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Practical Large-Scale Synthesis of the 2-Aminomethylpyrrolidin-4-ylthio-Containing Side Chain of the Novel Carbapenem Antibiotic Doripenem

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Abstract:

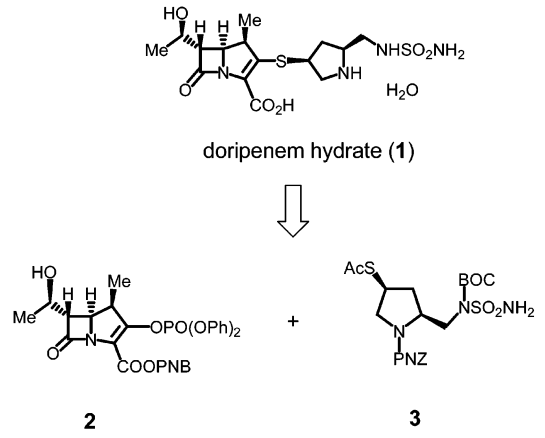
The first synthesis using an original procedure and a practical large-scale process using an improved procedure for the synthesis of the *N*-PNZ-protected 2-aminomethylpyrrolidin-4-ylthio-containing side chain of doripenem hydrate (S-4661), a novel parenteral 1β-methylcarbapenem antibiotic, are described. *trans*-4-Hydroxy-L-proline (4) was converted in an efficient process to (2*S*,4*S*)-4-acetylthio-2-(*N*-sulfamoyl-*tert*-butoxycarbonylaminomethyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (3) in 55−56% overall yield via a six-step sequence, which includes the two alternative routes to intermediate 13. This process requires no chromatographic purifications, no cryogenic temperatures, no haloalkane solvents, and short operating times and is amenable to a multikilogram-scale preparation. Several kilograms of the side chain 3 were successfully prepared by this process.

Introduction

Carbapenem compounds are noted for their broad and potent antibacterial activity.[1] Imipenem,[2] panipenem,[3] meropenem,[4] biapenem,[5] and ertapenem[6] have been launched on the market. In cases of meropenem, biapenem, and ertapenem, the introduction of a 1β-methyl group to the carbapenem skeleton enhances metabolic stability to renal dehydropeptidase-1 (DHP-1) and leads to high antibacterial potency.[7] Doripenem hydrate (S-4661: **1**), which was discovered by Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, Japan, is a novel parenteral 1β-methylcarbapenem antibiotic.[8] In our previous reports,[8,9] its synthesis, biology, and structure−activity relationships (SAR) have been reported. Compound **1** exhibits potent, broad, and well-balanced antibacterial activity against a wide range of both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*.

According to the conventional retrosynthetic analysis of a carbapenem, doripenem can be assembled from 4-nitrobenzyl-protected 1β-methylcarbapenem enolphosphate **2**[7,10] and 2-aminomethylpyrrolidin-4-ylthio-containing side chain **3** (Scheme 1). Enolphosphate **2** is also used as a starting material in the synthesis of ertapenem.[11] Both the enolphophate **2** and aminomethylpyrrolidine **3** are now commercially available. The syntheses of several *N*-BOC- and

Scheme 1



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(10) (a) There are many efficient approaches to this compound **2**, eg. Berks, A. H. *Tetrahedron* **1996**, *52*, 331−375. (b) This is commercially available from Takasago, Kaneka, and Nisso companies.

(11) Brands, K. M. J.; Jobson, R. B.; Conrad, K. M.; Williams, J. M.; Pipik, B.; Cameron, M.; Davies, A. J.; Houghton, P. G.; Ashwood, M. S.; Cottrell, I. F.; Reamer, R. A.; Kennedy, D. J.; Dolling, U.-H.; Reider, P. J. *J. Org. Chem*. **2002**, *67*, 4771−4776.

