Novel C-2 Substituted Carbapenem Derivatives

Part III. Synthesis and Biological Activity of 2-(Functionalised Ethenyl, Oxyiminomethyl and α-[Hydroxy]benzyl)-Carbapenems

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(Received for publication October 7, 1996)

The synthesis, antibacterial activity and stability to human dehydropeptidase-1 (DHP-1) of three small series of carbapenems carrying carbon-linked substituents at C-2 are described. C-2 Ethenyl carbapenems showed moderate antibacterial activity but poor stability to DHP-1. C-2 Oxyiminomethyl carbapenems demonstrated variable activity and stability. C-2 α-(Hydroxy)benzyl carbapenems were the most promising and showed good potency and DHP-1 stability.

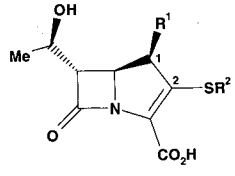
The exceptional antibacterial potency of thienamycin (**1**)[1] (Fig. 1) combined with its broad spectrum of activity and stability to β-lactamases, has stimulated a considerable and continuing interest in the chemistry of the carbapenem system. Although the inherent chemical and metabolic instability of thienamycin has precluded its clinical use, these respective problems have been addressed by the discovery of, among others, the carbapenem derivatives imipenem (**2**)[2] and meropenem (**3**)[3]. Imipenem alone is susceptible to hydrolysis by human renal dehydropeptidase (DHP-1) and is therefore co-administered with cilastatin, a DHP-1 inhibitor. Metabolic stability to DHP-1 has been achieved by the incorporation of a 1-β-methyl group into the carbapenem nucleus, as exemplified by meropenem, but this strategy can lead to reduced potency.[4] The discovery of C-2 aryl carbapenems with high potency and stability to DHP-1 demonstrated that both properties were attainable without the requirement of the 1-β-substituent.[4] It has been demonstrated that high antibacterial potency and stability to DHP-1 are combined in the related penem antibiotics bearing acyclic C-2 substituents linked directly to the penem ring *via* sp^2 and sp^3 hybridised carbon atoms.[5] As part of a series of investigations[6,7], this paper describes the synthesis, potency against targeted organisms and stability to DHP-1 of a small number of substituted C-2 ethenyl, C-2 oxyiminomethyl and C-2 α-(substituted)benzyl carbapenems to assess the potential for a subsequent full SAR study.

Chemistry

The synthesis of C-2 ethenyl carbapenems is depicted in Scheme 1. The 2-trifluoromethanesulfonyl enol ether **4** is readily prepared as described for the corresponding *p*-nitrobenzyl ester.[8] Displacement with substituted vinyl groups was effected by a cross-coupling reaction with the vinylstannanes **7a**～**c**[9～12] under palladium(0) catalysis. Desilylation of the products **5a**～**c** and ester hydrolysis with $AlCl_3$ gave the sodium salts **6a**～**c**.

The synthesis of C-2 oxyiminomethyl carbapenem derivatives was achieved by the intramolecular Wittig cyclisation route (Scheme 2).[13] Coupling of the silyl enol ether derivatives of **9a**～**b** with the commercially available 4-acetoxyazetidinone **8** in the presence of $ZnCl_2$ gave the azetidinones **10a**～**b** with retention of stereochemistry

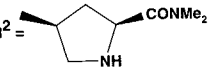
Fig. 1. Structures of thienamycin (**1**), imipenem (**2**) and meropenem (**3**).



1 R^1 = H, R^2 = $CH_2CH_2NH_2$

2 R^1 = H, R^2 = $CH_2CH_2NHCH{=}NH$

3 R^1 = Me, R^2 =



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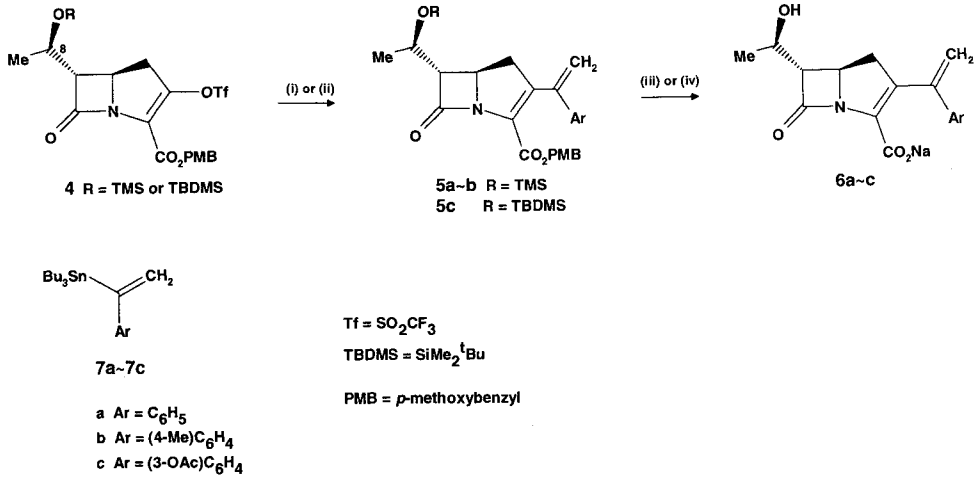
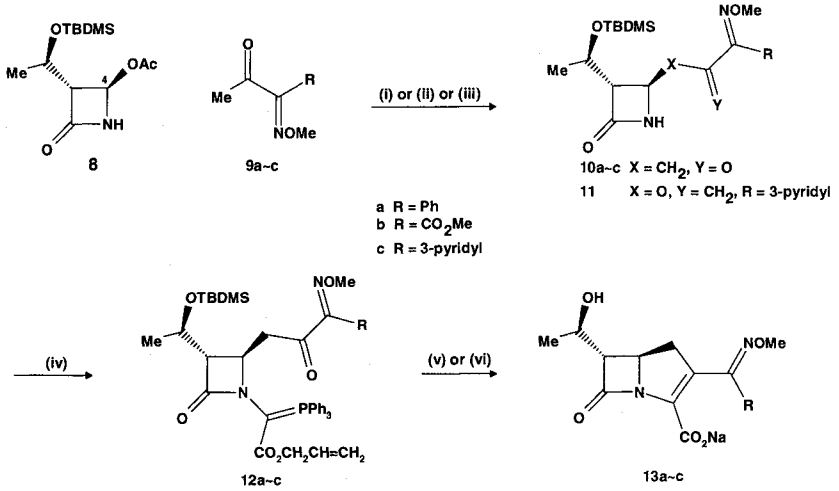
Scheme 1. Synthesis of ethenyl carbapenems (**6a**~**c**).



