Design, Synthesis, and SAR of Novel Carbapenem Antibiotics with High Stability to *Xanthomonas maltophilia* Oxyiminocephalosporinase Type II

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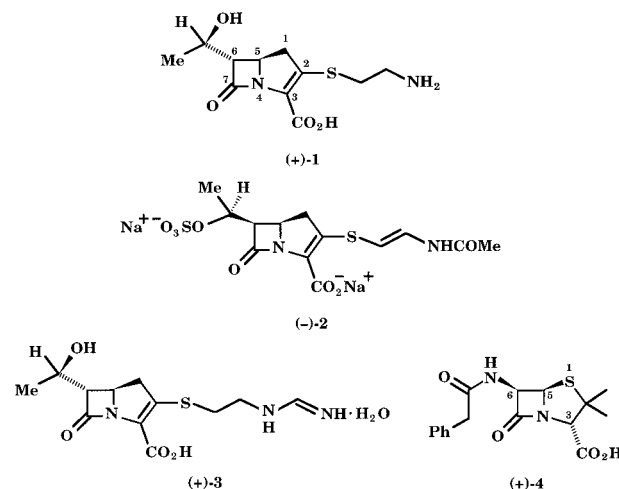
Racemic *cis*-6-(phenylacetamido)carbapenem **(21)**, 2-hydroxycarbonyl-*cis*-6-(phenylacetamido)-carbapenem **(22)**, 2-methoxycarbonyl-*cis*-6-(phenylacetamido)carbapenem **(30)**, 2-methoxycarbomethyl-*cis*-6-(phenylacetamido)carbapenem **(33)**, 2-hydroxyethyl-*cis*-6-(phenylacetamido)-carbapenem **(34)**, and 2-acetoxyethyl-*cis*-6-(phenylacetamido)carbapenem **(35)** were synthesized. Formation of the carbapenem nuclei in **21**, **22**, and **30** involved dehydrophosphonation of the corresponding 2-diphenylphosphono-6-(phenylacetamido)carbapenam precursors **14**, **15**, and **28** using trimethylsilyl triflate and 1,8-diazabicyclo[5.4.0]undec-7-ene in THF. Syntheses of carbapenems **33**−**35** involved a Wittig reaction of carbapenam **14** with methyl glyoxylate in the presence of lithium 2,2,6,6-tetramethylpiperidine in THF. For the antibacterial activities against *Staphylococcus aureus* FDA 209P, *S. aureus* 95, *Escherichia coli* ATCC 39188, *Klebsiella pneumoniae* NCTC 418, *Pseudomonas aeruginosa* 1101-75, and *P. aeruginosa* 18S-H, carbapenems (±)-**21**, (±)-**22**, (±)-**30**, and (±)-**33**−**35** were found comparable with imipenem ((+)-**3**), yet they were notably more potent than (+)-**3** against *Xanthomonas maltophilia* GN 12873. On the other hand, unlike (+)-**3**, carbapenems (±)-**21**, (±)-**22**, (±)-**30**, and (±)-**33**−**35** were stable to *X. maltophilia* oxyiminocephalosporinase type II. Their β-lactamase inhibitory properties, however, were found to be more comparable with those of penicillin G ((+)-**4**) than to those of imipenem ((+)-**3**). A combination of imipenem ((+)-**3**) with (±)-**21**, (±)-**22**, (±)-**30**, and (±)-**33**−**35** resulted in synergistic antibacterial activity against *X. maltophilia* GN 12873. Results from the biological tests were correlated with the distribution of the electron density at C_2=C_3 of carbapenems upon reaction with transpeptidases or β-lactamases.

Introduction

Thienamycin ((+)-**1**), isolated from *Streptomyces* spp, is the first naturally occurring compound containing the carbapenem nucleus.[1−3] Subsequently, many carbapenem derivatives (i.e., imipenem ((+)-**3**)),[6−10] have been discovered and some of them are the epimers of thienamycin (i.e., olivanic acid ((−)-**2**)).[4,5]

Two major differences exist between carbapenems and penicillins (e.g., penicillin G ((+)-**4**)). First, the sulfur atom in penicillins is absent in carbapenems, where a more strained azetidinone four-membered ring (A-ring) is fused with a pyrroline nucleus (B-ring). Second, the side chain at the C-6 position of most carbapenems possesses the trans configuration to the pyrroline nucleus, but the C-6 substituent in penicillins has a cis configuration to the 1,3-azathiolane nucleus.

Xanthomonas maltophilia produces oxyiminocephalosporinases type I (CXase-I) and type II (CXase-II).[11,12] β-Lactamase CXase-II can destroy all known carbapenems.[13a] Up to now, none of the structural modifica-

tions have been found to be successful in protecting the carbapenems against CXase-II.[13a]

Herein we report the synthesis of a new class of carbapenems that have antibacterial as well as β-lactamase inhibitory properties. They include *cis*-6-(phenylacetamido)carbapenems (±)-**21**, (±)-**22**, (±)-**30**, and (±)-**33**−**35**. A key finding of this work is that unlike other carbapenems (e.g., imipenem ((+)-**3**)), these new compounds were found to be resistant to CXase-II.

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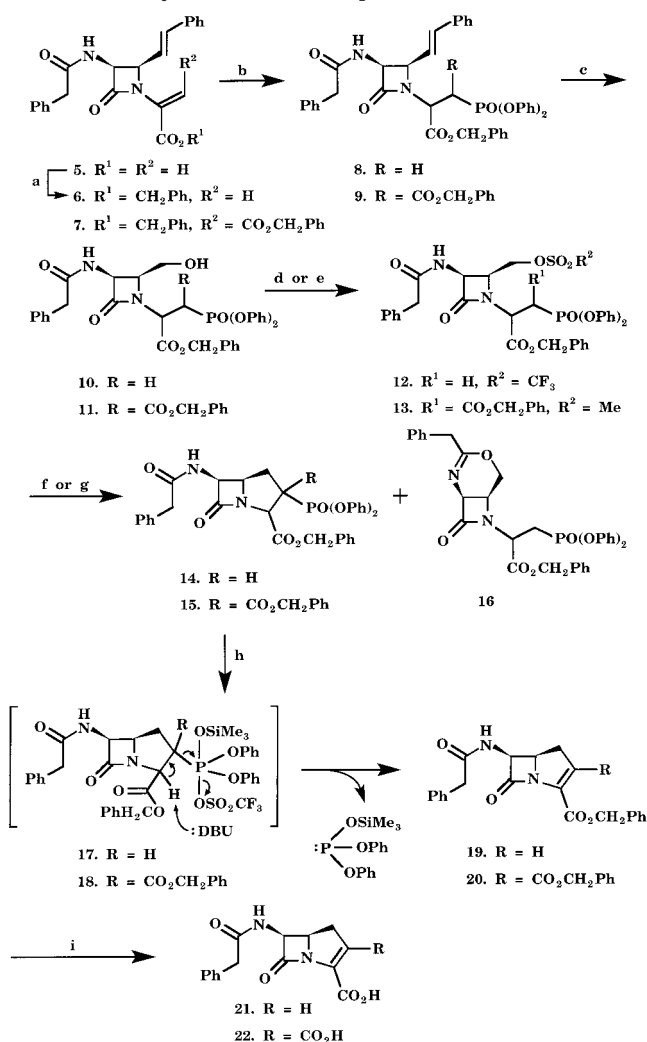† Institute of Chemistry, Academia Sinica.
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Scheme 1. Synthesis of Carbapenems **21** and **22**[a]

5. $R^1 = R^2 = H$
6. $R^1 = CH_2Ph, R^2 = H$
7. $R^1 = CH_2Ph, R^2 = CO_2CH_2Ph$

8. R = H
9. $R = CO_2CH_2Ph$

10. R = H
11. $R = CO_2CH_2Ph$

12. $R^1 = H, R^2 = CF_3$
13. $R^1 = CO_2CH_2Ph, R^2 = Me$

14. R = H
15. $R = CO_2CH_2Ph$

16

17. R = H
18. $R = CO_2CH_2Ph$

19. R = H
20. $R = CO_2CH_2Ph$

21. R = H
22. $R = CO_2H$

[a] Reagents: (a) PhCH$_2$Br, K$_2$CO$_3$, DMF (90%); (b) (PhO)$_2$POH, NaH(cat.), THF, **6** → **8** (96%), **7** → **9** (80%); (c) 1. O$_3$, MeOH, 2. NaBH$_4$, **8** → **10** (80%), **9** → **11** (85%); (d) CF$_3$SO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$, **10** → **12** (90%); (e) MeSO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$, **11** → **13** (95%); (f) LiTMP, THF, **12** → **14** (30%) + **16** (65%); (g) DBU, THF, **13** → **15** (90%); (h) Me$_3$SiOSO$_2$CF$_3$, DBU, THF, **14** → **19** (40%), **15** → **20** (65%); (i) PdCl$_2$, H$_2$ (50 psi), EtOAc, **19** → **21** (70%), **20** → **22** (68%).

