Organic Process Research & Development **2009,** *13,* 815–819

An Improved Process for the Preparation of Diphenylmethyl 7β-Phenylacetamido-3-hydroxymethyl-3-cephem-4-carboxylate

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Abstract:

An efficient and improved process for the preparation of diphenylmethyl 7β-phenylacetamido-3-hydroxymethyl-3-cephem-4-carboxylate was developed. With the commercially available 7-aminocephalosporanic acid (7-ACA) as starting material, up to 73.5% overall isolated yield of the titled compound was synthesized in two steps via direct phenylacetylation with phenylacetyl chloride, followed by basic hydrolysis and esterification with diphenyldiazomethane. The newly developed process obviated the use of protecting groups, reduced the environmental footprint, and could be easily controlled and conveniently scaled up for this pivotal intermediate in cephalosporin chemistry.

Introduction

Diphenylmethyl 7β-phenylacetamido-3-hydroxymethyl-3-cephem-4-carboxylate (**1**) is an important intermediate for the synthesis of a series of cephalosporin derivatives. The 3-hydroxymethyl group has extensively been leveraged as a pivot to install various C3-functional groups, providing generation of C3-substituted cephalosporins in quantities of thousands of metric tons to treat infectious diseases. [1,2] Compound **1** has also been directly used for the synthesis of a number of cephalosporins. [3] There were generally two types of routes for the preparation of **1** from the commercially available 7-aminocephalosporanic acid (7-ACA) in the literature.[1d,g,3a,c] In both routes, the synthesis of **1** started with basic hydrolysis of the acetoxy group of 7-ACA with sodium hydroxide to give intermediate 7β-amino-3-hydroxymethyl-3-cephem-4-carboxylic acid (**2**), followed by phenylacetylation of amino group at the 7β-position of intermediate **2** to give the corresponding 7β-phenylacetamido-3-hydroxymethyl-3-cephem-4-carboxylic acid (**3**), which was then esterified with diphenyldiazomethane to protect the carboxylic acid at the 4-position to provide compound **1** (Scheme 1). Among these, Takaya et al. performed hydrolysis of 7-ACA with 20% aqueous sodium hydroxide solution at 2−5 °C, acylation with phenylacetyl chloride in a mixture of water−acetone at the pH of 7.5−8.5, and final esterification with a large excess of diphenyldiazomethane. An overall yield of 48.5% was reported from 7-ACA under these conditions.[3a] However, only 32% overall yield was obtained following this procedure by Fini et al., who attributed the potential reason for the lower yield to the side esterification of the 3-hydroxymethyl group by phenylacetyl chloride during the acylation of 7-amino group of intermediate **2**.

To avoid the inherent competitive reactions, Fini et al. proposed an improved synthetic method (Scheme 2). In the optimized condition, 7-ACA was first hydrolyzed with sodium hydroxide in a mixture of water and methanol at the temperatures between −10 to −20 °C, and intermediate **2** was isolated with good yields (82%). The 3-hydroxymethyl group of purified intermediate **2** was then protected with trimethylsilyl (TMS) group via *N*,*O*-bis(trimethylsilyl)acetamide (BAS), so that phenylacetylation could be performed in organic solvent and the potential side reaction completely avoided. After the removal of the TMS protecting group under mild conditions, the final esterification was carried out with slightly excess diphenyldiazomethane. With these modifications, the process could be smoothly applied in the synthesis of the titled compound **1** with up to 48% overall yield from 7-ACA, but the optimized route required tedious additional protecting and deprotecting operations, with a substantial increase in the amount of organic solvent used and elongated processing time.[1g]

We describe a new route (Scheme 3) in this report, which is designed to overcome drawbacks inherent with these reported methods. Specifically, 7-ACA was first acylated with phenylacetyl chloride to afford intermediate **4** selectively, which was isolated and in turn hydrolyzed with NaOH in aqueous methanol to yield the unseparated intermediate **3-Na**. The reaction mixture was neutralized to pH 6−7 with 10% HCl, and then was added the solution of diphenyldiazomethane in ethyl acetate. The final esterification was smoothly promoted by dropwise addition of 10% HCl. The target compound **1** was easily isolated as a white

