Novel C-2 Substituted Carbapenem Derivatives

Part IV. Synthesis and Biological Activity of Five Membered Heteroaromatic Derivatives

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The synthesis, antibacterial activity, and stability to human dehydropeptidase-1 (DHP-1) of a novel series of (5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-2-heterocyclylcarbapen-2-em-3-carboxylates are described. Of the compounds investigated 1,5-disubstituted pyrazol-3-yl and 3-substituted isoxazol-5-yl derivatives have the best combination of antibacterial activity and stability to DHP-1. They are particularly active against community-acquired respiratory tract pathogens and have stabilities to DHP-1 superior to that of meropenem.

The aim of this series of investigations is the synthesis of potent and DHP-1 stable C-2 substituted carbapenems. The preceding papers[1~3] described the SAR of carbapenems bearing non-aromatic heterocyclic and acyclic groups. These derivatives possess variable potency and stability to DHP-1. Independent studies however have shown that DHP-1 stability can generally be improved by replacing the classical thio-linked C-2 substituents with directly attached aryl groups[4]. Nevertheless, only a limited number of compounds have been described which investigate the effect of direct attachment of heterocyclic substituents at C-2, particularly those containing more than one heteroatom.

Recently, epidemiological studies have demonstrated that community-acquired infections caused by penicillin-resistant *Streptococcus pneumoniae*[5] and penicillin-resistant, non β-lactamase producing *Haemophilus influenzae*[6] are increasing. Most β-lactams are ineffective in the therapy of infections caused by these bacteria, in which altered target site penicillin-binding proteins (PBPs) may be responsible for β-lactam resistance. However, the higher intrinsic affinity of carbapenems for a range of PBPs means that they do represent a potential therapy for infections caused by these pathogens.

Herein, we report the synthesis, antibacterial activity, and stability to DHP-1 of a range of novel C-2 aromatic heterocyclyl carbapenems which have activity and stability characteristics suitable for the treatment of community acquired infections, particularly those caused by *S. pneumoniae* and *H. influenzae*.

Chemistry

Three synthetic strategies were employed in the synthesis of the target carbapenems. The first utilised the chiral 4-acetoxyazetidinone (**1**) which was elaborated to the bicyclic carbapenem nucleus by established Wittig methodology (Method A). This approach proved particularly useful for the synthesis of a range of nitrogen containing heterocycles.

Thus, conversion of a suitably substituted ketone to the lithium enolate, followed by reaction with the azetidinone (**1**)[7] gave the *trans* functionalised azetidinone (**2**) (Scheme 1). The utility of the reaction was limited to the synthesis of carbapenems with nitrogen containing aromatic heterocycles because those containing oxygen or sulfur were not tolerant of the strong base used in

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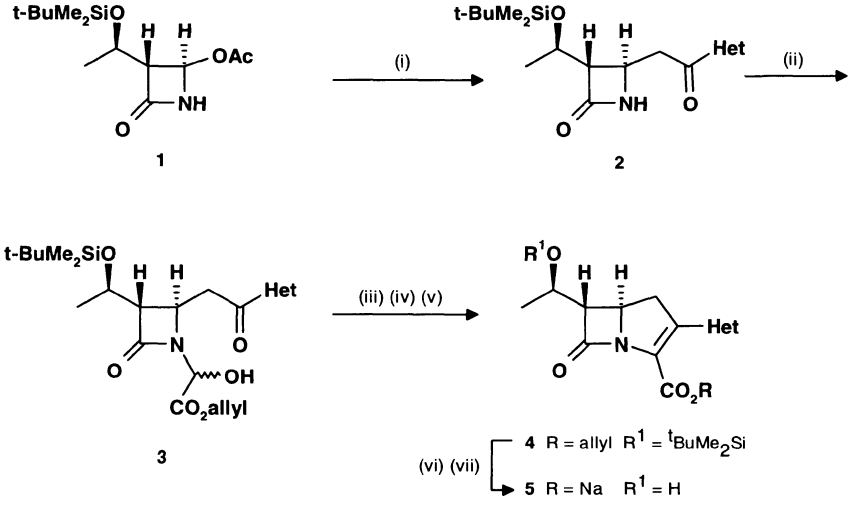
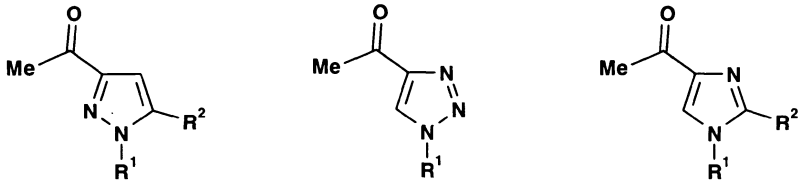
Scheme 1. Wittig route to carbapenem derivatives (method A).



Reagents: (i) LiHMDS, Het-C(O)Me (**6**, **7**, or **8**) THF, -70°C; (ii) allyl glyoxylate, $PhCH_3$, Δ; (iii) $SOCl_2$, 2,6-lutidine, THF; (iv) PPh_3, or P(*n*-Bu)$_3$, 2,6-lutidine, DMF; (v) $PhCH_3$, 80°C; (vi) Bu_4NF, HOAc, THF; (vii) $Pd(PPh_3)_4$, PPh_3, sodium 2-ethylhexanoate.



enolate formation. Azetidinones of general structure (**2**) were elaborated to the bicyclic carbapenem ester (**4**) by the well established Wittig cyclisation procedure, first reported by WOODWARD[8]. Steric congestion in the cyclisation reaction precluded the synthesis of the α-substituted C-2 heterocyclyl carbapenem derivatives by this method. Sequential deprotection was accomplished by established methods to give the carbapenem salts (**5**).