Results

Synthesis of Carbapenems (±)-21 and (±)-22 (Scheme 1). We treated racemic azetidione acrylic acid **5**[14] with benzyl bromide and K$_2$CO$_3$ in DMF to produce the corresponding benzyl ester **6** in 90% yield. Acrylate **6** and fumarate **7**[15] were converted to the corresponding diastereoisomeric phosphonates **8** (95% yield) and **9** (80% yield), respectively, using diphenyl phosphite and a catalytic amount of NaH in THF. Ozonolysis of the styryl groups in **8** and **9**, followed by reductive workup, gave alcohols **10** (80% yield) and **11** (85% yield), respectively. Sulfonation of alcohol **10** with trifluoromethanesulfonyl chloride and Et$_3$N in CH$_2$Cl$_2$ produced triflate **12** in 90% yield. Subsequently, reaction of **12** with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) in THF gave a mixture of carbapenam **14** (30% yield) and phosphonate **16** (65% yield). With a mesylate functionality in place of the triflate group in **12**, we also obtained a mixture of **14** (20% yield) and **16** (70% yield). On the other hand, the reaction of **12** with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) exclusively gave the undesired

Scheme 2. Synthesis of Carbapenem **30**[a]

23

24. R = OH
25. $R = OSO_2Me$

26

27

28

29. $R = CH_2Ph$
30. R = H
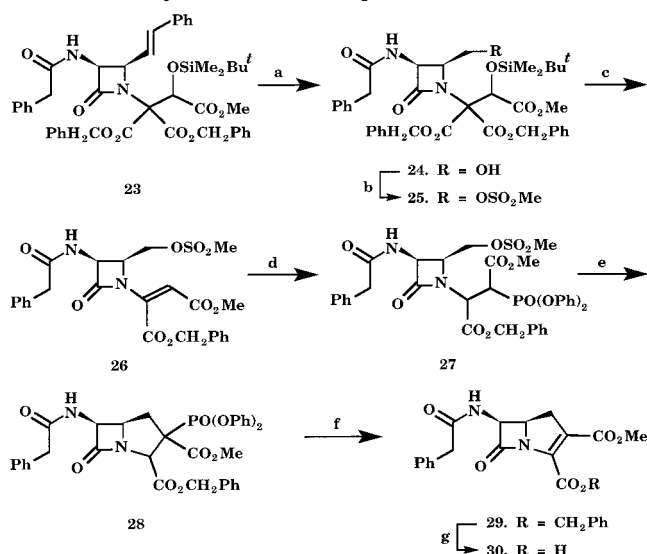
[a] Reagents: (a) 1. O$_3$, MeOH, 2. NaBH$_4$ (75%); (b) MeSO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$ (95%); (c) Pd/C, H$_2$ (40 psi), DBU, EtOAc (66%); (d) (PhO)$_2$ POH, NaH(cat.), THF (85%); (e) DBU, THF (87%); (f) Me$_3$SiOSO$_2$CF$_3$, DBU, THF (70%); (g) PdCl$_2$, H$_2$ (50 psi), EtOAc (80%).

phosphonate **16** (90% yield). Treatment of alcohol **11** with methanesulfonyl chloride and Et$_3$N in CH$_2$Cl$_2$ generated methanesulfonate **13** in 95% yield. Monocyclic β-lactam **13**, however, produced the desired carbapenam **15** (90% yield) exclusively upon treatment with DBU in THF. Thus, the difference in cyclization behavior between **12** and **13** is mainly due to a more stabilized anion derived from **13**.

Dehydrophosphonation of carbapenam **14** by use of trimethylsilyl trifluoromethanesulfonate and DBU in THF gave the corresponding carbapenem **19** in 40% yield, presumably via the intermediate **17**. By the same method, carbapenam **15** was successfully converted to **20** in 65% yield via **18**. Hydrogenolysis of **19** and **20**, by use of PdCl$_2$ in EtOAc at 50 psi of H$_2$, gave the target carbapenems (±)-**21** (70% yield) and (±)-**22** (68% yield), respectively.
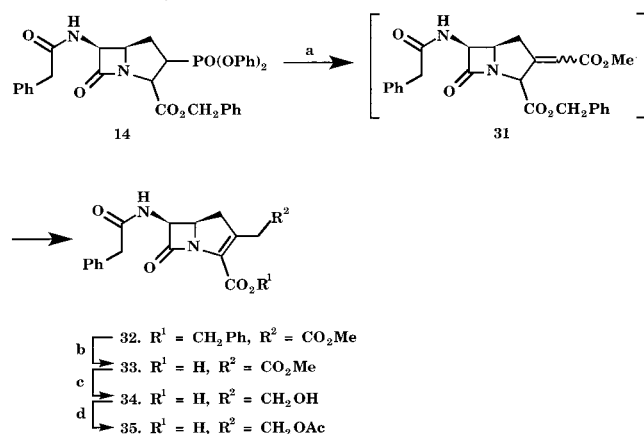
Synthesis of 2-(Methoxycarbonyl)carbapenem (±)-30 (Scheme 2). For the preparation of carbapenem (±)-**30**, we ozonolyzed diastereoisomeric β-lactam **23**[16] in MeOH to produce the corresponding aldehyde. Without isolation, the aldehyde was subsequently treated with NaBH$_4$ to give alcohol **24** in 75% overall yield. Reaction of **24** with methanesulfonyl chloride and Et$_3$N in CH$_2$Cl$_2$ gave methanesulfonate **25** in 95% yield. Hydrogenolysis of **25** by use of Pd/C and H$_2$ (40 psi) in the presence of DBU and EtOAc afforded β-lactam **26** in 66% yield through elimination. The ^{1}H NMR spectrum of β-lactam **26** indicates the two ester functionalities therein are cis to each other on the basis of the chemical shift of the olefinic proton at δ 5.62 (s, 1 H, =CHCO$_2$Me). The olefinic proton appears at higher field (δ ∼5.47−5.68) in maleate in comparison with that of the corresponding fumarate at δ ∼6.56−6.84.[17,18]

Reaction of maleate **26** with diphenyl phosphite and a catalytic amount of NaH in THF gave phosphonate adduct **27** in 85% yield. By using DBU in THF, we accomplished the cyclization of monocyclic β-lactam **27** to give bicyclic β-lactam **28** in 87% yield. Dehydrophos-

Table 1. Minimum Inhibitory Concentrations[a] (MIC, μg/mL) of Carbapenems ($\pm$)-**21**, ($\pm$)-**22**, ($\pm$)-**30**, and ($\pm$)-**33**−**35** as Well as the Reference Compounds (+)-**3** and (+)-**4** against Microorganisms

	S. aureus		*E. coli*	*K. pneumoniae*	*P. aeruginosa*		*X. maltophilia*[d]
β-lactam	FDA 209P	95[b,c]	ATCC 39188	NCTC 418	1101-75	18S-H[b]	GN 12873
(+)-**3**	0.020 ± 0.004	15.65 ± 1.71	0.35 ± 0.02	0.40 ± 0.03	4.71 ± 0.62	35.61 ± 4.17	>128
(+)-**4**	0.510 ± 0.010	>128	2.87 ± 0.42	>128	>128	>128	>128
(±)-**21**	0.120 ± 0.002	30.70 ± 2.80	0.98 ± 0.15	1.92 ± 0.12	8.91 ± 1.02	31.58 ± 2.70	10.27 ± 1.36
(±)-**22**	0.030 ± 0.012	13.87 ± 0.91	0.48 ± 0.03	0.56 ± 0.02	5.63 ± 0.90	28.16 ± 3.09	9.61 ± 1.02
(±)-**30**	0.010 ± 0.001	8.30 ± 1.01	0.20 ± 0.01	0.15 ± 0.01	0.89 ± 0.10	12.10 ± 0.93	12.13 ± 1.81
(±)-**33**	0.040 ± 0.004	18.53 ± 2.60	0.67 ± 0.06	0.77 ± 0.09	1.80 ± 0.25	21.30 ± 2.98	5.97 ± 0.58
(±)-**34**	0.070 ± 0.011	19.23 ± 3.43	0.75 ± 0.22	0.88 ± 0.10	3.51 ± 0.78	22.64 ± 3.07	6.73 ± 0.65
(±)-**35**	0.050 ± 0.003	14.92 ± 1.21	0.69 ± 0.08	1.08 ± 0.28	2.87 ± 0.50	17.21 ± 2.10	4.12 ± 0.30

[a] The lowest concentrations of antibiotics needed for the prevention of visible growth of microorganisms, reported as the average values of duplicate determinations (±standard error). MIC values were obtained by use of an agar dilution method whereby organisms were deposited onto medicated agar plates by the replication device of Steers et al.[20] [b] β-Lactamase-producing organism. [c] Methicillin-resistant organism. [d] Oxyiminocephalosporinases type I- and type II-producing organism.

Scheme 3. Synthesis of Carbapenems **33**−**35**[a]

- b ┌ **32.** R^1 = CH_2Ph, R^2 = CO_2Me
- c ├ **33.** R^1 = H, R^2 = CO_2Me
- d ├ **34.** R^1 = H, R^2 = CH_2OH
-   └ **35.** R^1 = H, R^2 = CH_2OAc

[a] Reagents: (a) $MeCO_2CHO$, LiTMP, THF (45%); (b) $PdCl_2$, H_2 (50 psi), EtOAc (77%); (c) $NaBH_4$, THF, H_2O (30%); (d) CH_3COCl, Et_3N, CH_2Cl_2 (90%).

phonation of carbapenam **28** with $Me_3SiOSO_2CF_3$ and DBU in THF produced carbapenem **29** in 70% yield. Finally, hydrogenolysis of **29** at 50 psi of H_2 in the presence of $PdCl_2$ in EtOAc afforded the desired carbapenem ($\pm$)-**30** in 80% yield.

