Synthesis of Novel 6-α and 6-β-Alkylcarbonylmethyl Substituted Penems

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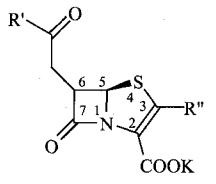
6-α and 6-β Alkylcarbonylmethyl penems were synthesized from 6-α-bromo and 6-oxo penicillanates respectively and their *in vitro* antibacterial activity was studied. The compounds were generally active against Gram-positive but not against Gram-negative strains, the compounds of the 6-β series being more active. Relatively to imipenem, taken as reference compound, the penems resulted more stable towards chemical hydrolysis in Tris-HCl buffered medium (pH 7.4) but more sensitive towards dehydropeptidase-I (DHP-I).

Since the disclosure of the first penem synthesis by WOODWARD[1], many research groups have prepared variously substituted penems, predominantly at the C-3 position, having an α-2-hydroxyethyl substituent in 6-position. Although this side chain is considered the best option for the antibacterial activity of penems, their sensitivity to dehydropeptidases-I (DHP-I) and their low serum elimination half life are serious disadvantages. Other subtituents have received relatively little attention[1~3]. With the aim of finding structurally novel penems combining activity with chemical and biochemical stability, we were interested in the synthesis of compounds with a 6α- or 6β-alkylcarbonylmethyl groups of general formula:



This type of substitution, in the case of 6β-phenoxyacetylmethylpenicillanic acid[4,5], is reported to improve the *in vitro* antibacterial activity and stability, also against penicillinase producing strains of *Bacillus cereus*.

Chemistry

All of the 6-β-alkylcarbonylmethyl penems described were prepared by way of an approach that involved the synthesis of the oxalimido derivatives **7a**~**7l** (Scheme 1).

The precursor 6-oxo penicillanates **3a**, **3b** were obtained by ozonolysis of the diazopenicillanates **2a**, **2b** prepared *in situ* from the 6-β-aminopenicillanates **1a**, **1b**[6]. The Wittig reaction of **3a**, **3b** with the appropriate alkylcarbonylmethyltriphenyl phosphoranes afforded the olefines **4a**~**4g** mainly as the *Z*-isomer, the *E*-isomer being detected by ^{1}H NMR in proportions up to 5%. Reduction of the olefines **4a**~**4g** with tris(triphenylphosphine)rhodium chloride catalyst gave the 6-alkylcarbonylmethyl compounds **5a**~**5g** as a mixture of 6-α and 6-β isomers, the yield of the 6-β isomer ranging between 95 to 70%, the bulkyness of the substituent in 6-position decreasing the selectivity. The separation of the isomers was easily obtained by chromatography. In the case of the 6-β methylcarbonylmethyl compounds, only the 6-β compounds were formed. By analogy with known procedures[7], the opening of the thiazolidine ring of penams **5a**~**5g** with phenylmercuric chloride and DBU, followed by the "*in situ*" acylation of the intermediate mercaptides, yielded the thioesters **6a**~**6l**. Finally, ozonolysis of the thioesters **6a**~**6l** afforded the oxalimido derivatives **7a**~**7l**.

To obtain the penems pivaloyloxymethyl esters **8a**, **8b** (Scheme 2) the oxalimides **7a**, **7b** were processed with triethylphosphite[8] in refluxing xylene. In the case of the penem **8a** the 3-chloromethyl derivative was converted into the (1-*N*-methyl-tetrazol-2-yl)thiomethyl derivatives **9** by reaction with 1-*N*-methyl-5-mercapto-tetrazole sodium salt, under phase transfer conditions[14].

