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TOTAL SYNTHESIS OF THIENAMYCIN ANALOGS—III

SYNTHESES OF 2-ARYL AND 2-HETEROARYL ANALOGS OF THIENAMYCIN

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Abstract—The total syntheses of 2-aryl and 2-heteroaryl carbapen-2-em-3-carboxylic acids with and without a 6-hydroxyethyl side chain, using a Wittig cyclization for formation of the bicyclic ring system is described. Antibacterial activity of the compounds synthesized is discussed.

The discovery of thienamycin (**1a**),[1] a β-lactam antibiotic with an unusually broad spectrum combined with very high potency and stability to β-lactamases, has been the stimulus for considerable interest in the chemistry of the carbapenem system, which is the basic structure of thienamycin.[2] Excellent as thienamycin is in its antibiotic properties, it was recognized quite early that the compound could best be regarded as an excellent lead rather than a commercial product candidate because of its chemical instability and its metabolism by mammalian dehydropeptidases in the kidney.[3] Chemical modification of thienamycin led to the chemically more stable N-formimidoyl derivative MK-787 (**1b**),[4] and the problem of metabolism by DHP-I in the kidney was solved by the co-administration of MK-791, a DHP-I inhibitor (**2**).[5a,b] This combination is presently undergoing clinical evaluation.[5c] The total synthesis of analogs not available by natural product modification represents an alternate approach which could give single entity DHP-I stable carbapenem antibiotics.

The antibiotic activity of the thienamycin nucleus (**3a**) and descysteaminyl thienamycin (**3b**)[6] indicated that the nucleus substituted by an α-(*R*)-hydroxyethyl group was a major contributor to the antibiotic activity of thienamycin and substitution at the 2-position could perhaps be varied without a major loss in activity of the resulting thienamycin derivatives. Therefore in the search for thienamycin analogs with increased chemical stability and stability to mammalian dehydropeptidases, we undertook a synthetic program directed toward 2-C-substituted thienamycin derivatives.

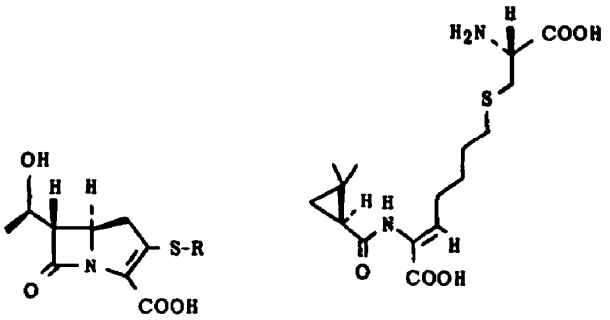
Our initial experiments[7] showed that 2-alkyl substituted carbapenem carboxylic acids had low chemical stability, but 2-aryl substitution resulted in stable compounds with good antibiotic activity. Aryl and heteroaryl substitution at the 2-position offers a number of interesting advantages. Like the S atom at the 2-position, the aromatic ring at 2 extends the conjugation of the Δ^2-carbapenem chromophore and leads to compounds more stable than 2-unsubstituted analogs. Substitution on the aryl or heteroaryl ring can be used to change the polarity, the basicity and the acidity as well as steric parameters of the molecule. Electron-withdrawing or donating groups on the ring may be expected to influence the reactivity of the β-lactam bond to which they are conjugated leading to changes in antibiotic activity. With these considerations in mind, we embarked on the total syntheses of several 2-aryl and heteroaryl substituted thienamycin analogs.

In order to identify as rapidly as possible those aromatic or heteroaromatic rings which were compatible with good antibiotic activity, our initial work was directed toward the synthesis of 6-unsubstituted-2-aryl thienamycin derivatives, wherein the lack of stereochemistry at C-6 gave a target somewhat simpler to synthesize. The best aromatic and heteroaromatic rings were then selected for incorporation into molecules which had the α-(*R*)-hydroxyethyl side chain at C-6.

In this article we describe the various synthetic routes leading to both 6-unsubstituted and 6-α-(*R*)-hydroxyethyl-2-aryl or heteroaryl thienamycin analogs. Though mention will be made of the antibiotic activity of some representative compounds, a full discussion of the structure–activity relationships will follow in a separate manuscript to be published elsewhere.

General synthetic considerations. A successful synthetic approach to the highly strained and reactive carbapenem system requires that a minimum number of synthetic operations be performed on the carbapenem once it is formed. A retrosynthetic analysis of the 2-aryl carbapenem system (**4**), Scheme 1, shows that a Wittig type closure of a suitable ketone (**5**) would be the best approach for closing the 5-membered ring and at the same time generating the Δ^2 double bond at the desired position. Such an approach has been successfully applied for the generation of Δ^3-cephalosporins[8] and has also been demonstrated to be useful in generating Δ^2-carbapenems[6a] and penems.[9]

Our strategy, shown in Scheme 1, was to design a general method which would allow us to introduce the ketone functionality at a late stage of the synthesis on a preconstructed β-lactam synthon with appropriate chirality and functionality. Such a strat-

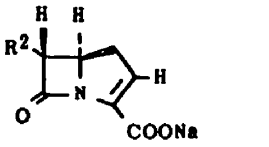


1

a, R = $CH_2CH_2NH_2$

b, R = $CH_2CH_2NHC(=NH)H$

2



3

a, R^2 = H

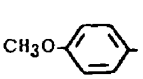
b, R^2 = (R)CH_3-C(OH)-H

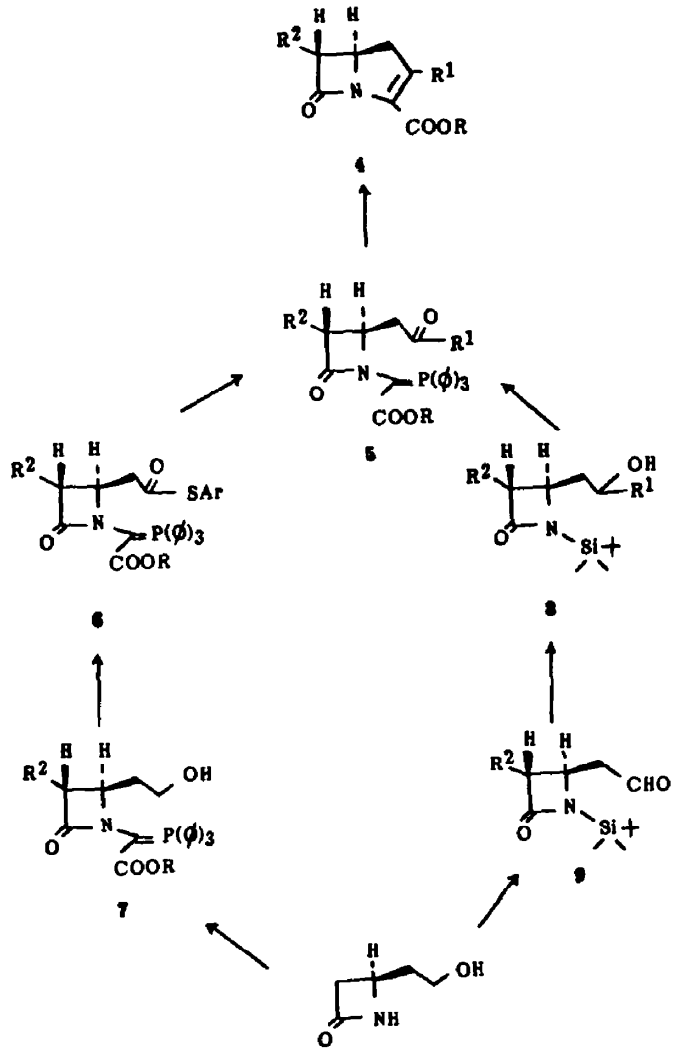
egy would allow us to synthesize a large number of ketones from a common intermediate. Aryl and heteroaryl organometallic reagents are easily available from a variety of aromatic and heteroaromatic systems by metalation with strong base or by halogen metal exchange reactions.[10] These reagents or their cuprate derivatives generally react with an aldehyde or thioester to give aryl alcohols ot ketones respectively. The aryl alcohols (**8**) are readily oxidized to the ketones. Thus the reaction of an aryl or heteroaryl Grignard reagent on a suitable aldehyde (followed by oxidation of the alcohol) or thioester, or the reaction of a lithium or magnesium aryl (heteroaryl) cuprate on a thioester was expected and found to be the ideal general reaction for the synthesis of the desired ketones **5** (Scheme 1).

The suitable thioesters **6** could be prepared from the known intermediate **7**[6a] [R^2 = H, or α-(*R*)-1-(*o*-nitrobenzyloxycarbonyloxy)ethyl] by oxidation of **5** to the acid followed by activation of the acid and reaction with a thiol. The required aldehyde **9** (R^2 = H) is a known compound.[11] Both **7** and **9** are derived from the achiral azetidinone derivative **10**.[12]

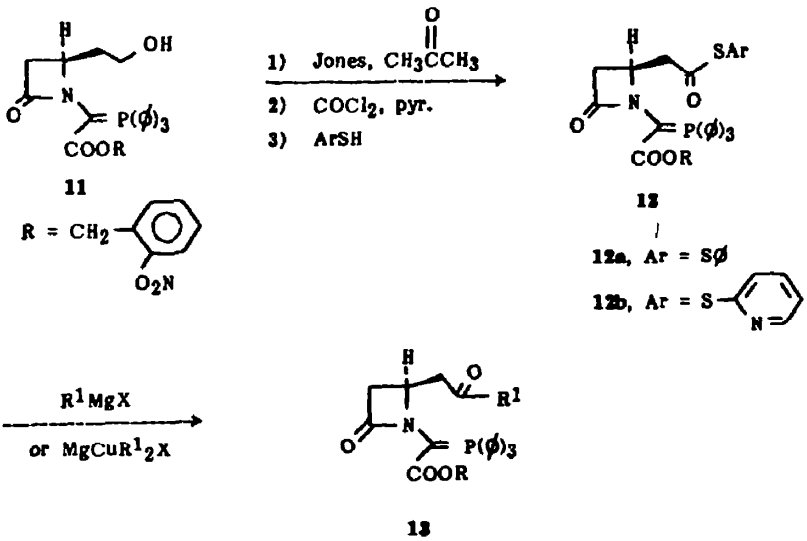
Syntheses of achiral 6-unsubstituted-2-aryl (heteroaryl)-carbapen-2-em-3-carboxylates. Both routes outlined in the general scheme, involving either the thioester or aldehyde intermediate, have been used for these compounds. Hydroxyethyl phos-

Table 1.

13	R^1	Yield	Reagent	Thiol ester	Reaction Conditions
a	C_6H_5-	(66%)	$R^1{}_2MgCuBr$	12a	Et_2O-THF, -15°, 20 min
b	CH_3O- 	(50%)	$R^1{}_2MgCuBr$	12a	Et_2O-THF, 0°, 20 min
c		(56%)	R^1MgBr	12b	Et_2O-THF, 0°, 15 min
d		(63%)	R^1MgBr	12b	Et_2O-THF, 0°, 10 min
e		(74%)	R^1MgBr	12b	THF, RT, 20 min
f		(69%)	R^1MgBr	12b	Et_2O-THF, RT, 30 min
g		(43%)	R^1MgBr	12b	THF, 0°, 1 hr



Scheme 1.



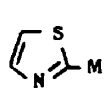
Scheme 2.

phorane **11**[6a] was oxidized using a slight excess of Jones reagent in acetone at 0° to give the acid which without purification was converted to the acid chloride with excess oxalyl chloride in the presence of pyridine or DMF (catalytic amount) in CH_2Cl_2. The acid chloride was treated with 1.5 eq of thiophenol or 2-mercaptopyridine in methylene chloride in the presence of pyridine to give the phenyl or 2-pyridyl thiolester in 66% and 50% overall yield respectively from **11**.

The phenylthioester **12a**, on treatment with 2 eq of R_2^1MgCuX in ether/THF, gave the ketone **13**.[13] Alternately and somewhat more conveniently, as formation of a cuprate was avoided, the pyridylthioester **12b** was treated with a Grignard reagent[14] to give the ketone **13**. The reagents used, the reaction conditions and yield of ketones **13** prepared by the thioester route are summarized in Table 1.

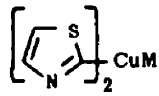
In certain cases the organometallic reagent, either the Grignard or the lithio or magnesium cuprate, failed to react with the thioesters **12a** or **12b** to give the desired ketones **13**. Examples of such organometallics are the thiazolyl reagent **14**, the tetrazole reagent **15**, the benzthiazole reagent **16**, and the pyrimydyl reagent **17**.

In these cases the Mg or Li derivatives successfully added to the aldehyde **18** to give the carbinol **19** (Scheme 3). Oxidation with MnO_2 or $CrO_3 \cdot 2$ pyr.



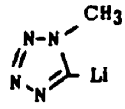
14a, M = Li

14b, M = MgBr

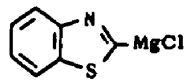


14c, M = Li

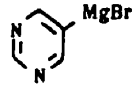
14d, M = MgBr



15

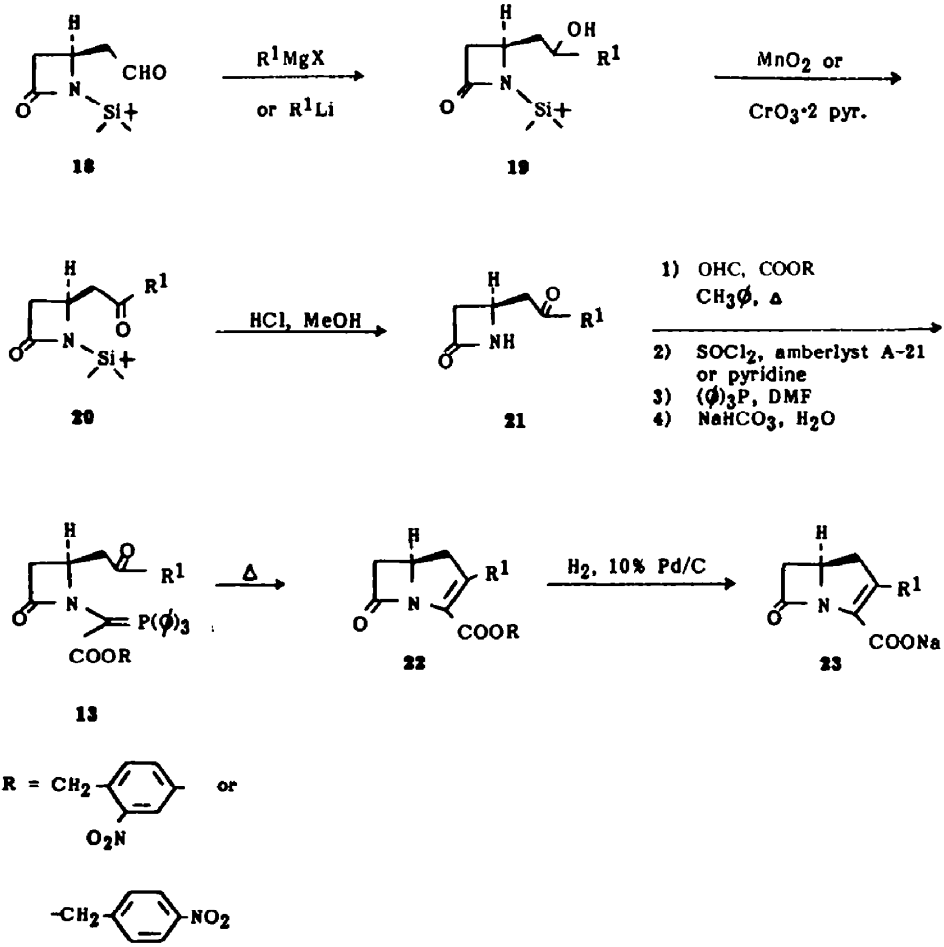


16



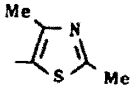
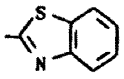
17

gave the keto azetidinones **20** which were desilylated using methanolic HCl to give the ketones **21**. The ylide side chain on the azetidinone nitrogen was elaborated by reaction with *o*-nitrobenzyl glyoxylate in refluxing toluene, treatment of the resulting carbinol with thionyl chloride in the presence of Amberlyst A-21 or pyridine in CH_2Cl_2 at 0°, followed by reaction of the chloro derivative with $(\phi)_3P$ in DMF and workup with aqueous bicarbonate, to give the keto-ylides **13**.



