Infected placebo control mice were injected with the vehicle [0.2% (carboxymethyl)cellulose with 0.2% Tween 80 in water (CMC/T)]. Mice were observed, for 21 days, for mortality. Statistical analysis and the probablity (P) value for the percent survival and the mean survival time were determined by Fisher's exact and Gehan–Wilcoxon tests, respectively.

d. Cutaneous HSV Infection in Guinea Pigs. We used the method described by Alenius and Oberg[32] with slight modification. Briefly, guinea pigs weighing 250–300 g (Charles River, Wilmington, MA) were anesthetized (Ketaset, Bristol-Myers Co., Syracuse, NY) and shaved and depilated on the back. The depilated areas were divided into six squares, and 20 μL of HSV 1, HL-34 strain with a titer of 6.5×10^7 PFU/mL was applied with a multiple puncture apparatus (Downs Surgical, Inc., Wilmington, MA). Treatment was initiated 3 h postinfection and continued twice daily for 5 consecutive days. Four areas on each animal were treated topically with preparations of either 5% FEAU, FMAU, or FIAU (prepared fresh daily in CMC/T in polyethylene glycol (PEG)) or with 5% acyclovir ointment (Zovirax, Burroughs Wellcome Co., Research Triangle, NC). One area on each animal was treated with PEG (placebo control) and one area was not treated (untreated control). Fifty microliters of the compound solution was applied each treatment and spread over the infected site. Each drug was tested in three to five animals, with one area/animal for each compound.

The scoring system used was similar to that described by Alenius and Oberg:[32] 1 = erythema and one or two small vesicles; 2 = erythema and numerous small vesicles; 3 = numerous large vesicles, if in close juxtaposition, coalesced; III = vesicles dried, large crusts; II = 50% of the crusts fallen off; I = 10% of the crusts remains; 0 = complete healing. Scoring was done blindly every day for 14 days. Statistical analysis and the mean area under the lesion score–day curve were determined by using a two-sample t test with a pooled error term. Comparisons were based on a logarithmic transformation of the areas. A P value less than 5% was considered significant.

Acknowledgment. We express our appreciation to Dan J. Speelman and Randy R. Brutkiewiez for their technical assistance in obtaining the biological data. We thank also the Bristol-Myers Analytical Department.

Registry No. 1, 83546-42-3; 7, 4212-49-1; 8, 31167-05-2; 9, 97614-44-3; 10, 95740-18-4; 11, 106835-91-0.

(32) Alenius, S.; Oberg, B. *Arch. Virol.* **1978**, *58*, 277.

Structure–Activity Relationships in the 2-Arylcarbapenem Series: Synthesis of 1-Methyl-2-arylcarbapenems

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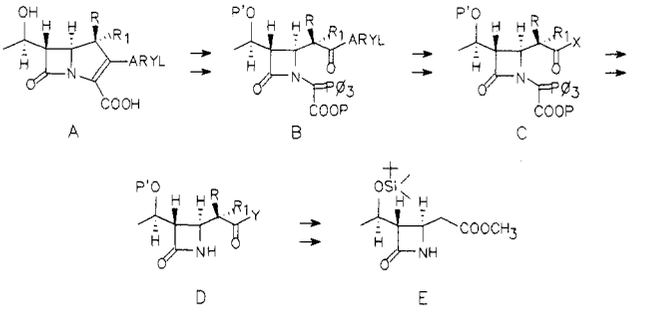
The labile *tert*-butyldimethylsilyl esters of the azetidinones **6–8b** served as the crucial synthons in the preparation of the potentially useful ylide pyridyl thio esters **18–20**. These intermediates were utilized to synthesize a host of title carbapenems **25–30d**, **32**, and **49–53**. The antimicrobial properties and DHP-I susceptibility of these carbapenems were studied with reference to thienamycin.

The discovery of thienamycin[1] and related members of the carbapenem family[2] ushered in a new era in antibiotics research. Excitement over the unprecedented potency and breadth of spectrum of these natural products was soon tempered by the recognition that many of the agents that showed the most promising antibacterial properties also suffered from both chemical instability and susceptibility to a mammalian dehydropeptidase, DHP-I.[3a,b] Previous work[3b] from these laboratories has shown that the chemical stability of thienamycin could be significantly enhanced by conversion to the N-formimidoyl derivative, imipenem.

Scheme I



However, this modification has little impact on metabolic stability, imipenem being approximately 90% as susceptible to DHP-I-mediated hydrolysis as thienamycin. Subsequent total synthesis studies[4,5] resulted in the discovery of two subclasses of carbapenems that combine chemical and metabolic stability with enhanced antibacterial potency. The properties of these structural variants, i.e., 1-substituted carbapenems and 2-arylcarbapenems, have been the subjects of previous reports from these laboratories.[4,5] Herein we detail the syntheses and structure–activity relationships for 1-methyl-2-arylcarbapenems, a new hybrid class of compounds that com-

(1) (a) Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B. 16th ICAAC, Chicago, 1976; p 227. (b) Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1–12. (c) Albers-Schonberg, G.; Arison, B. H.; Kaczka, E.; Kahan, F. M.; Kahan, J. S.; Lago, B.; Maiese, W. M.; Rhodes, R. E.; Smith, J. L. 16th ICAAC, Chicago, 1976; p 229. (d) Albers-Schonberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, F. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; and Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491.

(2) Ratcliffe, R.; Albers-Schonberg, G. In *Chemistry and Biology of Beta Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; pp 227–314.

(3) (a) Kropp, H.; Sundelof, J. G.; Hajdu, R.; Kahan, F. M. *Antimicrob. Agents Chemother.* **1982**, *22*, 62. (b) Leanza, W. J.; Wildonger, K. J.; Miller, T. W.; Christensen, B. G. *J. Med. Chem.* **1979**, *22*, 1435.

(4) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29–40 and references cited therein.

(5) Cama, L. D.; Wildonger, K. J.; Guthikonda, R. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron* **1983**, *39*, 2531–2549 and references cited therein.

0022-2623/87/1830-0871$01.50/0

Chart I

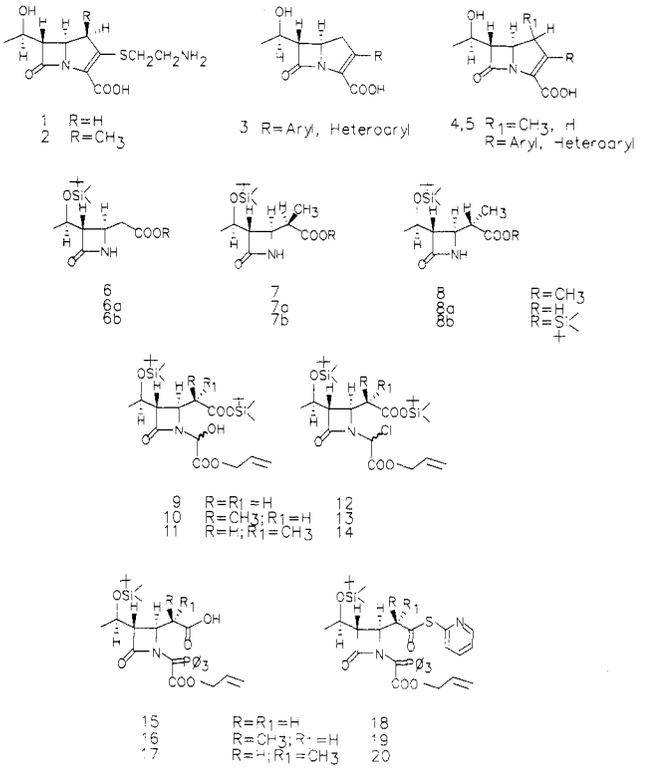
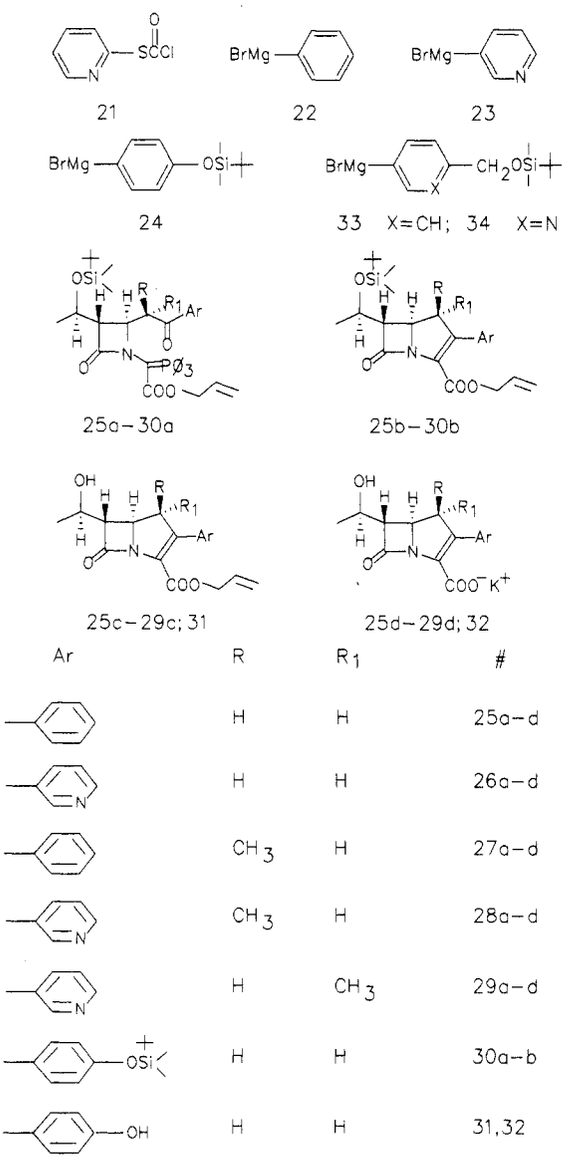


Chart II



bines those key structural features known to impart the favorable stability/potency profiles discussed above.