Reagents and conditions: (i) a) **7a** or **7b**, *n*BuLi, −78°→0°C, THF, 1 M $ZnCl_2$, b) tris(dibenzylideneacetone)dipalladium(0), tris(2,4,6-trimethoxyphenyl)phosphine, THF, −78°C→rt; (ii) **7c**, tris(dibenzylideneacetone)dipalladium(0), tris(2,4,6-trimethoxyphenyl)phosphine, *N*-methylpyrrolidinone, THF, 1 M $ZnCl_2$, 50°C; (iii) for **5a**~**b**, $AlCl_3$, anisole, CH_2Cl_2, −50°C, b) $NaHCO_3$, phosphate buffer (pH 7); (iv) for **5c**, nBu$_4$NF, AcOH, THF then (iii).

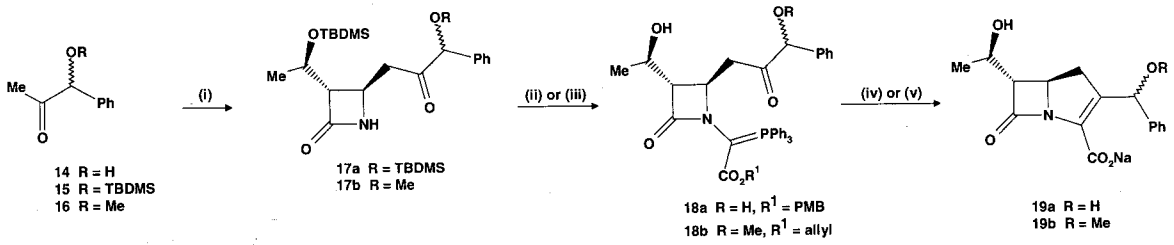
Scheme 2. Synthesis of oxyiminomethyl carbapenems (**13a**~**c**).



Reagents and conditions: (i) a) TBDMS-OTf, Et_3N, CH_2Cl_2, b) **8**, 1 M $ZnCl_2$, CH_2Cl_2 (→**10a**); (ii) a) TMS-OTf, $EtNiPr_2$, CH_2Cl_2, b) **8**, 1 M $ZnCl_2$, CH_2Cl_2 (→**10b**); (iii) a) LiHMDS, THF, b) **8**, (→**10c**, **11**); (iv) a) $(HO)_2CHCO_2$ allyl, Et_3N, toluene, b) $SOCl_2$, 2,6-lutidine, THF, c) PPh_3, 2,6-lutidine, dioxan; (v) a) HCl, MeOH, b) toluene, reflux, c) $Pd(PPh_3)_4$, sodium 2-ethylhexanoate, THF (→**13a**, **c**); (vi) a) Toluene, reflux, b) nBu$_4$NF, AcOH, c) $Pd(PPh_3)_4$, sodium 2-ethylhexanoate, THF (→**13b**).

at C-4. The silyl enol ether derivative of **9c** failed to react under these conditions so reaction between **8** and the lithium enolate derivative of **9c**, prepared by treatment with lithium hexamethyldisilazane (LiHMDS), was examined. This gave two products, the required material **10c** (23% yield) and the enol ether **11** (20%), demonstrating the ambident nucleophilicity of the lithium enolate species. Treatment of allyl glyoxylate[4] with **10a**~**c** gave intermediate epimeric hemiaminals, from which the corresponding phosphorane derivatives **12a**~**c** were prepared prior to the Wittig cyclisation step. Thereafter, higher overall yields of final products **13a**~**c** were obtained when the TBDMS protecting group was removed before rather than after cyclisation. Although all intermediates and final products in this series were identified as single geometrical isomers, no *E*/*Z* stereochemical assignments could be made either from ^{1}H NMR analysis or *via* NOE experiments.

Scheme 3. Synthesis of α-(substituted)benzyl carbapenems (**19a, b**).



14 R = H
15 R = TBDMS
16 R = Me

17a R = TBDMS
17b R = Me

18a R = H, R^1 = PMB
18b R = Me, R^1 = allyl

19a R = H
19b R = Me

Reagents and conditions: (i) **8** (Scheme 2), LiHMDS, THF; (ii) a) $(HO)_2CHCO_2PMB$, Et_3N, C_6H_6, b) $SOCl_2$, 2,6-lutidine, THF, c) PPh_3, 2,6-lutidine, dioxan, d) 2 M HCl, MeOH; (iii) a) $(HO)_2CHCO_2$ allyl, Et_3N, C_6H_6, b), c) and d) as (ii) above; (iv) a) toluene, reflux, b) $AlCl_3$, anisole, CH_2Cl_2, c) $NaHCO_3$, phosphate buffer (pH 7) (→**19a**); (v) a) toluene, reflux, b) $Pd(PPh)_4$, PPh_3, sodium 2-ethylhexanoate, EtOAc-CH_2Cl_2 (1 : 1) (→**19b**).

Table 1. Antibacterial activity and stability to human renal dehydropeptidase (DHP-1) of C-2 substituted carbapenems.

Compound	MIC (μg/ml)						Stability to DHP-1 (%)*
	E. c.	*H. i.*	*M. c.*	*S. a.*	*S. pn.*	*S. py.*	
6a	0.06	0.06	0.06	0.06	0.5	0.06	72
6b	0.06	0.06	0.13	0.13	0.5	0.13	NT
6c	0.25	0.25	0.06	0.5	2	0.13	NT
13a	0.25	0.25	0.25	0.5	2	0.06	79
13b	4	16	32	32	64	0.25	37
13c	0.25	1	2	1	4	0.06	63
19a	0.5	0.25	0.06	0.06	0.5	0.06	84[a]
19b	0.03	0.06	0.06	0.13	0.5	0.06	77[b]
Imipenem	0.06	0.25	0.06	0.06	0.06	0.06	68
Meropenem	0.03	0.06	0.03	0.03	1	0.03	88

Abbreviations: *E. c.*; *Escherichia coli* DC_2, *H. i.*; *Haemophilus influenzae* Q1 (β-lactamase − ve), *M. c.*; *Moraxella catarrhalis* Ravasio (β-lactamase + ve), *S. a.*; *Staphylococcus aureus* Russell (β-lactamase + ve), *S. pn.*; *Streptococcus pneumoniae* PU 7, *S. py.*; *Streptococcus pyogenes* CN 10, NT; not tested.

