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A Novel, Mild, and Facile Method To Prepare 6-Methylidene Penem Derivatives

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A novel and mild method was established to synthesize 6-methylidene penem compounds. This method entails a $MgBr_2/Et_3N$-promoted aldol-type condensation on 6-bromopenem **12** with an appropriately substituted aldehyde to yield the intermediate acetylated bromohydrin, which was smoothly converted to the final product with simultaneous deprotection of C3 carboxylic acid ester using activated zinc dust and phosphate buffer at pH 6.5. This process provides a useful variation of C−C bond formation method for penem derivatives and also serves as a practical synthetic method to prepare 6-exomethylenepenem derivatives without racemization at the C5 position.

Introduction

Penicillins and cephalosporins are among the most widely used antibiotics. However, the development of resistance to β-lactam antibiotics by different pathogens severely limits these agents in treating bacterial infections.[1] The most significant known mechanism related to the development of bacterial resistance to the β-lactam antibiotics is the production of class-A, class-B, and class-C β-lactamases.[2] In practice, only a few effective β-lactamase inhibitors are clinically approved, which are coadministered with a β-lactam antibiotics. Thus, clavulanic acid **1**[3a] (given in combination with amoxicillin), sulbactam **2**[3b] (given in combination with ampicillin), and tazobactam **3**[3c] (given in combination with piperacillin) are very effective inhibitors against class-A enzymes but do not inhibit either class-C or class-B β-lactamases.

It has been recently shown that a number of 6-substituted methylidene penems such as BRL-42715 (**4**) and SB-206999Z (**5**) are potent broad spectrum inhibitors of bacterial β-lactamases.[4] In particular, BRL-42715 was advanced to a development stage. Unlike other β-lactamase inhibitors, the 6-methylidene structural feature imparts a unique mechanism of action toward enzyme inhibition.[5] In addition to these synthetic penem derivatives, naturally occurring 6-methylidene carbapenem derivatives such as asparenomycins (A, B, and C, Figure 1) are known to be broad-spectrum antibiotics with potent β-lactamase inhibitor activity.[6] To

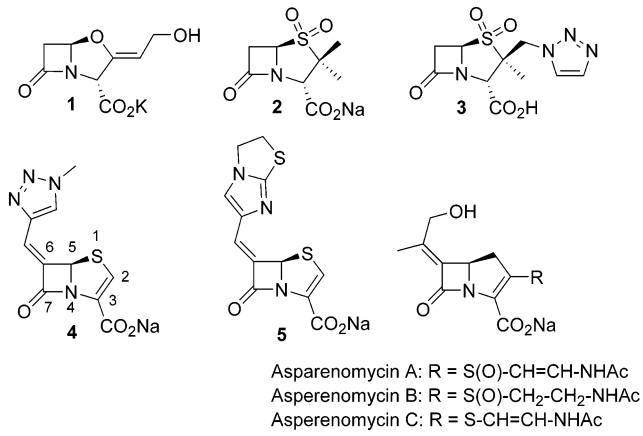

FIGURE 1. β-Lactamase inhibitors and 6-methylidene derivatives.

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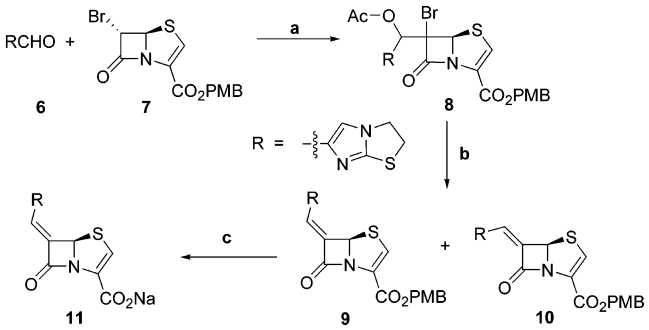
SCHEME 1[a]



[a] Key: (a) (1) Ph_2NLi, THF−MeCN, −78 °C, (2) Ac_2O; (b) Zn, AcOH, TMEDA; (c) (1) Et_2AlCl, anisole, CH_2Cl_2, −20 °C, (2) Na_2HPO_4.

design broad-spectrum β-lactamase inhibitors as well as to study their mechanism of action, we sought out an efficient and practical method to synthesize 6-methylidene penem derivatives.

The general synthesis of 6-(substituted methylidene) penems has been reported by the Beecham group (Scheme 1).[7] However, when this procedure was repeated in our laboratory, we encountered the following problems: First, the precursor ester **9** underwent racemization at the C5 center in the solution state. This proved to be a fatal aspect for scale-up synthesis and further evaluation of the penem derivatives. Next, the initial aldol-type condensation reaction using LHMDS or lithium diphenylamide (Ph_2NLi) was very difficult to control resulting in variable yields. Finally, the pivotal intermediate **7** was relatively unstable on standing at room temperature over a period of several days.[8]

Hence, to circumvent the above-mentioned problems, a novel and facile method was devised to accomplish this transformation. The instability issue relating to the *p*-methoxybenzyl (PMB) protected intermediate **7** was solved by replacing it with the more stable and crystalline *p*-nitrobenzyl (PNB) derivative **12** (Scheme 2). It has been shown that deprotection of PNB group on *N*-protected amino acids or carbapenems can be achieved by hydrogenolysis on Pd/C or zinc dust reduction in phosphate buffer.[9] Hence, we envisaged that this procedure could be applied to the present situation, which would not only deprotect the ester functionality, but also introduce the 6-methylidene linkage. Furthermore, introduction of the PNB group was expected to not only avoid the unstable precursor ester **9** but also improve the stability of the pivotal intermediate **12**.

Results and Discussion

PNB bromopenem **12** was synthesized from 6-aminopenicillanic acid in an overall 23% yield by a modification of the previously reported procedure.[7] To our satisfaction, the crystalline compound **12** demonstrated excellent stability in the solid state at 40 °C.[8] After solving this stability problem, we examined the crucial aldol-type condensation reaction using **12**. Thus, bromopenem **12** was sequentially treated with Ph_2NLi (Scheme 2) in THF at −78 °C and aldehyde **6**[7] at −78 °C for 1 h. The resulting bromohydrin comprising a mixture of diastereomers was proved to be relatively unstable and difficult to isolate, so it was acetylated in situ with Ac_2O at 0 °C to afford the corresponding bromoacetates **14** in 43% yield, along with the formation of PNB ester of thiazole-4-carboxylic acid **15** in 30% yield (Table 1, entry 1). Analyses of the crude products by a reverse phase HPLC and LC−MS techniques[10] showed that the product **14** consisted of a mixture of four diastereomeric isomers (**14a**−**d**) formed in the ratio of 40:22:25:13. These results indicate that the PNB protecting group is compatible with aldol-type condensation conditions, even though the yield of the desired product is low.

This promising result prompted us to investigate further Lewis acid mediated aldol-type condensation to improve the yield and diastereoselectivity of this reaction. It has been shown by Masamune, Seebach, and others[11] that metal enolates, such as aluminum, magnesium, boron, and other Lewis acids, can be utilized in aldol-type condensation reactions to achieve improved diastereoselectivity and yield. In addition to the selectivity profile, it has been reported independently by Mansour,[12] Rathke et al.,[13] and Moreno-Manas et al.[14] that the acidity of the proton involved in the anion formation process can be increased by the addition of Lewis acid. Hence, we anticipated that adding Lewis acid such as $MgBr_2$ could facilitate the anion formation at the C6-position of bromopenem **12**. Toward this end, aldehyde **6** was reacted with **12** using Ph_2NLi as a base (1.3 molar equiv) and $MgBr_2{\cdot}Et_2O$ (1.3 molar equiv) as the Lewis acid at −78 °C for 1 h (Scheme 2). The aldol product was isolated as bromoacetates **14** in excellent overall yield (Table 1, entry 2). Analysis of the reaction mixture using HPLC techniques revealed that only two diastereomers **14a** and **14b** were formed in the ratio of 1:6. It should be noted here that aldehyde **6** was added immediately after the formation of the lithium enolate. However, upon the slow addition of **6** to the enolate (over 10 min), we observed a decrease in the yield to 42%. On the basis of these results, the aldol-type condensation between **12** and **6** was investigated in the presence of anhydrous $MgBr_2$, $MgCl_2$, or MeMgBr/Ph_2NH. As seen in Table 1, replacing the $MgBr_2{\cdot}Et_2O$ with $MgBr_2$ resulted in a slight decrease

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(8) The PMB bromopenem **7** intermediate decomposed to an extent of 30% after standing at 40 °C for 7 days in the solid state while that of the PNB bromopenem **12** did not decompose over 15 days after standing under the same conditions.

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(10) A mixture of the bromoacetates **14a** and **14b** showed same retention time on the normal phase HPLC. The other minor diastereomers **14c** and **14d** were unstable to isolate but detected by LC−MS.