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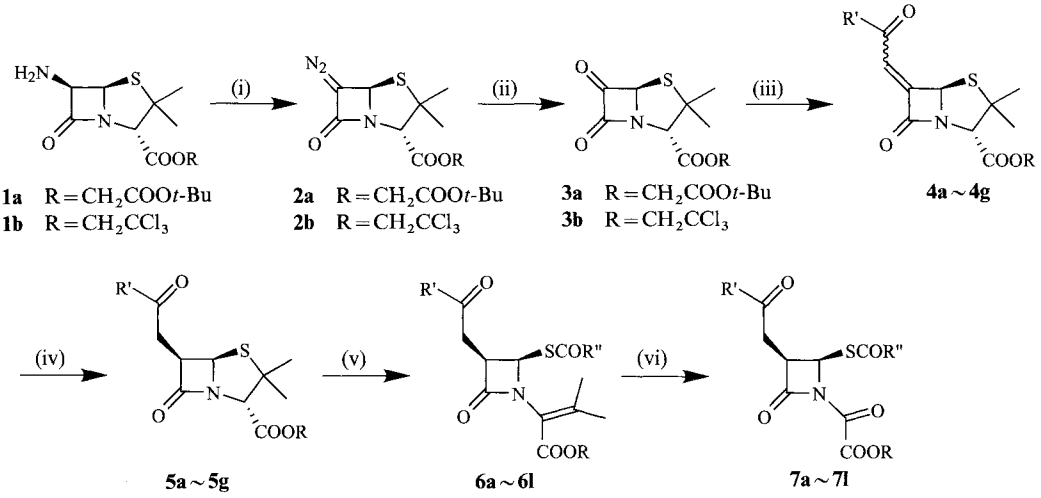
Scheme 1.



1a R=CH_2COOt-Bu
1b R=CH_2CCl_3

2a R=CH_2COOt-Bu
2b R=CH_2CCl_3

3a R=CH_2COOt-Bu
3b R=CH_2CCl_3

4a~4g

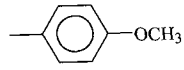
5a~5g

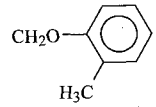
6a~6l

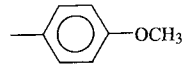
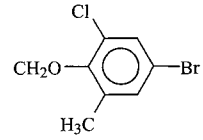
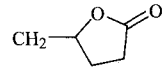
7a~7l

(i) $NaNO_2$, CH_2Cl_2
(ii) O_3, CH_2Cl_2, $-10°C$
(iii) $Ph_3P{=}CHCOR'$, CH_2Cl_2, 0°C
(iv) $(Ph_3P)_3RhCl$, MeOH, [H]
(v) a) PhHgCl, DBU b) R″COCl
(vi) O_3, CH_2Cl_2, $-60°C$

Compound	R	R′
4a, 5a	CH_2COOt-Bu	CH_3
4b, 5b	CH_2CCl_3	CH_3
4c, 5c	CH_2CCl_3	t-Bu
4d, 5d	CH_2CCl_3	CH_2Ph

Compound	R	R′
4e, 5e	CH_2CCl_3	
4f, 5f	CH_2COOt-Bu	n-C_5H_{11}
4g, 5g	CH_2COOt-Bu	$(CH_2)_2Ph$

Compound	R	R′	R″
6a, 7a	CH_2COOt-Bu	CH_3	CH_2Cl
6b, 7b	CH_2COOt-Bu	CH_3	CH_2Ph
6c, 7c	CH_2CCl_3	CH_3	Ph
6d, 7d	CH_2CCl_3	CH_3	CH_2OPh
6e, 7e	CH_2CCl_3	CH_3	
6f, 7f	CH_2CCl_3	t-Bu	CH_2OPh
6g, 7g	CH_2CCl_3	CH_2Ph	CH_2OPh

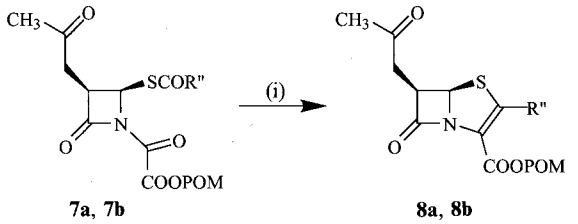
Compound	R	R′	R″
6h, 7h	CH_2CCl_3		CH_2OPh
6i, 7i	CH_2COOt-Bu	CH_3	
6j, 7j	CH_2COOt-Bu	n-C_5H_{11}	CH_2OPh
6k, 7k	CH_2COOt-Bu	$(CH_2)_2Ph$	CH_2OPh
6l, 7l	CH_2COOt-Bu	CH_3	