The synthetic strategy proposed for the preparation of 1-substituted 2-arylcarbapenems is outlined in retrosynthetic form in Scheme I. The critical cyclization to the carbapenem nucleus, A, was designed to be accomplished by the internal Wittig reaction of a keto phosphorane, B. Such a strategy has previously been demonstrated in the simpler 2-arylcarbapenems.[5] Keto phosphorane B would in turn be derived from an activated acylating agent, C, via reaction with the appropriate aryl organometallic reagent. Thus, intermediate C serves as the pivotal branch point for the synthesis of the entire series. The ultimate starting material for the synthetic effort was the known, optically pure azetidinone E, which, via chemospecific alkylation followed by appropriate manipulation of protecting groups (vide infra), was to be converted to D. Introduction of the phosphorane side chain would then provide key intermediate C.

As formulated in Scheme I, our synthetic strategy required the elaboration of an activated acylating agent on an intermediate of type C, presumably via intermediacy of the corresponding carboxylic acid. This would in turn necessitate the use of an ester protecting group that would be readily removable in the presence of potentially more labile functionality. Previous experience had shown us that the methyl esters present in the readily available[4,6] starting materials **6–8** were difficult to selectively hydrolyze in intermediates of type C. For this reason we chose to introduce a more labile ester protecting group early in the synthetic sequence.

Synthesis of Pyridyl Thio Esters

Toward this end, methyl esters **6–8** were hydrolyzed to the corresponding acids **6a**,[6] **7a**, and **8a**[4] in good yield (Chart I). Reesterification with *tert*-butyldimethylchlorosilane provided the silyl esters **6b**, **7b**, and **8b**.[10] The

(6) (a) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31. (b) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783. (c) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 616. (d) Cvetovich, R. J.; Melillo, D. G.; Ryan, K. M.; Sletzinger, M. U.S. Patent 4 360 684, Nov. 23, 1982.

(7) Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1979**, 2875.
(8) Just, G.; Liak, T. J. *Can. J. Chem.* **1978**, *56*, 211.
(9) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587.
(10) Most of the new compounds reported here are either noncrystalline solids or foams or unstable. Hence, their analytical data could not be obtained. Instead, where appropriate, high-resolution mass spectral measurements were obtained in addition to IR, NMR, and UV values, thus confirming the structures of all these new compounds directly or indirectly.
(11) The antibacterial activity of synthetic carbapenems was determined by a disc diffusion assay using thienamycin as an internal standard. Inhibitory concentration at the edge of the zone of inhibition was computed for each compound and for thienamycin by a rearrangement of eq 3 in ref 12, which takes into account the differing molecular weights and resultant diffusion constants of each compound. Strains were individually calibrated for their critical times. The ratio of inhibitory concentration to that of thienamycin is stated in the tables. For comparison, the mean MICs for thienamycin are shown for the strains employed.[13]
(12) Humphrey, J. H.; Lightbrown, J. W. *J. Gen. Microbiol.* **1952**, *7*, 129–143.

Table I. Preparation of Ylide Ketones from Pyridyl Thio Esters and Grignard Reagents

ylide ketone	pyridyl thio ester	Grignard reagent	reaction conditions	yield, %	silica gel chromatography solvent
25a	**18**	**22**	THF, 0 °C, 15 min	52	cyclohexane/EtOAc (1:1)
26a	**18**	**23**	ether, THF, 0 °C, 30 min	32	CH_2Cl_2/EtOAc (1:3)
27a	**19**	**22**	THF, 0 °C, 30 min	67	cyclohexane/EtOAc (1:1)
28a	**19**	**23**	ether, THF, 0 °C, 30 min	49	ether
29a	**20**	**23**	ether, THF, 0 °C, 1 h	40[a]	ether
30a	**18**	**24**	ether, THF, 0 °C, 20 min	51	ether/hexane (4:1)
35	**19**	**33**	THF, 0 °C, 1 h	68	cyclohexane/EtOAc (3:1)
36	**19**	**34**	THF, 0 °C, 1 h	56	cyclohexane/EtOAc (3:7)

[a] Ylide ketone **29a** is accompanied by 17% of its cyclization product **29b** under these reaction conditions.

Table II. Cyclizations of Aryl Keto Ylides to Carbapenems

carbapenem	aryl keto ylide	reaction conditions	yield, %	silica gel chromatography solvent
25b	**25a**	xylene (hydroquinone), 125 °C, 2 h	81	cyclohexane/EtOAc (4:1)
26b	**26a**	xylene (hydroquinone), 130 °C, 0.5 h	64	EtOAc/ether (1:4)
27b	**27a**	xylene, 130 °C, 15 h	58	cyclohexane/EtOAc (1:1)
28b	**28a**	xylene, 130 °C, 4 h	68	ether
29b	**29a**	toluene, 50 °C, 4.5 h	73	ether
30b	**30a**	xylene (hydroquinone), 130 °C, 3.5 h	69	ether
43	**41**	xylene, 130 °C, 6 h	71	cyclohexane/EtOAc (4:1)
44	**42**	xylene (hydroquinone), 130 °C, 1 h	90	cyclohexane/EtOAc (3:2)
47	**35**	xylene (hydroquinone), 130 °C, 16 h	70	cyclohexane/EtOAc (3:1)

Table III. Desilylation of the Carbapenem Silyl Ethers to the Carbapenem Alcohols

carbapenem		reaction time, h	yield, %	silica gel chromatography solvent
alcohol	silyl ether			
25c	**25b**	21	60	cyclohexane/EtOAc (1:1)
26c	**26b**	15	81	EtOAc
27c	**27b**	40	45	cyclohexane/EtOAc (1:1)
28c	**28b**	22	57	ether
29c	**29b**	24	35	EtOAc
31	**30b**	48	25	ether
45	**43**	40	44	cyclohexane/EtOAc (1:2)
46	**44**	28	82	EtOAc
48	**47**	**36**	**62**	EtOAc

conversion of these silyl esters to phosphoranylidene pyridyl thio esters **18–20** was carried out without purification of the synthetic intermediates. Thus, treatment with allyl glyoxalate in refluxing toluene provided carbinols **9–11**, which were converted to the relatively unstable chloro compounds **12–14**. In the case of compound **13**, subsequent treatment with triphenylphosphine in DMF at room temperature or in the presence of 2,6-lutidine at 80 °C gave carboxylic acid **16** directly. In contrast, conversion of compounds **12** and **14** to phosphoranylidene acids **15** and **17** using the same procedures required the inclusion of a deliberate hydrolysis step to effect complete removal of the silyl ester. Crude carboxylic acids **15–17** were converted to pyridyl thio esters **18–20** by reaction with 2-pyridyl chlorothioformate (**21**),[7] in the presence of triethylamine at 0 °C. Overall yields for the conversion of silyl esters **6b**, **7b**, and **8b** to pyridyl thio esters **18–20** (which correspond to intermediate C in Scheme I) were 15–44%.

Synthesis of Carbapenems

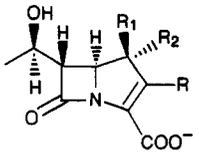
The desired aryl side chains were introduced via reaction of the appropriate Grignard reagent with the pyridyl thio esters prepared above. Thus, treatment of compounds **18–20** with Grignard reagents **22–24** in THF/ether at 0 °C provided aryl ketones **25a–30a** in good yields (Chart II and Table I). It is of note that these strongly basic reaction conditions did not effect epimerization of the methyl groups of either starting materials or final products. Thermolysis of phosphoranylidene ketones **25a–30a** in refluxing toluene or xylenes produced carbapenems **25b–30b** in good to excellent yields (Table II). It is noteworthy that the 1-α-methyl derivative **29b** was produced at considerably lower temperature than either the corresponding 1-unsubstituted or 1-β-methyl compounds. In addition, it was observed that the presence of pyridyl or azido moieties in the substrates significantly increased the rate of cyclization.

Desilylation of carbapenems **25b–30b** with tetra-*n*-butylammonium fluoride[8] buffered with acetic acid in THF at room temperature resulted in the formation of hydroxyethyl derivatives **25c–29c** and **31** (Table III). In general, moderate to high yields could be obtained after 24–48 h. Deallylation of esters **25c–29c** and **31** was accomplished by the method of Jeffrey and McCombie[9] to provide carbapenems **25d–29d** and **32**. The moderate yields that were obtained were independent of the nature of the side chain and the stereochemistry of the 1-substituent.

Previous work from these laboratories had demonstrated that the presence of a basic functionality in the carbapenem side chain was critical for the maintenance of activity against *Pseudomonas* species.[5] With this observation in mind, we initiated an effort to prepare 1-β-methyl-2-aryl derivatives that carried aminomethyl substitution. Toward this end, pyridyl thio ester **19** was treated with Grignard reagents **33** and **34** to afford the corresponding phosphoranylidene ketones **35** and **36** (Chart III and Table I). Selective deprotection of the benzylic alcohols was ac-

(13) Kropp, H.; Sundelof, J. G.; Kahan, J. S.; Kahan, F. M.; Birnbaum, J. *Antimicrob. Agents Chemother.* **1980**, *17*, 993.

Table IV. Antibiotic Activity (Relative Potency) and DHP-I Stability of the Carbapenems[a]



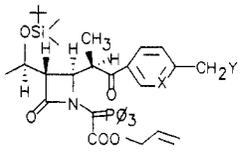
species (number)	R = ⬡ R_1 = H R_2 = H **25d**	R = ⬡ R_1 = CH_3 R_2 = H **27d**	**54**[b]	**55**[b]	R = ⬡N R_1 = H R_2 = H **26d**	R = ⬡N R_1 = CH_3 R_2 = H **28d**	R = ⬡N R_1 = H R_2 = CH_3 **29d**	MIC, μg/mL R = $SCH_2CH_2NH_2$ R_1 = H R_2 = H **1**
Staphylococcus aureus (5)	0.5	0.2	0.02	0.002	1.5	1	0.15	0.04
Enterococcus (3)	5.7	2	1	0.15	6	2.5	0.15	5
Escherichia coli (5)	2.5	0.5	0.1	0.01	9	12	3.5	0.3
Enterobacter sp. (6)	4.6	0.3	0.2	0.02	20	13	5	14
Klebsiella sp. (5)	1.4	0.3	0.04	0.02	7	7	2.5	1.3
Serratia sp. (2)	10	1	0.01	0.01	28	13	22	2.5
Proteus sp. (5)	10	3.5	0.03	0.03	17	7	2.5	7.5
Pseudomonas aeruginosa (5)	0.03	0.02	0.03	0.1	0.05	0.05	0.03	5.8
DHP-I[c] susceptibility	0.2	0.25	0.35	0.3	0.4	0.7	0.1	1

[a] See ref 11. [b] See ref 5. [c] DHP-I susceptibility is given relative to thienamycin = 1.