Scheme 3.

Table 2.

	R^1	Reaction Conditions and Yields for			
		19[a]	20	21	13
h		Et_2O, -78° 15 min (74%)	Et_2O, MnO_2 Δ, 2½ hrs (71%)	MeOH, HCl THF, H_2O (75%)	29%
i		THF, -78° 1 hr (65%)	Et_2O, MnO_2 Δ, 2½ hrs (80%)	MeOH, HCl THF, H_2O (49%)	27%
j		THF, -78° 30 min (67%)	Et_2O, MnO_2 Δ, 2½ hrs (67%)	MeOH, HCl THF, H_2O (87%)	9%
k		Et_2O, -78° 20 min (57%)	Et_2O, MnO_2 Δ, 2½ hrs (53%)	MeOH, HCl THF, H_2O (43%)	56%

a) In all cases, the side chain was added as the corresponding R^1Li reagent.

Table 2 shows the reagents, reaction conditions and yields of carbinol **19**, ketones **20** and **21** and ylide **13**, prepared by this route.

Cyclization of the keto-ylides **13** to the carbapenems **22** (Scheme 3) was accomplished in xylene or toluene under nitrogen or argon. The reaction temperatures and the yields varied considerably depending on the nature of the heteroaromatic or aromatic substituent R^1. The cyclized carbapenems **22** were deblocked by hydrogenation with 10% Pd/C as catalyst in aqueous THF or dioxane in the presence of 1 eq of sodium bicarbonate to give the sodium salts **23**. The yields and conditions of cyclization of **13** to **22** are given in Table 3.

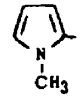
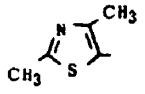
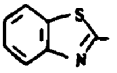
An alternate route to 6-unsubstituted 2-aryl(heteroaryl)carbapenems, which incidently gave chiral compounds, was suggested by the availability of the chiral azetidinone iodide **24**. Alkylation of S-stabilized anions such as **25a** with the chiral iodide is known,[15] and if anions such as **25b** underwent alkylation, this would lead to the protected derivative of the desired ketone.

Treatment of **25b, c, d,** ($R = C_6H_5$, 2-furyl, 3-furyl) with the chiral iodide gave the desired products **26** (Scheme 4). The thioacetal group was removed by treatment with mercuric chloride and mercuric oxide in aqueous methanol followed by removal of the silyl group by acid hydrolysis (CH_3OH, HCl) to give the desired ketone **21**. Further elaboration of **21** to the carbapenem carboxylic acids was carried out in a manner identical to that for the achiral compounds described earlier. Alternately, after acid hydrolysis of the N-silyl group, elaboration of the ylide side chain on the 1-position of azetidinone **27**, as described for **21** to **13**, was followed by hydrolysis of the thioacetal **28** to give the keto ylide **13** (R^1 = 2- and 3-furyl).

Synthesis of 6 - α - (R) - *hydroxyethyl* - 2 - *aryl(heteroaryl)carbapen* - 2 - *em* - 3 - *carboxylate.* The thiolester route was found to be the most versatile route for the synthesis of these compounds. The protected hydroxyethyl phosphorane **29**[6a] was oxidized to the acid **30** using Jones reagent in acetone at 0° (Scheme 5). The conversion of the carboxylic acid to the pyridyl thioester **31a** was accomplished in 70% yield by treatment with 2-pyridylthiochloroformate.[16] The carboxylic acid was also converted to the phenylthioester **31b** in 64% yield by activation as the N-methyl-2-pyridinium derivative using N-methyl-2-fluoropyridinium iodide and triethylamine followed by reaction with thiophenol in the presence of pyridine as base.[17]

Modifications of thienamycin in which the basic amino function of the side chain at 2 is modified to a non-basic function (e.g. by acylation) leads to loss of antibacterial activity against pseudomonas sp.,[18] indicating that a basic function is necessary for activity against these species of bacteria. Therefore aromatic and heteroaromatic rings substituted with an aminomethyl moiety became the groups of choice for substitution at the 2-position of the carbapenems. The zwitterionic final products would then have all the chemical functionality of thienamycin and might be expected to have activity against pseudomonas sp. For this purpose, the pyridyl thioester **31** was treated with the Grignard reagents **32** to give the corresponding aryl(heteroaryl)ylid-ketones **33a–d** in 40–58% yield (Scheme 6). Treatment of the phenylthioester **31b** with the magnesium cuprate **32e** gave the keto-

Table 3.

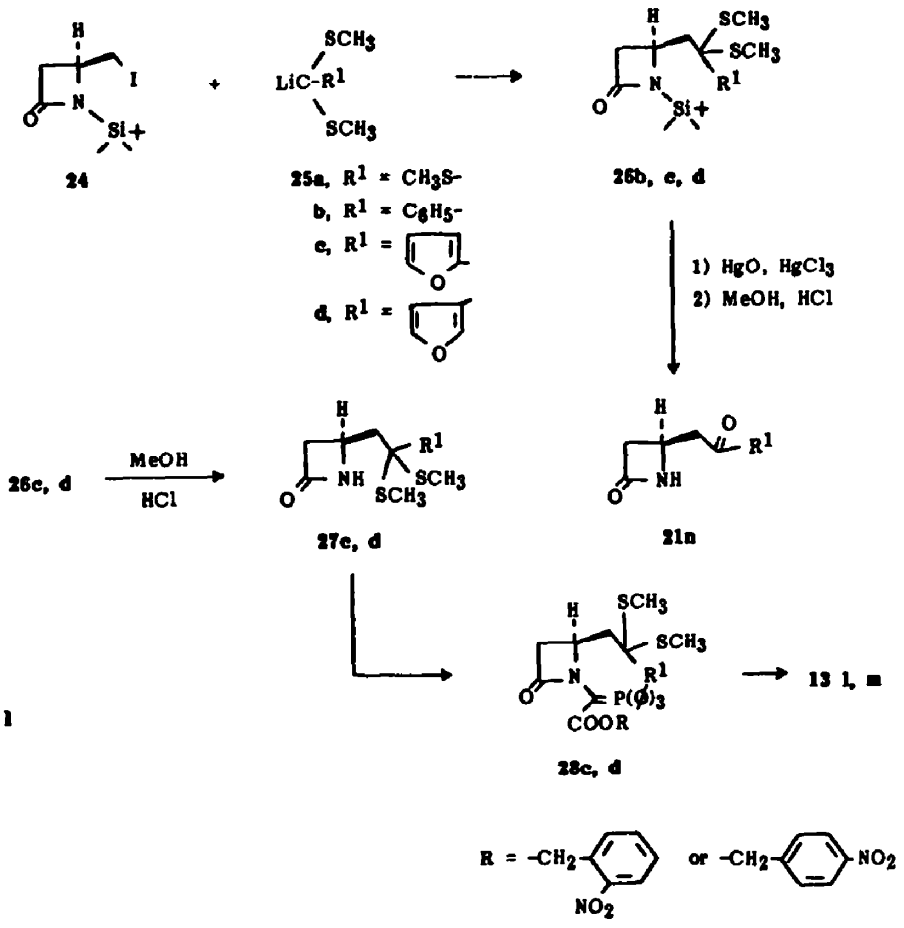
	R^1	Reaction Conditions & Yields 13 to 22
a	C_6H_5	Xylene, 145°, 45 min (23%) Recovered S.M. cyclized once
b	CH_3O- 	Xylene, 145°, 1+3+3 hrs (23%) Recovered S.M. cyclized twice
c		Xylene, 125°, 45 min (64%)
d		Xylene, 120°, 6 hrs (48%)
e		Xylene, 120°, 6 hrs (26%)
f		Xylene, 120°, 5.5 hrs (12%)
g		Xylene, 120°, 18 hrs (0%)
h		Toluene, RT, 17 hrs (88%)
i		Xylene, 120°, 29.5 hrs (11%)
j		Xylene, RT, 17 hrs (55%)
k		Toluene, 120°, 20 min (77%)
l		Xylene, 130°, 1.5 hrs (38%)
m		Xylene, 130°, 2 hrs (40%)
n	C_6H_5-	Xylene, 116°, 5.5 hrs (56%)

ylid **34e** in 56% yield. It is interesting to note that the reaction of the Grignard reagents is specific for the pyridyl thioester functionality of **31**, and the other functions such as the ester, β-lactam and especially the carbonate, which are normally reactive to Grignard reagents, are not affected.

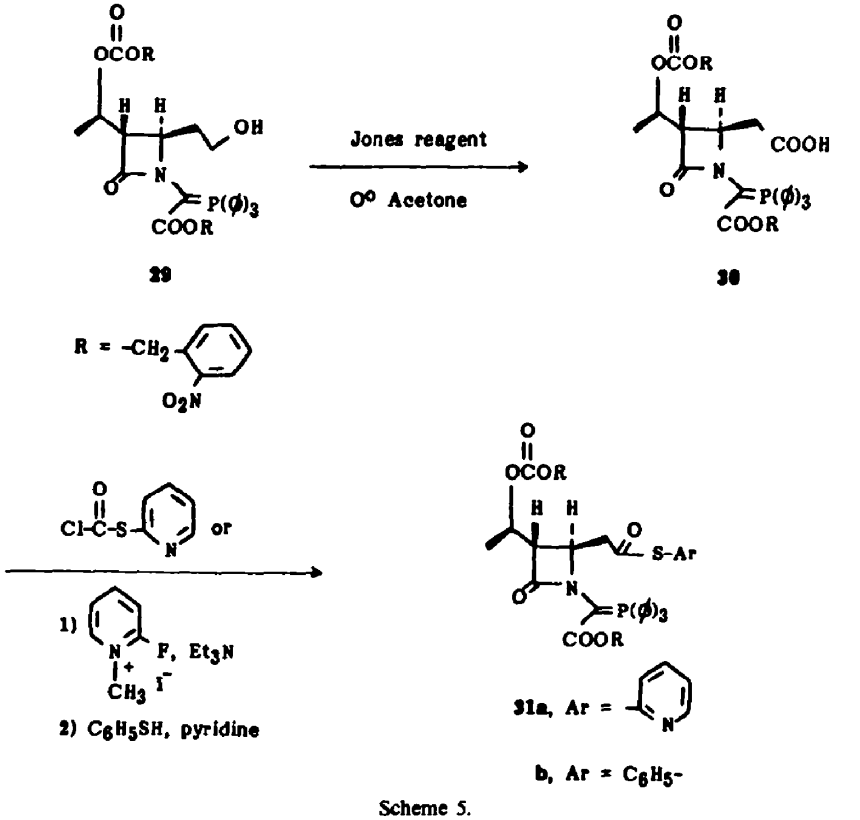
Because we anticipated that the cyclized carbapenems would not stand up to the conditions required to transform the protected hydroxymethyl function to an aminomethyl, these transformations were carried out at the keto-ylid stage. Hydrolysis of the protecting group (P = THP or t-BuMe$_2$Si) in **33** was accomplished by using 10% H_2SO_4 in CH_3COOH or HCl/MeOH/H_2O/THF respectively. The free alcohols **34** were converted to the methanesulfonates **35** with CH_3SO_2Cl and Et_3N which was then displaced with LiN_3 in DMF to give the azidomethyl derivative **36** (Scheme 6).

The azide function proved to be an ideal precursor for the amino function. The azide is a neutral, non-nucloephilic function stable to the cyclization conditions and unlike the basic and nucleophilic amino function, it is not expected to react with the β-lactam of the cyclized carbapenem. Since the protecting group R is removed by hydrogenation in the final step, the azide is converted to the desired amine in the same final step of the synthesis.

