New types of monocyclic β-lactams constitute an important class of compounds due to their unique structures and natures. Here, the design and synthesis of new 4-alkylthio monocyclic β-lactams 2a and 3a are reported. Significantly, compounds 2a and 3a, while keeping a monocyclic system, were designed to contain all of the substructures provided by the cleavage of C(2)-C(3) bond in penicillins. Efficient synthetic pathways for compounds 2a and 3a were established based on two different strategies. Compound 2a was synthesized from raw materials, using 4-acetoxyazetidin-2-one as a key intermediate, through a ten-step synthetic sequence in 3% overall yield. Compound 3a was synthesized from potassium salt of penicillin G (17), using the degraded product 20 as a key intermediate, through a six-step synthetic sequence in 11% overall yield. 4-Alkylthioazetidin-2-one derivatives, introduced in this study, could serve as valuable intermediates for the development of new monocyclic β-lactams.

Key Words: Monocyclic β-lactams, Penicillin, Isopropylthioazetidinone, t-Butylthioazetidinone, Degradation of penicillin

Introduction

The four-membered ring appears to be the smallest cyclic system that accommodates the amide function as a constituent. Such four-membered cyclic amides, commonly referred to as β-lactams, possess physical and chemical properties that diverge sharply from those of acyclic amides, partially due to ring strain. After numerous penicillins and cephalosporins, new types of nonclassical β-lactams have appeared. Monocyclic β-lactam compounds1 such as monobactams and nocardicins are included in these categories and differ from classical β-lactams in structural features and biological activities. In addition, the most important groups of monocyclic β-lactam antibiotics were discovered in the 1980s. The Imada2 and Sykes3 groups independently described a new class of compounds 1. As characteristic features, these monocyclic β-lactams have a 4-unsubstituted β-lactam ring, a 3-acylamido side chain, and a 1-sulfonate group, which rarely occur in nature.

Recently, monocyclic β-lactams have been found to display a range of non-antibacterial activities as well as bacterial activities,4,5 again highlighting the significance of these compounds. The studies on the structures and biological activities of monocyclic β-lactams were reviewed by Galletti and Giacominii.6 Some of the compounds in this series proved to be biologically active but were chemically unstable and therefore unsuitable for practical use.

As the biologically active principle of all β-lactam antibiotics is the β-lactam ring, the reactivity and stability of the β-lactam ring must be decisively influenced by substituents. However, the exact influence of each substituent on biological activities remains a puzzle in spite of the development of numerous analogues. Nevertheless, the substituent(s) might have significant effects on amide resonance and molecular geometry and, as a result, govern the amide bond stability and reactivity and the corresponding biological activities.

So, the synthesis of monocyclic β-lactam derivatives that could be more effective than the existing compounds has become an important subject of medicinal interest.7,8 Accordingly, here I report the design and synthesis of two new monocyclic β-lactams that contain penicillin-similar moieties.

Results and Discussion

Design and Structural Features of 2a and 3a. I wished to design new monocyclic β-lactams and so attempted to breakdown the bicyclic system in the penicillin structure. Based on the importance of the alkylthio group at C(4) and the carboxymethyl group at N(1), I was specifically interested in structures 2 and 3 that would be obtained by the cleavage of C(2)-C(3) bond in the penicillin structure. As a result, 2 and 3 should contain all of the penicillin moieties except the bicyclic ring system. In particular, compound 2a contained 2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido group at C(3) as an acyl side chain and isopropylthio group at C(4) (trans to acetamido group), and compound 3a contained phenylacetamido group at C(3) and t-butylthio group at C(4) (cis to acetamido group). Notably, compound 2a and 3a contained trans and cis configurations between the acetamido and the alkylthio groups, respectively. Although compound 2a contained trans configuration which is differ-
ent from that of penicillins, a number of monocyclic β-lactam derivatives of biological significance were found to have trans configurations. Carboxymethyl group (potassium salt) was retained at N(1) in both cases. Taken together, 2a and 3a might be structurally similar but less-strained than penicillin, and these new 4-alkylthio monocyclic β-lactams might therefore have comparable characteristics to penicillin. Thus, 2a and 3a could be meaningful analogues of monocyclic β-lactams derived from penicillins.