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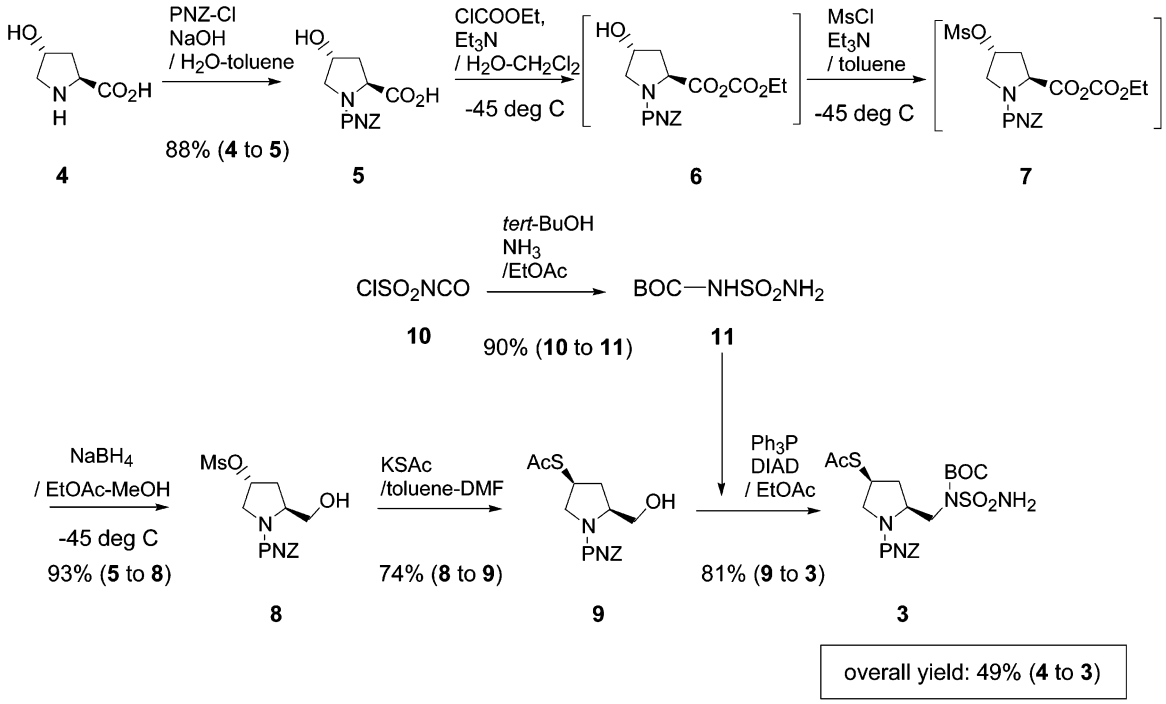
Scheme 2. **First-generation process**



N-PMZ-protected aminomethylpyrrolidine derivatives have been reported in our previous papers.[8,9] These procedures facilitated the SAR studies and led to a rapid optimization of lead derivatives. For the first time, *N*-PNZ-protected aminomethylpyrrolidine **3** was prepared by the sequence of six reaction steps from *trans*-4-hydroxy-L-proline (**4**) in overall yield of 49% using our first-generation process (Scheme 2), which was a modification of our previously reported procedure.[9] The average yield per reaction was 89%. However, the first-generation process for the synthesis of aminomethylpyrrolidine **3** included several undesirable conditions, for instance, cryogenic reaction temperatures, long operation times, and the use of haloalkane solvents. To reduce the cost or the processing time and to make the process more enviromentally suitable, we have developed an improved process which requires no cryogenic temperatures, no haloalkane solvents, and a shorter processing time than that for the first-generation process. In this contribution, we describe an efficient and practical synthesis of aminomethylpyrrolidine **3** that is amenable to large-scale production.[12] The coupling reaction of enolphosphate **2** to give the protected final intermediate, the deprotection, and the isolation to afford doripenem hydrate (**1**) will be reported separately.[13]

Results and Discussion

The First-Generation Process. For the first time, *N*-PNZ-protected aminomethylpyrrolidine **3** was prepared by the sequence of six reactions from hydroxyproline **4** as shown in Scheme 2. This is the first example for the synthesis of the aminomethylpyrrolidine **3**. This first-generation process was a modification of our previously reported procedure,[9] which we described as a medicinal chemical process for the synthesis of another *N*-BOC-protected aminomethylpyrrolidine derivatives. The hydroxyproline **4** was treated with 4-nitrobenzyl chloroformate (PNZ-Cl) in toluene−water to give *N*-protected 4-hydroxyproline **5**[14] in 88% yield. The hydroxyproline **5** was converted into hydroxymethylpyrrolidine **8** in a one-pot procedure in 93% overall yield by a sequence of three reactions at −45 °C, namely the formation of mixed anhydride **6** from hydroxyproline **5** with ethyl chloroformate and triethylamine (Et_3N), the *O*-mesylation of mixed anhydride **6** with methanesulfonyl chloride (MsCl) and Et_3N, and the reduction of the mixed anhydride **7** with sodium borohydride ($NaBH_4$). The hydroxymethylpyrrolidine **8** was treated with potassium thioacetate (KSAc) in DMF−toluene to afford acetylthiopyrrolidine **9** in 74% yield with the inversion of the C-4 configuration. The conversion of the hydroxyl group of acetylthiopyrrolidine **9** into the *N*-BOC-sulfamoyl group was successfully carried out by the Mitsunobu reaction to give the target compound **3** in 81% yield. The overall yield of aminomethylpyrrolidine **3** from hydroxyproline **4** was 49%. The average yield per reaction was 89%. This first-generation process required no chromatographic purification. We manufactured over 50 kg of aminomethylpyrrolidine **3** by this first-generation process on a pilot scale. However, this process for the synthesis of aminomethylpyrrolidine **3** included some undesirable conditions, for instance, cryogenic reaction temperatures (three reactions required −45 °C), the use of CH_2Cl_2 as a solvent (for the mixed anhydride formation), and long operating

(12) A portion of this study was patented. Nishino, Y.; Yuasa, T.; Komurasaki, T.; Kakinuma, M.; Masui, T.; Kobayashi, M. Patent Application No. JP 2001-140782.