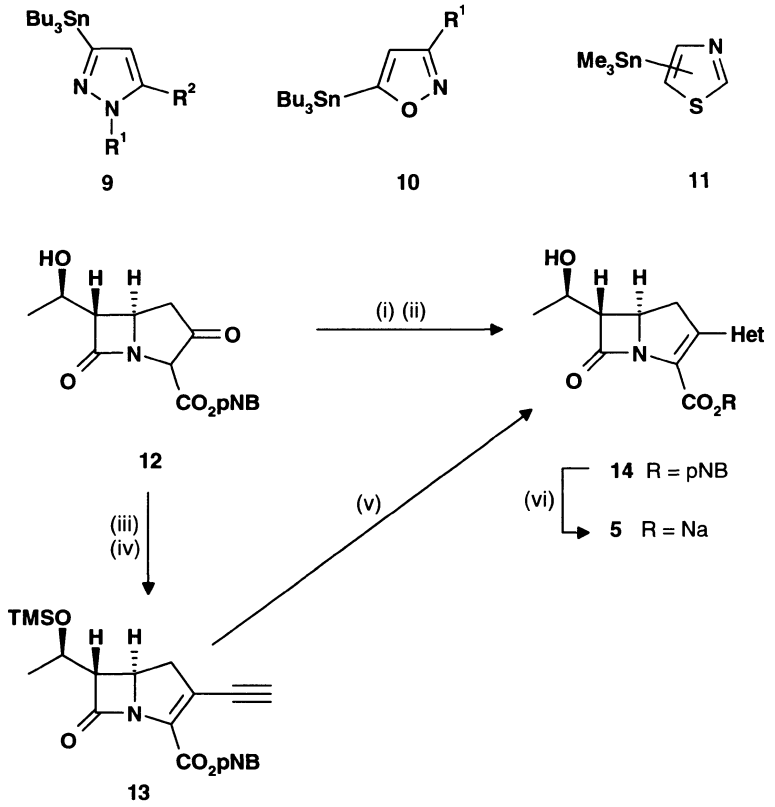
An alternative synthetic strategy was to remove the silyl protection prior to Wittig cyclisation. This deprotection was typically higher yielding than the corresponding reaction on the assembled carbapenem nucleus. However, the stability of the free hydroxy compound in the Wittig cyclisation was dependent on the functionalisation of the nascent 2-position.

The heterocyclic ketones (Scheme 1) required in this synthetic approach were prepared by a range of methodologies, each of which were designed such that functionality could be introduced which would be compatible with the rest of the synthesis (*vide infra*). Thus, pyrazol-3-yl ketones (**6**) were prepared by conversion of the corresponding esters to *N*-methoxy-*N*-methylcarboxamide[9] followed by reaction with methyl magnesium bromide. Similarly triazol-4-yl ketones (**7**) and imidazol-4-yl ketones (**8**) were prepared from known compounds by functional group manipulation.

Other, more convergent, approaches utilised the known carbapenam ketone[10] (**12**) as a convenient late stage intermediate. The vinyl triflate, derived from **12**, has been demonstrated to be an effective partner in the Stille cross coupling reaction[11] with both aryl and heteroaryl stannanes. Access to a range of heterocyclic stannanes which would be useful substrates for such a Stille coupling (Scheme 2) was therefore required.

3-Stannylpyrazoles (**9**) were prepared by the cycloaddition reaction of ethynyl tri-*n*-butylstannane with a *meso*-ionic sydnone derived from *N*-nitrosation of an amino acid, followed by cyclisation *via* the mixed trifluoroacetic anhydride[12]. 5-Stannylisoxazole (**10**) derivatives were available using a cycloaddition strategy involving reaction of nitrile oxide with ethynyl tri-*n*-butylstannane[13]. 4- and 5-Stannylthiazoles (**11**) were prepared using a literature protocol involving sequential protection, electrophilic introduction of tin, and

Scheme 2. Routes to C-2 substituted carbapenems *via* stille coupling (method B) and cycloaddition (method C).



Reagents: (i) $^{i}Pr_2NH$, Tf_2O, THF, -70°C; (ii) Het-SnR_3, (**9**, **10**, or **11**), $Pd_2(dba)_3$, Ph_3As, LiCl, $ZnCl_2$, THF; (iii) $^{i}Pr_2NH$, Tf_2O, THF, -70°C followed by NEt_3, TMSOTf; (iv) ethynyltri-*n*-butyltin, tri-(2-furyl)phosphine, $ZnCl_2$, N-methylpyrrolidinone; (v) Nitrile oxide or nitrile imine (generated *in situ*), CH_2Cl_2, 1,4-dioxan; (vi) H_2, Pd on C, $NaHCO_3$, THF. Tf = $-SO_2CF_3$.

deprotection[14].

The Stille coupling reaction (Method B) was carried out using tris(dibenzylideneacetone)dipalladium (0) with one of the following ligands; tris(2,4,6-trimethoxyphenyl)phosphine, tri(2-furyl)phosphine, or triphenyl arsine. The presence of both lithium chloride and zinc chloride were essential for effective coupling. Final deprotection of the *p*-nitrobenzyl ester (**14**) was accomplished in a phosphate buffered solution using zinc dust.

The final route involved construction of the dipolarophile attached to the C-2 position of the carbapenem nucleus (Method C). Whilst both C-2 vinyl and ethynyl carbapenems have been described[15], there has been only one example reported by others[16] of a cycloaddition reaction in which such substrates have been used. Earlier work in this series demonstrated that the 2-vinyl carbapenem derivative is an effective dipolarophile.[2] The current work shows that the 2-ethynyl derivative also reacts with 1,3-dipoles affording aromatic heterocycles directly.

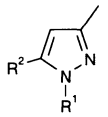
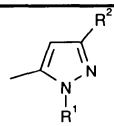
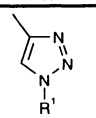
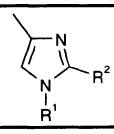
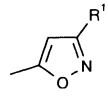
The dipolarophile (**13**) was constructed using the Stille coupling between the 8-silyl protected triflate derivative and ethynyl tri-*n*-butyltin. Reaction with an *in situ* generated nitrile oxide furnished the isoxazole derivatives. In a similar fashion nitrile imines could be used as the 1,3-dipole to give pyrazol-5-yl derivatives. Deprotections of the silyl ether and the *p*-nitrobenzyl ester (*vide infra*) gave the carbapenem salts (**5**). The heterocycles prepared by Methods A, B, and C are summarised in Table 1.

Biology

In general, the antibacterial activities of the new compounds were similar to those for imipenem[††] and

[††] See preceding paper for structures.

Table 1. Summary of preparative methods and substitution of C-2 heterocyclyl carbapenems.

Heterocycle	Compound	Method [a]	R^1	R^2
	**5a**	B	Me	-
	5b	B	Ph	-
	5c	B	CH_2CH_2Ph	-
	5d	A	Me	Me
	5e	B	Me	Bz
	5f	A	Et	Me
	5g	A	Et	Et
	5h	B	Ph	Me
	5i	A	CH_2CH_2Ph	Me
	5j	A	CH_2CH_2OH	Me
	5k	A	CH_2CH_2NCOMe	Me
	**5l**	C	Ph	Me
	5m	C	Ph	^iPr
	**5n**	A	Me	
	5o	A	CH_2CH_2Ph	
	**5p**	A	Me	Me
	5q	A	Me	SO_2Me
 4-	**5r**	B		
5-	**5s**	B		
	**5t**	C	Me	
	5u	C	^iPr	
	5v	C	Ph	
	5w	B	CH_2OMe	
	5x	B	$CH_2(CH_2)_3OH$	
	5y	B	CH_2Ph	
	5z	B	CH=CHPh	

[a] Method A: Wittig cyclisation. Method B: Stille coupling. Method C: cycloaddition with **13**

meropenem[††] against Gram-positive organisms as well as *Moraxella catarrhalis* and *H. influenzae* (Table 2). The good activity of the pyrazol-3-yl derivatives (**5a**~**k**) against the test organisms was largely independent of the nature of the functionalisation on the heterocycle. An exception to this was in the 1-monosubstituted series (**5a**~**c**) in which decreasing polarity paralleled an increase in the activity against *S. pneumoniae*. This characteristic was not observed in the case of the 1,5-disubstituted compounds (**5d**~**k**). There was also variable activity against *Escherichia coli* in which an increase in lipophilicity resulted in decreased activity. In comparison, pyrazol-3-yl derivatives (**5l**, **5m**) showed diminished potency against both Gram-positive and Gram-negative organisms.

