (N/R).

As mentioned, dibenzoyl-L-tartaric acid was identified as the best resolving agent from the screen. The highest ee for this resolving agent was obtained using ethyl acetate as the solvent (88.8% ee). A second screen was conducted using dibenzoyl-L-tartaric acid in four additional solvents: 1-butanol, isopropyl acetate, 2-methyltetrahydrofuran and methyl isobutyl ketone. Unfortunately, none of these solvents improved the enantiomeric excess over ethyl acetate. The dibenzoyl-L-tartaric acid/ethyl acetate conditions were selected for scale up. Treatment of **15** (containing 4% side product **16**) with diatomaceous earth (50% wt. to **15**) in ethyl acetate was effectively used to remove insoluble **16**. It was

found that 1.0 mole equivalent of resolving acid and 30 volumes of ethyl acetate (to reduce the viscosity for effective agitation) were required to successfully execute the classical resolution. Stress testing the reaction showed that ~30% decomposition occurred at reflux for 1 hour and a non-stirrable gel resulted at temperatures below 40 ^{o}C. Therefore, 60 ^{o}C for 45 to 60 minutes was chosen as reaction temperature and time. To facilitate filtration of the resolved diastereomeric salt **17**, another portion of diatomaceous earth (100% wt. to **15**) was added prior to addition of the resolving acid. Using this protocol, compound **17** was isolated as a ~1:1.1 mixture of salt and diatomaceous earth as determined by ^{1}H NMR. The yield for **17** was calculated as 45% (98% ee). Furthermore, CHN data suggested the salt was isolated as a half hydrate (~0.5 equivalent water).

Scheme 4. Classical resolution and amine liberation[a]



15 (racemate) **17** (single enantiomer) **18** (free amine)

[a]Reagents and conditions: a) L-(-)DBTA, EtOAc (45%, 98% ee); b) 5% aqueous K_3PO_4, EtOAc (80%, 99% ee).

With **17** in hand as a diatomaceous earth mixture, our efforts turned to the salt break and removing the filter aid to liberate the free amine without degrading the

sensitive β-lactam ring (Scheme 4). To our delight, basification of salt **17** with 5% aqueous K_3PO_4 at pH 8 − 9 followed by recrystallization from ~7:1 heptane and ethyl acetate provided free amine **18** (99% ee) in 80% yield as a white powder with no detectable presence of side products from ring opening or epimerization.

CONCLUSION

A practical five-step chemical process was developed for the multikilogram preparation of enantiopure amine **18** (99% ee), starting from commercially available diethyl acetal **7** and *N*-Boc-glycine in 20% overall yield. The process employs a Staudinger ketene-imine [2+2] cycloaddition reaction to prepare the β-lactam core that bears the necessary 4-aminomethyl group (racemate **13**, 66% yield). A classical resolution was developed to resolve racemic amine **15** using dibenzoyl-L-tartaric acid in ethyl acetate to provide single enantiomer **17** in 45% yield with 98% ee, and the salt was broken to afford target **18** in 80% yield and 99% ee . All isolated intermediates were obtained through crystallization or precipitation and filtration, avoiding chromatographic steps. Solvent usage and waste streams were reduced by telescoped operations. This synthesis dramatically improves upon the original seventeen-step linear sequence to generate this key intermediate. Process development efforts applied to the total synthesis of API **1** will be disclosed separately.

EXPERIMENTAL SECTION

General. All commercially available materials and solvents were used as received, unless otherwise stated. Reaction temperatures were measured internally, unless indicated otherwise (rt = 20 − 23 °C). Achiral HPLC analyses were carried out using Agilent Extended C-18 column (75 mm x 3 mm, 3.5 μm); column temperature 45 °C; flow rate 1.0 mL / minute; detection UV 230 nm; mobile phase: solvent A = acetonitrile (100%), solvent B = acetonitrile (5%) in 10 mM ammonium acetate; gradient elution: 0-1.5 minutes solvent B (100%), 1.5-10.0 minutes solvent B (5%), 10.0 − 13.0 minutes solvent B (100%); total run time 13.0 minutes. HPLC purity is reported by area %.