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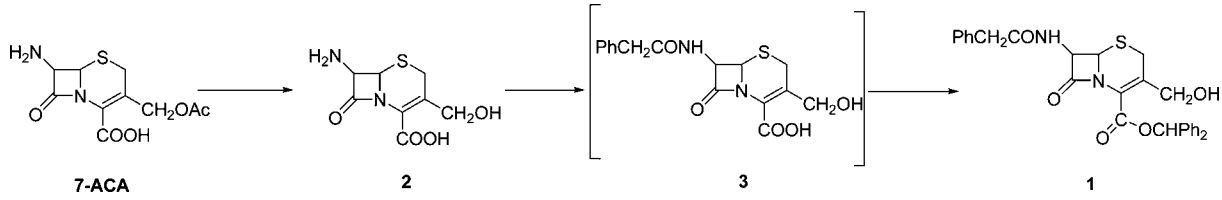
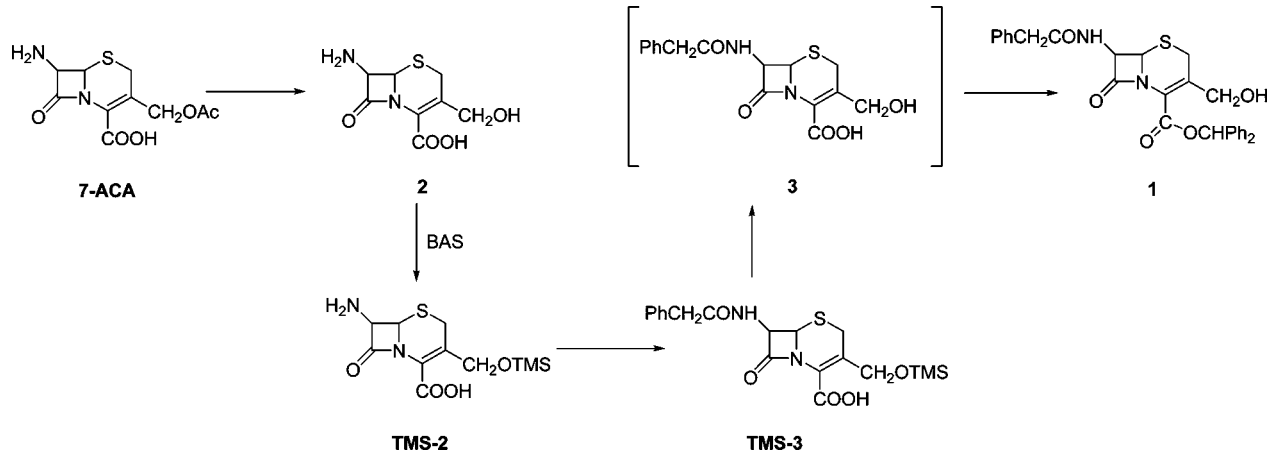
10.1021/op900063e CCC: $40.75
Published on Web 05/28/2009

Scheme 1



Scheme 2



solid, and a purity of more than 99% was obtained by HPLC analysis after being slurried with acetone. With this newly improved procedure, up to 73.5% of overall yield was achieved from 7-ACA.