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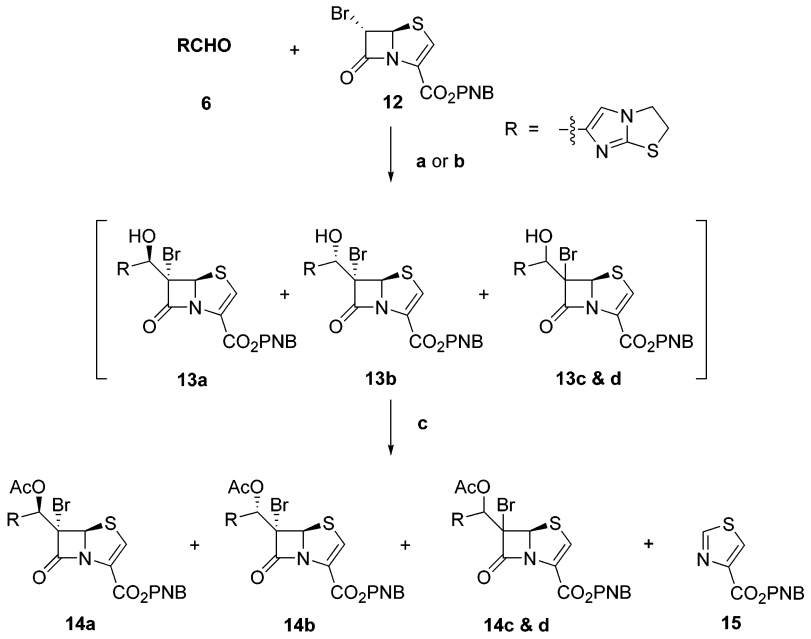
SCHEME 2[a]



[a] Key: (a) Ph_2NLi, −78 °C; (b) Ph_2NLi, $MgBr_2{\cdot}Et_2O$, −78 °C; (c) Ac_2O.

TABLE 1. Aldol-Type Condensation of the Bromopenem 12 and Aldehyde 6 Using Lithium Amides/Lewis Acids

	aldol reaction		acetylation		
entry	base (molar equiv)	additive (molar equiv)	Ac_2O (molar equiv)	time (h)	HPLC[a] yield of **14** (%)
1	Ph_2NLi (1.3)	−	1.3	1	43
2	Ph_2NLi (1.3)	$MgBr_2{\cdot}Et_2O$ (1.3)	1.3	1	90
3	Ph_2NLi (1.3)	$MgBr_2$ (1.3)	1.3	1	77
4	MeMgBr (1.3)	Ph_2NH (1.3)	1.3	2	0
5	LDA (2.0)	−	2.0	1	40
6	LDA (2.0)	$MgBr_2{\cdot}Et_2O$ (1.3)	2.0	1	47
7	Ph_2NLi (1.3)	$ZnCl_2$ (1.3)	1.3	1	0

[a] Analytical HPLC conditions are shown in the Supporting Information.

in the yield, and the other modifications resulted in significant reduction in the yield of the desired aldol products. Replacing the $MgBr_2$ with $ZnCl_2$ did not result in any desired product. Even changing the base from Ph_2NLi to LDA decreased the yield drastically.

Whereas utilization of $MgBr_2$ results in a satisfactory yield, the use of Ph_2NLi may pose some problems for large-scale production, because immediate and successive addition of Ph_2NLi and aldehyde **6** is not practical, and the resulting Ph_2NH has to be removed by silica gel column chromatography. An extensive literature[15] survey revealed that the C6-position of the penem nucleus is always deprotonated using strong bases such as LHMDS, LDA, or Ph_2NLi, while others[12,13] have shown that enolization of certain ketones can be achieved by using mild base such as *i*-Pr_2NEt in the presence of Lewis acid such as $MgCl_2$. Interestingly, it has been shown by Nagao et al.[16] that imines can undergo aldol-type condensation reaction with an aldehyde in the presence of $MgBr_2$ and Et_3N. These precedents seemed attractive to attempt the use of a mild and safe base such as Et_3N, because the C6-proton is further activated by the presence of the bromine substituent.

Accordingly, compound **12** was reacted with aldehyde **6** in the presence of $MgBr_2$ (1.2 molar equiv) and Et_3N (2.4 molar equiv) at −40 °C for 9 h (Table 2, entry 1). In this reaction, both the enolization and the aldol-type reaction proceeded smoothly, and the intermediate aldol products were trapped as bromoacetate **14** by using Ac_2O at 0 °C. After the isolation of the products, it was determined that the reaction proceeded in 75% yield with the formation of two major diastereomers **14a** and **14b** in a ratio of 1:10. We next investigated the effect of temperature on this reaction, and as shown in Table 2 (entry 2), the yield increased to 89−93% with a rise in the temperature from −40 to −20 °C. However, further increase in the reaction temperature led to a decrease in the yield (entries 4−6). When THF as the reaction solvent was replaced with CH_2Cl_2, the composition of **14a**−**d** was changed to 20:63:8:9 (entry 3). As can be seen in entries 7 and 8, when the amount of $MgBr_2$ was reduced from 2.4 to 0.6 molar equiv, the yield of **14** decreased dramatically. The use of $MgBr_2{\cdot}Et_2O$ did not alter the yield significantly. However, when the Lewis acid was changed to hydrated $MgBr_2$ or $MgCl_2$, the desired product was not produced. The above-mentioned aldol-type condensation reaction on **12** was further studied using different Lewis acids such as $AlCl_3$, $TiCl_4$, and $La(OTf)_3$ (entries 12−14). The use of $AlCl_3$ or $TiCl_4$ did not result in any of the desired product. However, $La(OTf)_3$ afforded **14** (diaster-

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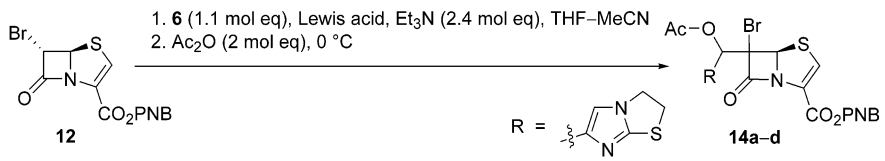
TABLE 2. Aldol-Type Condensation of the Bromopenem 12 Using Et_3N/Lewis Acids



entry	Lewis acid (molar equiv)	aldol reaction T (°C)	aldol reaction time (h)	acetylation time (h)	HPLC[a] yield of **14** (%)	comments
1	$MgBr_2$ (1.2)	−40	9	2	75	
2	$MgBr_2$ (1.2)	−20	2−3	16	89−93	**14a**/**14b**/**14c**/**14d** = 5:60:1:1[b]
3	$MgBr_2$ (1.2)	−20	2−3	16	55	THF was replaced with CH_2Cl_2, **14a**/**14b**/**14c**/**14d** = 20:63:8:9[b]
4	$MgBr_2$ (1.2)	0	1	2	73	
5	$MgBr_2$ (1.2)	0	1	17	79	
6	$MgBr_2$ (1.2)	rt	0.83	2	56	
7	$MgBr_2$ (2.4)	0	1	2	70	
8	$MgBr_2$ (0.6)	0	1	2	18	
9	$MgBr_2 \cdot Et_2O$ (1.2)	0	1	2	68	
10	$MgBr_2 \cdot 6H_2O$ (1.2)	0	1	2	0	
11	$MgCl_2$ (0.6)	0	1	2	1	
12	$AlCl_3$ (1.2)	−20	2	18	dec	solvent: CH_2Cl_2 only
13	$TiCl_2$ (2.4)	−78 to −10 rt	4 then 18	18	dec	solvent: CH_2Cl_2 only
14	$La(OTf)_3$ (1.2)	−45 −20	2 then 1.5	18	51	diastereomer ratio **14a**/**14b** = 1:7[b]

[a,b] Analytical HPLC conditions are shown in the Supporting Information.

eomeric ratio = 1:7) in a modest yield. It is clear that the nature of the metal ion and the choice of the base are crucial for an efficient aldol reaction to occur. Clearly, the use of $MgBr_2$ (1.2 molar equiv)/Et_3N (2.4 molar equiv) at −20 °C resulted in the best yield of **14** with the diastereomeric ratio of 1:10 (entry 2), thus avoiding the use of Ph_2NLi as the base.

It should be noted here that the stereochemistry of the major isomer formed via the magnesium enolate is different from that via the lithium enolate based on isolating each single component by silica gel column chromatography.[16a] Thus, the absolute stereochemistry of the major isomer obtained via the magnesium enolate was determined to be **14b** by X-ray crystallographic analysis of the *p*-nitrobenzoyl ester **16** (Figure 2), whereas that formed via the lithium enolate was not clearly assigned, but it could likely be **14a** based on the NOE experiments.[7] This stereochemical outcome clearly shows a preference for attack by the aldehyde **6** from the more hindered face, the concave side of the bromopenem, suggesting a degree of pyramidalization at the C6-position in the bromine-substituted enolate.

This stereochemical proposal was further supported by the ab initio calculations of the bromine substituted and unsubstituted enolates of penems (Figure 3). The dihedral angle of Br−C6−C7−C5 for the lithium enolate of bromopenem and unsubstituted penem was 166.23° and 173.74°, respectively. The HOMO potential map showed the reaction region was positioned on the concave site in the enolate of bromopenem, while it was spread over both the concave and convex site of the enolate of unsubstituted penem.

The difference in the stereochemical outcome that we observed in each metal enolate can be explained mechanistically as depicted in Figure 4. A possible explanation for the formation of **14b** can be due to the excess amount of $MgBr_2$ that interacts with the carbonyl group of the

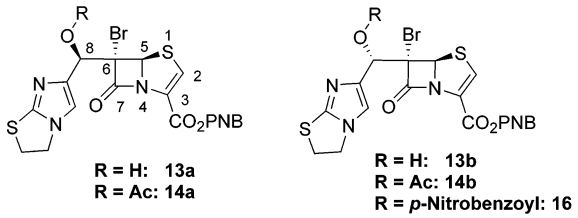


FIGURE 2. Stereochemistry of the bromoacetate, **14a**, **14b**, and the *p*-nitrobenzoyl ester **16**.

β-lactam ring facilitating deprotonation and resulting in the magnesium enolate approaching the magnesium coordinated aldehyde **6** subsequently, the transition state for the reaction between the enolate and the aldehyde adopts an open-chain conformation resulting in high diastereomeric selectivity for **14b**.