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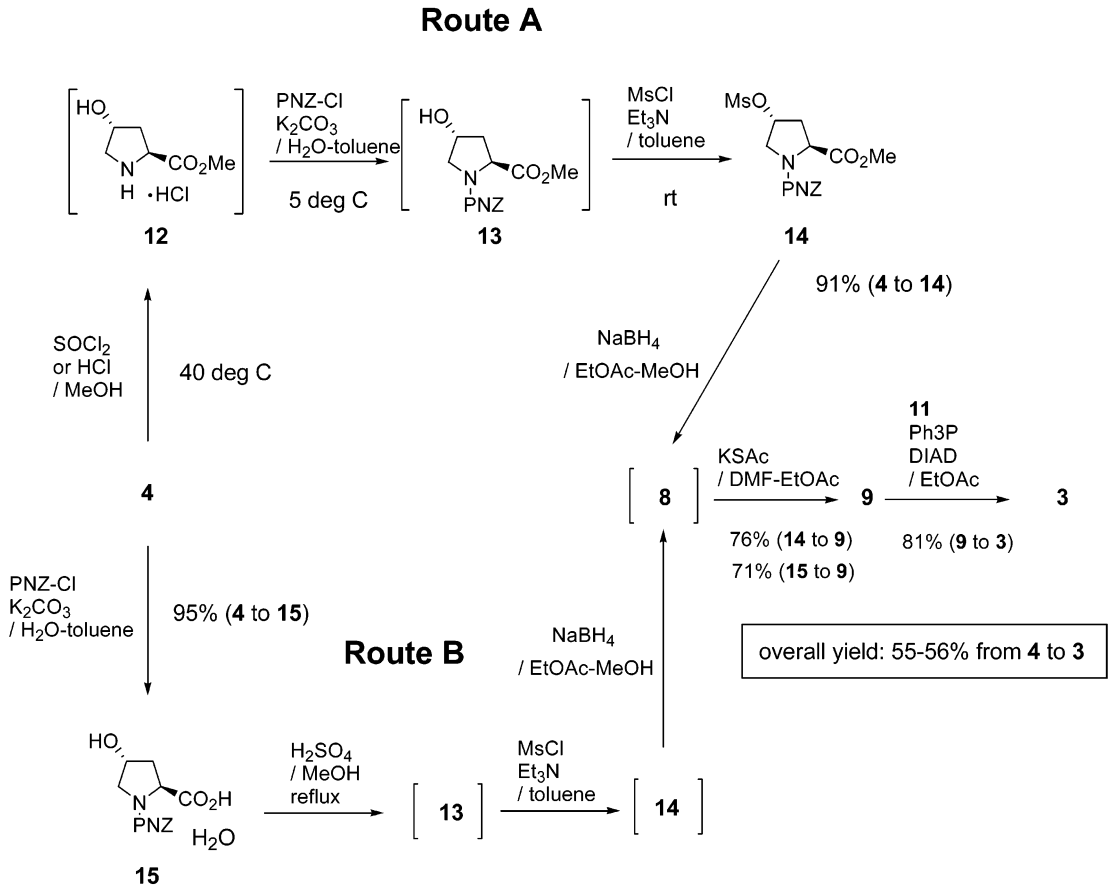
Scheme 3. **Improved process**



times (numerous separations of biphasic layers in extractions and four isolation steps of the crystalline intermediates **5**, **8**, **9**, and the product **3**). A cryogenic reaction temperature confines equipment and significantly increases the cost of production. It is difficult to recover CH_2Cl_2 completely, mainly due to its low boiling point. Unless CH_2Cl_2 can be 100% recovered, its use should be avoided due to the effect on the environment. The longer operating times lead to lower productivity and to higher manufacturing cost. Therefore, we have developed an improved process which requires no cryogenic temperatures, no haloalkane solvents, and operating times shorter than those for the first-generation process.

The Improved Process. We then developed the efficient process for the synthesis of aminomethylpyrrolidine **3** which is shown in Scheme 3. After the intermediate **13**,[15] the improved process is identical to the first-generation process. There are two alternative routes to afford **13** in the improved process. In Route A, hydroxyproline **4** was converted into mesylate **14**[15] in 91% yield by a sequence of three reactions, namely the esterification with methanol in the presence of HCl or $SOCl_2$ to give methyl ester hydrochloride **12**, the *N*-protection with PNZ-Cl to give methyl ester **13**, and the *O*-mesylation with MsCl and Et_3N without isolation of the two intermediates **12** and **13**. Acetylthiopyrrolidine **9** was prepared from mesylate **14** in 76% yield without isolation of hydroxymethylpyrrolidine **8**. The target compound **3** was prepared from acetylthiopyrrolidine **9** in 81% yield. The overall yield of **3** from **4** by Route A was 56%. In Route B, hydroxyproline **4** was treated with PNZ-Cl in toluene−water to give *N*-PNZ-protected carboxylic acid hydrate **15**[16] in 95% yield. The carboxylic acid hydrate **15** was converted into acetylthiopyrrolidine **9** in 71% overall yield by a sequence of four reactions, namely the esterification of hydroxyproline **4** with methanol in the presence of H_2SO_4, the *O*-mesylation with MsCl and Et_3N, the reduction of the methyl ester with $NaBH_4$, and the substitution of the C-4 position with KSAc without isolation of the three intermediates **13**, **14**, and **8**. The target compound **3** was prepared from acetylthiopyrrolidine **9** in 81% yield. The overall yield of **3** from **4** by Route B was 55%, which was quite similar to that by Route A (56%). The improved process provided 6−7% larger yields than the first-generation process and provides the flexibility of two routes to **13**. The average yield per reaction in each route was 91%. Route B is preferable because expensive PNZ-Cl is used in the later step. However, if PNZ-Cl is produced in-house cheaply, Route A can be chosen.

