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Development of a Second-Generation Process to Antibacterial Candidate Sulopenem

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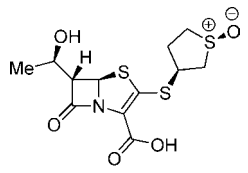
Supporting Information

ABSTRACT: The research, development, and scale-up of the broad-spectrum antibacterial candidate sulopenem are presented. An enabled medicinal chemistry synthesis of this active pharmaceutical ingredient was utilized for Phase 1 and early Phase 2 manufacture but was not conducive to larger scale. The limitations associated with the first-generation synthesis were partially addressed in an improved second-generation synthesis of the target molecule where the penem ring is constructed via a modified Eschenmoser sulfide contraction sequence. Other highlights of the second-generation process include an improved synthesis of an important trithiocarbonate intermediate and a superior process for Pd-catalyzed deallylation of the penultimate ester to obtain low levels of residual palladium.

INTRODUCTION

Sulopenem (**1**) is a broad-spectrum antibacterial candidate in the thiopenem class (Figure 1).[1] A limited but successful



1
sulopenem

Figure 1. Sulopenem.

clinical evaluation of **1** was carried out in Japan in the mid-1990s and involved nearly 1200 subjects. Although the studies suggested both safety and efficacy for the treatment of a range of infections, development of sulopenem was discontinued in the late 1990s in light of discouraging market projections and high development costs.

In 2003, development of sulopenem resumed as multidrug resistant bacteria threatened to render existing therapies ineffective.[2−5] The combination of a high-dose daily intravenous delivery, a challenging β-lactam structure, and an aggressive clinical development plan for this candidate required the identification of scalable technology for the manufacture of increasing quantities of active pharmaceutical ingredient (API). Because sulopenem exhibits antibacterial activity and contains a β-lactam structural motif related to that seen in penicillin,[6−9] all GMP manufacture was carried out in a dedicated single-product facility to eliminate cross-contamination concerns, as recommended by ICH Q7A.[10,11] This added considerable cost and complexity to the API development effort.

First GMP Synthesis. The first-generation sulopenem synthesis was developed and enabled for GMP manufacture in the late 1980s (Scheme 1).[12,13] This route was used to manufacture several lots of **1** in batch sizes up to 10 kg and consists of five distinct chemical transformations starting from chiral nonracemic sulfoxide **2** and the commodity building block 4-acetoxyazetidinone, **3**.[14]

In the key step of this synthesis, the fused thiazoline ring was prepared by treating oxalamide **6** with triethylphosphite in refluxing $CHCl_3$, in a modification of the well-established Woodward penem synthesis.[15−19] Unlike the Woodward method, which utilizes a Wittig reaction for the key cyclization, the triethylphosphite process is thought to proceed via formation of a stabilized carbene intermediate **9** that reacts in an intramolecular fashion with the trithiocarbonate group to afford episulfide **10a** (Scheme 2).[20,21] The episulfide presumably reacts with additional triethylphosphite (at least two molar equivalents are required for conversion of **6** to **7a**) to yield thiopenem **7a** via desulfurization to form triethylthiophosphate. Evidence for a carbene intermediate includes formation of cyclopropane byproducts if chloroallyl oxalyl fluoride **5** is replaced by its des-chloro analogue in this reaction sequence.

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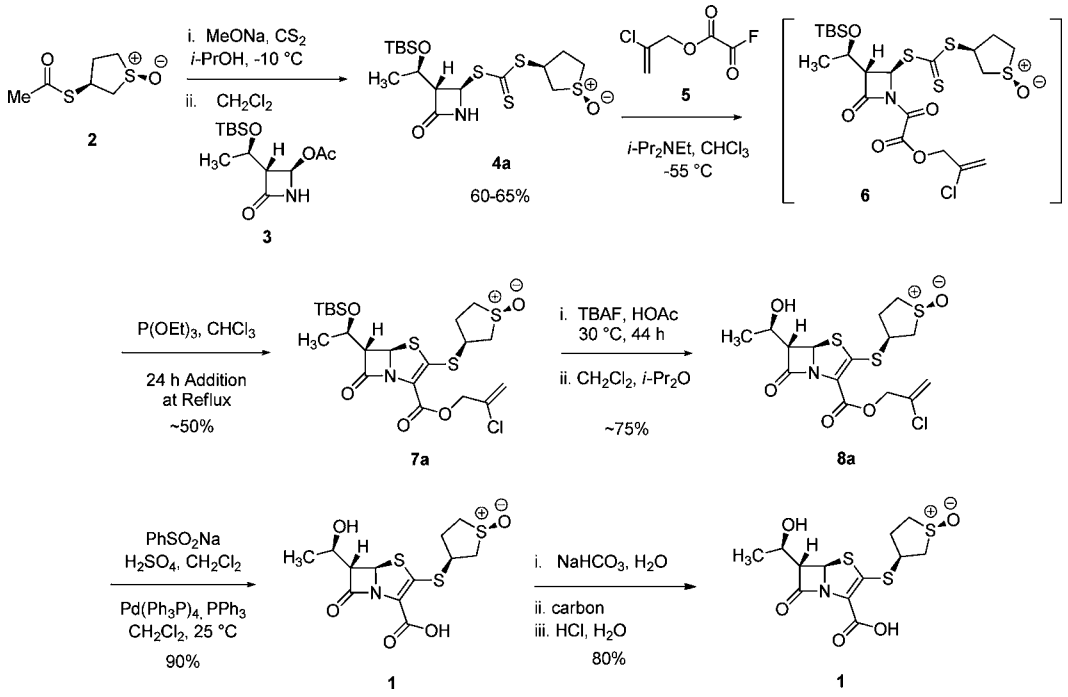
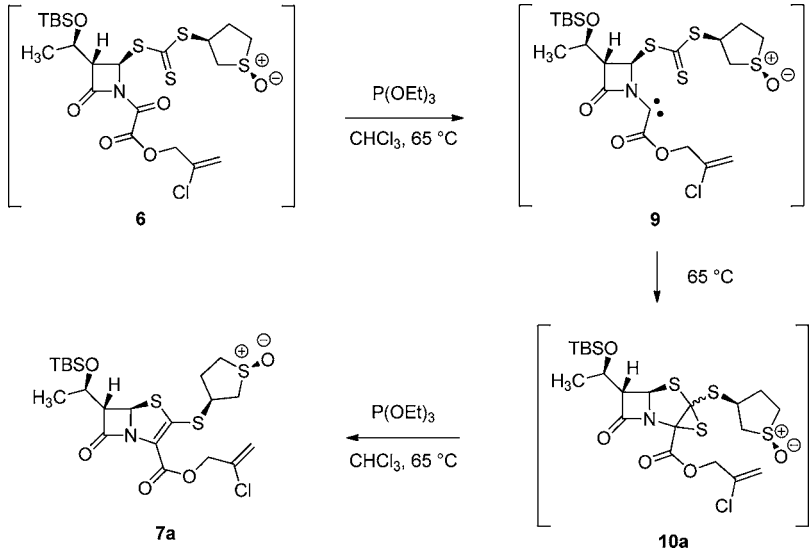
Scheme 1. Early enabled discovery route



