

# Development of a Practical and Convergent Process for the Preparation of Sulopenem

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## Supporting Information

**ABSTRACT:** Previous synthetic processes for the preparation of sulopenem involved multistep linear sequences in which the chiral sulfoxide side chain was introduced early in the process. This contribution summarizes the development of a practical and convergent process for the large-scale preparation of **1**. The key step in the synthesis involves cyclization of an oxalimide intermediate to provide the thiopenem core. This convergent strategy allows for late introduction of the expensive and labile chiral sulfoxide subunit. Additionally, a regioselective sulfur oxidation and an improved deprotection sequence were developed. The latter provides API of high purity without the need for recrystallization.

## INTRODUCTION

Penems, a class of  $\beta$ -lactam antibiotics, have been the subject of intense research over the last three decades.<sup>1–6</sup> Sulopenem (**1**) is a novel 2-thioalkyl penem that was in development for a broad range of indications (Figure 1).<sup>7,8</sup> In order to support this research program, a practical process for the large-scale preparation of this antibacterial was required.

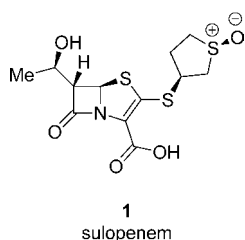


Figure 1. Chemical structure of sulopenem.

During the early phases of clinical development, sulopenem (**1**) was prepared at multikilogram scale via two distinct chemical processes (Scheme 1).<sup>9</sup> Both approaches utilized trithiocarbonate **2** as a key building block but differed in the chemistry used for construction of the thiopenem ring. The first-generation synthesis employed an oxalimide-derived carbene cyclization for construction of intermediate **5** via oxalimide **4**.<sup>10,11</sup> Penem **5** was then converted to sulopenem via two well-established deprotection steps (desilylation, followed by Pd-catalyzed deallylation). While this synthesis was fit for purpose, scale-related challenges prohibited larger-scale application. Primary drawbacks included low yield for the cyclization step (~40%) and high environmental impact associated with  $\text{CHCl}_3$  utilization. It became clear that a more efficient process was required to support development and commercialization.

The second-generation synthesis involved conversion of trithiocarbonate **2** to thiopenem **8** (analogous to **5**) via a base-induced cyclization, followed by desulfurization with triethylphosphite, in a process reminiscent of an Eschenmoser sulfide contraction.<sup>8,12</sup> Although this approach also comprised a linear synthetic sequence for the preparation of the penem core, several of the key issues that prevented larger-scale production of API were addressed. This route proved satisfactory for the production of phase 3 supplies; however, it was deemed unacceptable for commercial manufacture, primarily due to a poor yield (20–25%) for the key cyclization sequence. As a result, a process research program was initiated to identify an improved disconnection strategy. We report herein the development of an efficient, convergent process for the synthesis of **1**.

## RESULTS AND DISCUSSION

**Process Research. Identification of a Potential Commercial Route.** The combination of a high daily intravenous dose, a challenging  $\beta$ -lactam structure, and an aggressive clinical development plan for sulopenem (**1**) required the identification of scalable technology for the manufacture of rapidly escalating quantities of active pharmaceutical ingredient (API). To enable early alignment of suppliers for custom raw materials, 4-acetoxyazetidione (**9**) and the proprietary chiral sulfoxide **10** were selected as building blocks for all potential commercial processes (Figure 2). Furthermore, we committed to targeting the late-stage thiopenem intermediate **8**, since the end-game chemistry for conversion of this compound to sulopenem (**1**) was well-established by the first- and second-generation syntheses.<sup>9</sup> Conserving the same end-game strategy also

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Scheme 1. First- and second-generation routes for construction of key intermediates

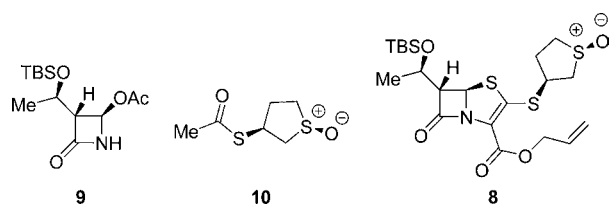
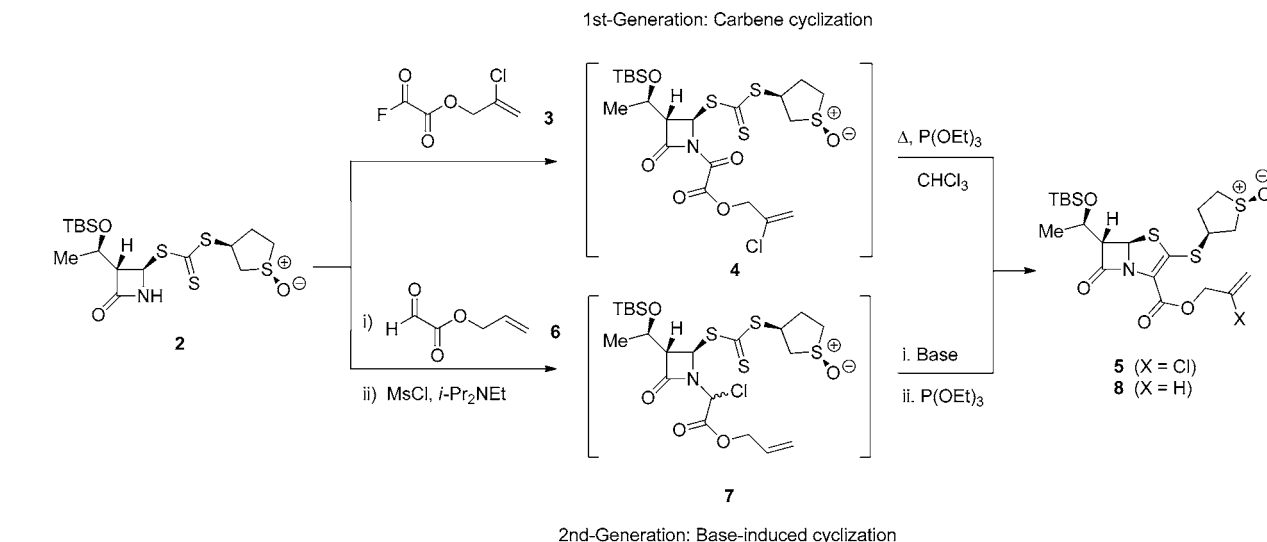


Figure 2. Key building blocks for sulopenem synthesis.

minimized the potential for introducing new process-related impurities.

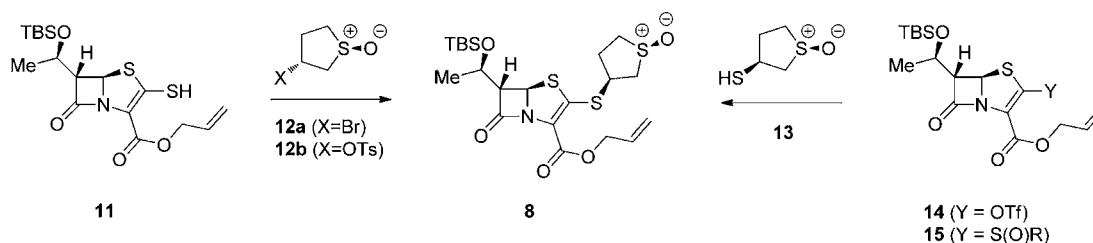
After a preliminary cost analysis, it became clear that commercial processes for the manufacture of **1** would need to be more convergent than the routes used during development. A late introduction of the chiral sulfoxide moiety would have a positive impact, since this subunit was both expensive and relatively labile. Two complementary approaches for the late-stage introduction of this group have been reported (Scheme 2).<sup>8,13,14</sup> The first method involves S-alkylation of the thioenolate derived from **11** with a suitable electrophile, such as **12a** (X = Br) via halogen–halogen displacement, or via  $\beta$ -elimination of the leaving group in **12b** (X = OTs) to afford a conjugate acceptor that reacts with poor facial selectivity.