Results and Discussion

Compound **1** is a pivotal intermediate in the history of cephalosporins. Lower yield and cumbersome operational procedures in the reported methods led us to believe that a new procedure for its preparation from 7-ACA might be developed by address the chemoselectivity problem in an efficient manner. Since intermediate **2** has two active groups, i.e., 7β-amino group and 3-hydroxymethyl group, that may react with phenylacetyl chloride, it is considered an uphill battle to drive the reaction to completion while avoiding acylation on the alcohol. On the other hand, the starting material, 7-ACA, has only one group reactive toward acyl chloride, i.e., 7β-amino group, and it seems well suited for selective phenylacetylation to obtain high purity of 7β-phenylacetamido-3-acetoxymethyl-3-cephem-4-carboxylic acid (**4**). Under this situation, the inherent acetoxy group in intermediate **4** actually acted as a protecting group as TMS in the above-described **TMS-2** and **TMS-3** (Scheme 2); thus, protecting and deprotecting steps in the later procedure can be totally eliminated. Indeed, hydrolysis of 3-acetoxymethyl of intermediate **4** into the corresponding alcohol with NaOH in aqueous methanol was achieved following a similar procedure in the literature as for the preparation of intermediate **2** from 7-ACA. While this seems to be an obvious choice, its lack of application is probably due to the common assumption from the literature that lactone (intermediate **5**, Scheme 4) formation is inevitable when the 3-hydroxymethyl meets an unprotected carboxylic group in close proximity. In reality, the amount of lactonization product of intermediate **3**, only becomes visible when the NaOH-mediated hydrolysis product mixture was acidified to lower pH. [4] Once formed, lactone **5** would become a byproduct as it would not react with diphenyldiazomethane to give target compound **1**. We reckoned this as the main reason for the lack of development for such a synthetic route. However, wide application of the routes in Schemes 1 and 2 led us to believe that the hydroxymethyl acid **3** can be a viable intermediate if its stability could be controlled.

Our initial experiments were carried out as outlined in Scheme 3. 7-ACA was uneventfully acylated with phenylacetic chloride following literature procedure, and the resulting intermediate **4** was isolated. Hydrolysis was carried out using NaOH in aqueous methanol. After the hydrolysis was completed, the reaction mixture was overlayered with ethyl acetate and subsequently acidified to pH 3 with 10% HCl. The ethyl acetate layer was separated, washing with brine, and dried over Na_2SO_4. The resulting solution was directly subjected to esterification with diphenyldiazomethane in ethyl acetate to afford the target product **1**. The overall yield of compound **1** from 7-ACA from this preliminary result was about 40%.

The initial success of preparing compound **1** by our proposed route inspirited us to pursue further improvement. The most important thing for us is to address what results in the lower yield. Removal of solvent from the ethyl acetate extracts from the hydrolysis mixture after acidification to pH 3 yielded a pale-yellow and viscous solid, whose amount was found far lower than the theoretical yield. Proton NMR showed two sets of peaks, which evidently came from two different compounds, and the ratio of these two compounds was about 0.4 to 1 (Figure 1 B). The MS and IR analyses further showed that these two compounds were intermediate **3** and lactone **5**, respectively. Recrystallization of this viscous solid with ethyl acetate provided