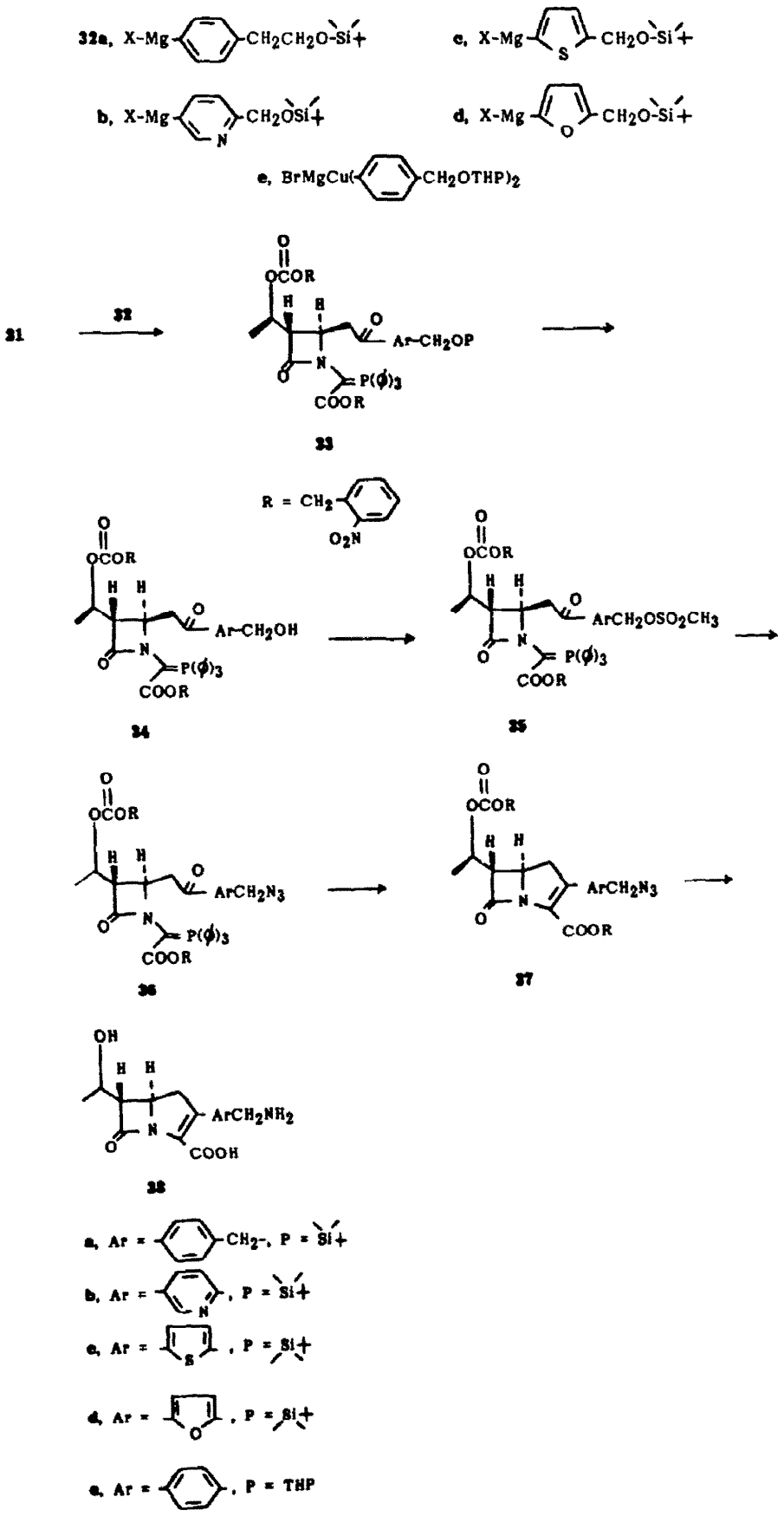
Heating the azide ketone ylide **36** in xylene at temperatures from 120 to 140° gave the cyclized carbapenems **37** which were deprotected to the zwitterion **38** by hydrogenolysis over Pd in aqueous THF or dioxame.



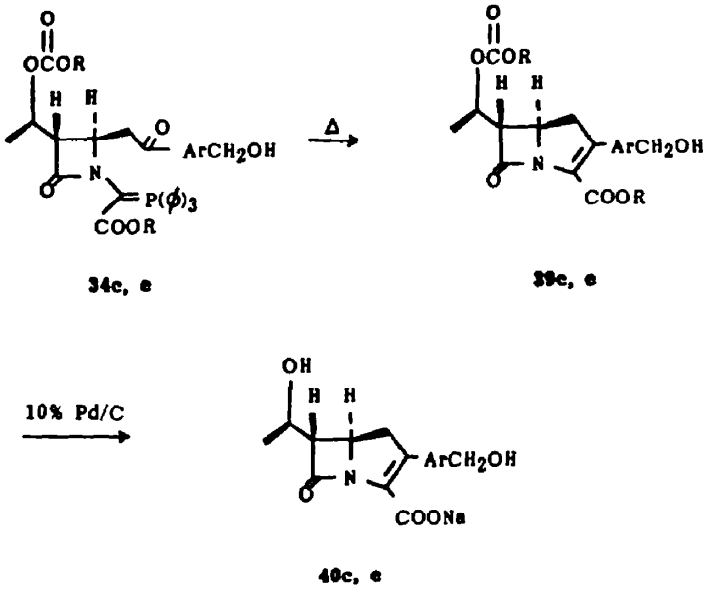
Scheme 4.



Scheme 5.


32a, X-Mg-C6H4-CH2CH2O-Si+
b, X-Mg-C5H3N-CH2OSi+
c, X-Mg-C4H3S-CH2O-Si+
d, X-Mg-C4H3O-CH2O-Si+
e, BrMgCu(C6H4-CH2OTHP)2
31
32
33
R = CH2-C6H4-O2N
34
35
36
37
38
a, Ar = C6H4-CH2-, P = Si+
b, Ar = C5H3N, P = Si+
c, Ar = C4H3S, P = Si+
d, Ar = C4H3O, P = Si+
e, Ar = C6H4, P = THP

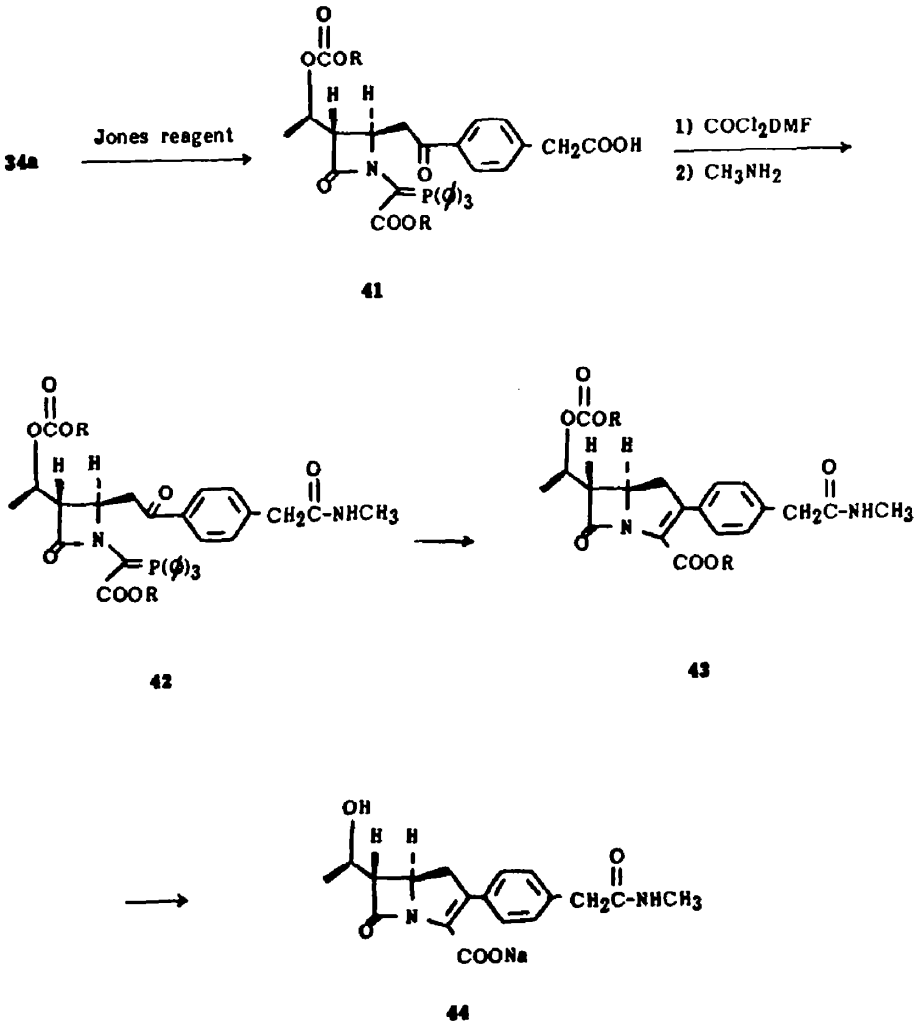
Scheme 6.



34c, e 39c, e

40c, e

Scheme 7.



41 42 43 44

Scheme 8.

Compounds **34** could also be cyclized by heating in xylene to give the hydroxymethylaryl derivatives **39** (Ar = $-C_6H_4-$, $-C_4H_2S$), which on deblocking gave the hydroxymethylaryl carbapenem carboxylic acids **40**.

Oxidation of **34a** (Ar = $-C_6H_4-CH_2-$) with Jones reagent (Scheme 8) and conversion of the acid **41** to the N-methyl amide gave the derivative **42** which was cyclized and deblocked to give **44**.

CONCLUSION

The synthesis of 6-unsubstituted-2-aryl(heteroaryl) compounds was carried out for identifying 2-aryl(heteroaryl) side chains compatible with antibiotic activity. That the 2-substitution has considerable effect on the antibiotic activity of the molecule and the stability to dehydropeptidase I (DHP-I) is shown by the 4 examples in Table 4, which are representative of the range of activity. Though there is considerable variation in the potency of the 2-aryl(heteroaryl) compounds, they all show better stability to DHP-I than thienamycin.

Table 5 shows the activity of 6-(*R*)-hydroxyethyl substituted carbapenems. As expected,[19] the hydroxyethyl side chain increases the potency of the carbapenems by a large factor so that these compounds become comparable in activity to thienamycin; however, activity against pseudomonas sp. is lacking in compounds which do not have a strongly basic side chain on the aryl ring as in **40e** and **43**. Compounds **38c** and **38e**, which have such a side chain, show activity against pseudomonas and are also highly stable to DHP-I. Thus total synthesis of 2-aryl(heteroaryl) analogs of thienamycin has provided compounds which are broad spectrum, highly potent antibiotics with activity against pseudomonas and are also stable to DHP-I, criteria necessary for a single entity antibiotic comparable to the combination MK-0787/0791.

EXPERIMENTAL

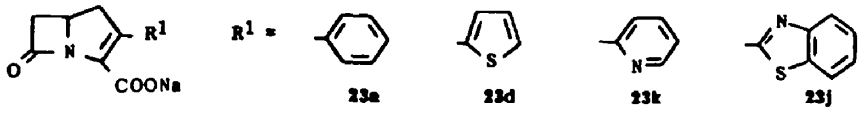
M.ps were determined on a Thomas–Hoover capillary m.p. apparatus and are uncorrected. IR spectra were run on thin film unless otherwise specified and were recorded on Perkin–Elmer 727B and 267 spectrophotometers; only selected absorptions are reported. UV spectra were recorded on a Perkin–Elmer 552A spectrophotometer. The NMR spectra were recorded on Varian T-60, SC-300 and XL-200 spectrometers in either $CDCl_3$ soln with TMS as an internal standard or in D_2O soln with DSS as an internal standard. Chemical shifts are reported in ppm δ relative to the standards.

All reactions were performed under a positive atmosphere of N_2 with the aid of a Firestone valve (Ace Glass). Organic solns obtained after workup were dried over $MgSO_4$ unless otherwise specified. Plate layer chromatography was performed on Analtech silica gel GF plates and column chromatography was conducted with E. Merck 60 silica gel.

Diisopropylethylamine (DIEA) was distilled from CaH_2 prior to use. Tetrahydrofuran (THF) and ether (Et_2O) were distilled from benzophenone ketyl or lithium aluminum hydride (LAH) prior to use. 2.2M n-BuLi in hexane (Alfa) was used as supplied. A specific example is provided as a general procedure, and the experimental parameters in Tables 1–3 should be consulted for any given compound.

1 - (O - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (*phenylthiocarbonyl)methyl* - *azetidin* - 2 - *one* (**12a**). Compound **11** (1.0 g, 1.7 mmol) in acetone

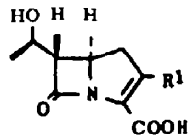
Table 4. Antibiotic activity and DHP-I stability of 6-unsubstituted carbapenems



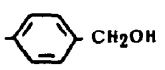
	23a	23d	23k	23j
Organisms	Relative Potency, Thienamycin = 1[a]			
S. aureus (4)	0.02	0.06	0.002	0.002
Enterococcus (3)	1.00	0.14	0.13	0.07
E. coli (5)	0.09	0.16	0.009	0.003
Enterobacter (6)	0.22	0.16	0.02	0.005
Klebsiella (5)	0.04	0.04	0.02	0.006
Serratia (2)	0.006	0.02	0.01	0.006
Proteus (5)	0.03	0.03	0.03	0.02
DHP-I Susceptibility[b]	0.34	0.51	0.67	0.48

a) Agar disc-diffusion assay. Activities are relative to thienamycin and are expressed as indices derived from the indicated number of strains in each species. b) DHP-I susceptibility is given relative to thienamycin = 1.

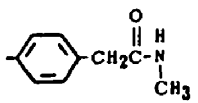
Table 5. Antibiotic activity and DHP-I stability of 6-hydroxyethyl-2-aryl(heteroaryl)-carbapenems



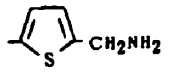
R^1 = $-SCH_2CH_2NH_2$ (38a)



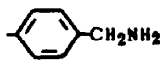
40



43



38c



38e

Organisms	MIC (μg/ml)[c]	Relative Potency, Thienamycin = 1[a]			
S. aureus (4)	0.03	1.0	0.33	0.9	1.5
Enterococcus (3)	3.6	4.9	3.4	2.8	9.2
E. coli (5)	0.37	2.0	2.3	0.7	3.5
Enterobacter (6)	0.67	4.0	1.4	1.7	10.6
Klebsiella (5)	0.88	2.3	0.70	1.4	3.2
Serratia (2)	0.93	7.0	2.4	3.9	5.3
Proteus (5)	1.9	14.9	10.6	1.6	6.5
Pseudomonas (5)	1.79	R[d]	R[d]	0.06	0.3
DHP-I Susceptibility[b]	1	0.28	0.18	0.1	0.02

a) Agar disc diffusion assay. Activities are relative to thienamycin and are expressed as indices derived from the indicated number of strains in each species. b) DHP-I susceptibility is given relative to thienamycin = 1. c) MIC (μg/ml) of thienamycin given as a reference. d) R = resistant.

(20 mL), cooled to 0° was treated with Jones reagent (4N, 1.0 mL). The soln was stirred for 10 min and filtered. The residue was washed with CH_2Cl_2 and the filtrate and washings were washed once with brine, dried and evaporated to give the crude acid (0.943 g). The acid in CH_2Cl_2 (40 ml) was cooled to 0° under N_2 treated with oxalyl chloride (1.0 mL) and DMF (20 μL). After 5 min the ice bath was removed and the mixture was stirred 1/2 hr. The solvent and excess oxalyl chloride were removed under reduced pressure to give the crude acid chloride as a foam. The acid chloride in CH_2Cl_2 (10 mL) was cooled to 0° under N_2 and treated with thiophenol (0.283 g, 2.5 mmol) followed by pyridine (0.283 g, 2.7 mmol). After stirring at 0° for 15 min and a further 15 min without the ice bath, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried and evaporated. Chromatography using 50% C_6H_6/EtOAc as eluant gave **12a** (0.805 g, 68%): IR 1740 (β-lactam), 1700 (thiolester), 1625 (ester); MS, *m/e* 674 (M).

1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (2 - *pyridylthiocarbonyl)methyl* - *azetidin* - 2 - *one* (**12b**). The crude acid chloride was prepared as above from the alcohol (7.94 g, 13.9 mmol), dissolved in CH_2Cl_2 (85 mL) under N_2 and treated with a soln of 2-mercaptopyridine (1.62 g, 14.5 mmol) and pyridine (1.15 g, 14.5 mmol). After 30 min, the reaction was diluted with EtOAc (500 mL), washed with water (3 × 300 mL), pH 3 phosphate buffer (2 × 300 mL) 5% $NaHCO_3$ soln (2 × 300 mL) and brine, dried and evaporated to a foam. Trituration with ether gave **13** as a light yellow solid (4.66 g, 50%): IR (CH_2Cl_2) 1745 (β-lactam), 1710 (thiolester), 1622 (ester); MS, *m/e* 676 (M).