Triazole (**5n**, **5o**) and imidazole (**5p**, **5q**) derivatives had similar broad spectra of activity to that of the pyrazoles, whilst the thiazole derivatives (**5r**, **5s**) displayed potent activity, particularly against the Gram-positive organisms. Substitution in the 3-position of isoxazol-5-yl derivatives demonstrated a more profound effect on activity than observed with the other heterocycles. Incorporation of a bulky lipophilic group (**5v**, **5y**, **5z**) substantially reduced activity against the Gram-negative

Table 2. Summary of antibacterial activity and stability to DHP-1 of C-2 heterocyclyl carbapenems.

Compound	*E.c.*	*H.i.*	*M.c.*	*S.a.*	*S.p.*	Pen. R. *H.i.*	Pen. R. *S.p.*	Stability to DHP-1†
	MIC (μg/ml)					MIC_{90}* (μg/ml)		
Imipenem	0.12	0.25	<0.06	<0.06	<0.06	2	0.25	15.1 (67%)
Meropenem	<0.03	0.13	<0.03	<0.03	1	-	-	1.0 (88%)
5a	0.25	0.25	0.5	<0.06	0.5	-	-	3.6
5b	8	0.12	<0.06	<0.06	0.25	-	-	3.3
5c	32	0.25	<0.06	<0.06	<0.06	-	-	6.9
5d	0.25	0.25	<0.06	<0.06	0.5	0.25	0.5	0.6
5e	>32	0.12	<0.03	<0.03	0.12	-	-	2.3
5f	2	0.25	<0.06	<0.06	0.25	0.25	0.25	0.6
5g	16	0.12	<0.06	<0.06	0.25	1	0.25	0.4
5h	32	0.12	<0.06	<0.06	0.12	0.25	0.12	2.1
5i	>64	0.5	0.12	<0.06	0.12	-	-	2.7
5j	1	0.5	<0.06	<0.06	0.5	1	1	0.1
5k	2	0.5	0.12	0.12	0.5	2	0.5	0.5
5l	32	0.5	0.25	-	0.25	-	1	0.1
5m	>64	0.5	0.5	0.25	0.25	8	2	0.4
5n	0.12	0.5	<0.06	<0.06	0.5	0.5	0.5	(83%)
5o	16	0.25	<0.06	<0.06	0.12	0.25	0.06	0.5
5p	1	1	0.12	<0.06	0.12	2	0.25	(94%)
5q	0.5	0.5	<0.06	<0.06	0.12	0.5	0.25	0.5
5r	0.06	0.25	<0.06	<0.06	<0.06	-	-	3.5
5s	0.12	0.12	<0.06	<0.06	<0.06	0.5	0.25	(88%)
5t	0.25	0.5	<0.06	<0.06	1	1	0.5	(91%)
5u	1	0.25	0.25	<0.06	0.25	0.5	0.25	0.2
5v	4	4	8	<0.06	0.5	-	-	0.4
5w	0.5	0.5	<0.06	0.12	0.25	1	0.25	0.7
5x	0.5	0.25	<0.06	<0.06	0.12	1	0.25	0.4
5y	8	0.5	4	<0.06	0.5	-	-	0.8
5z	32	8	4	<0.06	4	-	-	-

Abbreviations: *E.c., Escherichia coli* DCO (TEM 1 β-lactamase); *H.i., Haemophilus influenzae* WM493 (β-lactamase -ve), *M.c., Moraxella catarrhalis* Ravasio (β-lactamase +ve); *S.a. Staphylococcus aureus* Russell (β-lactamase +ve); *S.p., Streptococcus pneumoniae* PU7. Pen. R., penicillin resistant; NT, not tested.

* Pen. R. *H. i*: 20 non β-lactamase producing strains; Pen. R. *S. p*: 20~40 strains

†Stability to DHP-1: Rates of hydrolysis by human DHP-1 at 37°C, relative to meropenem in the spectrophotometric assay. Figures in parenthesis are percentage of carbapenem remaining after incubation with human DHP-1 at 37°C for 60 minutes in the HPLC assay. See experimental section for assay details.

organisms and, to a lesser extent, *S. pneumoniae*. Derivatives with smaller, or more polar groups (**5t**, **5u**, **5w**, **5x**), gave activity only slightly lower than that of the pyrazoles.

Representative compounds from each class were evaluated further against respiratory tract pathogens in a more stringent multistrain screen. Thus, compounds were tested against a range of penicillin-resistant *S. pneumoniae* (20) and penicillin-resistant, non β-lactamase producing *H. influenzae* (20) both of which have resistance mechanisms mediated by altered penicillin binding proteins. The MIC_{90} data for the relevant compounds is described in Table 2.

The results demonstrate that in the pyrazol-3-yl series, maximum potency is associated with small alkyl (**5d**, **5f**) or aryl (**5h**) functionalisation at both the 1 and 5 posi-

tion of the heterocycle. The triazoles, imidazoles and thiazoles exhibit similar potency to the pyrazoles. Isoxazoles were shown to be consistently less potent against *H. influenzae*.

The stability to DHP-1 of most derivatives was assessed, against purified human enzyme, in a UV spectrophotometric assay. However, when the chromophore of the hydrolysis product interfered with that of the starting material, an alternative HPLC assay was employed. In both cases meropenem was used as the comparator compound and control experiments were conducted to check the stability of the carbapenems in the buffer used in the experiments. The results, shown in Table 2, indicate that some examples of all of the classes of heterocycle investigated have stability to DHP-1 as good as, or better than, meropenem. The most stable pyrazol-3-yl derivatives were those with small alkyl groups at both N-1 and C-5 (**5d**, **5f**, **5g**) which were hydrolysed at approximately half the rate of meropenem. Pyrazol-5-yl compounds (**5l**, **5m**) were also more stable than meropenem. However, 1-monosubstitution (**5a**~**c**) or incorporation of lipophilic groups at N-1 (**5h**, **5i**) or C-5 (**5e**) in the pyrazol-3-yl series was detrimental to their stability to DHP-1. Triazole (**5n**, **5o**) and imidazole (**5p**, **5q**) had hydrolysis rates which were about half the rate for meropenem. In the case of thiazoles the degree of stability depended on the position of attachment of the heterocycle to the carbapenem C-2 position; thiazol-5-yl (**5s**) had stability to DHP-1 similar to meropenem whilst the thiazol-4-yl (**5r**) compound was less stable. Isoxazol-5-yl derivatives (**5t**~**5y**) were consistently more stable to DHP-1 than meropenem. An increase in the lipophilicity of the C-3 substituent caused a reduction in stability to DHP-1 which was less significant than that observed in the pyrazol-3-yl series.