To investigate the versatility of the above-mentioned procedure, various aldehydes were reacted with bromopenem **12**, and the results are shown in Table 3. These examples demonstrated the generality of this process, which is applicable to aliphatic, aromatic, and heterocyclic aldehydes.[17] The overall yields range from 42 to 84%. The absolute stereochemistry of the major bromohydrins **17a** and **17c** was determined by X-ray crystallographic analysis. In these cases, the stereochemistry at C8 was opposite to that of **13b**, the main product from aldehyde **6** and bromopenem **12** (Figure 5).

These results clearly demonstrate that the chelating ability of the aldehyde plays an important role in directing the stereoselectivity of the reaction as shown in Figure 4.

(17) The $MgBr_2$/Et_3N-promoted aldol-type condensation of **12** did not proceed with nitrile, ester, activated amide such as imidazolide, 1,3-thiazolidine-2-thione amide, and Weinreb's amide.

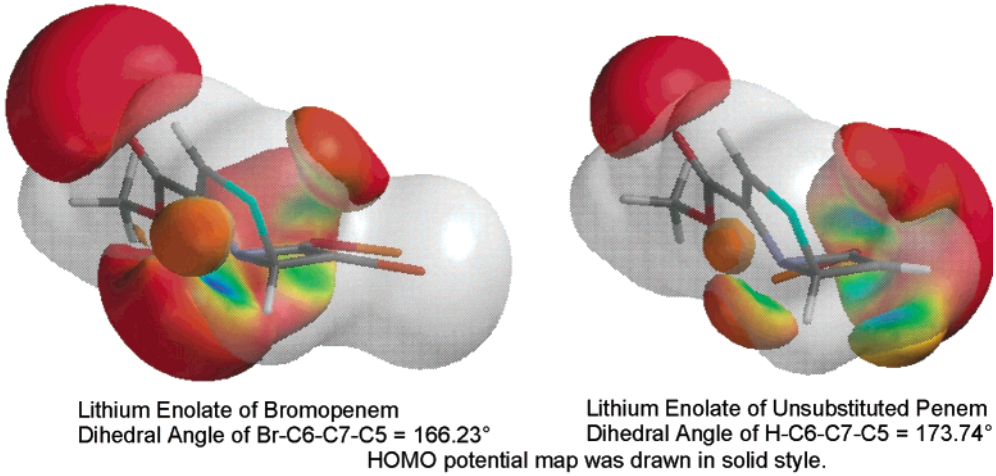


FIGURE 3. HOMO potential map of bromine-substituted and unsubstituted enolates of penems, calculated by Spartan 'O2 using the 3-21g* basis set.

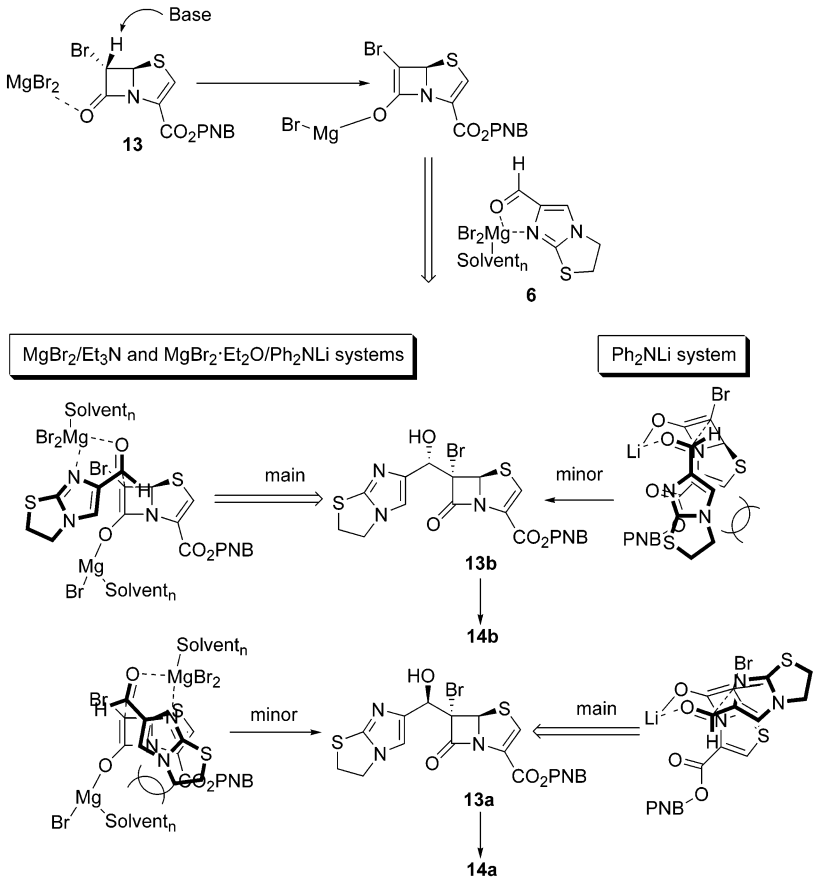
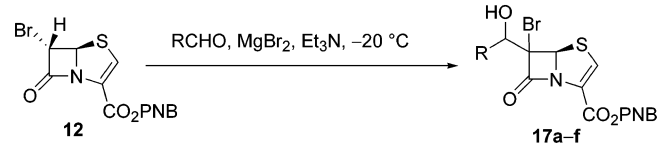


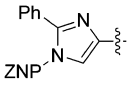
FIGURE 4. Plausible reaction mechanisms.

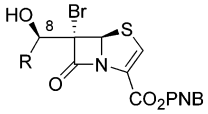
After standardizing this novel aldol-type condensation procedure, we next turned our attention to the reductive elimination procedure to introduce a *Z*-double bond between the C6 and C8 carbon atoms. Since the resulting 6-methylidene penem compounds are prone to decomposition at a pH >9 and <5, a neutral procedure[9c] was devised using freshly prepared activated zinc dust[18] and 0.5 M (pH 6.5) phosphate buffer. The amount of zinc dust required for this transformation was found to be about four times the weight of the bromoacetate. After exploring different solvent systems to carry out this transformation at room temperature, MeCN/THF (1:2) emerged as the most suitable combination. At this juncture, it is very important to mention that the use of activated zinc dust/phosphate buffer not only introduces exclusively the *Z*-double bond between the C6 and C8 carbon atoms, but also results in concomitant deprotection of the carboxyl

(18) Commercially available zinc dust was activated with 1 N HCl for 15 min and filtered. It was washed well with deionized water and used as such.

TABLE 3. $MgBr_2/Et_3N$-Promoted Aldol-Type Condensation of 12 with Various Aldehydes



entry	aldehyde (R)	product	isolated yield of main product (%)	
1	Me	**17a**	44	Single isomer was mainly obtained.
2		**17b**	59	Single isomer was mainly obtained.
3	Ph	**17c**	65	Single isomer was mainly obtained.
4	Cinnamoyl	**17d**	74	Single isomer was mainly obtained.
5		**17e**	84	Diastereomeric mixture was obtained.
6		**17f**	42	Single isomer was mainly obtained.



R = Me: 17a

R = Ph: 17c

FIGURE 5. Stereochemistry of **17a** and **17c**.

TABLE 4. Comparison of the Optical Purity of Compound 5

entry	ee[a] (%)	comments
1	0.1	enantiomeric mixture; prepared from the racemized precursor 9
2	96.3	a crystalline solid; procedure outlined in ref 7
3	>99	a re-crystallized solid; procedure outlined in ref 7
4	>99	a crude amorphous solid; prepared by $MgBr_2 \cdot Et_2O/Ph_2NLi$ method
5	>99	a crystalline solid; prepared by $MgBr_2 \cdot Et_2O/Ph_2NLi$ method
6	>99	a crude amorphous solid; prepared by $MgBr_2/Et_3N$ method
7	>99	a crystalline solid; prepared by $MgBr_2/Et_3N$ method

[a] Chiral HPLC conditions are shown in the Supporting Information.

functionality, thus avoiding an extra deprotection step. Additionally, this mild and direct transformation avoids racemization at the C5 position unlike the earlier literature reports and results in a product with high optical purity (Table 4) due to the avoidance of a stepwise procedure.[7]

Finally, the applicability of this process for scale-up synthesis was confirmed by preparing a 112-g batch of **5** in 50% isolated yield starting from 250 g of bromopenem **12**.

Conclusion

In conclusion, the formation of an anion at the C6-position of penem is extremely useful for the preparation of various penem-based antibiotics and β-lactamase inhibitors. Previously, this was achieved by using a strong base such as LHMDS, LDA, MeMgBr, or Ph_2NLi. In the present paper, it has been shown that the $MgBr_2/Et_3N$-mediated procedure can be applied to labile 6-bromo penem derivatives. This C6−C8 bond formation reaction was shown to be a rather mild, efficient, and useful variation of the aldol reaction. In this paper, we have also described a mild and efficient reductive elimination procedure that can be applied to other pH-sensitive molecules such as penems.

Experimental Section

2,3-Dihydroimidazo[2,1-*b*]thiazole-6-carboxaldehyde (6) and *p*-Methoxybenzyl (5*R*,6*S*)-6-Bromo-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (7). Compounds **6** and **7** were prepared by the procedure as described in the literature.[7]

6: ^{1}H NMR ($CDCl_3$) δ 3.88 (t, J = 7.3 Hz, 2H), 4.27 (t, J = 7.3 Hz, 2H), 7.65 (s, 1H), 9.72 (s, 1H).

7: ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 5.14 (d, J = 1.5 Hz, 1H), 5.18 and 5.22 (AB, J = 12.0 Hz, 2H), 5.75 (d, J = 1.5 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.25 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H).