Because of instability of the intermediates **6** and **7** in the first-generation process, −45 °C was necessary for the reactions. Significantly, in the improved process, we suc-

(15) The synthesis of the esters **13** and **14** from hydroxyproline **4** was described: The overall yield of ester **14** from **4** was 80%, which was 11% lower than that by our process (Route A). This process contained chromatographic purification of ester **13**. CH_2Cl_2 was used as a solvent for the reactions to give the both esters **13** and **14**: Oh, C.-H.; Lee, S. C.; Park, S.-J.; Lee, I.-K.; Nam, K. H.; Lee, K.-S.; Chung, B.-Y.; Cho, J.-H. *Arch. Pharm. Pharm. Med. Chem*. **1999**, *332*, 111−114.

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cessfully avoided the cryogenic temperature conditions in the original process by changing the intermediates **6** and **7** into the stable intermediates **13** and **14**, thereby, eliminating the need for a cryogenic reaction. In addition, CH_2Cl_2 was removed from the process by employing toluene as the reaction solvent. The process throughput (product produced per unit time)[17] of the improved process was 3-fold higher than that of the first-generation process. A total production period is the sum of an operation time for the reactions, extractions, concentrations, crystallizations, drying, cleaning up the equipment, quality control, and so on. According to our simulation, the total production period for 1 MT of **3** from **4** by the improved process on a commercial scale would be almost one-third of that required by the first-generation process. The operation time was shortened by reducing the number of phase cuts in the extractions from 13 times to 4 times, by reducing the number of isolated crystalline products from 4 (**5**, **8**, **9**, and **3**) to 3 (**14** or **15**, **9**, and **3**), and by reducing the amounts of solvent concentrated during the workup after the reactions or extractions. For example, the weight of solvent for the Mitsunobu reaction was reduced from 18- to 7-fold of the weight of **3**.

Since the improved process does not require chromatographic purification, cryogenic temperature, or haloalkane solvent and provides shorter operation time, it is a practical, efficient, and enviromentally friendly process. This new process has been scaled up in the pilot plant to produce the compound **3** in over 50 kg scale.

Conclusions

We described the first example for the synthesis of (2*S*,4*S*)-4-acetylthio-2-(*N*-sulfamoyl-*tert*-butoxycarbonylaminomethyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (**3**), which is the side chain of the new parenteral carbapenem antibiotic doripenem hydrate (**1**). Further, we developed the process including the two alternative routes to intermediate **13** and demonstrated its use for the practical multikilogram-scale synthesis of **3**. The improved process can provide **3** from **4** in overall yield of 55−56% (by six reactions with an average of yield of 91%), and requires no chromatographic purification, no cryogenic temperature, no haloalkane solvent, and short operation time. This makes it practical, efficient, and industrial. In fact, this new process has been scaled up in the pilot plant to produce over 50 kg of the compound **3**.

Experimental Section

Materials and Instrumentation. All commercially available materials and solvents were used as received. Melting points are uncorrected. NMR experiments were conducted by using a Mercury 300 or a Unity 600 NMR spectrometer (Varian). IR spectra were obtained on a Magna 560 FT-IR spectrophotometer (Nicolet).

The First-Generation Process (Scheme 2). *Preparation of (2S,4R)-4-Hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-2-carboxylic Acid (**5**).* A 50% solution of PNZ-Cl (130.0 kg, 1.1 equiv) in toluene was added dropwise to a solution of *trans*-4-hydroxy-L-proline (**4**) (36.0kg, 275 mol) and NaOH (24.2 kg) in water (240 L) at 5 °C. The reaction mixture was stirred for 1 h at 5 °C. After the addition of toluene (100 L), the layers were separated. The aqueous layer was washed with toluene (90 L). Each organic layer was back-extracted with aqueous 2% NaOH (67.5 kg). EtOAc (360 L) was added to the combined aqueous extracts. The pH was adjusted to 2.0 by slow addition of concentrated HCl (ca. 36 kg). Extraction with EtOAc (144 L) followed by crystallization from toluene gave *N*-protected proline **5**[14] (75.06 kg, 88%) as a colorless crystalline powder: mp 182−183 °C (lit. 181.6−182.6 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85−2.25 (m, 2H, H-3), 3.30 (br s, 1H, −O*H*), 3.40 (m, 2H, H-5), 4.28 (m, 2H, H-2 and H-4), 5.20 (m, 2H, −OCH_2−Ar), 7.60 (m, 2H, meta-H of nitrophenyl), 8.20 (m, 2H, ortho-H of nitrophenyl), 12.65 (br s, 1H, −CO_2H).