1 - o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (*phenylcarbonyl)methyl* - *azetidin* - 2 - *one* (**13a**). CuI (76 mg, 0.39 mmol) was suspended in Et_2O (2 mL), cooled to 0° under N_2 and treated with C_6H_5MgBr soln (0.8 mL of 1M soln in Et_2O). The mixture was stirred at 0° for 10 min and THF (1.0 mL) was added. The thiolester **12a** (128 mg, 0.19 mmol) in THF (1.0 mL) was added dropwise and stirring continued for 45 min. Satd NH_4Cl soln was added and the reaction was stirred open to the atmosphere for 10 min to oxidize the cuprous salts to water-soluble cupric salts. The mixture was dilulted with CH_2Cl_2, the organic phase was separated, washed with brine, dried and evaporated. The residue was purified by preparative TLC (50% EtOAc/C_6H_6, 2 elutions) to give ketone **13a** (55 mg, 42.6%): IR 1740 (β-lactam), 1680 (ketone), 1620 (ester).

1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (4 - *methoxyphenylcarbonyl)methyl* - *azetidin* - 2 - *one* (**13b**). Prepared by the procedure used for **13a**: IR ($CHCl_3$) 1740 (β-latcam), 1670 (ketone), 1610 (ester); NMR 3.65 (d of d, H4), 3.86 (s, OCH_3).

1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (3 - *pyridylcarbonyl)methyl* – *azetidin* - 2 - *one* (**13c**). Mg (24 mg, 1 mmol) was suspended in THF (3 mL) in a dry flask under N_2 and treated with 1,2-dibromoethane (125 μL, 0.13 mmol). The mixture was warmed to 50° and allowed to stir until the Mg dissolved. In another dry flask under N_2, 3-bromopyridine (0.065 mL, 0.065 mmol) in Et_2O (1 mL), cooled to −78° was treated with n-BuLi (0.25 mL of a 2.2M soln, 0.55 mmol). An immediate yellow colored ppt was formed. After stirring 25 min, the soln of MgBr prepared above was added and stirring was continued 5 min. The mixture was warmed to 0° (ice bath) and stirred 20 min to give a soln of 3-pyridyl–magnesium bromide (0.1M).

The thiolester **12b** (67.5 mg, 0.1 mmol) in THF (2 mL) cooled to 0° under N_2 was treated with the 3-pyridyl–magnesium bromide soln (1 mL). The mixture was stirred 15 min, satd NH_4Cl soln was added, the mixture was extracted with EtOAc (3 ×), dried and evaporated. Purification by preparative TLC (EtOAc) gave **13g** (38 mg, 56%): R_f 0.15; IR 1740 (β-lactam), 1685 (ester), 1620 (ketone) and recovered **12b** (23 mg, 34%).

Using the above procedure, the following compounds were prepared using the appropriate Grignard reagent and thiolester **12b**

1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (2 - *thienylcarbonyl)methyl* – *azetidin* - 2 - *one* (**13d**). IR (CH_2Cl_2) 1745 (β-lactam), 1655 (ketone), 1620 (ester); MS, *m/e* 648 (M), 386, 370, 328.

1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (3 - *thienylcarbonyl)methyl* – *azetidin* - 2 - *one* (**13e**). IR (CH_2Cl_2), 1735 (β-lactam), 1670 (ketone), 1620 (ester); MS, *m/e* 648 (M), 496.

1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (2 - *pyrrolycarbonyl)methyl* – *azetidin* - 2 - *one* (**13f**). IR (CH_2Cl_2) 1740 (β-lactam), 1640 (ketone), 1620 (ester); MS, *m/e*, 631 (M), 496.

1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (1 - *methyl* - 2 - *pyrrolylcarbonyl)methyl* – *azetidin* - 2 - *one* (**13g**). IR (CH_2Cl_2) 1738 (β-lactam), 1640 (ketone), 1620 (ester); MS, *m/e* 645 (M), 496.

1 - (t - *Butyldimethylsilyl*) - 4(2 - *thiazolyl* - 2 - *hydroxy)ethyl* – *azetidin* - 2 - *one* (**19h**). A stirred soln of 2-bromothiazole (0.079 mL, 0.87 mmol) in Et_2O (4.0 mL) under N_2 was cooled to −78° and treated with n-BuLi in hexane (0.380 mL, 0.87 mmol). After 45 min a soln of **18** (199 mg, 0.87 mmol) in Et_2O (0.6 mL) was added and stirring continued for 15 min. The mixture was treated with water and extracted with EtOAc, the organic extract was washed with brine, dried and evaporated to an oil (259 mg). TLC (EtOAc/CH_2Cl_2, 3/1) gave **19h** (201 mg, 74%): IR (CH_2Cl_2), 1730 (β-lactam); MS, *m/e* 313 (M + 1), 297, 255.

The following were prepared using the procedure for **19h**

1 - (t - *Butyldimethylsilyl*) - 4 - (2,5 - *dimethyl* - 4 - *thiazolyl* - 2 - *hydroxy)ethyl* – *azetidin* - 2 - *one* (**19i**). IR (CH_2Cl_2), 1735 (β-lactam); MS, *m/e* 341 (M + 1), 325, 283, 265.

1 - (t - *Butyldimethylsilyl*) - 4 - (2 - *benzthiazolyl* - 2 - *hydroxy)ethyl* – *azetidin* - 2 - *one* (**19j**). IR (CH_2Cl_2) 1725 (β-lactam); MS, *m/e* 362 (M^+), 305, 263.

1 - (t - *Butyldimethylsilyl*) - 4 - (2,2' - *pyridyl* - 2 - *hydroxy)ethyl* – *azetidin* - 2 - *one* (**19k**). IR 3360 (OH), 1720 (β-lactam).

1 - (t - *Butyldimethylsilyl*) - 4 - (2 - *thiazolylcarbonyl*) *methyl* – *azetidin* - 2 - *one* (**20h**). A soln of **19h** (83 mg, 0.27 mmol) in Et_2O (8.0 mL) was mixed with activated MnO_2 (585 mg, 6.71 mmol) and the mixture heated at reflux 2–1/2 hr. The mixture was cooled and filtered. The residue was washed with Et_2O. The combined filtrate and washings were evaporated to a colorless oil (59 mg, 71%). IR (CH_2Cl_2) 1735 (β-lactam), 1690 (ketone); MS, *m/e* 253, 184.

The following were prepared by the procedure for **20h**

1 - (t - *Butyldimethylsilyl*) - 4 - (2,5 - *dimethyl* - 4 - *thiazolyl* - 2 - *carbonyl)methyl* – *azetidin* - 2 - *one* (**20i**). IR (CH_2Cl_2 1740 (β-lactam), 1668 (ketone); MS, *m/e* 323 (M-15), 281 (M-57).

1 - (t - *Butyldimethylsilyl*) - 4 - (2 - *benzthiazolylcarbonyl)methyl* – *azetidin* - 2 - *one* (**20j**). IR (CH_2Cl_2) 1735 (β-lactam), 1680 (ketone); MS, *m/e* 360 (M), 303, 234.

1 - (t - *Butyldimethylsilyl*) - 4 - (2 - *pyridylcarbonyl)methyl* – *azetidin* - 2 - *one* (**20k**). IR 1735 (β-lactam), 1695 (ketone); NMR 2.7 (dd, J = 16 and 4 Hz, H3-β), 3.3 (dd, J = 16 and 5 Hz, H3-α), 3.4 (dd, J = 10 and 16 Hz, CH_2–C=O), 3.84 (dd, J = 5 and 16 Hz, CH_2–C=O), 4.2 (m, H4), 7.3–8.9 (m, ArH).

4 - (2 - *Thiazolylcarbonyl)methyl* – *azetidin* - 2 - *one* (**21h**). A soln of **20h** (203 mg, 0.655 mmol) in MeOH (2 mL), H_2O (2 mL) and conc HCl (0.005 mL) was stirred at RT and monitored by TLC for disappearance of starting material. After 4 hr, the soln was neutralized with 5% $NaHCO_3$aq and extracted with EtOAc (3 × 15 mL). The combined EtOAc extracts were washed with brine, dried and evaporated under vacuum to give **21h** as a white solid (97 mg, 73%); IR (CH_2Cl_2) 1745 (β-lactam), 1685 (ketone); MS, *m/e* 196 (M), 168, 153.

The following compounds were made by the procedure used for **21h**

4 - (2,5 - *Dimethyl* - 4 - *thiazolylcarbonyl)methyl – azetidin* - 2 - *one* (**21i**). IR (CH_2Cl_2) 1760 (β-lactam), 1665 (ketone); MS, *m/e* 224 (M), 207, 196, 182.

4 - (2 - *Benzthiazolylcarbonyl)methyl – azetidin* - 2 - *one* (**21j**). IR (CH_2Cl_2) 1763 (β-lactam), 1690 (ketone); MS, *m/e* 246 (M), 218, 189, 162.

4 - (2 - *Pyridylcarbonyl)methyl – azetidin* - 2 - *one* (**21k**). IR 1730 (β-lactam), 1695 (ketone); NMR 2.76 (m, H3-β), 3.26 (m, H3-α), 3.68 (d, J = 5 Hz, $CH_2C{=}O$), 4.1 (m, H4), 6.46 (broad s, NH), 7.3–8.9 (m, pyridyl H).

(4R)-4-*Phenacyl–azetidin*-2-*one* (**21n**). A soln of **26b** (1.29 g, 3.38 mmol) in anhyd MeOH (34 mL) was treated with HgO (1.10 g, 5.08 mmol) and $HgCl_2$ (2.02 g, 7.44 mmol). The resulting mixture was stirred at RT for 30 min, then filtered to remove the salts which were washed with more MeOH. The filtrate was evaporated under vacuum to a residue which was taken up in Et_2O, washed with H_2O and brine, dried with $MgSO_4$, filtered, and evaporated to provide (4R) - 1 - (t - butyldimethylsilyl) - 4 - (2,2 - dimethoxy - 2 - phenylethyl) – azetidin - 2 - one (1.16 g, 98%) as a white solid: m.p. 111–113° (hexane); IR (CH_2Cl_2) 1725; NMR 0.17 (s, $SiCH_3$), 0.18 (s, $SiCH_3$), 0.92 (s, Si-t-C_4H_9), 1.87 (dd, J = 2.8 and 15.8 Hz, H3-β), 1.92 (dd, J = 10.8 and 13.8 Hz, H4'a), 2.52 (dd, J = 2.2 and 13.8 Hz, B4b), 2.57 (dd, J = 5.0 and 15.8 Hz, H 3-α), 3.11 (s, OCH_3), 3.25 (s, OCH_3), 3.38 (m, H4), 7.35 (m, phenyl); Anal. ($C_{19}H_{31}NO_3Si$) C, H, N.

A soln of the acetal (1.16 g, 3.32 mmol) in THF (11 mL) was diluted with MeOH (11 mL) and H_2O (10 mL) and then treated with 1N HCl (1.1 mL). The resulting soln was kept at RT for 15 hr then diluted with 5% $NaHCO_3$aq (50 mL) and extracted with EtOAc (50 mL, 2 × 25 mL). The extracts were washed with brine, dried with $MgSO_4$, filtered, and evaporated under vacuum to afford a white solid (0.62 g) which was recrystallized from EtOAc to give the title compound (0.51 g, 81%) as white needles: m.p. 154–156°; IR (Nujol mull) 3210, 1738, 1707, 1673; NMR (200 MHz) 2.73 (ddd, J = 1.0, 2.5 and 15.2 Hz, H3-β), 3.24 (dd, J = 8.9 and 17.7 Hz, H4'a), 3.26 (ddd, J = 2.4, 5.1 and 15.2 Hz, H3-α), 3.49 (dd, J = 4.3 and 17.7 Hz, H4'b), 4.14 (m, H4), 6.24 (br s, NH), 7.57 and 7.98 (two m, phenyl) Anal. ($C_{11}H_{11}NO_2$) C, H, N.

Preparation of (4R) - 1 - (p-*nitrobenzyloxycarbonyl*) *triphenylphosphoranylidenemethyl* - 4 - *phenacyl* - 2 - *azetidinone* (**13n**). Phenacyl azetidinone **21n** (189 mg, 1 mmol) and *p*-nitrobenzyl glyoxalate hemihydrate (240 mg, 1.1 mmol) were suspended in anhyd toluene (5 mL) and the mixture was stirred and heated at reflux under N_2. After 3 hr, more glyoxalate (87 mg, 0.4 mmol) was added and heating was continued a further 5 hr. The mixture was diluted with EtOAc and evaporated under vacuum to an oil which was chromatographed on EM silica gel (25 g) using Et_2O as the eluting solvent. The appropriate fractions were combined and evaporated under vacuum to afford (4R) - 1 - (*p* - nitrobenzyloxycarbonyl)hydroxymethyl - 4 - phenacyl - 2 - azetidinone (305 mg, 77%) as a clear oil: IR 3350, 1740, 1675, 1605; MS, *m/e* 398 (M), 380, 262, 218, 136, 120.

The hydroxy ester intermediate (305 mg, 0.77 mmol) in anhyd CH_2Cl_2 (7.7 mL) was treated with Amberlyst A21 resin (512 mg, 2.30 mmol) and the resulting mixture was stirred under N_2 with ice–MeOH cooling while thionyl chloride (0.112 mL, 1.54 mmol) was added dropwise by syringe. The resulting mixture was stirred for 3 hr with gradual warming from −18 to 0°. The mixture was filtered to remove the resin which was washed with more CH_2Cl_2. The filtrate was evaporated under vacuum to give crude (4*R*) - 1 - (*p* - nitrobenzyloxycarbonyl)chloromethyl - 4 - phenacyl - 2 - azetidinone (308 mg, 96%) as a yellow oil: IR 1765, 1680, 1605.

A soln of the crude chloro ester (308 mg, 0.74 mmol) in anhyd DMF (3.7 mL) was cooled in an ice-bath under N_2, treated with triphenylphosphine (213 mg, 0.81 mmol), and kept at *ca* 2° for 19 hr. The resulting yellow soln was evaporated under vacuum to an oil which was dissolved in CH_2Cl_2 (50 mL) and shaken vigorously with 5% $NaHCO_3$aq (50 mL) for several min. The organic phase was separated, dried with $MgSO_4$, filtered, and evaporated under vacuum to a yellow gum. This material was chromatographed on silica gel (25 g) using EtOAc as the eluting solvent. The appropriate fractions were evaporated and the residue lyophilized from benzene to give the title compound (377 mg, 79%, 59% overall) as a pale yellow, amorphous powder: IR (CH_2Cl_2) 1745, 1685, 1622, 1608; MS, *m/e* 642 (M), 364, 322, 278, 262, 143.