4-Methoxybenzyl (5*R*)-(*Z*)-6-(2,3-Dihydroimidazo[2,1-*b*]thiazol-6-ylmethylene)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic Acid (9). The ester **9** was synthesized by the procedure as outlined by Osborne et al.[7] Enantiomeric excess (%) of **9** was determined to be 93% ee by chiral HPLC (system B): mp 144 °C dec; HPLC area ratio 100%, contents 100% (system A); $[\alpha]^{20}_D$ +577.40 (*c* 0.001, MeCN) [lit.[7] a yellow form $[\alpha]^{20}_D$ +522 (*c* 0.001, MeCN)]; IR (KBr) 1768, 1699, 1235 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 3.82 (t, J = 7.4 Hz, 2H), 4.18 (t, J = 7.4 Hz, 2H), 5.14 and 5.25 (AB, J = 12.1 Hz, 2H), 6.58 (d, J = 0.8 Hz, 1H), 6.84 (d, J = 0.8 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 7.20 (s, 1H), 7.23 (s, 1H), 7.36 (d, J = 8.6 Hz, 2H).

Racemization of 9. The ester **9** (604 mg, 1.4 mmol, 93% ee) was dissolved in a mixture of toluene−EtOAc−CH_2Cl_2 mixed solvent (7:2:1, 200 mL) and allowed to stand in a light-resistant bottle for 8 days at 35 °C. The solvent of the mixture was evaporated under reduced pressure, and the resulting residue was dried in vacuo to obtain a yellow solid (594 mg, 98% yield by HPLC assay (system A), 3% ee, $[\alpha]^{20}_D$ +8.72 (*c* 0.002, MeCN)). The solid (519 mg) was triturated with EtOAc (13 mL) for 1.5 h at rt to obtain a racemate of **9** as a yellow crystalline solid [484 mg, HPLC area ratio 100%, contents 100% (system A), 93% yield, 1.3% ee (system B)]: mp 180 °C dec; $[\alpha]^{20}_D$ +3.33 (*c* 0.001, MeCN); IR (KBr) 1778, 1701, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 3.82 (t, J = 7.3 Hz, 2H), 4.18 (t, J = 7.3 Hz, 2H), 5.17 and 5.23 (AB, J = 12.1 Hz, 2H), 6.58 (d, J = 0.8 Hz, 1H), 6.84 (d, J = 0.8 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 7.20 (s, 1H), 7.23 (s, 1H), 7.36 (d, J = 8.6 Hz, 2H). Anal. Calcd for $C_{20}H_{17}N_3O_4S_2$: C, 56.19; H, 4.01; N, 9.83. Found: C, 56.07; H, 4.00; N, 9.69.

Sodium (5*RS*)-(*Z*)-6-(2,3-Dihydroimidazo[2,1-*b*]thiazol-6-ylmethylene)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (Racemized 5, Prepared from the Racemate of 9). The PMB protective group of the above racemate **9** (214 mg, 0.5 mmol) was deprotected by a modified Beecham's procedure.[7] The reaction vessel was covered with foil to exclude light. Et_2AlCl (1 M) in hexane solution (1.56 mL) was added to a dry CH_2Cl_2 (2.6 mL) solution of anisole (0.07 mL) at −20 °C. A dry CH_2Cl_2 (12 mL) solution of the racemate **9** (214 mg) was added gradually to the mixture for 15 min at −20 °C. The reaction mixture was stirred for 1 h 40 min at −10 °C. A solution of $Na_2HPO_4 \cdot 12H_2O$ (3.6 g) in H_2O (13 mL) was added to the reaction mixture below −5 °C and stirred for 30 min at ice-bath temperature. Celite (428 mg) was added to the reaction solution and stirred for 30 min. The mixture was filtered through a pad of Celite. The pad was washed with water and CH_2Cl_2, and then the aqueous layer was separated. The aqueous layer was concentrated to 25 mL under high vacuum at 30 °C. The concentrate was applied to Diaion HP-21 (30 mL, Mitsubishi Kasei Co. Ltd.) resin column chromatography. After adsorbtion, the column was eluted with water and then with 2.5−5% MeCN−water. The combined active fractions were concentrated to 770 mg under high vacuum at 30 °C. Acetone (1.5 mL) was added to the concentrate at rt, and it was stirred for 30 min in an ice bath. More acetone was added to the mixture in 0.75 mL portions every 30 min over a 1.5 h period at ice-bath temperature (total 3 mL of acetone was added). After being stirred for 30 min in an ice bath, the resulting precipitate was filtered, washed with acetone, and dried in vacuo for 15.5 h at rt. The racemized **5** was obtained as a yellow crystalline solid (81 mg, HPLC area ratio 100% (system C). HPLC contents 94.8% as a monohydrate form, yield 46%, 0.1% ee by chiral HPLC (system D): mp 190 °C dec; $[\alpha]^{20}_D$ +1.87 (*c* 0.0011, MeCN); IR (KBr) 1755, 1684 cm^{-1}; ^1H NMR (D_2O) δ 3.70 (t, J = 7.4 Hz, 2H), 4.06 (t, J = 7.4 Hz, 2H), 6.32 (s, 1H), 6.75 (s, 1H), 6.82 (s, 1H), 7.32 (s, 1H); HRMS (FAB) calcd for $C_{12}H_8N_3O_3S_2Na_2$ (MW + Na) 351.9802, found *m*/*z* 351.9788 (M^+ + Na). Anal. Calcd for $C_{12}H_8N_3O_3S_2Na \cdot 2.1H_2O$: C, 39.25; H, 3.35; N, 11.44. Found: C, 39.02; H, 2.97; N, 11.31.

Synthesis of *p*-Nitrobenzyl (5*R*,6*S*)-6-Bromo-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate 12. *p*-Nitrobenzyl 6-Bromopenicillanate 1-Oxide (18). 6-Aminopenicillanic acid (500 g. 2.31 mol) was added to a cooled solution of MeOH (3.5 L), water (1.36 L), and 48% w/w hydrobromic acid (1.36 L, 12.02 mol) at −10 °C. After the addition was complete, the mixture was cooled to −15 °C. $NaNO_2$ solution (235 g dissolved in 660 mL of water) was added over 30 min, and the resulting solution was stirred without cooling for a further 30 min. To the resulting reaction mixture was added NaCl (240 g), and the mixture was extracted with CH_2Cl_2 (2 × 3 L). The combined organic layers were washed with brine (3 L), dried ($MgSO_4$), and concentrated to 1.6 L under reduced pressure at 25 °C. The residual solution of 6-bromopenicillanic acid was taken to next step without any purification.

Anhydrous K_2CO_3 (288 g, 2.08 mol), DMF (2.8 L), and *p*-nitrobenzyl bromide (500 g, 2.31 mol) were successively added to the 6-bromopenicillanic acid, and the mixture was stirred at 35−40 °C for 1 h. The reaction solution was poured into a mixture of water (2.8 L) and extracted with CH_2Cl_2 (3.4 L). The organic layer was washed with water (2.8 L) and brine (3 L) and cooled to −2 °C. The resulting *p*-nitrobenzyl 6-bromopenicillanate was taken to the next step without purification.

In order for analytical characterization, a small portion (1/100 w/w) of the organic layer was applied to silica gel column chromatography and eluted with EtOAc−hexane (4:1) to obtain *p*-nitrobenzyl 6-bromopenicillanate as a colorless solid (7.2 g, 75% yield): mp 74−76 °C; $[\alpha]^{20}_D$ +130.54 (*c* 0.002, $CHCl_3$); IR (KBr) 1786, 1742, 1523, 1347 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.62 (s, 3H), 4.61 (s, 1H), 4.83 (d, J = 1.5 Hz, 1H), 5.25 and 5.34 (AB, J = 13.0 Hz, 2H), 5.41 (d, J = 1.5 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 8.26 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{15}H_{15}N_2O_5SBr$ (MW) 413.9885, found *m*/*z* 413.9868 (M^+). Anal. Calcd for $C_{15}H_{15}N_2O_5SBr$: C, 43.39; H, 3.64; N, 6.75. Found: C, 43.49; H, 3.62; N, 6.86.

m-CPBA (355 g, 2.06 mol) was added to the stirred solution of *p*-nitrobenzyl 6-bromopenicillanate over a period of 15 min, and the mixture was stirred for an additional 10 min. The reaction mixture was diluted with EtOAc (4.8 L) and washed with a saturated solution of $NaHCO_3$ (7.6 L). The organic layer was separated, and the aqueous layer was reextracted with EtOAc (3.9 L). The combined organic layers were washed with water (3.9 L) and brine (3.9 L), dried ($MgSO_4$), and evaporated under reduced pressure at 30 °C. The residual solid was triturated with EtOAc (1.8 L) for 30 min, and hexane (5.4 L) was added dropwise to this mixture over 1 h. The solid was filtered off, and the filter cake was washed with EtOAc−hexane (1:4, 0.8 L). The solid was air-dried for 1 h and dried in vacuo overnight at rt. Sulfoxide **18** was obtained as a pale-yellow crystalline solid (768 g, 77% yield). The obtained material was used as is for the next reaction.

A small portion of the solid was applied to silica gel column chromatography, eluted with EtOAc−hexane (1:1) and recrystallized from EtOAc. Sulfoxide **18** was obtained as a colorless solid: mp 118−120 °C dec; $[\alpha]^{20}_D$ +161.58 (*c* 0.004, $CHCl_3$); IR (KBr) 1794, 1739, 1521, 1347, 1051 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 3H), 1.69 (s, 3H), 4.60 (s, 1H), 5.04 (d, J = 1.5 Hz, 1H), 5.10 (d, J = 1.5 Hz, 1H), 5.30 and 5.37 (AB, J = 12.9 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 8.27 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{15}H_{15}N_2O_6SBr$ (MW) 429.98342, found *m*/*z* 429.9797 (M^+). Anal. Calcd for $C_{15}H_{15}N_2O_6SBr$: C, 41.78; H, 3.51; N, 6.50. Found: C, 41.76; H, 3.47; N, 6.41.