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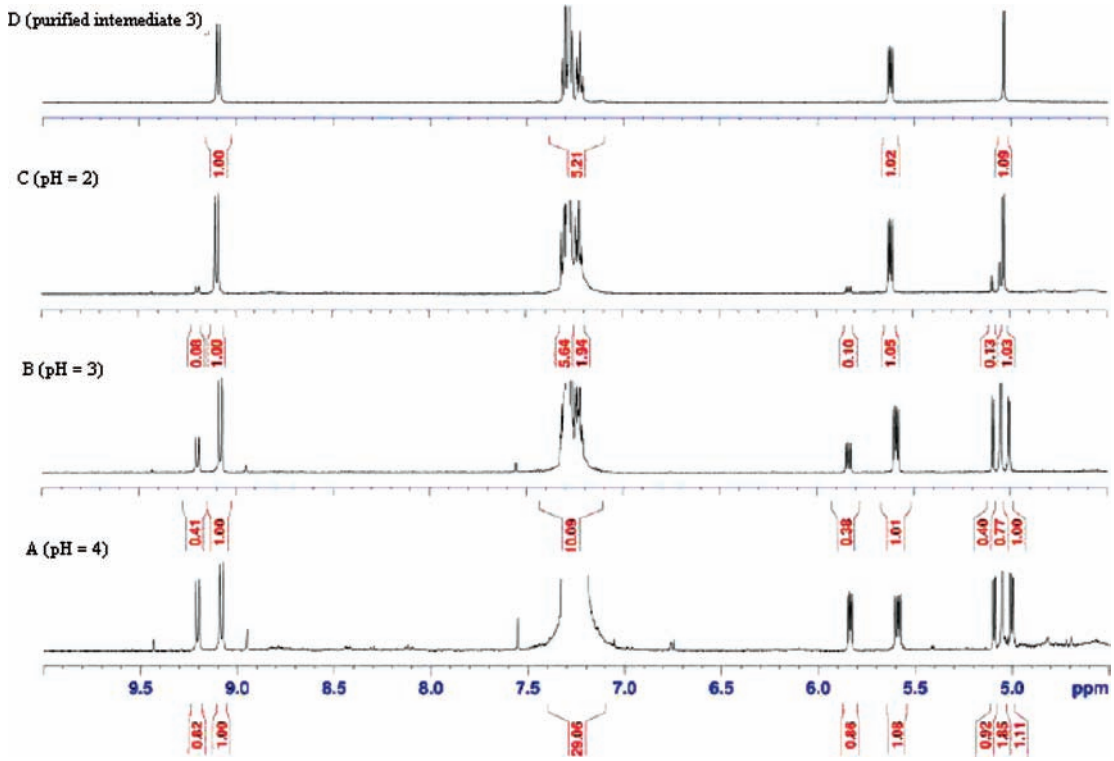
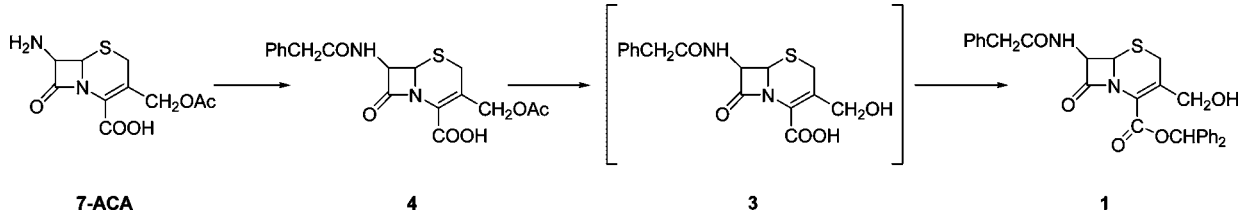


Figure 1

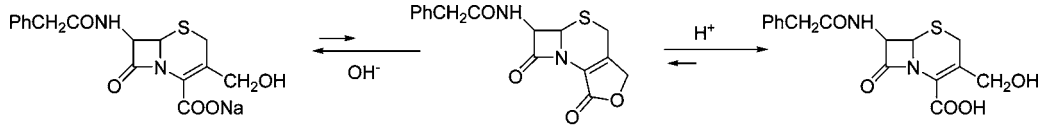
a pale-yellow crystal, whose structure was confirmed to be intermediate **3** by proton NMR and MS. According to the proton NMR spectrum (Figure 1 D) of purified intermediate **3**, we can assign the set of doublet peaks at 9.08 ppm and 5.57 ppm to intermediate **3**, and the set of doublet peaks at 9.20 ppm and 5.83 ppm in Figure 1B to lactone **5**. On the other hand, we came back to analyze the residual aqueous phase by HPLC. Indeed we found a substantial amount of the sodium salt of intermediate **3** (**3-Na**, Scheme 4) in the aqueous layer. When another portion of 10% HCl was added to the aqueous phase the precipitate was observed again. This precipitate was shown to be a mixture of intermediate **3** and lactone **5**. Interestingly, there still existed some amount of hydrolyzed product in the aqueous phase.