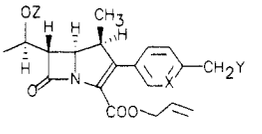
complished by brief treatment with tetra-*n*-butylammonium fluoride/acetic acid in THF to provide compounds **37** and **38**. Activation of alcohols **37** and **38** with methanesulfonyl chloride (triethylamine, CH_2Cl_2) followed by displacement of the resulting mesylates **39** and **40**, by azide (lithium azide, DMF), gave azidomethyl derivatives **41** and **42** in excellent overall yields. Thermolysis of **41** and **42** in refluxing xylenes produced carbapenems **43** and **44** in very good yield (Table II). Consistent with observations in the 1-unsubstituted series, the pyridyl analogue **42** cyclized approximately six times faster than the corresponding phenyl analogue **41**, again pointing out the profound influence of electronic factors in these intramolecular cyclizations. Desilylation (Table III) and deallylation were carried out by using procedures analogous to those described above to provide the penultimate intermediates **49** and **50**. Reduction of the azido functions of **49** and **50** by hydrogenation (45 psi of H_2, 10% Pd/C, water/pH 7 buffer) gave the desired aminomethyl derivatives **51** and **52**.

In order to provide an isosteric control compound for ascertaining the effect of the basic substituents of **51** and **52** on the antibacterial spectrum, the corresponding hydroxymethyl derivative **53** was prepared from intermediate **35** by using the general methodologies described above.

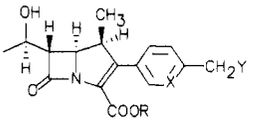
Chart III



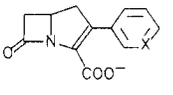
#	X	Y
35	CH	OSi<
36	N	OSi<
37	CH	OH
38	N	OH
39	CH	OMs
40	N	OMs
41	CH	N_3
42	N	N_3



#	X	Y	Z
43	CH	N_3	Si<
44	N	N_3	Si<
45	CH	N_3	H
46	N	N_3	H
47	CH	OSi<	Si<
48	CH	OH	H



#	X	Y	R
49	CH	N_3	K
50	N	N_3	K
51	CH	NH_2	H
52	N	NH_2	H
53	CH	OH	K

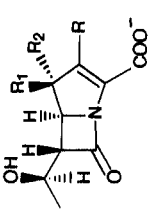


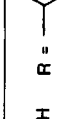
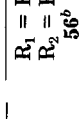
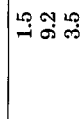
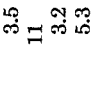
54	X=CH
55	X=N

Discussion

Examination of the biological activities of the various analogues as summarized in Tables IV and V reveals some interesting trends. As was anticipated, on the basis of previous work[5] in carbapenems bearing simple substituents at the 2-position, elaboration of the hydroxyethyl side chain to the 6-unsubstituted derivatives **54** and **55** results in analogues **25d** and **26d**, which exhibit markedly increased potency. This enhanced potency can be attributed in large part to the increased β-lactamase stability imparted by the hydroxyethyl substituent. The effect of this substituent on DHP stability is relatively minor, with compound **25d** showing an approximately twofold increase in stability while **26d** remains essentially equivalent to the 6-unsubstituted analogue. Synthesis of the corresponding 1-β-methyl analogues **27d** and **28d** resulted in compounds that exhibited decreased potency relative to the 1-unsubstituted compounds. While this result might have been predicted on the basis of work in other series, the effect of 1-methylation on the DHP susceptibility of these analogues was quite surprising. Thus, in the case of the 2-phenyl analogue **27d**, the DHP susceptibility actually increased slightly relative to that of **25d**, a result that is counter to previous observations in other series.[5] The effect of altering the stereochemistry of the substituent at the 1-position can be seen in the comparison of compounds **28d** and **29d**. Thus, while there is a negative effect on the antibacterial potency in changing the stereochemistry of the 1-methyl substituent from α to β, there is a concomitant sevenfold enhancement in stability to hydrolysis by DHP. It is significant to note that none of the

Table V. Antibiotic Activity (Relative Potency) and DHP-I Stability of the Carbapenems[a]



	R = 		R = 		R = 		R = 		MIC, μg/mL R = $SCH_2CH_2NH_2$	
species (number)	$R^1 = CH_3$ $R_2 = H$ 53	$R_1 = H$ $R_2 = H$ 57[b]	$R_1 = H$ $R_2 = H$ 32		$R_1 = H$ $R_2 = H$ 56[b]	$R_1 = CH_3$ $R_2 = H$ 51	$R_1 = CH_3$ $R_2 = H$ 52	$R_1 = H$ $R_2 = H$ 58[b]	$R_1 = H$ $R_2 = H$ 1	
Staphylococcus aureus (5)	0.2	1	0.4		1.5	0.4	0.5	1.9	0.04	
Enterococcus (3)	1.4	5	7.5		9.2	3	2.8	8	5	
Escherichia coli (5)	0.9	2	2.8		3.5	1.6	1.5	3	0.3	
Enterobacter sp. (6)	1.1	4	1.7		11	2.5	3.5	5.7	1.4	
Klebsiella sp. (5)	0.7	2.3	0.7		3.2	1.7	2.8	3	1.3	
Serratia sp. (2)	1.2	7	2.3		5.3	6.5	3.2	5.3	2.5	
Proteus sp. (5)	5.3	15	8		6.5	2	2.5	3.2	7.5	
Pseudomonas aeruginosa (5)	0.02	0.02	0.06		0.3	0.13	0.08	0.2	5.8	
DHP-I[c] susceptibility	0.22	0.28	0.2		0.02	0.07	0.16	0.1	1	

[a] See ref 11. [b] See ref 5. [c] DHP-I susceptibility is given relative to thienamycin = 1.

above derivatives demonstrate useful antipseudomonal activity. Compound **26d** appears to provide the best compromise between antibacterial activity and DHP susceptibility.

A comparison of the biological properties of the analogues bearing basic side chains (Table V), i.e., compounds **51**, **52**, **56**, and **58**, reveals that although antipseudomonal activity is enhanced relative to that of the isosteric but nonbasic analogues **53** and **57**, it is still significantly below that for thienamycin. As anticipated, relative DHP susceptibility for the isosteric pairs shows that the presence of the basic side chain enhances stability in both cases, however, this enhancement is much more significant in the 1-unsubstituted pair, **56** and **57**, wherein a 14-fold stability improvement is seen. Once again, two related pairs of compounds, **51**,**56** and **52**,**58**, demonstrate that the presence of the β-methyl substituent at the 1-position has a net detrimental effect on both in vitro antibacterial potency and stability to DHP-mediated hydrolysis.

In conclusion, the synthetic examples detailed above indicate that the desirable effects imparted individually to the potency and dehydropeptidase stability of carbapenems by either 1-methyl or 2-aryl side chains are not additive phenomena. On the contrary, in the 2-aryl cases examined to date, the opposite effect, i.e., diminution of activity and metabolic stability by 1-substitution, is observed. Although several of these analogues possess high levels of activity against most Gram-positive and Gram-negative organisms, efforts to build in therapeutically useful levels of antipseudomonal activity have been unsuccessful.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were run on thin film unless otherwise specified and were recorded on Perkin-Elmer 727B and 267 spectrophotometers; only selected absorptions are reported. UV spectra were recorded on a Perkin-Elmer 552A spectrophotometer. The NMR spectra were recorded on Varian T60A and XL-200 spectrometers in either $CDCl_3$ solution with Me_4Si as an internal standard or D_2O solution with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. Chemical shifts are reported in ppm relative to the standards. Mass spectral data were recorded on Varian MAT731 and LKBN9000 instruments. High-resolution mass spectra were recorded on a Finnigan MAT212 instrument at 3 kV. Peaks were matched by using perfluorokerosene (PFK) as internal standard. Although some of the Grignard reagents are commercially available and are known in the literature in different concentrations in different solvents, we have observed that the yields obtained by using the Grignard reagents described in this Experimental Section are superior to the ones described above.

All reactions were performed under a positive atmosphere of nitrogen. Organic solutions obtained after workup were dried over anhydrous $MgSO_4$ unless otherwise specified. Plate layer chromatography was performed on Analtech regular or reverse-phase silica gel GF plates, and column chromatography was conducted with Merck 60 silica gel.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone ketyl or lithium aluminum hydride (LAH) prior to use. *n*-Butyllithium in hexane (Aldrich), tetra-*n*-butylammonium fluoride in THF (1 M) (Aldrich), tetrakis(triphenylphosphine)palladium (Aldrich), and potassium 2-ethylhexanoate (Aldrich) were used as supplied.