**Synthesis of Monocyclic β-Lactam 2a.** After considering several synthetic pathways, I established a plausible synthetic scheme through azetidin-2-one as an intermediate, as shown in Scheme 1. In particular, 4-substituted azetidin-2-ones were considered as very important intermediates in the synthesis of various nonclassical β-lactams. The preparations of these compounds were developed by the Clauss group and later further exploited period. However, most of these methods suffered from side reactions and low yields (~20%). Thus, I applied minor modifications to these methods. At first, vinyl acetate (4) was treated with chlorosulfonyl isocyanate (CSI, 5) in CH2Cl2 to provide azetidinone 6, which was applied in situ for reductive hydrolysis of the N-S bond, leading to the generation of compound 7 in moderate yield (35%, for two steps). Unfortunately, further efforts to improve the yield of this step did not lead to better results. Intermediate 7 could be functionalized by displacing the acetoxy group with various nucleophiles to form new C-S or C-C bond. In our experiments, the acetoxy group was displaced by sulfur-containing nucleophiles such as sodium isopropanethiolate at 0 oC for 15 h. The reaction of compound 7 with sodium isopropanethiolate at 0 oC for 30 min gave 4-isopropylthio compound 9 in 78% yield. Also, sodium t-butanethiolate (or thiol) and thioacetate anions (or thiolacetic acids) were employed to react with compound 7 to give the corresponding thioderivatives. For example, the reaction of 7 with sodium t-butanethiolate at room temperature for 1 h afforded 4-t-butylthioazetidin-2-one in 65% yield. This type of carbon-sulfur bond forming reaction has been regarded as an important step for further functionalization. Then, for the functionalization at C(3) it was required to protect NH group due to its high reactivity. Accordingly, compound 9 was reacted with t-butyldimethylsilyl chloride (TBSCl) in CH2Cl2, which smoothly proceeded within 4 h to give 10 in near quantitative yield. Then, the formation of anion at C(3) in 10 with LDA in THF (~78 oC, 2 h) was followed by treatment with p-toluenesulfonyl azide and trimethylsilyl chloride (TMSCl), affording the 3-azido compound 11 in 65% yield, along with the minor desilylated compound 12. At this step I was also interested in the stereochemistry of 11 (cis or trans-isomer). However, analysis of the NMR signals was not clear since the two proton signals for C(3)H and C(4)H overlapped near δ 4.60-4.40. However, 11 was found to be a trans-isomer since the stereochemistry of compound 12 in the next step was determined. Treatment of compound 11 with tetrabutylammonium fluoride (TBAF) in THF at ~78 oC for 2 h produced the desilylated compound 12 in 70% yield. Treatment with HF-pyridine in acetonitrile at room temperature also led to the formation of 12. However, the condition using TBAF gave slightly better results than that using HF-pyridine. As mentioned above, I analyzed the stereochemistry of 12 using 1H NMR and found that it was a trans-isomer based on the coupling constant (J = 1.5 Hz) of the signals of C(3)H and C(4)H, which is diagnostic for a trans-isomer.

The intermediate 12 was then converted to N-alkyl compound 13 in 84% yield by treatment with ethyl bromoacetate and potassium carbonate in DMF at room temperature for 4 h, as shown in Scheme 2. The IR spectrum of the product 13 showed the expected amide, azide, and ester absorptions at 1780, 2120, and 1745 cm⁻¹, respectively.

Then, the azido compound 13 was transformed into primary amine 14. Among various reducing agents that have been employed in the conversion of aliphatic or aromatic azido groups into corresponding amines, two methods were tested. First, azido derivative 13 was mixed with triphenyl-
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phosphine in THF\(^{16}\) and then treated with water to afford the amine product. Second, the azido group was treated with Pd/C in THF under 40 psi (H\(_2\) gas) at room temperature\(^{17}\) to give the amine product \(14\) in 71% yield. When compared, the latter method (Pd/C) gave slightly better results.