From these results, we conclude that the degree of acidification may not be enough during the workup of the reaction mixture. In another experiment, we increased the amount of 10% HCl (1.1 mol equiv to NaOH) during the acidification. At this moment, the pH value of the mixture was about 2. HPLC analysis indicated that no hydrolysis product existed in the aqueous layer and all hydrolysis product was extracted into the ethyl acetate layer. After performing the same workup as described above, removal of solvent under reduced pressure afforded a crude product. To our surprise, proton NMR showed that the ratio of intermediate **3** and lactone **5** remarkably varied to about 1.0 to 0.1 (C in Figure 1). From these results, it is evident that that final pH value of the hydrolysis mixture affected not only the transformation of **3-Na** to free acid **3** and lactone **5** but also the ratio of free acid **3** and lactone **5** during the acidification. In order to further clarify the relationship between the pH value and the ratio of free acid **3** and lactone **5**, an experiment of adjusting pH value to 4 was carried out during the acidification. With a similar operation, not as much of the more viscous oil was obtained. Proton NMR of this oil is shown in Figure 1 A, which indicates that the ratio of free acid **3** and lactone **5** is about 1.0 to 0.8. All proton NMR spectra under different pH values, together with the proton NMR spectrum of the purified free acid **3** are listed in Figure 1, demonstrating a clear trend that free acid **3** and lactone **5** were coproduced when the hydrolysis product **3-Na** was treated with 10% HCl, and the ratio of these two compounds varied with the amount of HCl added. As more HCl was added and the pH of the mixture turned more acidic, the more **3-Na** was transformed to lactone **5** and the more lactone **5** was transformed to free acid **3**. Thus, there existed an equilibrium between **3-Na**, lactone **5** and free acid **3**, with the content of each component varying with the pH value (Scheme 4). When the pH value of the mixture was adjusted to 2, **3-Na** was disappeared and a

Scheme 3



Scheme 4



3-Na **5** **3**

ratio of free acid **3** and lactone **5** was reached to more than 90% to 10% according to proton NMR. However, more acidity did not favor moving the equilibrium.

With the purified intermediate **4** as the starting material, we used HPLC to monitor the conversion and selectivity during the hydrolysis with NaOH in the water/methanol solution at −20 °C. The amount of water, methanol, and NaOH and also the ratio of water and methanol were carefully optimized. Experimental results showed that increasing the amount of methanol would slow down the rate of hydrolysis, while the quantity of NaOH would obviously affect the conversion. The best result of the hydrolysis of intermediate **4** to **3-Na** was obtained with 9 volumes (v/w) of a mixture of aqueous methanol (MeOH/water = 3:4) and 1.5 mol equiv of NaOH. The optimum conversion obtained was up to 95% by HPLC normalization. After hydrolysis was complete, ethyl acetate was added and the mixture was acidified to pH 2 with 10% HCl (*ca.* 1.1 mol equivalents to NaOH) below 0 °C. The organic layer was separated, washed with brine and dried over anhydrous Na_2SO_4. Then, diphenyldiazomethane (∼1.05 mol equiv to intermediate **4**) in ethyl acetate was dropwisely added into the above solution at 0−5 °C. Precipitate gradually appeared, and the mixture was stirred at the same temperature until complete conversion. The formed solid was collected and washed with ethyl acetate to afford about 70% (from intermediate **4**) of product **1** as white crystalline powder with 99% purity by HPLC normalization.

Although great progress was achieved in the preparation of the target compound **1** in the laboratory, a tedious workup procedure and a large amount of ethyl acetate could not be avoided for the above esterification procedure if the process was applied to scale-up. We further made efforts to simplify the process. To avoid using a large amount of solvent, we tried to separate solid-free acid **3** by direct acidification of the hydrolysis mixture but failed because the mixture turned into a heavy slurry at pH lower than 4 during the acidification with 10% HCl. It was also found that a large excess of diphenyldiazomethane was needed to complete the esterification if addition of the solution of diphenyldiazomethane in ethyl acetate was made directly to the crude hydrolysis mixture whose pH was adjusted to 2. This could be ascribed to the partial decomposition of diphenyldiazomethane under the strong acidic conditions. Considering the equilibrium between **3**-Na, lactone **5**, and free acid **3** shown in Scheme 4 and the fact that free acid **3** can quickly react with diphenyldiazomethane to form the target compound **1**, we could imagine that the equilibrium of the mixture of **3**-Na, lactone **5**, and free acid **3** would move in the desired direction as the consuming of free acid **3** by diphenyldiazomethane under a suitable pH value, which could be conveniently controlled by addition of HCl. Thus, we neutralized the hydrolysis mixture to pH 6−7 by 10% HCl below 0 °C at the first stage; then a solution of diphenyldiazomethane in ethyl acetate was charged to the resulting clear solution, followed by dropwise addition of 10% HCl. We were pleased to find that the esterification reaction was smoothly initialized when the pH of the mixture was adjusted about 3. With this success, the reaction conditions, such as the amount of 10% HCl, the amount of diphenyldiazomethane and the reaction temperature, were also investigated. Experimental results showed that 1.1 mol equiv (to NaOH) of 10% HCl and 1.1 mol equiv of diphenyldiazomethane (to intermediate **4**) were appropriate to complete the esterification. The temperature of 0−5 °C was suitable for the reaction. Moreover, the isolated crude product can be purified to afford white crystalline product with 99% purity by a hot slurry in reflux acetone. Under the optimal conditions, up to 76.6% (calculated from intermediate **4**) of product **1** was obtained. Contrasted to the previous ethyl acetate extraction procedure, this esterification process was easy to manipulate and greatly decreased the usage of ethyl acetate.