Scheme 2. Carbene-mediated penem formation



Although this original carbene-mediated process proved suitable for the manufacture of small- to medium-sized lots of **1** in the 1990s, there were several drawbacks associated with running this same process at larger scale:

(1) The synthesis of intermediate **4a** utilized a large excess of toxic, highly flammable carbon disulfide.
(2) Removal of *i*-PrOH from bulk **4a** required two extended drying cycles separated by a milling operation.
(3) Synthesis of oxalamide **6** was carried out at cryogenic temperatures to avoid acylation of the sulfoxide oxygen.
(4) Conversion of **6** to thiopenem **7a** was carried out under high dilution in the highly undesirable solvent $CHCl_3$ to minimize formation of phosphorous ylide byproduct **11** (Figure 2).
(5) Conversion of **7** to penultimate intermediate **8a** required greater than 40 h of reaction time at 30 °C; heating to higher temperatures led to degradation.
(6) Isolation of **8a** required large quantities of isopropyl ether, which is capable of forming hazardous peroxides.[22]

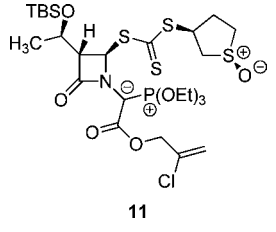


Figure 2. Ylide byproduct **11**.

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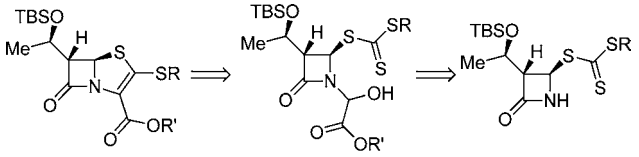
(7) The chloroallyl group, introduced via toxic and expensive acyl fluoride **5**, was required to minimize intramolecular cyclopropanation byproducts during the carbene cyclization step; this introduced alerting structures to downstream intermediates and impurities and thus required extensive purge procedures.
(8) Cleavage of the chloroallyl group required high loading of an expensive palladium catalyst as well as benzenesulfinic acid (freshly prepared from its stable sodium salt).[23]
(9) Although the deallylation conditions provided **1** in excellent yield, the API was found to contain consistently high levels of residual palladium metal.[24] Since sulopenem was to be administered as its sodium salt via an intravenous dosage form, meeting the specification for residual metals was expected to be a challenge.[25]

Despite the considerable amount of process knowledge gained from years of enabling R&D studies, performance of this route was disappointing and highly variable due to fundamental limitations related to increasing scale and the general instability of each β-lactam intermediate to aqueous workup conditions—even near neutral pH. Perhaps most disconcerting was the low yield (~40%) and high $CHCl_3$ utilization (3550 volumes) associated with the penem ring construction. As a result of these issues, the overall yield of this route reached a maximum of 12% on pilot-plant scale, which contributed to high development costs for the program as demand for API continued to escalate. Thus, we began to target second-generation syntheses that would alleviate these concerns prior to phase 3 development.

RESULTS AND DISCUSSION

Development of a Second-Generation Synthesis. Several methods for penem ring construction have been reported in the literature, and many were evaluated for potential application prior to phase 3.[26] During several months of laboratory investigation, we revisited a synthetic strategy first reported by Pfizer medicinal chemists (Scheme 3).[27,28]

Scheme 3. Synthesis of thiopenems via Eschenmoser sulfide contraction

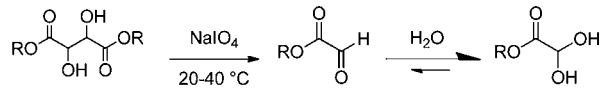


As described through internal communications,[29] protected thiopenems of type 7 can be prepared from α-hydroxyesters **12** through activation and nucleophilic ring closure followed by desulfurization using a variation of the Eschenmoser sulfide contraction.[30] Hydroxyesters **12** can be prepared via alkylation of β-lactam **4** with a glyoxylic acid ester.

In this process, the thiopenem ring is constructed under mildly basic conditions instead of the high-temperature carbene reaction that had been employed previously. This promised to eliminate the large volumes of $CHCl_3$ solvent as well as the cryogenic reaction temperatures required for N-acylation of the β-lactam. Improved reaction concentration in the penem formation step and replacement of the chloroallyl protecting group with a less expensive alternative were also significant advantages offered by this methodology.

Base-Mediated Construction of the Thiopenem. The N-alkylation of β-lactam compounds with glyoxylic acid esters to prepare aminal compounds has been described.[31−35] In an attempt to maximize yield for this transformation on our substrate, obtain optimal physical properties of both glyoxalate and product, and simplify the downstream processing, several glyoxalate derivatives were evaluated. Each compound was prepared via oxidative cleavage of the appropriate tartrate precursor **13** with periodic acid,[36−43] or preferably, with sodium periodate[44−46] as depicted in Scheme 4. Unfortunately, none of

Scheme 4. Preparation of glyoxalates



the glyoxalates **14** were crystalline solids at room temperature, and each existed primarily in hydrated form **15**.[47] Thus, glyoxalates were utilized as crude oils in the laboratory and as concentrated solutions on larger scale.

Allyl glyoxalate hydrate **15a** was eventually selected for further development, as it was the least expensive, was effective in the downstream chemistry, and was relatively easy to prepare. Furthermore, the use of an allyl protecting group on the carboxylic acid (vs chloroallyl utilized in the previous synthesis) mitigated risk during API development, since the identical end-game process chemistry would still apply. Thus, the number and identity of new process-related impurities that made their way into the final API were expected to be less impactful.