Synthesis of 2-(Methoxycarbonylmethyl)carbapenem ($\pm$)-33, 2-(Hydroxyethyl)carbapenem ($\pm$)-34, and 2-(Acetoxyethyl)carbapenem ($\pm$)-35 (Scheme 3). To condense methyl glyoxylate with racemic carbapenam **14**, we applied LiTMP in THF at −30 °C. The resultant carbapenem **32** was obtained in 45% yield through C−C double bond migration in the intermediate **31**. Debenzylation of **32** at 50 psi of H_2 in the presence of $PdCl_2$ in EtOAc afforded carbapenem ($\pm$)-**33** in 77% yield. Reduction of the ester group in **33** with $NaBH_4$ in wet THF gave hydroxyethylcarbapenem ($\pm$)-**34** in 30% yield. Finally, acetylation of the hydroxyl functionality in **34** with acetyl chloride and Et_3N in CH_2Cl_2 produced the desired acetoxyethylcarbapenem ($\pm$)-**35** in 90% yield.

Biological Activity. We carried out the screening experiments in vitro for the antibacterial activity of the carbapenems ($\pm$)-**21**, ($\pm$)-**22**, ($\pm$)-**30**, and ($\pm$)-**33**−**35**.[19,20] Imipenem ((+)-**3**) and penicillin G ((+)-**4**) were used as reference compounds. The results are summarized in Table 1.

Minimum inhibitory concentrations were also determined for the newly synthesized carbapenems ($\pm$)-**21**, ($\pm$)-**22**, ($\pm$)-**30**, and ($\pm$)-**33**−**35** in combination (1:1 w/w)

Table 2. Minimum Protective Concentrations[a] (MPC, μg/mL) of Carbapenems ($\pm$)-**21**, ($\pm$)-**22**, ($\pm$)-**30**, and ($\pm$)-**33**−**35** as Well as the Reference Compounds (+)-**3** and (+)-**4** against β-Lactamases

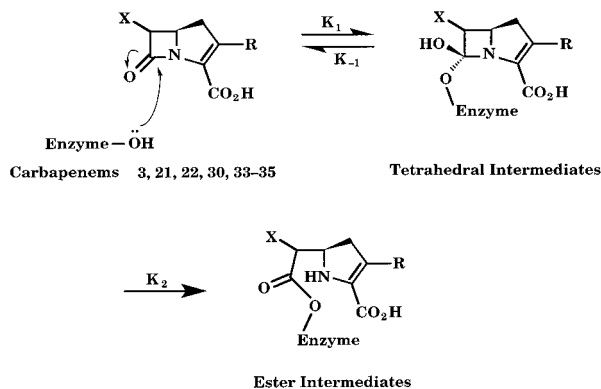|	β-lactamase of		β-lactamase of *X. maltophilia* GN 12873	
compd[b]	*S. aureus* 95	*P. aeruginosa* 18S-H	CXase-I	CXase-II
(+)-**3**	30.12 ± 3.30	35.61 ± 6.40	46.78 ± 7.01	0.87 ± 0.03
(+)-**4**	1.85 ± 0.30	1.03 ± 0.18	23.56 ± 3.24	28.84 ± 2.13
(±)-**21**	3.45 ± 0.70	4.21 ± 1.01	29.98 ± 3.12	33.64 ± 4.95
(±)-**22**	2.20 ± 0.18	2.38 ± 0.77	25.50 ± 4.09	29.43 ± 2.97
(±)-**30**	0.98 ± 0.06	1.02 ± 0.09	14.61 ± 0.78	16.73 ± 1.56
(±)-**33**	6.87 ± 0.94	8.74 ± 1.40	30.36 ± 3.06	34.97 ± 2.89
(±)-**34**	7.18 ± 0.76	6.98 ± 1.06	36.74 ± 4.02	42.15 ± 3.93
(±)-**35**	6.12 ± 0.55	5.87 ± 0.42	27.48 ± 2.11	47.83 ± 4.68

[a] The average values of duplicate determinations (±standard error) for the ability of compounds to inhibit the hydrolysis of 3-[(*E*)-2,4-dinitrostyryl]-(6*R*,7*R*)-7-(2-thienylacetamido)-3-cephem-4-carboxylic acid by β-lactamases from *S. aureus* 95, *P. aeruginosa* 18S-H, and *X. maltophilia* GN 12873. MPC values, determined by the procedure of O'Callaghan et al.,[21] are the lowest concentrations of β-lactams needed to protect the indicator from hydrolysis by β-lactamases under standard test conditions within 1.0 h. The hydrolysis of indicator was evidenced by a distinct red color. [b] All compounds were stable (>15 h) in the absence of β-lactamases at 37 °C in a phosphate buffer solution (pH 6.5), except for **30**. The β-lactam ring in carbapenem **30** was destroyed within 8.0 h.

with imipenem ((+)-**3**) against *X. maltophilia* GN 12873. The values (μg/mL), expressed as mean ± standard error from two independent determinations, were 2.15 ± 0.74 for **3** + **21**, 1.58 ± 0.66 for **3** + **22**, 2.01 ± 0.85 for **3** + **30**, 0.98 ± 0.12 for **3** + **33**, 0.77 ± 0.08 for **3** + **34**, and 0.39 ± 0.10 for **3** + **35**.

Moreover, we tested the β-lactamase inhibitory properties of carbapenems ($\pm$)-**21**, ($\pm$)-**22**, ($\pm$)-**30**, and ($\pm$)-**33**−**35**. Imipenem ((+)-**3**) and penicillin G ((+)-**4**) were also used in vitro as reference compounds.[21] The results are summarized in Table 2.

Discussion

Imipenem ((+)-**3**) exhibits potent activity against a broad spectrum of pathogenic microorganisms.[7,8,22] This compound is stable to most β-lactamases,[8] yet highly susceptible to CXase-II (Table 2). Consequently, imipenem did not show activity against *X. maltophilia* (see Table 1). In contrast to imipenem, the newly synthesized carbapenems ($\pm$)-**21**, ($\pm$)-**22**, ($\pm$)-**30**, and ($\pm$)-**33**−**35** were found to be much more stable to CXase-II (see Table 2). Consequently, they showed notable activity against *X. maltophilia* (Table 1). Carbapenems ($\pm$)-**21**, ($\pm$)-**22**, ($\pm$)-**30**, and ($\pm$)-**33**−**35** share the basic carbapenem nucleus with imipenem but differ in the stereoconfigu-

Scheme 4. Mode of Action of Carbapenems with Transpeptidases or β-Lactamases

Table 3. NBO Bond Charges[a] (e) for Carbapenems **3**, **21**, **22**, **30**, and **33**−**35** and Their Model Tetrahedral Intermediates at the HF/6-31G*//HF/3-21G* Level of Theory

compd	R	carbapenems		tetrahedral intermediates
		$C_7=O$ δq	$C_2=C3$ δq	$C_2=C3$ δq
3	$S(CH_2)_2NHCH=NH$	−1.52	−0.12	−0.20
21	H	−1.51	−0.11	−0.11
22	COOH	−1.50	−0.26	−0.17
30	COOMe	−1.50	−0.23	−0.34
33	CH_2COOMe	−1.52	0.10	0.09
34	CH_2CH_2OH	−1.53	0.12	0.12
35	CH_2CH_2OAc	−1.52	0.12	0.10

^{a} $C_7=O$ $\delta q = O$ $q - C_7$ q; $C_2=C_3$ $\delta q = C_2$ $q - C_3$ q.

Figure 1. Geometries of **3**, **3a**, **30**, and **30a** fully optimized at the HF/3-21G* level.

ration of the side chain at the C-6 position. Unlike imipenem, which has a trans configuration at the C-5 and C-6 positions, the new carbapenems possess a cis configuration like penicillin G ((+)-**4**).

Apart from *X. maltophilia,* the activity of *cis*-6-(phenylacetamido)carbapenems (±)-**21**, (±)-**22**, (±)-**30**, and (±)-**33**−**35** against the other microorganisms, *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa,* is similar to that of imipenem ((+)-**3**), as shown in Table 1. Thus the common carbapenem nucleus in these compounds could play a prominent role in their biological activities. On the other hand, the β-lactamase inhibitory property of carbapenems (±)-**21**, (±)-**22**, (±)-**30**, and (±)-**33**−**35** is more comparable with that of penicillin G ((+)-**4**), indicating that the *cis*-6-phenylacetamido substituent on the β-lactam nucleus is likely to be vital for β-lactamase inhibition (see Table 2). It reduced the ability of CXase-II to destroy the β-lactam nucleus relative to imipenem. Similarly penicillin G appears to be stable to the enzyme, yet it is not active against *X. maltophilia.* This may be due to the impermeability of the outer membrane of *X. maltophilia* to penicillin G relative to carbapenems (±)-**21**, (±)-**22**, (±)-**30**, and (±)-**33**−**35**.[23,24]