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[[(*tert*-butyldimethylsilyl)oxy]carbonyl]ethyl]azetidin-2-one (7b). To a solution of the crude acid **7a** (5.7 g, 18.94 mmol) in 30 mL of anhydrous DMF was added *tert*-butyldimethylsilyl chloride (3.14 g, 20.4 mmol) followed by imidazole (1.417 g, 20.4 mmol). The resulting homogeneous solution was heated at 47 °C for 4 h under nitrogen. The reaction mixture was cooled, and the solvent was removed in vacuo at <30 °C. The residue was shaken with 100 mL of petroleum ether and

25 mL of ice water. The aqueous layer was separated and washed with 3 × 25 mL of petroleum ether. The combined organic layers were washed with 20 mL of ice-cold 1 N HCl solution, 50 mL of ice-cold saturated $NaHCO_3$ solution, and finally 20 mL of saturated NaCl solution. The organic phase was dried, and the solvent was removed to give the desired silyl ester **7b** as a white solid melting at 101–103 °C in 73% yield. NMR: 0.03, 0.23 ($SiCH_3$, 2 s), 0.82 and 0.90 (Si-*t*-Bu, 2 s), 1.16 (CH_3, d, J = 6 Hz), 1.20 (CH_3, d, J = 8 Hz), 2.66 ($CHCO_2$, m), 2.92 (H3, dd, J = 2,4 Hz), 3.94 (H4, dd, J = 2.5, 5 Hz), 4.18 (SiOCH, m), 5.93 (NH, br). MS: m/e 415 (M^+).

Via the above procedure, the following silyl esters were synthesized.

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[[[(*tert*-butyldimethylsilyl)oxy]carbonyl]methyl]azetidin-2-one (6b) was obtained from the corresponding acid **6a** as white crystals melting at 115–116 °C in 66% yield. NMR: 0.14 and 0.28 ($SiCH_3$, 2 s), 0.86 and 0.93 (Si-*t*-Bu, 2 s), 1.20 (CH_3, d, J = 6 Hz), 2.50–2.90 (H3 and CH_2C=O), 3.80–4.40 (H4 and SiOCH), 6.03 (NH, br). MS: m/e 401 (M^+).

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*S*)-1-[[(*tert*-butyldimethylsilyl)oxy]carbonyl]ethyl]azetidin-2-one (8b) was prepared from the respective acid **8a** as white crystals melting at 110–114 °C in 73% yield. NMR: 0.08 and 0.28 ($SiCH_3$, 2 s), 0.88 and 0.95 (Si-*t*-Bu, 2 s), 1.26 (CH_3, d, J = 8 Hz), 2.52 (SiOOCCH, m), 2.80 (H3, m), 3.75 (H4, dd, J = 2, 9.5 Hz), 4.25 (SiOCH, m), 6.11 (NH, br). MS: m/e 415 (M^+).

Allyl Glyoxylate. To a solution of *dl*-tartaric acid (30 g, 0.2 mol) in 150 mL of sieve-dried DMF at 0 °C under nitrogen was added triethylamine (111.2 mL, 0.8 mol). While the reaction mixture was allowed to warm to room temperature, a solution of allyl bromide (69.15 mL, 0.8 mol) in 100 mL of sieve-dried DMF was added over a period of 3 h. The reaction mixture was stirred overnight at ambient temperature. The solvent was removed in vacuo at <35 °C. The residue was taken up in 400 mL of ethyl acetate and washed with 2 × 100 mL of ice water, 2 × 100 mL of ice-cold saturated $NaHCO_3$ solution, and 2 × 50 mL of saturated NaCl solution. The organic layer was dried. Solvent removal in vacuo gave 43 g of *dl*-diallyl tartrate as a light orange oil, which was pumped overnight at room temperature in vacuo with stirring.

To a stirred solution of periodic acid (42.6 g, 0.187 mol) in anhydrous THF (700 mL) under nitrogen at room temperature (in water bath) was added dropwise a solution of diallyl tartrate in 150 mL of anhydrous THF. At the end of the addition, turbidity was observed. The reaction mixture warmed up, and a white solid precipitated. The reaction mixture was stirred for 1 h. The solids were filtered and washed with cold THF. Concentration of the filtrate in vacuo at room temperature gave a residue, which was taken up in ethyl acetate (500 mL) and washed with 4 × 50 mL of saturated NaCl solution containing 15% sodium thiosulfate. The organic layer was dried over anhydrous Na_2SO_4. Solvent removal afforded 32.9 g of allyl glyoxylate as an oil, which was used without further purification, although this compound is distillable.

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl]hydroxymethyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[[(*tert*-butyldimethylsilyl)oxy]carbonyl]ethyl]azetidin-2-one (10). A solution of the crude azetidinone silyl ester **7b** (8.3 g, 20 mmol) and allyl glyoxylate monohydrate (3.42 g, 26 mmol) in 100 mL of toluene was heated to reflux for 12 h with use of a Dean–Stark trap containing calcium hydride solid (5 g) to remove traces of water from the reaction mixture. The reaction mixture was then cooled and filtered, and the solvent was removed to give a thick oil, which was stirred and pumped in vacuo for 3 h at room temperature to give 11.2 g of the desired condensation product **10** as a colorless oil. IR: 3300 (OH), 1764 (β-lactam C=O), 1725 (ester C=O). NMR: 0.04 and 0.25 ($SiCH_3$, 2 s), 0.84, 0.85, and 0.91 (Si-*t*-Bu, 3 s), 1.21 and 1.40 (CH_3, 2 dd, J = 6, 8, Hz), 4.60–6.00 (CH_2CH=CH_2, m). MS: m/e 529 (M^+).

The condensation products **9** and **11** were also obtained by following the above procedure for **10**.

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl]hydroxymethyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[[[(*tert*-butyldimethylsilyl)oxy]carbonyl]methyl]azetidine-2-one (9) was synthesized from the azetidinone silyl ester **6b** and allyl glyoxylate in almost quantitative yield. IR: 3400 (OH), 1765 (β-lactam C=O), 1725 (ester C=O). MS: m/e 515 (M^+).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl]hydroxymethyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*S*)-1-[[(*tert*-butyldimethylsilyl)oxy]carbonyl]ethyl]azetidin-2-one (11) was prepared in quantitative yield from the azetidinone silyl ester **8b** and allyl glyoxylate. IR: 3450 (OH), 1775 (β-lactam C=O), 1735 (ester C=O). NMR: 0.06, 0.07, 0.08, and 0.27 ($SiCH_3$, 4 s), 0.88, 0.89, and 0.94 (Si-*t*-Bu, 3 s), 0.12–0.13 (CH_3, m), 4.64–6.10 (CH_2CH=CH_2, m). MS: m/e 529 (M^+).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-2′-[(pyridylthio)carbonyl]ethyl]azetidin-2-one (19). To a solution of the crude hydroxy azetidinone **10** (5.983 g, 11.31 mmol) in freshly distilled THF at −40 °C to −20 °C under nitrogen was added dropwise pyridine (1.60 mL, 20 mmol) followed by thionyl chloride (1.44 mL, 20 mmol). The reaction mixture with the resulting white precipitate was stirred for 45 min at −40 °C to −20 °C. Solids were then filtered and washed with 2 × 5 mL of cold anhydrous THF. The solvent was removed in vacuo at room temperature. The resulting oily solid was taken up in sieve-dried ethyl acetate (50 mL) and filtered, and the filtrate was concentrated. The residue, pumped in vacuo at room temperature for 0.5 h, gave 6.2 g of the desired chloro azetidinone **13**. IR: 1785 (β-lactam C=O), 1760 (esters C=O).

To this thick oil was added a solution of triphenylphosphine (5.24 g, 20 mmol) in 15 mL of sieve-dried DMF. This reaction mixture was stirred for 1.5 h under nitrogen at room temperature. The solvent was then removed in vacuo at <30 °C. The residue was taken up in ethyl acetate (200 mL) and washed with 3 × 50 mL of pH 7 phosphate buffer (0.5 M) and 2 × 50 mL of saturated NaCl solution. The organic phase was dried. Solvent removal in vacuo at room temperature for 3 h gave the ylide acid **16** as a light brown thick oil (13.9 g). IR: 3400–2600 (OH), 1765 (β-lactam C=O), 1600 (ylide ester).

To a solution of this crude ylide acid **16** in 70 mL of sieve-dried methylene chloride at 0 °C under nitrogen was added triethylamine (2.78 mL, 20 mmol), followed after 5 min by freshly prepared 2-pyridyl chlorothioformate (**21**) (2.52 mL, 20 mmol). The reaction mixture was stirred then for 1 h, diluted with 100 mL of ethyl acetate, and washed with 2 × 60 mL of 1 N hydrochloric acid, 2 × 60 mL of 10% $NaHCO_3$, and 2 × 40 mL of saturated NaCl solution. After the organic layer was dried, it was concentrated to give a brown thick oil, which was chromatographed on silica gel using a 4:1 ether/petroleum ether or 7:3 ethyl acetate/cyclohexane mixture to afford the ylide pyridyl thio ester **19** as yellow foam in 15–32% yield (based on the starting silyl ester **7b**). This material formed plates in ether. IR: 1755 (β-lactam C=O), 1725 (ester C=O), 1665 (ylide ester), 1635 and 1585 (pyridyl thio). NMR: 0.72, 0.74, and 0.80 (Si-*t*-Bu, 3 s), 0.98 and 1.14 (CH_3, d, J =6, 8 Hz), 2.6–3.42 and 4.0–6.15 (β-lactam protons, CH_2CH=CH_2, CHOSi), 7.31–7.95 (phenyl H and pyridyl H), 8.64 (pyridyl H, d, J = 5 Hz). MS: m/e 752 (M^+), 753 (M + 1), 262.

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[[(2′-pyridylthio)carbonyl]methyl]azetidin-2-one (18). The crude hydroxy azetidinone **9** (5.15 g, 10 mmol) was converted into the thick oily chloro azetidinone **12** as described above for **13** from **10**. Ylide ester **18** was then prepared from **12** by employing one of the two following methods.

Method I. The thick oil **12** was dissolved in a solution of triphenylphosphine (2.62 g, 10 mmol) in 50 mL of sieve-dried DMF, and dry pyridine (0.8 mL, 10 mmol) was then added. The reaction mixture was then heated under nitrogen at 80 °C for 2 h and cooled to room temperature, concentrated HCl (0.75 mL) was added, and the mixture was stirred for 5 min. The solvents were removed in vacuo at <30 °C. The residue was taken up in 125 mL of ethyl acetate and washed with 50 mL of pH 7 phosphate buffer (0.5 M), 100 mL of 10% $NaHCO_3$, and 50 mL of saturated NaCl solution. The organic layer was dried. Solvent removal in vacuo gave 6.5 g of the ylide acid **15** as a brown oil.