3-Amino compound \(14\) was considered a highly important intermediate because it could react with various acids using appropriate coupling agents to give a range of 3-substituted azetidinone compounds. For this purpose, I considered employing organophosphate coupling agents since these agents have attracted a great deal of interest in peptide synthesis. Among these agents, I chose benzotriazol-1-yl diethylphosphatate (BDP)\(^{18}\) as an appropriate coupling agent that was prepared by mixing equimolar amounts of diethylchlorophosphate, 1-hydroxybenzotriazole (HOBT), and triethylamine in THF. On the other hand, I also intended to choose an appropriate acid as an acyl side chain. Among numerous acids, aminothiazole moiety has been extensively explored, and in particular, 2-(2-aminothiazol-4-yl)-2-(methoxymimo)acetic acid (15) has been widely employed in clinically important β-lactam antibiotics\(^{19}\) and in investigations of structure-activity relationships.\(^{20}\) Based on this fact, I chose 15 as an exemplary acid for our study. So, compound 15 was first mixed with 3-amino compound 14 in the presence of triethylamine in DMF at room temperature, and to this mixture was slowly added a solution of BDP in DMF, leading to the formation of the product 16 in 63% yield. Similar results were obtained in the absence of triethylamine, probably due to the role of the amino group attached to the thiazole ring. In general, the size and number of substituents in a small ring molecule could be very important factors that stabilize the ring; thus, more substituted β-lactams would be more stable than less substituted β-lactams. Accordingly, compound 16 would be stabilized more or less by introducing the large acid as a side chain in the monocyclic β-lactam ring. Finally, ethyl ester in 16 was hydrolyzed in methanol by treatment with aqueous potassium hydroxide (KOH). Here, I wished to examine, in advance, the stability of the β-lactam carbonyl group against potassium hydroxide. When treated with aqueous potassium hydroxide, the less substituted monocyclic β-lactam 9 was found to be slightly decomposed after 1 h and severely decomposed after 7 h, while the more substituted monocyclic β-lactam, 3-phenylacetamido-4-isopropylthiazetidin-2-one, was found to be resistant for 5 h. Based on these results, I carefully conducted the hydrolysis reaction using only 1.0 equiv. of potassium hydroxide as a base, for fear of ring opening and further decomposition. Fortunately, the reaction proceeded without severe decomposition of 16 in this condition. However, after the reaction was complete, isolation and purification of the salt were difficult. After extensive efforts, I succeeded in recrystallizing the crude product by fine modulation of the solvent mixture (methanol and Et\(_2\)O), affording purified salt 2a in 65% yield. Consequently, the target compound 2a was synthesized from 4 and 5 through a 10-step synthetic sequence in 3% overall yield.

**Synthesis of Monocyclic β-Lactam 3a.** In order to synthesize monocyclic β-lactam 3a, I wished to apply a different strategy from that for compound 2a. Oftentimes, penicillin G has been regarded as one of the best starting materials for the synthesis of various β-lactams, because it is currently available at low cost via fermentation and could be stereospecifically transformed to important key intermediate(s).\(^{21}\) In particular, the methods whereby penicillin acid derivatives could be degraded to monocyclic azetidinones were of my interest. Thus, I intended to transform penicillin G to 4-

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\begin{align*}
\text{PhCH}_2\text{CO-} & \quad \text{PhCH}_2\text{CO-} \\
\text{HN} & \quad \text{HN} \\
\text{N} & \quad \text{N} \\
\text{CO} & \quad \text{CO} \\
\text{Et} & \quad \text{PhCH}_2\text{Ph} \\
\text{Ac} & \quad \text{Ac} \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{CO} & \quad \text{CO} \\
\text{Et} & \quad \text{Et} \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{CO} & \quad \text{CO}
\end{align*}
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acetoxyazetidin-2-one derivatives that could be used to synthesize monocyclic β-lactams in many ways. As shown in Scheme 3, potassium salt of penicillin G (17) was treated with benzyl bromide in DMF to give benzyl ester of penicillin G (18) in 84% yield. Then, according to previous procedures, I attempted to convert the bicyclic system in 18 to monocyclic compound 19. Mercury acetate was heated with acetic anhydride in acetic acid at 80 °C for 30 min and to the resulting solution was added compound 18, affording monocyclic compound 19 in 60% yield.