The following compounds **13h** *to* **13j** *were prepared by the method described for* **13n**

1 - (p - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (2 - *thiazolylcarbonyl)methyl – azetidin* - 2 - *one* (**13h**). IR (CH_2Cl_2) 1740 (β-lactam), 1670 (ketone), 1620 (ester) MS, *m/e* 371 [M-P(C_6H_5)$_3$], 329.

1 - (p - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (2,5 - *dimethyl* - 4 - *thiazolylcarbonyl)methyl – azetidin* - 2 - *one* (**13i**). IR (CH_2Cl_2) 1740 (β-lactam), 1660 (ketone), 1620 (ester); MS, *m/e* 677 (M), 606, 361.

1 - (p - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (2 - *benzthiazolyl – carbonyl)methyl – azetidin* - 2 - *one* (**13j**). IR (CH_2Cl_2) 1740 (β-lactam), 1685 (ketone), 1610 (ester).

1 - (p - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (2 - *pyridinylcarbonyl)methyl – azetidin* - 2 - *one* (**13k**). This compound was prepared from **21k** by the procedure for **28c**. IR 1740 (β-lactam), 1695 (ketone), 1620 (ester).

(4R) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (2 - *furanylcarbonyl)methyl – azetidin* - 2 - *one* (**13l**). To a suspension of **28c** (105 mg, 0.15 mmol) in MeOH/H_2O 10:1 (2 mL) were added red HgO (30 mg, 1.35 eq) and $HgCl_2$ (82 mg, 2 eq). The stirred mixture was heated to reflux for 1 hr, cooled and filtered in the residue washed with MeOH. The filtrate and washings were concentrated and the residue was taken up in 10 mL EtOAc, washed with satd NH_4Cl soln (3 × 5 mL), dried and evaporated. Purification by preparative TLC (cyclohexane/EtOAc 1:3) gave **13l** (62 mg, 67%); IR 1740 (β-lactam), 1665 (ketone), 1625 (ester).

(4R) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 4 - (3 - *furanylcarbonyl)methyl – azetidin* - 2 - *one* (**13m**). Prepared in 63% yield from **28d** by using the above procedure; IR 1740 (β-lactam), 1665 (ketone), 1625 (ester).

The following carbapenem esters **22** were obtained by heating in toluene or xylene under N_2 or A as specified in Table 3, followed by purification by preparative TLC:

o - *Nitrobenzyl* - 2 - *phenyl* - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**22a**). IR 1780 (β-lactam), 1725 (ester) 1610 (C=C), 1525 (NO_2); NMR (300 MHz), 3.1 (dd, J = 15 and 3 Hz, H6-β), 3.3 (octet H-1), 3.59 (dd, J = 15 and 5 Hz, H6-α), 4.4 (m, H5), 5.57 and 5.78 (2d, J = 16 Hz, CH_2Ar), 7.2–8.2 (m, ArH), UV λ_{max} (CH_2Cl_2) 268, 300 (ϵ = 5000, NH_2OH extinguishable).

o - *Nitrobenzyl* - 2 - (4 - *methoxyphenyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**22b**). IR 1770 (β-lactam), 1720 (ester), 1600 (C=C); NMR (300 MHz), 3.15 (dd, J = 17 and 3 Hz, H6-β), 3.28 (d, J = 10 Hz, H1), 3.56 (dd, J = 17 and 6 Hz, H6-α), 3.81 (s, OCH_3), 4.34 ((m, H4), 5.58 and 5.83 (2d, J = 16 Hz, CH_2Ar), 6.8–8.2 (m, ArH).

o - *Nitrobenzyl* - 2 - (3 - *pyridyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**22c**). IR 1780 (β-lactam), 1725 (ester); NMR (300 MHz) 3.12 (dd, J = 3 and 15 Hz, H6-β), 3.33 (m, H1), 3.6 (dd, J = 6 and 15 Hz, H6-α), 4.42 (m, H4), 5.58 and 5.7 (2d, J = 18 Hz, CH_2Ar), 7.2–8.8 (m, ArH).

o - *Nitrobenzyl* - 2 - (2 - *thienyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**22d**). IR (CH_2Cl_2) 1775 (β-lactam), 1710 (ester); NMR (300 MHz), 3.03 (dd, J = 16 and 3 Hz,

H6-β), 3.38 (dd, J = 17.5 and 9 Hz, H4-α), 3.51 (dd, J = 17.5 and 9.5 Hz, H1-β), 3.55 (dd, J = 16 and 6 Hz, H6-α), 4.32 (dddd, J = 9.5, 9, 6 and 3 Hz, H 5), 5.79 (ABq, J = 16 Hz, $ArCH_2$), 7.1 (dd, J = 5 and 4 Hz, ArH), 7.52 (dd, J = 5 and 1 Hz, ArH), 7.65 (dd, J = 4 and 1 Hz, ArH), 7.48 (ddd, J = 9, 8 and 1 Hz, ArH), 7.70 (dt, J = 8 and 1 Hz, ArH), 8.05 (dd, J = 8 and 1 Hz, ArH), 8.18 (dd, J = 9 and 1 Hz, ArH); MS, *m/e* 370 (M), 328.

o - *Nitrobenzyl* - 2 - (3 - *thienyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**22e**). IR (CH_2Cl_2) 1775 (β-lactam), 1715 (ester); NMR (300 MHz) 3.05 (dd, J = 16 and 3.0 Hz, H 6-β), 3.32 (dd, J = 17.5 and 9 Hz, H1-α), 3.42 (dd, J = 17.5 and 9 Hz, H 1-β), 3.56 (dd, J = 16 and 5.0 Hz, H 6-α), 4.34 (dddd, J = 9, 9, 5 and 3.0 Hz, H 5), 5.75 (ABq, J = 16.0 Hz, CH_2Ar), 7.30 (dd, J = 3 and 1 Hz, ArH), 7.49 (dd, J = 5 and 1 Hz, ArH), 7.89 (dd, J = 3 and 1 Hz, ArH), 7.47 (t, J = 8 Hz, ArH), 7.69 (dt, J = 8 and 1 Hz), 7.98 (d, J = 8 Hz, ArH), 8.17 (dd, J = 8 and 1 Hz, ArH); MS, *m/e* 370 (M), 328.

o - *Nitrobenzyl* - 2 - (2 - *pyrrolyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**11f**). IR (CH_2Cl_2) 1770 (β-lactam), 1685 (ester); NMR (300 MHz), 2.97 (dd, J = 16 and 2 Hz, H 6-β), 3.29 (dd, J = 17 and 9 Hz, H 1-α), 3.49 (dd, J = 17.5 and 9 Hz, H 1-β), 3.51 (dd, J = 16 and 5 Hz, H 6-α), 4.25 (dddd, J = 9, 9, 5 and 2 Hz, H 5), 5.8 (ABq, J = 16 Hz, CH_2Ar), 6.3 (m, ArH), 6.53 (m, ArH), 7.03 (m, ArH), 7.48 (t, 8 Hz, ArH), 7.71 (t, J = 7 Hz, ArH), 8.11 (d, J = 7 Hz, ArH), 8.18 (d, J = 8 Hz, ArH); MS, *m/e* 353 (M), 311.

p - *Nitrobenzyl* - 2 - (2 - *thiazolyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**22h**). IR (CH_2Cl_2) 1782 (β-lactam), 1715 (ester); NMR (300 MHz), 3.12 (dd, J = 16 and 3 Hz, H 6-β), 3.51 (dd, J = 19 and 9 Hz, H 1-α), 3.6 (dd, J = 16 and 6 Hz, H 6-α), 3.89 (dd, J = 19 and 9.5 Hz, H 1-β), 4.35 (dddd, J = 9.5, 9, 6 and 3 Hz, H 5), 5.48 (ABq, J = 14 Hz, CH_2Ar), 8.29 (d, J = 9 Hz, ArH), 7.74 (d, J = 9 Hz, ArH), 7.6 (d, J = 3 Hz, ArH), 7.99 (d, J = 2.0 Hz, ArH). MS, *m/e* 371 (M), 329, 284.

p - *Nitrobenzyl* - 2 - (2,5 - *dimethyl*)*thiazol* - 4 - *yl* - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**22i**). IR (CH_2Cl_2) 1785 (β-lactam), 1735 (ester), NMR (300 MHz), 2.23 (s, CH_3), 2.65 (s, CH_3), 3.09 (dd, J = 17 and 3 Hz, H 6-β), 3.17 (d, J = 9.5 Hz, H 4-α and -β), 3.57 (dd, J = 17 and 5 Hz, H 6-α), 4.36 (dddd, J = 9.5, 9.5, 5 and 3 Hz, H 5), 5.32 (ABq, J = 14 Hz, CH_2Ar), 7.53 (d, J = 9 Hz, ArH), 8.82 (d, J = 9 Hz, ArH).

p - *Nitrobenzyl* - 2 - (2 - *benzthiazolyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**22j**). IR (CH_2Cl_2) 1780 (β-lactam), 1720 (ester); NMR (300 MHz), 3.14 (dd, J = 17.0 and 3.0 Hz, H 6-β), 3.58 (dd, J = 19 and 9.0 Hz, H 1-α), 3.60 (dd, J = 17.0 and 5.5 Hz, H 6-α), 3.92 (dd, J = 19.0 and 10 Hz, H 4-β), 4.37 (dddd, J = 10, 9, 5.5 and 3 Hz, H 5), 5.46 (ABq, J = 14 Hz, CH_2Ar), 7.69 (d, J = 9.0 Hz, ArH), 8.24 (d, J = 9.0, ArH), 7.5 (m, ArH), 7.92 (d, J = 8 Hz, ArH), 8.05 (d, J = 8 Hz, ArH), MS, *m/e* 379 (M-42).

o - *Nitrobenzyl* - 2 - (2 - *pyridyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**22k**). IR 1790 (β-lactam), 1722 (ester); NMR 2.95–3.95 (m, H 2 and H 6), 4.3 (m, H 4), 5.7 (ABq, CH_2Ar), 7.1–8.75 (m, ArH).

o - *Nitrobenzyl* (5R) - 2 - (2 - *furanyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**22l**). M.p. 129–130°; IR 1775 (β-lactam), 1710 (ester); NMR (300 MHz), 3.05 (dd, J = 16 and 3 Hz, H 6-β), 3.28 (dd, J = 18 and 9 Hz, H 1-α), 3.54 (dd, J = 16 and 6 Hz, H 6-α), 3.60 (dd, J = 18 and 9 Hz, H 1-β), 4.33 (dddd, J = 9, 9, 6 and 3 Hz, H 5, 5.8 (ABq, J = 15 Hz, CH_2Ar), 6.40–8.25 (m, ArH).

o - *Nitrobenzyl* (5R) - 2 - (3 - *furanyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**22m**). IR 1773 (β-lactam), 1715 (ester); NMR (300 MHz), 3.03 (dd, J = 16 and 3 Hz, H 6-β), 3.20 and 3.3 (2 dd, J = 18 and 9 Hz, H 1-α and -β), 3.54 (dd, J = 15 and 5 Hz, H 6-α), 4.3 (dddd, J = 9, 9, 5 and 3 Hz, H 5), 5.77 (ABq, J = 16, CH_2Ar), 6.90–8.20 (m, ArH).

Preparation of p-*nitrobenzyl* (5R)-2-*phenyl*-1-*carbapen*-2-*em*-3-*carboxylate* (**22n**). A soln of **13n** (100 mg, 0.156 mmol) in anhyd xylene (100 mL) was degassed by bubbling Ar through it for 15 min. The soln was heated in an oil bath at 116° for 5.5 hr while continuously bubbling Ar through it. After cooling to RT, the soln was evaporated under vacuum to a residue which was chromatographed on four 0.25 mm × 20 × 20 cm silica gel GF plates using 1:1 pet. ether–EtOAc as developing solvent. The UV visible bands at R_f 0.44 were extracted with EtOAc to give, after evaporation of the solvent and lyophilization of the residue from benzene, the bicyclic product (32 mg, 56%) as an off-white, amorphous powder: IR (CH_2Cl_2) 1782, 1725; UV (dioxane) λ_{max} 274 (ε 12,800), 315 (sh) nm; UV (dioxane + $Me_4NOH \cdot 5\,H_2O$) λ_{max} extinguished, 313 (ε 7900) nm; NMR ($CDCl_3$) 3.08 (dd, J = 3.1 and 16.6 Hz, H 6-β), 3.22 (dd, J = 9.8 and 18.5 Hz, H 1a), 3.34 (dd, J = 8.9 and 18.5 Hz, H 1b), 3.58 (dd, J = 5.5 and 16.6 Hz, H 6-α), 4.38 (m, H 5), 5.23 and 5.40 (two d, J = 14.0 Hz, CO_2CH_2), 7.37 (m, phenyl and 2 aryl), 8.18 (d, J = 8.7 Hz, 2 aryl); MS, *m/e* 364 (M), 322 (MCH_2CO), 143.

Sodium 2-*phenyl*-1-*carbapen*-2-*em*-3-*carboxylate* (**23a**). The carbapenem **22a** (8 mg) was dissolved in dioxane (2 mL), water (2 mL), EtOH (0.4 mL), $NaHCO_3$ (1.8 mg), and 10% Pd/C (8 mg) were added. The mixture was hydrogenated at 40 lb for 1 hr. The catalyst was filtered off and washed with water (3 mL). The filtrate and washings were extracted with EtOAc (3 × 5 mL) and the aqueous phase was evaporated to 5 mL, the pH was adjusted to 6.5 and the soln was freeze-dried to give **23a** (18%): UV (H_2O), λ_{max} 297 nm (NH_2OH extinguishable) NMR (300 MHz, D_2O) 3.07 (dd, J = 18 and 7 Hz, H 1-α or -β), 3.16 (dd, J = 18 and 3 Hz, H 6-β), 3.23 (dd, J = 16 and 9 Hz, H 1-α or -β), 3.5 (dd, J = 18 and 5 Hz, H 6-α), 4.37 (m, H 5), 7.39 (s, ArH).

The Na salts **23b–m** were prepared from their *o*-nitro or *p*-nitrobenzyl esters following the above procedure. Because of their relative instability, they were only characterized by their UV spectrum in H_2O (extinguishable by addition of NH_2OH).

Sodium 2 - (4 - *methoxy*)*phenyl* - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**23b**). UV $(H_2O)_{max}$ 305 nm (NH_2OH extinguishable).

Sodium 2 - (3 - *pyridyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**23c**). UV (H_2O) λ_{max} 300 nm (NH_2OH extinguishable).

Sodium 2 - (2 - *thienyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**23d**). UV (H_2O) λ_{max} 323 nm (NH_2OH extinguishable).

Sodium 2 - (3 - *thienyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**23e**). UV (H_2O) λ_{max} 300 nm (NH_2OH extinguishable).

Sodium (2 - (2 - *pyrrolyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**23f**). UV (H_2O) λ_{max} 335 nm (NH_2OH extinguishable).