To obtain the penems potassium salts *via* cleavage of the trichloroethyl esters, the oxalimides **7c~7h** were cyclised to penems **10a~10f** as previously described[8] (Scheme 3). The cleavage of the trichloroethyl ester with activated zinc[9] under sonication, in the presence of phosphate buffer, followed by treatment with potassium hydrogencarbonate yielded the penem potassium salts **11a~11f**.

The synthesis of penem allyl esters (Scheme 4) required a different synthetic approach, due to the incompatibility of the allylic system with the ozonolysis of the secopenams. This approach[10] involved the synthesis of azetidinones **12a~12d** by methanolysis of the oxalimido intermediates **7i~7l**. Acylation of the azetidinones with allyloxalylchloride and treatment of the oxalimido intermediates **13a~13d** with triethylphosphite yielded the penem allyl esters **14a~14d**. Deprotection of the allyl esters was achieved with triphenylphosphine and tetrakis(triphenylphosphine)palladium(0)[11] in the presence of potassium-2-ethylhexanoate to obtain the penem potassium salts **15a~15d**.

The synthesis of the 6-α-methylcarbonylmethylpenems is outlined in Scheme 5. According to known procedures[12,13], stereoselective 6-α-allylation of pivaloy-

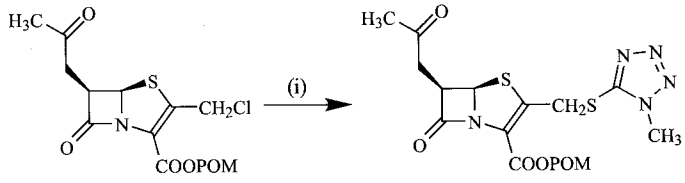
Scheme 2.



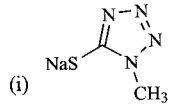
7a, 7b 8a, 8b

(i) $P(OEt)_3$, *m*-xylene, reflux

Compound	R″
7a, **8a**	CH_2Cl
7b, **8b**	CH_2Ph



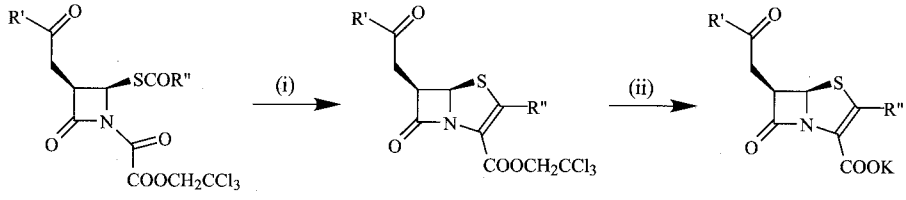
8a **9**



(i) $[CH_3(CH_2)_3]_4NBr$, CH_2Cl_2, H_2O

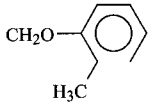
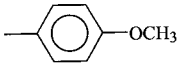
POM CH_2COOt-Bu

Scheme 3.