A second, more desirable, approach involves conjugate addition of thiol **13** (obtained from thioacetate **10**) to an appropriately activated penem derivative (e.g., **14** or **15**). For carbapenems, leaving groups (Y) such as enol phosphates or enol tosylates have been used for coupling the carbapenem

nucleus with mercaptan side chains.<sup>16–18</sup> Unfortunately, analogous reactions with thioenems proved largely unsuccessful. Conversely, more reactive enol triflates, or certain alkyl sulfinate derivatives, have been reported to be effective for coupling a wide range of thiols to prepare substituted thioenems. Preparation and use of an enol triflate (e.g., **14**) would be problematic on large scale for several reasons.<sup>19</sup> Therefore, initial efforts were focused on developing alkyl sulfinate analogues (e.g., **15**) for the introduction of the sulopenem side chain.<sup>11,20</sup>

**Construction of the 2-Thioalkylpenem Core.** Numerous synthetic approaches were evaluated in the laboratory for the preparation of the challenging penem core (Figure 3). The most promising hits were further assessed for synthetic viability on larger scale.

A number of methods for construction of carba- and thioenems have been reported in the synthetic chemistry literature.<sup>21–23</sup> Key strategies include C–C,<sup>1,3,24–26</sup> C–N,<sup>27</sup> and C–S<sup>28–30</sup> bond formation for preparation of the five-membered ring. However, many of the methods that have proven successful for carbapenems are not applicable to thioenems. For instance, incompatibility between sulfur-containing substrates and a necessary catalyst or promoter (e.g., Rh) beset the metallo–carbenoid insertion approach.<sup>31</sup> Difficulties in the construction and handling of starting materials for a key transformation complicated the vinyl halide cross-coupling<sup>32</sup> and intramolecular imine formation strategies. Finally, other routes reached a proof-of-concept phase in the laboratory, but were either too lengthy (e.g., thiolactonization and enolate addition to thiocarbonate<sup>33</sup> approaches) or

Scheme 2. Convergent approaches to protected penem **8**

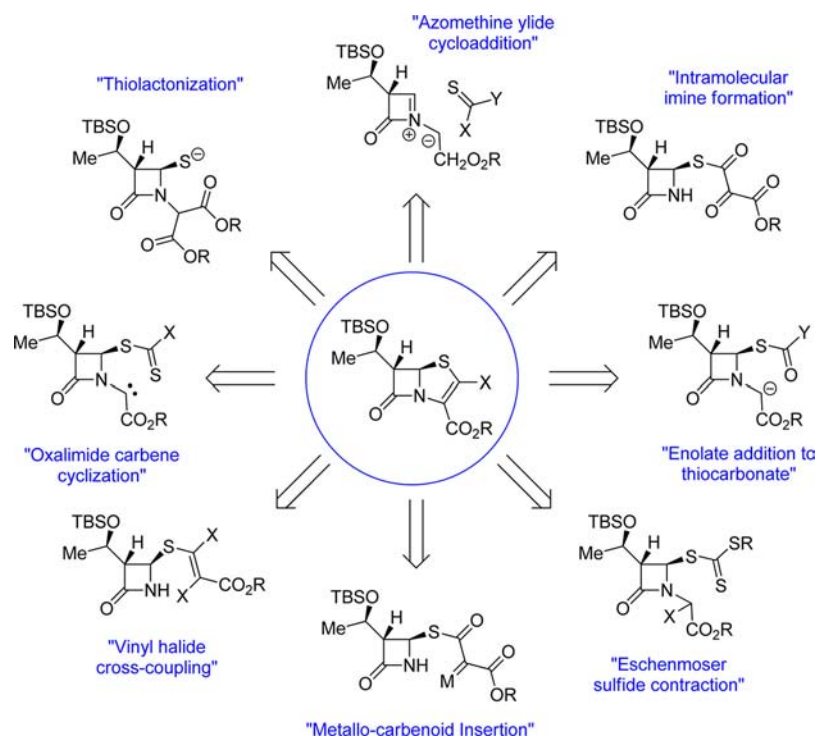
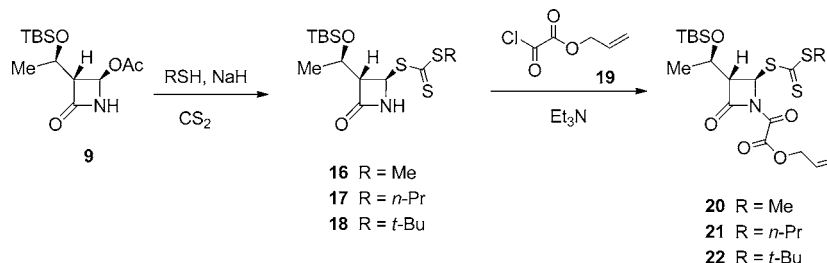


Figure 3. Survey of methods for thiopenem synthesis.

### Scheme 3. Preparation of oxalimide derivatives from 9



technically challenging/costly for commercial-scale application (azomethine ylide<sup>34</sup> and Eschenmoser sulfide contraction<sup>9</sup> routes).

After extensive evaluation of potential methods, a variation of the oxalimide carbene cyclization approach was selected.<sup>10</sup> Despite poor performance of this strategy in the first-generation process, the use of more stable oxalimide cyclization precursors led to significantly increased viability as a commercial approach. Key to the success of this modification was introduction of the chiral sulfoxide side chain *after* thiopenem construction, which offered several advantages.

**Preparation of Oxalimides from Azetidinone 9.** As in the first-generation synthesis, the commercially available azetidinone 9 was utilized in the preparation of several oxalimides for evaluation in the key carbene cyclization step (Scheme 3).<sup>8</sup> Azetidinone 9 was converted to a range of alkyl trithiocarbonates 16–18 utilizing simple, inexpensive thiols and carbon disulfide. Aliphatic thiols were chosen due to their performance in the cyclization sequence, coupled with the knowledge that the resulting 2-thioalkylpenems could be further converted to sulopenem (1) via established methods.<sup>20</sup>

Methyl, *n*-propyl, and *tert*-butyl thiols were treated with sodium hydride in MtBE, followed by addition of carbon disulfide to afford the corresponding trithiocarbonate salts.

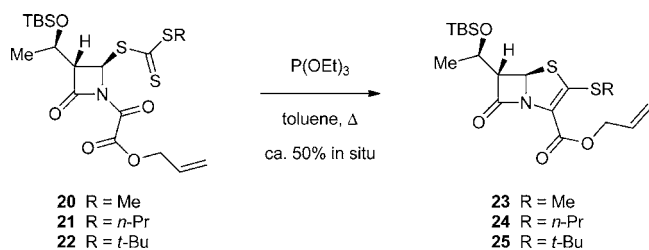
These salts were subsequently reacted with azetidinone 9 to provide 16–18 in good yields. Compounds 16–18 were each crystalline solids that exhibited improved stability relative to trithiocarbonate 2, which was utilized in the first- and second-generation syntheses.

The trithiocarbonates 16–18 were then treated with allyl oxalyl chloride 19 in the presence of triethylamine to form the desired oxalimides 20–22. These oxalimides were each carried into the carbene cyclization step, in order to compare their performances in this key reaction.

**Cyclization of Oxalimides to Thiopenems.** Cyclizations of oxalimides of this type have traditionally been performed using trialkyl phosphites under high dilution in chlorinated solvents.<sup>10,11</sup> During the first-generation process (Scheme 1) the optimal conditions for conversion of 4 to 5 involved the use of triethylphosphite in  $\text{CHCl}_3$ .<sup>8</sup> Toluene was also identified as being compatible with the carbene cyclization, and was chosen as a more environmentally friendly alternative for the current study. Oxalimides 20–22 were treated with two molar equivalents of triethylphosphite in toluene at elevated temperature to provide the corresponding thiopenems 23–25 (Scheme 4) in similar in situ yields (~50%).