Sodium 2 - (2 - *thiazolyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**23h**). UV (H_2O) λ_{max} 328 nm (NH_2OH extinguishable).

Sodium 2 - (2,5 - *dimethyl* - 4 - *thiazolyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**23i**). UV (H_2O) λ_{max} 305 nm (NH_2OH extinguishable).

Sodium 2 - (2 - *benzthiazolyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**23j**). UV (H_2O) λ_{max} 335 nm (NH_2OH extinguishable).

Sodium 2 - (2 - *pyridyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**23k**). UV (H_2O) λ_{max} 305 nm (NH_2OH extinguishable).

Sodium (5R) - 2 - (2 - *furanyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**23l**). UV (H_2O) λ_{max} 314 nm (NH_2OH extinguishable).

Sodium (5R) - 2 - (3 - *furanyl*) - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**23m**). UV (H_2O) λ_{max} 289 nm (NH_2OH extinguishable).

2-*Dimethylthiomethylfuran* (**25c**). To a stirred soln of freshly distilled furfural (2.88 g, 30 mmol) in Et_2O (100 mL) was added trimethylthioorthoborate[20] (3.86 g, 20 mmol). The

soln was heated to reflux for 2 hr. The light pink ppt formed was filtered off and washed with Et_2O. The filtrate and washings were evaporated and the residue was chromatographed (20% Et_2O, petroleum ether, 30–60) to give **25c** (2.61 g, 50%) which slowly turned brown. NMR 2.15 (s, CH_3), 4.94 [s, ArCH–$(SMe)_2$], 6.33 and 7.30 (furyl H).

3-*Dimethylthiomethylfuran* (**25d**). Oxidation of the commercially available 3-hydroxymethylfuran with DMSO, trifluoroacetic anhydride and Et_3N[21] in CH_2Cl_2 gave 3-furaldehyde in 59% yield; NMR 6.75, (m, ArH), 7.47 (m, ArH), 8.05 (m, ArH), 10.0 (s, aldehyde H). Using the procedure for preparation of **25c** on 3-furaldehyde gave **25d** (84%); NMR 2.10 (s, SCH_3), 4.73 [s, ArCH–$(SMe)_2$], 6.40 (m, ArH), 7.33 (m, ArH).

Preparation of (4S) - 1 - (t - *butyldimethylsilyl*) - 4 - (2,2 - *dimethylthio* - 2 - *phenylethyl*) - 2 - *azetidinone* (**26b**). A soln of benzaldehyde dimethylthioacetal (1.014 g, 5.5 mmol) in anhyd THF (20 mL) was cooled to −23° (dry ice–CCl_4 bath) under N_2 and treated dropwise with n-BuLi in hexane (2.4 mL of a 2.3M soln, 5.5 mmol) over 2.5 min. The resulting soln was stirred for 1 hr at −20°, then cooled to −78° and treated dropwise over 8 min with a soln of (4*S*)-1-(*t*-butyldimethylsilyl)-4-iodomethyl-2-azetidinone (1.627 g, 5 mmol) in THF (5 mL). The mixture was stirred at −78° for an additional 1 hr and at 0° for 1 hr; then diluted with sat NH_4Claq (5 mL) and H_2O (50 mL) and extracted with Et_2O (50 mL, 2 × 25 mL). The ether extracts were washed with dilute $Na_2S_2O_3$aq and brine, dried with $MgSO_4$, filtered, and evaporated under vacuum to a pale yellow semi-solid (2.05 g). This material was crystallized from hexane (20 mL) by slow evaporation to give the title compound (1.29 g) as off-white clusters. Chromatography of the mother liquors on silica gel (20 g) using 10:1 pet. ether–Et_2O as eluting solvent gave additional product (0.52 g, total yield 95%) as white crystals: m.p. 94–95°; IR (Nujol mull) 1735; NMR (200 MHz) 0.16 (s, $SiCH_3$), 0.19 (s, $SiCH_3$), 0.92 (s, Si-t-C_4H_9), 1.99 (s, SCH_3), 2.05 (dd, J = 2.5 and 15.8 Hz, H 3-β), 2.06 (s, SCH_3), 2.16 (dd, J = 10.8 and 13.9 Hz, H 4'a), 2.58 (dd, J = 1.8 and 13.9 Hz, H 4'b), 2.68 (dd, J = 5.2 and 15.8 Hz, H 3-α), 3.60 (m, H 4), 7.37 and 7.75 (two m, phenyl); Anal. ($C_{19}H_{31}NOS_2Si$) C, H, N, S.

(4R) - 1 - t - *Butyldimethylsilyl* - 4 - [2,2 - *dimethylthio* - 2 - (2 - *furanyl*]*ethyl* – *azetidin* - 2 - *one* (**26c**). Prepared from **25c** and **24** by the above procedure in 80% yield. IR 1745 (β-lactam); NMR 0.23 (s, CH_3Si), 0.95 (s, t-butyl Si), 1.97 and 2.0 (2s, SCH_3), 2.6–3.8 (m, H 3 and H 4), 2.15–2.55 [m, CH_2–$C(SCH_3)_2$], 6.33 (m, furyl H), 7.75 (m, furyl H).

(4R) - 1 - *t* - *Butyldimethylsilyl* - 4 - [2,2 - *dimethylthio* - 2 - (3 - *furanyl*]*ethyl* – *azetidin* - 2 - *one* (**26d**). Prepared from **25d** and **24** in 73% yield by the above procedure. IR 1745 (β-lactam); NMR 0.20 (s, $SiCH_3$), 0.94 (s, t-butyl Si), 2.00 and 2.03 (2s, SCH_3), 1.90–3.8 [m, H 3, H 4 and –CH_2–$C(SCH_3)_2$], 6.43 (m, furyl H), 7.37 (m, furyl H).

(4R) - 4 - [2 - (2 - *Furanyl*) - 2,2 - *dimethylthio*]*ethyl* – *azetidin* - 2 - *one* (**27c**). To a soln of **26c** (371 mg, 1 mmol) in a mixture of MeOH, H_2O and THF (3 mL each) was added conc HCl (0.025 mL) at RT. The mixture was stirred and followed by TLC. When starting material disappeared, the mixture was diluted with EtOAc (50 mL) and washed with water (5 × 10 mL). The organic phase was dried and evaporated and the residue chromatographed to give **27c** (195 mg, 76%): IR 3350 (NH), 1740 (β-lactam); NMR 1.97 and 2.03 (2s, SCH_3), 2.43 [m, CH_2–$C(SCH_3)_2$], 2.56–3.36 (m, H 3), 3.76 (m, H 4), 5.9 (broad s, NH), 6.36 (m, furyl H), 7.4 (m, furyl H).

(4R) - 4[2 - (3 - *Furanyl*) - 2,2 - *dimethylthio*]*ethyl* – *azetidin* - 2 - *one* (**27d**). Prepared from **26d** by the above procedure in 64% yield. IR 3350 (NH), 1740 (β-lactam); NMR 1.94 and 2.0 (s, SCH_3), 2.2–3.9 [m, H 3, H 4 and CH_2–$(SCH_3)_2$], 6.0 (broad s, NH), 6.43 (m, furyl H), 7.40 (m, furyl H).

(4R) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene*)*methyl* - 4 - (2,2' - *furanyl* - 2,2 - *dimethylthio*) *ethyl* – *azetidin* - 2 - *one* (**28c**). A soln of **27c** (1.28 g, 5 mmol), and *o*-nitrobenzylglyoxylate (2.1 g, 10 mmol) in C_6H_6 (50 mL) was heated to reflux using a Dean Stark water separator with CaH_2 in the water trap. After refluxing overnight, the solvent was evaporated and the residue was chromatographed (1:1, Et_2O:petroleum ether 30–60°) to give (4*R*) - 1 - *o* - nitrobenzyloxycarbonylhydroxymethyl - 4 - (2 - furanyl - 2,2 - dimethylthio)ethyl – azetidin - 2 - one (1.12 g, 56%). IR 3375 (OH), 1740 (β-lactam and ester); NMR 1.97, 2.0, 2.03 and 2.06 (4s, SCH_3, 2 isomers), 2.20–4.00 [H 3, H 4 and CH_2–$(SCH_3)_2$], 5.65 (s, $ArCH_2$), 6.33 (m, furyl H), 7.3–8.2 (m, ArH).

To a soln of the hydroxy compound (1.12 g, 1.93 mmol) in THF (50 mL) at −30° to −20°, under N_2 were added pyridine (0.4 mL, 5 mmol) and thionyl chloride (0.36 mL, 5 mmol). After stirring for 40 min, the mixture was filtered and the residue washed with THF (3 × 10 mL). The filtrate and washings were evaporated under reduced pressure and the residue pumped at high vacuum for 1 hr. The residue was taken up in DMF (20 mL) under N_2, triphenylphosphine (787 mg, 3 mmol) was added and the mixture stirred at RT overnight. The solvent was removed under vacuum at *ca* 35°, the residue was taken up in EtOAc (100 mL) and washed with 0.5M phosphate buffer, pH 7 (3 × 50 mL). The organic phase was dried and evaporated and the residue chromatographed (Et_2O) to give **28c** as a yellow foam (795 mg, 50%). IR 1740 (β-lactam), 1670 (ester).

(4R) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene*)*methyl* - 4 - (2,3' - *furanyl* - 2,2 - *dimethylthio*) *ethyl*–*azetidin* - 2 - *one* (**28d**). This ylid was obtained in 42% overall yield employing the above procedure on **27d**. IR 1740 (β-lactam), 1620 (ester).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene*)*methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy*)*ethyl*] - 4 - (2 - *pyridylthiocarbonyl*) *methyl* – *azetidin* - 2 - *one* (**31a**). A soln of **29** (9.22 g, 11.6 mmol) in acetone (120 mL) was oxidized with Jones reagent as described for **12a** to give the crude acid **30** (9.04 g, 96%).

To a stirred soln of **30** (5.1 g, 6.32 mmol) under N_2, cooled to 0°, was added Et_3N (1.01 mL, 7.27 mmol), and 2-pyridylthiochloroformate. The soln was stirred 40 min, diluted with EtOAc (250 mL), washed with IN HClaq, 5% $NaHCO_3$aq and brine, then dried and evaporated to a foam (5.33 g). Chromatography on a Waters prep LC/500 using one silica gel cartridge, elution with EtOAc/cyclohexane (1.2:1.0) gave **31a** as a yellow foam (3.05 g, 54%). IR (CH_2Cl_2), 1750 (β-lactam and carbonate), 1615 (ester); NMR (200 MHz), 1.21 (d, J = 6.4 Hz, CH_3), 2.8–3.6 (m, H 3 and CH_2–C=O), 3.88 (m, H 4), 5.0–6.0 (m, CH_2Ar ester and carbonate and CH_3–CH–O), 7.1–8.6 (m, ArH). MS, FD/MCA high resolution. (Found: 898.2061. Calc.: 898.2072.)

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene*)*methyl* - 3 - [(R*) - 2 - (o - *nitrobenzyloxycarbonyloxy*)*ethyl*] - 4 - (*phenylthiocarbonyl*) *methyl*–*azetidin* - 2 - *one* (**31b**). The crude **30** (407 mg, 0.5 mmol) in CH_2Cl_2 (8 mL), under N_2 cooled to 0°, was treated with Et_3N (0.080 mL, 0.57 mmol) and N-methyl-2-fluoropyridinium iodide[21] (132 mg, 0.53 mmol) and stirred 15 min at 0° followed by 30 min without the ice bath. Thiophenol (0.110 mL, 1.07 mmol) and pyridine (0.080 mL, 1 mmol) were added and the mixture was allowed to stir 20 min. The solvent was removed under reduced pressure and the residue chromatographed (50% EtOAc, cyclohexane) to give **31b** (290 mg, 64%). IR 1750 (β-lactam and carbonate), 1700 (thioester), 1625 (ester).

Procedures for the preparation of aryl bromo compounds for the preparation of Grignard Reagents (**32**)

4-[2-(*t*-*Butyldimethylsilyloxy*)*ethyl*]-*bromobenzene*. To a soln of commercially available 2-(4-bromophenyl)ethanol

(2.1 g, 10 mmol) in 10 mL of CH_2Cl_2 at 0° under N_2 was added Et_3N (1.40 mL, 10 mmol) followed by t-butyldimethylsilyl chloride (1.51 g, 10 mmol). The mixture was stirred overnight. It was then washed with 3 × 25 mL water and dried. Solvent removal afforded crude silyl ether, which was chromatographed on silica gel (90 g) using petroleum ether (35–60° b.p.) as eluant to give 78% of 4-[2-(t-butyldimethylsilyloxy)ethyl]bromobenzene. This material was distilled using a short path distillation apparatus at 0.1 mm and 90° oil bath temp. NMR 0.09 (s, $SiCH_3$), 1.06 (s, Si-t-butyl), 2.94 (t, CH_2Ar), 3.97 (t, $SOCH_2$), 7.40 (q, ArH).

2-Bromo-5-[t-butyldimethylsilyloxymethyl]thiophene. A stirred soln of 2-bromo-5-carboxythiophene (5.00 g, 24.1 mmol) in THF (10 mL) under N_2 cooled to 0° in an ice–water bath was treated with a soln of diborane in THF (32 mL, 32 mmol) added dropwise over 15 min. After addition, the reaction was allowed to warm to RT and stirred overnight. The soln was then treated with water–THF (1:1, 10 mL), followed by a soln of satd K_2CO_3aq (25 mL). The mixture was extracted with EtOAc (2 × 25 mL) and the combined organic extracts washed with brine, dried, filtered, and evaporated under vacuum to a colorless clear oil of 2-bromo-5-hydroxymethylthiophene. NMR 3.27 (s, OH), 4.67 (s, CH_2), 6.67 (d, J = 4 Hz, ArH), 6.90 (d, J = 4 Hz, ArH). A stirred soln of this 2-bromo-5-hydroxymethylthiophene (4.30 g, 22.5 mmol) under N_2 in DMF (10 mL) was treated with imidazole (3.83 g, 56.3 mmol) and t-butyldimethylsilyl chloride (4.07 g, 27 mmol) and the resulting soln stirred overnight at RT. The soln was diluted with EtOAc (125 mL) and washed with water (5 × 125 mL), brine, dried, filtered and evaporated under vacuum to a nearly colorless clear oil (6.26 g). Purification by column chromatography using petroleum ether (b.p. 35–60°) followed by distillation (b.p. 108°, 0.3 mm) of the chromatographed product afforded a colorless clear oil (3.62 g, 53%). NMR 0.13 (s, $SiCH_3$), 0.96 (s, Si-t-butyl), 4.38 (s, CH_2), 6.63–7.00 (m, ArH). (Found: C, 43.21; H, 6.27; S, 10.69. Calc. for $C_{11}H_{19}BrOSSi$: C, 42.99; H, 6.23; S, 10.43%.)