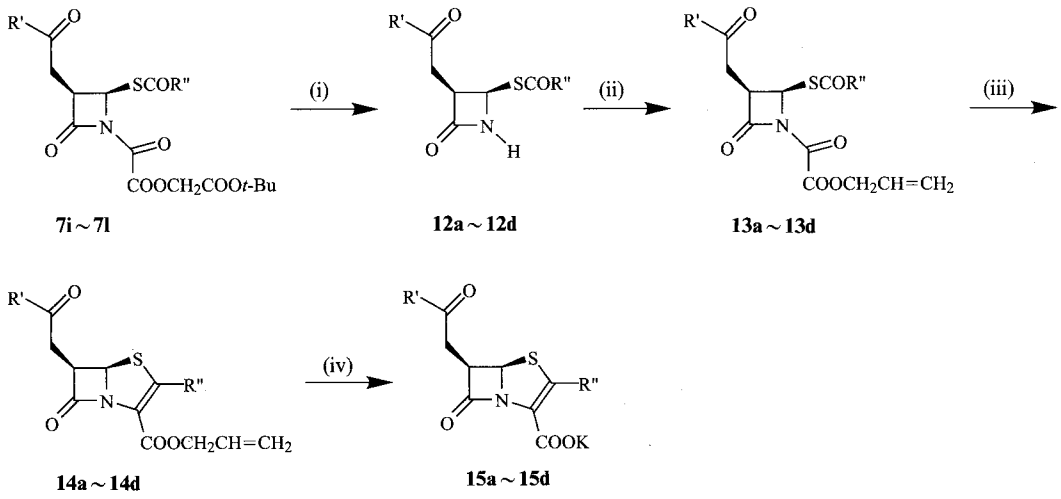
7c～7h **10a～10f** **11a～11f**

(i) $P(OEt)_3$, *m*-xylene, reflux
(ii) Zn(Cu), THF, 0°C

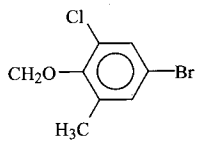
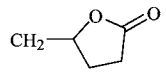
Compound	R′	R″
10a, **11a**	CH_3	Ph
10b, **11b**	CH_3	CH_2OPh
10c, **11c**	CH_3	
10d, **11d**	*t*-Bu	CH_2OPh
10e, **11e**	CH_2Ph	CH_2OPh
10f, **11f**		CH_2OPh

loxymethyl 6-α-bromopenicillanate **16** with 2-methyl-2-propenyl-tri-*n*-butyltin, in the presence of a catalytic amount of α,α′-Azoisobutyronitrile (AIBN), yielded the 6-α-(2-methyl-2-propenyl)penams **17**. The thiazolidine ring opening with phenylmercuric chloride and DBU followed by acylation of the mercaptides yielded the thioesters **18a**, **18b** which were submitted to ozonolysis to obtain the 3-α-acetylmethyl-oxalimides **19a**, **19b**. The Wittig cyclization yielded the corresponding penems **20a**, **20b**. Finally, the chloromethylpenem **20a** was converted

Scheme 4.



(i) MeOH, H_2O
(ii) CH_2=$CHCH_2OOCCOCl$, TEA, K_2CO_3, CH_2Cl_2, 0°C
(iii) $P(OEt)_3$, *m*-xylene, reflux
(iv) $Pd(PPh_3)_4$, potassium 2-ethylhexanoate, THF

Compound	R′	R″
12a~15a	CH_3	
12b~15b	*n*-C_5H_{11}	CH_2OPh
12c~15c	$(CH_2)_2Ph$	CH_2OPh
12d~15d	CH_3	

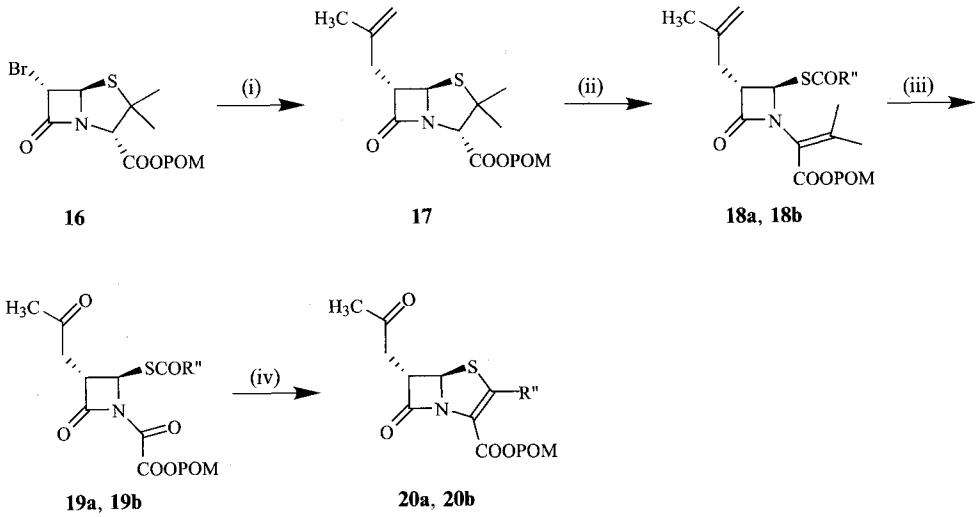
into the (1-*N*-methyl-tetrazol-2-yl)thiomethyl derivative **21** by reaction with 1-*N*-methyl-5-mercapto-tetrazole sodium salt, under phase transfer conditions[14].