Increased API demand necessitated preparation of glyoxalate **15a** via periodate oxidation at 400-L scale. Following a successful reaction, the excess periodate and iodate were removed via filtration and packaged. Within hours of packaging this waste material, an exothermic event was observed that led to iodine release. The issue was found to be associated with residual methyl *tert*-butyl ether remaining on the waste solids. A full discussion of the oxidative cleavage of diallyl tartrate, including safe handling conditions for the waste material, will be the subject of a future publication.[48]

Unfortunately, all glyoxalate derivatives studied were extremely sensitive to ester hydrolysis. In the case of allyl glyoxalate, this resulted in the formation of allyl alcohol and glyoxylic acid, which proved to be a strong inhibitor of the N-alkylation of **4a**. Fortunately, the addition of 0.3−0.5 equiv of 2,4,6-collidine buffered the acidity that caused reactions to stall. Collidine was also sufficiently mild to avoid the base-promoted degradation of **4a** that eroded yields of **6** during reaction with acyl fluoride **5** in the historical process (Scheme 1).

With allyl glyoxalate, smooth alkylation of **4a** proceeded near ambient temperature in a range of solvents (Scheme 5). The use of azeotropic distillation with a Dean−Stark trap or the addition of 3 Å molecular sieves helped to drive the reaction to completion and minimize glyoxalate ester hydrolysis. The Dean−Stark trap was more practical in the pilot plant, although the use of sieves was more robust on laboratory scale.

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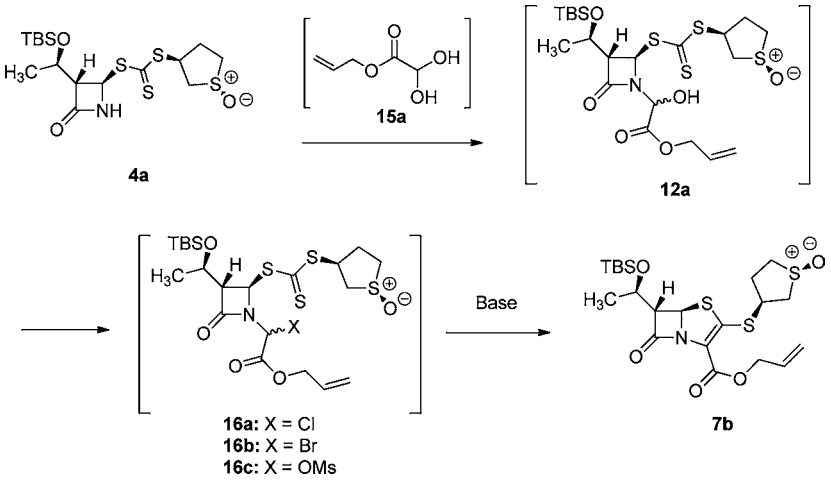
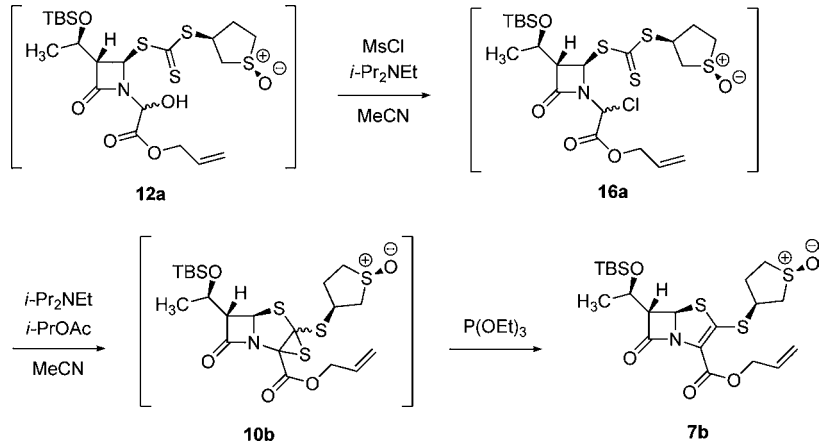
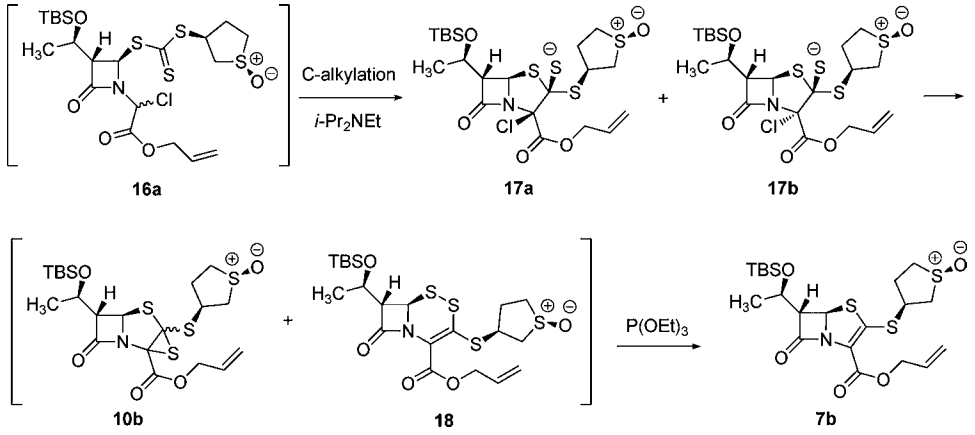
Scheme 5. Construction of the penem



Scheme 6. Penem construction via Eschenmoser sulfide contraction



Scheme 7. Proposed C-alkylation pathway to penem 7b



The diastereomeric mixture of aminals **12a** was further converted to activated intermediates **16** in order to evaluate the base-promoted ring closure. Both the formation of **16** and subsequent cyclization to penem **7b** required optimization of several parameters, including base, solvent, reaction temperature, and activating agent.