(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)acetaldehyde (8). To a nitrogen-purged glass-lined reactor A was charged **7** (14.5 kg, 55.07 mol) and dichloromethane (28.0 L), and the solution was stirred for 30 min at 20 °C. In a separate nitrogen-purged glass-lined reactor B was charged trifluoroacetic acid (14.0 L, 185.15 mol) and the resulting solution was transferred to reactor A over 15 min while maintaining the reaction temperature at 20 °C. The reaction mixture was stirred at 20 °C for 20 hours. HPLC analysis indicated reaction completion. The dichloromethane and trifluoroacetic acid were distilled with toluene (2 x 42.0 L, then 3 x 70.0 L) using vacuum at 40 °C to a final volume of 34.0 L. The toluene solution was cooled to 20 °C and charged with heptane (70.0 L) over 45 min while maintaining the reaction temperature at 20 °C. The resulting mixture was crystallized over 2 h. The batch was filtered and the solids washed with a mixture of toluene and heptane (1 : 3, 16.8 L), followed by heptane (14.0 L). The solids were dried under vacuum with a nitrogen sweep at 50 °C over 8 h to afford the desired product **8** as a white solid. Yield: 9.89 kg, 52.13 mol, 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.86 - 7.93 (m, 2H), 7.73 - 7.80 (m, 2H), 4.57 (s, 2H). HPLC retention time 5.1 minutes.

***tert*-Butyl{*cis*-1-(2,4-dimethoxybenzyl)-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-4-oxoazetidin-3-yl}carbamate (13).** To a nitrogen-purged glass-lined reactor A was charged **8** (3.40 kg; 17.97 mol) and dichloromethane (56.78 L), and the reactor was cooled to 0 ^{o}C. The solution was treated with 2,4-dimethoxybenzylamine (3.01 kg, 17.97 mol) over 20 min while maintaining the temperature at 0 °C. The 2,4-dimethoxybenzylamine charging equipment was rinsed with dichloromethane (3.40 L) and the rinsate added to reactor A.

The solution was stirred for 15 min at 0 °C and then treated with molecular sieves (5.85 kg, Type 3A). The reactor was warmed to 20 ^{o}C and the reaction slurry was stirred for 2 h. The slurry was filtered and the filter cake was rinsed with dichloromethane (13.60 L). The dichloromethane filtrate (imine solution) was used directly in the next step.

To a nitrogen-purged glass-lined reactor B was charged *N*-(*tert*-butoxycarbonyl)glycine **11** (6.30 kg, 35.96 mol) and tetrahydrofuran (64.60 L). After stirring for 1 h under nitrogen, the reactor was cooled to -50 °C and treated with triethylamine (4.0 kg, 39.53 mol) over 30 min while maintaining the temperature at -50 °C. The triethylamine charging equipment was rinsed with tetrahydrofuran (1.7 L) and the rinsate added to reactor B. The mixture was stirred for 30 minutes at -50 °C and then treated with ethyl chloroformate (5.07 kg, 46.73 mol) over 30 minutes while maintaining the temperature at -50 °C. The ethyl chloroformate charging equipment was rinsed with tetrahydrofuran (1.7 L) and the rinsate added to reactor B. The reaction mixture was stirred at -50 °C for 3 hours.

The previously prepared imine solution was transferred to reactor B over 1 h while maintaining the temperature at -50 °C. The imine solution charging equipment was rinsed with

dichloromethane (3.40 L) and the rinsate added to reactor B. The slurry was treated with triethylamine (1.82 kg, 17.98 mol) and the reaction mixture was slowly warmed to 16 °C over 6 h and then stirred for an additional 12 h. The reaction slurry was charged with water (13.60 L) and the volatiles removed under vacuum at 35 °C until a volume of 40.0 L remains. Reactor B was charged with additional water (40.80 L) and the volatiles removed under vacuum at 35 °C until a volume of 60.0 L remained. The mixture was treated with methyl *tert*-butyl ether (40.80 L) and the resulting mixture was crystallized over 2 h. The batch was filtered and the solids washed with water (2 x 14.96 L), followed by methyl *tert*-butyl ether (2 x 12.0 L). The solids were dried under vacuum with a nitrogen sweep at 50 °C over 18 h to afford the desired product **13** as a white solid. Yield: 5.87 kg, 11.86 mol, 66%. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.85 (s, NH), 7.80 (s, 4H), 6.78 (d, J = 7.8 Hz, 1H), 6.25 (m, 1H), 6.10 (m, 1H), 4.83 (m, 1H), 4.38 (d, J = 9.5 Hz, 1H), 3.77-3.95 (m, 3H), 3.62 (s, 3H), 3.45 (m, 1H), 3.40 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.5, 166.5, 160.0, 157.6, 155.0, 134.3, 131.5, 130.0, 122.9, 114.7, 104.3, 98.0, 78.6, 58.4, 55.0, 54.4, 40.0, 38.3, 28.0; HRMS (IS) Calcd for 496.2084, found 496.2077. HPLC retention time 6.05 minutes; XBridge C8 column (4.6 x 75 mm, 3.5 μm); column temperature 45°C; flow rate 2.0 mL/minute; detection UV 210 nm, 230 nm, and 254 nm; mobile phase: solvent A = methanesulfonic acid (5%) in 10 mmol sodium octylsulfonate, solvent B = acetonitrile (100%); gradient elution: 0 − 1.5 minutes solvent A (95%) and solvent B (5%), 1.5 − 8.5 minutes solvent A (5%) and solvent B (95%), 8.5 − 10.0 minutes solvent A (5%) and solvent B (95%), 10.0 − 12.0 minutes solvent A (95%) and solvent B (5%); total run time 12.0 minutes.