Antibacterial Activity

The minimum inhibitory concentration (MIC) values of the 6-alkylcarbonylmethyl penems for selected strains of Gram-positive and Gram-negative bacteria were determined according to the broth dilution method recommended by N.C.C.L.S.[15,16]. The MIC was defined as the lowest drug concentration which inhibited visible growth of microorganisms. The human renal dehydropeptidases-I (DHP-I) was isolated using a known methodology[17,18] and the stability of the penems was determined following the method reported by CAMPBELL[19]. The chemical stability (t/2) was determined in a 25 mmol Tris-HCl buffer at pH 7.4. The *in vitro* antibacterial activities for the acids, determined after enzymatic hydrolysis with pig liver esterase of the corresponding 6-α and 6-β-methylcarbonylmethyl penems pivaloyloxymethyl esters **8b**, **9**, **20b** and **21**, are reported in Table 1.

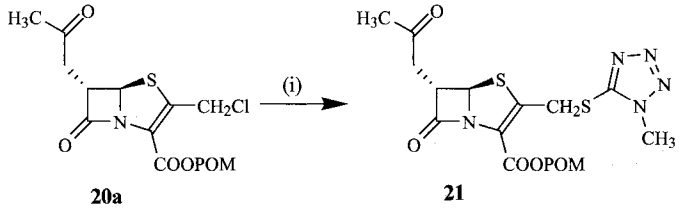
In contrast to what known in the case of the 6-α-hydroxyethylpenems, the antibacterial activity of the 6-β compounds was better than the activity of the 6-α compounds. On the basis of these results, some 6-β-alkylcarbonylmethyl penem potassium salts were prepared and tested (Table 2). We found a moderate activity against Gram-positive aerobes and anaerobes (*e.g. Clostridium perfringens 615/E*) particularly for products bearing a 3-phenoxymethyl chain. None of the tested substances showed any significant activity against the Gram-negative strains. All the compounds were less stable to human renal DHP-I than imipenem taken as reference compound, whereas the chemical stability was generally increased.

Scheme 5.

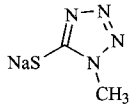


(i) $CH_3CH(=CH_2)CH_2SnBu_3$, AIBN, toluene, reflux
(ii) a) PhHgCl, DBU b) R″COCl
(iii) O_3, CH_2Cl_2, −78°C
(iv) $P(OEt)_3$, *m*-xylene, reflux

Compound	R″
18a ~ 20a	CH_2Cl
18b ~ 20b	CH_2Ph



20a **21**

(i)  $[CH_3(CH_2)_3]_4NBr$, CH_2Cl_2, H_2O

POM CH_2COOt-Bu

Conclusion

A series of 6-β-alkylcarbonylmethyl penems was synthesized through a new and versatile method involving the 6-oxo penicillanate intermediates **3** and tested against Gram-positive and Gram-negative strains, in comparison with some of the 6-α isomers. Tested compounds showed a moderate activity against aerobic and anaerobic Gram-positive strains, whereas the activity against Gram-negative strains was negligible. Finally, with respect to imipenem, the compounds were less stable to DHP-I, but exhibited an increased chemical stability.

