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Technical Notes

Novel Synthetic Route of a Pivotal Intermediate for the Synthesis of 1β-Methyl Carbapenem Antibiotics

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Abstract:

A novel synthetic method using an original and practical procedure for the preparation of the *N*-PNZ protected 2-aminomethylpyrrolidin-4-ylthio-containing side chain of doripenem hydrate (S-4661), a new parenteral 1β-methylcarbapenem antibiotic, is described. *trans*-4-Hydroxy-L-proline was converted through an efficient process to (2*S*,4*S*)-4-acetylthio-2-(*N*-sulfamoyl-4-nitro-benzyloxycarbonyl-aminomethyl)-1-(4-nitrobenzyloxycarbonyl) pyrrolidine with 60−70% overall yield via a two-step sequence. This procedure requires no chromatographic purifications, no cryogenic temperatures, no haloalkane solvent, and shorter operating times and avoids the side reaction brought by acid hydrolysis. Furthermore, the product was obtained as a crystal rather than an oil, which made it to be an advantage for quantization in the pilot-scale manufacture. Several kilograms of the side chain were prepared by using this method.

1. Introduction

Members of the carbapenem family are important among the β-lactam antibiotics for their broad and potent antibacterial activity and their relatively high resistance to most clinically encountered β-lactamases.[1] So far many products, such as imipenem,[2] panipenem,[3] meropenem,[4] biapenem,[5] and ertapenem,[6] have been put into market. The introduction of a 1β-methyl group to the carbapenem skeleton in meropenem, biapenem, and ertapenem enhances metabolic stability to renal dehydropeptidase-1 (DHP-1) and leads to high antibacterial potency.[7] Doripenem hydrate (S-4661, **1**, Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, Japan) is a novel parenteral 1β-methylcarbapenem antibiotic.[8] Compound **1** is superior to meropenem against Gram positive bacteria and, meanwhile, is superior to imipenem against Gram negative bacteria. Furthermore, **1** has an antibacterial potency against *Pseudomonas aeruginosa* which is up to twice as strong as that of imipenem or meropenem. With its potent, broad, and well-balanced antibacterial activity against a wide range of both Gram-positive and Gram-negative bacteria, doripenem is now under phase 3 clinical trials for the treatment of serious infections such as pneumonia, pyelonephritis, and respiratory tract infections.

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-aminomethyl-pyrrolidin-4-ylthio-containing side chain **3** (Scheme 1). SAR studies revealed that the acylation and sulfamoylamination of the side chain pyrrolidine would benefit the enhancement of the antibacterial activity.

Several papers have been published regarding the synthesis of the side chain aminomethylpyrrolidine derivatives,[8,9,11a,11b] among which two are important. In 1996, Iso and co-workers reported the synthesis of *N*-*p*-methoxybenzyl (PMZ)-protected aminomethylpyrrolidine **3a** (R^2 = PMZ) or *N*-BOC-protected aminomethylpyrrolidine **3b** (R^2 =

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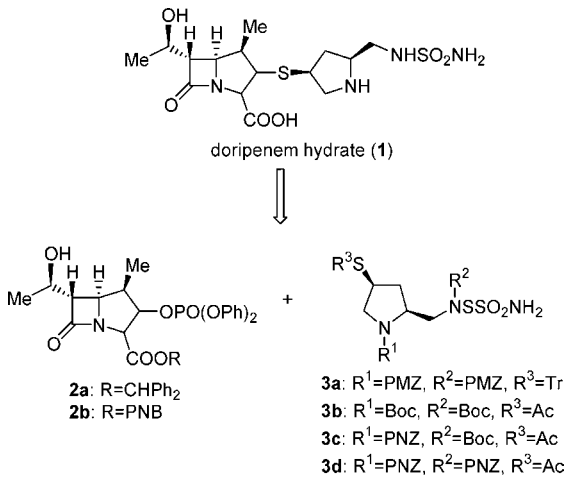
Scheme 1. **Retrosynthetic analysis of a carbapenem**



BOC),[8] after coupling with the diphenylmethyl-protected enolphosphate **2a**, compound **1** was prepared by deprotection with $AlCl_3$-anisole.

