Supporting Information

Development of a Second-Generation Process to Antibacterial Candidate Sulopenem

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I. Process Scheme

\[ \text{2} \xrightarrow{\text{i. MeONa, i-ProOH, -10 °C}} \text{21} \]

\[ \text{3} \xrightarrow{\text{i. MeCl, i-Pr}_{2}\text{NEt, -20 to 30 °C}} \text{4a} \]

\[ \text{15a} \xrightarrow{\text{i-ProAC, collidine, 50 °C, (-H}_2\text{O)}} \text{12a} \]

\[ \text{8b} \xrightarrow{\text{TBAr, AcOH, THF, MeBz, 75%}} \]

\[ \text{1} \xrightarrow{\text{cat. Ph}_{3}\text{P, CH}_2\text{Cl}_2, \text{H}_2\text{O, then, HCl, H}_2\text{O, 80%}} \]
II. $^1$HNMR and $^{13}$C NMR spectra of compound 4a

Acquisition Time (sec) 4.2467  
Date 01 Apr 2010 16:43:44

File Name NUCLEUS 1H  
Number of Transients 8
Owner staff  
Sweep Width (Hz) 7715.81

Acquisition Time (sec) 0.7783  
Date 01 Apr 2010 16:45:52

File Name NUCLEUS 13C  
Number of Transients 133
Owner staff  
Sweep Width (Hz) 42016.17
III. $^1$HNMR and $^{13}$C NMR spectra of compound 7b
IV. $^1$HNMR and $^{13}$C NMR spectra of compound 8b
V. $^1$HNMR and $^{13}$C NMR spectra of compound 1
VI. Kilogram Scale Experimental Procedures

(2R,3S)-3-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-4-oxoazetidin-2-yl ((1R,3S)-1-oxidotetrahydrothiophen-3-yl) carbonotritioate (4a): A solution of 2 (14.0 kg, 78.5 mol) in isopropyl alcohol (144 L) was cooled to -15 °C, and then solid sodium methoxide (4.6 kg, 85.2 mol) was added in nine portions over 30 min at ≤ -8 °C (CAUTION: exothermic addition). The reaction was stirred for 20 to 30 minutes at -8 to -15 °C. The mixture was cooled to -20 to -25 °C, and then precooled (-10 °C) dichloromethane (45 L) was added. The resulting mixture was cooled to -25 °C, and then a solution of carbon disulfide (CAUTION: toxic, highly flammable substance) (8.0 kg, 105.1 mol) in dichloromethane (10 L) was added over 60 minutes at -18 to -25 °C. The reaction was stirred for 30 min at -20 to -25 °C, and then a pre-cooled (-20 °C) solution of 3 (22.6 kg, 78.6 mol) in dichloromethane (95 L) was added at -15 to -25 °C over 5 min. The reaction was stirred for 25 to 35 min, additional dichloromethane (70 L) was added, and then a solution of 12 N hydrochloric acid (3.8 L, 45.6 mol) in water (93 L) was added at < 10 °C (CAUTION: exothermic addition). The mixture was stirred for 5-10 min, and then the phases were separated. The organic phase was washed with two portions of cool (≤ 15 °C) water (2x 90 L), and then was concentrated to remove all solvent under reduced pressure (≤ 100 mbar) at ≤ 30 °C. Dichloromethane (80 L) and MtBE (100 L) were added and the resulting mixture was concentrated by 100 L under reduced pressure (≤ 100 mbar) at ≤ 30 °C. MtBE (150 L) and heptanes (160 L) were added and the mixture was granulated at 5-15 °C for 2h. Solids were collected by filtration, were washed with MtBE (2x 25 L) and dried under vacuum to constant weight at 25 °C to afford 4a (20.9 kg, 47.5 mol, 60.5%) as a bright yellow fluffy solid.
(5R,6S)-allyl 6-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-3-(((1R,3S)-1-oxidotetrahydrothiophen-3-ylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (7b):

A 10% solution of sodium bicarbonate (336 L) was charged to allyl glyoxalate monohydrate 15a in dichloromethane (494 kg, 3.74 kmol) and i-PrOAc (1359 L) in order to neutralize the glyoxylic acid impurity that slowly forms in 15a during storage. The solution was tested for pH (target specification pH > 7) prior to further processing. The organic phase was then washed with saturated sodium chloride (171 L). Trithiocarbonate 4a (275 kg, 625 mol) was then added and the contents were concentrated at 50 °C under reduced pressure (300 mbar) to remove dichloromethane. S-collidine (22.8 kg, 188 mol) was then added and the mixture was heated at 50 °C under reduced pressure (450 mbar) for 2-4 h (IPC target specification ≤ 5 area% residual 4a according to HPLC). The reaction was then cooled to 20 °C and filtered. The solution was washed with 1N HCl (303 L) and aqueous sodium bisulfite (2x 303 L), and then was concentrated under reduced pressure (50 °C / 200-300 mbar) to a volume of 550 L (IPC target specification ≤ 0.40% water according to KF). The crude aminal 12a in i-PrOAc was used in the next step without purification. Solution potency of 12a was determined by HPLC analysis of the crude reaction mixture to determine stoichiometry for the subsequent reaction.