Experimental

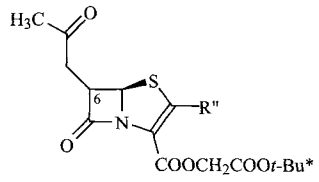
IR spectra were obtained using a Perkin-Elmer 377 or a Perkin-Elmer 681 spectrometer. The 80 MHz ^1H NMR spectra were recorded on a Brucker WP 80. Chemical shifts are listed in ppm. (δ scale) using tetramethylsilane (TMS) as internal standard. Column chromatography was performed on Merck silica gel (230 ~ 400 mesh).

General Procedures for the Preparation of 6-β-Alkylcarbonylmethyl Penicillanate **5a ~ 5g**

Pivaloyloxymethyl (2*S*,5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-(2-oxo-propyl)-4-thia-1-azabicyclo[3.2.0]eptane-2-carboxylate (**5a**)

A solution of the compound **4a**[8] (3.28 g) in

Table 1. *In vitro* antibacterial activity (MIC), human renal dehydropeptidases (DHP-I) stability and chemical stability (Chem.).

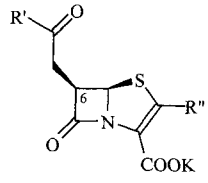


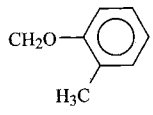
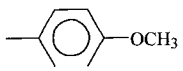
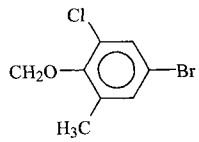
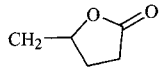
Compound		R″	MIC (mg/ml)				DHP-I t/2 (minute)	Chem. t/2 (minute)
			S.a. 663/E	*S.a.* 853/E	*E.c.* 851/E	*C.p.*		
8b	6β	CH_2Ph	0.8	3.1	n.e.	n.e.	n.e.	n.e.
20b	6α	CH_2Ph	6.2	25	>50	n.e.	115.5	693
9	6β	CH_2Tet	<0.06	<0.06	0.4	2	9.9	n.e.
21	6α	CH_2Tet	6.2	6.2	>50	n.e.	n.e.	n.e.

* The tested compounds were preincubated with pig liver esterases.

Abbreviation: *S.a.*; *Staphylococcus aureus*, *S.a.* 853/E; *Staphylococcus aureus* penicillin-resistant, *E.c.*; *Escherichia coli*, *C.p.*; *Clostridium perfringens*. Tet = (1-*N*-methyl-tetrazol-2-yl)thio, n.e. = not evaluated.

Table 2. *In vitro* antibacterial activity (MIC), human renal dehydropeptidases (DHP-I) stability and chemical stability (Chem.).



Compound	R′	R″	MIC (mg/ml)				DHP-I t/2 (minute)	Chem. t/2 (minute)
			S.a. 663/E	*S.a.* 853/E	*E.c.* 851/E	*C.p.*		
11a	CH_3	Ph	1	4	>32	4	6	347
11b	CH_3	CH_2OPh	<0.25	1	>32	<0.25	3	231
11c	CH_3		0.5	1	32	4	3	623
11d	*t*-Bu	CH_2OPh	0.1	3	>32	0.2	19	347
11e	CH_2Ph	CH_2OPh	0.25	4	32	2	3	345
11f		CH_2OPh	<0.25	16	>32	n.e.	3	344
15a	CH_3		0.25	0.25	32	n.e.	2	>60
15b	n-C_5H_{11}	CH_2OPh	0.25	4	32	n.e.	3	346
15c	CH_2CH_2Ph	CH_2OPh	<0.25	8	>32	n.e.	3	99
15d	CH_3		2	8	16	2	9	730
Imipenem			<0.06	<0.06	0.5	0.1	87	195

Abbreviation: *S.a.*; *Staphylococcus aureus*, *S.a.* 853/E; *Staphylococcus aureus* penicillin-resistant, *E.c.*; *Escherichia coli*, *C.p.*; *Clostridium perfringens*, n.e. = not evaluated.