* Stability to DHP-1: Assessed by incubation at 37°C in a homogenate of human kidney. The numbers represent the percentage of compound remaining after 1 hour incubation.

[a] Tested as a 1 : 1 mixture of diastereomers.

[b] Tested as a single diastereomer of undetermined configuration.

Carbapenems **19a**～**b** bearing the C-2 α-(substituted)-benzyl grouping were also prepared by the Wittig route (Scheme 3). The racemic α-hydroxy ketone **14**[14] was derivatised to give compounds **15** and **16**. These products were converted to their lithium enolates by treatment with LiHMDS and then reacted with the azetidinone **8** (Scheme 2) to give the monocyclic derivatives **17a**～**b**. Elaboration to the phosphorane derivatives **18a**～**b** was carried out as described previously. Intramolecular cyclisation of **18a**～**b** and deprotection of the esters gave compounds **19a** and **19b** each as a mixture of two diastereomers; only separation of one diastereomer of the mixture **19b** was achieved by chromatography.

Biology

The antibacterial activities and stabilities to human DHP-1 of the three series of C-2 substituted carbapenems in comparison with imipenem and meropenem are shown in the Table 1.

The C-2 ethenyl substituted carbapenem **6a** showed good antibacterial potency across the range of organisms but stability to DHP-1 was significantly less than that of meropenem. The substituted aryl analogues **6b** and **6c** were slightly less potent than **6a**.

The antibacterial activities of the C-2 oxyiminomethyl derivatives were disappointing. The phenyl derivative **13a** was the most active compound in this series and also showed the best stability to DHP-1. The methyl ester derivative **13b** and the 3-pyridyl derivative **13c**, both showed poor antibacterial activity and poor stability to DHP-1.

The most promising series of compounds was the C-2 α-(substituted)benzyl carbapenems. Both **19a** and **19b** demonstrated good potency and good stability to DHP-1,

albeit less than the stability of meropenem.

As a result of this investigation, further work in these laboratories has been directed away from acyclic C-2 substituents and towards the synthesis of carbapenems bearing sp^2 and sp^3 carbon linked aromatic[15] and non-aromatic[6,7] heterocycles.

In summary, the synthesis of three series of carbapenems substituted at C-2 with either ethenyl, oxyiminomethyl or α-(substituted)benzyl groupings has been achieved. Their antibacterial activities against selected organisms have been assessed and their stabilities to DHP-1 have been measured and compared with imipenem and meropenem. Of the three series, C-2 α-(substituted)benzyl carbapenems displayed the best combination of antibacterial activity and stability to DHP-1.

Experimental

General

Mp's were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ soln 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 soln unless otherwise stated and NMR spectra on a Bruker AC 250 spectrometer (250 MHz)in $CDCl_3$ soln unless otherwise stated. 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) or fast atom bombardment (FAB) mode, as specified. Flash chromatography was performed on Merck silica 60, <230 mesh.

4-Methoxybenzyl (5*R*,6*S*)-2-(1-Phenylethenyl)-6-[(1*R*)-1-trimethylsilyloxyethyl]carbapen-2-em-3-carboxylate (**5a**)

A stirred soln of (**7a**) (0.786 g, 2.0 mmol) in dry THF (8 ml) was treated with a 1.5 M soln of *n*BuLi in hexane (1.33 ml) under argon at −78°C. After 10 minutes, the temperature was raised to 0°C and a soln of 1 M $ZnCl_2$ in Et_2O (2 ml) was added after which the temperature was further raised to 20°C for 0.5 hours. This soln was then added to a stirred mixture of the TMS ether derivative (**4**) (0.806 g, 1.5 mmol), tris(dibenzylideneacetone)dipalladium (45 mg, 49 μmmol) and tris(2,4,6-trimethoxyphenyl)phosphine (105 mg, 0.2 mmol) in THF (5 ml) at −78°C. The mixture was quickly warmed to room temperature and stirred for 1.5 hours. The mixture was diluted with EtOAc (50 ml) and the soln was washed with H_2O (50 ml), dried, and concd to an oil. The oil was purified by flash chromatography on silica gel eluting with a gradient of EtOAc-hexane (3:17→3:7) to give the title compound as a gum (185 mg, 25%) IR cm^{-1} 1780, 1720, 1615; ^1H NMR δ 0.13 (9H, s), 1.27 (3H, d, J=6.2 Hz), 2.96 (1H, dd, J=9.9, 18.8 Hz), 3.08 (1H, dd, J=11.1, 18.1 Hz), 3.18 (1H, dd, J=6.7 Hz), 3.79 (3H, s), 4.1~4.25 (2H, m), 4.84 (1H, d, J=12.2 Hz), 4.98 (1H, d, J=12.2 Hz), 5.24 (1H, s), 5.51 (1H, s), 6.80 (2H, d, J=8.7 Hz), 7.16 (2H, d, J=8.7 Hz), 7.29 (5H, s); MS (EI) m/z 491 (M^+), 121.

The preparation of (**5b**) followed a similar process using (**7b**) and the TMS compound (**4**).

4-Methoxybenzyl (5*R*,6*S*)-2-[1-(3-Acetoxyphenylethenyl)-6-[(1*R*)-1-trimethylsilyloxyethyl]carbapen-2-em-3-carboxylate (**5c**)

A soln of the TBDMS ether derivative (**4**) (0.4 g, 0.7 mmol) in dry THF (2.5 ml) was successively treated with *N*-methylpyrrolidinone (0.7 ml), tris(dibenzylideneacetone) dipalladium (25 mg, 0.028 mmol) and tris(2,4,6-trimethoxyphenyl)phosphine (62 mg, 0.117 mmol). A soln of (**7c**) (0.42 g, 0.95 mmol) in THF (2.5 ml) was then added followed by a soln of 1 M $ZnCl_2$ in Et_2O (0.9 ml) and the whole was heated at 50°C for 17 hours. To the mixture was added with shaking EtOAc (20 ml) and H_2O (20 ml) and then the layers were separated and the organic phase was washed with brine (20 ml), dried, and concd to an oil. The oil was purified by flash chromatography on silica gel eluting with a gradient of EtOAc-hexane (1:4→3:7) to afford the title compound as an oil (140 mg, 34%) (Found MS m/z 591.2678. $C_{33}H_{40}NO_7Si$ requires 571.2652).