To a solution of this crude ylide acid **15** in sieve-dried methylene chloride (100 mL) at 0 °C under nitrogen was added 2-pyridyl chlorothioformate[7] (**21**) (1.26 mL, 10 mmol) followed by triethylamine (1.39 mL, 10 mmol). The reaction mixture was stirred

at 0 °C for 1 h, diluted with 125 mL of ethyl acetate, and washed with 2 × 50 mL of ice water, 100 mL of ice-cold 1 N HCl solution, 100 mL of 10% $NaHCO_3$ solution, and finally 100 mL of saturated NaCl solution. The organic layer was dried. Solvent removal gave a yellow crude oil, which was chromatographed on silica gel using a 1:1 ethyl acetate/cyclohexane mixture to afford the desired ylide pyridyl thio ester **18** as a yellow foam in 18% yield (from the starting silyl ester azetidinone **6b**).

Method II. The chloro azetidinone **12**, obtained from 10 mmol of the hydroxy azetidinone **9**, was dissolved in sieve-dried DMF (50 mL), and triphenylphosphine (2.62 g, 10 mmol) was added, followed by 2,6-lutidine (1.165 mL, 10 mmol). The reaction mixture was heated under nitrogen at 80 °C for 2 h and cooled to room temperature, and DMF was removed in vacuo at <30 °C. The residue was taken up in 125 mL of ethyl acetate and washed with 50 mL of pH 7 phosphate buffer (0.5 M), 100 mL of 10% $NaHCO_3$, and 50 mL of saturated NaCl. The organic phase was dried. Solvent removal in vacuo gave 6.15 g of crude oil. This was dissolved in dry THF and cooled to 0 °C under nitrogen with stirring, and acetic acid (1.15 mL, 20 mmol) followed by tetra-*n*-butylammonium fluoride (10 mL of 1 M solution in THF, 10 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, diluted with 150 mL of ethyl acetate, and washed with 3 × 25 mL of water, 25 mL of pH 7 phosphate buffer (0.5 M), and 25 mL of saturated NaCl solution. The organic layer was dried. Solvent removal afforded 5.9 g of the ylide acid **15** as a thick brown oil.

This ylide acid **15** was converted as described in method I above into the desired ylide pyridyl thio ester **18** in 25% yield, based on the starting silyl ester azetidinone **6b**. IR: 1755 (β-lactam C=O), 1710 (ester C=O), 1625 (ylide ester), 1575 (pyridyl thio). MS: *m/e* 738 (M^+), 739 (M + 1), 262.

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*S*)-2′-[(pyridylthio)carbonyl]ethyl]azetidin-2-one (20). This compound was synthesized in 44% yield as a yellow foam from the hydroxy azetidinone **11** by following the above method I employed for the synthesis of the pyridyl thio ester **18** from **9**. IR: 1755 (β-lactam C=O), 1720 (ester C=O), 1650 (ylide ester), 1625 and 1575 (pyridyl thio). NMR: 0.74 (Si-*t*-Bu, s), 1.06 (CH_3, d, J = 6 Hz), 1.24 (CH_3, d, J = 6 Hz), 4.24–6.16 (H3, H4, $CH_2CH{=}CH_2$, SiOCH), 7.27–7.80 (phenyl H and pyridyl H), 8.65 (1 pyridyl H). MS: *m/e* 752 (M^+), 753 (M + 1), 262.

2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-5-bromopyridine (34a). 2-Picoline (46.565 g, 0.5 mol) was added under nitrogen to mechanically stirred solid aluminum chloride (200 g, 1.5 mol). This slurry was heated with stirring to 100 °C, and bromine (40 g, 0.25 mol) was added over a period of 1 h. The heating was continued at 100 °C for 0.5 h. The reaction mixture was poured into 2 L of ice water containing 75 mL of concentrated HCl. Additional concentrated HCl was added until the mixture became acidic. Excess $NaHSO_3$ solid was added, and the mixture was left overnight at room temperature, decanted, and washed with 3 × 150 mL of methylene chloride. The aqueous phase was made alkaline with 50% NaOH solution and extracted with ether (4 × 150 mL). The organic phase was washed with brine (100 mL) and dried. Solvent removal gave 57 g of residue, which was chromatographed on silica gel using a mixture of ether/petroleum ether (1:9) as solvent to give 14.4 g of 5-bromo-2-picoline (solid, R_f 0.5) and 9.5 g of 3-bromo-2-picoline (oil, R_f 0.4).

m-Chloroperbenzoic acid (85% pure, 12.2 g, 60 mmol) was added to a solution of 5-bromo-2-picoline (9.4 g, 54.6 mmol) in chloroform (50 mL). After 1 h of stirring at room temperature, the solid was filtered and the filtrate was washed with 2 × 25 mL of saturated $NaHCO_3$ solution, dried, and concentrated to afford 10 g of crude product, which was chromatographed on silica gel using ethyl acetate/cyclohexane (1:1) as solvent to yield 9.4 g of the *N*-oxide of 5-bromo-2-picoline (R_f 0.15).

To this *N*-oxide of 5-bromo-2-picoline (9.4 g, 50 mmol) was added trifluoroacetic anhydride (35 mL) under nitrogen, and the mixture was stirred for 0.5 h at room temperature and for 0.5 h at 53 °C bath temperature. The reaction mixture was cooled, $NaHCO_3$ solution (150 mL, 10%) was added, and the mixture was stirred at room temperature for 6 h, extracted with 3 × 50 mL of methylene chloride, and dried. Solvent removal gave crude product, which was chromatographed on silica gel using a mixture of ethyl acetate/cyclohexane (1:1) (R_f 0.35) as solvent to afford 5.7 g of 2-(hydroxymethyl)-5-bromopyridine.

To a solution of this 2-(hydroxymethyl)-5-bromopyridine (5.657 g, 30 mmol) in dry DMF (25 mL) were added *tert*-butyldimethylsilyl chloride (5.43 g, 36 mmol) and triethylamine (5.04 mL, 36 mmol). The mixture was stirred under nitrogen overnight, diluted with 100 mL of ethyl acetate, washed with 2 × 25 mL of ice water, and dried. Solvent removal in vacuo gave a colorless oil, which was distilled in a short-path distillation apparatus at 110–112 °C (0.1 mm) to afford 7.5 g of 2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5-bromopyridine (**34a**) as a colorless oil. NMR: 0.19 ($SiCH_3$, s), 1.0 (Si-*t*-Bu, s), 4.73 (CH_2OSi, s), 7.0–8.2 (pyridine H, m).

4-[(*tert*-Butyldimethylsilyl)oxy]bromobenzene (24a). To a stirred solution of reagent grade 4-bromophenol (1.4 g, 8 mmol) in 16 mL of dry methylene chloride at 0 °C was added triethylamine (1.4 mL, 10 mmol), followed by a catalytic amount of 4-(dimethylamino)pyridine and *tert*-butyldimethylsilyl chloride (1.33 g, 8.8 mmol). A white precipitate appeared immediately. The reaction mixture was warmed to room temperature, stirred for 3 h, and washed with 1 N HCl/ice, followed by washing with brine. The organic phase was dried over Na_2SO_4 and filtered. The solution was concentrated and distilled at 95 °C (1.5 mm) to give 73% of the desired 4-[(*tert*-butyldimethylsilyl)oxy]-bromobenzene (**24a**) as a colorless oil.

Phenylmagnesium Bromide (22). To a stirred suspension of magnesium turnings (108 mg, 4.5 mmol) in dry THF (8 mL) was added reagent grade bromobenzene (0.628 mL, 4 mmol). A trace of 1,2-dibromoethane was added, and the reaction mixture was stirred for 2 h at room temperature under nitrogen, during which period digestion of the magnesium metal was complete. The resulting clear liquid was used as 0.5 M phenylmagnesium bromide (**22**) in THF solution.

[4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]phenyl]magnesium bromide (33) was also prepared similarly from 4-**[[(*tert*-butyldimethylsilyl)oxy]methyl]bromobenzene**[5] **(33a).**

3-Pyridylmagnesium Bromide (23). A stirred solution of freshly distilled reagent grade 3-bromopyridine (316 mg, 2 mmol) in anhydrous ether (5 mL) under nitrogen at −78 °C was treated with 1.3 M *n*-butyllithium in hexane (1.69 mL, 2.2 mmol) dropwise. The resulting yellow suspension was stirred at −78 °C for 0.5 h. A turbid solution of magnesium bromide, preformed in situ from magnesium (72 mg, 3 mmol) and 1,2-dibromoethane (0.257 mL, 3 mmol) in dry THF (10 mL), was then added dropwise at −78 °C. After 15 min at −78 °C, the reaction mixture was stirred for 20 min at 0 °C. The resulting clear brown solution (16 mL) with a small amount of brown oil at the bottom was used as a 0.125 M solution of 3-pyridylmagnesium bromide.

Via the above procedure, **[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]magnesium bromide (24)** was obtained from 4-**[(*tert*-butyldimethylsilyl)oxy]bromobenzene (24a)** and **[2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5-pyridyl]magnesium bromide (34)** was obtained from **2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5-bromopyridine (34a).**

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(phenylcarbonyl)methyl]azetidin-2-one (25a). A stirred solution of the ylide pyridyl thio ester **18** (221.5 mg, 0.3 mmol) in THF (5 mL) under nitrogen cooled to 0 °C in an ice-water bath was treated with the Grignard reagent **22** (1.2 mL, 0.6 mmol). After 5 min, TLC of an aliquot indicated the complete disappearance of the starting material. Saturated NH_4Cl solution (5 mL) was added after 15 min. The resulting mixture was extracted with 3 × 5 mL of methylene chloride. The combined organic layers were dried. Evaporation of the solvent gave a thick oil, which was chromatographed on silica gel using ethyl acetate/cyclohexane (1:1) as solvent to afford 52% of the desired phenyl ketone **25a** as a white foam. IR: 1740 (β-lactam C=O), 1675 (phenyl ketone C=O), 1625 (ylide ester). MS: *m/e* 706 (M + 1).