MeOH - EtOAc (1 : 1) (200 ml) was hydrogenated at 2 atm for 2 hours in the presence of tris(triphenylphosphine)rhodium chloride (1.7 g) as catalyst. The reaction mixture was filtered, the solvent was concentrated *in vacuo* and the crude material was purified by column flash chromatography (cyclohexane - EtOAc, 9 : 1) to give the title compound **5a** (2.8 g).

IR (CH_2Cl_2) cm^{-1} 1770 (β-lactam, ester, C=O), 1720 (C=O); ^1H NMR ($CDCl_3$, ppm) 5.82 (2H, dd), 5.58 (1H, d), 4.41 (1H, s), 4.00 (1H, m), 3.00 (2H, m), 2.19 (3H, s), 1.62 (3H, s), 1.49 (3H, s), 1.22 (3H, s).

2,2,2-Trichloroethyl (2*S*,5*R*,6*R*)-3,3-Dimethyl-6-(3,3-dimethyl-2-oxo-butyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-eptane-2-carboxylate (**5c**)

A solution of the compound **4c**[8] (7.5 g) in MeOH - EtOAc (1 : 1) (350 ml) was hydrogenated at 3 atm for 48 hours in the presence of tris(triphenylphosphine)-rhodium chloride (3.5 g) as catalyst. The reaction mixture was filtered, the solvent was concentrated *in vacuo* and the crude material was purified by column flash chromatography (cyclohexane - EtOAc, 9 : 1) to give the title compound **5c** (5 g).

IR (CH_2Cl_2) cm^{-1} 1770 (β-lactam, ester, C=O), 1705 (C=O); ^1H NMR ($CDCl_3$, ppm) 5.63 (1H, d), 4.78 (2H, dd), 4.51 (1H, s), 3.99 (1H, m), 3.10 (2H, m), 1.68 (3H, s), 1.56 (3H, s), 1.18 (9H, s).

General Procedure for the Preparation of Secopenams **6a ~ 6l**

(3*R*,4*R*)-3-(3,3-Dimethyl-2-oxo-butyl)-4-(phenyloxy-acetyl)thio-1-[1-(2,2,2-trichloroethyloxycarbonyl)-2-methyl-1-propenyl]-azetidin-2-one (**6f**)

To a stirred solution of phenylmercuric chloride (0.24 g) and DBU (0.12 ml) in acetonitrile (15 ml) at 0°C was added dropwise a solution of the compound **5c** (0.3 g) in acetonitrile (20 ml). The reaction mixture was stirred for 3 hours at room temperature, then a solution of phenoxyacetyl chloride (0.13 g) in acetonitrile (10 ml) was added. After 2 hours the solution was concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with brine and the separated organic layer was dried over Na_2SO_4. After evaporation of the solvent *in vacuo* the crude material was purified by flash column chromatography (cyclohexane - EtOAc, 7 : 3) to give the title compound **6f** (0.27 g).

IR (CH_2Cl_2) cm^{-1} 1770 (C=O), 1740 ~ 1700 (C=O), 1630 (C=C), 1600 (aromatic, C=C); ^1H NMR ($CDCl_3$, ppm) 7.6 ~ 6.75 (5H, m), 6.09 (1H, d), 5.6 (1H, d), 4.90 (2H, dd), 4.64 (2H, s), 4.10 (1H, m), 3.2 (2H, m), 2.28 (3H, s), 1.98 (3H, s), 1.16 (9H, s).

General Procedure for the Preparation of Oxalimides **7a ~ 7l**

(3*R*,4*R*)-3-(3,3-Dimethyl-2-oxo-butyl)-4-(phenyloxy-acetyl)thio-1-[1-(2,2,2-trichloroethyloxycarbonyl)-1-oxo]-azetidin-2-one (**7f**)

A stirred solution of the azetidinone **6f** (2.8 g) in dichloromethane (150 ml) at −78°C was treated with ozone for 15 minutes (flux 4.4 g/hour). The solution was dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to give the crude title compound **7f** (2.6 g).