The β-lactamase inhibitory property of imipenem ((+)-**3**) against CXase-II allowed it to exert a large synergistic effect on antimicrobial agents (±)-**21**, (±)-**22**, (±)-**30**, and (±)-**33**−**35**. Thus a 1:1 mixture of (+)-**3** with (±)-**21**, (±)-**22**, (±)-**30**, and (±)-**33**−**35** exhibited notable activity against *X. maltophilia* GN 12873.
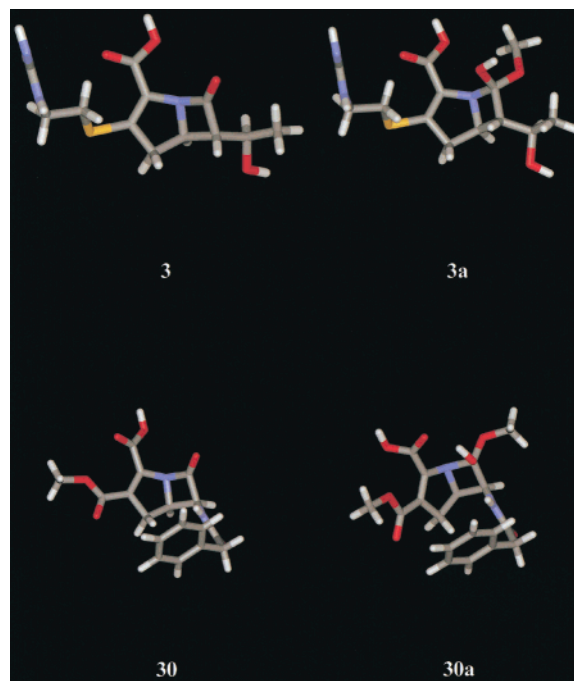
β-Lactam antibiotics (e.g., carbapenems) exert certain biological activity by acylating serine residues of transpeptidases (Scheme 4).[25] Thus, the presence of electron-withdrawing groups at the C-2 position of carbapenems may enhance the antibacterial properties. To evaluate this hypothesis, we calculated bond charges (δq's) for $C_7=O$ and $C_2=C_3$ in carbapenems **3**, **21**, **22**, **30**, and **33**−**35** as well as $C_2=C_3$ δq in the respective tetrahedral intermediates. As shown in Table 3, the nature of the substituents at the C-2 position of carbapenems did not affect the polarity of the $C_7=O$ bond: the δq's for the entire series are similar, −1.50e to −1.53e. This indicates that the susceptibility of the β-lactam ring toward nucleophilic attack by the transpeptidase or β-lactamase was not affected by electron-withdrawing or electron-donating groups at the C-2 position of carbapenems.

Changing the substituent at the C-2 position of carbapenems, however, affects the distribution of the electron density at the neighboring $C_2=C_3$ bond. For carbapenems **3**, **21**, **22**, and **30** the electron density flows toward the C-2 position (negative $C_2=C_3$ δq), while for **33**−**35** the electron density moves toward the C-3 position (positive $C_2=C_3$ δq). The highest $C_2=C_3$ δq values were calculated for carbapenems **22** (−0.26e) and **30** (−0.23e) with strong electron-withdrawing groups, CO_2H and CO_2Me, respectively. For the other carbapenems **3**, **21**, and **33**−**35**, the $C_2=C_3$ δq values were similar in magnitude (see Table 3).

As shown in Scheme 4, the reversibility of tetrahedral intermediates results in regeneration of transpeptidase or β-lactamase enzymes. However, the rate-limiting step is the breakdown of the tetrahedral intermediate to the corresponding ester, which is the first chemical step in the antibacterial activity or β-lactamase inhibitory property of β-lactams.[13] Consequently, the biological activities of carbapenems may be correlated with the $C_2=C_3$ bond polarity in the respective tetrahedral intermediates upon enzyme attack. Indeed, the ability of carbapenems (±)-**21**, (±)-**22**, (±)-**30**, and (±)-**33**−**35** to inhibit the β-lactamases of the pathogenic microorganisms in Table 2 correlates well with the $C_2=C_3$ bond polarity in their tetrahedral intermediates (Table 3). In particular, the carbapenems (±)-**21**, (±)-**22**, and (±)-**30**, whose $C_2=C_3$ δq values in the ground state as well as

for the tetrahedral intermediate are negative, inhibit the β-lactamases in Table 2 more than carbapenems ($\pm$)-**33**−**35**, whose $C_2=C_3$ bond polarities in the ground state and for the respective tetrahedral intermediates are positive. Carbapenems ($\pm$)-**33**−**35** exhibit similar β-lactamase inhibition, and their tetrahedral intermediates showed similar $C_2=C_3$ δq values (0.09e to 0.12e). The other new carbapenems exhibit increasing β-lactamase inhibition in the order: ($\pm$)-**21** < ($\pm$)-**22** < ($\pm$)-**30**, which correlates with the increasing $C_2=C_3$ bond polarity in their tetrahedral intermediates: ($\pm$)-**21** (−0.11e) < ($\pm$)-**22** (−0.17e) < ($\pm$)-**30** (−0.34e).

The ability of carbapenems (+)-**3**, ($\pm$)-**21**, ($\pm$)-**22**, and ($\pm$)-**30** to prevent growth of *S. aureus* FDA 209P and 95, *E. coli* ATCC 39188, *K. pneumoniae* NCTC 418, and *P. aeruginosa* 1101−75 (Table 1) correlates well with the $C_2=C_3$ bond polarity in their tetrahedral intermediates (Table 3). In particular, these carbapenems exhibit increasing antibacterial activity in the order: ($\pm$)-**21** (−0.11e) < ($\pm$)-**22** (−0.17e) ∼ ($\pm$)-**3** (−0.20e) < ($\pm$)-**30** (−0.34e). Nevertheless, carbapenems ($\pm$)-**33**−**35** exhibit greater antibacterial activity than carbapenem ($\pm$)-**21** even though their tetrahedral intermediates have *positive* $C_2=C_3$ bond polarities. In contrast to other carbapenems, ($\pm$)-**21** has a hydrogen at the C-2 position. Thus, a substituent at the C-2 position of carbapenems may be essential for effective interaction with the target enzyme,[13a] such as penicillin-binding proteins.

Our results indicate that enhancement of the antibacterial activity or β-lactamase inhibitory property of electronically activated carbapenems is probably due to reduction of the reversibility of tetrahedral intermediates, which facilitates the formation of ester intermediates.

Conclusions

A series of new carbapenems were synthesized by chemical methods and their structure−activity relationship (SAR) was explored. These compounds include ($\pm$)-*cis*-6-(phenylacetamido)carbapenem **(21)**, ($\pm$)-2-hydroxycarbonyl-*cis*-6-(phenylacetamido)carbapenem **(22)**, ($\pm$)-2-methoxycarbonyl-*cis*-6-(phenylacetamido)carbapenem **(30)**, ($\pm$)-2-methoxycarbomethyl-*cis*-6-(phenylacetamido)-carbapenem **(33)**, ($\pm$)-2-hydroxyethyl-*cis*-6-(phenylacetamido)-carbapenem **(34)**, and ($\pm$)-2-acetoxyethyl-*cis*-6-(phenylacetamido)-carbapenem **(35)**. Results from the biological tests indicate that the carbapenems **21**, **22**, **30**, and **33**−**35** were reasonably stable to *X. maltophilia* oxyiminocephalosporinase type II (CXase-II). Thus, they showed notable activity against *X. maltophilia.* Moreover, all of these newly synthesized carbapenems were found to be active against *S. aureus* FDA 209P, *E. coli* ATCC 39188, *K. pneumoniae* NCTC 418, and *P. aeruginosa* 1101-75 as well as the β-lactamase producing organism *P. aeruginosa* 18S-H and methicillin-resistant organism *S. aureus* 95.

The A-ring in the synthesized carbapenems is structurally similar to that of penicillin G ((+)-**4**); the B-ring therein is identical to that of imipenem ((+)-**3**). These new carbapenems exhibited imipenem-like antibacterial activity and penicillin G-like β-lactamase inhibitory property. Thus, the antibacterial spectrum of ($\pm$)-**21**, ($\pm$)-**22**, ($\pm$)-**30**, and ($\pm$)-**33**−**35** may have its origin in the structural features of the B-ring. Their β-lactamase inhibitory property, however, may have resulted from the feature of the A-ring and its C-6 substituent with a cis configuration. Moreover, a combination of imipenem ((+)-**3**) and carbapenems ($\pm$)-**21**, ($\pm$)-**22**, ($\pm$)-**30**, and ($\pm$)-**33**−**35** in a ratio of 1:1 (w/w) was found to possess notable activity against *X. maltophilia* GN 12873 in vitro.

Results from the biological tests were also correlated with the distribution of the $C_2=C_3$ electron density of carbapenem tetrahedral intermediates. We found that the antibacterial activity and the β-lactamase inhibitory property of carbapenems are enhanced substantially by possessing a potential electron-withdrawing group at the C-2 position.

Experimental Section

General. For anhydrous reactions, glassware was dried overnight in an oven at 120 °C and cooled in a desiccator over anhydrous $CaSO_4$ or silica gel. Reagents purchased from Fluka Chemical Co. Solvents, including dry ether and tetrahydrofuran (THF), were obtained by distillation from the sodium ketyl of benzophenone under nitrogen. Other solvents, including chloroform, dichloromethane, ethyl acetate, and hexanes were distilled over CaH_2 under nitrogen. Absolute methanol and ethanol were purchased from Merck and used as received.

Melting points were obtained with a Büchi 510 melting point apparatus. Infrared (IR) spectra were recorded on a Beckman IR-8 spectrophotometer. The wavenumbers reported are referenced to the 1601 cm^{-1} absorption of polystyrene. Proton NMR spectra were obtained on a Varian XL-300 (300 MHz) spectrometer. Chloroform-*d* and dimethyl sulfoxide-d_6 were used as solvents; Me_4Si (δ 0.00) was used as an internal standard. All NMR chemical shifts are reported as δ values in parts per million (ppm) and coupling constants (*J*) are given in hertz (Hz). The splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, unresolved multiplet due to the field strength of the instrument; and dd, doublet of doublets. Mass spectra were carried out on a VG 70-250 S mass spectrometer. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer.

Purification on silica gel refers to gravity column chromatography on Merck silica gel 60 (particle size 230−400 mesh). Analytical TLC was performed on precoated plates purchased from Merck (silica gel 60 F_{254}). Compounds were visualized by use of UV light, I_2 vapor, or 2.5% phosphomolybdic acid in ethanol with heating.