Details of the cyclization sequence are outlined in Scheme 6. Crude aminal intermediate **12a** was treated with MsCl and Hünig's base to yield alkyl chloride **16a** as a 1:1 mixture of diastereomers. It is proposed that this reaction involves competitive mesylation on the sulfoxide oxygen, since excess MsCl led to sulfoxide reduction,[49] epimerization (presumably via Pummerer-type reaction),[50,51] and elimination byproducts. The reaction of sulfoxides with electrophiles is well precedented.[52−54] However, the efficiency of these undesired reactions demanded that MsCl stoichiometry be carefully controlled during scale-up of the process. The corresponding bromide **16b** and mesylate **16c** were prepared in an analogous

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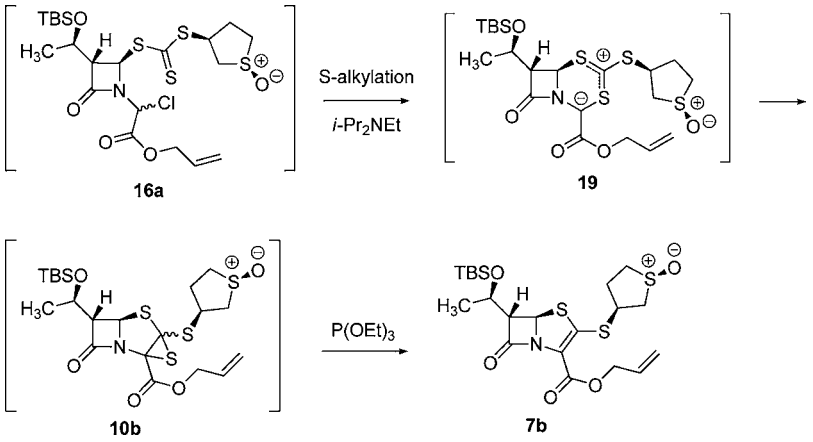
Scheme 8. Proposed S-alkylation pathway to episulfide 16



fashion utilizing MsBr and Ms_2O, respectively; these intermediates were less successful in the cyclization process to **7b**.

The intermediate mesylate was not detected analytically, since conversion to the corresponding chloride **16a** was extremely rapid at 0 °C. Chloride **16a** was fairly stable in solution at 0 °C, but after the addition of excess *i*-Pr_2NEt and warming above 30 °C, cyclization afforded a mixture of the desired penem product **7b** and a compound we tentatively assigned as episulfide **10b** according to mass spectral data. Addition of a small quantity of a thiophilic reagent (e.g., $P(OEt)_3$) to the crude reaction mixture instantly converted this component to the desired penem **7b**. A small percentage of the C4 diastereomer of **7b** was also formed during the process.[55]

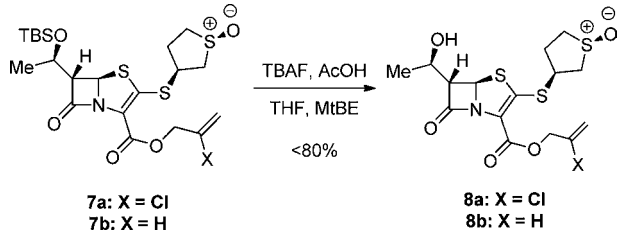
The mechanism for conversion of chloride **16a** to episulfide **10b** has not been thoroughly investigated. O'Neill and Volkmann previously proposed addition of the α-chloroester enolate to the trithiocarbonate, leading to a mixture of diastereomeric chlorothiolates *syn*-**17a** and *anti*-**17b** (Scheme 7).[13] Presumably, the anti diastereomers **17b** lead to episulfide **10b** via direct nucleophilic substitution, whereas the syn diastereomers **17a** cannot. O'Neill and Volkmann thus proposed the rearrangement of *syn*-chlorothiolates **17a** to carbacephem **18**, followed by selective sulfur extraction (by treatment with a thiophilic phosphorous compound) to convert **18** to penem **7b**.[56,57] Although this proposal is consistent with our limited analytical data, the formation of adjacent quaternary centers via enolate addition to a poorly electrophilic trithiocarbonate is not well precedented.[58]

An alternative mechanism would involve S-alkylation of the electron-rich trithiocarbonate by the activated alkyl chloride (Scheme 8). This reactivity is well precedented for the Eschenmoser sulfide contraction[59−62] and would provide a stabilized zwitterion intermediate **19** in the presence of a suitable base (e.g., *i*-Pr_2NEt). Subsequent intramolecular ring closure would provide episulfide **16** as a diastereomeric mixture. One diastereomer may spontaneously desulfurize, while the other may require the addition of triethylphosphite. Both mechanisms are consistent with our experimental observations, and at this time, we have not collected conclusive evidence that would support one proposal over the other.

Despite the complexity of this chemistry, the conversion of **4a** to penem **7b** performed in 35−40% overall isolated yield in laboratory trials up to 100 g, making it essentially equivalent to the historical carbene-mediated process. The isolation of **7b** from the complex mixture of reactants, reagents, and byproducts was not straightforward. Extensive solubility screening was carried out on purified product, as well as on crude reaction mixtures. Eventually, an aqueous extractive workup was designed to remove inorganic residues and many of the reagents used in excess that were found to inhibit crystallization (e.g., *i*-Pr_2NEt). A process was eventually developed for the isolation of 80−85% of **7b** available in the crude reaction mixture. It was also demonstrated that any new impurities introduced by this cyclization sequence were effectively purged at or before the isolation of sulopenem (**1**).

Removal of the Protecting Groups. Removal of the TBS group from penems **7** has traditionally resulted in low isolated yield of alcohols **8**. For related substrates, this deprotection has been carried out with acids[63,64] and with numerous fluoride reagents.[65−71] However, the only effective conditions identified for the desilylation of **7a**/**b** utilized TBAF in the presence of a significant quantity of AcOH (Scheme 9).[66] Not surprisingly,

Scheme 9. Desilylation of TBS ethers 7



the presence of water in the solvent and/or reagents led to competitive β-lactam hydrolysis, and loss of the sulfoxide side chain became a significant issue at temperatures above 35 °C. Furthermore, the presence of AcOH impacted workup and isolation, since penems **8a**/**b** are appreciably soluble in this solvent.

In the historical process, isolation of chloroallyl ester **8a**, was accomplished by trituration with isopropyl ether (Scheme 1). This is not ideal, due to the tendency of this solvent to form hazardous peroxides during storage.[72] As a result, our second-generation process involved a direct drop isolation of **8b** using MtBE as a cosolvent (with THF and AcOH). After extensive screening and optimization, the in situ yield for the conversion of **7b** to **8b** reached nearly 90%. Isolated yield of **8b**, however, rarely exceeded 75%.