Although this route facilitated the SAR studies and led to rapid optimization of the lead derivatives, it had several drawbacks for multikilogram-scale preparation of compound **1**. The two most serious problems resided in the isolation and deprotection steps. Compound **1** was isolated as a foam, which needed further purification on a Diaion HP-20. Later, a modified process was developed, and compound **1** was obtained as a crystalline monohydrate.[9] However, the process still required chromatographic purification, and the yield of compound **1** through the deprotection, purification, and crystallization steps on a pilot scale (49%) was lower than that through the deprotection and purification steps on a bench scale (72%). During the column chromatography and concentration of the eluents, decomposition of the target compound **1** was observed, resulting in a 16% yield decrease due to longer operating times on scale-up. Furthermore, this process included several severe conditions such as cryogenic reaction temperatures (three reactions required −45 °C), long operation times, and the use of haloalkane solvent (CH_2Cl_2). To reduce the cost of processing time and to make the process more environmentally suitable, Nishino and co-workers[11b] reported *N*-PNZ-protected aminomethylpyrrolidine (R^2 = Boc) **3c**, which was prepared from *trans*-4-hydroxy-L-proline. But the deprotection of the *tert*-butylcarbonyl group by 98% H_2SO_4 results in an oily product at room temperature, and the carbonium ion brought many side reactions, while scavenger usage will increase the producing cost.

To increase the yield and to avoid the chromatographic purification, we developed an improved process. Compound **1** was synthesized from PNB-protected enolphosphate **2b** and *N*-[*p*-nitrobenzyloxycarbonyl] (PNZ)-protected aminomethylpyrrolidine **3d**. In this contribution, we describe the preparation of the new pyrrolidine derivative **3d** and its coupling with enolphosphate **2b** (Scheme 2). This process avoided the side reaction brought by deprotection of the *tert*-butoxycarbonyl group and made it easier for purification. Furthermore, the product was obtained as a crystal rather than an oil, which made it an advantage for quantization in the pilot-scale manufacture.

2. Experimental Section

2.1. Materials and Instrumentations. ESI-MS spectral data were measured on a Finnigan LCQ^{DECA} mass spectrometer. ^{1}H NMR and ^{13}C NMR experiments were measured on a Bruker Avance 600 spectrometer. Chemical shifts are reported in ppm (δ scale) using tetramethylsilane as an internal standard. Melting points were determined with a micromelting point apparatus and are uncorrected. All commercially available materials and solvents were used as received without any further purification. 4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(diphenylphosphono)oxy]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3, 2, 0]hept-2-ene-2-carboxylate (**2b**) is commercially available.

2.2. Preparation of the Compounds. 2.2.1. Preparation of the *N*-PNZ-Protected Pyrrolidine Derivative 3d. 2.2.1.a. Preparation of *N*-4-Nitrobenzyloxycarbonyl-sulfonamide (5). To a solution of 4-nitrobenzyl alcohol (38.25 g, 250 mmol) in THF, chlorosulfonyl isocyanate (21.75 mL, 250 mmol) was added dropwise at −40°C, and the mixture was stirred at −40 °C for 30 min. After cooling the mixture to −60°C, gaseous amine was bubbled into the reaction with stirring. After bubbling, the mixture was stirred for 30 min at 15 °C and then acidified with 1 N HCl until no more precipitation was generated. The precipitate was collected by filtration and dissolved in EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated in a vacuum. The residue was crystallized from EtOAc−hexane to give 55 g of *N*-4-nitrobenzyl sulfonamide as a colorless crystal (80%). Mp: 160−162 °C (dec). FT-IR (KBr, cm^{-1}): 3348, 3258, 3223, 1721, 1610, 1473, 1454, 1348, 1260, 1156, 847. ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.29 (2H, s, −O−CH_2−Ar), 7.54 (br, 2H, −SO_2NH_2), 7.64 (A_2B_2, 2H, J = 8.7 Hz, −ArH), 8.26 (A_2B_2, 2H, J = 8.7 Hz, −ArH), 11.38 (br, 1H, −CO−NH−SO_2−). ^{13}C NMR (600 MHz, DMSO-d_6) δ 65.6 (−O−CH_2−Ar), 124.1 (o, −Ar−NO_2), 128.8 (m, −Ar−NO_2), 144.3 (p, −Ar−NO_2), 147.6 (−Ar−NO_2 in situ), 152.0 (C=O, PNZ−). ESI-MS: 298 [M + Na]$^+$, 314 [M + K]$^+$. FTICR/MS: Calculated for [$C_8H_9N_3Na_1O_6S_1$], 298.0110; found, 298.0104.