Ab initio calculations were carried out by using the Gaussian 98 program.[26] Full geometry optimization of carbapenems **3**, **21**, **22**, **30**, and **33**−**35** was performed at the HF/3-21G* level. Structures of the respective tetrahedral intermediates in Scheme 4, modeled by replacing the covalently bound serine of the enzyme with MeOH, were also optimized at the same level. The geometries of *cis*-carbapenem **30** and its tetrahedral intermediate **30a** as well as the *trans*-carbapenem **3** and its respective tetrahedral intermediate **3a** are shown in Figure 1. Single-point HF/6-31G* calculations were carried out to evaluate the natural bond orbital (NBO) partial atomic charges.[27] The results were analyzed in terms of a bond charge (δq), which is defined as the difference between the atomic charges of the terminal and initial atoms of a given bond: $\delta q = q_t - q_i$. The bond charge can be regarded as a measure of the chemical bond polarity.

($\pm$)-**Benzyl 2-(*cis*-2-Oxo-3-phenylacetamido-4-styryl-1-azetidinyl)acrylate (6).** To a solution containing β-lactam ($\pm$)-**5** (3.76 g, 10.0 mmol) in DMF (40 mL) were added anhydrous K_2CO_3 (2.07 g, 15.0 mmol) and benzyl bromide (1.71 g, 10.0 mmol). The solution was stirred at 25 °C for 12 h, then partitioned between Et_2O (150 mL) and water (200 mL). The organic layer was washed with H_2O (3 × 200 mL), dried over $MgSO_4(s)$, filtered, and concentrated under reduced pressure. The crude product was purified by use of column chromatography (CH_2Cl_2 as eluant) to give ($\pm$)-**6** (4.19 g, 8.99 mmol) in

90% yield: mp (recrystallized from MeOH) 129−131 °C; ^{1}H NMR (CDCl$_3$) δ 3.50 (s, 2H, CH$_2$CO), 4.61−4.70 (m, 1H, HC-(4)), 5.28 (s, 2H, CH$_2$O), 5.55 (dd, J = 10.0, 5.0 Hz, 1H, HC-(3)), 5.82 (s, 1H, CH=C), 6.07 (s, 1H, CH=C), 6.00−6.88 (m, 3H, CH=CH + NH), 7.01−7.38 (m, 15H, 3 × Ph); IR (CH$_2$Cl$_2$) 3300 (NH), 1765 (β-lactam), 1730 (ester), 1670 (amide) cm^{-1}. Anal. (C$_{29}$H$_{26}$N$_2$O$_4$) C, H, N.

(±)-**Benzyl 2-(*cis*-2-Oxo-3-phenylacetamido-4-styryl-1-azetidinyl)-3-diphenylphosphonopropionate (8).** To a solution containing (±)-**6** (4.66 g, 10.0 mmol) and diphenyl phosphite (2.34 g, 10.0 mmol) in dry THF (70 mL) was added a catalytic amount of NaH at 0 °C. After the solution was stirred at 0 °C for 1.0 h, Et$_2$O (60 mL) was added and the solution was washed with water (2 × 100 mL). The organic layer was then dried over MgSO$_4$(s), filtered, and concentrated under reduced pressure. The crude product was purified by use of column chromatography (CHCl$_3$ as eluant) to give (±)-**8** (6.66 g, 9.50 mmol) as an oil in 95% yield: ^{1}H NMR (CDCl$_3$) δ 2.43−2.79 (m, 2H, CH$_2$P), 3.45 (s, 2H, CH$_2$CO), 4.50−4.62 (m, 1H, CHCO$_2$), 4.65−4.93 (m, 1H, HC(4)), 5.26 (br s, 2H, CH$_2$O), 5.60 (dd, J = 9.4, 5.0 Hz, 1H, HC(3)), 5.89−6.92 (m, 2H, CH=CH), 6.98−7.68 (m, 25H, 5 × Ph), 7.78 (d, J = 9.4 Hz, 1H, NH); IR (CH$_2$Cl$_2$) 3420 (NH), 1760 (β-lactam), 1740 (ester), 1680 (amide) cm^{-1}. Anal. (C$_{41}$H$_{37}$N$_2$O$_7$P) C, H, N.

(±)-**Dibenzyl 2-(*cis*-2-Oxo-3-phenylacetamido-4-styryl-1-azetidinyl)-3-diphenylphosphonosuccinate (9).** Compound **9** (6.67 g, 8.00 mmol) was prepared as a foam in 80% yield from **7** (6.00 g, 10.0 mmol), diphenyl phosphite (2.34 g, 10.0 mmol), and a catalytic amount of NaH in dry THF (70 mL) by the method used for the synthesis of **8** from **6**: ^{1}H NMR (CDCl$_3$) δ 3.31 (br d, J = 20.0 Hz, 1H, CHP), 3.51 (br s, 2H, CH$_2$CO), 4.68 (d, J = 6.8 Hz, 1H, CHCO$_2$), 4.66−4.75 (m, 1H, HC(4)), 5.17 (s, 2H, CH$_2$O), 5.29 (s, 2H, CH$_2$O), 5.60 (dd, J = 10.0, 5.0 Hz, 1H, HC(3)), 5.90−6.91 (m, 2H, CH=CH), 7.00−7.67 (m, 30H, 6 × Ph), 7.80 (br d, J = 10.0 Hz, 1H, NH); IR (CH$_2$Cl$_2$) 3410 (NH), 1765 (β-lactam), 1743−1730 (esters), 1680 (amide) cm^{-1}. Anal. (C$_{49}$H$_{43}$N$_2$O$_9$P) C, H, N.

(±)-**Benzyl 2-(*cis*-2-Oxo-3-phenylacetamido-4-hydroxymethyl-1-azetidinyl)-3-diphenylphosphonopropionate (10).** Ozone was passed through a solution of (±)-**8** (0.70 g, 1.0 mmol) in MeOH (40 mL) at −78 °C for 1.0 h. After the solution was purged with N$_2$, NaBH$_4$ (0.19 g, 5.0 mmol) was added at −20 °C. After 1.0 h of stirring, 5% HCl aqueous solution (3.0 mL) was added and the solution was partitioned between EtOAc (40 mL) and water (50 mL). The organic layer was dried over MgSO$_4$(s), filtered, and concentrated under reduced pressure. The crude product was purified by use of column chromatography (EtOAc as eluant) to give (±)-**10** (0.50 g, 0.80 mmol) as a foam in 80% yield: ^{1}H NMR (CDCl$_3$) δ 2.41−2.76 (m, 2H, CH$_2$P), 3.47 (s, 2H, CH$_2$CO), 3.60−4.25 (m, 4H, CH$_2$OH + HC(4)), 4.49−4.82 (m, 1H, CHCO$_2$), 5.15 (s, 2H, CH$_2$O), 5.17 (s, 2H, CH$_2$O), 5.56 (2 dd, J = 10.0, 5.0 Hz, 1H, HC(3)), 7.01−7.63 (m, 20H, 4 × Ph), 7.76 (br s, 1H, NH); IR (CH$_2$Cl$_2$) 3435−3340 (OH, NH), 1758 (β-lactam), 1735 (ester), 1680 (amide) cm^{-1}. Anal. (C$_{34}$H$_{33}$N$_2$O$_8$P) C, H, N.

(±)-**Dibenzyl 2-(*cis*-2-Oxo-3-phenylacetamido-4-hydroxymethyl-1-azetidinyl)-3-diphenylphosphonosuccinate (11).** Compound **11** (0.65 g, 0.85 mmol) was prepared as a foam in 85% yield from **9** (0.84 g, 1.0 mmol) by the method used for the synthesis of **10** from **8**: ^{1}H NMR (CDCl$_3$) δ 3.38 (br d, J = 22.0 Hz, 1H, CHP), 3.57 (br s, 2H, CH$_2$CO), 3.69−4.39 (m, 4H, CH$_2$CO + HC(4)), 4.70 (d, J = 7.0 Hz, 1H, CHCO$_2$), 5.15 (br s, 2H, CH$_2$O), 5.25 (br s, 2H, CH$_2$O), 5.42 (dd, J = 8.5, 5.0 Hz, 1H, HC(3)), 7.10−7.62 (m, 25H, 5 × Ph), 7.70 (br s, 1H, NH); IR (CH$_2$Cl$_2$) 3420−3355 (OH, NH), 1768 (β-lactam), 1745 (esters), 1680 (amide) cm^{-1}. Anal. (C$_{42}$H$_{39}$N$_2$O$_{10}$P) C, H, N.

(±)-**Benzyl 2-[*cis*-2-Oxo-3-phenylacetamido-4-(trifluoromethanesulfonyl)oxymethyl-1-azetidinyl]-3-diphenylphosphonopropionate (12).** To a solution containing (±)-**10** (0.63 g, 1.0 mmol) and Et$_3$N (0.20 g, 2.0 mmol) in CH$_2$Cl$_2$ (30 mL) was added CF$_3$SO$_2$Cl (0.17 g, 1.0 mmol) at −5 °C. After the solution was stirred for 1.0 h, it was washed with water (30 mL). The organic layer was dried over MgSO$_4$(s), filtered, and concentrated under reduced pressure. Purification of the

residue by use of column chromatography (CHCl$_3$ as eluant) gave (±)-**12** (0.68 g, 0.90 mmol) as an oil in 90% yield: ^{1}H NMR (CDCl$_3$) δ 2.42−2.84 (m, 2H, CH$_2$P), 3.47 (s, 2H, CH$_2$CO), 4.42−4.49 (br m, 1H, HC(4)), 4.52−4.68 (m, 1H, CHCO$_2$), 4.80−4.91 (br, 2H, CH$_2$OSO$_2$), 5.20 (br s, 2H, CH$_2$O), 5.63 (dd, J = 9.5, 5.0 Hz, 1H, HC(3)), 7.15−7.50 (m, 20H, 4 × Ph), 7.70 (br s, 1H, NH); IR (CH$_2$Cl$_2$) 3410 (NH), 1780 (β-lactam), 1745 (ester), 1680 (amide) cm^{-1}. Anal. (C$_{35}$H$_{32}$N$_2$O$_{10}$F$_3$PS) C, H, N, S.