Upon completion of this initial screen, the advantages of employing 1-propanethiol in this sequence became apparent.

Scheme 4. Cyclization of oxalimide to penem



This thiol is inexpensive and nonvolatile (vs MeSH) and led to highly crystalline, isolable compounds at both the oxalimide (21) and thiopenem (24) stages. Therefore, intermediate 21 was selected to evaluate downstream chemistry. As described in Scheme 5, conversion of thiopenem 24 to the known late-stage intermediate 8 was envisioned to include selective sulfur oxidation, followed by displacement of the sulfinate of intermediate 26 with the thiol derived from deacetylation of 10.

**Formation of Penem Sulfoxide 26 by Oxidation of Penem 24.** A survey of the literature indicated that the most common methods for oxidation of compounds of type 24 employed either *m*-chloroperoxybenzoic acid (*m*-CPBA)<sup>20</sup> or bleach, and proceeded in modest yields.<sup>24,25,35</sup> Due to its simplicity and reported regioselectivity favoring the exocyclic sulfur, *m*-CPBA was initially selected for conversion of 24 to 26. This oxidant provided the desired sulfoxide 26 as the major product, albeit as a mixture of diastereoisomers contaminated by significant levels of sulfone 27 and regioisomer 28 (Scheme 6).

Nevertheless, the ability to produce sulfoxide 26 in multigram quantities enabled us to focus on preparation of a suitable nucleophile for introducing the chiral side-chain moiety. Initial trials using historical methods<sup>8</sup> involved treatment of thioacetate 10 with aqueous sodium hydroxide to liberate the corresponding sodium thiolate 29 (Scheme 7). The reaction mixture was then acidified to afford thiol 13, which unfortunately proved to be highly water-soluble.

Although 13 could be partially extracted into CH<sub>2</sub>Cl<sub>2</sub>, concentration of solutions resulted in the formation of disulfide 30 (Figure 4). Disulfide formation occurred primarily during concentration of the solution of 13 even when care was taken to exclude oxygen. In order to avoid handling thiol 13, direct addition of thiolate 29 to sulfoxide 26 was investigated. Unfortunately, this approach led to poor yields of the desired coupling product.

To avoid the issues experienced with extraction of thiol 13 from an aqueous solution, thioacetate 10 was converted to thiolate 29 with sodium ethoxide in ethanol. This was followed by acidification with acetic acid to give crude thiol 13 containing minimal disulfide 30. Although thiol 13 proved incapable of addition to 26 directly, addition of nitrogen bases

(e.g., triethylamine) promoted the reaction to provide thiopenem 8 (Scheme 8), an advanced intermediate in the second-generation process to sulopenem (1).<sup>9</sup>

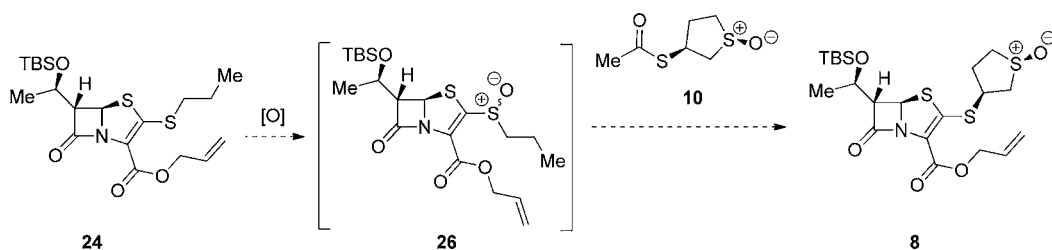
**Process Optimization for the Preparation of Penem 8. Telescoped Synthesis of Oxalimide 21.** While trithiocarbonate 17 could be isolated via crystallization from heptanes, several crops were required to maximize recovery. Therefore, a telescoped process for the preparation of oxalimide 21 was developed that took advantage of the high in situ yield of 17. 1-Propanethiol was treated with sodium hydride to afford the corresponding thiolate. After addition of carbon disulfide, the resulting intermediate was combined with 4-acetoxyazetidione (9) to provide trithiocarbonate 17 in nearly quantitative yield (Scheme 9).

The crude reaction mixture in MtBE was filtered through a pad of silica gel and then treated with allyl oxalyl chloride 19 and triethylamine at -10 °C to provide oxalimide 21 in 89–92% yield from 9.

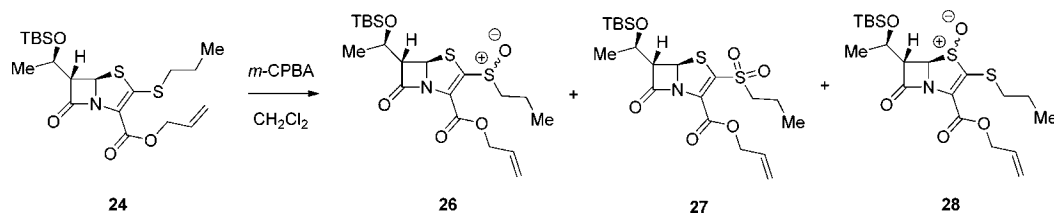
**Carbene Cyclization to Prepare Thiopenem 24.** Although the conversion of oxalimide 21 to thiopenem 24 in toluene had been demonstrated, the reaction was far from optimal in terms of yield, throughput and scalability. Initial cyclization conditions utilizing triethylphosphite in toluene at 75 °C resulted in 35–40% in situ yield of penem 24. Cyclization proceeded in a range of solvents, but CHCl<sub>3</sub>, toluene and trifluorotoluene gave the highest yields. Evaluation of reaction parameters including concentration, temperature and phosphite addition rate did not lead to substantial improvement. Alternative phosphite reagents (e.g., P(O<sup>*i*</sup>Pr)<sub>3</sub>, P(OPh)<sub>3</sub>) gave inferior results, but a breakthrough was realized when dialkylphosphonite reagents (P(OR)<sub>2</sub>R') were used (Table 1).<sup>36,37</sup> For example, the use of dimethyl phenylphosphonite or diethyl methylphosphonite, in toluene, provided thiopenem 24 in an improved 69% and 68% in situ yield, respectively (entries 4 and 5). Further evaluation of this class of reagents showed generally enhanced performance compared to phosphites. Of the phosphonites evaluated, diethyl methylphosphonite provided the best combination of performance and bulk reagent cost, so it was selected for further development.

With the substantial increase in yield attained by using a more effective phosphorous reagent, focus shifted to evaluation of the mass balance for this cyclization. As suspected from previous experience on the first-generation synthesis, the allyl protecting group on oxalimide 21 led to 5–10% of the cyclopropanation byproduct 31 (Scheme 10).<sup>10</sup> Oxalimide 32, which contains a chloroallyl protecting group, was prepared in order to compare performance in the cyclization.<sup>11</sup> Chloroallyl protection was found to minimize intramolecular cyclopropanation byproducts in the first-generation carbene synthesis through added steric hindrance, as well as by rendering the alkene less electron-rich. Under equivalent conditions,

Scheme 5. Proposed introduction of the chiral side chain



Scheme 6. Selective oxidation of thiopenem 24



Scheme 7. Preparation of thiolate 29 and thiol 13

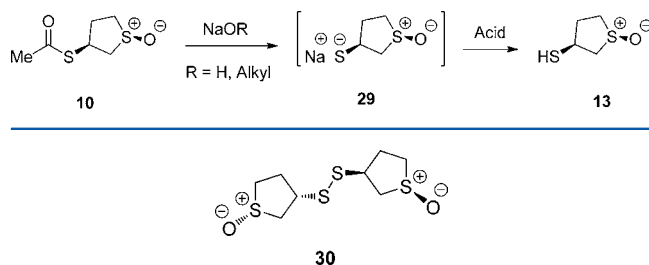
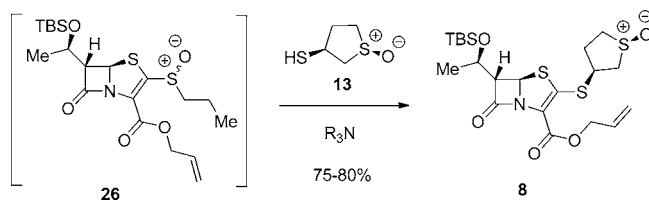


Figure 4. Disulfide impurity 30.