Sodium (5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-2-(1-phenylethenyl)carbapen-2-em-3-carboxylate (**6a**)

A soln of (**5a**) (195 mg, 1.46 mmol) in CH_2Cl_2 (2 ml) was added to a stirred mixture of $AlCl_3$ (57 mg, 0.42 mmol) and anisole (4 ml, mmol) in CH_2Cl_2 (2 ml) at −60°C under argon. The mixture was stirred at −40°C for 30 minutes and then quenched by the addition of $NaHCO_3$ (0.55 g, 6.5 mmol) in 0.1 M pH 7 phosphate buffer (10 ml) and stirred at room temperature for 20 minutes. The precipitate was removed by filtration through a celite pad, washed with H_2O (4 ml), and the filtrate was then extracted with EtOAc (2 × 10 ml). The aq phase was concd *in vacuo* to 5 ml and then applied to an HP20SS chromatography column eluting with a gradient of THF-H_2O (1:49→1:24→1:9). The relevant pooled fractions were concd to half the vol and the soln was then freeze-dried to give the title compound as an amorphous solid (51 mg, 43%); UV λ_{max} (H_2O) nm 245 and 292 (shoulder); IR (KBr) cm^{-1} 1751, 1596, 1491; ^1H NMR δ (D_2O) 1.25 (3H, d, J=6.3 Hz), 2.94 (1H, dd, J=9.8, 17.0 Hz), 3.21 (1H, dd, J=8.5, 17.0 Hz), 3.43 (1H, dd, J=2.8, 5.9 Hz), 4.15~4.30 (2H, m), 5.26 (1H, s), 5.40 (1H, s), 7.3 (5H, m); MS (FAB) m/z 322 ($M+H^+$).

Sodium (5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-[1-(4-methylphenylethenyl)carbapen-2-em-3-carboxylate (**6b**)

Compound (**6b**) was prepared in 10% yield from the deprotection of (**5b**) by the method described for (**6a**); IR (KBr) cm^{-1} 1753; UV λ_{max} (H_2O) nm (ε) 300 (3730),

251 (7020); ^{1}H NMR (D_2O) δ 1.23 (3H, d, J=6.9 Hz), 2.29 (3H, s), 2.90 (1H, dd, J=17.1, 9.8 Hz), 3.18 (1H, dd, J=17.1, 8.5 Hz), 3.42 (1H, dd, J=6.0, 2.8 Hz), 4.16~4.29 (12H, m), 5.22 (1H, s), 5.38 (1H, s), 7.16 (2H, d, J=8.1 Hz), 7.26 (2H, d, J=8.1 Hz); MS (FAB) m/z 336 ($M+H^+$).

Sodium (5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-[1-(3-acetoxyphenylethenyl)carbapen-2-em-3-carboxylate (**6c**)

A soln of (**5c**) (130 mg, 0.25 mmol) in THF (3 ml) was treated with glacial AcOH (0.176 ml, 3.1 mmol) followed by a 1 M soln of tetrabutylammonium fluoride in THF (0.92 ml). After stirring for 18 hours, EtOAc (10 ml) and H_2O (10 ml) were added. The organic extract was separated, dried and concd to an oil which was purified by flash chromatography on silica gel eluting with a gradient of EtOAc-hexane (1:1→3:2→7:3→4:1) to afford *p*-methoxybenzyl (5*R*,6*S*)-2-[1-(3-acetoxyphenyl)-ethenyl]-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (28 mg, 26%). IR cm^{-1} 3608, 1779, 1772, 1718, 1613; ^{1}H NMR δ 1.33 (3H, d, J=6.5 Hz), 2.30 (3H, s), 2.98 (1H, dd, J=10.1, 18.1 Hz), 3.09 (1H, dd, J=8.8, 18.1 Hz), 3.24 (1H, dd, J=2.9, 6.6 Hz), 3.79 (3H, s), 4.20~4.32 (2H, m), 4.90 and 5.00 (ABq, J=12.1 Hz), 5.26 (1H, s), 5.53 (1H, s), 6.7~7.5 (8H, m).

This intermediate ester was deprotected as described for (**6a**) to give the title compound (24% yield from ester). UV λ_{max} (H_2O) nm (ε) 292 (4360) 242 (7658); ^{1}H NMR δ (D_2O) 1.26 (3H, d, J=6.3 Hz), 2.30 (3H, s), 2.94 (1H, dd, J=9.7, 17.6 Hz), 3.21 (1H, dd, J=7.6, 17.6 Hz), 3.43 (1H, dd, J=2.7, 4.8 Hz), 4.18~4.32 (2H, m), 5.30 (1H, br s), 5.44 (1H, br s), 7.0~7.45 (4H, m); MS (FAB) m/z 380 ($M+H^+$).

1-Methoxyimino-1-phenylacetone (**9a**)

Anhydr K_2CO_3 (7.8 g, 56.4 mmol) was added to a soln of 1-hydroxyimino-1-phenylacetone[16] (4.2 g, 25.7 mmol) in DMSO (20 ml) at room temperature. After 15 minutes stirring, iodomethane (3.2 ml) was added to the mixture and the whole was stirred for 24 hours. The reaction mixture was diluted with EtOAc (200 ml) and was washed with H_2O (4 × 100 ml). The organic extract was dried and concd to an orange oil which was purified by flash chromatography on silica gel eluting with a gradient of EtOAc-hexane (1:50→2:25) to yield a single isomer of the title compound as a colourless oil (3.9 g, 87%) (Found: C, 67.8; H, 6.3; N, 7.9%. $C_{10}H_{11}NO_2$ requires C, 67.8; N, 6.3; N, 7.9%); IR cm^{-1} 3000, 1688 and 1060; ^{1}H NMR δ 2.52 (3H, s), 4.06 (3H, s) and 7.24~7.43 (5H, m); MS (CI) m/z 195 ($M+NH_4^+$) and 178 ($M+H^+$).

Preparation of (**9b**) (78%) and (**9c**) (82%) followed similar processes using the appropriate substituted oximes.