The oxidation procedures that were employed for other N-alkylidene derivatives of azetidinone were applied to achieve the transformation of compound 19 to compound 20. When I tested several methods, I found that ozonolysis was the most efficient procedure for oxidation of the side chain. Ozonolysis of compound 19 in CH₂Cl₂-methanol at −78 °C led to the production of compound 20 in 80% yield. Then, 4-acetoxy derivative 20 was transformed to t-butythioazetidin-2-one compound 21 by nucleophilic displacement of the acetoxy group with sodium t-butanethiolate that was prepared by dissolving sodium metal in t-butanethiol. We found that the reaction rate of 20 with t-butanethiolate anion at 0 °C was slower than that with isopropanethiolate anion probably due to steric hindrance. This reaction therefore required higher temperature (room temperature) and longer reaction time (4 h) to give compound 21 in 51% yield, compared to the reaction with isopropanethiolate (0 °C, 2 h, 60% yield). Although this reaction could work through nucleophilic displacement and/or elimination-addition processes, we mainly observed the formation of cis-isomer 21 due to inversion by nucleophilic displacement, which was identified by the chemical shifts and coupling constants of the signals of C(3)H and C(4)H in 1H NMR.

Before the alkylation of the NH group, I was interested in the influence of the alkylthio groups at C(4) on the reactivity of the NH group. I therefore conducted a model study for N-alkylation in two cases; 4-isopropylthioazetidin-2-one and 4-t-butythioazetidin-2-one. In the former case, the reaction with ethyl bromoacetate in the presence of potassium carbonate in DMF at room temperature was complete in 5 h to give the corresponding product in 79% yield. However, in the latter case, the reaction did not work efficiently under the same conditions, and higher temperature (60 °C) and longer reaction time (10 h) were required to give the corresponding product in similar yield (77%). Thus, we believed that the reactivity of the NH group was strongly influenced by the substituent at C(4), probably due to steric effect. On the basis of the results of the model study, I performed the reaction under the similar condition, in which compound 21 was treated with ethyl bromoacetate at 60 °C for 10 h to provide compound 22 in 74% yield. Finally, I carefully conducted the hydrolysis reaction using only 1.0 equiv. of potassium hydroxide as a base and further purification by recrystallization in methanol and Et₂O, finally affording the potassium salt 3a in good yield (75%). Consequently, the target monocyclic β-lactam 3a was synthesized from 17 through a six-step synthetic sequence in 11% overall yield.

Conclusions

The design and synthesis of monocyclic β-lactams 2a and 3a are reported. These compounds were specifically designed by cleavage of the C(2)-C(3) bond of the penicillin structure and aimed to retain all of the penicillin moieties except the bicyclic ring system. Compound 2a contained a useful aminothiazolylacetamido group as a side chain at C(3) and an isopropylthio group at C(4). Compound 3a contained a phenylacetamido group as a side chain at C(3) and a t-butythio group at C(4). Both compounds kept the same carboxymethyl group (its potassium salt) at N(1). These substructures would exactly represent the structures that would be obtained by the cleavage of the C(2)-C(3) bond in the penicillins. Compound 2a was synthesized from 4 and 5 through a ten-step synthetic sequence in 3% overall yield. Compound 3a was obtained from the degradation of the potassium salt of penicillin G (17) through a six-step synthetic sequence in 11% overall yield.

Experimental

General. 1H NMR spectra were recorded on a Varian FT-80A Spectrometer and chemical shifts are expressed as δ units relative to tetramethylsilane (TMS). Infrared (IR) spectra were measured on a Perkin-Elmer 267 spectrometer and frequencies are given in reciprocal centimeters. Analytical thin layer chromatography (TLC) was performed on glass plates (0.25 mm) coated with silica gel 60F-254 (Merck). Column chromatography was conducted using Merck silica gels (0.040-0.063 mm). Most of the reagent grade chemicals were purchased commercially and distilled before use, if necessary. Some compounds were prepared by known procedures, and spectral and physical data of the products were in accord with reported data.