2.2.1.b. Preparation of Acetylthiol-pyrrolidine Derivative (3d). A solution of diisopropyl azodicarboxylate (DIAD, 22 mL, 130 mmol) in EtOAc was added dropwise to a mixture of (2*S*,4*S*)-4-acetylthio-2-hydroxymethyl-1-(4-nitrobenzyl-oxycarbonyl)pyrrolidine (**6**, 35.5 g, 100 mmol), *N*-4-nitrobenzylsulfamide (**5**, 41.25 g, 150 mmol), triphenyl phospine (34.125 g, 130 mmol), and THF (1000 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 2 h. After the reaction was completed, the reaction mixture was concentrated to 200 mL, and 500 mL of anhydrate alcohol were then added. The solution was stored in a refrigerator over-

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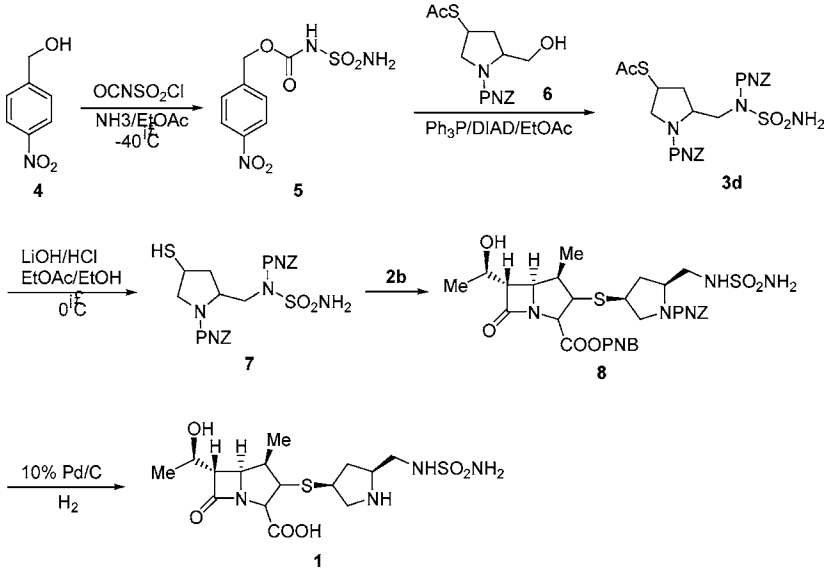
Scheme 2. **Improved method for the preparation of 1**