The finding on the esterification process greatly inspired our interests in the optimization of the previous acylation step. Several acylation procedures of synthesizing intermediate **4** from 7-ACA with phenylacetic chloride were reported under Schotten−Baumann conditions. [5] Usually, the acylation was carried out in an organic solvent with Et_3N or $NaHCO_3$ as base, and the yield of the phenylacetylation product typically ranged from 83−85%. During the process optimization, we focused on screening some other potential bases. It was found that Na_2CO_3 can provide a more feasible operation and better results. The advantage of Na_2CO_3 was that it first reacted with 7-ACA to form 7-ACA-Na salt and generated $NaHCO_3$, which can act as the base to buffer the HCl during the later acylation. We also tried to test the acylation in organic media, and found that aqueous acetone can significantly accelerate the reaction and also improved the isolated yield. Up to 96% of isolated yield of pure phenylacetylated 7-ACA (intermediate **4**) was obtained under optimal conditions with 1.1 mol equiv of Na_2CO_3 in aqueous acetone.

Conclusion

In conclusion, we have successfully developed a more practical route for the synthesis of useful intermediate, diphenylmethyl 7β-phenylacetamido-3-hydroxymethyl-3-cephem-4-carboxylate (**1**). In our newly developed process, 7-ACA was first directly acylated with phenylacetyl chloride to yield intermediate **4** under a modified Schotten−Baumann procedure with Na_2CO_3 as base in aqueous acetone. The purified intermediate **4** was hydrolyzed with NaOH in aqueous methanol.

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The resulting hydrolyzed mixture was neutralized to pH 6−7 and then charged with a solution of diphenyldiazomethane in ethyl acetate. The esterification was promoted by dropwise addition of 10% HCl. The obtained crude product was treated with acetone to afford pure compound **1**. Under the optimal condition, up to 73.5% overall yield of **1** was obtained with this two-step process starting from 7-ACA.

Experimental Section

Materials and Instruments. All solvents and reagents were purchased from commercial sources and were used without further purification. Diphenyldiazomethane was prepared following the literature procedure. [6] Melting points (mp) were determined on BUCHI B-545 apparatus and were uncorrected. Proton NMR spectra were recorded on Bruker AVANCE III 500 MHz spectrometer in DMSO-d_6 with tetramethylsilane (TMS) as internal standard. IR spectra were performed on NICOLET AVATAR 370 FT-IR instrument. ESI-MS was recorded on Perkin-Elmer Elan DRC-e instrument. HPLC analyses were performed on Waters 1525 instrument with UV detector (280 nm) using an Atlantis ODS column (150 mm × 4.6 mm (i.d.), 3.5 μ) at room temperature and mobile phase (60:40 CH_3CN/0.005 mol/L hexadecyltrimethyl ammonium bromide water solution, adjusted to pH 3.0 with H_3PO_4) with a flow rate of 0.8 mL/min.