Scheme 8. Preparation of thiopenem 8



oxalimide 32 was converted to thiopenem 33 in a slightly improved yield (~10% greater than 21→24), as the corresponding chlorocyclopropane 34 was not observed. Since 2-chloroallyl oxalyl chloride is significantly more expensive than the allyl derivative, the minimal yield improvement did not justify a change in strategy. Therefore, allyl oxalimide 21 was utilized for further development.

In addition to the cyclopropanation byproduct, the thiol derivative 11, and *S*-ethyl penem 35 were each identified (Figure 5). These two compounds contributed <10% to the overall mass balance. These impurities formed in detectable levels under all reaction conditions explored, but neither compound was problematic in downstream chemistry.<sup>38</sup>

A design of experiment (DoE) approach was utilized to further optimize reaction conditions for the cyclization of oxalimide 21 in toluene with diethyl methylphosphonite. These investigations revealed that concentration and reaction temperature were important factors. The optimal reaction temperature appeared to be in the range of 80–90 °C. Below 65 °C, the reaction failed to reach completion after extended periods, while elevated temperatures led to thermal decomposition

Scheme 9. Telescoped synthesis of oxalimide 21

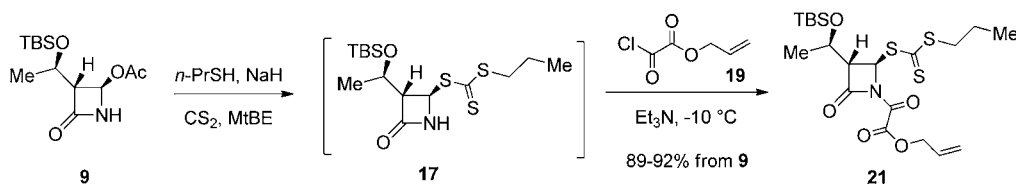
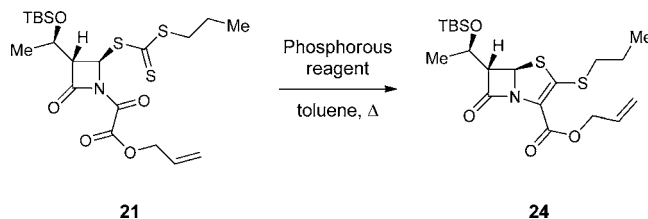


Table 1. Phosphorous reagent screen



entry	phosphorous reagent	yield <sup>a,b</sup>
1	triethyl phosphite, $\text{P}(\text{OEt})_3$	35–40
2	triisopropyl phosphite, $\text{P}(\text{O}i\text{-Pr})_3$	15–20
3	triphenyl phosphite, $\text{P}(\text{OPh})_3$	trace
4	dimethyl phenylphosphonite, $\text{PhP}(\text{OMe})_2$	69
5	diethyl methylphosphonite, $\text{MeP}(\text{OEt})_2$	68
6	diisopropyl phenylphosphonite, $\text{PhP}(\text{O}i\text{-Pr})_2$	53
7	diethyl phenylphosphonite, $\text{PhP}(\text{OEt})_2$	39

<sup>a</sup>In situ yields determined by HPLC analysis. <sup>b</sup>Conditions: 21 (2 mmol), phosphorous reagent (2.25 equiv) added over 4 h, toluene (30 mL/g), 90 °C.

products. Although the intramolecular carbene cyclization is optimally carried out under high dilution, reasonable yields could be achieved with as little as 20 volumes (L/kg substrate) of toluene.<sup>10</sup> Utilizing the findings from the experimental design, optimal conditions were determined. This process involved addition of 2.5 equiv of methyl diethylphosphonite over 4–5 h to a solution of 21 in toluene (30 volumes) at 90 °C. In situ yields of 63–69% were reproducibly achieved with isolated yields typically 54–60%. After completion of the reaction, toluene was displaced with *i*-PrOH under reduced pressure. The product was subsequently crystallized from an *i*-PrOH concentrate as large, high density laths, which effectively excluded process-related impurities (see Figure 6). The high bulk density of this material also enabled high throughput manufacture.

**Identification of Optimal Sulfur Oxidation Conditions.** Initial oxidation of penem 24 with *m*-CPBA was suitable for proof of concept; however, only low yields of desired sulfoxide 26 were obtained. Despite significant optimization, the *m*-CPBA oxidation unfortunately resulted in maximum yields of only 55–59% of sulfoxide 26. In addition, safety concerns associated with the use of *m*-CPBA on large scale,<sup>39</sup> led to an

## Scheme 10. Formation of cyclopropanation byproduct 31

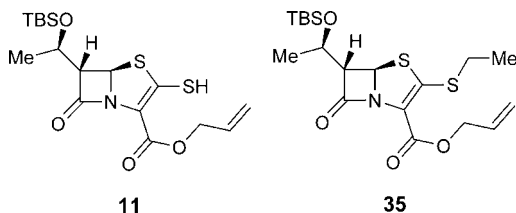
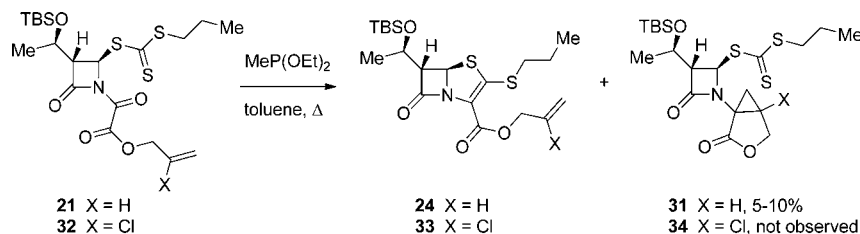


Figure 5. Cyclization byproducts 35 and 11.

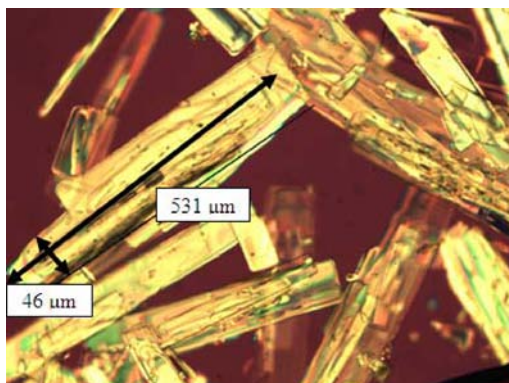
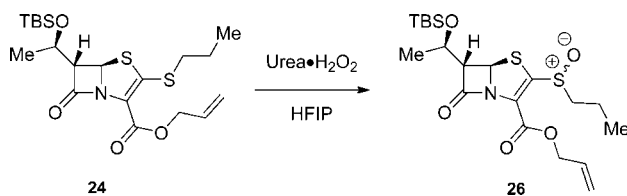


Figure 6. Crystals of thiopenem 24.

evaluation of alternatives. Extensive screening of catalytic (e.g., V, Mo, W, Au) and stoichiometric oxidants was performed. These efforts resulted in identification of two highly regioselective oxidation systems for the formation of sulfoxide **26**. A catalytic system utilizing methyltrioxorhenium (MTO)<sup>40,41</sup> and urea–hydrogen peroxide (UHP) in trifluoroethanol (TFE), as well as a noncatalytic system using urea–hydrogen peroxide (UHP) in hexafluoroisopropanol (HFIP),<sup>42–44</sup> each produced sulfoxide **26** in 70–75% yield. Due to the limited availability and high cost of MTO, the latter method was selected for further development (Scheme 11).