***tert*-Butyl{*cis*-2-((1,3-dioxoisoindolin-2-yl)methyl)-1-((*R*)-1-(4-methoxyphenyl)ethyl)-4-oxoazetidin-3-yl}carbamate (14).** A solution of **8** (15.0 g; 79.3 mmol) in dichloromethane (250 mL) under nitrogen was cooled to 2°C. The solution was treated with *(R)*-4-methoxy-α-methylbenzylamine (12.0 g, 79.3 mmol) in dichloromethane (50 mL) added drop wise over 15 minutes, maintaining the temperature at 2°C. The solution was stirred for 15 minutes at 2°C and then treated with magnesium sulfate (25.8 g, 214 mmol). The reaction slurry was stirred for 2.5 hours at 2 °C. The slurry was filtered through a pad of Celite (34.5 g) and the filter cake was rinsed with dichloromethane (2 x 30 mL). The dichloromethane filtrate (imine solution) was used directly in the next step.

A solution of *N*-(*tert*-butoxycarbonyl)glycine **11** (27.8 g, 159 mmol) in tetrahydrofuran (300 mL) under nitrogen was cooled to -45 °C and treated with triethylamine (17.7 g, 175 mmol). The mixture was stirred for 15 minutes at -45 °C and then treated with ethyl chloroformate (22.4 g, 200 mmol) in tetrahydrofuran (60 mL) over 22 minutes. The reaction mixture was stirred at -45 °C for 1.25 hours. The previously prepared imine solution was added via an addition funnel over 25 minutes while maintaining the reaction mixture temperature below -40 °C. The slurry was treated with triethylamine (8.04 g, 79.4 mmol) over 1 hour at -40 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for an additional 12 hours. The reaction slurry was charged with water (300 mL) and the volatiles removed using a rotary evaporator. The mixture was treated with methyl *tert*-butyl ether (393 mL) and vigorously stirred for 1 hour. The solids were collected by vacuum filtration and the filter cake was rinsed with methyl *tert*-butyl ether (200 mL). The solid was collected and dried in a vacuum oven at 50 °C for 16 hours to afford **14**. Yield: 27.0 g, 56.3 mmol, 70%). ^{1}H-NMR (400 MHz, DMSO-d_6): Diastereomer A δ 7.83 − 7.77 (m, 4H), δ 7.81 (s, NH), 7.15 − 7.13 (d, *J*

= 8.5 Hz, 2H), 6.69 − 6.66 (d, *J* = 8.5 Hz, 2H), 4.90 − 4.86 (m, 1H), 4.66 − 4.61 (dd, *J* = 11.6, 7.0 Hz, 1H), 4.18 − 4.13 (dd, *J* = 11.6, 6.2 Hz, 1H), 3.77 − 3.67 (m, 2H), 3.64 (s, 3H), 1.57 (d, *J* = 6.2 Hz, 3H), 1.36 (s, 9H). Diastereomer B δ 7.83 − 7.77 (m, 4H), δ 7.81 (s, NH), 7.06 − 7.04 (d, *J* = 8.5 Hz, 2H), 6.63 − 6.61 (d, *J* = 8.8 Hz, 2H), 4.83 − 4.79 (m, 1H), 4.52 − 4.47 (dd, *J* = 13.6, 6.8 Hz, 1H), 4.10 − 4.06 (dd, *J* = 13.6, 6.4 Hz, 1H), 3.62 (s, 3H), 3.60 − 3.53 (m, 2H), 1.58 (d, *J* = 7.0 Hz, 3H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.6, 166.7, 166.4, 158.3, 155.2, 134.4, 133.1, 132.3, 131.7, 128.0, 127.5, 123.0, 113.7, 78.7, 78.6, 58.3, 58.1, 55.0, 52.1, 51.8, 40.0, 38,2, 37.9, 28.1, 19.9; HRMS (IS) Calcd for 480.2135, found 480.2131. HPLC retention time 6.22 minutes; XBridge C8 column (4.6 x 75 mm, 3.5 μm); column temperature 45 °C; flow rate 2.0 mL/minute; detection UV 210 nm, 230 nm, and 254 nm; mobile phase: solvent A = methanesulfonic acid (5%) in 10 mmol sodium octylsulfonate, solvent B = acetonitrile (100%); gradient elution: 0 − 1.5 minutes solvent A (95%) and solvent B (5%), 1.5 − 8.5 minutes solvent A (5%) and solvent B (95%), 8.5 − 10.0 minutes solvent A (5%) and solvent B (95%), 10.0 − 12.0 minutes solvent A (95%) and solvent B (5%); total run time 12.0 minutes.