One unexpected advantage offered by the new process was realized during removal of the allyl ester protecting group in **8b**.

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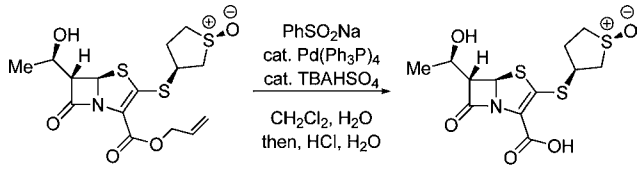
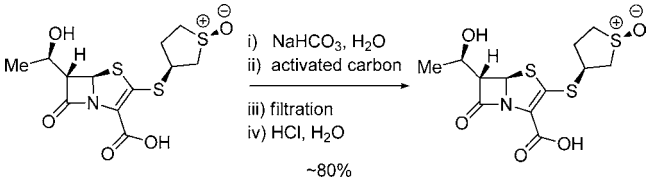
In the carbene process, a chloroallyl protecting group was necessary to avoid intramolecular cyclopropanation during the phosphite-mediated cyclization of oxalimide **6** (Scheme 1). However, cleavage of the chloroallyl group in **8a** required 4−5 mol % of the $Pd(Ph_3P)_4$ catalyst in order to achieve an acceptable reaction rate and yield of free acid **1**, presumably due to steric and electronic deactivation by the 2-chloro substituent during oxidative addition by Pd(0).[23] Conversely, removal of the allyl group from **8b** proceeded much more efficiently, allowing a reduction in catalyst loading to less than 1 mol % while maintaining acceptable reaction rates and isolated yields of **1** (Scheme 10).

Scheme 10. Deallylation of ester 8b to afford sulopenem (1)



This decrease in loading was important not only due to the high cost of $Pd(Ph_3P)_4$ catalyst but also since use of less catalyst resulted in lower levels of residual Pd in the isolated API.[73] Previously, purging Pd below the specified level of <5 ppm required repeated carbon treatments **1**, but this had a negative impact on yield due to background β-lactam hydrolysis in the aqueous solution (Scheme 11). A single aqueous rework of **1**

Scheme 11. Process for palladium removal



on multikilogram scale resulted in the loss of approximately 20% of our valuable API, while the residual Pd level was decreased by only 50%.

In combination with the lower initial Pd catalyst loading required for deallylation, we found that residual Pd levels could be addressed by adding additional Ph_3P to the reaction mixture. This addition had no observable impact on the reaction rate but ensured that Pd(0) remained in the organic phase during workup, while the product sodium salt was taken into the aqueous phase prior to acidification and isolation.

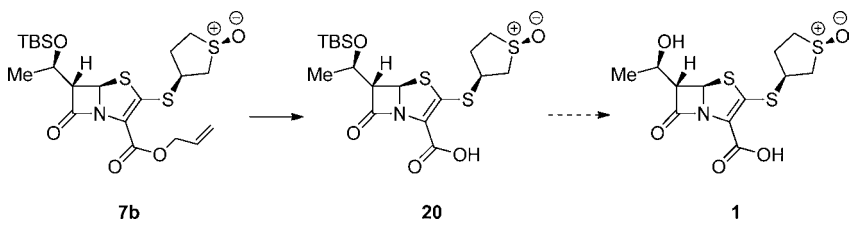
In an attempt to remove Pd entirely from the final reaction step, a simple reordering of the deprotection sequence was evaluated (Scheme 12). Palladium-catalyzed deallylation of **7b** proceeded well under the standard conditions to yield acid **20**; however, cleavage of the TBS protecting group with TBAF in AcOH led to considerable degradation. Furthermore, solubility studies suggested that isolation of carboxylic acid **1** in the presence of AcOH would be challenging. It was clear that significant development would be required in order to implement new end-game chemistry, and thus, the historical deprotection sequence was utilized.

The Second-Generation Process for Phase 3 API Production. Optimized conditions for synthesis of **1** are described in Scheme 13. Chiral sulfoxide **2** was treated with sodium methoxide in isopropyl alcohol, followed by the addition of carbon disulfide and dichloromethane to yield a sparingly soluble sodium trithiocarbonate intermediate **21**. The low solubility of the trithiocarbonate in this solvent system helped drive the reversible reaction toward completion, thereby allowing for a decreased charge of CS_2. Addition of 4-acetoxyazetidinone **3** at approximately −10 °C provided trithiocarbonate **4** in 60−65% yield after a careful neutralization and isolation procedure.

N-Alkylation of **4a** with allyl glyoxalate hydrate **15a** in the presence of 0.3 equiv of collidine provided aminal **12a** as a mixture of diastereomers in 85−90% yield. Due to poor physical properties, aminal **12a** was not isolated. Instead, the reaction mixture was diluted with MeCN, cooled to −20 °C, and treated with MsCl and *i*-Pr_2NEt to provide the intermediate chloride **16a** (Scheme 8). A second charge of base and an increase in the reaction temperature to 30 °C promoted conversion of **16a** to a mixture of penem **7b** and, presumably, episulfide **10b**. A small charge of $P(OEt)_3$ was required for full conversion of this intermediate to the desired penem.

Unfortunately, a considerable drop in overall yield for the penem construction sequence was observed as this process was scaled from the laboratory to the pilot plant. As we transferred this chemistry from 100 g to 4 kg of input trithiocarbonate **4a** (laboratory to kilo lab), the yield plummeted from ~40% to <10% of penem **7b**. The fundamental instability of these β-lactam intermediates toward background hydrolysis and thermal decomposition led us to expect a decrease in yield during scale-up. However, the magnitude of the decline came as a surprise. We engaged in thorough stress testing of every unit operation in the process in an attempt to understand and overcome the scale-related yield losses. These studies identified several operations that contributed to decomposition of one or more reactive intermediates. Principal degradation pathways included competitive sulfoxide activation by MsCl (followed by Pummerer-type pathways) and base-mediated lactam hydrolysis during neutralization of *i*-Pr_2NEt with aqueous HCl. The latter could be addressed by incorporating an inverse quench of the crude reaction into aqueous acid. Careful control of MsCl stoichiometry (challenging solution potency determination that