***p*-Nitrobenzyl 2-[(3*S*,4*R*)-3-Bromo-4-formylthio-2-oxoazetidin-1-yl]-3-methylbut-2-enoate (19).** Sulfoxide **18** (766 g, 1.78 mol) and mercaptobenzothiazole (294 g, 1.76 mol) were heated in refluxing toluene (2.4 L) with a provision for the azeotropic removal of water (Dean−Stark apparatus) for 1 h. The reaction mixture was cooled to 0 °C and used as is for the next reaction.

A small portion (0.56% w/w) of the mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography by eluting with EtOAc−hexane (2:5) to obtain *p*-nitrobenzyl (2*R*)-2-[(3*S*,4*R*)-4-(benzothiazol-2-yldithio)-3-bromo-2-oxoazetidin-1-yl]-3-methylbut-3-enoate as a pale-yellow solid (5.67 g, 98% yield): mp 120−122 °C (toluene); $[\alpha]^{20}_D$ −154.19 (*c* 0.005, $CHCl_3$); IR (KBr) 1792, 1737, 1520, 1347 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (s, 3H), 4.87 (s, 1H), 5.05 (brs, 1H), 5.10 (d, J = 1.7 Hz, 1H), 5.17−5.25 (m, 4H), 7.37−7.41 (m, 1H), 7.41−7.50 (m, 3H), 7.81 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.8 Hz, 2H); HRMS (EI) calcd for $C_{22}H_{18}N_3O_5S_3Br$ (MW) 578.9592, found *m*/*z* 578.9606 (M^+). Anal. Calcd for $C_{22}H_{18}N_3O_5S_3Br$: C, 45.52; H, 3.13; N, 7.24. Found: C, 45.79; H, 3.15; N, 7.10.

The cooled reaction mixture was treated with Et_3N (25 mL, 0.18 mol) and stirred at 0 °C for 2 h, and the resulting suspension was used as is for next step.

A small portion (0.49% w/w) of the above-mentioned reaction mixture was washed with 1 N HCl, water, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by silica gel column chromatography for structure assignment and eluted with EtOAc−hexane (1:3) to obtain *p*-nitrobenzyl 2-[(3*S*,4*R*)-4-(benzothiazol-2-yldithio)-3-bromo-2-oxoazetidin-1-yl]-3-methylbut-2-enoate as a colorless crystalline solid (4.16 g, 80% yield from **18**): mp 121−122 °C (EtOAc); $[\alpha]^{20}_D$ −71.50 (*c* 0.005, $CHCl_3$); IR (KBr) 1767, 1723, 1518, 1349 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H), 2.24 (s, 3H), 5.01 (d, J = 1.7 Hz, 1H), 5.24 and 5.30 (AB, J = 13.1 Hz, 2H), 5.35 (d, J = 1.7 Hz, 1H), 7.34−7.42 (m, 1H), 7.48−7.57 (m, 3H), 7.80 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{22}H_{18}N_3O_5S_3Br$ (MW) 578.9592, found *m*/*z* 578.9548 (M^+). Anal. Calcd for $C_{22}H_{18}N_3O_5S_3Br$: C, 45.52; H, 3.13; N, 7.24. Found: C, 45.46; H, 3.14; N, 7.15. The polar fraction contained the symmetric disulfide as a colorless solid (0.68 g, 19% yield). *p*-Nitrobenzyl 2-[(3*R*,4*R*)-3-bromo-4-[(3*R*′,4*R*′)-3′-bromo-1′-[2′-methyl-1′-(*p*-nitrobenzyloxycarbonyl)prop-1-enyl]-2′-oxoazetidin-4′-yldithio]-2-oxo-azetidin-1-yl]-3-methylbut-2-enoate: ^1H NMR ($CDCl_3$) δ 2.01 (s, 6H), 2.29 (s, 6H), 4.73 (d, J = 1.7 Hz, 2H), 5.06 (d, J = 1.7 Hz, 2H), 5.32 (s, 4H), 7.54 (d, J = 8.6 Hz, 4H), 8.24 (d, J = 8.6 Hz, 4H).

The resulting suspension was cooled to −20 °C. HCO_2H (360 g, 7.82 mol), Ac_2O (798 g, 7.82 mol), and pyridine (145 g, 1.83 mol) were added sequentially maintaining the temperature below −10 °C. The mixture was cooled to −20 °C. Ph_3P (473 g, 1.80 mol) was added in portions over a period of 10 min maintaining the temperature between −15 and −10 °C. After being stirred at −15 to −10 °C for further 1 h, the resulting suspension was cooled to −30 °C and then filtered. The residual solid was rinsed with cold (−30 °C) toluene (500 mL). The combined filtrate was washed successively with a mixture of ice−water (2 L), ice-cold brine (0.26 L), and $NaHCO_3$ solution (2 × 2.6 L). The organic layer was dried ($MgSO_4$) and evaporated. The residue was applied to silica gel (6 kg) column chromatography and eluted with EtOAc−hexane (1:2), and the title compound was crystallized from a cold 2-propanol (800 mL). The solid was filtered off, washed with a cold 2-propanol (400 mL), air-dried for 1 h, and dried over P_2O_5 in vacuo at rt overnight. The title compound **19** was obtained as a reddish-yellow crystalline solid (567 g, 72% yield). The obtained material was used for next reaction as is: mp 107−108 °C (EtOAc−hexane); $[\alpha]^{20}_D$ +63.22 (*c* 0.007, $CHCl_3$); IR (KBr) 1780, 1723, 1682, 1519, 1344 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.30 (s, 3H), 4.82 (d, J = 1.9 Hz, 1H), 5.32 and 5.38 (AB, J = 13.3 Hz, 2H), 5.81 (d, J = 1.9 Hz, 1H), 7.61 (d, J = 8.6 Hz, 2H), 8.25 (d, J = 8.6 Hz, 2H), 10.09 (s, 1H); HRMS (EI) calcd for $C_{16}H_{15}N_2O_6SBr$ (MW) 441.9834, found *m*/*z* 441.9831 (M^+). Anal. Calcd for $C_{16}H_{15}N_2O_6SBr$: C, 43.35; H, 3.41; N, 6.32. Found: C, 43.21; H, 3.43; N, 6.22.

***p*-Nitrobenzyl(5*R*,6*S*)-6-Bromo-7-oxo-4-thia-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (12).** Compound **19** (300 g, 0.68 mol) was dissolved in EtOAc (7.5 L) and cooled to −70 °C. Ozonized oxygen was passed through the reaction mixture for ca. 1.5 h until a blue color persisted. The solution was purged with nitrogen for 2.5 h and treated with $P(OMe)_3$ (383 mL, 3.25 mol) at −70 °C. The mixture was warmed slowly and stirred at ambient temperature for 17 h. The solution was then heated to gentle reflux for 45 min. After cooling to rt, the mixture was diluted with EtOAc (1.25 L) and washed with water (2 × 2.5 L) and then brine (2.5 L). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure at 25 °C. The residual solid was triturated with EtOAc (0.6 L). Hexane (0.45 L) was added dropwise to this mixture over 50 min. The separated solid was filtered off, and the filter cake was washed with EtOAc−hexane (1:1, 2 × 200 mL) and then EtOAc−hexane (1:2, 300 mL). The solid was air-dried for 1 h and dried in vacuo overnight at rt. Bromopenem **12** (109.6 g, 42% yield) was obtained as a pale-brown crystalline solid. The obtained material was quantified and used for next reaction as it is. A small portion of the material was further triturated with EtOAc for structure assignment to obtain a colorless crystalline solid [cont 100% by HPLC (system F)]: mp 148−151 °C; $[\alpha]^{20}_D$ +41.69 (*c* 0.004, $CHCl_3$); IR (KBr) 1791, 1723, 1516, 1328 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (d, J = 1.5 Hz, 1H), 5.29 and 5.43 (AB, J = 13.5 Hz, 2H), 5.81 (d, J = 1.5 Hz, 1H), 7.37 (s, 1H), 7.60 (d, J = 8.7 Hz, 2H), 8.25 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{13}H_9N_2O_5SBr$ (MW) 383.9416, found *m*/*z* 383.9417 (M^+). Anal. Calcd for $C_{13}H_9N_2O_5SBr$: C, 40.54; H, 2.36; N, 7.27. Found: C, 40.57; H, 2.44; N, 7.15.

Stability of *p*-Methoxybenzyl Bromopenem 7 and *p*-Nitrobenzyl Bromopenem 12 in a Solid State. Each of the bromopenems **7** and **12** were weighed accurately (∼10 mg) into light-resistant vials (1 mL × 14) and allowed to stand at 40 °C for 14 days. Samples were quantified by HPLC (condition F) on 1, 2, 4, 7, and 14 days. Each remaining ratio (%) was shown as follows.

7: 100% (initial), 99.7% (1 d), 95.3% (2 d), 72.9% (4 d), 69.8% (7 d).

12: 100% (initial), 100% (1 d), 99.6% (2 d), 100% (4 d), 98.7% (7 d), 98.4% (14 d).