night and resulted in 54 g of amorphous yellowish powder (88%). FT-IR (KBr, cm^{-1}): 3383, 3082, 2960, 1695, 1607, 1522, 1430, 1395, 1296, 1267, 1181, 1154, 1114, 850. ^1H NMR (600 MHz, $CDCl_3$) δ 1.60 (1H, m, pyrrolidine, H-3β), 2.33 (3H, s, AcS—), 2.59 (dt, 1H, J = 14.0, 8.7 Hz, pyrrolidine, H-3α), 3.17 (dd, 1H, J = 11.9, 6.24 Hz, pyrrolidine H-5β), 3.71 (dd, 1H, J = 14.9 Hz, —$CH_2N(PNZ)SO_2$—), 3.92 (1H, m, pyrrolidine H-4), 4.10 (dd, 1H, J = 15.3,10.2 Hz, —$CH_2N(PNZ)SO_2$—), 4.20 (dd, 1H, J = 11.7, 7.5 Hz, pyrrolidine H-5α), 4.52 (1H, m, pyrrolidine H-2α), 5.16 (AB_q, 2H, J = 13.4 Hz, —O—CH_2—Ar), 5.25 (br, 2H, —O—CH_2—Ar), 5.86 (br, 2H, —SO_2NH_2), 7.47 (A_2B_2, m, 2H, J = 8.46 Hz, —$ArNO_2$), 7.51 (A_2B_2, m, 2H, J = 8.46 Hz, —$ArNO_2$), 8.21 (A_2B_2, 2H, o, J = 8.52 Hz, —$ArNO_2$), 8.23 (A_2B_2, 2H, o, J = 8.28 Hz, —$ArNO_2$). ^{13}C NMR (600 MHz, $CDCl_3$) δ 30.5 (Me—, AcS—), 34.7 (pyrrolidine C-3), 39.1 (pyrrolidine C-4), 50.6 (—CH_2NSO_2—), 52.2 (pyrrolidine C-5), 56.7 (pyrrolidine C-2), 66.1 (—OCH_2—Ar), 74.0 (—OCH_2—Ar), 123.9 (o, —$ArNO_2$), 124.0 (o, —$ArNO_2$), 128.0 (m, —$ArNO_2$), 128.5 (m, —$ArNO_2$), 141.7 (p, —$ArNO_2$), 143.1 (p, —$ArNO_2$), 147.8 (—$ArNO_2$, in situ), 148.0 (—$ArNO_2$, in situ), 152.7 (C═O, PNZ—), 155.4 (C═O, PNZ—), 194.6-(C═O, AcS—). ESI-MS: 610.2 $[M - H]^-$. FTICR/MS: Calculated for $[C_{23}H_{25}N_5O_{11}S_2Na]$, 634.0890; found, 634.0884.

2.2.2. Preparation of Doripenem (S-4661). 2.2.2.a. Preparation of Thiol-pyrrolidine Derivative (2*S*,4*S*)-1-*tert*-Nitrobenzyl-oxycarbonyl-2—4*S*)-1-*tert*-nitrobenzyloxycarbonyl-2-(*N*-4-nitrobenzyloxycarbonylbenzyl-*N*-sulfamoulaminomethyl)-4-mercaptopyrrolidine (7). To a solution of 50 g (81.8 mmol) of (2*S*,4*S*)-1-*tert*-nitrobenzyl-2-(*N*-*tert*-nitrobenzylcarbonyl-*N*-aminosulfamide)methyl-4-acetylthiopyrrolidine (**3d**) in 200 mL of THF, 6 g of lithium hydroxide in 20 mL of water were added with an ice bath. After stirring for 2 h, the mixture was acidified with 6 N HCl and gave a sticky solid. The solid was collected by filtration, was dissolved with EtOAc and alcohol, and then stored in a refrigerator overnight. The product was precipitated as a yellowish amorphous powder (32 g, 68.8%). FT-IR (KBr, cm^{-1}): 3381, 2959, 1717, 1607, 1521, 1432, 1393, 1347, 1268, 1181, 1154, 1112, 850. ^1H NMR (600 MHz, $CDCl_3$) δ 1.52 (m, 1H, H-3β of pyrrolidine), 1.83 (d, 1H, J = 6.12 Hz, H of HS—), 2.62 (m, 1H, H-3α of pyrrolidine), 3.13 (dd, 1H, J = 11.64 and 7.68 Hz, H-5β of pyrrolidine), 3.39 (m, 1H, H-4 of pyrrolidine), 3.75 (d, 1H, J = 15.3 Hz, one of —$CH_2N(PNZ)SO_2$—), 4.10 (dd, 1H, J = 11.64 and 7.26 Hz, H-5α of pyrrolidine), 4.27 (dd, 1H, J = 15.3 and 10.32 Hz, one of —$CH_2N(PNZ)SO_2$—), 4.48 (m, 1H, H-2α of pyrrolidine), 5.15 (AB_q, 2H, J = 13.74 Hz, —OCH_2—Ar), 5.26 (AB_q, 2H, J = 13.74 Hz, —OCH_2—Ar), 5.84 (br, 2H, —SO_2NH_2), 7.45 (A_2B_2, 2H, J = 8.22 Hz, meta-H of nitrophenyl), 7.51 (A_2B_2, 2H, J = 8.40 Hz, *meta*-H of nitrophenyl), 8.21 (m, 4H, *ortho*-H of nitrophenyl). ^{13}C NMR (600 MHz, $CDCl_3$) δ: 34.5 (pyrrolidine C-3), 39.4 (pyrrolidine C-4), 50.9 (—$CH_2N(PNZ)SO_2$—), 55.3 (pyrrolidine C-5), 57.2 (pyrrolidine C-2), 66.1 (—OCH_2—Ar), 67.3 (—OCH_2—Ar), 123.9 and 124.0 (nitrophenyl *ortho*-C), 128.0 and 128.5 (nitrophenyl *meta*-C), 141.9 and 143.2 (nitrophenyl *para*-C), 147.8 and 148.0 (nitrophenyl ipso-C), 152.8 and 155.3 (C═O of PNZ—). ESI-MS: 592.1 $[M + Na]^+$, 608.1 $[M + K]^+$. FTICR/MS: Calculated for $[C_{21}H_{23}N_5Na_1O_{10}S_2]$, 592.0784; found, 592.0779.