Scheme 12. Attempted end-game reordering



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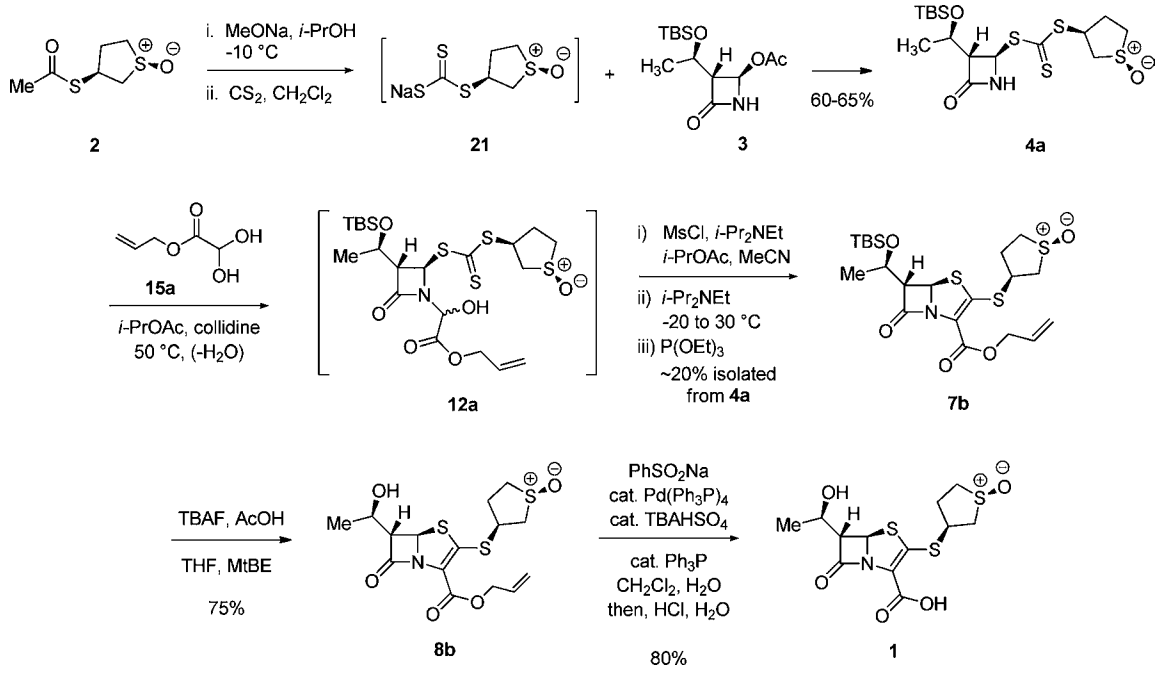
Scheme 13. Pilot-plant synthesis of sulopenem (1)



accounted for multiple substances capable of reaction with MsCl) and addition time/temperature partially addressed the former. Although we were eventually able to achieve 23% yield for this reaction sequence on 266-kg scale (**4a** as basis), the laboratory performance standard could not be achieved.

Conversion of advanced intermediate **7b** to sulopenem (**1**) was accomplished in two steps. The TBS ether in **7b** was cleaved with TBAF in the presence of AcOH to provide **8b** in 75% yield. Subsequent deallylation of ester **8b** was carried out via Pd(0)-catalyzed allyl transfer to benzenesulfinic acid sodium salt under biphasic reaction conditions in dichloromethane and water. By including an additional 5−10 mol % of triphenylphosphine in the reaction mixture, levels of Pd in the isolated API were maintained below 5 ppm, obviating the need for costly recrystallization to meet the specified acceptable level for this product. Each batch of **1** has been processed under conditions appropriate for an injectable therapy. This included extensive cleaning and testing of all equipment, utilization of water for injection (WFI) at all stages of processing to ensure that endotoxins are at acceptably low levels, treatment with activated carbon to purge Pd as low as reasonably practicable, and a microfiltration prior to crystallization and isolation.

■ CONCLUSION

Although the historical carbene-mediated route to antibacterial candidate **1** was effective for the preparation of gram-to-kilogram quantities of API during phases 1 and 2, our API team concluded that a more efficient, environmentally friendly synthesis would be required to support phase 3 development. After rapidly evaluating several reported methods for the construction of thiopenems, a second-generation process was nominated for development and implementation. The second-generation route offered several distinct advantages for manufacture of API on increasing scale. The β-lactam N-alkylation strategy eliminated the need for a costly, hazardous acyl fluoride reagent. Shifting from a carbene-mediated cyclization to a base-promoted mechanism negated the need for large quantities of $CHCl_3$ solvent. Furthermore, the new route offered the potential for increased throughput and thus generated less waste.

However, the key reaction sequence in this synthesis involved an Eschenmoser sulfide contraction that proved to be extremely difficult to scale into a pilot-plant environment. Laboratory trials predicted the second-generation penem formation method to perform with essentially the same overall yield as the carbene-mediated cyclization. This proved not to be the case, with actual yields at only 40−50% of the predicted value. The tendency of the substituted chiral sulfoxide to undergo β-elimination and the hydrolytic instability of the lactam ring during alkaline aqueous treatments were primarily responsible for the scale effect. Nevertheless, sulopenem was prepared by the process described in Scheme 13 to support the short-term program need.

On the basis of the disappointing performance of the penem formation sequence, exploration of alternate chemistry that could be developed for potential commercial-scale manufacturing continued. The results of this effort are described in the subsequent manuscript.[74]

■ EXPERIMENTAL SECTION

General. Mass spectral data was obtained on a Thermo LTQ FT-MS mass spectrometer with flow injection analysis and electrospray ionization (ESI). Reactions were monitored by reverse phase liquid chromatography using an Agilent 1100 series HPLC equipped with a Waters Symmetry Shield RP18 (150 mm × 4.6 mm, 3.5 μm) column utilizing an acetonitrile and aqueous phosphoric acid elution at a column temperature of 40 °C (Methods 1−2). Method 1 is an isocratic 50−50% acetonitrile/aqueous phosphoric acid elution at a flow rate of 2.0 mL/min. Approximate retention times (min): **4a** (4.1), **12a** (4.9, 5.2), **7b** (6.5), **16a** (11.9), and **10b**/**18** (13.0). Method 2 is 30−100% acetonitrile/aqueous phosphoric acid gradient elution at a flow rate of 1.0 mL/min over 12 min. Approximate retention times (min): **1** (1.5) and **8b** (3.6).