*One-Pot Preparation of (2S,4R)-2-Hydroxymethyl-4-methylsulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (**8**) from 5.* Ethyl chloroformate (11.9 kg, 1.1 equiv) and Et_3N (12.1 kg, 1.2 equiv) were added to a solution of *N*-protected proline **5** (31.0 kg, 99.9 mol) in CH_2Cl_2 (250 L) at 0 °C. The reaction mixture was stirred for 0.5 h at 0 °C and then was cooled to −45 °C. MsCl (12.6 kg, 1.1 equiv) and Et_3N (12.1 kg, 1.2 equiv) were added dropwise to the reaction mixture at −45 °C. After the reaction mixture was stirred for 0.5 h at −45 °C, 2-propanol (78 kg) was added dropwise at −45 °C, followed by the dropwise addition of a solution of $NaBH_4$ (5.7 kg, 1.5 equiv) in water (23 L) to the reaction mixture at −45 °C. The reaction mixture was stirred for 0.5 h at −45 °C and then was poured into aqueous 2.4% HCl (234 kg). After the layers were separeted, the organic layer was washed with aqueous 2% $NaHCO_3$ and 3% NaCl. Each aqueous layer was back-extracted with CH_2Cl_2. The combined extracts were concentrated to 50 L. EtOAc (250 L) was added to the concentrate, and the mixture was concentrated to 110 L. Crystallization by addition of hexane (62 L) to the concentrate gave **8** (34.9 kg, 93%) as a colorless crystalline powder: mp 113−116 °C. A thermal equilibrium of the single C−N bond rotation in a solution of $CDCl_3$ at 0 °C to give a 5:2 mixture of cis and trans isomers was observed. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.05 (m, 1H, one of H-3 of pyrrolidine), 2.42 (m, 1H, one of H-3 of pyrrolidine), 3.07 (minor) and 3.09 (major) (s, 3H, Ms-), 3.60 (minor) and 3.64 (major) (m, 1H, one of −CH_2OH), 3.65 (minor) and 3.72 (major) (m, 1H, one of H-5 of pyrrolidine), 3.89 (major) and 3.95 (minor) (m, 1H, one of −CH_2OH), 3.90−4.10 (br, 1H, −O*H*), 4.04 (m, 1H, one of H-5 of pyrrolidine), 4.21 (m, 1H, H-2 of pyrrolidine), 5.23 (d, 1H, J = 13.7 Hz, one of −CH_2−Ar of minor isomer), 5.26 (s, 2H, −CH_2−Ar of major isomer), 5.27 (major) and 5.30 (minor) (m, 1H, H-4 of pyrrolidine), 5.30 (d, 1H, J = 13.7 Hz, one of −CH_2−Ar of minor isomer), 7.54 (minor) and 7.67 (major) (d, 2H, J = 9.1 Hz, meta-H of nitrophenyl), 8.24 (d, 2H, J = 9.1 Hz, ortho-H of nitrophenyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 35.1 (major) and 35.4 (minor) (C-3 of pyrrolidine), 38.8 (minor) and 38.9 (major) (Ms-), 53.7 (minor) and 53.8 (major) (C-5 of pyrrolidine), 57.5 (minor) and 59.3 (major) (C-2 of pyrrolidine), 63.2 (minor) and 65.1

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(major) (−*C*H$_2$OH), 66.3 (major) and 67.2 (minor) (−*C*H$_2$−Ar), 78.3 (major) and 79.0 (minor) (C-4 of pyrrolidine), 124.1 (ortho-C of nitrophenyl), 128.3 (major) and 128.4 (minor) (meta-C of nitrophenyl), 143.6 (major) and 143.7 (minor) (para-C of nitrophenyl), 147.7 (ipso-C of nitrophenyl), 155.9 (*C*═O of PNZ−). IR (KBr) 3439, 1699, 1684, 1523, 1342, 1169 cm^{-1}. MS (Ion Mode: FAB$^+$) *m*/*z* 375 [M + H]$^+$, 749 [2M + H]$^+$. Anal. Calcd for $C_{14}H_{18}N_2O_8S$: C, 44.92; H, 4.85; N, 7.48; S, 8.57. Found: C, 44.82; H, 4.68; N, 7.50; S, 8.40.