The solution of aminal 12a in i-PrOAc (∼ 550 L) is diluted with acetonitrile (121 L) and cooled to -20 °C, where methanesulfonyl chloride (76 kg, 663 mol) was added at a rate to maintain temperature below -10 °C. Diisopropylethylamine (128 kg, 990 mol) was then added to the reaction at a rate of 0.5 L/min. The reaction was tested for completion (IPC target specification < 5 area% 12a according to HPLC). A second charge of methanesulfonyl chloride (13.5 kg, 118 mol) was added to complete the reaction. The
reaction was stirred for 30 min following the second MsCl charge to provide intermediate chlorides 16a. Additional diisopropylethylamine (155 kg, 1.20 kmol) was then added, the mixture was warmed to 30 °C and stirring continued for 2 h (IPC target specification < 1 area% 16a according to HPLC). Triethylphosphite (70 kg, 421 mol) was added and the solution was stirred for 30 min (IPC target specification < 3 area% 10b + 18 according to HPLC). After dilution with i-PrOAc (1100 L), the reaction mixture was added to a pre-cooled solution (5-10 °C) of 0.5 N HCl (1733 L). The organic layer was washed successively with 0.5 M phosphate buffer (pH 6; 1448 L) and 10% aqueous sodium chloride (1440 L). The organic layer was concentrated (35 °C / 100 mbar) to 1000 L (IPC target specification < 4% acetonitrile according to HPLC). Solids formed during the concentration. The slurry was cooled to 20 °C and MtBE (688 mL) was added. The slurry was further cooled to 0 °C and allowed to granulate for 11 h. The solid product was filtered and washed twice with MtBE (275 L, 550 L). The product cake was dried on a filter dryer at 25 °C for ≥ 16 h to afford thiopenem 7b (58.8 kg, 18.7% from 4a) of as an off-white solid.

(5R,6S)-allyl 6-((R)-1-hydroxyethyl)-3-(((1R,3S)-1-oxidotetrahydrothiophen-3-yl)thio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (8b). A solution of thiopenem 7b (177 kg, 351 mol) in THF (986 L) was stirred for 15 minutes at 20 °C, and then was added through an in-line filter to a solution of tetrabutylammonium fluoride trihydrate (188 kg, 596 mol) and acetic acid (211 kg, 3.51 kmol) in MtBE (986 L) at 28 °C. Following complete addition, the reaction was stirred for 40 h (IPC target specification ≤ 3 area% 7b according to HPLC). MtBE (986 L) was added and the contents were cooled to 5 °C over 3 h. The slurry was allowed to stir at 5 °C for 4 h, solids were collected by filtration,
and then were washed with MtBE (986 L) and dried to constant weight in a filter dryer at 13-17 °C to afford alcohol 8b (84.3 kg, 62%) as an off-white solid.

![Chemical Structure of 1](image)

**1**

(5R,6S)-6-((R)-1-hydroxyethyl)-3-(((1R,3S)-1-oxidotetrahydrothiophen-3-yl)thio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (1). To a solution of alcohol 8b (84 kg, 216 mol) in dichloromethane (840 L) was charged tetrabutylammonium hydrogen sulfate (7.3 kg, 22 mol), benzene sulfinic acid sodium salt (37.8 kg, 230 mol), triphenylphosphine (4.2 kg, 16 mol) and water (840 L). The biphasic mixture was stirred vigorous under nitrogen. After several inertion cycles, tetrakis(triphenylphosphine) palladium(0) (6.3 kg, 5.5 mol) was added and the reaction was stirred at 18 °C for 30 minutes (IPC target specification ≤ 1 area% 8b according to HPLC). The layers were then separated and the aqueous layer was washed with dichloromethane (3 x 840 L). The aqueous layer was then cooled to 5 °C and treated with activated carbon (3 x 4.2 kg). 1.0 N HCl (208 L) was then added over 150 min at 5 °C to precipitate 1; precipitation was complete at pH 2.5. The slurry was granulated for 15 min at 5 °C then filtered. The filter cake was washed with cold (5 °C) water (2 x 420 L) then dried under vacuum at 25 °C to yield sulopenem 1 (57.8 kg, 77%) as an off-white solid.