Preparation of 7β-Phenylacetamido-3-acetoxymethyl-3-cephem-4-carboxylic Acid (4). To a solution of 35.0 g of Na_2CO_3 (0.33 mol) in 500 mL of water and 400 mL of acetone cooled to −5 °C was added 81.3 g of 7-ACA (0.30 mol). The resulting solution was stirred for 10 min at this temperature. Then 50.1 g of phenylacetyl chloride (0.33 mol) in 100 mL of acetone was dropwise added in a period of 2.5−3 h. After the addition was complete, an extra 400 mL of water was added, and the reaction mixture was stirred for another 1 h. The reaction conversion was monitored by HPLC. After 7-ACA was totally converted, 500 mL of ethyl acetate was added, and the reaction mixture was acidified to pH 3.0−3.5 with 10% HCl (∼210 mL). The organic layer was separated, and the aqueous layer was further extracted with 200 mL of ethyl acetate. The combined organic layers were washed with 300 mL of brine, dried over anhydrous Na_2SO_4, and filtered; the solvent was removed to dryness in vacuo. The residue was slurried with 300 mL of petroleum ether for 30 min at room temperature, and the suspension was filtered, washed with petroleum ether, and dried to afford 112.0 g of intermediate **4** (96.0%) as an off-white powder. Chromatographic purity by HPLC was shown to be >98%. Mp 160−162 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.03 (s, 3H), 3.48−3.64 (m, 4H), 4.67−5.02 (m, 2H), 5.08 (d, J = 5.0 Hz, 1H), 5.69 (dd, J_1 = 5.0 Hz, J_2 = 8.5 Hz, 1H), 7.21−7.32 (m, 5H), 9.12 (d, J = 8.5 Hz, 1H), 13.70 (s, 1H); IR (cm^{-1}): 3262.4, 1784.1, 1743.1, 1714.8, 1660.2; ESI-MS (*m*/*z*): 413 [M + Na]$^+$.

Preparation of Diphenylmethyl 7β-Phenylacetamido-3-hydroxymethyl-3-cephem-4-carboxylate (1). To a mixture of 400 mL of water and 300 mL of methanol cooled to −20 °C was added 77.8 g of intermediate **4** (0.20 mol). A cooled solution of 12.0 g of NaOH (0.3 mol) in 80 mL of water was added in a period of 40 min at this temperature. The reaction mixture was stirred for another 20 min, and monitored by HPLC. After the conversion reached a plateau, 35 mL of 10% HCl was gradually added to neutralize the mixture to pH ∼6 at a temperature below 0 °C. Then a solution of diphenyldiazomethane (40.7 g, 0.21 mol) in ethyl acetate (200 mL) was added to the above neutral mixture, and the mixture was kept at the temperature of 0−5 °C. Eighty milliliters of 10% HCl was dropwisely added into the mixture in a period of 1.5 h. Emission of N_2 was observed during the addition of 10% HCl, and a precipitate gradually appeared to a slurry during the stirring. The slurry was kept stirring for another 2 h at the same temperature until no N_2 evolution was observed. The resulting precipitate was collected by suction and washed with ethyl acetate (100 mL × 2) to afford crude product. The dried crude product was slurried with 450 mL of acetone under reflux for 2 h and filtered after cooling down to room temperature to afford 78.8 g of target compound **1** (76.6% from intermediate **2**) as a white crystalline powder after drying. Chromatographic purity by HPLC was shown to be >99%. Mp 178−180 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.50−3.59 (m, 2H), 3.61 (s, 2H), 4.20 (t, J = 5.5 Hz), 5.11 (d, J = 5.0 Hz, 1H), 5.18 (t, J = 5.5 Hz, 1H), 5.72 (dd, J_1 = 5.0 Hz, J_2 = 8.5 Hz 1H), 6.90 (s, 1H), 7.22−7.52 (m, 15H), 9.15 (d, J = 8.5 Hz, 1H); IR (cm^{-1}): 3501.6, 3283.6, 1762.3, 1713.8, 1665.7; ESI-MS(*m*/*z*): 537 [M + Na]$^+$.

Acknowledgment

This project was financially supported by the project of Science and Technology Department of Zhejiang Province, China. (Grant No. 2008C21028). We thank Dr. Tony Y. Zhang at Eli Lilly and Company for his helpful discussion.

Supporting Information Available

Proton NMR and mass spectra of compounds **1**, **3**, and **4** and HPLC diagrams of compounds **1** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review March 18, 2009.

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