(3*R*,4*S*)-3-{[(1*R*)-1-*tert*-Butyldimethylsilyloxy]ethyl}-4-(1-methoxyimino-1-phenylaceton-3-yl)azetidin-2-one (**10a**)

To an ice-cooled soln of (**9a**) (3.8 g, 21.4 mmol) in CH_2Cl_2 (56 ml) was added Et_3N (4.4 ml, 31.6 mmol) followed by *t*-butyldimethylsilyltrifluoromethane sulfonate (5.8 ml, 25.3 mmol) during 20 minutes under argon. The soln was allowed to warm to room temperature during 2 hours after which it was washed with H_2O (60 ml), dried, and concd to an orange oil. The oil was purified by flash chromatography on silica gel eluting with a gradient of EtOAc-hexane (1:50→3:50) to afford 2-*tert*-butyldimethylsilyloxy-3-methoxyimino-3-phenylprop-1-ene as a colourless oil (5.9 g, 95%) (Found: C, 65.6; H, 8.4; N, 4.8%. $C_{16}H_{25}NO_2Si$ requires C, 65.9; H, 8.7; N, 4.8%). IR cm^{-1} 2935, 2860, 1608 and 1348; ^{1}H NMR δ 0.21 (6H, s), 0.93 (9H, s), 3.89 (3H, s), 4.41 (1H, d, J=1.1 Hz), 4.70 (1H, d, J=1.1 Hz) and 7.23~7.43 (5H, m); MS (CI) m/z 292 ($M+H^+$), 262, 234 (M^+-Bu).

A 1 M $ZnCl_2$ soln in Et_2O (20 ml) was added during 5 minutes to a stirred soln of (**8**) (5.2 g, 18.1 mmol) in CH_2Cl_2 (75 ml). A soln of the silyl compound described above (5.8 g, 19.9 mmol) in CH_2Cl_2 (50 ml) was then added during 1 hour to this stirred soln under argon at room temperature. After 24 hours, the mixture was washed with H_2O (3 × 150 ml) and the organic extract was dried, and concd *in vacuo* to a yellow oil which was chromatographed on silica gel [EtOAc-hexane (1:9→1:1 gradient elution)] to give the title compound as a white solid (3.9 g, 53%) mp 135~140°C (Found: C, 62.2; H, 8.2; N, 7.0%. $C_{21}H_{32}N_2O_4Si$ requires C, 62.3; H, 8.0; N, 6.9%). IR cm^{-1} 3460, 1755, 1685 and 1038; UV λ_{max} nm (ε) 202 (13,800), 224 (8800) and 261 (5500); ^{1}H NMR δ 0.08 (6H, s), 0.88 (9H, s), 1.24 (3H, d, J=6.2 Hz), 1.24 (3H, d, J=6.2 Hz), 2.90 (1H, dd, J=2.2, 4.9 Hz), 3.11 (1H, dd, J=10.2, 18.0 Hz), 3.53 (1H, dd, J=3.3, 18.0 Hz), 4.05 (1H, m), 4.08 (3H, s), 4.22 (1H, quin., J=6.1 Hz), 6.03 (1H, br s) and 7.26~7.43 (5H, m); MS (CI) m/z 422 ($M+NH_4^+$); 405 ($M+H^+$), 121.

The preparation of (**10b**) (53% yield), using TMS-OTf in place of TBDMS-OTf, followed a similar process starting from (**9b**).

(3*R*,4*S*)-3-{[(1*R*)-1-*tert*-Butyldimethylsilyloxy]ethyl}-4-[1-methoxyimino-1-(3-pyridyl)aceton-3-yl]azetidin-2-one (**10c**)

A soln of (**9c**) (3.9 g, 21.9 mmol) in THF (20 ml) was added over 15 minutes to a stirred soln of LiHMDS (21.7 ml; 1 M in hexane) in THF (20 ml) at −78°C under argon. The reaction mixture was stirred at −78°C for 45 minutes then a soln of (**8**) (9.4 g, 32.7 mmol) in THF (20 ml) was added over 10 minutes. After stirring at −78°C for 45 minutes the mixture was warmed to −5°C and stirred for a further 45 minutes. The cold mixture was then poured into a satd NH_4Cl soln (100 ml) which was extracted with EtOAc (2 × 100 ml). The combined organic extracts were washed with brine (50 ml), dried

and concd *in vacuo* to an oil which was flash chromatographed on silica gel [acetone - toluene (1 : 100→3 : 7 gradient elution)] to give the title compound as a white solid (2.0 g, 23%) mp 120～121°C (Found: C, 59.29; H, 7.70; N, 10.33%. $C_{20}H_{31}N_3O_4Si$ requires C, 59.23; H, 7.70; N, 10.36%); IR cm^{-1} 3420, 1760, 1690; ^1H NMR δ 0.08 (6H, s), 0.89 (9H, s), 1.24 (3H, d, J=6.3 Hz), 2.90 (1H, dd, J=2.3, 4.9 Hz), 3.14 (1H, dd, J=10.1, 18.0 Hz), 3.52 (1H, dd, J=3.4, 18.0 Hz), 4.05 (1H, dt, J=9.8, 2.9 Hz), 4.11 (3H, s), 4.23 (1H, quint J=6.1 Hz), 6.07 (1H, br s), 7.38 (1H, dd, J=4.9, 7.9 Hz), 7.67 (1H, dt, J=1.9, 7.9 Hz), 8.58 (1H, s), and 8.63 (1H, d, J=4.9 Hz); MS (CI) m/z 406 ($M+H^+$).

Compound (**11**) (1.81 g, 20%) was also eluted from the chromatography column and isolated as an oil; IR cm^{-1} 3420, 1780; UV λ_{max} nm (ε) 202 (12900), 239 (9800); ^1H NMR δ 0.06 and 0.08 (total 6H, both s), 0.87 (9H, s), 1.25 (3H, d, J=6.2 Hz), 3.23 (1H, d, J=3.4 Hz), 3.94 (3H, s), 4.17～4.26 (1H, m), 4.59 and 4.63 (each 1H, d, J=3.1 Hz), 5.55 (1H, s), 6.6 (1H, s), 7.37 (1H, dd, J=4.9, 7.8 Hz), 7.70 (1H, dt, J=1.8, 7.8 Hz), 8.6～8.63 (2H, m); MS (CI) m/z 406 ($M+H^+$).