HFIP is a highly polar specialty solvent, commercially available on multiton scale from several suppliers.<sup>45</sup> However, due to the relatively high cost of HFIP compared to that of more traditional solvents, it was evident that maximizing concentration and/or recycling this material would be

## Scheme 11. Selective oxidation of 2-thioalkyl penems with UHP in HFIP



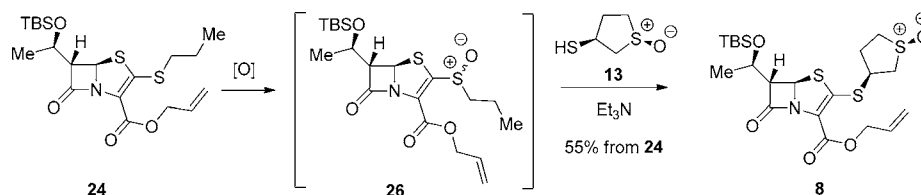
required.<sup>46</sup> Unfortunately, optimal yield and selectivity for the formation of sulfoxide **26** required at least 4–5 volumes of HFIP. The use of polar cosolvents (e.g., THF, ethyl acetate, acetonitrile, and ethanol) inhibited the reaction, while nonpolar cosolvents (e.g., toluene and heptanes) could be used successfully. The use of toluene significantly slowed the reaction rate, but reactions eventually reached completion with similar yield. Heptanes and HFIP are immiscible, but use of the biphasic mixture produced desired sulfoxide **26** in similar yield and selectivity to that using neat HFIP, without a significant rate reduction. Presumably, the desired oxidation occurs in the HFIP layer. Although the use of heptanes cosolvent did not decrease the required HFIP volume, it enabled the development of a suitable recycling process for this expensive solvent.

The reaction could be run in the presence of heptanes. However, the optimal process was carried out in neat HFIP (4–5 L/kg), and upon reaction completion, heptanes were added. The biphasic solution could then be distilled under reduced pressure.<sup>47</sup> The distillate was collected as a biphasic mixture, and the lower HFIP layer could be easily separated and reused without further purification. The concentrated reaction mixture was carried on to the next step without isolation.

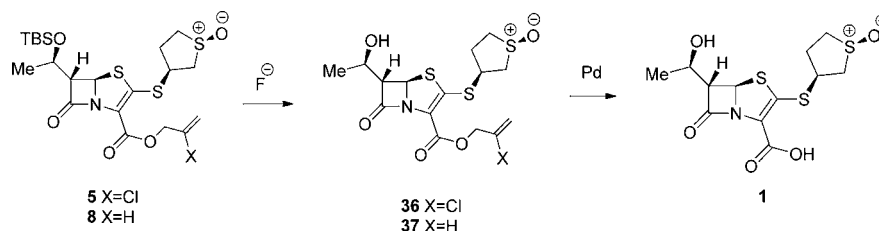
**Coupling thiol 13 with sulfoxide 26.** Thioacetate **10** is efficiently converted to thiol **13** via hydrolysis to thiolate **29** with sodium ethoxide followed by acidification with acetic acid (Scheme 7). Direct coupling of thiol **13** with sulfoxide **26**, in the presence of a trialkylamine, provided thiopenem **8** in scouting experiments. In order to maximize efficiency at large scale, a telescoped process was desired. Therefore, an extensive screen of base and solvent combinations was carried out. Isopropyl acetate emerged as the optimal solvent for hydrolysis of **10** to **13** and also proved suitable for the coupling step. For the coupling, no amine base proved to be superior to triethylamine in terms of cost and effectiveness. A two-step telescoped process was developed that provided thiopenem **8** in 80–83% in situ yield. This process tolerated crude solutions of sulfoxide **26**, allowing a multistep telescoped sequence to be utilized (Scheme 12), which further improved the efficiency of the overall synthesis. After aqueous workup and isolation from heptanes, **8** was obtained in 55% overall yield from thiopenem **24**.

**End-Game Development. Developing an Ideal Deprotection Strategy.** The synthesis described herein proved efficient and robust at moderate-to-large laboratory scale, providing thiopenem **8** in an overall yield of 30% (five steps) from 4-acetoxyazetidinone (**9**). Therefore, focus shifted to improvements in the end game. The end-game strategy utilized in both first- and second-generation syntheses of sulopenem (**1**) involved desilylation of the secondary hydroxyl group, followed by palladium-catalyzed deallylation to provide the free carboxylic acid (Scheme 13).<sup>9,11,48</sup>

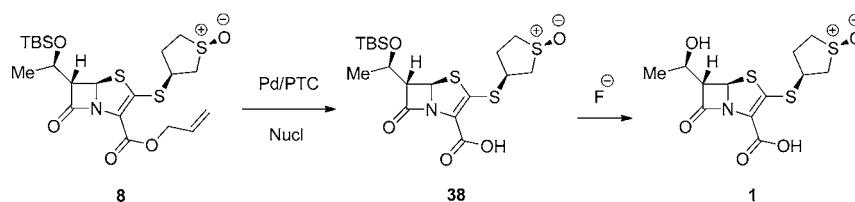
Scheme 12. Preparation of thiopenem 8



Scheme 13. Historical deprotection sequence



Scheme 14. Reordered deprotection sequence



Utilizing this strategy, the final API consistently required remediation due to high levels of residual palladium. Aqueous reprocessing of crude **1** was effective in purging Pd to an acceptable level; however, this resulted in unfortunate product losses of 15–20%. Late in the development of the second-generation route, it was discovered that the addition of a slight excess of triphenylphosphine to the deallylation led to isolated API that met tight Pd specifications.<sup>49</sup> This addition did not hinder the deprotection step, but it precluded the need for reprocessing by maintaining a soluble form of Pd throughout isolation. High Pd and/or triphenylphosphine oxide levels nevertheless remained a potential risk and were closely monitored. For commercial manufacturing, a reordered end-game sequence was desired (Scheme 14).

**Deprotection of 8 Leading to Formation of Sulopenem (1).** Performing the deallylation before the desilylation provided a two-fold advantage. The step involving Pd is further removed from the end of the synthesis, and the resulting TBS-protected acid is a fine crystalline solid that is relatively insoluble in water and most common organic solvents. The new strategy would provide another opportunity for purification via crystallization prior to isolation of sulopenem (**1**).

The Pd-catalyzed deallylation of **8** was studied closely to optimize catalyst, solvent, and allyl scavenger.<sup>50</sup> Initial screening provided conditions that included Pd(Ph<sub>3</sub>P)<sub>4</sub> in dichloromethane/water with the use of a phase transfer catalyst (Scheme 14). Sodium benzene sulfinate was an effective allyl scavenger, affording free acid **38** as a crystalline solid after acidification of the aqueous phase. While these conditions were adequate and gave reproducibly high yields, several factors urged us to reevaluate, including high cost and poor stability for the Pd catalyst and the use of a chlorinated solvent. Furthermore, the sulfinate was a relatively expensive stoichiometric reagent that required a phase transfer catalyst for

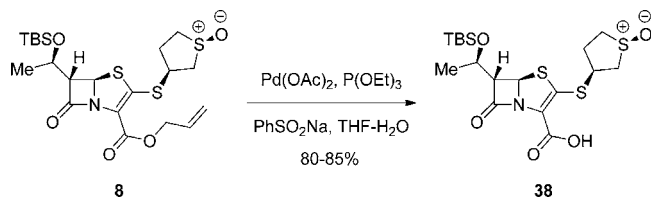
solubility in the organic phase. Optimization of these parameters would not only affect the chemistry output, but there were also questions around scalability, commercial availability of reagents, and overall cost.

The most significant parameter for both scalability and cost was the choice of Pd catalyst precursor. Typically, Pd(II) catalyst precursors are preferred, owing to their increased stability under standard handling conditions. Therefore, several Pd(II) compounds, ligands, and additives were evaluated.<sup>51,52</sup> After extensive screening, it was determined that a mixture of Pd(OAc)<sub>2</sub> and P(OEt)<sub>3</sub> could serve as a viable replacement for Pd(Ph<sub>3</sub>P)<sub>4</sub> in terms of performance, economics, and stability. The catalyst prepared in situ from these two components proved effective for conversion of **8** to **38**, leading to a less expensive, more robust process.