2-t-Butyldimethylsilyloxymethyl-5-bromopyridine. 2-Hydroxymethyl-5-bromopyridine (2 g, 10.6 mmol) was dissolved in DMF (30 mL) and treated with t-butyldimethylsilyl chloride (1.92 g, 12.8 mmol) and Et_3N (1.8 mL, 12.8 mmol). The mixture was stirred 0.5 hr at RT, diluted with Et_2O (100 mL), washed with water (5 × 20 mL), dried and evaporated. The residual oil was distilled at 0.1 mm using a short path distillation apparatus to give the silyl ether (2.5 g, 83%). NMR 0.19 (S, $SiCH_3$), 1.0 (S,Si-t-butyl), 4.73 (S, CH_2–OSi), 7.0–8.2 (m, pyridyl H).

2-Bromo-5-(t-butyldimethylsilyloxymethyl)furan. To a suspension of commercially available 5-bromo-2-furoic acid (19.1 g, 0.1 mol) in aqueous MeOH (1:1, 100 mL) was added 2.5N NaOH (39 mL, 0.0975 mol) slowly. The mixture warmed up and turned brown. After 5 hr stirring at RT, the solvent was removed and the residue azeotroped with EtOAc (3 × 250 mL). The resulting sodium 5-bromo-2-furoate was left at 0.05 mm and RT for 15 hr. This brown Na-salt was suspended in dry DMF (100 mL) and MeI (2 eq.) was added under N_2. The mixture was stirred for 24 hr when all the solid was digested. Most of the solvent was removed *in vacuo* at 60°. The residue was taken up in water (250 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and dried. Solvent removal gave 20 g of crude methyl ester, which was chromatographed (ether–petroleum ether, b.p. 35–60°, 1:4) as eluant to give 67.3% yield of methyl 5-bromo-2-furoate.

A soln of this methyl ester (4.1 g, 20 mmol) in dry THF (25 mL) was added dropwise to an ice-cooled suspension of LAH (420 mg, 11 mmol) in dry THF (50 mL). Effervescence was observed during the addition. After the addition was complete, the mixture was heated to reflux for 2 hr and kept overnight at RT. Satd Na_2SO_4aq (20 mL) was added cautiously to ice-cooled light pink mixture. The solids were filtered and washed with THF (2 × 10 mL). The solvent was removed from the filtrate. The residue was taken up in ether and dried. Removal of ether gave crude 2-bromo-5-hydroxymethylfuran. To a soln of this crude alcohol in CH_2Cl_2 (100 mL) was added Et_3N (5.56 mL, 40 mmol), followed by t-butyldimethylsilyl chloride (6.1 g, 40 mmol) under N_2 at 0°. The mixture was stirred overnight at RT, washed with water (3 × 25 mL), dried and solvent removed to give the crude silyl ether (4.95 g). Chromatography (ether–petroleum ether, b.p. 35–60°, 1:9) as eluant gave 3.0 g of the desired 2-bromo-5-t-butyldimethylsilyloxymethylfuran. This material was distilled using a short path distillation apparatus at 0.1 mm and 100° oil bath temperature. NMR 0.09 (s, $SiCH_3$), 0.90 (s, Si-t-butyl), 4.50 (s, CH_2), 6.09 (furyl H).

4-(2-Tetrahydropyranyloxy)methyl bromobenzene. To a soln of 4-hydroxy–methyl bromobenzene (5.6 g, 30 mmol) in CH_2Cl_2 (200 mL) were added dihydropyran (5.0 g, 60 mmol) and *p*-TsOH (0.1 g). The mixture was stirred at RT for 2 hr, washed with 5% $NaHCO_3$aq, dried and evaporated. The residue was distilled using a short path distillation unit at 0.1 mm and an oil bath temp of 110° (a trace of K_2CO_3 was added to the distillation flask) to give 7.5 g (92%) of the desired product. NMR 1.8 (m, CH_2 of THP ether), 3.73 (m, CH_2–O), 4.63 (ABq, J = 14, $ArCH_2O$), 4.73 (m, –O–CH–O–), 7.4 (q, ArH).

(3S,4R*)-1-(o-Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl-3-[(R*)-1-o-nitrobenzyloxycarbonyloxyethyl]-4-(2'-t-butyldimethylsilyloxymethyl-5'-thienylcarbonyl)methyl-azetidin-2-one* (**33c**). A stirred soln of 2-bromo-5-(t-butyldimethylsilyloxy) methylthiophene (3.0 g, 9.76 mmol) in THF (10 mL) under N_2 was cooled to −78° and treated with a soln of n-BuLi in n-hexane (4.43 mL, 9.76 mmol) added dropwise. After 1 hr, the soln was transferred at −78° via Teflon tubing to a mixture of $MgBr_2$, preformed *in situ* from Mg (261 mg, 10.7 mmol) and 1,2-dibromoethane (0.88 mL, 10.2 mmol) in THF (10 mL) under N_2 at −78°. The resulting mixture was stirred at −23° in a CCl_4–dry ice bath. After $1\frac{1}{2}$ hr, a soln resulted, *ca* 0.3 molar.

A stirred soln of **31a**, (1.0 g, 1.11 mmol) in THF (13.0 mL) under N_2 cooled at 0° in an ice–water bath was treated with Grignard reagent (4.5 mL, 1.35 mmol). After 30 min, the soln was treated with additional Grignard reagent (4.0 mL, 1.2 mmol). The reaction was followed by TLC. After 50 min the solution was treated with sat NH_4Claq. The reaction was extracted with EtOAc (100 mL) and the organic phase was washed with water (100 mL), brine, dried, filtered and evaporated under vacuum to an oil (1.8 g). This crude product was chromatographed on silica gel using EtOAc:cyclohexane mixture (3:2) as solvent to give the desired **33c** as a foam (452 mg, 40%). IR (CH_2Cl_2) 1750 (β-lactam and carbonate), 1650 (ketone), 1620 (ester). MS, *m/e* 540, 499, 415, 348.

The following analogous ketones, **33a**, **33b** and **33d** *were prepared by the above procedure*

(3S,4R*)-1-((o-Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl-3-[(R*)-1-(o-nitrobenzyloxycarbonyloxy)ethyl]-4-[4'-(2-t-butyldimethylsilyloxyethyl)phenylcarbonyl]methyl-azetidin-2-one* (**33a**). Was obtained from 4-[2-(t-butyldimethylsilyloxy)ethyl]-bromobenzene and **31a** in 46% yield as a foam. IR 1745 (β-lactam and carbonate), 1673 (ketone), 1625 (ester). NMR 0.10 (s, CH_3Si), 0.94 (s, Si-t-butyl), 1.04 (d, J = 6 Hz, CH_3), 5.50 (s, CH_2 phenyl), 7.00–8.20 (m, ArH).

(3S,4R*)-1-(o-Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl-3-[(R*)-1-(o-nitrobenzyloxycarbonyloxy)ethyl]-4-[2-t-butyldimethylsilyloxymethyl-5'-pyridylcarbonyl)methyl-azetidin-2-one* (**33b**). Was obtained from 2-t-butyldimethylsilyloxymethyl-5-bromopyridine and **31a** in 58% yield. IR, 1750 (β-lactam and carbonate), 1690 (ketone), 1635 (ester). NMR 0.16 (s,

$SiCH_3$), 1.0 (s, Si-t-butyl), 1.1 (d, CH_3), 4.83 (s, CH_2OSi), 5.48 (s, CH_2–phenyl).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - [2 - *t - butyldimethylsilyloxymethyl-5' - furanylcarbonyl)methyl – azetidin* - 2 - *one* (**33b**). The Grignard reagent from 2-bromo-5-(t-butyldimethylsilyloxymethyl)furan was prepared and kept at −20 to −30° instead of 0° prior to its reaction with **31a**. The ketone **33d** was obtained from this Grignard reagent and **31a**, in 48.5% yield as a foam. IR, 1740 (β-lactam), 1730 (carbonate), 1655 (ketone), 1620 (ester). NMR 0.10 (s, $SiCH_3$), 0.94 (s, Si-t-butyl), 1.01 (d, J = 6 Hz, CH_3), 4.73 (broad d, CH_2OSi), 5.60 (broad s, CH_2–Ar), 6.50 d, ArH), 7.10–8.20 (m, ArH).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - [4' - (2 - *pyranyloxymethyl)phenylcarbonyl]methyl – azetidin* - 2 - *one* **33e**. Mg (25 mg) was suspended in THF (2 mL) under N_2, 4-(2-pyranyloxymethyl)bromobenzene (0.48 mL), and one drop of dibromomethane were added and the mixture stirred at RT for 2 hr, during which time the Mg dissolved. The mixture was cooled to 0° and treated with CuI (95 mg). After 5 min, 2.5 mL of ether was added and the mixture was stirred another 25 min. The bath temp was cooled to −10° and the mixture was treated dropwise with **31b** (200 mg, 0.22 mmol) in 2.5 mL THF/ether (1:1). The mixture was stirred 45 min at 0°. Workup as described for **33c** gave **33e** (122 mg, 56%) after chromatography on preparative TLC plates (1:1 EtOAc:cyclohexane). IR, 1742 (β-lactam and carbonate), 1670 (ketone), 1620 (ester).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - (2' - *hydroxymethyl* - 5 - *thienylcarbonyl)methyl – azetidin* - 2 - *one* (**34c**). A soln of **33c** (100 mg, 0.098 mmol) in THF (1.2 mL), MeOH (0.4 mL), water (0.4 mL) and conc HCl (16 μL) was stirred at RT and monitored by TLC. After $2\frac{1}{2}$ hr, the soln was treated with 5% $NaHCO_3$aq (5 mL) and extracted with EtOAc (5 mL). The organic phase was washed with brine, dried, filtered and evaporated under vacuum to an oil (93.2 mg). This crude product was chromatographed on silica gel using EtOAc/cyclohexane mixture (3:1) as solvent to give **34c** as an oil (63 mg, 71%). IR (CH_2Cl_2), 1750 (β-lactam and carbonate), 1650 (ketone), 1620 (ester); MS, *m/e* 901 (M).

The following analogous alcohols **34a, 34b** and **34d** *were prepared by the above procedure*

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - [4' - 2 - *hydroxyethylphenyl) carbonylmethyl – azetidin* - 2 - *one* (**34a**). This alcohol was obtained in 65% yield from **33a**, using 2 eq conc HCl in DMF for 12 min at RT instead of the above procedure for **34c**. IR 3375 (broad, OH), 1740 (β-lactam and carbonate), 1670 (ketone), 1620 (ester); NMR 1.20 (d, J = 6 Hz, CH_3), 5.50 (broad s, CH_2–phenyl), 7.00–8.20 (ArH).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - (2' - *hydroxymethyl* - 5' - *pyridylcarbonyl)methyl – azetidin* - 2 - *one* (**34b**). Was obtained in 62% yield from **33b**. IR, 3325 (OH), 1740 (β-lactam and carbonate), 1685 (ketone), 1620 (ester).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - [2 - *hydroxymethyl* - 5' - *furanycarbonyl)methyl – azetidin* - 2 - *one* (**34d**). Was obtained as foam in 50% yield from **33d**. IR, 3350 (broad, OH), 1740 (β-lactam and carbonate), 1655 (ketone), 1620 (ester); NMR, 1.23 (d, J = 3 Hz, CH_3), 4.67 (broad d, CH_2O), 5.57 (s, CH_2–phenyl), 6.50 (broad d, ArH), 7.00–8.20 (m, ArH).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - (4' - *hydroxymethylphenylcarbonyl)methyl – azetidin* - 2 - *one* (**34e**). The THP ether **33e** (163 mg, 0.166 mmol) in AcOH (8 mL) was treated with 10% H_2SO_4aq (4 mL) at RT for 0.5 hr. The mixture was poured into 50 mL 5% $NaHCO_3$aq and brought to neutrality by addition of further amounts of solid $NaHCO_3$. The aqueous phase was extracted with 3 × 20 mL CH_2Cl_2 and the organic phase was dried and evaporated. The residue was pruified by preparative TLC (silica gel, 1:1 EtOAc:cyclohexane) gave **34e** (115 mg, 78%). IR, 3300 (OH), 1755 (β-lactam), 1742 (carbonate), 1680 (ketone), 1620 (ester), 1525 (NO_2); NMR, 1.23 (d, J = 7 Hz, CH_3), 4.73 (s, $-CH_2O$), 5.56 (s, CH_2Ar).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - (4' - *methylsulfonyloxymethylphenylcarbonyl)methyl – azetidin* - 2 - *one* (**35e**). The alcohol **34e** (214 mg, 0.239 mmol) in 10 mL CH_2Cl_2 cooled to 0° under N_2 was treated with CH_3SO_2Cl (55.4 μL, 0.717 mmol) and Et_3N (99.6 μL, 0.717 mmol). The mixture was stirred at 0° for 0.5 hr and at RT overnight. The mixture was diluted with CH_2Cl_2, washed with water, dried and evaporated. The residue was chromatographed on preparative TLC (silica gel, 1:1 EtOAc:cyclohexane) to give **35e** (168 mg, 72.4%). IR, 1745 (β-lactam and carbonate), 1680 (ketone), 1620 (ester), 1522 (nitro); NMR, 1.25 (d, J = 6 Hz, CH_3), 3.1 (s, CH_3OSO_2), 4.6 (s, CH_2OSO_2), 5.56 (s, CH_2Ar).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - [2' - *methylsulfonyloxymethyl* - 5' - *furanylcarbonyl)methyl – azetidin* - 2 - *one* (**35d**). Was obtained as a foam in almost quantitative yield from **34d** in accordance with the above procedure. IR, 1740 (β-lactam and carbonate), 1665 (ketone), 1625 (ester).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - (4' - *azidomethylphenylcarbonyl) methyl – azetidin* - 2 - *one* (**36e**). Lithium azide (65 mg, 1 mmol) and LiBr (84 mg, 1 mmol) were added to DMF (1 mL) under N_2 at RT amd the mixture was stirred 0.5 hr. To this was added **35e** (168 mg, 0.172 mmol) and the mixture was stirred at RT for 2 hr. The mixture was diluted with CH_2Cl_2, washed with water, dried and evaporated. The residual DMF was removed under high vacuum at 50° and the residue was purified by preparative TLC (silica gel, 1:1 EtOAc:cyclohexane) to give **36e** (130 mg, 82%). IR, 2100 (N_3), 1745 (β-lactam and carbonate), 1680 (ketone), 1620 (ester); NMR, 1.2 (d, J = 6 Hz, CH_3), 4.48 (s, CH_2N_3).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - (2' - *azidomethyl* - 5' - *pyridylcarbonyl)methyl – azetidin* - 2 - *one* (**36b**). Was obtained in 74% yield from **34b** following the procedures for **35e** and **36e**. IR, 2120 (N_3), 1750 (β-lactam and carbonate), 1680 (ketone), 1635 (ester); NMR, 1.1 (d, CH_3), 4.52 (s, CH_2N_3), 5.5 (s, CH_2Ar).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - (2' - *azidomethyl* - 5' - *thienylcarbonyl)methyl – azetidin* - 2 - *one* (**36c**). Was obtained in 87% yield from **34c** following the procedures for **35e** and **36e**. IR (CH_2Cl_2), 2100 (N_3), 1745 (β-lactam and carbonate), 1650 (ketone), 1620 (ester); MS, *m/e* 568, 277, 262.