(3*S*,4*R*)-3-{[(1*R*)-1-*tert*-Butyldimethylsilyloxy]ethyl}-1-[allyloxycarbonyl(triphenylphosphoranylidene)-methyl]-4-(1-methoxyimino-1-phenylaceton-3-yl)-azetidin-2-one (**12a**)

Allyl glyoxylate hydrate[4] (0.36 g, 2.7 mmol) in benzene (30 ml) was refluxed for 1 hour in apparatus fitted with a Dean-Stark water separator. The reaction mixture was cooled and diluted with Et_3N (0.069 ml, 0.5 mmol). Compound (**10a**) (1 g, 2.5 mmol) was then added and the whole was stirred at room temperature for 18 hours under argon. The mixture was concd to give a yellow foam. The foam was dissolved in THF (15 ml) and the soln cooled to −10°C under argon and treated with 2,6-lutidine (0.43 ml, 3.7 mmol) followed by $SOCl_2$ (0.27 ml, 3.7 mmol). After stirring at this temperature for 15 minutes the mixture was diluted with dry toluene (13 ml) and the precipitated solid was filtered off and washed with toluene. The filtrate and washings were combined and concd to an oily residue which was re-concd with toluene (2×20 ml). The residue was dried for 1 hour *in vacuo* and then dissolved in dry 1,4-dioxane (8 ml) and the soln was treated with Ph_3P (2.6 g, 9.9 mmol). After stirring this mixture for 15 minutes under argon, it was concd to half the vol and then treated with 2,6-lutidine (0.32 ml, 2.7 mmol). The resulting mixture was stirred for 48 hours and then diluted with EtOAc (150 ml). This soln was washed successively with 5% citric acid (150 ml), brine (150 ml), satd $NaHCO_3$ soln (150 ml), and brine (150 ml), dried, and concd to an oil. The oil was flash chromatographed on silica gel [EtOAc - hexane (2 : 25→3 : 2 gradient elution)] to yield the title compound (73%); IR cm^{-1} 1732, 1688, 1630 and 1612; MS (FAB) m/z 865 ($M+Na^+$), 843 ($M+H^+$), 121.

The preparations of (**12b**) and (**12c**) followed a similar process starting from (**10b**) and (**10c**), respectively.

Sodium (5*R*,6*S*)-2-(*N*-Methoxyiminomethoxycarbonylmethyl)-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (**13b**)

A solution of the crude phosphorane (**12b**), (5.0 g, 6.8 mmol) in toluene (40 ml) was heated under reflux for 1.75 hours. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with EtOAc - hexane (1 : 4) to yield allyl (5*R*,6*S*)-2-(*N*-methoxyiminomethoxycarbonylmethyl)-6-[(1*R*)-1-*tert*-butyldimethylsilyloxymethylcarbapen-2-em-3-carboxylate [1.64 g, 51% based on (**10b**)] (Found MS m/z 466.2139. $C_{22}H_{34}N_2O_7Si$ requires 466.2135); IR cm^{-1} 1783, 1746, 1728; ^1H NMR δ 0.076 (6H, s), 0.88 (9H, s), 1.24 (3H, d, J=6.2 Hz), 3.05～3.30 (3H, m), 3.85 (3H, s), 3.99 (3H, s), 4.08～4.27 (2H, m), 4.63～4.77 (2H, m), 5.22～5.73 (1H, m), 5.37～5.46 (1H, m), 5.85～6.00 (1H, m); MS (EI) m/z 466 (M^+).

A soln of this allyl ester (0.7 g, 1.5 mmol) in THF (20 ml) was treated with glacial AcOH (0.86 ml, 15 mmol) followed by a 1 M soln of tetrabutylammonium fluoride in THF (4.5 ml). After stirring for 20 hours, EtOAc (150 ml) and H_2O (50 ml) were added. The organic extract was separated, dried and concd to an oil which was purified by flash chromatography on silica gel eluting with EtOAc - hexane (1 : 1) to afford a solid (0.308 g) mp 115～118°C.

A soln of this solid (0.2 g) in a 1 : 1 mixture of CH_2Cl_2 - EtOAc (12 ml) was treated with Ph_3P (13 mg, 0.05 mmol) followed by sodium 2-ethylhexanoate (94 mg, 0.57 mmol) then tetrakis(triphenylphosphine)palladium (0) (22 mg, 0.019 mmol) and the mixture was stirred for 45 minutes Et_2O (80 ml) was then added and the mixture was centrifuged. The supernatant was discarded and the solid purified by chromatography on HP20SS resin eluting with a THF - H_2O gradient (1 : 49→3 : 47). The relevant pooled fractions were concd to half the vol and the soln was then freeze-dried to give the title compound as an amorphous solid (73 mg, 38% based on carbapenem ester). IR (KBr) cm^{-1} 1760, 1735, 1617; UV λ_{max} (H_2O) nm (ε) 309 (9882), 220 (5089); ^1H NMR (D_2O) δ 1.25 (3H, d, J=6.4 Hz), 3.09 (2H, d, J=9.5 Hz) 3.51 (1H, dd, J=3.1, 5.7 Hz), 3.76 (3H, s), 3.90 (3H, s), 4.16～4.27 (2H, m); MS (FAB) m/z 335 ($M+H^+$), 357 ($M+Na^+$).

Sodium (5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(*N*-methoxyiminobenzyl)carbapen-2-em-3-carboxylate (**13a**)

The phosphorane (**12a**) (1.35 g, 1.77 mmol) in MeOH (60 ml) was treated with aq 2 M HCl (15 ml) at room temperature for 3 hours. Satd $NaHCO_3$ soln was cautiously added to attain pH 8. The MeOH was removed *in vacuo* and the aq soln was extracted with EtOAc (60 ml). The extract was dried and concd *in vacuo* to give (3*S*,4*R*)-3-[(1*R*)-1-hydroxyethyl]-1-[allyloxycarbonyl-(triphenylphosphoranylidene)methyl]-4-(1-methoxyimino-1-phenylaceton-3-yl)azetidin-2-one as a pale yellow foam (1.16 g, 100%); (Found: MS m/z 648.2400. $C_{38}H_{37}N_2O_6P$ requires 648.2389); IR cm^{-1} 3500 (br),

1742, 1683 and 1615.

The cyclisation of this material and subsequent removal of the allyl group were carried out as described for (**13b**) to afford the title compound as an amorphous solid in 50% yield. IR (KBr) cm^{-1} 1759, 1605, 1491, 1444 and 1396 cm^{-1}; UV λ_{max} (H_2O) nm (ε) 299 (9682); ^1H NMR (D_2O) δ 1.27 (3H, d, J=6.4 Hz), 3.14 (2H, d, J=10.0 Hz), 3.52 (1H, dd, J=2.9, 5.5 Hz), 3.81 (3H, s), 4.18~4.33 (2H, m) and 7.28~7.44 (5H, m); MS (FAB) m/z 353 ($M+H^+$), 375 ($M+Na^+$).