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(2*R*,3*S*)-3-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-oxoazetidin-2-yl((1*R*,3*S*)-1-oxidotetrahydrothiophen-3-yl)carbonotrithioate(4a). A mixture of thioacetate **2** (505 g, 2.83 mol) and *i*-PrOH (4.0 L) cooled to 10 °C was treated with solid sodium methoxide (168 g, 3.11 mol) in portions at ≤ −8 °C. The mixture was stirred for 30 min at 10 °C, and then was further cooled to −15 °C. While stirring vigorously, carbon disulfide (680 mL, 11.32 mol) in dichloromethane (2 L) was added at ≤ −12 °C. The resulting thick, bright yellow slurry of the trithiocarbonate intermediate **21** was stirred for 30 min at −15 °C, and then was cooled to −25 °C. A solution of acetoxyazetidinone **3** (814 g, 2.83 mol) in dichloromethane (3 L) was then added over 30 min. After stirring for 30−60 min at 20 °C, the mixture was quenched into dilute aqueous AcOH (120 mL in 5 L) containing sodium chloride (500 g). The organic layer was separated. The aqueous layer was extracted with dichloromethane (1 L). The combined organic layers were washed with 10% aqueous sodium chloride (2 × 2 L) and concentrated under reduced pressure, at a maximum internal temperature of 30 °C, to a volume of 2 L. Heptanes (11.2 L) were then added with vigorous stirring. The mixture began to solidify during the first half of the heptanes addition. After complete addition, the mixture was stirred for at least 2 h at 20−25 °C and then 2 h at 4 °C. The resulting yellow solids were collected via filtration, washed with heptanes (3 × 500 mL), and dried to constant weight at an oven temperature of ≤30 °C to give trithiocarbonate **4a** (780 g, 63%).

^{1}H NMR (700 MHz, $CDCl_3$) 6.69 (br s, 1H), 5.67 (d, *J* = 2.6 Hz, 1H), 4.59−4.54 (m, 1H), 4.30 (dq, 1H, *J* = 6.2, 6.2, 6.2, 4.0 Hz), 3.77 (dd, *J* = 14.7, 8.8 Hz, 1H), 3.24 (t, *J* = 3.1 Hz, 1H), 3.19−3.17 (m, 1H), 2.86 (ddd, *J* = 14.8, 6.5, 2 Hz, 1H), 2.79−2.71 (m, 3H), 1.22 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) 165.90, 64.35, 63.74, 59.18, 57.19, 52.72, 47.81, 31.02, 25.64, 22.39, 17.88, −4.30, −5.17. HRMS (ESI) exact mass calcd for $C_{16}H_{30}NO_3S_4Si$ (M + H) 440.0878, found: *m*/*z* 440.0880.

Allyl 2,2-Dihydroxyacetate (15a). A mixture of diallyl tartrate (65 g, 282 mmol), dichloromethane (455 mL), and water (32.5 mL) was stirred vigorously at 25−30 °C. Sodium periodate (108.7 g, 508 mmol) was added in three equal portions. Each portion was charged over 10 min and stirred for 30 min between each addition. The resulting white heterogeneous reaction mixture was stirred vigorously under a nitrogen atmosphere at 30−35 °C for 16 h. The solids were filtered and washed with dichloromethane (2 × 65 mL). The reaction vessel and filter cake were then washed thoroughly with dichloromethane (400 mL) to remove highly flammable material. The solid waste cake was disposed of as a slurry in 260 mL of water.

CAUTION: The final dichloromethane wash removes the last traces of highly flammable organic material from the oxidant cake, minimizing the potential for exothermic side reactions that have been shown to liberate iodine. This is critical for safe handling and disposal of the periodate−iodate solid cake.

Combined organic filtrates were washed with 18% aqueous sodium chloride (65 mL). The organic layer was dried over sodium sulfate (25 wt %), filtered and concentrated under vacuum at ≤40 °C to provide allyl glyoxalate hydrate **15a** (48.1 g, 65% yield) as a colorless oil (GC area% purity 86.1%). This material was used as a crude oil in the subsequent reaction step without further purification.

(5*R*,6*S*)-Allyl 6-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)-ethyl)-3-(((1*R*,3*S*)-1-oxidotetrahydrothiophen-3-yl)thio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (7b). A mixture of trithiocarbonate **4a** (100.0 g, 227 mmol), allyl glyoxalate monohydrate **15a** (60.1 g, 455 mmol), *i*-PrOAc (400 mL), and Scollidine (8.26 g, 240 mmol) were heated for 2−4 h at 50 °C under reduced pressure (450 mbar). The reaction mixture was cooled to 25 °C and extracted with 1 N HCl (100 mL), followed by aqueous sodium bisulfite (2 × 100 mL). The organic phase was concentrated under reduced pressure (50 °C/200−300 mbar) to 150 mL. The reaction was diluted with *i*-PrOAc (400 mL) and then concentrated (50 °C/200−300 mbar) to a final volume of 150 mL. This cycle was repeated until the water content was <0.5% according to KF analysis. The crude aminal **12a** was then used in the next step without purification, after determination of approximate solution potentcy by HPLC.

A solution of aminal **12a**, acetonitrile (200 mL), and *i*-PrOAc (175 mL) was cooled to −10 °C. Methanesulfonyl chloride (41.75 g, 511 mmol) was added. Diisopropylethylamine (61.4 g, 475 mmol) was added at a rate of 0.5 mL/min. The reaction mixture was stirred for 30 min to produce chloride intermediate **16a** (IPC target specification <5 area % **12a** according to HPLC). Additional diisopropylethylamine (58.9 g, 456 mmol) was added; the mixture was warmed to 30 °C and then stirred for 2 h (IPC target specification <1 area % **16a** according to HPLC). Triethylphosphite (26.5 g, 160 mmol) was added, and the solution was stirred for 30 min. *i*-PrOAc (400 mL) and 0.5 N HCl (600 mL) were added, and the layers were separated. The organic layer was washed successively with 10% brine (500 mL), 0.5 M phosphate buffer (pH 6; 500 mL), and 10% brine (500 mL). The organic layer was concentrated (50 °C/100 mbar) to 500 mL; solids formed during the concentration (IPC target specification <4% acetonitrile according to HPLC). The temperature was adjusted to 25 °C, and MtBE (250 mL) was added. The slurry was cooled to 5 °C and allowed to granulate for 4 h. The solid product was filtered and washed with MtBE (200 mL). The product cake was dried at 25 °C for ≥16 h to yield thiopenem **7b** (26.58 g, 23% from **4a**) of as an off-white solid (HPLC potency 97.8%). The in situ yield of **7b** was 37% following aqueous washes.