(±)-**Dibenzyl 2-[*cis*-2-Oxo-3-phenylacetamido-4-(methanesulfonyl)oxymethyl-1-azetidinyl]-3-diphenylphosphonosuccinate (13).** Compound **13** (0.80 g, 0.95 mmol) was prepared in 95% yield from **11** (0.76 g, 1.0 mmol) by the same method used for the synthesis of **12** from **10** except that MeSO$_2$Cl (0.12 g, 1.0 mmol) was used to replace CF$_3$SO$_2$Cl: ^{1}H NMR (CDCl$_3$) δ 2.80, 2.83 (2 s, 3H, SO$_2$CH$_3$), 3.36 (br d, J = 22.0 Hz, 1H, CHP), 3.59 (br s, 2H, CH$_2$CO), 3.99−4.16 (br, 2H, CH$_2$OSO$_2$), 4.30−4.51 (m, 1H, HC(4)), 4.70 (br, 1H, CHCO$_2$), 5.10 (s, 2H, CH$_2$O), 5.20 (s, 2H, CH$_2$O), 5.43 (dd, J = 8.5, 5.0 Hz, 1H, HC(3)), 7.15−7.60 (m, 25H, 5 × Ph), 7.69−7.76 (br, 1H, NH); IR (CH$_2$Cl$_2$) 3410 (NH), 1771 (β-lactam), 1750−1740 (esters), 1685 (amide) cm^{-1}. Anal. (C$_{43}$H$_{41}$N$_2$O$_{12}$-PS) C, H, N, S.

(±)-**Benzyl (2*RS*,3*RS*,5*RS*,6*SR*)-7-Oxo-6-(phenylacetamido)-3-diphenylphosphono-1-azabicyclo[3.2.0]heptane-2-carboxylate (14)** and (±)-**Benzyl 2-{2-[*a*-Benzyl]-6-oxoazetidino[3,2-*d*]-4a,6a-dihydro[1,3]oxazin-5-yl}diphenylphosphonopropionate (16).** To a stirred solution containing triflate (±)-**12** (0.76 g, 1.0 mmol) in dry THF (20 mL) was added a THF solution of LiTMP (2.8 mL, 1.2 mmol) dropwise under an argon atmosphere at −20 °C. The reaction mixture was warmed to 25 °C within 2.0 h; then it was partitioned between EtOAc (40 mL) and water (50 mL). The organic layer was dried over MgSO$_4$(s), filtered, and concentrated under reduced pressure. Purification of the residue by use of column chromatography (CH$_2$Cl$_2$/CHCl$_3$ (1:1)) gave bicyclic β-lactam (±)-**16** (0.40 g, 0.65 mmol) as an oil in 65% yield. Further elution of the column with CHCl$_3$/EtOAc (4:1) afforded carbapenam (±)-**14** (0.18 g, 0.30 mmol) as a foam in 30% yield.

For (±)-**14**: ^{1}H NMR (CDCl$_3$) δ 1.95 (ddd, J = 12.9, 5.9, 5.5 Hz, 1H, HC(4)), 2.12 (ddd, J = 13.3, 12.9, 9.4 Hz, 1H, HC(4)), 2.56−2.70 (m, 1H, HC(3)), 3.46 (br s, 2H, CH$_2$CO), 3.98−4.21 (m, 1H, HC(5)), 4.60−4.72 (m, 1H, HC(2)), 5.14 (2 dd, J = 9.6, 4.9 Hz, 1H, HC(6)), 5.27 (br s, 2H, CH$_2$O), 7.10−7.56 (m, 20H, 4 × Ph), 7.69 (br s, 1H, NH); IR (CH$_2$Cl$_2$) 3405 (NH), 1780 (β-lactam), 1740 (ester), 1681 (amide) cm^{-1}; CI-MS 611 (M$^+$ + 1); MS m/e 435 (M$^+$ − PhCH$_2$CONHCH=C=O). Anal. (C$_{34}$H$_{31}$N$_2$O$_7$P) C, H, N.

For (±)-**16**: ^{1}H NMR (CDCl$_3$) δ 2.45−2.69 (m, 2H, CH$_2$P), 3.52 (s, 2H, CH$_2$), 3.90−4.08 (br m, 2H, OCH$_2$), 4.51−4.71 (m, 1H, CHCO$_2$), 4.70−5.25 (m, 2H, NCHCH), 5.20 (s, 2H, CH$_2$-OCO), 7.20−7.55 (m, 20H, 4 × Ph); IR (CH$_2$Cl$_2$) 1779 (β-lactam), 1742 (ester) cm^{-1}. Anal. (C$_{34}$H$_{31}$N$_2$O$_7$P) C, H, N.

(±)-**Dibenzyl (2*RS*,3*RS*,5*RS*,6*SR*)-7-Oxo-6-(phenylacetamido)-3-diphenylphosphono-1-azabicyclo[3.2.0]-heptane-2,3-dicarboxylate (15).** A solution containing mesylate (±)-**13** (0.84 g, 1.0 mmol) and DBU (0.16 g, 1.1 mmol) in THF (20 mL) was heated at reflux for 3.0 h. Then EtOAc (40 mL) was added and the solution was washed with water (2 × 50 mL), dried over MgSO$_4$(s), filtered, and concentrated under reduced pressure. Purification of the residue by use of flash chromatography (EtOAc/hexane (1:1)) afforded (±)-**15** (0.67 g, 0.90 mmol) in 90% yield: ^{1}H NMR (CDCl$_3$) δ 1.98 (dd, J = 13.5, 6.0 Hz, 1H, HC(4)), 2.20 (dd, J = 13.5, 11.0 Hz, 1H, HC(4)), 3.50 (s, 2H, CH$_2$CO), 3.95−4.18 (m, 1H, HC(5)), 4.50, 4.52 (2 s, 1H, HC(2)), 5.01−5.19 (m, 1H, HC(6)), 5.25 (s, 2H, CH$_2$O), 5.35 (s, 2H, CH$_2$O), 6.98−7.70 (m, 26H, 5 × Ph + NH); IR (CH$_2$Cl$_2$) 3410 (NH), 1782 (β-lactam), 1750−1740 (esters), 1680 (amide) cm^{-1}. Anal. (C$_{42}$H$_{37}$N$_2$O$_9$P) C, H, N.

(±)-**Benzyl (5*RS*,6*SR*)-7-Oxo-6-(phenylacetamido)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (19).** Trimethylsilyl trifluoromethanesulfonate (0.46 g, 2.1 mmol) and DBU (0.32 g, 2.1 mmol) were added to a THF solution (35 mL) containing carbapenam (±)-**14** (0.61 g, 1.0 mmol) at 0 °C. The

stirred mixture was warmed to 25 °C within 1.0 h and then heated at reflux for 2.0 h. Then water (20 mL) was added and then the aqueous solution was extracted with Et_2O (3 × 40 mL). The organic layer was dried over $MgSO_4(s)$, filtered, and concentrated under reduced pressure. Purification of the residue by use of column chromatography (CH_2Cl_2 as eluant) gave carbapenem (±)-**19** (0.15 g, 0.40 mmol) as an oil in 40% yield: ^{1}H NMR (CDCl$_3$) δ 2.95–3.45 (m, 2H, $H_2C(4)$), 3.58 (s, 2H, CH_2CO), 3.89–4.28 (m, 1H, HC(5)), 4.89 (dd, J = 10.0, 5.0 Hz, 1H, HC(6)), 5.18 (s, 2H, CH_2O), 5.95 (br t, J = 3.21 Hz, 1H, HC(3)), 7.20 (s, 5H, Ph), 7.41 (s, 5H, Ph), 7.70 (d, J = 10.0 Hz, 1H, NH); IR (CH_2Cl_2) 3415 (NH), 1787 (β-lactam), 1745 (ester), 1680 (amide) cm^{-1}. Anal. ($C_{22}H_{20}N_2O_4$) C, H, N.

(±)-Dibenzyl (5*RS*,6*SR*)-7-Oxo-6-(phenylacetamido)-1-azabicyclo[3.2.0]hept-2-ene-2,3-dicarboxylate (20). Compound **20** (0.33 g, 0.65 mmol) was prepared as a foam in 65% yield from carbapenam **15** (0.75 g, 1.0 mmol), trimethylsilyl trifluoromethanesulfonate (0.46 g, 2.1 mmol), and DBU (0.32 g, 2.1 mmol) in dry THF (35 mL) by the method used for the synthesis of **19** from **14**: ^{1}H NMR (CDCl$_3$) δ 3.21 (dd, J = 18.0, 8.0 Hz, 1H, HC(4)), 3.47 (dd, J = 18.0, 10.0 Hz, 1H, HC(4)), 3.60 (s, 2H, CH_2CO), 3.95–4.14 (m, 1H, HC(5)), 4.91 (dd, J = 9.5, 5.0 Hz, 1H, HC(6)), 5.15 (s, 2H, CH_2O), 5.21 (s, 2H, CH_2O), 7.25–7.42 (m, 15H, 3 × Ph), 7.69 (d, J = 9.5 Hz, 1H, NH); IR (CH$_2$Cl$_2$) 3415 (NH), 1790 (β-lactam), 1750–1740 (esters), 1680 (amide) cm^{-1}. Anal. ($C_{30}H_{26}N_2O_6$) C, H, N.