*Preparation of (2S,4S)-4-Acetylthio-2-hydroxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (**9**) from **8** Using DMF−Toluene as Reaction Solvents.* A mixture of **8** (40.0 kg, 107 mol), potassium thioacetate (16.0 kg, 1.3 equiv), DMF (80 L), and toluene (120 L) was stirred at 65 °C for 4 h. After the reaction was completed, the reaction mixture was added to a mixure of EtOAc (600 L) and water (300 L). The layers were separated, and the organic layer was washed with aqueous 5% NaCl (200 kg × 2). Each aqueous layer was back-extracted with EtOAc (120 L). The combined organic extracts were concentrated to 290 L. Toluene (340 L) was added to the concentrate. The mixture was concentrated to 290 L. The mixture was stored at room temperature overnight. The resultant precipitate was collected by filtration, washed with EtOAc−toluene, and dried to give **9** (27.9 kg, 74%) as a slightly yellow crystalline powder: mp 132−133 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.66 (m, 1H, H-3 of pyrrolidine), 2.33 (s, 3H, Ac−), 2.50 (m, 1H, H-3 of pyrrolidine), 3.26 (dd, 1H, J = 7.6 and 11.2 Hz, H-5 of pyrrolidine), 3.74 (m, 2H, C*H*$_2$−OH), 3.88 (m, 1H, H-4 of pyrrolidine), 4.07 (m, 1H, H-2 of pyrrolidine), 4.14 (dd, 1H, J = 8.8 and 11.2 Hz, H-5 of pyrrolidine), 4.42 (dd, 1H, J = 3.5 and 8.6 Hz, −O*H*), 5.22 (s, 2H, C*H*$_2$−Ar), 7.53 (d, 2H, J = 9.1 Hz, meta-H of nitrophenyl), 8.28 (d, 2H, J = 9.1 Hz, *ortho*-H of nitrophenyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 30.8 (Me− of Ac−), 34.0 (C-3 of pyrrolidine), 38.5 (C-4 of pyrrolidine), 52.9 (C-5 of pyrrolidine), 60.9 (C-2 of pyrrolidine), 66.2 (*C*H$_2$−Ar), 66.5 (−*C*H$_2$OH), 124.0 (ortho-C of nitrophenyl), 128.4 (meta-C of nitrophenyl), 143.5 (para-C of nitrophenyl), 147.6 (ipso-C of nitrophenyl), 156.2 (*C*═O of PNZ−), 195.5 (*C*═O of Ac−). IR (KBr) 3419, 1693, 1670, 1604, 1519, 1429, 1340, 1126 cm^{-1}. MS (Ion Mode: FAB$^+$) *m*/*z* 355 [M + H]$^+$, 709 [2M + H]$^+$. Anal. Calcd for $C_{15}H_{18}N_2O_6S$: C, 50.84; H, 5.12; N, 7.90; S, 9.05. Found: C, 50.88; H, 4.82; N, 7.97; S, 8.87.

*Preparation of N-tert-Butoxycarbonylsulfamide (**11**) According to the Literature Method.*[9] Chlorosulfonyl isocyanate (**10**) (62.5 kg, 442 mol) was added to a solution of *tert*-butyl alcohol (32.7 kg) in EtOAc (626 L) at −40 °C. The reaction mixture was stirred at −40 °C for 40 min, and then was cooled to −65 °C. After dry liquid ammonia (NH_3, 45.1 kg) was added dropwise to the reaction mixture at −60 °C, and the reaction mixture was warmed to 15 °C. Aqueous 22% H_2SO_4 (ca. 150 kg) was added to the reaction mixture to adjust the pH to 9.5 with cooling. Water (100 L) was added to the mixture. The layers were separated. The aqueous layer was washed with EtOAc (230 L) and then was acidified with aqueous 22% H_2SO_4 (ca. 170 kg) to adjust the pH to 2.0. The resulting precipitate was collected by filtration, washed with water, and dried to give **11**[9] (78.4 kg, 90%) as a colorless crystalline powder: mp 131−133 °C (lit. 130−131 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.43 (s, 9H, *tert*-Bu-), 7.27 (s, 2H).

*Preparation of (2S,4S)-4-Acetylthio-2-(N-sulfamoyl-tert-butoxycarbonylaminomethyl)-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (**3**).* A solution of diisopropyl azodicarboxylate (DIAD) (16.7 kg, 1.2 equiv) in EtOAc (24 L) was added dropwise to a mixture of **9** (24.3 kg, 68.6 mol), triphenylphosphine (21.9 kg, 1.2 equiv), *N*-BOC-sulfamide **11** (20.2 kg, 1.5 equiv), and EtOAc (560 L) at 20 °C. The reaction mixture was stirred at 20 °C for 2 h. After the reaction was completed, the reaction mixture was concentrated to 110 L, and the residual EtOAc was exchanged into MeOH by evaporation to give the concentrate (160 L). Water (19 L) was added to the concentrate at 65 °C. After addition of seed cryatal (40 g), the mixure was stirred at 50 °C for 2 h and then was stored at room temperature overnight. The resultant precipitate was collected by filtration, washed with 85% aqueous MeOH, and dried to give **3** (29.6 kg, 81%) as a slightly yellow crystalline powder: mp 139−142 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.48 (s, 9H, *tert*-Bu-), 1.57−1.61 (ddd, 1H, J = 14.1, 5.4 and 3.6 Hz, H-3β of pyrrolidine), 2.35 (s, 3H, AcS−), 2.59 (dt, 1H, J = 14.1 and 8.6 Hz, H-3α of pyrrolidine), 3.27 (dd, 1H, J = 12.1 and 6.5 Hz, H-5β of pyrrolidine), 3.62 (dd, 1H, J = 14.9 and 2.7 Hz, one of −C*H*$_2$N(BOC)SO$_2$−), 3.96 (m, 1H, H-4 of pyrrolidine), 4.02 (dd, 1H, J = 14.9 and 8.5 Hz, one of −C*H*$_2$N(BOC)SO$_2$−), 4.27 (dd, 1H, J = 12.1 and 7.8 Hz, H-5α of pyrrolidine), 4.55 (m, 1H, H-2α of pyrrolidine), 5.18 (ABq, 2H, J = 13.4 Hz, −OC*H*$_2$−Ar), 5.86 (br, 2H, −SO$_2$N*H*$_2$), 7.49 (A_2B_2, 2H, J = 8.7 Hz, meta-H of nitrophenyl), 8.24 (A_2B_2, 2H, J = 8.7 Hz, ortho-H of nitrophenyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.1 (Me- of *tert*-Bu−), 30.5 (Me− of AcS−), 34.5 (C-3 of pyrrolidine), 39.2 (C-4 of pyrrolidine), 49.9 (−*C*H$_2$NSO$_2$−), 52.2 (C-5 of pyrrolidine), 56.7 (C-2 of pyrrolidine), 66.1 (−OC*H*$_2$−Ar), 84.2 (*quat*-C of *tert*-Bu−), 123.9 (ortho-C of nitrophenyl), 128.2 (meta-C of nitrophenyl), 143.1 (para-C of nitrophenyl), 147.8 (ipso-C of nitrophenyl), 151.8 (*C*═O of BOC−), 155.1 (*C*═O of PNZ−), 194.9 (*C*═O of AcS−). IR (KBr) 3361, 3226, 2978, 1708, 1692, 1523, 1381, 1336, 1187,1149 cm^{-1}. MS (Ion Mode: FAB$^+$) *m*/*z* 533 [M + H]$^+$, 555 [M + Na]$^+$. Anal. Calcd for $C_{20}H_{28}N_4O_9S_2$: C, 45.10; H, 5.30; N, 10.52; S, 12.04. Found: C, 45.00; H, 5.27; N, 10.52; S, 11.99.