The following analogous ketones (**26a–30a**, **35**, and **36**) were also prepared by the above procedure (refer to Table I for conditions and yields).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldi-

methylsilyl)oxy]ethyl]-4-[(3′-pyridylcarbonyl)methyl]azetidin-2-one (26a). IR (CH_2Cl_2): 1732 (β-lactam C=O), 1680 (pyridyl ketone C=O), 1610 (ylide ester).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-(phenylcarbonyl)ethyl]azetidin-2-one (27a). IR: 1750 (β-lactam C=O), 1680 (phenyl ketone C=O), 1620 (ylide ester). MS: *m/e* 720 (M + 1).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-(3′-pyridylcarbonyl)ethyl]azetidin-2-one (28a). IR: 1730 (β-lactam C=O), 1675 (pyridyl ketone C=O), 1615 (ylide ester).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*S*)-1-(3′-pyridylcarbonyl)ethyl]azetidin-2-one (29a). IR: 1740 (β-lactam C=O), 1680 (pyridyl ketone C=O), 1625 (ylide ester).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[[[4′-[(*tert*-butyldimethylsilyl)oxy]phenyl]carbonyl]methyl]azetidin-2-one (30a). IR: 1735 (β-lactam C=O), 1670 (phenyl ketone C=O), 1595 (ylide ester).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[[4′-[[(*tert*-butyldimethylsilyl)oxy]methyl]phenyl]carbonyl]ethyl]azetidin-2-one (35). IR: 1745 (β-lactam C=O), 1680 (phenyl ketone C=O), 1625 (ylide ester). MS: *m/e* 863 (M^+), 864 (M + 1).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[[2′-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5′-pyridyl]carbonyl]ethyl]azetidin-2-one (36). IR: 1740 (β-lactam C=O), 1680 (pyridyl ketone C=O), 1625 (ylide ester). MS: *m/e* 865 (M + 1).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[[4′-(hydroxymethyl)phenyl]carbonyl]ethyl]azetidin-2-one (37). To a solution of the silyl ether **35** (374 mg, 0.433 mmol) in anhydrous THF (5 mL) at room temperature under nitrogen was added glacial acetic acid (0.0744 mL, 1.299 mmol), followed by tetra-*n*-butylammonium fluoride[8] (1 M in THF, 0.433 mL, 0.433 mmol). The reaction mixture was stirred for 4.5 h, diluted with 15 mL of ethyl acetate, and washed with ice water (5 mL), 10% $NaHCO_3$ solution (5 mL), and saturated NaCl solution (5 mL). The organic phase was dried. Solvent removal gave a foam, which was chromatographed on silica gel using ethyl acetate as solvent. The desired alcohol was obtained as a white foam in 79% yield. IR: 3500 (OH), 1760 (β-lactam C=O), 1680 (phenyl ketone C=O), 1620 (ylide ester).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[[2′-(hydroxymethyl)-5′-pyridyl]carbonyl]ethyl]azetidin-2-one (38). This alcohol was prepared from the silyl ether **36** in 80% yield by following the procedure described above for the alcohol **37**. IR: 3400 (OH), 1750 (β-lactam C=O), 1690 (pyridyl ketone C=O), 1640 (ylide ester). MS: *m/e* 750 (M^+), 751 (M + 1), 262.

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[[4′-[[(methylsulfonyl)oxy]methyl]phenyl]carbonyl]ethyl]azetidin-2-one (39). The alcohol **37** (250 mg, 0.33 mmol) in dry methylene chloride (5 mL) cooled to 0 °C under nitrogen was treated with methanesulfonyl chloride (0.04 mL, 0.5 mmol) and triethylamine (0.09 mL, 0.66 mmol). The mixture was stirred at 0 °C for 0.5 h and at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with ice water (5 mL) and saturated NaCl solution (5 mL). The organic phase was dried. The solvent was removed to give the crude methanesulfonate **39** as a foam in 96% yield. This material was used in the next reaction without further purification. IR: 1740 (β-lactam C=O), 1675 (phenyl ketone C=O), 1625 (ylide ester).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[[2′-[[(methylsulfonyl)oxy]methyl]-5′-pyridyl]carbonyl]ethyl]azetidin-2-one (40). This methanesulfonate was prepared from the alcohol **38** in quantitative yield following the procedure described above for the methanesulfonate **39**. IR: 1750 (β-lactam C=O), 1690 (pyridyl ketone C=O), 1625 (ylide ester).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[[4′-(azidomethyl)phenyl]carbonyl]ethyl]azetidin-2-one (41). Lithium azide (98 mg, 2 mmol) was added to a solution of the methanesulfonate **39** (262 mg, 0.32 mmol) in dry DMF (2 mL), and the mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo at <35 °C. The residue was taken up in ethyl acetate (10 mL), washed with ice water (5 mL), and dried. Solvent removal gave a foam, which was chromatographed on silica gel, with ethyl acetate/cyclohexane (7:3) as solvent. The desired azide **41** was obtained as a white foam in 85% yield. IR: 2100 (azide), 1750 (β-lactam C=O), 1680 (phenyl ketone C=O), 1625 (ylide ester). MS: *m/e* 774 (M^+), 775 (M + 1), 262.

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[[2′-(azidomethyl)-5′-pyridyl]carbonyl]ethyl]azetidin-2-one (42) was prepared from the methanesulfonate **40** in 53% yield as a yellow foam by following the procedure described above for the azide **41**. IR: 2110 (azide), 1750 (β-lactam C=O), 1685 (pyridyl ketone C=O), 1620 (ylide ester).

Allyl (5*R*,6*S*)-2-Phenyl-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]carbapen-2-em-3-carboxylate (25b). A solution of the phosphorane phenyl ketone **25a** (80 mg, 0.1135 mmol) in anhydrous xylene (3 mL) was heated with two small crystals of hydroquinone at 125 °C under nitrogen for 2 h. The progress of the reaction was followed by TLC (EtOAc/cyclohexane, 1:4, silica gel), which indicated the disappearance of the starting ylide ketone and the appearance of a new less polar UV-active spot. After 2 h, the solvent was removed in vacuo and the residue was purified on silica gel using ethyl acetate/cyclohexane (1:4) as solvent to give 39.3 mg (81%) of the desired carbapenem **25b** as a white foam. IR: 1780 (β-lactam C=O), 1725 (ester C=O). NMR: 0.09 and 0.1 ($SiCH_3$, 2 s), 0.90 (Si-*t*-Bu, s), 3.21 (H6, dd, *J* = 1.5, 3 Hz), 3.23 (H1, m), 4.26 (H5 and H8, m), 4.62–5.96 (CH_2=$CHCH_2$, m), 7.36 (phenyl H). MS: *m/e* 427 (M^+).

Via the above procedure for **25b**, carbapenem silyl ethers **26b–30b**, **43**, **44**, and **47** were also prepared from the ylide ketones **26a–30a**, **41**, **42**, and **35** as specified in Table II.

Allyl (5*R*,6*S*)-2-(3′-Pyridyl)-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]carbapen-2-em-3-carboxylate (26b). IR (CH_2Cl_2): 1778 (β-lactam C=O), 1715 (ester C=O). NMR: 0.095 ($SiCH_3$, s), 0.90 (Si-*t*-Bu, s), 1.30 (CH_3, d, *J* = 8 Hz), 3.12–3.40 (H6 and H2, m), 4.22–4.40 (H5 and H8, m), 4.60–6.00 (CH_2CH=CH_2, m), 7.28–8.73 (pyridyl H, m).

Allyl (1*R*,5*R*,6*S*)-2-Phenyl-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (27b). IR: 1785 (β-lactam C=O), 1725 (ester C=O). NMR: 0.14 and 0.15 ($SiCH_3$, 2 s), 0.93 (Si-*t*-Bu, s), 1.09 (CH_3, d, *J* = 8 Hz), 1.33 (CH_3, d, *J* = 6 Hz), 3.35 (H6, dd, *J* = 1.5, 3 Hz), 3.44 (H1, m), 4.31 (H8, m), 4.36 (H5, dd, *J* = 1.5, 5 Hz), 4.57–5.97 (CH_2CH=CH_2, m), 7.41 (phenyl H).

Allyl (1*R*,5*R*,6*S*)-2-(3′-Pyridyl)-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (28b). IR: 1785 (β-lactam C=O), 1725 (ester C=O). NMR: 0.1 and 0.11 ($SiCH_3$, 2 s), 0.91 (Si-*t*-Bu, s), 1.08 (CH_3, d, *J* = 8 Hz), 1.30 (CH_3, d, *J* = 6 Hz), 3.36 (H6, dd, *J* = 1.5, 3 Hz), 3.46 (H1, m), 4.3 (H8, m), 4.40 (H5, dd, *J* = 1.5, 5 Hz), 4.54–5.92 (CH_2CH=CH_2, m), 7.3–8.68 (pyridyl H, m).

Allyl (1*S*,5*R*,6*S*)-2-(3′-Pyridyl)-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (29b). IR: 1795 (β-lactam C=O), 1735 (ester C=O). NMR: 0.11 ($SiCH_3$, s), 0.94 (Si-*t*-Bu, s), 1.14 (CH_3, d, *J* = 7 Hz), 1.30 (CH_3, d, *J* = 6 Hz), 3.29 (H6, dd, *J* = 1.5, 3 Hz), 3.64 (H1, m), 3.89 (H5, dd, *J* = 1.5, 5 Hz), 4.26 (H8, m), 4.58–5.90 (CH_2CH=CH_2, m), 7.36, 7.56 and 8.44 (pyridyl H).