***tert*-Butyl[*cis*-2-(aminomethyl)-1-(2,4-dimethoxybenzyl)-4-oxoazetidin-3-yl]carbamate (15).** To a nitrogen-purged glass-lined reactor was charged **13** (10.72 kg, 21.64 mol) and ethyl acetate (96.50 L). After stirring for 30 min at 20 °C the reactor was charged with ethanolamine (19.83 kg, 324.56 mol). The ethanolamine charging equipment was rinsed with ethyl acetate (10.72 L) and the rinsate added to the reactor. The reaction mixture was heated at 78 °C for 2 h and then cooled to 20 °C. The reaction mixture was charged with water (107.22 L) while maintaining the temperature at 20°C and the phases separated. The aqueous phase was back extracted with ethyl acetate (53.61 L) and the combined ethyl acetate organic layers washed

with water (2 x 107.22 L) followed by saturated aqueous sodium chloride (107.22 L). The organic layer was dried over magnesium sulfate (1.72 kg), filtered and the filtrate concentrated under vacuum at 30 °C to a volume of 27 L. The reactor was cooled to 20 °C, treated with heptane (107.22 L) and the resulting mixture was crystallized over 2 h. The batch was filtered and the solids washed with heptane (13.94 L). The solids were dried under vacuum with a nitrogen sweep at 50 °C over 12 h to afford the desired product **15** as a white solid. Yield: 7.01 kg, 19.19 mol, 88%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, J = 9.4 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 6.56 (s, 1H), 6.49 (dd, J = 8.20, 2.3 Hz, 1H), 4.78 (dd, J = 9.37, 5.1 Hz, 1H), 4.30 (d, J = 14.8 Hz, 1H), 4.14 (d, J = 14.8 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.45 − 3.53 (m, 1H), 2.65 − 2.75 (m, 1H), 2.56 − 2.64 (m, 1H), 1.38 (s, 9H), 1.30 − 1.35 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.7, 160.2, 157.9, 154.9, 130.3, 115.9, 104.6, 98.3, 78.5, 58.4, 55.4, 55.1, 39.7, 38.8, 28.0; HRMS (IS) Calcd for 366.2029, found 366.2021. HPLC retention time 5.1 minutes.

***tert*-Butyl[(2*R*,3*S*)-2-(aminomethyl)-1-(2,4-dimethoxybenzyl)-4-oxoazetidin-3-yl]carbamate, (-)-L-dibenzoyltartarate salt (17).** To a nitrogen-purged glass-lined reactor was charged **15** (4.80 kg, 13.14 mol) and ethyl acetate (108.0 L). The mixture was stirred at 20 °C for 1 h. The reactor was treated with diatomaceous earth (2.40 kg) and stirred for 30 min while maintaining the temperature at 20 °C. The solids were filtered and the filter cake washed with ethyl acetate (36.0 L). The filtrate was charged with diatomaceous earth (4.8 kg) and treated with (-)-L-dibenzoyltartaric acid (4.71 kg, 13.14 mol). The slurry was heated at 60 °C for 1 h and then cooled to 20 °C. The slurry was held at 20 °C for 1 h with stirring. The batch was filtered and the solids washed with ethyl acetate (21.6 L). The solids were dried under vacuum