In conclusion, the novel carbapenems described herein have demonstrated that both activity against respiratory tract pathogens, and stability to DHP-1, can be incorporated in the same molecule by direct attachment of a five membered aromatic heterocycle at the C-2 position. The 1,5-dialkylpyrazol-3-yl (*e.g.* **5d**, **5f**) and the 3-alkylisoxazol-5-yl (*e.g.* **5t**) derivatives combined the necessary activity for the treatment of community-acquired infections with stability to DHP-1 superior to that of meropenem. The further evaluation of the most promising novel C-2 heterocyclyl carbapenems will be the subject of future publications.

Experimental

M.p.s were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded in CH_2Cl_2 solution unless otherwise stated, either on a Perkin Elmer 983 or a Philips PU9706 spectrometer. UV spectra were recorded on a Beckman DU spectrophotometer in EtOH or H_2O solution. NMR spectra were recorded on a Bruker AC 250 spectrometer in the solvents specified. Mass spectra were recorded either on a VG ZAB1F or a VG Trio-2 spectrometer in electron impact (EI), chemical ionisation using NH_3 gas (CI), electrospray (ESI-MS) or fast atom bombardment (FAB) mode, as specified. Chromatography was performed on Merck silica 60, <230 or $230\sim400$ mesh.

Chemistry Method A

(3*S*,4*R*)-3-[(*R*)-1-*t*-Butyldimethylsilyloxyethyl]-4-[(1,5-dimethylpyrazol-3-yl carbonyl)methyl]azetidin-2-one (**2d**)

3-Acetyl-1,5-dimethylpyrazole (0.770 g, 5.1 mmol) was dissolved in dry THF (10 ml) under an atmosphere of argon. The solution was cooled to $-78°C$ and lithium hexamethyldisilazide (1 M solution in hexane; 5.1 ml; 5.1 mmol) added by rapid dropwise addition. After stirring at $-78°C$ for 30 minutes a solution of azetidinone (**1**) (0.73 g, 2.55 mmol) in THF (10 ml) was added. Stirring was continued for 2 hours at $-78°C$. The reaction was treated with saturated ammonium chloride solution followed by ethyl acetate. After allowing to warm to room temperature the organic phase was washed with water and brine before drying ($MgSO_4$). Purification was accomplished by chromatography on silica gel which gave (**2d**) as a gum (0.539 g, 58%). IR ν_{max} (CH_2Cl_2) cm^{-1} 3411 (NH), 1761 (β-lactam C=O); MS *m/z* 365.2134 (M, $C_{18}H_3N_3O_3S$, requires 365.2135); ^1H NMR (250 MHz, $CDCl_3$) δ 6.54 (1H, s), 6.09 (1H, bs), 4.13~4.25 (1H, m), 4.09 (1H, dt, $J=2.5$, 9.1 Hz), 3.84 (3H, s), 3.13 (1H, dd, $J=10.1$, 17.1 Hz) and 3.48 (1H, dd, $J=3.4$, 17.1 Hz) (ABq), 2.89 (1H, dd, $J=2.4$, 4.8 Hz), 2.31 (3H, s), 1.21 (3H, d, $J=6.28$ Hz), 0.86 (9H, s), 0.08 (6H, s).

Allyl (5*R*,6*S*)-6-[(*R*)-1-*t*-Butyldimethylsilyloxyethyl]-2-(1,5-dimethylpyrazol-3-yl) carbapen-2-em-3-carboxylate (**4d**)

Azetidin-2-one (**2d**) (0.736 g, 2.0 mmol) and allyl glyoxylate monohydrate (0.662 g, 5.0 mmol) were dissolved in benzene (25 ml) and the mixture warmed to reflux, with provision for azeotropic removal of water, whilst under an atmosphere of argon. The reaction was held at reflux

for 1 hour and then allowed to cool to room temperature. Triethylamine (~4 drops) was added and the reaction stirred for 16 hours at room temperature. Purification of the crude material was accomplished by chromatography on silica gel which gave the hemiaminals (**3d**) as a 1 : 1 diastereomeric mixture (0.983 g), IR ν_{max} (CH_2Cl_2) cm^{-1} 3517 (broad, OH), 1757 (β-lactam C=O). The diastereomeric mixture (**3d**) (0.983 g, 2.0 mmol) in THF (15 ml) was treated with 2,6-lutidine (0.357 ml, 3.0 mmol) and thionyl chloride (0.225 ml, 3.0 mmol) whilst at $-10°C$ under an atmosphere of argon. The mixture was stirred for 1 hour at $-10°C$. The heterogeneous solution which resulted was treated with toluene and then filtered through Keiselguhr. Removal of solvent under reduced pressure gave a diastereomeric mixture of chlorides as a yellow oil (~1 g).

The above product was dissolved in dioxan (6 ml) and treated with triphenylphosphine (2.15 g, 8 mmol) and 2,6-lutidine (0.262 ml, 2.2 mmol) whilst under an atmosphere of argon. The reaction was stirred at room temperature for 4 hours. Ethyl acetate was added to the reaction mixture and the resulting organic phase was washed sequentially with 5% aq. citric acid, saturated aq.sodium bicarbonate and brine. After drying ($MgSO_4$) and removal of solvent the crude material was purified by chromatography on silica gel (10 × 4.5 cm), loading in dichloromethane and eluting with 70% ethyl acetate in hexane. The resulting phosphorane (0.75 g, 68% after three steps) was dissolved in dry toluene (75 ml) with hydroquinone (1 mg) whilst under argon. The reaction was warmed to reflux and stirred for 5 hours. Chromatography and crystallisation (ethyl acetate/hexane) gave (**4d**) as an off white solid (0.31 g, 68%): MP 119°C; IR ν_{max} (CH_2Cl_2) cm^{-1} 1773 (β-lactam C=O), 1716, (ester C=O); MS *m/z* 445.2395 (M, $C_{23}H_{35}N_3O_4Si$ requires 445.2397); ^1H NMR (250 MHz, $CDCl_3$) δ 7.02 (1H, s), 5.91~6.07 (1H, m), 5.45 (1H, dd, J=1.6, 17.3 Hz), 5.25 (1H, dd, J=1.2, 10.5 Hz), 4.67~4.86 (2H, m), 4.11~4.27 (2H, m), 3.77 (3H, s), 3.23 (1H, dd, J=9.1, 18.4 Hz) and 3.54 (1H, dd, J=10.0, 18.3 Hz) (ABq), 3.12 (1H, dd, J=2.7, 6.7 Hz), 2.27 (3H, s), 1.27 (3H, d, J=6.2 Hz), 0.88 (9H, s), 0.09 (6H, s).