^{1}H NMR (700 MHz, $CDCl_3$) 5.92 (ddt, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.65 (d, *J* = 1.4 Hz, 1H), 5.39 (ddt, *J* = 17.2, 1.5 (×3) Hz, 1H), 5.23 (ddt, *J* = 10.5, 1.4 (×3) Hz, 1H), 4.74−4.65 (m, 2H), 4.24 (dq, *J* = 6.3, 6.3, 6.3, 4.5, 1H), 3.96 (dd, *J* = 14.3, 8.4 Hz, 1H), 3.70 (dd, *J* = 4.7, 1.5 Hz, 1H), 3.64 (dt, *J* = 8.3, 8.3 Hz, 1H), 3.13−3.10 (m, 1H), 2.79 (ddd, *J* = 14.3, 8.7, 1.8 Hz, 1H), 2.74−2.64 (m, 3H), 1.24 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) 172.02, 159.60, 150.96, 131.81, 118.63, 71.92, 65.87, 65.34, 64.21, 61.58, 52.87, 46.86, 33.32, 25.85, 22.67, 18.11, 4.13, 4.97. HRMS (ESI) exact mass calcd for $C_{21}H_{34}NO_5S_3Si$ (M + H) 504.1368, found: 504.1380.

(5*R*,6*S*)-Allyl 6-((*R*)-1-hydroxyethyl)-3-(((1*R*,3*S*)-1-oxidotetrahydrothiophen-3-yl)thio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (8b). Thiopenem **7b** (5.47 g, 9.57 mmol) and THF (26.84 mL) were stirred for 15 min at 20−25 °C, and then added to a second vessel containing MtBE (26.84 mL), tetrabutylammonium fluoride trihydrate (5.16 g, 14.6 mmol) and acetic acid (5.17 mL, 90.3 mmol). The reaction was heated to 27 °C and stirred for 24 h (IPC target specification ≤3 area% **7b** according to HPLC). MtBE (26.84 mL) was added and the mixture was cooled to 5 at 0.2 °C/min. The slurry was stirred for 4 h at 5 °C, filtered, washed with MtBE (2 × 26.84 mL) and dried to constant weight at 20 °C to yield alcohol **8b** (2.95 g, 77%) as an off-white solid (HPLC area% purity 97.6% at 210 nm).

^{1}H NMR (700 MHz, $CDCl_3$) 5.98−5.93 (m, 1H), 5.71 (br s, 1H), 5.42 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.26 (d, *J* = 10.6 Hz, 1H),

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4.80−4.77 (m, 1H), 4.70−4.67 (m, 1H), 4.23 (dq, J = 6.5, 6.5 Hz, 1H), 3.94 (dd, J = 14.4, 8.5 Hz, 1H), 3.74 (d, J = 7.1 Hz, 1H), 3.69 (dddd, J = 8.2, 8.2, 8.2, 8.2 Hz, 1H), 3.15 (d, J = 13.2 Hz, 1H), 2.84 (ddd, J = 14.4, 8.2, 8.2 Hz, 1H), 2.76−2.66 (m, 3H), 1.36 (d, J = 6.4 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) 171.80, 159.40, 151.44, 131.60, 118.60, 118.33, 71.35, 65.83, 65.55, 64.75, 61.25, 52.65, 46.63, 33.19, 21.93. HRMS (ESI) exact mass calcd for $C_{15}H_{19}NNaO_5S_3$ (M + Na) 412.0323, found: 412.0322.

(5*R*,6*S*)-6-((*R*)-1-Hydroxyethyl)-3-(((1*R*,3*S*)-1-oxidotetrahydrothiophen-3-yl)thio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (1). To a mixture of alcohol **8b** (5 g, 12.8 mmol) and dichloromethane (65 mL) was added tetrabutylammonium hydrogen sulfate (0.44 g, 1.3 mmol), benzene sulfinic acid sodium salt (2.25 g, 13.7 mmol), and water (63 mL). The biphasic mixture was stirred vigorously under nitrogen. Tetrakis (triphenylphosphine) palladium(0) (0.44 g, 0.38 mmol) and triphenylphosphine (0.50 g, 0.9 mmol) were added, and the mixture was stirred for 30 min at 20 °C (IPC target specification ≤1 area % **8b** according to HPLC). The layers were separated, the aqueous layer containing product was washed with dichloromethane (3 × 50 mL) and then treated with activated carbon (1.1 g) and Hyflo Supercel (1.1 g). The suspension was stirred for 10 min and then filtered. The filtrate was cooled to 5 °C, and then 1 M HCl was added to precipitate **1**; precipitation was complete when pH reached 2−2.5. The slurry was granulated for 60 min and then filtered at 5 °C. The filter cake was washed with cold (∼5 °C) water (2 × 25 mL) and then dried under vacuum at 25 °C to yield sulopenem (**1**) (1.97 g, 82%) as an off-white solid (HPLC area % purity 99.1% at 210 nm).

^{1}H NMR (700 MHz, DMSO-d_6) 5.71 (br s, 1H), 5.21 (br s, 1H), 4.00−3.96 (m, 1H), 3.90−3.85 (m, 1H), 3.80 (dd, J = 6.0, 1.2 Hz, 1H), 3.76 (dd, J = 14.4, 8.9 Hz, 1H), 3.01−2.98 (m, 1H), 2.84 (ddd, J = 12.7, 12.7, 6.6 Hz, 1H), 2.72 (ddd, J = 14.4, 5.6, 1.9 Hz, 1H), 2.65 (ddt, J = 13.1, 6.5, 2.3 Hz, 1H), 2.39 (ddt, J = 12.6, 9.2, 6.4 Hz, 1H), 1.16 (d, J = 6.4 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) 173.34, 160.86, 151.56, 117.75, 71.09, 64.31, 63.94, 60.53, 52.17, 46.26, 33.46, 21.51. HRMS (ESI) exact mass calcd for $C_{12}H_{16}O_5NS_3$ (M + H) 350.0185, found: 350.0188.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra and kilogram-scale experimental procedures. 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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