An extensive screen of alternatives to the sodium benzene sulfinate allyl scavenger was largely unsuccessful; most led to either a significant decline in rate or a poor purity profile for acid **38**. Triethylammonium acetate proved suitable for the deallylation but caused complications during workup. With sodium benzene sulfinate as the best choice for allyl scavenger, a survey of alternative solvents was carried out. It was determined that THF/water was an excellent replacement for the CH<sub>2</sub>Cl<sub>2</sub>/water combination. This miscible pair allowed for deallylation of **8** without the need for a PTC. With this solvent system change, the reaction conditions were further simplified and made more environmentally friendly. Final conditions for deallylation involved reaction of ester **8** with P(OEt)<sub>3</sub>, Pd(OAc)<sub>2</sub> (5 mol % catalyst), and sodium benzene sulfinate in a mixture of THF and water (2:1) at 20–25 °C, which provided acid **38** in 80–85% yield (Scheme 15).

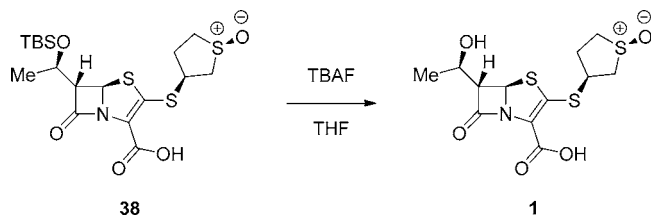
**Preparation of Sulopenem Acid 1 from 38.** For the final step of the synthesis of sulopenem acid **1**, a desilylation is performed on TBS ether **38**. Adopting conditions gleaned from

Scheme 15. Improved deallylation conditions



the first-generation synthesis, tetrabutylammonium fluoride (TBAF) in acetic acid was investigated for the reaction.<sup>9,11,53</sup> Under these conditions, significant decomposition of both starting material and product was observed. Therefore, other fluoride reagents (e.g., aqueous HF, CsF, KF,  $\text{Et}_3\text{N}\cdot 3\text{HF}$ ) were evaluated.<sup>33,54–59</sup> These reagents also proved ineffective for the reaction, showing poor product conversion or significant substrate decomposition. After carrying out pH-dependent stability studies on 38 and 1, it became apparent that the acetic acid cosolvent was primarily responsible for the degradation observed. Therefore, TBAF in THF was reevaluated in the absence of AcOH and was found to be effective. Silyl ether 38 was cleanly converted to alcohol 1 at 20–25 °C, resulting in excellent in situ yield (Scheme 16). Elevated temperatures resulted in thermal degradation of the  $\beta$ -lactam. Therefore, longer reaction times (~18 h) near 25 °C proved optimal.

Scheme 16. Desilylation of TBS ether 38



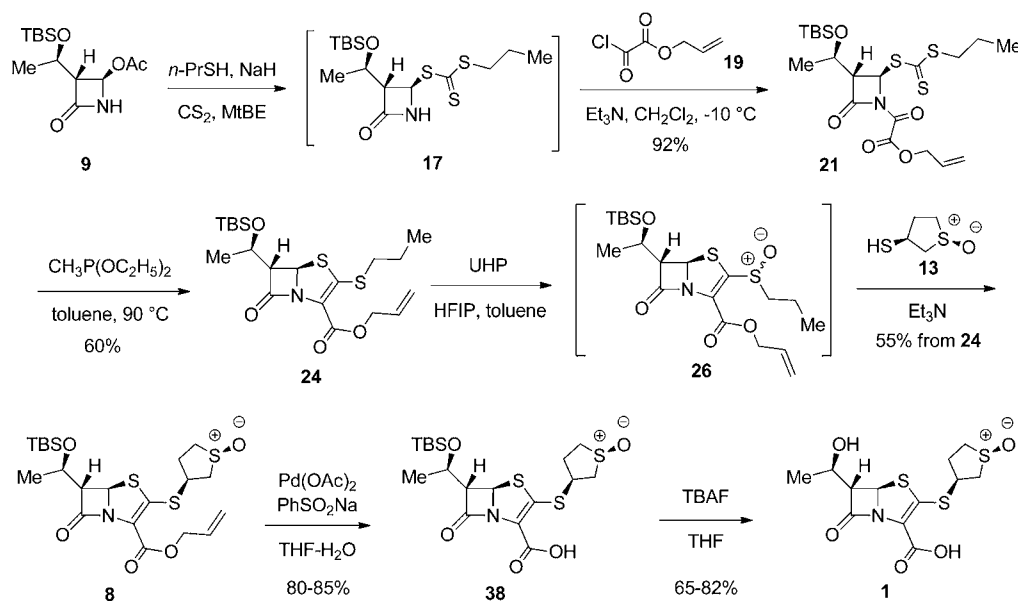
The isolation of 1 was surprisingly complicated. Partition of the crude reaction mixture between organic and aqueous phases allowed the product to be separated from organic impurities as

its salt form. However, simple acidification of the aqueous phase failed to result in precipitation of acid 1, despite the success of a related protocol in the first- and second-generation routes. Presumably, tetrabutylammonium salts were inhibiting the crystallization of sulopenem (1) from the aqueous solution. After extensive screening, it was discovered that addition of sodium benzenesulfinate to the aqueous solution, followed by  $\text{CH}_2\text{Cl}_2$  extractions, allowed for smooth crystallization of 1, upon acidification of the aqueous mixture (e.g.,  $\text{H}_2\text{SO}_4$  or HCl). This final process for workup and isolation of sulopenem (1) provided API of very high quality in up to 82% yield. While the role of sodium benzenesulfinate has not been definitively established, we suspect that dynamic salt metathesis allows for extraction of the more organic soluble tetrabutylammonium benzenesulfinate into the  $\text{CH}_2\text{Cl}_2$  layer.

## CONCLUSION

Following extensive route-scouting studies, a practical, cost-effective, and convergent third-generation process to sulopenem (1) was identified and developed for potential commercial application (Scheme 17). Conditions were discovered for telescoping the first two steps of the synthesis, affording oxalimide 21 in high yield from commercially available 4-acetoxyazetidione (9). The cyclization of oxalimide 21 to penem 8 was accomplished in good yield by replacing a phosphite reagent with a phosphonite, which enabled the carbene cyclization to proceed in a more environmentally friendly solvent. A highly regioselective oxidation procedure was developed for the preparation of sulfoxide 26 from penem 17, utilizing UHP/HFIP. The practical utility of this oxidation was enhanced by development of a recovery and recycle process for the HFIP solvent. Due to the relative instability of thiol 13, mild conditions were developed that enabled efficient coupling of thiol 13 with sulfoxide 26 to give thiopenem 8 via a telescoped process from penem 24. Additionally, an alternative end-game process was identified for palladium-catalyzed deallylation of ester 8, affording the penultimate penem acid 38. The reordered end game alleviated concerns over residual palladium and triphenylphosphine oxide in the API, in addition

Scheme 17. Final process scheme





to providing a crystalline intermediate for purification. Finally, desilylation conditions were developed, for the conversion of **38** to API, that addressed poor chemical stability and unique solubility properties of **1**, while obviating the need for recrystallization. The process to sulopenem described herein was intended for commercial application. Unfortunately, the program was discontinued before the chemistry was performed beyond laboratory scale.

## EXPERIMENTAL SECTION

**General.** (*R*)-4-Acetoxyazetidione **9** and allyl oxalyl chloride **19** were obtained from Kaneka Corporation and Interchem Corporation, respectively. All reactions were monitored by reverse phase liquid chromatography using an Agilent 1100 series HPLC equipped with a Halo C18 (50 mm × 4.6 mm, 2.7 μm) column utilizing an isocratic elution of 25% acetonitrile and 75% aqueous methanesulfonic acid with a flow rate of 1.0 mL/min and a column temperature of 30 °C. Approximate retention times (min): **1** (0.45), **38** (3.4), **8** (6.2), **26** (8.4, 8.6), **24** (11.6) and **21** (12.0).