Sodium (5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-(1,5-dimethylpyrazol-3-yl)carbapen-2-em-3-carboxylate (**5d**)

Silylether (**4d**) (0.355 g, 0.68 mmol) was dissolved in dry THF (40 ml) and treated with glacial acetic acid (0.411 mg) and tetra-*n*-butyl ammonium fluoride (2.0 mml of 1.0 M solution in THF) before stirring at room temperature for 24 hour. The mixture was diluted with ethyl acetate and washed with sat. sodium hydrogen carbonate solution and brine before drying ($MgSO_4$). The desilylated compound was isolated after chromatography on silica gel (0.07 g, 31%); IR ν_{max} (CH_2Cl_2) cm^{-1} 3603 (OH), 1774 (β-lactam C=O). Ester deprotection was accomplished by treatment of the allyl ester (0.071 g, 0.021 mmol) with triphenyphosphine (0.006 g, 0.021 mmol), sodium 2-ethylhexanoate (0.428 ml of 0.5 M solution in ethyl acetate) and tetrakis (triphenylphosphine)palladium (0) (0.008 mg, 0.006 mmol) in dichloromethane/ethylacetate (1 : 1, 8 ml) and stirring under an atmosphere of argon for 1 hour. Solvent was removed *in vacuo* until precipitation occurred and the resulting heterogeneous mixture transferred to centrifuge tube. Ether was added and the mixture triturated prior to centrifugation and removal of the supernatant (two times). Dissolution of the solid in water, filtration (GF/F, 0.7 μm), and lyophilization gave (**5d**) as a white fluffy solid (0.04 g, 65%); UV (H_2O) λ_{max} 297.5 nm (ε 8769); FAB-MS *m/z* 314 $(M+H)^+$, 336 $(M+Na)^+$; IR ν_{max} (KBr disc) cm^{-1} 1771 (β-lactam C=O); ^1H NMR (250 MHz, D_2O) δ 6.43 (1H, s), 4.21~4.28 (2H, m), 3.70 (3H, s), 3.47 (1H, dd, J=2.9, 5.9 Hz), 3.16~3.21 (2H, m), 2.23 (3H, s), 1.28 (3H, d, J=6.4 Hz).

Compounds **5n** and **5o** were prepared by identical methodology. Compounds **5p** and **5q**[†††] required conversion of the *tert*-butyldimethylsilyl- to trimethylsilyl- protecting group prior to Wittig cyclisation. Compounds **5f**~**5k** utilised the tri-*n*-butylphosphorane as the Wittig precursor and the hydroxyl protection was removed prior to cyclisation. See Table 3 for analytical data on the carbapenem sodium salts.

Method B

p-Nitrobenzyl (5*R*,6*S*)-6-[(1*R*)-Hydroxyethyl]-2-(1-phenylpyrazol-3-yl)-carbapen-2-em-3-carboxylate (**14b**)

To a solution of carbapenam-2-ketone (**12**) (460 mg, 1.32 mmol) in THF (14 ml), cooled in an acetone/CO_2 bath under argon atmosphere, was added diisopropylamine (0.215 ml, 1.53 mmol) followed after 5 minutes by trifluoromethanesulfonic anhydride (0.255 ml, 1.52 mmol). The resultant yellow solution was stirred with cooling for 30 minutes.

Meanwhile triphenyl arsine (42 mg, 0.14 mmol) was

[†††] Formation of **2q** required condensation of **1** with 1-methyl-2-thiomethyl-4-acetylimidazole followed by oxidation of the thioether to the sulfone using *m*-chloroperoxybenzoic acid.

Table 3-1. Analytical data on carbapenem sodium salts.

No.	^{1}H NMR (250MHz, D_2O) δ ppm	$(M+H)^+$ m/z	IR* cm^{-1}
5a	7.54 (1H, d, *J*= 2.4Hz), 6.65 (1H, d, *J*= 2.4Hz), 4.28 (2H, m), 3.86 (3H, s), 3.50 (1H, m), 3.28 (1H, dd, *J*= 8.6, 17.0Hz), 3.18 (1H, dd, *J*= 9.7, 17.0Hz), 1.31 (3H, d, *J*= 6.5Hz)	NT	1761
5c	7.25-7.41 (4H, m), 7.12-7.21 (2H, m), 6.57 (1H, d, *J*= 2.5Hz), 4.43 (2H, t,*J*= 6.5Hz), 4.25-4.40 (2H, m), 3.55 (1H, m), 3.20-3.35 (2H, m), 3.17 (2H, t, *J*= 6.5Hz), 1.36 (3H, d, *J*= 6.5Hz)	390	1753
5e	7.31-7.52 (5H, m), 6.63 (1H, s), 4.28-4.39 (2H, m), 4.15 (2H, s), 3.76 (3H, s), 3.58 (1H, dd, *J*= 2.8, 5.9Hz), 3.24-3.35 (2H, m), 1.39 (3H, d, *J*= 1.39Hz)	NT	1750
5f	6.41 (1H, s), 4.15-4.25 (2H, m), 4.04 (2H, q, *J*= 7.3Hz), 3.44 (1H, dd, *J*= 2.9, 6.0Hz), 3.14-3.19 (2H, m), 2.23 (3H, s), 1.24-1.29 (6H, m)	328*	1761
5g	6.48 (1H, s), 4.14-4.26 (2H, m), 4.05 (2H, q, *J*= 7.2Hz), 3.46 (1H, dd, 2.7, 5.9Hz), 3.18 (2H, d, *J*= 9.8Hz), 2.60 (2H, q *J*= 7.2Hz), 1.25-1.38 (6H, m), 1.19 (3H, t, *J*=7.6Hz)	342*	1752
5h	7.39-7.57 (5H, m), 6.61 (1H, s), 4.16-4.28 (2H, m), 3.46 (1H, dd, *J*= 2.9, 5.9Hz), 3.10-3.29 (2H, m), 2.20 (3H, s), 1.26 (3H, d, *J*= 6.4Hz)	NT	1786
5i	7.23 (3H, m), 6.90-7.08 (2H, m), 6.28 (1H, s), 4.22 (4H, m), 3.45 (1H, m), 3.17 (2H, m), 3.04 (2H, t, *J*=6.5Hz), 1.77 (3H, s), 1.28 (3H, d, *J*= 6.4Hz)	404	1752
5j	6.45 (1H, s), 4.05-4.30 (2H, m), 4.18 (2H, t, *J*= 5.0Hz), 3.88 (2H, t, *J*= 5.0Hz), 3.42-3.56 (1H, m), 3.13-3.30 (2H, m), 2.29 (3H, s), 1.31 (3H, d, *J*= 6.5Hz)	344	1752
5k	6.39 (1H, s), 4.19-4.28 (2H, m), 4.12 (2H, dd, *J*= 5.0, 6.1Hz), 3.50 (2H, dd, *J*= 5.0, 6.1Hz), 3.46 (1H, dd, *J*= 2.9, 6.0Hz), 3.15-3.21 (2H, m), 2.20 (3H, s), 1.88 (3H, s), 1.27 (3H, d, *J*= 6.4Hz)	383	1766
5l	7.30-7.56 (5H, m), 6.32 (1H, s), 4.11-4.25 (2H, m), 3.34 (1H, dd, *J*= 2.9, 5.8Hz), 2.96 (1H, dd, *J*= 8.6, 17.5Hz), 2.84 (1H, dd, *J*= 9.8, 17.5Hz), 2.29 (3H, s), 1.17 (3H, d, *J*= 6.4Hz)	354* (free acid)	1758