***p*-Nitrobenzyl (5*R*,6*S*)-6-Bromo-6-[(*R*)-hydroxy-(2,3-dihydroimidazo[2,1-*b*]thiazol-6-yl)methyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (13a), by Using Ph_2NLi.** *n*-BuLi (7.5 mL, 12 mmol, 1.57 M in hexane) was added to a dry THF solution (24 mL) of Ph_2NH (2030 mg, 12 mmol) at −40 °C. The mixture was cooled to −78 °C, and a dry THF (76 mL) solution of bromopenem **12** (3080 mg, 8 mmol) was added to the Ph_2NLi solution over a period of 5 min. After being stirred for 5 min, the vigorously stirred mixture was treated, in one portion, with a dry MeCN solution (51 mL) of aldehyde **6** (1360 mg, 8.8 mmol). The reaction mixture was stirred for 1.5 h at −78 °C, quenched with aqueous solution of NH_4Cl, and extracted with EtOAc. The organic layer was separated and washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The HPLC analysis (system H) of the crude product showed the product was a mixture of four diastereomers in the ratio of **13a**/**13b**/**13c**/**13d** = 57:21:16:6. The residue was applied to silica gel column chromatography and eluted with EtOAc−hexane (1:2 to 1:1) to obtain **13a** as a pale-yellow amorphous solid (357 mg, 8% yield): $[\alpha]^{20}_D$ +146.03 (*c* 0.0039, MeCN); IR (KBr) 1790, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61 (brd, J = 6.0 Hz, 1H), 3.80−3.84 (m, 2H), 4.13−4.17 (m, 2H), 5.26 and 5.48 (AB, J = 13.5 Hz, 2H), 5.51 (brd, J = 6.0 Hz, 1H), 6.13 (s, 1H), 7.07 (s, 1H), 7.44 (s, 1H), 7.62 (d, J = 8.8 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H); HRMS (FAB) calcd for $C_{19}H_{16}N_4O_6S_2Br$ (MW + H) 538.9695, found *m*/*z* 538.9695 (M^+ + H).

***p*-Nitrobenzyl (5*R*,6*S*)-6-Bromo-6-[(*R*)-acetoxy(2,3-dihydroimidazo[2,1-*b*]thiazol-6-yl)methyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (14a).** To a stirred CH_2Cl_2 (2 mL) solution of bromohydrin **13a** (148 mg, 0.275 mmol) were added pyridine (22 mg, 0.275 mmol), Ac_2O (28 mg, 0.275 mmol), and DMAP (3 mg, 0.025 mmol) at rt successively. The reaction mixture was stirred for 3 h at rt. The mixture was diluted with $CHCl_3$ and washed with dilute $NaHCO_3$ solution, saturated NH_4Cl solution, and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was applied to silica gel column chromatography and eluted with EtOAc−hexane (1:2 to 1:1) to obtain **14a** as yellow viscous oil (145 mg, 91% yield): $[\alpha]^{20}_D$ +127.44 (*c* 0.0045, $CHCl_3$); IR (KBr) 1798, 1753, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (s, 3H), 3.76−3.86 (m, 2H), 4.10−4.21 (m, 2H), 5.27 and 5.45 (AB, J = 13.6 Hz, 2H), 6.08 (s, 1H), 6.79 (s, 1H), 6.91 (s, 1H), 7.44 (s, 1H), 7.59−7.65 (m, 2H), 8.24 (d, J = 8.6 Hz, 2H); HRMS (FAB) calcd for $C_{21}H_{18}N_4O_7S_2Br$ (MW + H) 580.9800, found *m*/*z* 580.9775 (M^+ + H).

***p*-Nitrobenzyl (5*R*,6*S*)-6-Bromo-6-[(*S*)-hydroxy(2,3-dihydroimidazo[2,1-*b*]thiazol-6-yl)methyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (13b), by Using Anhydrous $MgBr_2$ and Et_3N.** To a stirred solution of anhydrous $MgBr_2$ (1100 mg, 6 mmol) in dry MeCN (40 mL) was added the aldehyde **6** (826 mg, 5.5 mmol) under an argon atmosphere at rt. A white solid deposited over 30 min. A dry THF solution (40 mL) of bromopenem **12** (1950 mg, 5 mmol) was added, and the mixture was cooled to −20 °C. Et_3N (1.68 mL, 12 mmol) was added to the mixture in one portion. The reaction vessel was covered with foil to exclude light. The reaction mixture was stirred for 2.5 h at −20 °C. The reaction mixture was diluted with EtOAc and washed with 5% citric acid aqueous solution, saturated $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and filtered through a pad of Celite. The pad was washed with EtOAc. The filtrate was concentrated under reduced pressure. The HPLC and LC−MS analyses (system H and G) of the crude product showed the product was a mixture of four diastereomers in the ratio of **13a**/**13b**/**13c**/**13d** = 11:85:2:1. The residue was applied to silica gel column chromatography and eluted with EtOAc−hexane (1:2 to 1:1) to give **13b** as a pale-yellow amorphous solid (452 mg, 17% yield): $[\alpha]^{20}_D$ +105.1 (*c* 0.0039, $CHCl_3$); IR (KBr) 1794, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72−3.88 (m, 3H), 4.13−4.25 (m, 2H), 5.22 (brd, J = 4.4 Hz, 1H), 5.28 and 5.46 (AB, J = 13.5 Hz, 2H), 6.12 (s, 1H), 7.11 (s, 1H), 7.41 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 8.25 (d, J = 8.6 Hz, 2H); HRMS (FAB) calcd for $C_{19}H_{16}N_4O_6S_2Br$ (MW + H) 538.9695, found *m*/*z* 538.9645 (M^+ + H). The mixed fraction contained the diastereomeric mixtures of **13a** and **13b** (1044 mg, 39% yield).

***p*-Nitrobenzyl (5*R*,6*S*)-6-Bromo-6-[(*S*)-acetoxy(2,3-dihydroimidazo[2,1-*b*]thiazol-6-yl)methyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (14b).** To a stirred solution of bromohydrin **13b** (120 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) were added Ac_2O (35 mg, 0.3 mmol), pyridine (27 mg, 0.3 mmol), and DMAP (2.5 mg, 0.02 mmol) at 0 °C successively. The reaction mixture was warmed to rt and stirred for 16 h. The mixture was diluted with EtOAc and washed with 1 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was applied to silica gel column chromatography and eluted with EtOAc−hexane (1:1) to obtain **14b** as a yellow amorphous solid (89 mg, 69% yield): $[\alpha]^{20}_D$ +266.3 (*c* 0.0036, $CHCl_3$); IR (KBr) 1798, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H), 3.76−3.86 (m, 2H), 4.10−4.21 (m, 2H), 5.27 and 5.45 (AB, J = 13.6 Hz, 2H), 6.23 (s, 1H), 6.30 (s, 1H), 7.15 (s, 1H), 7.48 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 8.24 (d, J = 8.6 Hz, 2H); HRMS (FAB) calcd for $C_{21}H_{18}N_4O_7S_2Br$ (MW + H) 580.9800, found *m*/*z* 580.9764 (M^+ + H).

Sequential Synthesis of *p*-Nitrobenzyl (5*R*)-6-Bromo-6-[acetoxy(2,3-dihydroimidazo[2,1-*b*]thiazol-6-yl)methyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate 14 by Using Ph_2NLi (Table 1, Entry 1). A dry THF (4 mL) solution of bromopenem **12** (154 mg, 0.4 mmol) was cooled to −78 °C under an argon atmosphere. The reaction vessel was covered with foil to exclude light. Ph_2NLi, prepared by adding *n*-BuLi (0.33 mL, 1.57 M in hexane) to a dry THF solution (1 mL) of Ph_2NH (88 mg, 0.52 mmol) at −40 °C, was added to the vigorously stirred suspension in one portion. After being stirred for 5 min, the vigorously stirred mixture was treated, in one portion, with a dry MeCN solution (3 mL) of aldehyde **6** (75 mg, 0.49 mmol). The reaction mixture was stirred for 1 h at −78 °C and treated with Ac_2O (53 mg, 0.52 mmol) in one portion. The reaction mixture was warmed to 0 °C and stirred for 1 h at 0 °C. The mixture was diluted with EtOAc and washed with water and brine. LC−MS and HPLC analyses (system G and H) of the organic layer showed **14** was formed in 43% yield as a mixture of four diastereomers in the ratio of **14a**/**14b**/**14c**/**14d** = 40:22:25:13 (2:1:1:0.2 by ^1H NMR). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was applied to silica gel column chromatography and eluted with EtOAc−hexane (1:2 to 1:1) to obtain **14** as two diastereomeric mixture (**14a**/**14b** = 4:1, a yellow amorphous solid, 58 mg, 25% yield) along with the PNB ester of thiazole-4-carboxylic acid **15** (a yellow solid, 32 mg, 30% yield).

14: ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H × 1/5), 2.24 (s, 3H × 4/5), 3.76−3.86 (m, 2H), 4.10−4.21 (m, 2H), 5.27 and 5.45 (AB, J = 13.6 Hz, 2H), 6.08 (s, 1H × 4/5), 6.23 (s, 1H × 1/5), 6.30 (s, 1H × 1/5), 6.79 (s, 1H × 4/5), 6.91 (s, 1H × 4/5), 7.15 (s, 1H × 1/5), 7.44 (s, 1H × 4/5), 7.48 (s, 1H × 1/5), 7.59−7.65 (m, 2H), 8.24 (d, J = 8.6 Hz, 2H).