**Allyl 2-((3*S*,4*R*)-3-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-2-oxo-4-(propylthiocarbonothioylthio)azetidinyloxy)-2-oxoacetate (**21**).** To sodium hydride (60% w/w in mineral oil, 28 g, 690 mmol) was added MtBE (1.0 L), and the resulting slurry was cooled to 20 °C. To the heterogeneous reaction mixture, was added slowly at ≤25 °C a solution of 1-propanethiol (34 g, 450 mmol) in MtBE (200 mL). (**CAUTION:** hydrogen gas evolution!) The resulting slurry was stirred at 20 °C for 1 h, and then carbon disulfide (53 g, 690 mmol) was added at ≤35 °C. The resulting yellow slurry was stirred at 20 °C for 1 h, and then anhydrous magnesium sulfate (6.0 g) was added; the reaction mixture was filtered through a pad of dry diatomaceous earth under a nitrogen atmosphere. The filter cake was rinsed with MtBE (100 mL). The combined filtrates were transferred to a clean and dry reactor to which **9** (100 g, 370 mmol) was added as a solid. The resulting slurry was stirred at 20 °C for 1 h and then filtered through a pad of silica gel under nitrogen atmosphere. The filter cake was rinsed with MtBE (100 mL), and then the combined filtrates containing **17** were cooled to -10 °C. Allyl oxalyl chloride (**19**) was then added at a rate to ensure the internal temperature was maintained below 0 °C. To the resulting solution was added a solution of triethylamine in MtBE at a rate to maintain temperature below 0 °C. After the addition of triethylamine was complete, the resulting mixture was warmed to 20 °C and stirred for 1 h. The reaction was quenched with water (200 mL), and the layers were separated. The organic layer was then washed with aqueous 10% sodium bicarbonate solution (2 × 200 mL), dried over magnesium sulfate (6.0 g), and filtered. The filtrate was diluted with heptanes (500 mL). The solution was then distilled at atmospheric pressure to a final temperature of 93 °C to ensure removal of MtBE. The resulting solution was cooled to 0 °C and the product precipitated. The resulting slurry was stirred for a minimum of 12 h, then was filtered and washed with heptanes (200 mL), and dried under reduced pressure for a minimum of 8 h to give **21** as an off-white solid (152 g, 89%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.77 (d, 1H, *J* = 3.4 Hz), 6.00–5.92 (m, 1H), 5.41 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.33 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.80–4.79 (m, 2H), 4.40 (dddd, *J* = 6.3, 6.3, 6.3, 2.4 Hz, 1H), 3.58 (t, *J* = 3.0 Hz, 1H), 3.45–3.36 (m, 2H), 1.78 (sxt, *J* = 7.4 (×5) Hz, 2H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.04 (t, *J* = 7.4, 7.4 Hz, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.05 (s,

3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 218.3, 163.4, 159.1, 154.4, 130.4, 120.2, 67.4, 66.1, 64.5, 58.9, 39.0, 25.6, 22.0, 21.3, 17.8, 13.4, -5.3, -4.3. HRMS (ESI) exact mass calcd for (M + H) 492.1363; found: 492.1365.

**(5*R*,6*S*)-Allyl 6-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-7-oxo-3-(propylthio)-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**24**).** A solution of toluene (3.0 L) and **21** (100 g, 0.20 mol) was heated to 90 °C under nitrogen. Diethyl methyl phosphonite (30% w/w solution in toluene; 230 mL, 0.46 mol) was added over 2 h, and the solution was stirred for an additional 2 h (IPC target specification <5% **21** according to HPLC). The reaction mixture was cooled to 50 °C and concentrated to 1.5 L under reduced pressure. The solution was further cooled to 20–25 °C and sequentially washed with aqueous 0.1 N HCl (500 mL), 5% aqueous sodium bicarbonate (500 mL), and 23% aqueous sodium chloride (500 mL). The organic layer was concentrated under reduced pressure at 50 °C to 200 mL. Isopropyl alcohol (500 mL) was added, and the mixture was concentrated under reduced pressure at 50 °C to 150 mL. The product slurry was cooled to 30 °C and stirred for 30 min. The solids were then filtered, washed with cold isopropyl alcohol (150 mL), and dried under vacuum at 20–25 °C to afford of penem **24** (54.1 g, 60%) as a yellow solid.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.99–5.91 (m, 1H), 5.61 (d, *J* = 1.2 Hz, 1H), 5.42 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.23 (ddt, *J* = 10.5, 1.2, 1.2) Hz, 1H), 4.77–4.66 (m, 2H), 4.25 (dq, *J* = 6.3 (x4), 1H), 3.68 (dd, *J* = 5.1, 1.5 Hz, 1H), 3.00–2.87 (m, 2H), 1.75 (sxt, *J* = 7.2 Hz, 2H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 172.1, 159.8, 155.5, 132.0, 118.1, 117.0, 71.5, 65.3, 63.7, 37.9, 25.7, 23.4, 22.5, 17.9, 13.2, -5.1, -4.3. HRMS (ESI) exact mass calcd for (M + H) C<sub>20</sub>H<sub>34</sub>NO<sub>4</sub>S<sub>2</sub>Si<sup>+</sup> 444.1693; found: 444.1701.

**(5*R*,6*S*)-Allyl 6-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-7-oxo-3-(propylsulfinyl)-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**26**).** Urea-hydrogen peroxide (5.75 g, 60 mmol) was added to penem **24** (25 g, 56 mmol) in hexafluoroisopropanol (HFIP) (125 mL) at 20–25 °C. The mixture was stirred for 12–14 h (IPC target specification <7% **24** according to HPLC), and then heptanes (38 mL) were added. The reaction mixture was distilled under reduced pressure at 35 °C to remove HFIP. Solvent displacement was continued by adding heptanes and concentrating until the HFIP was removed. The distillate was collected as two layers; the lower HFIP layer was separated for reuse in subsequent batches. The reaction mixture was concentrated to a slurry under reduced pressure to a final volume of 100–125 mL. To this was added isopropyl acetate (50 mL), and the heterogeneous mixture containing sulfoxide **26** (70–75% in situ yield according to HPLC analysis) was carried into the next step without purification.

A portion of the crude product was purified by silica gel column chromatography using ethyl acetate/heptane (30:70) as eluent to afford an analytically pure sample of a mixture of sulfoxide diastereomers **26**.

<sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>): δ 5.93–5.86 (m, 1H), 5.80 (d, *J* = 1.4 Hz, 0.6H), 5.67 (d, *J* = 1.4 Hz, 0.4H), 5.43–5.38 (m, 1H), 5.27 (br d, *J* = 10.8 Hz, 1H), 4.73–4.64 (m, 2H), 4.26–4.22 (m, 1H), 3.86 (dd, *J* = 4.0, 1.7 Hz, 0.4H), 3.84 (dd, *J* = 4.2, 1.7 Hz, 0.6H), 3.14 (ddd, *J* = 12.8, 9.2, 5.1 Hz, 0.6H), 3.09 (ddd, *J* = 12.6, 9.2, 5.1 Hz, 0.6H), 3.03–2.96 (m, 1H), 1.98–1.84 (m, 2H), 1.24 (d, *J* = 6.3 Hz, 1.8H), 1.24 (d, *J* = 6.3 Hz,

1.2H), 1.11 (t,  $J = 7.4$  Hz, 1.2H), 1.11 (t,  $J = 7.4$  Hz, 1.8H), 0.87 (s, 3.6H), 0.86 (s, 5.4H), 0.06 (s, 3.6H), 0.06 (s, 2.4H).  $^{13}\text{C}$  NMR (176 MHz,  $\text{CDCl}_3$ ):  $\delta$  173.0, 172.0, 164.6, 164.2, 158.5, 158.4, 131.0, 130.0, 121.7, 119.3, 119.2, 73.9, 73.6, 66.6, 65.2, 65.0, 62.7, 57.6, 57.2, 27.1, 25.8, 22.5, 22.4, 18.1, 16.6, 16.3, 13.2, -4.1, -5.1. HRMS (ESI) exact mass calcd for (M + H)  $\text{C}_{20}\text{H}_{34}\text{NO}_5\text{S}_2\text{Si}$  460.1642 found: 460.1645.