All MS conducted by FAB-MS except * assayed by ESI-MS.

* IR absorption of the β-lactam carbonyl. NT not tested

added to a solution of $Pd_2(dba)_3$ (6 mmg, 0.07 mmol) in THF (5 ml) under argon. After stirring at room temperature for 5 minutes, the deep red solution was then added to the crude triflate solution and the flask rinsed with THF (2 ml). Zinc chloride (2.76 ml of a 1.0 M solution in ether, 2.76 mmol) and solid lithium chloride (117 mg, 2.76 mmol) were added to the mixture followed by a solution of 1-phenyl-3-tri-*n*-butylstannyl-pyrazole (600 mg, 1.38 mmol) in THF (10 ml). The reaction mixture was removed from the cooling bath and stirred for 3 hours. The mixture was then concentrated, chromatographed on silica gel, and the partially purified product triturated with ether to afford (**14b**) (41 mmg, 67%). IR ν_{max} (CH_2Cl_2) cm^{-1} 1776 (β-lactam C=O), 1722; MS *m/z* 474 (M, $C_{25}H_{22}N_4O_6$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.24 (2H, d, *J*=8.8 Hz), 7.92 (1H, d, *J*=2.7 Hz), 7.70 (4H, m), 7.47 (3H, m), 7.32 (1H, t, *J*=7.3 Hz), 5.56 (1H, d, *J*=13.9 Hz), 5.30 (1H, d, *J*=13.9 Hz), 4.31 (2H, m), 3.78 (1H, dd, *J*=10.0, 18.8 Hz), 3.45 (1H, dd, *J*=9.0, 18.8 Hz), 3.28 (1H, dd, *J*=2.8, 6.4 Hz), 1.74 (1H, d, *J*=4.9 Hz), 1.41 (3H, d, *J*=6.3 Hz).

Sodium (5*R*,6*S*)-6-[(1*R*)-Hydroxyethyl]-2-(1-phenyl-pyrazol-3-yl)-carbapen-2-em-3-carboxylate (**5b**)

Compound (**14b**) (206 mg, 0.43 mmol) was suspended in THF (1 ml) and treated with (1:3) THF/0.35 M phosphate buffer (pH 6) (5 ml) followed by zinc dust (2 g, 0.03 mol). The mixture was then rapidly stirred at room temperature for 2 hours. The mixture was then filtered and the residue thoroughly washed with water. The pH of the filtrate was checked at pH 7, and then washed with ethyl acetate. Concentration of the aqueous phase to approximately 10 ml and purification by reverse phase chromatography (HP20SS, THF/water mixtures) gave the sodium salt (**5b**) after lyophilisation (72 mg, 46%). UV (H_2O) λ_{max} 307 nm (ε 16027); IR ν_{max} (KBr disc) cm^{-1} 1750 (β-lactam C=O); FAB-MS *m/z* 362 $(MH)^+$

Table 3-2. Analytical data on carbapenem sodium salts.