4-Acetoxyazetidin-2-one (7). To a stirred solution of vinyl acetate (4, 5.0 mL, 54 mmol) in dry CH₂Cl₂ (5 mL) was added chlorosulfonyl isocyanate (5, 1.0 mL, 11 mmol) dropwise at 0 °C. After stirring for 2 h at 0 °C, the mixture was poured into an aqueous solution (150 mL) of NaHCO₃ (8 g) and Na₂SO₃ (8 g) at 0 °C with stirring. Stirring was again continued for 30 min at 0 °C and the mixture was extracted with CH₂Cl₂. Evaporation of the solvent gave a yellow oil that was chromatographed on silica gel to afford the title compound (0.50 g, 35%). 1H NMR (CDCl₃, 80 MHz) δ 7.60 (br s, 1H), 6.05-5.80 (m, 1H), 3.60-2.86 (m, 2H), 2.25 (s, 3H); IR (KBr) v 1750, 1740 cm⁻¹.

4-Isopropylthioazetidin-2-one (9). To a stirred solution of compound 7 (2.4 g, 19 mmol) in THF (30 mL) at 0 °C was added a solution of sodium propanethiolate (8, 2.03 g, 21 mmol) in H₂O (10 mL). After being stirred for 30 min at 0 °C, the reaction mixture was diluted with CH₂Cl₂ (30 mL) and washed with brine three times. The organic layer was dried over MgSO₄ and evaporated to give the title compound (2.1 g, 78%). 1H NMR (CDCl₃, 80 MHz) δ 7.60 (br s, 1H), 5.94-5.70 (m, 1H), 3.61-2.68 (m, 3H), 1.36 (d, J = 6.0 Hz, 6H); IR (KBr) v 3200, 1750 cm⁻¹.
1-Butylidimethylsilyl-4-isopropylthiazetidin-2-one (10). To a stirred solution of compound 9 (2.1 g, 15 mmol) in CH₂Cl₂ was added t-butylidimethylsilyl chloride (TBSCI, 2.7 g, 18 mmol) in the presence of disopropylethylamine (DIEA, 3.1 mL, 18 mmol) at 0 °C. Then the ice bath was removed and stirring was continued for 4 h at room temperature. The reaction mixture was added with CH₂Cl₂ (50 mL) and washed with brine. The organic layer was dried over MgSO₄ and evaporated to dryness. The crude product was purified by column chromatography to give the title compound in quantitative yield. ¹H NMR (CDCl₃, 80 MHz) δ 4.90-4.62 (m, 1H), 3.80-2.80 (m, 3H), 1.39 (d, J = 6.0 Hz, 6H), 1.09 (s, 9H), 0.35 (s, 6H); IR (KBr) ν 3400, 2120, 1780 cm⁻¹.

trans-3-Azido-1-t-butylidimethylsilyl-4-isopropylthiazetidin-2-one (11). To a stirred solution of compound 10 (1.9 g, 7.2 mmol) at –78°C in THF (20 mL) was added compound 13 (0.39 g, 2.1 mmol) in DMF (2 mL), and the resulting solution was stirred at the same temperature, the reaction mixture was filtered and the filtrate was diluted with CH₂Cl₂ (1.8 mL, 14 mmol) was added. Then the reaction mixture was maintained at room temperature for 1 h, followed by heating to 50°C for 4 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was diluted with CH₂Cl₂ (50 mL) and washed with brine at neutral conditions. The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude product was purified by silica gel column chromatography to afford the title compound (1.4 g, 65%). ¹H NMR (CDCl₃, 80 MHz) δ 4.60-4.40 (m, 2H), 3.25-3.00 (m, 1H), 1.39 (d, J = 6.0 Hz, 6H), 1.09 (s, 9H), 0.35 (s, 6H); IR (KBr) ν 3400, 2120, 1780 cm⁻¹.