The Improved Process (Scheme 3). *Preparation of Methyl (2S,4R)-4-Methylsulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-2-carboxylate (**14**) from **4**.* $SOCl_2$ (10.0 g, 1.0 equiv) was added dropwise to a mixture of hydroxyproline **4** (10.0 g, 76.3 mmol) and MeOH (50 mL) at 0 °C. The reaction mixture was then stirred at 40 °C for 2 h. After cooling the reaction mixture to 0 °C, a 48% aqueous solution of NaOH (7.0 g) was added dropwise at 0 °C. After addition of water (30 mL), K_2CO_3 (15.8 g) was added slowly below 20 °C by controlling the amount of gaseous CO_2 evolution. A solution of PNZ-Cl (16.4 g, 1.0 equiv) in toluene (17 mL)

was added dropwise to the mixture at 5 °C. The reaction mixture was stirred for 1 h at 2 °C and then was concentrated to remove MeOH. After addition of EtOAc (100 mL) and water (60 mL) to the concentrate, the layers were separated. The organic layer was concentrated to replace EtOAc into toluene. Et_3N (9.3 g, 1.2 equiv) was added to the residue. MsCl (9.6 g, 1.1 equiv) was added dropwise to the mixture at room temperature. After the reaction mixture was stirred at room temperature for 20 min, water (60 mL) was added. The precipitate was collected and dried to give **14**[15] (27.8 g, 91%) as a colorless crystalline powder: mp 87−90 °C (lit. 78.0−80.0 °C). A thermal equilibrium of the single C−N bond rotation in a solution of $CDCl_3$ at 0 °C to give a 1:1 mixture of cis and trans isomers was observed. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.30 and 2.35 (m, 1H, H-3 of pyrrolidine), 2.67 and 2.76 (m, 1H, H-3 of pyrrolidine), 3.10 (s, 3H, Ms−), 3.68 and 3.79 (s, 3H, C*H*$_3$OCO−), 3.83 (m, 1H, H-5 of pyrrolidine), 3.88 (m, 1H, H-5 of pyrrolidine), 4.55 and 4.57 (t, J = 8.1 Hz, H-2 of pyrrolidine), 5.14−5.35 (s and 2d, 2H, J = 13.7 Hz, −C*H*$_2$−Ar), 5.31 and 5.33 (m, 1H, H-4 of pyrrolidine), 7.48 and 7.54 (d, 2H, J = 9.0 Hz, meta-H of nitrophenyl), 8.24 (d, 2H, J = 9.0 Hz, ortho-H of nitrophenyl). ^{13}C NMR (150 MHz, $CDCl_3$) δ 36.4 and 37.7 (C-3 of pyrrolidine), 38.8 and 38.9 (Ms−), 52.8 and 53.2 (C-5 of pyrrolidine), 52.9 and 53.1 (MeO−), 57.3 and 57.6 (C-2 of pyrrolidine), 66.2 (−*C*H$_2$−Ar), 77.7 and 78.1 (C-4 of pyrrolidine), 124.0 (ortho-C of nitrophenyl), 128.1 and 128.3 (meta-C of nitrophenyl), 143.6 (para-C of nitrophenyl), 147.6 and 147.7 (ipso-C of nitrophenyl), 153.6 and 154.2 (*C*═O of PNZ−), 172.2 and 172.4 (*C*═O of −*C*O$_2$Me). IR (KBr) 1745, 1707, 1523, 1440, 1345. MS (Ion Mode: FAB$^+$) *m*/*z* 403 [M + H]$^+$, 805 [2M + H]$^+$. Anal. Calcd for $C_{15}H_{18}N_2O_9S$: C, 44.77; H, 4.51; N, 6.96; S, 7.97. Found: C, 44.79; H, 4.34; N, 7.05; S, 7.78.