No.	^{1}H NMR (250MHz, D_2O) δ ppm	$(M+H)^+$ m/z	IR[a] cm^{-1}
5m	7.38-7.58 (5H, m), 6.44 (1H, s), 4.17-4.28 (2H, m), 3.38 (1H, dd, *J*= 2.9, 5.9Hz), 3.00 (1H, quintet, *J*= 7.0Hz), 2.97 (1H, dd, *J*= 8.6, 17.4Hz), 2.88 (1H,dd, *J*= 9.9, 17.4Hz), 1.28 and 1.29 (6H, 2d, each *J*= 7.0Hz), 1.24 (3H, d, *J*= 6.6Hz)	382* (free acid)	1759
5n	8.33 (1H, s), 4.12-4.33 (2H, m), 4.07 (3H, s), 3.47 (1H, dd, *J*= 2.8, 5.9Hz), 3.32 (1H, dd, *J*= 8.9, 17.5Hz) and 3.39 (1H, dd, *J*= 9.5, 17.5Hz) (ABq), 1.28 (3H, d, *J*= 6.4Hz)	NT	1752
5o	8.23 (1H, s), 7.29 (3H, m), 7.13 (2H, m), 4.70 (2H, t, *J*= 6.5Hz), 4.20-4.34 (2H, m), 3.49 (1H, dd, *J*= 3.0, 6.0Hz), 3.34 (2H, dd, *J*= 4.0, 9.0Hz), 3.22 (3H, t, *J*= 6.5Hz), 1.31 (3H, d, *J*= 6.0Hz)	391*	1755
5p	7.51 (1H, s), 4.28-4.34 (2H, m), 3.78 (3H, s), 3.51 (1H, dd, *J*= 2.7, 6.1Hz), 3.32 (2H, d, *J*= 9.3Hz), 2.62 (3H, s), 1.36 (3H, d, *J*= 6.4Hz)	NT	1750
5q	7.81 (1H, s), 4.18-4.26 (2H, m), 3.93 (3H, s), 3.64 (1H, dd, *J*= 3.0, 6.0Hz), 3.32 (3H, s), 3.25 (2H, dd, *J*= 3.0, 9.0Hz), 1.26 (3H, d, *J*= 6.0Hz)	378	1752
5r	8.88 (1H, s), 7.69 (1H, s), 4.19-4.27 (2H, m), 3.51 (1H,m), 3.20 (1H, dd, *J*= 10.1, 17.3Hz), 3.35 (1H, dd, *J*= 8.4, 17.1Hz), 1.26 (3H, d, *J*= 6.4Hz)	303	1754
5s	8.88 (1H, s), 7.87 (1H, s), 4.20-4.28 (2H, m), 3.36 (1H, dd, *J*= 2.8, 5.3Hz), 3.35 (1H, d, *J*= 1.7Hz), 3.31 (1H, d, *J*= 3.1Hz), 1.28 (3H, d, *J*= 6.4Hz)	303	1752
5t	6.50 (1H, s), 4.33 (1H, dt, *J*= 3.1, 9.3Hz), 4.25 (1H, quintet, *J*= 6.2Hz), 3.57 (1H, dd, *J*= 3.1, 5.7Hz), 3.26 (1H, d, *J*= 9.3Hz), 2.26 (3H, s), 1.28 (3H, d, *J*= 6.4Hz)	301	1761
5u	6.50 (1H, s), 4.35 (1H, dt, *J*= 3.1, 9.2Hz), 4.27 (1H, quintet, *J*= 6.3Hz), 3.59 (1H, dd, *J*= 3.1, 9.2Hz), 3.28 (2H, d, *J*= 9.2Hz), 3.05 (1H, quintet, *J*= 7.0Hz), 1.31 (3H, d, *J*= 6.4Hz), 1.26 (6H, d, *J*= 7.0Hz)	329	1766
5w	6.64 (1H, s), 4.56 (2H, s), 4.21-4.35 (2H, m), 3.56 (1H, dd, *J*= 3.0, 5.4Hz), 3.38 (3H, s), 3.25 (2H, d, *J*= 9.2Hz), 1.25 (3H, d, *J*= 6.3Hz)	309* (free acid)	1760
5x	6.50 (1H, s), 4.31 (1H, dt, *J*= 3.1, 9.3Hz), 4.23 (1H, m), 3.57 (2H, t, *J*= 6.6Hz), 3.55 (1H, dd, 3.1, 5.7Hz), 3.24 (2H, d, *J*= 9.3Hz), 2.67 (2H, t, *J*= 7.4Hz), 1.49-1.74 (4H, m), 1.26 (3H, d, *J*= 6.4Hz)	359*	1770
5y	7.31-7.42 (5H, m), 6.50 (1H, s), 4.32 (1H, dt, *J*= 3.1, 9.2Hz), 4.25 (1H, quintet, *J*= 6.2Hz), 4.03 (2H, s), 3.56 (1H, dd, *J*= 3.1, 5.7Hz), 3.22 (2H, d, *J*= 9.3Hz), 1.28 (3H, d, *J*= 6.4Hz)	377	1762
5z	7.30-7.60 (5H, m), 7.14 (1H, d, *J*=16.5Hz), 6.92 (1H, d, *J*= 16.5Hz), 6.84 (1H, s), 4.10-4.25 (2H, m), 3.43 (1H, dd, *J*= 3.0, 5.6Hz), 3.06 (1H, s), 3.01 (1H, s), 1.25 (3H, d, *J*= 6.2Hz)	389*	1759

All MS conducted by FAB-MS except * assayed by ESI-MS.

[a] IR absorption of the β-lactam carbonyl. NT not tested

384 $(MNa)^+$; ^{1}H NMR (250 MHz, D_2O) δ 8.02 (1H, d, J=2.5 Hz), 7.61 (2H, d, J=8.3 Hz), 7.49 (2H, t, J=7.6 Hz), 7.36 (1H, t, J=6.9 Hz), 6.82 (1H, d, J=2.5 Hz), 4.23 (2H, m), 3.48 (1H, dd, J=2.4, 5.4 Hz), 3.27 (2H, d, J=9.0 Hz), 1.27 (3H, d, J=6.3 Hz).

Compounds **5a**~**c**, **5e**, **5h**, **5r**, **5s**, and **5w**~**5z** were all prepared using the same methodology.

Method C

p-Nitrobenzyl (5*R*,6*S*)-2-Ethynyl-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (**13v**)

Diisopropylamine (0.88 ml, 6.3 mmol) was added dropwise to a stirred solution of carbapenam ketone (**12**) (2.0 g, 5.7 mmol) in dry tetrahydrofuran (30 ml) at −78°C under argon. After 10 minutes trifluoromethanesulfonic anhydride (1.1 ml, 6.3 mmol) was added dropwise followed by stirring for 15 minutes and then the addition of triethylamine (0.87 ml, 6.3 mmol). Trimethylsilyl

trifluoromethanesulfonate (1.2 ml, 6.3 mmol) was then slowly added to the cooled mixture and the whole was stirred at −78°C for 20 minutes. The crude triflate was warmed from −78°C to 0°C and then diluted with *N*-methyl-2-pyrrolidinone (NMP) (10 ml). A solution of tris(dibenzylideneacetone)dipalladium (0) (105 mg, 2 mol%), tri(2-furyl)phosphine (53 mg, 4 mol%) and ethynyltributyltin (2.8 g, 6.3 mmol) in NMP (10 ml) was added to the ice-cold solution and this was followed by the addition of 1 M zinc chloride in ether (11.5 ml, 11.5 mmol). The mixture was then allowed to warm to ambient temperature and stirred for 2 hours. The mixture was diluted with ethyl acetate (25 ml) and the solution was washed with saturated brine (2 × 20 ml), dried and evaporated to an orange liquid. The liquid was stirred with hexane (10 ml) to form a gummy solid which was separated by filtration and the solid purified by chromatography on silica gel, yielding the disilylated carbapenem as a white solid (0.911 g, 32%) MP 129~130°C; IR ν_{max} ($CHCl_3$) cm^{-1} 3020, 1786, 1719, 1524; CI-MS *m/z* 501 $(M+H)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 8.22 (2H, d, J=8.7 Hz), 7.64 (2H, d, J=8.7 Hz), 5.48 (1H, d, J=14.0 Hz), 5.31 (1H, d, J=14.0 Hz), 4.14~4.23 (2H, m), 3.21 (1H, dd, J=3.0, 6.2 Hz), 3.04 (1H, d, J=9.8 Hz), 3.02 (1H, d, J=9.1 Hz), 1.26 (3H, d, J=6.2 Hz), 0.13 and 0.19 (18H, s+s). Deprotection was accomplised by dissolution in ice cold THF (25 ml) followed by treatment with glacial acetic acid (0.72 ml) followed by 1 M tetra-*n*-butylammonium fluoride in THF (4.12 ml). The reaction was stirred at 0°C for 15 minutes followed by stirring at room temperature for 90 minutes. The reaction mixture was then diluted with ethyl acetate and the solution was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Stirring the residue with hexane prior to filtration gave (**13v**) as a solid (0.542 g, 85%). MP 100°C (dec.); CI-MS *m/z* 374 $(M+NH_4)^+$, 357 $(M+H)^+$; ν_{max} ($CHCl_3$) cm^{-1} 3690, 3020, 1786, 1725 and 1605; UV (EtOH) λ_{max} 267 nm (ε 9980), 292 nm (ε 8330); ^1H NMR (250 MHz, $(CD_3)_2CO$) δ 8.27 (2H, d, J=9.0 Hz), 7.83 (2H, d, J=9.0 Hz), 5.53 (1H, d, J=14.1 Hz), 5.38 (1H, d, J=14.1 Hz), 4.39 (1H, s), 4.33 (1H, ddd, J=3.2, 8.7, 10.2 Hz), 4.16 (1H, quint. J=6.1 Hz), 3.48 (1H, dd, J=3.2, 6.1 Hz), 3.19 (1H, dd, J=8.7, 18.2 Hz), 3.10 (1H, dd, J=10.2, 18.2 Hz), 1.26 (3H, d, J=6.3 Hz).