Compound (**13c**) was prepared from (**12c**) following a similar reaction sequence to that described for (**13a**).

Sodium (5*R*,6*S*)-6-[1-(*R*)-1-Hydroxyethyl]-2-[*N*-methoxyimino-(3-pyridyl)methyl]carbapen-2-em-3-carboxylate (**13c**)

Found: MS m/z 354.1063, $C_{16}H_{18}N_3NaO_5$ requires 354.1066 (MH^+); IR (KBr) cm^{-1} 1762, 1607 br, 1401 and 1054; UV λ_{max} (H_2O) nm (ε) 264 (5650), 301 (6520); ^1H NMR (D_2O) δ 1.27 (3H, J=6.4 Hz), 3.18 (2×1H, 2×d, J=3.1, 1.8 Hz), 3.54 (1H, dd, J=3.1, 5.7 Hz), 3.84 (3H, s), 4.21~4.33 (2H, m), 7.42~7.47 (1H, m), 7.76~7.80 (1H, m), 8.42~8.50 (2H, m); MS (FAB) m/z 354 ($M+H^+$), 376 ($M+Na^+$).

(3*S*,4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-(3-*tert*-butyldimethylsilyloxy-3-phenyl-2-oxopropyl)azetidin-2-one (**17a**)

LiHMDS (14.4 ml of a 1 M soln in THF) was added dropwise to a soln of (**15**) (2.86 g, 10.8 mmol) in THF (100 ml) under argon at −78°C. The resulting orange soln was stirred for 20 minutes, and a soln of (**8**) (2.07 g, 7.2 mmol) in THF (20 ml) was added dropwise, and the mixture was stirred for 18 hours at −78°C. Satd NH_4Cl soln (100 ml) was added, and the mixture was extracted with Et_2O (3×100 ml) and the combined organic extracts were dried, concd and flash chromatographed on silica gel eluting with an EtOAc - hexane gradient (1:9→1:4→1:3) to give the title compound as a mixture of diastereomers (1.48 g, 42%); IR (KBr) cm^{-1} 3197, 2930, 1764, 1723, 1471, 1375, 1257, 1139 and 1094 cm^{-1}; ^1H NMR δ −0.05~0.10 (12H, m), 0.80 (s) and 0.86 (s) [9H], 0.95 (9H, s), 1.13 (d, J=6.2 Hz) and 1.20 (d, J=5.9 Hz) [3H], 2.60~2.71 (2H, m), 3.02 (dd, J=3.4, 18.2 Hz) and 3.12 (dd, J=3.0, 18.3 Hz) [1H], 3.72 (dt, J=10.2, 3.4 Hz) and 3.86 (dt, J=9.7, 2.9 Hz) [1H], 4.03~4.15 (1H, m), 5.65 (s) and 5.87 (s) [1H, exch], 7.28~7.44 (5H, m); MS (CI) m/z 492 ($M+H^+$).

Compound (**17b**) was prepared as a mixture of diastereomers in 66% yield as described for (**17a**). The two isomers were separated by flash chromatography on silica gel. Diastereomer A: IR (KBr) cm^{-1} 3318, 2956, 1759, 1720, 1458, 1375, 1255 and 1099; ^1H NMR δ 0.01 and 0.05 (total 6H, both s), 0.83 (9H, s), 1.16 (3H, d, J=6.2 Hz), 2.71 (1H, dd, J=2.2, 5.4 Hz), 2.77 (1H, dd, J=9.9, 18.1 Hz), 3.02 (1H, dd, J=3.4, 18.1 Hz), 3.40 (3H, s), 3.81 (1H, ddd, J=2.5, 3.1, 9.8 Hz); 4.12 (1H, m), 4.68 (1H, s), 6.01 (1H, br s, exch), 7.25~7.48 (5H, m); MS (CI) m/z 392 ($M+H^+$). Diastereomer B: IR (KBr) cm^{-1} 3303, 2956, 1748, 1705, 1458, 1387, 1255 and 1100; ^1H NMR δ 0.03 and 0.07 (total 6H, both s), 0.85 (9H, s), 1.19 (3H, d, J=6.3 Hz), 2.63 (1H, dd, J=3.0, 6.2 Hz), 2.68 (1H, dd, J=10.0, 18.2 Hz), 3.06 (1H, dd, J=3.3, 18.1 Hz), 3.40 (3H, s), 3.86 (1H, ddd, J=2.6, 2.9, 10.0 Hz), 4.13 (1H, m), 4.69 (1H, s), 5.89 (1H, br s, exch), 7.23~7.45 (5H, m); MS (CI) m/z 392 ($M+H^+$).

(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-1-[*p*-methoxybenzyloxycarbonyl(triphenylphosphorylidene)methyl]-4-(3-*tert*-butyldimethylsilyloxy-3-phenyl-2-oxopropyl)azetidin-2-one (**18a**)

The TBDMS ether derivative of the title compound was prepared in 53% yield from the azetidinone (**17a**) and 4-methoxybenzyl glyoxylate by the method described for (**12a**); IR cm^{-1} 1744, 1646, 1616; m/z (FAB) 930 ($M+H^+$). A soln of this material (0.70 g, 0.75 mmol) in MeOH (90 ml) and 2 M hydrochloric acid (10 ml) was stirred for 16 hours and adjusted to pH 6 with satd $NaHCO_3$ soln. The soln was concd to a vol of 20 ml, diluted with H_2O (50 ml) and the mixture was then extracted with EtOAc (3×100 ml). The combined extracts were washed with brine (100 ml), dried, and concd. The residue was purified by flash chromatography on silica gel eluting with MeOH - CH_2Cl_2 (1:99) to give the title compound as a colourless foam (0.35 g, 66%); (Found: MS m/z 701.2558. $C_{42}H_{40}NO_7P$ requires 701.2542).

The TBDMS ether derivative of (**18b**) was similarly prepared in 50% yield from the diastereomeric mixture (**17b**) and allyl glyoxylate hydrate as described for (**12a**); IR cm^{-1} 1745, 1641, 1620 (Found: MS m/z 749.3312. $C_{44}H_{52}NO_6SiP$ requires 749.3302). Compound (**18b**) was then prepared by the desilylation procedure described for (**18a**); MS (CI) m/z 636 ($M+H^+$).