(±)-(5*RS*,6*SR*)-7-Oxo-6-(phenylacetamido)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (21). A solution of (±)-**19** (0.38 g, 1.0 mmol) in EtOAc (50 mL) was hydrogenated with H$_2$ at 50 psi on PdCl$_2$ (100 mg, 0.564 mmol) at room temperature for 5.0 h. The solution was then dried over $MgSO_4(s)$, filtered and concentrated under reduced pressure. Purification of the residue by use of column chromatography (EtOAc as eluant) afforded (±)-**21** (0.20 g, 0.70 mmol) in 70% yield: mp (recrystallized from ether) 112–114 °C; ^{1}H NMR (CDCl$_3$/DMSO-d_6/D$_2$O) δ 2.89–3.37 (m, 2H, $H_2C(4)$), 3.56 (s, 2H, CH_2-CO), 3.90–4.16 (m, 1H, HC(5)), 4.98 (d, J = 5.0 Hz, 1H, HC(6)), 5.90–6.10 (br, 1H, HC(3)), 7.35 (s, 5H, Ph); IR (Nujol) 3415–3300 (NH, CO_2H), 1783 (β-lactam), 1695 (acid), 1670 (amide) cm^{-1}. Anal. ($C_{15}H_{14}N_2O_4$) C, H, N.

(±)-(5*RS*,6*SR*)-7-Oxo-6-(phenylacetamido)-1-azabicyclo[3.2.0]hept-2-ene-2,3-dicarboxylic Acid (22). Compound **22** (0.23 g, 0.68 mmol) was prepared in 68% yield from **20** (0.51 g, 1.0 mmol), PdCl$_2$ (100 mg, 0.564 mmol), and H$_2$ (50 psi) in EtOAc (50 mL) by the method used for the synthesis of **21** from **19**: mp (recrystallized from EtOAc/ether 1:1) 145–147 °C; ^{1}H NMR (CDCl$_3$/DMSO-d_6/D$_2$O) δ 3.18 (dd, J = 18.0, 8.0 Hz, 1H, HC(4)), 3.43 (dd, J = 18.0, 10.5 Hz, 1H, HC(4)), 3.60 (s, 2H, CH_2CO), 3.98–4.13 (m, 1H, HC(5)), 4.97 (d, J = 4.5 Hz, 1H, HC(6)), 7.34 (s, 5H, Ph); IR (Nujol) 3415–3300 (NH, 2 × CO$_2$H), 1788 (β-lactam), 1700–1695 (acids), 1670 (amide) cm^{-1}. Anal. ($C_{16}H_{14}N_2O_6$) C, H, N.

(±)-Dibenzyl 2-(*cis*-2-Oxo-3-phenylacetamido-4-hydroxymethyl-1-azetidinyl)-2-[*tert*-butyldimethylsilyloxy-(methoxycarbonyl)methyl]malonate (24). Compound **24** (0.54 g, 0.75 mmol) was obtained in 75% yield from **23** (0.75 g, 1.0 mmol) by the method used for the synthesis of **10** from **8**: ^{1}H NMR (CDCl$_3$) δ 0.10 (s, 3H, SiCH$_3$), 0.11 (s, 3H, SiCH$_3$), 0.92, 1.00 (2 s, 9H, C(CH$_3$)$_3$), 3.58 (br s, 2H, CH_2CO), 3.60, 3.66 (2 s, 3H, OCH$_3$), 3.70–4.40 (m, 4H, CH$_2$OH + HC(4)), 5.10–5.28 (m, 5H, 2 × CH$_2$O + CHOSi), 5.44 (dd, J = 9.0, 5.0 Hz, 1H, HC(3)), 7.00–7.40 (br, 16H, 3 × Ph + NH); IR (CH$_2$Cl$_2$) 3415–3350 (NH, OH), 1770 (β-lactam), 1747–1735 (esters), 1675 (amide) cm^{-1}. Anal. ($C_{38}H_{46}N_2O_{10}Si$) C, H, N.

(±)-Dibenzyl 2-[*cis*-2-Oxo-3-phenylacetamido-4-(methanesulfonyl)oxymethyl-1-azetidinyl]-2-[*tert*-butyldimethylsilyloxy(methoxycarbonyl)methyl]malonate (25). Sulfonate **25** (0.76 g, 0.95 mmol) was prepared in 95% yield from **24** (0.72 g, 1.0 mmol) by the method used for the synthesis of **12** from **10** except that MeSO$_2$Cl (0.12 g, 1.0 mmol) was used to replace CF$_3$SO$_2$Cl: ^{1}H NMR (CDCl$_3$) δ 0.12 (s, 3H, SiCH$_3$), 0.15 (s, 3H, SiCH$_3$), 1.05, 1.13 (2 s, 9H, C(CH$_3$)$_3$), 2.83 (br s, 3H, SO$_2$CH$_3$), 3.53 (s, 2H, CH_2CO), 3.70 (s, 3H, OCH$_3$), 3.88–4.09 (br, 2H, CH$_2$OSO$_2$), 4.15–4.38 (m, 1H, HC(4)), 5.12–5.32

(m, 5H, 2 × CH$_2$O + CHOSi), 5.50 (dd, J = 10.0, 5.0 Hz, 1H, HC(3)), 7.01–7.49 (br, 16H, 3 × Ph + NH); IR (CH$_2$Cl$_2$) 3410 (NH), 1776 (β-lactam), 1750–1740 (esters), 1680 (amide) cm^{-1}. Anal. ($C_{39}H_{48}N_2O_{12}SSi$) C, H, N, S.

(±)-1-Benzyl 4-Methyl 2-[*cis*-2-Oxo-3-phenylacetamido-4-(methanesulfonyl)oxymethyl-1-azetidinyl]maleate (26). A solution containing (±)-**25** (0.80 g, 1.0 mmol) and DBU (0.32 g, 2.1 mmol) in EtOAc (50 mL) was hydrogenated over 10% Pd/C (300 mg, 1.69 mmol) and H$_2$ (40 psi) at 45 °C for 6.0 h. The mixture was filtered and AcOH (2.0 mL) was added. The organic layer was dried over $MgSO_4(s)$, filtered, and concentrated under reduced pressure. Purification of the residue by use of column chromatography (CHCl$_3$ as eluant) afforded (±)-**26** (0.35 g, 0.66 mmol) in 66% yield: mp (recrystallized from ether/hexanes 2:1) 118–119 °C; ^{1}H NMR (CDCl$_3$) δ 2.82 (s, 3H, SO$_2$CH$_3$), 3.58 (s, 2H, CH_2CO), 3.88 (s, 3H, OCH$_3$), 3.90–4.03 (br, 2H, CH$_2$OSO$_2$), 4.20–4.31 (m, 1H, HC(4)), 5.24 (dd, J = 8.5, 5.0 Hz, 1H, HC(3)), 5.41 (s, 2H, CH$_2$O), 5.62 (s, 1H, CHCO), 6.98 (d, J = 8.5 Hz, 1H, NH), 7.30 (s, 5H, Ph), 7.45 (s, 5H, Ph); IR (CH$_2$Cl$_2$) 3410 (NH), 1793 (β-lactam), 1735–1730 (esters), 1680 (amide) cm^{-1}. Anal. ($C_{25}H_{26}N_2O_9S$) C, H, N, S.

(±)-1-Benzyl 4-Methyl 2-[*cis*-2-Oxo-3-phenylacetamido-4-(methanesulfonyl)oxymethyl-1-azetidinyl]-3-diphenylphosphonosuccinate (27). Compound **27** (6.50 g, 8.50 mmol) was prepared in 85% yield from **26** (5.31 g, 10.0 mmol) as the method used for the synthesis of **8** from **6**: ^{1}H NMR (CDCl$_3$) δ 2.81, 2.83 (2 s, 3H, SO$_2$CH$_3$), 3.39 (br d, J = 20.0 Hz, 1H, CHP), 3.60 (br s, 2H, CH_2CO), 3.63 (br s, 3H, CH$_3$), 3.95–4.20 (br, 2H, CH$_2$OSO$_2$), 4.25–4.39 (m, 1H, HC(4)), 4.69 (br s, 1H, CHCO$_2$), 5.15 (s, 2H, CH$_2$O), 5.40 (dd, J = 8.5, 5.0 Hz, 1H, HC(3)), 7.15–7.53 (m, 20H, 4 × Ph), 7.72 (br s, 1H, NH); IR (CH$_2$Cl$_2$) 3410 (NH), 1771 (β-lactam), 1750–1740 (esters), 1685 (amide) cm^{-1}. Anal. ($C_{37}H_{37}N_2O_{12}SP$) C, H, N, S.

(±)-2-Benzyl 3-Methyl (2*RS*,3*RS*,5*RS*,6*SR*)-7-Oxo-6-(phenylacetamido)-3-diphenylphosphono-1-azabicyclo[3.2.0]heptane-2,3-dicarboxylate (28). Compound **28** (0.58 g, 0.87 mmol) was obtained in 87% yield from **27** (0.77 g, 1.0 mmol) as the method used for the synthesis of **15** from **13**: ^{1}H NMR (CDCl$_3$) δ 1.97 (dd, J = 13.5, 6.0 Hz, 1H, HC(4)), 2.21 (dd, J = 13.5, 11.0 Hz, 1H, HC(4)), 3.56 (s, 2H, CH_2CO), 3.68 (s, 3H, OCH$_3$), 3.89–4.11 (m, 1H, HC(5)), 4.55 (br s, 1H, HC(2)), 5.06–5.29 (m, 1H, HC(6)), 5.20 (s, 2H, CH$_2$O), 6.83 (br s, 1H, NH), 7.01–7.65 (m, 20H, 4 × Ph); IR (CH$_2$Cl$_2$) 3405 (NH), 1782 (β-lactam), 1750–1740 (esters), 1680 (amide) cm^{-1}. Anal. ($C_{36}H_{33}N_2O_9P$) C, H, N.