with a nitrogen sweep at 50 °C over 12 h to afford the desired product **17** on diatomaceous earth as a white solid (9.028 kg). Note, the isolated amount (9.028 kg) is based on the total weight. Correcting for the diatomaceous earth of 4.8 kg, this would result in 4.228 kg of product. Therefore, product yield is 4.228/9.51 x 100% = 45%. Yield: 4.22 kg, 5.84 mol, 45%, 98% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 − 7.91 (m, 4H), 7.59 − 7.65 (m, 3H), 7.44 − 7.49 (m, 4H), 7.09 (d, J = 8.3 Hz, 1H), 6.53 (d, J = 2.3 Hz, 1H), 6.49 (dd, J = 8.3, 2.3 Hz, 1H), 5.65 (s, 2H), 4.85 (dd, J = 9.3, 4.9 Hz, 1H), 4.30 (d, J = 15.3 Hz, 1H), 4.10 (d, J = 15.3 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.68 − 3.70 (m, 1H), 2.92 − 2.96 (dd, J = 13.6, 5.4 Hz, 1H), 2.85 − 2.90 (dd, J = 13.6, 6.3 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.1, 166.3, 164.9, 160.2, 157.9, 155.0, 133.4, 130.2, 129.5, 129.2, 128.7, 115.6, 104.5, 98.3, 78.9, 72.5, 59.7, 58.8, 55.4, 55.1, 40.0, 37.5, 28.0; HRMS (IS) Calcd for 366.2029, found 366.2023. HPLC retention time 5.1 minutes. Chiral HPLC retention time 9.1 minutes; column: Chiralcel OD-H column (250 mm x 4.6 mm); column temperature 40 °C; flow rate 1.0 mL / minute; detection UV 208 nm; mobile phase: solvent A = ethanol (18%), solvent B = heptane (85%); isocratic elution; total run time 20.0 minutes.

***tert*-Butyl[(2*R*,3*S*)-2-(aminomethyl)-1-(2,4-dimethoxybenzyl)-4-oxoazetidin-3-yl]carbamate (18).** To a nitrogen-purged glass-lined reactor was charged **17** (6.24 kg, 8.62 mol) on diatomaceous earth and ethyl acetate (112.24 L). The reactor was treated with 5% aqueous potassium phosphate tribasic (76.12 L) solution. The slurry was stirred for 1 h at 20 °C. The solids were filtered under vacuum and the filter cake washed with ethyl acetate (2 x 24.96 L). The phases were separated and the aqueous phase was back extracted with ethyl acetate (24.96 L). The combined organic phases were washed with 5% aqueous potassium phosphate tribasic

(6.99 L) solution. The phases were separated and the organic phase was washed with saturated sodium chloride (32.95 L) solution. The phases were separated and the organic layer was dried over magnesium sulfate (3.12 kg). The solids were filtered and washed with ethyl acetate (12.48 L). The filtrate was concentrated under vacuum at 30 ^{o}C to a volume of 15-16 L. The reactor was cooled to 20 ^{o}C, treated with heptane (93.6 L) over 30 min and the resulting mixture was crystallized over 1 h. The batch was filtered and the solids washed with heptane (18.72 L). The solids were dried under vacuum with a nitrogen sweep at 50 ^{o}C over 8 h to afford the desired product **18** as a white solid. Yield: 2.51 kg, 6.87 mol, 80%, 99% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, J = 9.4 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 6.56 (s, 1H), 6.49 (dd, J = 8.20, 2.3 Hz, 1H), 4.78 (dd, J = 9.37, 5.1 Hz, 1H), 4.30 (d, J = 14.8 Hz, 1H), 4.14 (d, J = 14.8 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.45 − 3.53 (m, 1H), 2.65 − 2.75 (m, 1H), 2.56 − 2.64 (m, 1H), 1.38 (s, 9H), 1.30 − 1.35 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.7, 160.2, 157.9, 154.9, 130.3, 115.9, 104.6, 98.3, 78.5, 58.4, 55.4, 55.1, 39.7, 38.8, 28.0; HRMS (IS) Calcd for 366.2029, found 366.2022. HPLC retention time 5.2 minutes. Chiral HPLC retention time 8.7 minutes; column: Chiralcel OD-H column (250 mm x 4.6 mm); column temperature 40 ^{o}C; flow rate 1.0 mL / minute; detection UV 208 nm; mobile phase: solvent A = ethanol (18%), solvent B = heptane (85%); isocratic elution; total run time 20.0 minutes.

ASSOCIATED CONTENT

Supporting Information Available

^{1}H NMR spectra of all intermediates and final product, as well as ReactIR and classical resolution studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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