trans-3-Azido-4-isopropylthiazetidin-2-one (12). To a stirred solution of compound 11 (0.90 g, 3.0 mmol) in THF was added tetraethyl ammonium fluoride (TBAF, 4.5 mL of 1 M solution in THF, 4.5 mmol) at –78°C. After being stirred for 2 h at the same temperature, the reaction mixture was slowly diluted with EtOAc (10 mL) and washed with brine (30 mL) three times. The organic layer was dried over MgSO₄ and evaporated in vacuo to give the title compound (0.39 g, 70%). ¹H NMR (CDCl₃, 80 MHz) δ 7.20 (br s, 1H), 4.64 (d, J = 1.5 Hz, 1H), 4.46 (d, J = 1.5 Hz, 1H), 3.60-3.05 (m, 1H), 1.39 (d, J = 6.0 Hz, 6H); IR (KBr) ν 3300, 2120, 1780 cm⁻¹.

trans-3-Azido-1-ethoxycarbonylmethyl-4-isopropylthiazetidin-2-one (13). To a stirred solution of ethyl bromoacetate (0.26 mL, 2.3 mmol) in DMF (6 mL) was added a solution of compound 12 (0.39 g, 2.1 mmol) in DMF (2 mL) in the presence of potassium carbonate (0.32 g, 2.3 mmol) at room temperature. The reaction mixture was then stirred for 4 h at room temperature. The resulting mixture was diluted with CH₂Cl₂ (35 mL) and subsequently, washed with brine (30 mL). The organic layer was dried over MgSO₄ and evaporated in vacuo, affording an oily residue that was chromatographed on Merck silica gel using EtOAc-hexanes (1:5) as an eluent. The fractions were combined and solvent was removed in vacuo to give the title compound (0.48 g, 84%). ¹H NMR (CDCl₃, 80 MHz) δ 4.81 (d, J = 2.0 Hz, 1H), 4.53-3.74 (m, 5H), 3.18-3.00 (m, 1H), 1.34 (d, J = 4.1 Hz, 6H), 1.26 (t, J = 7.0 Hz, 3H); IR (KBr) ν 2120, 1785, 1750 cm⁻¹.

trans-3-Amino-1-ethoxycarbonylmethyl-4-isopropylthiazetidin-2-one (14). Azido lactam 13 (0.48 g, 1.8 mmol) was hydrogenated in EtOAc (10 mL) using a 10% Pd on carbon catalyst (0.32 g, 0.30 mmol) under 40 psi (hydrogen gas). After the mixture was shaken for 2 h at room temperature, hydrogen gas was replaced by nitrogen gas and the catalyst was removed by filtration. The filtrate was concentrated in vacuo and the residue was chromatographed on Merck silica gel using EtOAc as an eluent. The fractions with R₂ 0.4 were combined and the solvent was removed in vacuo to afford the title compound (0.24 g, 63%). ¹H NMR (CDCl₃, 80 MHz) δ 4.60 (d, J = 2.0 Hz, 1H), 4.42-3.73 (m, 3H), 3.15-2.90 (m, 1H), 2.02 (br s, 2H), 1.34 (d, J = 6.5 Hz, 6H), 1.26 (t, J = 7.0 Hz, 3H); IR (KBr) ν 3400, 1780, 1750 cm⁻¹; MS (EI) m/z 247 [M⁺]⁺.

trans-3-(2-Amino-thiazol-4-yl)-2-(methoxyimino)acetamido)-1-ethoxycarbonylmethyl-4-isopropylthiazetidin-2-one (16). To a solution of thiazole acetic acid derivative 15 (0.18 g, 0.88 mmol), 3-aminolactam 14 (0.22 g, 0.88 mmol), and TEA (0.12 mL, 0.88 mmol) at room temperature was added benzotriazol-1-yl diethylphosphosphate (0.26 g, 0.97 mmol) in DMF (4 mL), and the resulting solution was stirred at room temperature until completion of the reaction (2 h). Solvent was removed in vacuo and the residue was chromatographed on Merck silica gel using EtOAc as an eluent to give the title compound (0.24 g, 63%). ¹H NMR (CDCl₃, 80 MHz) δ 8.43 (d, J = 8.0 Hz, 1H), 6.70 (s, 1H), 6.00 (br s, 2H), 5.25-5.00 (m, 2H), 4.40-3.60 (m, 7H), 3.19-2.98 (m, 1H), 1.35 (d, J = 6.5 Hz, 6H), 1.28 (t, J = 7.0 Hz, 3H); IR (KBr) ν 3350, 1775, 1750, 1680 cm⁻¹.