(±)-2-Benzyl 3-Methyl (5*RS*,6*SR*)-7-Oxo-6-(phenylacetamido)-1-azabicyclo[3.2.0]hept-2-ene-2,3-dicarboxylate (29). Compound **29** (0.30 g, 0.70 mmol) was prepared in 70% yield from **28** (0.67 g, 1.0 mmol) as the method used for the synthesis of **19** from **14**: ^{1}H NMR (CDCl$_3$) δ 3.21 (dd, J = 18.5, 8.0 Hz, 1H, HC(4)), 3.47 (dd, J = 18.5, 10.0 Hz, 1H, HC-(4)), 3.59 (s, 2H, CH_2CO), 3.86 (s, 3H, OCH$_3$), 3.99–4.20 (m, 1H, HC(5)), 4.95 (dd, J = 9.5, 5.0 Hz, 1H, HC(6)), 5.35 (s, 2H, CH$_2$O), 7.30 (s, 5H, Ph), 7.44 (s, 5H, Ph), 7.68 (d, J = 9.5 Hz, 1H, NH); IR (CH$_2$Cl$_2$) 3415 (NH), 1790 (β-lactam), 1750–1740 (esters), 1680 (amide) cm^{-1}. Anal. ($C_{24}H_{22}N_2O_6$) C, H, N.

(±)-3-Methyl 2-Hydrogen (5*RS*,6*SR*)-7-Oxo-6-(phenylacetamido)-1-azabicyclo-[3.2.0]hept-2-ene-2,3-dicarboxylate (30). Carboxylic acid **30** (0.28 g, 0.80 mmol) was obtained in 80% yield from **29** (0.43 g, 1.0 mmol) as the method used for the synthesis of **21** from **19**: mp (recrystallized from ether) 119–121 °C; ^{1}H NMR (CDCl$_3$/DMSO-d_6/D$_2$O) δ 3.20 (dd, J = 17.0, 7.8 Hz, 1H, HC(4)), 3.46 (dd, J = 17.0, 9.6 Hz, 1H, HC-(4)), 3.59 (s, 2H, CH_2CO), 3.90 (s, 3H, OCH$_3$), 4.01–4.29 (m, 1H, HC(5)), 4.99 (d, J = 5.0 Hz, 1H, HC(6)), 7.36 (s, 5H, Ph); IR (Nujol) 3426–3320 (NH, CO_2H), 1789 (β-lactam), 1726 (ester), 1705 (acid), 1675 (amide) cm^{-1}. Anal. ($C_{17}H_{16}N_2O_6$) C, H, N.

(±)-Benzyl (5*RS*,6*SR*)-7-Oxo-6-(phenylacetamido)-3-methoxycarbomethyl-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (32). To a solution containing phosphonate (±)-**14** (1.2 g, 2.0 mmol) and methyl glyoxylate (0.44 g, 5.0 mmol)

in dry THF (30 mL) was added a THF solution of LiTMP (5.13 mL, 2.20 mmol) dropwise under an argon atmosphere at -30 °C. The solution was stirred at -30 °C for 1.5 h and then at 25 °C for another 4.0 h. The reaction mixture was quenched with 10% NH$_4$Cl aqueous solution (20 mL) and extracted with CHCl$_3$ (2 × 35 mL). The combined organic layers were dried over MgSO$_4$(s), filtered, and concentrated under reduced pressure. Purification of the residue by use of column chromatography (CHCl$_3$/EtOAc (4:1)) gave ($\pm$)-**32** (0.40 g, 0.90 mmol) as a foam in 45% yield: ^{1}H NMR (CDCl$_3$) δ 2.98 (dd, J = 17.0, 6.7 Hz, 1H, HC(4)), 3.20 (s, 2H, H$_2$CC(3)), 3.38 (dd, J = 17.0, 9.8 Hz, 1H, HC(4)), 3.62 (s, 2H, CH$_2$CO), 3.47 (s, 3H, OCH$_3$), 3.92–4.28 (m, 1H, HC(5)), 4.98 (dd, J = 9.0, 5.0 Hz, 1H, HC(6)), 5.38 (s, 2H, CH$_2$O), 6.95 (d, J = 9.0 Hz, 1H, NH), 7.20 (s, 5H, Ph), 7.46 (s, 5H, Ph); IR (CH$_2$Cl$_2$) 3410 (NH), 1789 (β-lactam), 1745, 1720 (esters), 1680 (amide) cm^{-1}. Anal. (C$_{25}$H$_{24}$N$_2$O$_6$) C, H, N.

($\pm$)-(5RS,6SR)-7-Oxo-6-(phenylacetamido)-3-methoxy-carbomethyl-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (33). Carboxylic acid **33** (0.28 g, 0.77 mmol) was prepared in 77% yield from **32** (0.45 g, 1.0 mmol) as the method used for the synthesis of **21** from **19**: mp (recrystallized from ether) 98–99 °C; ^{1}H NMR (CDCl$_3$/D$_2$O) δ 2.97 (dd, J = 17.0, 7.0 Hz, 1H, HC(4)), 3.25 (s, 2H, H$_2$CC(3)), 3.35 (dd, J = 17.0, 9.7 Hz, 1H, HC(4)), 3.60 (s, 2H, CH$_2$CO), 3.50 (s, 3H, OCH$_3$), 3.89–4.15 (m, 1H, HC(5)), 4.95 (d, J = 4.8 Hz, 1H, HC(6)), 7.34 (s, 5H, Ph); IR (CH$_2$Cl$_2$) 3426–3310 (NH, CO$_2$H), 1787 (β-lactam), 1740 (ester), 1698 (acid), 1675 (amide) cm^{-1}. Anal. (C$_{18}$H$_{18}$N$_2$O$_6$) C, H, N.

($\pm$)-(5RS,6SR)-7-Oxo-6-(phenylacetamido)-3-hydroxy-ethyl-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (34). To a stirred solution containing ester ($\pm$)-**33** (0.36 g, 1.0 mmol) and water (0.50 mL) in THF (10 mL) was added NaBH$_4$ (0.38 g, 10 mmol). After the solution was stirred for 4.0 h, the reaction mixture was neutralized to pH = 7.0 by use of 10% HCl aqueous solution. Solvent was evaporated under reduced pressure and the aqueous layer was extracted with EtOAc (3 × 50 mL), dried over MgSO$_4$(s), filtered, and concentrated under reduced pressure. Purification of the residue by use of column chromatography (CHCl$_3$/EtOAc (1:1)) gave ($\pm$)-**34** (0.10 g, 0.30 mmol) in 30% yield: mp (recrystallized from ether) 107–108 °C; ^{1}H NMR (CDCl$_3$/D$_2$O) δ 2.11 (t, J = 7.2 Hz, 2H, H$_2$-CC(3)), 2.90 (dd, J = 17.5, 6.8 Hz, 1H, HC(4)), 3.29 (dd, J = 17.5, 9.8 Hz, 1H, HC(4)), 3.57 (s, 2H, CH$_2$CO), 3.80–4.15 (m, 3H, HC(5) + CH$_2$O), 4.90 (d, J = 5.0 Hz, 1H, HC(6)), 7.33 (s, 5H, Ph); IR (CH$_2$Cl$_2$) 3450–3300 (NH, OH, CO$_2$H), 1787 (β-lactam), 1688 (acid), 1680 (amide) cm^{-1}. Anal. (C$_{17}$H$_{18}$N$_2$O$_5$) C, H, N.

($\pm$)-(5RS,6SR)-7-Oxo-6-(phenylacetamido)-3-acetoxy-ethyl-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (35). To a solution containing alcohol ($\pm$)-**34** (0.33 g, 1.0 mmol) and Et$_3$N (0.20 g, 2.0 mmol) in CH$_2$Cl$_2$ (10 mL) was added CH$_3$-COCl (0.16 g, 2.0 mmol) at 0 °C. After the solution was stirred for 2.0 h, it was washed with water (20 mL), dried over MgSO$_4$-(s), filtered, and concentrated under reduced pressure. Purification of the residue by use of column chromatography (CHCl$_3$/EtOAc (1:1)) gave ($\pm$)-**35** (0.34 g, 0.90 mmol) as a foam in 90% yield: ^{1}H NMR (CDCl$_3$/D$_2$O) δ 1.96 (s, 3H, CH$_3$CO), 2.30 (t, J = 8.0 Hz, 2H, H$_2$CC(3)), 2.91 (dd, J = 18.0, 7.0 Hz, 1H, HC(4)), 3.29 (dd, J = 18.0, 10.0 Hz, 1H, HC(4)), 3.60 (s, 2H, CH$_2$CO), 3.85–4.13 (m, 1H, HC(5)), 4.40 (t, J = 8.0 Hz, 2H, CH$_2$O), 4.92 (d, J = 5.0 Hz, 1H, HC(6)), 7.34 (s, 5H, Ph); IR (CH$_2$Cl$_2$) 3450–3320 (NH, CO$_2$H), 1787 (β-lactam), 1750 (ester), 1689 (acid), 1680 (amide) cm^{-1}. Anal. (C$_{19}$H$_{20}$N$_2$O$_6$) C, H, N.

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