2.2.2.b. Preparations of 8. To a DMF solution (250 mL) of (1*R*,5*S*,6*S*)-2-diphenoxy-phosphonyloxy-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid-4-nitrobenzyl ester (**7**, 17.82 g, 30 mmol) and the corresponding mercaptopyrrolidine (**2b**, 22 g, 38.66 mmol), diisopropylethylamine (7.23 mL, 42.5 mmol) was added with an ice bath. After stirring for 2 h, the mixture was diluted with 500 mL of EtOAc and washed with 1 N HCl, saturated Na_2CO_3, and saturated brine, dried over anhydrous Na_2SO_4, and evaporated in a vacuum. Toluene was added to deposit the product. After filtration, the product was obtained as a yellowish amorphous powder (27 g, 98.5%). FT-IR (KBr cm^{-1}): 3405, 2969, 1771, 1716, 1607, 1522,1433, 1392, 1347, 1276, 1181, 1141, 1111, 850.^1H NMR (600 MHz, $CDCl_3$) δ 1.26 (d, 3H, J = 7.14 Hz, CH_3— on 4-position), 1.37 (d, 3H, J = 6.18 Hz, CH_3CHOH—), 1.64 (m, 1H, H-3β of pyrrolidine), 2.62 (m, 1H, H-3α of pyrrolidine), 3.27 (m,

1H, H-4α), 3.27 (m, 1H, H-6), 3.27 (m, 1H, H-5β of pyrrolidine), 3.73 (m, 1H, one of —CH_2N(PNZ)SO_2—), 3.73 (m, 1H, H-4 of pyrrolidine), 4.10 (m, 1H, H-5α of pyrrolidine), 4.25 (m, 1H, H-5), 4.25 (m, 1H, —CH(OH) CH_3), 4.25 (m, 1H, one of —CH_2N(PNZ)SO_2—), 4.54 (m, 1H, H-2α of pyrrolidine), 5.12−5.48 (m, 6H, —OCH_2—Ar), 5.85 (br, 2H, —SO_2NH_2), 7.47 (m, 4H, *meta*-H of nitrophenyl), 7.63 (A_2B_2, 2H, J = 8.70 Hz, *meta*-H of nitrophenyl), 8.16 (A_2B_2, 2H, J = 8.28 Hz, *ortho*-H of nitrophenyl), 8.20 (m, 4H, *ortho*-H of nitrophenyl).^{13}C NMR (600 MHz, $CDCl_3$) δ 16.9 (Me— of 4-position), 22.0 (Me— of CH_3CHOH—), 34.7 (pyrrolidine C-3), 40.5 (pyrrolidine C-4), 44.0 (C-4), 50.7 (C of —CH_2N-(PNZ)SO_2—), 54.0 (pyrrolidine C-5), 56.2 (C-5), 56.8 (pyrrolidine C-2), 59.8 (C-6), 65.5 (—CH— of CH_3CHOH—), 66.2 and 67.4 and 68.4 (—OCH_2—Ar), 123.8 and 123.9 and 124.0 (*ortho*-C of nitrophenyl), 125.8 (C-2), 128.3 and 128.4 (*meta*-C of nitrophenyl), 141.8 and 142.6 and 143.0 (*para*-C of nitrophenyl), 147.7 and 147.8 and 148.0 (ipso-C of nitrophenyl), 148.2 (C-3), 152.7 and 155.0 (C═O of PNZ—), 160.0 (C═O of PNB—), 172.4(C═O of C-7). FTICR/MS:

Calculated for [$C_{38}H_{39}N_7Na_1O_{16}S_2$], 936.1792; found, 936.1787.

2.2.2.c. Deprotection and Preparation of Doripenem (S-4661, 1). To a solution (180 mL) of (1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-1-*p*-nitrobenzyloxycarbonyl-5-(*N*-*p*-nitrobenzyloxycarbonyl-*N*-aminosulfonyl-amide)methylpyrrolidine]-sulfur-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid-4-nitrobenzyl ester (**8**, 10 g, 10.95 mmol), 120 mL of water and 10 g of 10% Pd/C (contents 54% H_2O) were added, and the reaction mixture stirred under 0.5 mpa H_2 pressure for 4 h and then was filtered to remove the catalyst. Then 4 g of $MgCl_2 \cdot H_2O$ were added followed by partitioning with 300 mL of THF. 2-Propanol was added to the separated aqueous layer, which was then stored in a refrigerator overnight. The product S-4661 was precipitated and collected by filtration and dried in a vacuum as a white powder (2.269 g, 49%). FT-IR(KBr cm^{-1}): 3532, 3391, 3261, 3080, 2949, 2922, 2853, 1713, 1630, 1567, 1455, 1378, 1350, 1321, 1278, 1264, 1162, 1092, 1071, 930, 764. ^{1}H NMR (600 MHz, D_2O) δ 1.11 (d, J = 7.26 Hz, 3H), 1.18 (d, J = 6.48 Hz, 3H), 1.62−1.67 (m, 1H), 2.60−2.65 (m, 1H), 3.25−3.35 (m, 3H), 3.36 (dd, J = 2.58, 6 Hz, 1H), 3.43 (dd, J = 4.77, 10.11 Hz, 1H), 3.60 (dd, J = 6.96, 12.48 Hz, 1H), 3.8−3.84 (m, 1H), 3.92−3.96 (m, 1H), 4.12−4.16 (m, 2H). ^{13}C NMR (600 MHz, D_2O) δ 15.76, 20.05, 32.67, 39.22, 42.42, 43.06, 52.15, 55.88, 58.08, 59.57, 65.03, 133.69, 138.11, 167.63, 176.60. ESI-MS: 421.1 $[M + H]^+$. FTICR/MS: Calculated for [$C_{15}H_{24}N_4Na_1O_6S_2$], 443.4940; found, 443.1029. The data are coincident with literature.

3. Conclusions

We developed and described a practical multikilogram scale synthesis of doripenem hydrate (**1**) by deprotection of compound **8**, which was prepared from enolphosphate **2b** and *N*-PNZ protected aminomethylpyrrolidine **3d**. We found effective extraction conditions to remove *p*-toluidine and most other organic impurities using THF/water and $MgCl_2$. The reported process requires no chromatographic purification and affords compound **1** as a sterile crystalline monohydrate in satisfactory yield. This process is practical and efficient. In fact, this process is now under pilot-scaled study to make compound **1** for clinical studies.

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