*Preparation of Hydroxymethylpyrrolidine **9** from **14**.* After dissolving **14** (27.6 g, 68.6 mmol) in a mixture of EtOAc (120 mL) and MeOH (16.5 mL) at 34 °C, the solution was cooled to 0 °C. $NaBH_4$ (13.2 g, 5.1 equiv) was added slowly to the solution, maintaining the temperature at 5 °C. The reaction mixture was stirred at 5 °C for 3 h and then was poured into aqueous 5% H_2SO_4 (138 mL). The layers were separated. The organic layer was washed with aqueous 5% NaCl (55 mL × 2) and then was concentrated. Potassium thioacetate (10.2 g), DMF (50 mL), and EtOAc (66 mL) were added to the residue. The mixture was stirred at 65 °C for 8 h. After cooling the mixture below 30 °C, water (44 mL) and aqueous 5% H_2SO_4 (11 mL) were added to the mixture. After removal of EtOAc, the precipitate was collected and dried to give **9** (18.4 g, 76%) as a slightly yellow crystalline powder.

*Preparation of (2S,4R)-4-Hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-2-carboxylic Acid Hydrate (**15**) from **4**.* A solution of PNZ-Cl (16.4 g, 1.0 equiv) in toluene (17 mL) was added dropwise to a solution of hydroxyproline **4** (10.0 g, 76.3 mmol) and K_2CO_3 (19.0 g) in water (50 mL) at 5 °C. After stirring the reaction mixture for 1 h at 2 °C, the layers were separated. Concentrated HCl (15.4 g) was added to the aqueous layer. After the mixture was stirred for 0.5 h at 10 °C, concentrated HCl (4.6 g) was added to the suspension. Filtration followed by drying gave **15**[16] (23.8 g, 95%) as a colorless crystalline powder: mp 136−138 °C (lit. 133−135 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85−2.25 (m, 2H, H-3), 3.30 (br s, 1H, −O*H*), 3.40 (m, 2H, H-5), 4.28 (m, 2H, H-2 and H-4), 5.20 (m, 2H, −OC*H*$_2$−Ar), 7.60 (m, 2H, *meta*-H of nitrophenyl), 8.20 (m, 2H, ortho-H of nitrophenyl), 12.65 (br s, 1H, −CO$_2$*H*).

*Preparation of Hydroxymethylpyrrolidine **9** from **15**.* H_2SO_4 (98%, 0.6 g) was added to a solution of **15** (10.0 g, 30.4 mmol) in MeOH (50 mL). The reaction mixture was stirred at 60 °C for 7 h. After cooling the mixture below 10 °C, the reaction mixture was neutralized with aqueous 5% NaOH to adjust the pH to 5 and then was concentrated. The residue (17.8 g) was poured into a mixture of EtOAc (50 mL) and aqueous 10% NaCl (50 mL). The layers were separated. The organic layer was concentrated to remove water. After the residual organic solution cooled to 0 °C, MsCl (3.8 g, 1.1 equiv) and Et_3N (3.7 g, 1.2 equiv) were added to the solution. After the reaction was completed, the reaction mixture was washed with aqueous 5% H_2SO_4 and water. The organic layer was concentrated to remove water. EtOAc (48 mL) and MeOH (7.5 mL) were added to the residue (14.5 g). $NaBH_4$ (0.46 g × 5, 2.0 equiv) was added slowly to the solution at 0 °C. After the reaction was completed, the reaction mixture was washed with aqueous 5% H_2SO_4 and water. The organic layer was concentrated. DMF (23 mL), EtOAc (34 mL), and potassium thioacetate (4.5 g) were added to the residue (11.8 g). The reaction mixture was stirred at 65 °C for 7 h. After cooling the mixture below 40 °C, aqueous 1% H_2SO_4 (24 mL) was added to the mixture. After removal of EtOAc, the aqueous mixture (60.0 g) was stirred at room temperature for 1 h. The precipitate was collected and dried to give **9** (7.62 g, 71%) as a slightly yellow crystalline powder.

*Preparation of Aminomethylpyrrolidine **3**.* DIAD (68.3 g, 1.2 equiv) was added dropwise to a mixture of **9** (100.0 g, 282 mmol), triphenylphosphine (90.2 g, 1.2 equiv), *N*-BOC-sulfamide **11** (83.0 g, 1.5 equiv), and EtOAc (1 L) at 20 °C. The reaction mixture was stirred at 20 °C for 7 h. After the reaction was completed, the reaction mixture was concentrated, and the residual EtOAc was replaced into MeOH by evaporation to give the concentrate (700 g). Water (75 mL) was added to the concentrate at 65 °C. The mixure was stirred at 50 °C for 2 h. After cooling, it was stored at room temperature overnight. The resultant precipitate was collected by filtration, washed with 85% aqueous MeOH, and dried to give **3** (121.7 g, 81%) as a slightly yellow crystalline powder.

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