Hydrolysis of 16 to Give Potassium Salt 2a. To a stirred solution of compound 16 (0.15 g, 0.35 mmol) in methanol (3 mL) was added aqueous potassium hydroxide (0.30 mL of 1.0 N solution, 0.30 mmol) at room temperature. After being stirred for 30 min, the reaction mixture was diluted with EtOAc (30 mL) and subsequently poured into distilled water (30 mL). The aqueous layer was washed three times with EtOAc to remove excess starting material. The aqueous layer was dried by freeze dryer to give the corresponding potassium salt. The salt was then purified by recrystallization from a methanol-Et₂O mixture to give the title compound (86 mg, 65%). ¹H NMR (D₂O, 80 MHz) δ 6.70 (s, 1H), 5.25-5.00 (m, 2H), 4.40-3.60 (m, 5H), 3.25-2.92 (m, 1H), 1.35 (d, J = 6.5 Hz, 6H); IR (KBr) ν 3380, 1770, 1685, 1620 cm⁻¹.

Benzyl Ester of Penicillin G (18). A suspension of potassium salt of penicillin G (17, 3.0 g, 8.11 mmol) in DMF (25 mL) and benzyl bromide (1.1 mL, 9.3 mmol) was stirred for 2 h at room temperature. The mixture was filtered and the filtrate was poured into ice water (100 mL). The resulting oil was extracted with EtO (50 mL), and the organic layer was washed with saturated NaHCO₃ solution (50 mL) and dried over MgSO₄. Evaporation of the solvent in vacuo gave the title compound (2.9 g, 84%). ¹H NMR (CDCl₃, 80 MHz) δ 7.46-7.39 (m, 5H), 7.38-7.29 (m, 5H), 6.36 (br s, 1H), 5.80-5.46 (m, 2H), 5.20 (s, 2H), 4.42 (s, 1H), 3.63 (s,
2H), 1.38 (d, J = 5.5 Hz, 6H); IR (KBr) ν 3400, 1795, 1725, 1690 cm⁻¹.

**trans-45-Acetoxy-1-(benzoyloxy carbonyl-2-methylpropenyl)-(3S)-phenylacetoamidoazetidin-2-one (19).**²⁴ Mercuric acetate (1.9 mg, 6.0 mmol) was dissolved in acetic acid (8.5 mL) and acetic anhydride (0.85 mL), and the mixture was heated to 80°C in an oil bath and stirred for 30 min. While the temperature was maintained at 80-85°C, compound 18 (1.7 g, 4.0 mmol) was added in small portions and stirred for 2 h at the same temperature range. Then, the reaction mixture was cooled, filtered through celite, and evaporated to give an oily residue. The residue was dissolved in CH₂Cl₂ and the resulting mixture was washed with 5% NaHCO₃ and 5% NaCl solutions. The organic layer was dried over Na₂SO₄ and evaporated to dryness. Column chromatography of the residue on a silica gel column by EtOAc-hexanes (1:1) as an eluent gave the title compound (0.86 g, 80%).

**Hydrolysis of 22 to Give Potassium Salt 3a.** To a stirred solution of compound 22 (0.15 g, 0.40 mmol) in methanol (3 mL) was added aqueous potassium hydroxide (0.35 mL of 1.0 N solution, 0.35 mmol) at room temperature. After being stirred for 30 min, the reaction mixture was diluted with EtOAc (30 mL) and poured into distilled water (30 mL). The aqueous layer was washed two times with EtOAc to remove excess starting material. The aqueous layer was dried by freeze dryer to afford the corresponding potassium salt. The salt was further purified by recrystallization from methanol-Et₂O mixture to afford the title compound (0.15 g, 74%).

H NMR (CDCl₃, 80 MHz) δ 7.33-7.24 (m, 5H), 5.04-4.80 (m, 2H), 4.61-3.77 (m, 4H), 3.57 (s, 2H), 2.11-1.04 (m, 12H); IR (KBr) ν 3300, 1785, 1755, 1670 cm⁻¹.

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