15: mp 173−174 °C; IR (KBr) 1728, 1511, 1343 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.51 (s, 2H), 7.64 (d, J = 8.7 Hz, 2H), 8.25 (d, J = 8.7 Hz, 2H), 8.32 (d, J = 2.0 Hz, 1H), 8.89 (d, J = 2.0 Hz, 1H); HRMS (FAB) calcd for $C_{11}H_9N_2O_4S$ (MW + H) 265.0283, found *m*/*z* 265.0294 (M^+ + H). Anal. Calcd for $C_{11}H_8N_2O_4S$: C, 50.00; H, 3.05; N, 10.60. Found: C, 50.02; H, 3.19; N, 10.45.

Sequential Synthesis of *p*-Nitrobenzyl (5*R*)-6-Bromo-6-[acetoxy(2,3-dihydroimidazo[2,1-*b*]thiazol-6-yl)methyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate 14 by Using Ph_2NLi and $MgBr_2$·Et_2O (Table 1, Entry 2). $MgBr_2$·Et_2O (335 mg, 1.3 mmol) was added to a dry THF (12 mL) solution of bromopenem **12** (385 mg, 1.0 mmol) under an argon atmosphere at rt. The suspension was cooled to −78 °C. The reaction vessel was covered with foil to exclude light. Ph_2NLi, prepared by adding *n*-BuLi (0.87 mL, 1.57 M in hexane) to a dry THF solution (4 mL) of Ph_2NH (220 mg, 1.3 mmol) at −20 °C, was added to the vigorously stirred suspension in one portion. After 15−20 s, the vigorously stirred mixture was treated, in one portion, with a dry MeCN solution (5 mL) of aldehyde **6** (170 mg, 1.1 mmol). The reaction mixture was stirred for 1 h at −78 °C and treated with Ac_2O (133 mg, 1.3 mmol) in one portion. The reaction mixture was warmed to 0 °C and stirred for 1 h at 0 °C. The mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. LC−MS and HPLC analyses (system G and H) of the crude product showed **14** was formed in 90% yield as a mixture of four diastereomers in the ratio of **14a**/**14b**/**14c**/**14d** = 14:82:2:1. The residue was applied to silica gel column chromatography and eluted with EtOAc−hexane (1:2 to 1:1) to obtain **14** as two diastereomeric mixture (**14a**/**14b** = 1:6 by ^1H NMR, a colorless amorphous solid, 447 mg, 77% yield): ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H × 6/7), 2.24 (s, 3H × 1/7), 3.76−3.86 (m, 2H), 4.10−4.21 (m, 2H), 5.27 and 5.45 (AB, J = 13.6 Hz, 2H), 6.08 (s, 1H × 1/7), 6.23 (s, 1H × 6/7), 6.30 (s, 1H × 6/7), 6.79 (s, 1H × 1/7), 6.91 (s, 1H × 1/7), 7.15 (s, 1H × 6/7), 7.44 (s, 1H × 1/7), 7.48 (s, 1H × 6/7), 7.59−7.65 (m, 2H), 8.24 (d, J = 8.6 Hz, 2H).

Sequential Synthesis of *p*-Nitrobenzyl (5*R*)-6-Bromo-6-[acetoxy(2,3-dihydroimidazo[2,1-*b*]thiazol-6-yl)methyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate 14 by Using Anhydrous $MgBr_2$ and Et_3N (Table 2, Entry 2). Aldehyde **6** (88 mg, 0.57 mmol) was added to a dry MeCN (4 mL) solution of anhydrous $MgBr_2$ (115 mg, 0.62 mmol) under an argon atmosphere at rt, and a colorless powder deposited over 30 min. A dry THF solution (4 mL) of bromopenem **12** (200 mg, 0.52 mmol) was added, and the mixture was cooled to −20 °C. Et_3N (0.17 mL, 1.25 mmol) was added to the mixture in one portion. The reaction vessel was covered with foil to exclude light. The reaction mixture was stirred for 3 h at −20 °C and treated with Ac_2O (106 mg, 1.04 mmol) in one portion. The reaction mixture was warmed to 0 °C and stirred for 16 h at 0 °C. The mixture was diluted with EtOAc and washed with 5% citric acid aqueous solution, saturated $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and filtered through a pad of Celite. The pad was washed with EtOAc. HPLC and LC−MS analysis (system H and G) of the organic layer showed **14** was produced in 90% yield as a mixture of four diastereomers in the ratio of **14a**/**14b**/**14c**/**14d** = 5:60:1:1. The filtrate was concentrated under reduced pressure. The residue was applied to silica gel column chromatography and eluted with EtOAc−hexane (1:2 to 1:1) to

obtain **14** as two diastereomeric mixture (**14a**/**14b** = 1:10 by ^{1}H NMR, a pale-yellow amorphous solid, 257 mg, 85% yield): ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3H × 10/11), 2.24 (s, 3H × 1/11), 3.76−3.86 (m, 2H), 4.10−4.21 (m, 2H), 5.27 and 5.45 (AB, J = 13.6 Hz, 2H), 6.08 (s, 1H × 1/11), 6.23 (s, 1H × 10/11), 6.30 (s, 1H × 10/11), 6.79 (s, 1H × 1/11), 6.91 (s, 1H × 1/11), 7.15 (s, 1H × 10/11), 7.44 (s, 1H × 1/11), 7.48 (s, 1H × 10/11), 7.59−7.65 (m, 2H), 8.24 (d, J = 8.6 Hz, 2H).

***p*-Nitrobenzyl (5*R*,6*S*)-6-Bromo-6-[(*S*)-*p*-nitrobenzoyloxy(2,3-dihydroimidazo[2,1-*b*]thiazol-6-yl)methyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (16).** Aldehyde **6** (1.24 g, 8.0 mmol) was added to a dry MeCN (50 mL) solution of anhydrous $MgBr_2$ (1.61 g, 8.8 mmol) under an argon atmosphere at rt. Colorless powder deposited over 30 min. A dry THF solution (45 mL) of bromopenem **12** (2.80 g, 7.3 mmol) was added, and the mixture was cooled to −20 °C. Et_3N (2.43 mL, 17.5 mmol) was added in one portion, and the reaction vessel was covered with foil to exclude light. The reaction mixture was stirred for 2.5 h at −20 °C and treated with a dry THF solution (5 mL) of the *p*-nitrobenzoyl chloride (2.03 g, 10.9 mmol) in one portion. The reaction mixture was warmed to 0 °C and stirred for 1 h at this temperature and subsequently diluted with EtOAc. The organic layer was washed with 5% citric acid aqueous solution, saturated $NaHCO_3$, and brine. It was dried ($MgSO_4$) and filtered through a pad of Celite. The pad was washed with EtOAc. The filtrate was concentrated under reduced pressure. The residue was applied to silica gel column chromatography and eluted with $CHCl_3$ to obtain **16** as a colorless crystalline solid (663 mg, 13% yield). The material was recrystallized several times from EtOA−DMF, and a single crystal was obtained. The stereochemistry was supported by an X-ray crystallographic structure determination: mp 153−156 °C dec; $[\alpha]^{20}_D$ +327.1 (*c* 0.0037, DMF); IR (KBr) 1779, 1730, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.77−3.86 (m, 2H), 4.11−4.24 (m, 2H), 5.26 and 5.43 (AB, 2H, J = 13.5 Hz), 6.41 (s, 1H), 6.51 (s, 1H), 7.26 (s, 1H), 7.58−7.60 (m, 3H), 8.09−8.12 (m, 2H), 8.20−8.22 (m, 4H); HRMS (FAB) calcd for $C_{26}H_{19}N_5O_9S_2Br$ (MW + H) 687.9808, found *m*/*z* 678.9781 (M^+ + H). Anal. Calcd for $C_{26}H_{18}N_5O_9S_2Br$: C, 45.36; H, 2.64; N, 10.17. Found: C, 45.15; H, 2.66; N, 10.07.

General Procedure for $MgBr_2$/Et_3N-Promoted Aldol-Type Condensation (Table 3). To a dry MeCN mixture of aldehyde (1.1−3 molar equiv) and anhydrous $MgBr_2$ (1.2−4 molar equiv) was added a dry THF solution of bromopenem **12** under a nitrogen atmosphere at rt. The reaction mixture was cooled to −20 °C, and Et_3N (2.4−4 molar equiv) was added in one portion. The reaction vessel was covered with foil to exclude light. The mixture was stirred for 3 to 4 h at −20 °C. The mixture was diluted with EtOAc and washed with water, saturated $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to obtain an isolated aldol adduct.

***p*-Nitrobenzyl (5*R*,6*S*)-6-Bromo-6-[(*R*)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (17a).** The stereochemistry was supported by an X-ray crystallographic structure determination. Single isomer: pale-yellow crystals; mp 148−151 °C dec ($CHCl_3$−hexane); $[\alpha]^{20}_D$ +9.26 (*c* 0.00396, $CHCl_3$); IR (KBr) 1784, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J = 6.1 Hz, 3H), 2.40 (d, J = 5.1 Hz, 1H), 4.36−4.41 (m, 1H), 5.29 and 5.45 (AB, J = 13.4 Hz, 2H), 5.98 (s, 1H), 7.37 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H); HRMS (FAB) calcd for $C_{15}H_{13}N_2NaO_6SBr$ (MW + Na) 450.9575, found *m*/*z* 450.9540 (M^+ + Na). Anal. Calcd for $C_{15}H_{13}N_2O_6SBr$: C, 41.97; H, 3.05; N, 6.53. Found: C, 41.60; H, 3.03; N, 6.41.