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene)methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 4 - (2' - *azidomethyl* - 5' - *furanylcarbonyl)methyl – azetidin* - 2 - *one* (**36d**). Was obtained as a foam in 65% yield from **34d** following the procedures for **35d** and **36e**. IR, 2075 (N_3), 1740 (β-lactam and carbonate), 1665 (ketone), 1620 (ester); NMR, 1.53 (d, J = 6 Hz, CH_3), 4.30 (s, CH_2N_3), 5.61 (s, CH_2Ar). 5.77 (dd, J = 10 and 8 Hz, CH_2Ar), 6.47 (d, J = 3 Hz, furanyl H), 7.0–8.2 (m, ArH).

o - *Nitrobenzyl* - (5R*,6S*) - 2 - (4' - *azidomethylphenyl*) - 6 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)*

ethyl] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**37e**). The azide, **36e** (130 mg, 0.141 mmol) in xylene (5 mL) was refluxed under N_2 for 1.5 hr (oil bath at 145°). The solvent was removed under reduced pressure and the residue purified by preparative TLC (1:1 EtOAc:cyclohexane) to give **37e** (53 mg, 58.4%). IR, 2100 (N_3), 1775 (β-lactam), 1745 (carbonate), 1720 (ester), 1525 (nitro); NMR (300 MHz), 1.55 (d, J = 6 Hz, CH_3), 3.30 (octet, H 1), 3.66 (dd, J = 4 and 5 Hz, H 6), 4.30 (app. t, J = 4 and 9 Hz, H 5), 4.35 (s, CH_2N_3), 5.26 (m, –CH–O), 5.57 and 5.79 (2d, J = 17 Hz, CH_2Ar), 5.62 and 5.68 (2d, J = 18 Hz, CH_2Ar), 7.20–8.20 (m, ArH).

o - *Nitrobenzyl* - (5R*,6S*) - 2 - (2' - *azidomethyl* - 5' - *pyridyl*) - 6 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy*) *ethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**37b**). Was obtained in 72% yield (toluene, 125°, 2 hr) from **36b** according to the procedure used for **37e**. IR, 2100 (N_3), 1780 (β-lactam), 1745 (carbonate), 1725 (ester), 1530 (nitro); NMR, 1.52 (d, J = 6 Hz, CH_3), 3.35 (m, H 1), 3.53 (dd, J = 3 and 7 Hz, H 6), 4.46 (m, H 5), 4.5 (s, CH_2N_3), 5.3 (m, –CH–O), 5.6 (s, CH_2Ar), 5.66 (ABq, CH_2Ar), 7.3–8.6 (m, ArH).

o - *Nitrobenzyl* - (5R*,6S*) - 2 - (2' - *azidomethyl* - 5' - *thienyl*) - 6 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy*) *ethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**37c**). Was obtained in 64% yield from **36c** using the conditions employed for **37e** (xylene, 120°, 4.5 hr). IR (CH_2Cl_2) 2100 (azide), 1780 (β-lactam), 1750 (carbonate), 1715 (ester); MS, *m/e* 451, 409, 342, 206; NMR (300 MHz), 1.54 (d, J = 6.8 Hz, CH_3), 3.42 (dd, J = 18 and 9.1 Hz, H 1-α), 3.46 (dd, J = 7.5 and 3.0 Hz, H 6-β), 3.56 (dd, J = 18.0 and 9.6 Hz, H 1-β), 4.32 (dt, J = 9.5 and 3.0 Hz, H 5), 4.50 (s, CH_2N_3), 5.28 (m, H 8), 5.59 and 5.67 (d, J = 14.5 Hz, CH_2 carbonate), 5.63 and 5.98 (d, J = 16.1 Hz, CH_2 ester), 7.07 (d, J = 4 Hz, thienyl proton), 7.5–7.7 (m, ArH), 8.04 (d, J = 8 Hz, ArH), 8.2 (dd, J = 8.5 Hz, ArH).

o - *Nitrobenzyl* - (5R*,6S*) - 2 - (2' - *azidomethyl* - 5' - *furanyl*) - 6 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy*) *ethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**37d**). Was obtained in 49% yield from **36d**, according to the procedure (xylene, 130°, 4 hr), used for **37e**. IR, 2100 (azide), 1765 (β-lactam), 1742 (carbonate), 1715 (ester); NMR (300 MHz), 1.54 (d, J = 6 Hz, CH_3), 3.47 (dd, J = 6 and 2 Hz, H 6), 3.34 and 3.64 (dd, J = 6 and 12 Hz, H 1), 4.32 (s, CH_2N_3), 4.30 (m, H 5), 5.26 (m, H 8), 5.74 (m, CH_2Ar), 5.96 (m, CH_2Ar), 6.51 (d, J = 3 Hz, furanyl H), 7.40–8.20 (m, ArH).

(5R*,6S*) - 2 - (4' - *Aminomethylphenyl*) - 6 - [(R*) - 1 - *hydroxyethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylic acid* (**38e**). The azide **37e** (4 mg) was dissolved in 4 mL dioxane, 4 mL water, and 0.2 mL EtOH. The pH of the soln was adjusted to 3.4 with 0.001N HCl, 4 mg of 10% Pd/C was added, and the mixture was hydrogenated at 40 psi for 20 min. The catalyst was filtered off and washed with water (8 mL). The filtrate and washings were extracted with ether (3 × 20 mL), and the aqueous phase was evaporated to 2 mL below RT to give a soln of **38e** which was purified by chromatography on XAD-2 resin, elution with H_2O followed by 10% THF/H_2O. UV λ_{max} (H_2O) 300 nm; ϵ = 12500. NMR (300 MHz, D_2O), 1.36 (d, J = 7 Hz, CH_3), 3.14 (dd, J = 10 and 17 Hz, H 1), 3.48 (dd, J = 9 and 17 Hz, H 1), 3.58 (dd, J = 3 and 6 Hz, H 6), 4.2 (s, CH_2N), 4.36 (m, H 5 and –CH–O), 7.6 (s, ArH).

(5R*,6S*) - 2 - (2' - *Aminomethyl* - 5' - *pyridyl*) - 6 - [(R*) - 1 - *hydroxyethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**38b**). The azide **37b** (4 mg) was dissolved in THF (4 mL), 3.2 mL water, 8 mg 10% Pd/C and 240 μL 0.5M pH 7 "MOPS" buffer were added. The mixture was hydrogenated at 40 psi for 10 min. The workup for **38e** was followed to give a soln of **38b**. UV λ_{max} (H_2O) 305 nm (NH_2OH extinguishable).

(5R*,6S*) - 2 - (2' - *Aminomethyl* - 5' - *thienyl*) - 6 - [(R*) - 1 - *hydroxyethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylic acid* (**38c**). Was obtained from **37c** using the procedure for **38b**. IR (CH_2Cl_2) 1747 (β-lactam), 1603 (carboxylate); UV λ_{max} (H_2O) 326 nm (ϵ = 5900) which is 94% NH_2OH extinguished); NMR (D_2O; 300 MHz), 1.33 (d, J = 6.8 Hz, CH_3), 3.34 (dd, J = 17 and 9.6 Hz, H 1), 3.37 (dd, J = 17 and 8.3 Hz, H 1), 3.51 (dd, J = 5.9 and 3.0 Hz, H 6), 4.2–4.5 (m, H 5 and H 8), 4.37 (s, CH_2Ar), 7.16 (s, ArH).

(5R*,6S*) - 2 - (2' - *Aminomethyl* - 5' - *furanyl*) - 6 - [(R*) - 1 - *hydroxyethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylic acid* (**38d**). Was obtained from **37d** by employing the procedure for **38b** as white fluffy material after freeze drying the aqueous soln: UV λ_{max} (H_2O) 314 (NH_2OH extinguishable).

o - *Nitrobenzyl* - (5R*,6S*) - 2 - (2' - *hydroxymethyl* - 5' - *thienyl*) - 6 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy*) *ethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**39c**). Was obtained in 28% yield from **34c** (xylene, 120°, 8 hr) according to the procedure used for **37e**. IR (CH_2Cl_2), 1778 (β-lactam), 1750 (carbonate), 1716 (ester); MS, *m/e* 512, 444, 426, 358, 340; NMR (300 MHz), 1.56 (d, J = 6.5 Hz, CH_3), 1.90 (t, J = 5.9, OH), 3.39 (dd, J = 17.9 and 9.7 Hz, H 1), 3.45 (dd, J = 8.0 and 2.5 Hz, H 6), 3.53 (dd, J = 17.9 and 9.7 Hz, H 1), 4.30 (dt, J = 9.7 and 2.5 Hz, H 5), 4.85 (d, J = 5.9 Hz, CH_2 thienyl), 5.28 (m, H 8), 5.58 and 5.65 (d, J = 14.9 Hz, CH_2Ar carbonate), 5.64 and 5.96 (d, J = 16 Hz, CH_2Ar ester), 7.03 (d, J = 4 Hz, ArH), 7.5–7.7 (m, ArH), 8.04 (d, J = 8 Hz, ArH), 8.19 (dd, J = 8 Hz, ArH).

o - *Nitrobenzyl* - (5R*,6S*) - 2 - (4' - *hydroxymethylphenyl*) - 6 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy*) *ethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**39e**). Was obtained in 68% yield from **34e** using the procedure employed for **37e**. IR, 3330 (OH), 1775 (β-lactam), 1740 (carbonate), 1720 (ester), 1525 (nitro); NMR (300 MHz), 1.55 (d, J = 7 Hz, CH_3), 3.30 (dd, J = 9 and 18 Hz, H 1-α), 3.36 (dd, J = 8.5 and 18 Hz, H 1-β), 3.51 (dd, J = 3 and 8 Hz, H 6), 4.29 (app. t, J = 9 and 3 Hz, H 5), 4.66 (s, CH_2 alcohol), 5.28 (m, H 8), 5.58 and 5.8 (2d, J = 15 Hz, CH_2 ester), 5.61 and 5.68 (2d, J = 15 Hz, CH_2 of carbonate), 7.2–8.2 (m, ArH).

Sodium (5R*,6S*) - 2 - (4' - *hydroxymethylphenyl*) - 6 - [(R*) - 1 - *hydroxyethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**40e**). The carbapenem **39e** (2 mg) was dissolved in *p*-dioxane (2 mL). An aqueous soln of $NaHCO_3$ (0.41 mg, 2 mL) was added followed by absolute EtOH (0.2 mL) and 10% Pd/C (2 mg). The mixture was hydrogenated at 45 psi for 45 min. The catalyst was filtered off and washed with water. The filtrate and washings were extracted with EtOAc (3 × 10 mL) and then evaporated to 5 mL. UV λ_{max} (H_2O) 305 nm (NH_2OH extinguishable). Assuming an ϵ = 12500 for **40e** similar to that of **37e**, the yield was calculated to be 50%.

Sodium (5R*,6S*) - 2 - (2' - *hydroxymethyl* - 5' - *thienyl*) - 6 - [(R*) - 1 - *hydroxyethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**40c**). Was obtained from **39c** using the above procedure. UV λ_{max} H_2O 325 nm; NMR (300 MHz, D_2O), 1.3 (m, CH_3), 3.3 (m, H 1), 3.48 (m, H 6), 4.3 (s, $-CH_2O-$), 4.2–4.3 (m, H 5 and H 8), 7.0 (m, ArH), 7.12 (m, ArH).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene*)*methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy*)*ethyl*] - 4 - (4' - *carboxymethylphenyl*) *carbonylmethyl* – *azetidin* - 2 - *one* (**41**). To a soln of **34a** (250 mg, 0.275 mmol) in acetone (5 mL) was added 145 l. (0.58 mmol) of Jones reagent (4 molar in O_2). After 1 hr stirring at RT, the solvent was removed and the residue was taken up in 10 mL water and extracted with 3 × 10 mL EtOAc. The combined organic extracts were dried. Solvent removal yielded crude **41** (245 mg). IR, 3000 (broad, COOH), 1740 (β-lactam and carbonate), 1680 (ketone), 1610 (ester). NMR 1.23 (d, J = 5 Hz, CH_3), 5.31 (s, CH_2), 7.0–8.2 (m, ArH).

(3S*,4R*) - 1 - (o - *Nitrobenzyloxycarbonyltriphenylphosphoranylidene*)*methyl* - 3 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy*)*ethyl*] - 4 - [4' - (N - *methylamidomethyl*) *phenylcarbonylmethyl*] - *azetidin* - 2 - *one* (**42**). To a soln of **41** (132 mg, 0.15 mmol) in dry CH_2Cl_2 (5 mL) under N_2 was

added carbonyldiimidazole (81 mg, 0.5 mmol). After stirring the mixture for 2 hr at RT, 10% methylamine soln in CH_2Cl_2 (155 l., 0.5 mmol) was added followed by Et_3N (70 μL, 0.5 mmol). After stirring for 4 hr at RT, the mixture was diluted with 10 mL EtOAc and washed with 2 × 5 mL 1N HCl and 2 × 5 mL 10% $NaHCO_3$aq. The organic layer was dried. Solvent removal, followed by chromatography on silica gel using EtOAc as solvent gave 85 mg of the desired **42**. IR, 3350 (broad, NH), 1740 (β-lactam and carbonate), 1670 (ketone, amide, strong peak), 1620 (ester).

o - *Nitrobenzyl* - (5R*,6S*) - 2 - [4' - (N - *methylamidomethyl)phenyl*] - 6 - [(R*) - 1 - (o - *nitrobenzyloxycarbonyloxy)ethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylate* (**43**). Was obtained in 40–60% yield from **42** using the procedure (xylene, 130°, 4.5 hr) employed for **37e**. IR, 3350 (NH), 1780 (β-lactam), 1750 (carbonate), 1720 (ester), 1660 (amide), 1525 (nitro). NMR (200 MHz), 1.56 (d, J = 7 Hz, CH_3 of C 8), 2.80 (d, J = 5 Hz, CH_3 of amide), 3.32 (dd, J = 9 and 18 Hz, H 1), 3.52 (dd, J = 3 and 8 Hz, H 6), 3.58 (s, CH_2 of amide), 4.38 (app. t, J = 9 and 3 Hz, H 5), 5.27 (m, H 8), 5.56 and 5.80 (2d, J = 15 Hz, CH_2 of ester), 5.65 and 5.69 (2d, J = 15 Hz, CH_2 of carbonate), 7.26–8.24 (m, ArH).

(5R*,6S*) - 2 - [4' - *Methylamidomethyl)phenyl*] - 6 - [(R*) - 1 - *hydroxyethyl*] - 1 - *carbapen* - 2 - *em* - 3 - *carboxylic acid* (**44**). Was obtained from **43** in acorrdance with the procedure used for **38b**: UV λ_{max} (H_2O) 301 nm.

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