p-Nitrobenzyl (5*R*,6*S*)-2-[3-(Phenyl)isoxazol-5-yl]-6-[(1*R*)-hydroxyethyl]carbapen-2-em-3-carboxylate (**14v**)

α-Chlorobenzaldehyde oxime (50 mg, 0.32 mmol) was added to a solution of (**13**) (50 mg, 0.14 mmol) in dichloromethane and hexane (1 : 1, 2 ml) whilst under argon at room temperature. Triethylamine (0.03 ml, 0.21 mmol) in dichloromethane and hexane (1 : 1, 1 ml) was added by dropwise addition and the resulting suspension stirred for 1 hour. After diluting the reaction with dichloromethane it was washed with water and brine and then dried ($MgSO_4$). Purification was accomplished by chromatography on silica gel to give (**14v**) as a cream solid (41 mg, 62%). MP 161~164°C; UV (EtOH) λ_{max} 229 nm (ε 18400), 261 nm (ε 12730) and 334 nm (ε 14410); IR ν_{max} ($CHCl_3$) cm^{-1} 3438 (br), 3020, 1783, 1722, 1607 and 1524; MS *m/z* 475 (M, $C_{25}H_{21}N_3O_7$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.26 (2H, d, J=8.8 Hz), 7.81~7.85 (2H, m), 7.70 (2H, d, J=8.8 Hz), 7.68 (1H, s), 7.46~7.48 (3H, m), 5.57 (1H, d, J=14.1 Hz), 5.33 (1H, d, J=14.1 Hz), 4.30~4.45 (2H, m), 3.68 (1H, dd, J=10.3, 18.7 Hz), 3.41 (1H, dd, J=8.9, 18.7 Hz), 3.38 (1H, dd, J=3.2, 6.5 Hz), 1.75 (1H, d, J=4.8 Hz, D_2O-exch.), 1.41 (3H, d, J=6.3 Hz).

Sodium (5*R*,6*S*)-2-[3-(Phenyl)isoxazol-5-yl]-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (**5v**)

Ester (**14v**) (67 mg, 0.14 mmol) was suspended in THF along with sodium hydrogen carbonate (22 mg) in 0.2 M phosphate buffer (4 ml). The mixture was shaken with hydrogen at room temperature and atmospheric pressure for 15 minutes. The mixture was filtered and concentrated prior to chromatography on DIAION HP20SS resin. The sodium salt (**14v**) was isolated after lyophilization as a white solid (32 mg, 63%). UV (H_2O) λ_{max} 223 nm (ε 12720), 312 nm (ε 14070); IR ν_{max} (KBr) cm^{-1} 3422 br, 1758, 1597 and 1394; FAB-MS *m/z* 385 $(MNa)^+$, 363 $(MH)^+$; δ (D_2O) 7.79~7.83 (2H, m), 7.52~7.45 (3H, m), 7.02 (1H, s), 4.35 (1H, dt, J=3.1, 9.3 Hz), 4.29 (1H, quint, J=6.1 Hz), 3.59 (1H, dd, J=3.1, 5.7 Hz), 3.30 (2H, d, J=9.3 Hz), 1.30 (3H, d, J=6.4 Hz).

Compounds **5l**, **5m**, **5t**, and **5u** were prepared using the same methodology.

Biology

Determination of MIC

Antibacterial activity was determined by a broth microdilution technique in microtitre plates using Hamilton AT+ liquid handling technology, and defined as the minimum inhibitory concentration (MIC in μg/ml) needed to inhibit growth of the micro-organism. Mueller-Hinton Broth (Difco) was used as the growth medium; for growth of the more fastidious micro-organisms (*S. pneumoniae*, *H. influenzae* and *M. catarrhalis*) this was supplemented with sterile heat-

inactivated donor horse serum (ICN Biomedicals)-5%; hematin (Sigma)-0.02 mg/ml and NAD (-nicotinamide adenine dinucleotide, Sigma)-0.08 mg/ml (all final concentrations). Overnight broth cultures were added to give a final concentration of 5×10^5 cfu/ml. Plates were incubated at 37°C for 18 hours.

Determination of Stability to DHP-1

(i) HPLC method: The test compound (0.5 mmol solution in 0.02 M MOPS at pH 7.0) (0.08 ml) was challenged with pure, human DHP-1 enzyme (0.08 ml of 2.5μg/ml solution) at 37°C. Samples were removed at 0, 30, 60, and 90 minute time points and analysed by reverse phase HPLC. The hydrolysis of the carbapenem was monitored by integration of the area under the peak for the test compound. The results were submitted to a statistical evaluation programme which allowed for the calculation of the percentage of test compound remaining intact after 60 minutes. Control experiments were conducted for each test compound to check its stability in buffer alone.

(ii) Spectrophotometric method: The test compounds were challenged with the pure, human DHP-1 enzyme as described above. Rates of hydrolysis were recorded on a UV spectrophotometer at time points between 0 and 90 minutes. Absorbance changes were converted to concentration changes by prior analysis of wavelength scans for each test compound (concentration as above) in the presence of *Bacillus cereus* metallo-β-lactamase (100 ng). Assumptions made are that each compound is completely hydrolysed by the β-lactamase, that the absorbance changes caused by each enzyme are the same, and that the rate of change of the hydrolysis by metallo-β-lactamase is linear. The standard compound, meropenem, is assayed in each screen and the results quoted as hydrolysis rates relative to meropenem. Control experiments were conducted for each test compound to check its stability in buffer alone.

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