Allyl (1*R*,5*R*,6*S*)-2-[4′-(Azidomethyl)phenyl]-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (43). IR: 2100 (azide), 1775 (β-lactam C=O), 1725 (ester C=O). NMR: 0.1 ($SiCH_3$, 2 s), 0.89 (Si-*t*-Bu, s), 1.06

(CH_3, d, J = 8 Hz), 1.29 (CH_3, d, J = 6 Hz), 3.31 (H6, dd, J = 1.5, 3 Hz), 3.43 (H1, m), 4.46 (H5, dd, J = 1.5, 5 Hz), 4.48 (CH_2N_3, s), 4.64–6.00 ($CH_2CH{=}CH_2$, m), 7.49 (aromatic H, 2 d, J = 4 Hz).

Allyl (1*R*,5*R*,6*S*)-2-[2′-(Azidomethyl)-5′-pyridyl]-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (44). IR: 2100 (azide), 1785 (β-lactam C=O), 1725 (ester C=O). NMR: 0.1 ($SiCH_3$, 2 s), 0.9 (Si-*t*-Bu, s), 1.08 (CH_3, d, J = 8 Hz), 1.28 (CH_3, d, J = 6 Hz), 3.34 (H6, dd, J = 1.5, 3 Hz), 3.48 (H1, m), 4.40 (H5, dd, J = 1.5, 5 Hz), 4.53 (CH_2N_3, s), 4.63, 5.24 ($CH_2CH{=}CH_2$, m), 7.60 (pyridine 5′H, d, J = 4 Hz), 7.77 (pyridine 4′H, dd, J = 1.2, 4 Hz, 1 H), 8.58 (pyridine 2′H, d, J = 1.2 Hz). MS: m/e 497 (M^+), calcd for M − 57 (*t*-Bu) = $C_{11}H_{26}N_5O_4Si$ 440.17541, found 440.1754.

Allyl (1*R*,5*R*,6*S*)-2-[4′-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]phenyl]-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]-ethyl]-1-methylcarbapen-2-em-3-carboxylate (47). IR: 1795 (β-lactam C=O), 1740 (ester C=O). NMR: 0.11 and 0.12 ($SiCH_3$, 2 s), 0.92 and 0.96 (Si-*t*-Bu's, 2 s), 1.04 (CH_3, d, J = 8 Hz), 1.30 (CH_3, d, J = 7 Hz), 3.30 (H6, dd, J = 1.5, 3 Hz), 3.43 (H1, m), 4.35 (H5, dd, J = 1.5, 5 Hz), 4.30 (H8, m), 4.78 (CH_2OSi, s), 4.56–5.96 ($CH_2CH{=}CH_2$, m), 7.37 (aromatic H).

Allyl (5*R*,6*S*)-2-Phenyl-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (25c). To a solution of the carbapenem silyl ether **25b** (113 mg, 0.2646 mmol) in freshly distilled anhydrous THF (5 mL) were added first glacial acetic acid (0.227 mL, 3.969 mmol) and then a 1 M solution of tetra-*n*-butylammonium fluoride in THF (1.323 mL, 1.323 mmol). After stirring for 30 h at room temperature under nitrogen, TLC (silica gel, ethyl acetate/cyclohexane, 1:1) indicated the disappearance of most of the starting material. The reaction mixture was diluted with ethyl acetate, washed with ice water (2 × 5 mL), 10% sodium bicarbonate solution (5 mL), and saturated sodium chloride solution (5 mL), and dried. Removal of the solvent gave 65 mg of crude product, which was chromatographed on silica gel with ethyl acetate/cyclohexane (1:1) as solvent to give 60% of the required carbapenem alcohol **25c** as a white foam. IR: 3450 (OH), 1780 (β-lactam C=O), 1725 (ester C=O). NMR: 1.35 (CH_3, d, J = 6 Hz), 3.26 (H1, m), 3.28 (H6, dd, J = 1.5, 3 Hz), 4.24 (H8, m), 4.31 (H5, dd, J = 1.5, 5 Hz), 4.53–5.94 ($CH_2CH{=}CH_2$, m), 7.36 (phenyl H). MS: m/e 312 (M − 1).

The following carbapenem alcohols (**26c–29c**, **31**, **45**, **46**, and **48**) were also prepared by the above procedure (see Table III for details).

Allyl (5*R*,6*S*)-2-(3′-Pyridyl)-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (26c). IR: 3450 (OH), 1780 (β-lactam C=O), 1724 (ester C=O). NMR: 1.38 (CH_3, d, J = 8 Hz), 3.24–3.33 (H6 and H2, m), 4.20–4.40 (H5 and H8), 4.56–5.96 ($CH_2CH{=}CH_2$, m), 7.25–8.62 (pyridyl H, m).

Allyl (1*R*,5*R*,6*S*)-2-Phenyl-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (27c). IR: 3450 (OH), 1770 (β-lactam C=O), 1725 (ester C=O). NMR: 1.05 (CH_3, d, J = 8 Hz), 1.35 (CH_3, d, J = 6 Hz), 2.56 (hydroxyl, br), 3.33 (H6, dd, J = 1.5, 3 Hz, 1 H), 3.36 (H1, m), 4.33 (H5, dd, J = 1.5, 5 Hz), 4.27 (H8, m), 4.5–6.05 ($CH_2CH{=}CH_2$, m), 7.33 (phenyl H).

Allyl (1*R*,5*R*,6*S*)-2-(3′-Pyridyl)-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (28c). IR: 3200 (OH), 1775 (β-lactam C=O), 1725 (ester C=O). NMR: 1.1 (CH_3, d, J = 8 Hz), 1.39 (CH_3, d, J = 6 Hz), 2.07 (hydroxyl, br), 3.40 (H6, dd, J = 1.5, 3 Hz), 3.50 (H1, m), 4.34 (H8, m), 4.44 (H5, dd, J = 1.5, 5 Hz), 4.58–5.95 ($CH_2CH{=}CH_2$, m), 7.35, 7.75, and 8.61 (pyridyl H). MS: m/e 328, calcd for $C_{18}H_{20}N_2O_4$ 328.1423, found 328.1419.

Allyl (1*S*,5*R*,6*S*)-2-(3′-Pyridyl)-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (29c). IR: 3200 (OH), 1785 (β-lactam C=O), 1735 (ester C=O). NMR: 1.15 (CH_3, d, J = 7 Hz), 1.37 (CH_3, d, J = 6 Hz), 3.37 (H6, dd, J = 1.5, 3 Hz), 3.68 (H1, m), 3.97 (H5, dd, J = 1.5, 4 Hz), 4.30 (H8, m), 4.46–5.92 ($CH_2CH{=}CH_2$, m), 7.36, 7.58, 8.46, and 8.57 (pyridyl H, m).

Allyl (5*R*,6*S*)-2-(4′-Hydroxyphenyl)-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (31). IR: 1735 (β-lactam C=O). NMR: 1.31 (CH_3, d, J = 8 Hz), 3.1–3.24 (H6 and H1, m), 4.14–4.30 (H5 and H8, m), 4.5–5.96 ($CH_2CH{=}CH_2$, m), 6.75 and 7.27 (phenyl H, dd, J = 4, 52 Hz).

Allyl (1*R*,5*R*,6*S*)-2-[4′-(Azidomethyl)phenyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (45). IR: 3460 (OH), 2100 (azide), 1775 (β-lactam C=O), 1725 (ester). NMR: 1.08 (CH_3, d, J = 8 Hz), 1.39 (CH_3, d, J = 6 Hz), 2.09 (hydroxyl, br), 3.38 (H6, dd, J = 1.5, 3 Hz), 3.47 (H1, m), 4.24–4.44 (CH_2N_3, H5 and H8, m), 4.54–5.94 ($CH_2CH{=}CH_2$, m), 7.36 (aromatic H, 2 d, J = 4 Hz). MS: m/e 382 (M^+), calcd for $C_{20}H_{22}N_4O_4$ 382.1641, found 382.1640.

Allyl (1*R*,5*R*,6*S*)-2-[2′-(Azidomethyl)-5′-pyridyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (46). IR: 3400 (OH), 2115 (azide), 1780 (β-lactam C=O), 1725 (ester C=O). NMR: 1.08 (CH_3, d, J = 7 Hz), 1.26 (CH_3, d, J = 7 Hz), 2.64 (hydroxyl, br), 3.39 (H6, dd, J = 1.5, 3 Hz), 3.50 (H1, m), 4.30 (H8, m), 4.43 (H5, dd, J = 1.5, 5 Hz), 4.53 (CH_2N_3, s), 4.58–5.60 ($CH_2CH{=}CH_2$, m), 7.39 (pyridine 5′H, d, J = 4 Hz), 7.76 (pyridine 4′H, dd, J = 1.2, 4 Hz), 8.56 (pyridine 2′H, d, J = 1.2 Hz). MS: m/e 383 (M^+), calcd for $C_{19}H_{21}N_5O_4$ 383.15935, found 383.1593.

Allyl (1*R*,5*R*,6*S*)-2-[4′-(Hydroxymethyl)phenyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (48). IR: 3400 (OH), 1770 (β-lactam C=O), 1730 (ester C=O). NMR: 1.08 (CH_3, d, J = 8 Hz), 1.38 (CH_3, d, J = 6 Hz), 2.16 (hydroxyls, br), 3.37 (H6, dd, J = 1.5, 3 Hz), 3.47 (H1, m), 4.30 (H8, m), 4.38 (H5, dd, J = 1.5, 5 Hz), 4.74 (CH_2O, s), 4.54–5.97 ($CH_2CH{=}CH_2$, m), 7.40 (aromatic H, 2 d, J = 4 Hz).