Sodium (5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(1-hydroxybenzyl)carbapen-2-em-3-carboxylate (**19a**)

Compound (**18a**) (0.35 g, 0.5 mmol) in toluene (150 ml) was heated under reflux under argon for 2 hours, cooled, concd *in vacuo* and flash chromatographed on silica gel eluting with a gradient of MeOH - CH_2Cl_2 (1:199→1:99→1:49) to give 4-methoxybenzyl (5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-2-(α-hydroxybenzyl)carbapen-2-em-3-carboxylate as a 1:1 mixture of diastereomers (0.15 g, 71%) (Found: MS m/z 423.1682. $C_{24}H_{25}NO_6$ requires 423.1682); ^1H NMR δ 1.27 (d, J=6.3 Hz) and 1.28 (d, J=6.3 Hz) [1.82 (d, J=4.9 Hz) and 1.86 (d, J=4.9 Hz) [inter alia 1H], 2.61 (dd, J=8.7,18.9 Hz) and 2.93 (dd, J=8.7, 19.0 Hz) [inter alia 1H], 2.72 (dd, J=10.1, 19.0 Hz) and 3.15(dd, J=10.1, 19.0 Hz) [inter alia, 1H], 3.04 (dd, J=2.9, 6.6 Hz) and 3.13 (dd, J=2.9, 6.5 Hz) [inter alia 1H), 3.22 (d, J=4.8 Hz) and 3.39 (d, J=4.9 Hz) [1H, exch], 4.00~4.25 (2H, m), 5.3 (d, J=11.5 Hz) and 5.25 (d, J=12.2 Hz) and 5.30 (d, 12.0 Hz) and 5.33 (d, J=11.5 Hz) [2H], 6.15 (d, J=4.9 Hz) and 6.22 (d, J=4.7 Hz) [1H], 6.90 (2H, d, J=7.8 Hz), 7.25~7.65 (7H,

m); MS (EI) *m/z* 423 (M^+), 121, 77.

The deprotection of this material followed a similar process to that described for the preparation of (**6a**). The title compound was isolated as a 1:1 mixture of diastereomers in 55% yield; UV λ_{max} nm (ε) 272 (6112); IR (KBr) cm^{-1} 3414, 2969, 1753, 1592; ^1H NMR δ (D_2O) 1.22 (3H, d, J=6.4 Hz), 2.62 (dd, J=8.6, 17.9 Hz) and 2.76 (dd, J=9.6, 18.2 Hz) and 2.91 (dd, J=9.8, 18.0 Hz) [2H], 3.22 (dd, J=2.6, 6.1 Hz) and 3.25 (dd, J=2.7, 6.3 Hz) [1H], 4.00~4.20 (2H, m), 5.96 (1H, s), 7.25~7.50 (5H, m); MS (FAB) *m/z* 326 ($M+H^+$), 348 ($M+Na^+$).

Sodium (5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(*p*-methoxybenzyl)-carbapen-2-em-3-carboxylate (**19b**)

Compound (**18b**) was cyclised to allyl (5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-2-(*p*-methoxybenzyl)carbapen-2-em-3-carboxylate in 53% yield by the method described for compound (**19a**) (Found: MS *m/z* 357.1582. $C_{20}H_{23}NO_5$ requires 357.1576); IR cm^{-1} 1780, 1716, 1624; ^1H NMR δ 1.28 (3H, d, J=6.4 Hz), 1.65 (1H, d, J=4.8 Hz, exch), 2.56 (dd, J=8.7, 18.7 Hz) and 2.87 (dd, J=8.9, 19.0 Hz) [1H], 2.81 (dd, J=9.5, 19.0 Hz) and 3.15 (dd, J=10.1, 18.7 Hz) [1H], 3.00 (dd, J=2.9, 6.6 Hz) and 3.19 (dd, J=2.9, 7.1 Hz) [1H], 3.36 (s) and 3.38 (s) [3H], 4.13~4.25 (2H, m), 4.71~4.96 (2H, m), 5.24~5.66 (2H, m), 5.91~6.10 (1H, m), 6.01 (s) and 6.06 (s) [inter alia 1H], 7.24~7.45 (5H, m); MS (EI) *m/z* 357 (M^+), 121, 77.

Deprotection of this material was carried out as follows. Ph_3P (18 mg, 70 mmol), sodium 2-ethylhexanoate (0.12 g, 0.7 mmol) then tetrakis(triphenyl-phosphine)-palladium (27 mg, 23 μmol) were added to a soln of the carbapenem ester (0.25 g, 0.7 mmol) in CH_2Cl_2 - EtOAc (3:2). The reaction was stirred for 2 hours, concd *in vacuo* and then twice chromatographed on HP20SS resin eluting each time with a gradient of THF - H_2O (1:49→1:24→3:47→2:23→1:9) to yield the title compound as a single diastereomer A (52 mg, 22%) and as a mixture of diastereomers (100 mg, 42%). Diastereomer A: IR (KBr) cm^{-1} 3399, 2933, 1762, 1598; ^1H NMR δ (D_2O) 1.19 (3H, d, J=6.4 Hz), 2.54 (1H, dd, J=8.4, 18.0 Hz), 2.93 (1H, dd, J=9.9, 17.9 Hz), 3.16 (1H, dd, J=2.7, 5.9 Hz), 3.35 (3H, s), 4.10~4.22 (2H, m), 5.97 (1H, s), 7.25~7.45 (5H, m); UV nm 273 (ε 6457); MS (FAB) *m/z* 340 ($M+H^+$), 362 ($M+Na^+$).

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 concentration). 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

Human kidney homogenates were prepared by the method previously described[17] and stored at −70°C. The test compound (40 μl of a 500 μM soln in 0.02 M MOPS buffer at pH 7.0) was added to 30% w/v of human kidney homogenate (40 μl) and 0.02 M MOPS buffer control at 37°C. Samples (25 μl) from the test and control tubes were assayed by HPLC immediately and after 1 hour. Peak area values were used for all calculations. A correction factor was calculated from the control AUC (t=0/t=1 hour) and used in the calculation of % test compound remaining after 1 hour.

Acknowledgments

We thank Dr. I. S. BENNETT for microbiological tests, Mr. E. A. CUTMORE, Mr. G. D. RISBRIDGER and Mr. J. W. TYLER for IR, MS and NMR spectra.

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