**(3S)-3-((5R,6S)-6-[(1R)-1-((tert-Butyl(dimethyl)silyloxy)ethyl)-7-oxo-2-[(prop-2-en-1-yloxy)carbonyl]-4-thia-1-azabicyclo[3.2.0]hept-2-en-3-yl)sulfanyl]tetrahydrothiophenium-1-olate (8).** A solution of sodium ethoxide in ethanol (35 mL, 90 mmol) was charged to a solution of **10** (16.05 g, 90 mmol) in degassed isopropyl acetate (110 mL) at 0–5 °C. The reaction was stirred for 30 min, and then the pH was adjusted to 6–7 with acetic acid (5.4 mL) to provide a solution of thiol **13**. Triethylamine (13.8 mL, 10 mmol) was then charged, and the resulting suspension was added to a crude solution of sulfoxide **26** (~45 mmol) in heptanes/isopropyl acetate (~150 mL) at -20 to -30 °C over 1 h. The reaction was warmed to 0–5 °C and stirred for 1 h. HPLC analysis of the reaction mixture indicated ~1% sulfoxide **26** remained. The reaction mixture was then quenched by addition of 1 M HCl (25 mL), and the layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate solution (100 mL) followed by saturated aqueous sodium chloride (100 mL). The organic layer was then concentrated under reduced pressure to a final volume of 25–50 mL. Heptanes (100 mL) were added, and the slurry was stirred at -20 °C for 30 min, filtered, washed with additional cold heptanes (100 mL), and dried under vacuum at 25 °C for 16 h to provide **8** (15.6 g, 55%) as an off-white solid.

$^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ ) 5.92 (ddt,  $J = 17.3, 10.6, 5.4$  Hz, 1H), 5.65 (d,  $J = 1.4$  Hz, 1H), 5.39 (ddt,  $J = 17.2, 1.5$  (x3) Hz, 1H), 5.23 (ddt,  $J = 10.5, 1.4$  (x3) 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).  $^{13}\text{C}$  NMR (176 MHz,  $\text{CDCl}_3$ ) ppm 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  $\text{C}_{21}\text{H}_{34}\text{NO}_5\text{S}_3\text{Si}$  (M + H) 504.1368, found: 504.1380.

**(3S)-3-((5R,6S)-6-[(1R)-1-((tert-Butyl(dimethyl)silyloxy)ethyl)-2-carboxy-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-en-3-yl)sulfanyl]tetrahydrothiophenium-1-olate (38).** Pd(OAc)<sub>2</sub> (4.46 g, 20 mmol), triethylphosphite (20.2 g, 120 mmol), THF (800 mL), and water (400 mL) were combined and stirred at 20–25 °C for 10 min under nitrogen. Solid penem **8** (200 g, 400 mmol) was added, followed by sodium benzenesulfinate (73.2 g, 440 mmol). The reaction was stirred for 4 h at 25 °C. After reaction completion was confirmed (IPC target specification <1% **38** according to HPLC), the mixture was cooled to 5 °C and 1 M aqueous HCl (495 mL) was added over 60 min (pH 2.5). The slurry was stirred at 0–5 °C for 30 min, and then filtered. The solids were reslurried in THF (800 mL), filtered, washed with THF (400 mL) and dried under reduced pressure for 16 h to afford **38** (176.02 g, 95.6%, potency =85.8%, assay corrected yield =82%).

$^1\text{H}$  NMR (700 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.82 (br s, 1H), 5.70 (d,  $J = 1.1$  Hz, 1H), 4.20 (dq,  $J = 6.2, 6.0$  Hz, 1H), 3.93 (dd,  $J = 4.2, 1.3$  Hz, 1H), 3.89–3.84 (m, 1H), 3.77 (dd,  $J = 14.4, 8.9$  Hz,

1H), 3.10–3.07 (m, 1H), 3.01–2.97 (m, 1H), 2.84 (ddd,  $J = 12.7, 12.7, 6.5$  Hz, 1H), 2.70 (ddd,  $J = 14.4, 5.7, 2.1$  Hz, 1H), 2.66–2.62 (m, 1H), 2.41–2.36 (m, 1H), 1.18 (d,  $J = 6.5$  Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).  $^{13}\text{C}$  NMR (176 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  172.8, 160.9, 151.3, 117.8, 70.7, 64.9, 63.7, 60.6, 52.2, 46.3, 33.4, 25.6, 21.8, 17.7, -4.5, 5.2. HRMS (ESI) exact mass calcd for (M + Na);  $\text{C}_{18}\text{H}_{29}\text{O}_5\text{NNaS}_3\text{Si}$  486.0869 found: 486.0875.

**(3S)-3-((5R, 6S)-2-Carboxy-6-[(1R)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-en-3-yl)sulfanyl]tetrahydrothiophenium-1-olate (1).** Tetrabutylammonium fluoride (1 M solution in THF) (113 mL, 113 mmol) was added to TBS ether **38** (35 g, 75.5 mmol) and THF (105 mL) at 25 °C, and the mixture was stirred for 18 h under nitrogen. After reaction completion was confirmed by HPLC analysis (IPC target specification <2% **38**), dichloromethane (245 mL) and a solution of sodium benzenesulfinate (13.3 g, 79.3 mmol) dissolved in water (245 mL) were added. The resulting biphasic mixture was separated, and the aqueous layer was washed with dichloromethane (2 × 87.5 mL). The aqueous layer was treated with activated carbon (3.5 g) for 20 min at 20–25 °C and then was filtered and washed with water (35 mL). The filtrates were combined and cooled to 5 °C. A 1.0 M HCl solution was added to obtain pH 2.5. The resulting slurry was stirred at 5 °C for 5 min, filtered, washed with water (35 mL), and dried under reduced pressure for 24 h to afford sulopenem (**1**) as a white solid (21.1 g, 72%).

$^1\text{H}$  NMR (700 MHz,  $\text{DMSO}-d_6$ ) 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).  $^{13}\text{C}$  NMR (176 MHz,  $\text{CDCl}_3$ ) ppm 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  $\text{C}_{12}\text{H}_{16}\text{O}_5\text{NS}_3$  (M + H) 350.0185, found: 350.0188.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, X-ray crystal structure for compound **24**, and design of experiment parameter and result information for the preparation of compound **24**. 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.

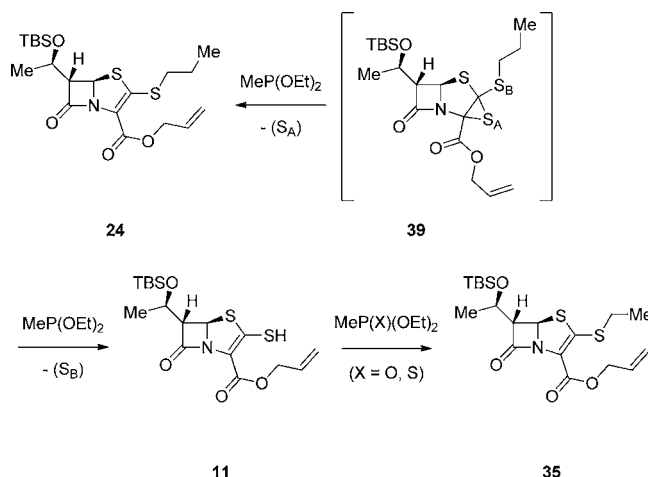
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