Potassium (5*R*,6*S*)-2-Phenyl-6-[(1*R*)-1-hydroxyethyl]-carbapen-2-em-3-carboxylate (25d). To a stirred solution of the carbapenem allyl ester **25c** (60 mg, 0.183 mmol) in a mixture of sieve-dried ethyl acetate and methylene chloride (1.5 mL/1.5 mL) in a centrifuge tube under nitrogen were added triphenylphosphine (4.2 mg, 0.016 mmol), 0.5 M potassium 2-ethylhexanoate (0.366 mL, 0.183 mmol), and then tetrakis(triphenylphosphine)palladium (7 mg, 0.00604 mmol). After 5 min of stirring, the reaction mixture was diluted with 6 mL of anhydrous ether and centrifuged and the supernatant liquid was separated. Anhydrous ether (10 mL) was added to the residual solid, and the mixture was stirred and centrifuged. Solvent was then decanted. This last step was repeated with 10 mL of dry ethyl acetate and 10 mL of dry ether. The residual solid was dissolved in 0.5 mL of water and applied on two 500-μm reverse-phase silica gel plates. After elution with a mixture of ethanol and water (1:9), the UV-active areas were scraped and the scrapings were stirred in 10 mL of an acetonitrile and deionized water mixture (2:5). The filtrate was extracted with 4 × 5 mL of hexane. The aqueous phase was concentrated to 0.5 mL in vacuo at <25 °C and then lyophilized to give 24 mg of the desired potassium salt **25d** as a white foamy material. NMR (D_2O): 1.17 (CH_3, d, J = 6 Hz), 2.94 (H1, dd, J = 5, 8 Hz), 3.31 (H1, dd, J = 4.25, 8.5 Hz), 3.38 (H6, dd, J = 1.5, 3 Hz), 4.13 (H8, m), 4.20 (H5, ddd, J = 1.5, 4.25, 5 Hz), 7.26 (phenyl H, m). UV: λ_{max} (H_2O) 299 nm (NH_2OH extinguishable).

The following potassium salts of carbapenems **26d–29d**, **32**, **49**, **50**, and **53** were prepared according to the above-described procedure for **25d**.

Potassium (5*R*,6*S*)-2-(3′-pyridyl)-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (26d) was obtained from allyl ester **26c** in 23% yield. UV: λ_{max} (H_2O) 302 nm (NH_2OH extinguishable).

Potassium (1*R*,5*R*,6*S*)-2-phenyl-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (27d) was prepared from allyl ester **27c** in 49% yield. NMR (D_2O): 0.96 (CH_3, d, J = 8 Hz), 1.20 (CH_3, d, J = 6 Hz), 3.34 (H1, m), 3.38 (H_6, dd, J = 1.5, 3 Hz), 4.16 (H8, m), 4.18 (H5, dd, J = 1.5, 5 Hz), 7.32 (phenyl H, m). UV: λ_{max} (H_2O) 285 nm (NH_2OH extinguishable). MS: 286 (M − K), 378 (M − K + glycerol matrix).

Potassium (1*R*,5*R*,6*S*)-2-(3′-pyridyl)-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (28d) was obtained from allyl ester **28c** in 50% yield. NMR (D_2O): 1.02 (CH_3, d, J = 8 Hz), 1.24 (CH_3, d, J = 6 Hz), 3.45 (H1, m), 3.46 (H6, dd, J = 1.5, 3 Hz), 4.22 (H8, m), 4.28 (H5, dd, J = 1.5, 5 Hz), 7.45, 7.87, and 8.45 (pyridyl H, m). UV: λ_{max} (H_2O) 290 nm (NH_2OH extinguishable). MS: 379 (M − K + glycerol matrix).

Potassium (1*S*,5*R*,6*S*)-2-(3′-pyridyl)-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (29d) was prepared from allyl ester **29c** in 38% yield. NMR (D_2O): 0.94 (CH_3, d, J = 7 Hz), 1.16 (CH_3, d, J = 6 Hz), 3.47 (H6, dd, J = 1.5, 3 Hz), 3.73 (H1, m), 3.80 (H5, dd, J = 1.5, 3.75 Hz), 4.14 (H8, m), 7.36, 7.62, and 8.24 (pyridyl H, m). UV: λ_{max} (H_2O) 295 nm

(NH_2OH extinguishable). MS: 379 (M – K + glycerol matrix).

Potassium (5*R*,6*S*)-2-(4′-hydroxyphenyl)-6-[(1*R*)-1-hydroxyethyl]-carbapen-2-em-3-carboxylate (32) was obtained from the allyl ester **31** in 30% yield. IR: 1735 (β-lactam C=O). NMR (D_2O): 1.16 (CH_3, d, J = 8 Hz), 2.9 and 3.26 (H2), 3.34 (H6, dd, J = 2, 4 Hz), 4.04–4.22 (H5 and H8, m), 6.74 and 7.17 (phenyl H, dd, J = 4, 43 Hz). UV: λ_{max} (H_2O) 300 nm (NH_2OH extinguishable).

Potassium (1*R*,5*R*,6*S*)-2-[4′-(azidomethyl)phenyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (49) was prepared from allyl ester **45** in 39% yield. NMR (D_2O): 0.9 (CH_3, d, J = 8 Hz), 1.14 (CH_3, d, J = 6 Hz), 3.30 (H6, dd, J = 1.5, 3 Hz), 3.22–3.40 (H1, m), 4.14 (H5, dd, J = 1.5, 5 Hz), 4.04–4.20 (H8, m), 4.27 (CH_2N_3, s, 2 H), 7.29 (aromatic H, 2 d, J = 4 Hz). UV: λ_{max} (H_2O) 286 nm (NH_2OH extinguishable).

Potassium (1*R*,5*R*,6*S*)-2-[2′-(azidomethyl)-5′-pyridyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (50) was obtained from allyl ester **46** in 32% yield. NMR (D_2O): 0.94 (CH_3, d, J = 8 Hz), 1.16 (CH_3, d, J = 8 Hz), 3.39 (H6, dd, J = 1.5, 3 Hz, 1 H), 3.30–3.46 (H1, m), 4.21 (H5, dd, J = 1.5, 5 Hz), 4.16 (H8, m), 4.42 (CH_2N_3, s), 7.3–8.5 (pyridyl H, m). UV: λ_{max} (H_2O) 290 nm (NH_2OH extinguishable).

Potassium (1*R*,5*R*,6*S*)-2-[4′-(hydroxymethyl)phenyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (53) was prepared from allyl ester **48** in 68% yield. NMR (D_2O): 1.36 (CH_3, d, J = 8 Hz), 1.60 (CH_3, d, J = 6 Hz, 3 H), 3.78 (H6 and H1, m, 2 H), 4.59 (H5 and H8, m, 2 H), 4.92 (CH_2O, s, 2 H), 7.70 (phenyl H, 2 d, J = 4 Hz, 4 H). UV: λ_{max} (H_2O) 288 nm (NH_2OH extinguishable).

(1*R*,5*R*,6*S*)-2-[4′-(Aminoethyl)phenyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic Acid (51). The carbapenem azide **49** (37 mg, 0.0974 mmol) was dissolved in 3 mL of water. Ten milligrams of 10% Pd/C and 0.39 mL (0.195 mmol) of 0.5 M pH 7 4-morpholinepropanesulfonic acid buffer were added. The mixture was hydrogenated at 45 psi on a Parr shaker apparatus for 15 min at room temperature. The solids were filtered and washed with 2 × 2 mL of water. The filtrate was concentrated to 0.5 mL, applied on reverse-phase silica gel plates, and worked up as described for **25d** to give 72% of the carbapenem amino acid **51**. UV: λ_{max} (H_2O) 287 nm (NH_2OH extinguishable). MS: FAB positive ion, 319 (M + H); FAB negative ion, 317 (M – H).

(1*R*,5*R*,6*S*)-2-[2′-(Aminomethyl)-5′-pyridyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid (52) was similarly obtained from the azide **50** as described above for **51** in 80% yield. NMR: 0.95 (CH_3, d, J = 6 Hz), 1.16 (CH_3, d, J = 6 Hz), 3.25–3.45 (H6 and H1), 4.0–4.30 (H5 and H8), 7.20–8.50 (pyridyl H). UV: λ_{max} (H_O) 290 nm (NH_2OH extinguishable).

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Anticonvulsant *O*-Alkyl Sulfamates. 2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose Sulfamate and Related Compounds†

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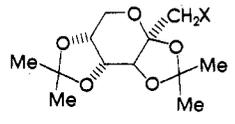
Novel sugar sulfamate **1** (McN-4853, topiramate) has been found to exhibit potent anticonvulsant activity analogous to that of phenytoin. In the maximal electroshock seizure test, orally at 2 h in mice, **1** had an ED_{50} of 39 mg/kg. Orally, **1** had a duration of action in excess of 8 h. Other aspects of the pharmacology of **1**, as well as neurochemistry and carbonic anhydrase inhibition, are discussed. The conformational behavior of **1** in solution and in the solid state is discussed. A series of analogues of **1** were synthesized and examined for anticonvulsant properties.

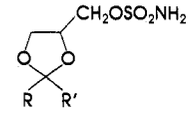
Anticonvulsants are the primary drugs used for the treatment of epileptic disorders.[1] However, despite the availability of several drugs, only about 75% of the epileptic population significantly benefits from current pharmacotherapy, and many of these patients experience adverse side effects, such as drowsiness, ataxia, or gingival hyperplasia.[1] Thus, the search for less toxic, more efficacious agents for the treatment of seizure disorders has been a continuing endeavor.

A wide diversity of chemical structure types exhibit anticonvulsant antivity. These compounds, many of which are cyclic amides (e.g., imides, carboxamides, sulfonamides, carbamates, hydantoins, and ureas),[1a-c] can be classified into two groups. There are agents (e.g., phenytoin and carbamazepine) effective for tonic–clonic seizures and agents (e.g., ethosuximide and nitrazepam) effective for petit mal seizures, which can be characterized pharmaco-

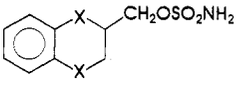
Chart I



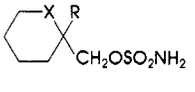
1 X = OSO_2NH_2
2 X = OSO_2NHMe
3 X = OSO_2NMe_2
4 X = OH
5 X = $OC(O)NH_2$
6 X = OSO_2N_3
7 X = OSO_2NHPh
8 X = OC(O)NHPh



9 R = R′ = Me
10 R/R′ = $(CH_2)_5$
11 R = Me; R′ = $(CH_2)_8CH_3$



14 X = CH_2
15 X = O



12 X = O; R = H
13 X = CH_2; R = CH_3

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