***p*-Nitrobenzyl (5*R*)-6-Bromo-6-[1-hydroxy-2-methylpropyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (17b).** Single isomer: pale-yellow amorphous solid; $[\alpha]^{20}_D$ +52.78 (*c* 0.00396, $CHCl_3$); IR (KBr) 1782, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.99−1.06 (m, 1H), 1.78 (ddd, J = 3.9, 10.2, 14.2 Hz, 1H), 1.92−1.98 (m, 1H), 2.26 (d, J = 5.2 Hz, 1H), 4.27 (dd, J = 5.2, 10.2 Hz, 1H), 5.29 and 5.46 (AB, J = 13.4 Hz, 2H), 5.97 (s, 1H), 7.38 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H); HRMS (FAB) calcd for $C_{18}H_{20}N_2O_6SBr$ (MW + H) 471.0225, found *m*/*z* 471.0186 (M^+ + H).

***p*-Nitrobenzyl (5*R*,6*S*)-6-Bromo-6-[(*R*)-hydroxyphenylmethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (17c).** The stereochemistry was supported by an X-ray crystallographic structure determination. Single isomer: pale-yellow crystals; mp 160−163 °C dec ($CHCl_3$−EtOAc); $[\alpha]^{20}_D$ +64.78 (*c* 0.00372, $CHCl_3$); IR (KBr) 1782, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.96 (brs, 1H), 5.30 and 5.47 (AB, J = 13.5 Hz, 2H), 5.44 (s, 1H), 6.04 (s, 1H), 7.37−7.44 (m, 4H), 7.49−7.53 (m, 2H), 7.62 (d, J = 8.7 Hz, 2H), 8.25 (d, J = 8.7 Hz, 2H); HRMS (FAB) calcd for $C_{20}H_{16}N_2O_6SBr$ (MW + H) 490.9912, found *m*/*z* 490.9907 (M^+ + H).

***p*-Nitrobenzyl (5*R*)-6-Bromo-6-(1-hydroxy-3-phenylallyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (17d).** Single isomer: pale-yellow amorphous solid; $[\alpha]^{20}_D$ +123.74 (*c* 0.00396, $CHCl_3$); IR (KBr) 1794, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.63 (d, J = 5.1 Hz, 1H), 4.95 (dd, J = 5.1, 7.0 Hz, 1H), 5.29 and 5.46 (AB, J = 13.4 Hz, 2H), 5.96 (s, 1H), 6.22 (dd, J = 6.0, 7.0 Hz, 1H), 6.84 (d, J = 6.0 Hz, 1H), 7.29−7.38 (m, 3H), 7.38−7.44 (m, 3H), 7.60 (d, J = 8.6 Hz, 2H), 8.24 (d, J = 8.6 Hz, 2H); HRMS (FAB) calcd for $C_{22}H_{17}N_2O_6SBrNa$ (MW + Na) 538.9888, found *m*/*z* 538.9913 (M^+ + Na).

4-Formyl-2-phenylimidazole-1-carboxylic Acid 4-Nitrobenzyl Ester. The title aldehyde was synthesized from 4-formyl-2-phenylimidazole by a conventional procedure using *p*-nitrobenzyl chloroformate: colorless solid; mp 122−125 °C; IR (KBr) 3153, 1760, 1689, 1515, 1398, 1347, 985 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.40 (s. 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.41−7.52 (m, 3H), 7.56−7.58 (m, 2H), 8.18−8.21 (m, 2H), 8.22 (s, 1H), 9.97 (s, 1H); HRMS (EI) calcd for $C_{18}H_{13}N_3O_5$ (MW) 351.0855, found *m*/*z* 351.0855 (M^+).

***p*-Nitrobenzyl (5*R*)-6-Bromo-6-[hydroxy[1-(*p*-nitrobenzyloxycarbonyl)-2-phenyl-1*H*-imidazol-4-yl]methyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (17e).** Diastereomeric mixture: pale-yellow amorphous solid; IR (KBr) 1794, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.84 (d, J = 6.6 Hz, 1H × 0.54), 3.49 (d, J = 6.1 Hz, 1H × 0.07), 3.75 (d, J = 6.1 Hz, 1H × 0.13), 3.86 (d, J = 8.5 Hz, 1H × 0.26), 5.21−5.64 (m, 5H), 6.13 (s, 1H × 0.26), 6.15 (s, 1H × 0.54), 6.40 (s, 1H × 0.07), 6.50 (s, 1H × 0.13), 7.32−7.73 (m, 11H), 8.18−8.25 (m, 4H); HRMS (FAB) calcd for $C_{31}H_{23}N_5O_{10}SBr$ (MW + H) 736.0349, found *m*/*z* 736.0317 (M^+ + H).

***p*-Nitrobenzyl (5*R*)-6-Bromo-6-(hydroxythiazol-2-ylmethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (17f).** Single isomer: colorless amorphous solid; mp 83−85.5 °C dec; $[\alpha]^{20}_D$ +233.91 (*c* 0.00369, $CHCl_3$); IR (KBr) 1783, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.26 (d, J = 6.5 Hz, 1H), 5.29 and 5.47 (AB, J = 13.4 Hz, 2H), 5.83 (d, J = 6.5 Hz, 1H), 6.19 (s, 1H), 7.40 (d, J = 3.2 Hz, 1H), 7.46 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 3.2 Hz, 1H), 8.24 (d, J = 8.8 Hz, 2H); HRMS (FAB) calcd for $C_{17}H_{13}N_3O_6S_2Br$ (MW + H) 497.9429, found *m*/*z* 497.9453 (M^+ + H).

Sodium (5*R*)-(*Z*)-6-(2,3-Dihydroimidazo[2,1-*b*]thiazol-6-ylmethylene)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (5), Prepared from Bromopenem 12. Aldehyde **6** (110.1 g, 0.714 mol) was added to a dry MeCN (5 L) solution of anhydrous $MgBr_2$ (143.4 g, 0.779 mol) under an argon atmosphere at rt. Colorless powder deposited over a period of 30 min. A dry THF solution (5 L) of bromopenem **12** (250 g, 0.649 mol) was transferred to the suspension via a PTFE tube under positive argon pressure over 12 min. After the reaction mixture was cooled to −20 °C, Et_3N (217 mL, 1.557 mol) was added in one portion. The reaction vessel was covered with foil to exclude light. The reaction mixture was stirred for 3 h at −20 °C and treated with Ac_2O (133 g, 1.303 mol) in one portion. The reaction mixture was warmed to 0

°C and stirred for 16 h at 0 °C. The mixture was diluted with EtOAc (20 L) and washed with 5% citric acid (10 L) aqueous solution, saturated $NaHCO_3$ (10 L), and brine (10 L). The organic layer was dried ($MgSO_4$) and filtered through a pad of Celite. The pad was washed with EtOAc (1.4 L). The filtrate was concentrated under reduced pressure at 30 °C. The residual brown oil contains 327 g (87% yield) of **14** from HPLC assay (system G). The resulting oil was used for the next reaction as is.

The residual brown oil of **14** was dissolved in THF (5.4 L) and MeCN (2.5 L). Freshly activated zinc dust (1.5 kg) was added rapidly with 0.5 M phosphate buffer (pH 6.5, 7.9 L). The reaction vessel was covered with foil to exclude light. The reaction mixture was vigorously stirred for 2.5 h maintaining the temperature about 35 °C. The mixture was cooled to 3 °C, and an ice-cold 1 M NaOH (ca. 1750 mL) was added to adjust pH to 8 at below 3 °C. The mixture was diluted with EtOAc (4 L) and filtered through a pad of Celite. The pad was washed with water (2.5 L), and the aqueous layer was separated. The aqueous layer, containing 150 g of **5** (81% yield from **14**, 70% yield from **12**) from the HPLC assay (system C), was concentrated to 8.85 kg (ca. 8 L) under high vacuum at 35 °C.

The concentrate was applied to Sepabeads SP-207 (7 L, Mitsubishi Kasei Co. Ltd.) resin column chromatography. After absorbing, the column was eluted with water (14 L) and then with 20% MeCN−water to give the purified active fractions of the title compound.

The combined fractions were concentrated to 1.25 kg (ca. 1 L) under high vacuum at 35 °C. Acetone (2.5 L) was added to the concentrate with stirring at rt. The mixture was cooled to 3 °C and then stirred for 30 min. Acetone was added to the mixture in 625 mL portions every 30 min over a period of 4 h at 3 °C (total 5 L of acetone). After the mixture was stirred for 1 h at 3 °C, the solid was filtered off, and the filter cake was washed with acetone (800 mL). The solid was air-dried under excluding light for 1 h and dried in vacuo overnight at rt to give **5** (112 g, HPLC area ratio 100%, contents 96.5% (system C), 100% ee by chiral HPLC (system D), 57% yield from **14**, 50% yield from **12**) as a yellow crystalline solid. A small portion of the solid was further purified by recrystallization to obtain a pure material (HPLC contents, 100%): mp 208 °C dec; $[\alpha]^{20}_D$ +521.4 (*c* 0.0053, H_2O); IR (KBr) 1752, 1679 cm^{-1}; ^1H NMR (D_2O) δ 3.80 (t, J = 7.4 Hz, 2H), 4.14−4.20 (m, 2H), 6.42 (s, 1H), 6.82 (s, 1H), 6.96 (s, 1H), 7.42 (s, 1H); HRMS (FAB) calcd for $C_{12}H_8N_3O_3S_2Na_2$ (MW + Na) 351.9802, found *m*/*z* 351.9815 (M^+ + Na). Anal. Calcd for $C_{12}H_8N_3O_3S_2Na\cdot 1.2H_2O$: C, 41.07; H, 2.99; N, 11.96. Found: C, 41.06; H, 2.91; N, 11.96.

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Supporting Information Available: HPLC analytic conditions, ^1H NMR spectra of all compounds, chiral HPLC charts of compounds **5** and **9**, and ORTEP drawings of compounds **16**, **17a**, and **17c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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