General Procedure for the Preparation of Penems **8a**, **8b** and **10a ~ 10f**

2,2,2-Trichloroethyl (5*R*,6*R*)-6-(3,3-Dimethyl-2-oxo-butyl)-3-(phenyloxymethyl)-7-oxo-4-thia-1-azabicyclo-[3.2.0]ept-2-ene-2-carboxylate (**10d**)

To a stirred solution of the oxalimide **7f** (2.6 g) in xylene (130 ml) was added triethylphosphite (2.74 ml) and the reaction mixture was heated at 100°C for one hour and at 120°C for 2.5 hours. The solvent was concentrated *in vacuo* and the residue was purified by flash column chromatography (cyclohexane - EtOAc, 9 : 1) to give the title compound **10d** (0.95 g).

IR ($CDCl_3$) cm^{-1} 1795 (β-lactam, C=O), 1720 ~ 1700 (C=O), 1600 ~ 1590 (aromatic, C=C), 1580 (penem, C=C); ^1H NMR ($CDCl_3$, ppm) 7.0 (5H, m), 5.93 (1H, d), 5.30 (2H, dd), 4.88 (2H, s), 4.20 (1H, m), 3.2 (2H, m), 1.16 (9H, s).

General Procedure for the Preparation of Penems Potassium Salts **11a ~ 11f**

Potassium (5*R*,6*R*)-6-(3,3-Dimethyl-2-oxo-butyl)-3-(phenyloxymethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]ept-2-ene-2-carboxylate (**11d**)

To a stirred solution of the penem **10d** (0.5 g) in THF - potassium phosphate buffer (5 : 1) (pH 4.2) (12 ml) was added Zn/Cu (0.45 g) and the reaction mixture was sonicated for 20 minutes at room temperature. The mixture was filtered and the solution was concentrated *in vacuo*. The residue was partitioned between EtOAc and a 1.0 M solution of citric acid (20 ml) at pH 4. The separated organic phase was treated with a 1.0 M solution of potassium hydrogencarbonate (10 ml). The aqueous phase was purified by column chromatography (Lichoprep Rp-8; elution with H_2O then MeOH - H_2O, 9 : 1) to give, after lyophilization, the title penem **11d** (0.16 g).

IR (Nujol) cm^{-1} 1763 (β-lactam, C=O), 1699 (C=O), 1599 (aromatic, C=C), 1588 (penem, C=C); ^1H NMR (D_2O, ppm) 7.3 ~ 7.1 (2H, m), 7.05 ~ 6.7 (3H, m), 5.78 (1H, d), 5.46 (2H, dd), 4.02 (1H, m), 3.15 (2H, m), 1.07 (9H, s).

Pivaloyloxymethyl (5*R*,6*R*)-3-(1-*N*-Methyl-tetrazol-2-yl)thiomethyl-7-oxo-6-(2-oxo-propyl)-4-thia-1-azabi-cyclo[3.2.0]ept-2-ene-2-carboxylate (**9**)

To a stirred solution of the oxalimide **7a** (0.4 g) in xylene (10 ml) was added triethylphosphite (0.32 ml) and the reaction mixture was heated at 80°C for 3 hours. The solvent was concentrated *in vacuo* and the residue dissolved in CH_2Cl_2 - H_2O (5 : 1) (12 ml). 1-*N*-methyl-5-mercapto-tetrazole sodium salt (0.16 g) and tetra-butylammonium bromide (0.043 g) were added and the

reaction mixture was vigorously stirred for 2 hours, then the organic layer was washed with water and dried over Na_2SO_4. After evaporation of the solvent *in vacuo*, the crude material was purified by flash column chromatography (cyclohexane - EtOAc, 7 : 3) to give the title compound **9** (0.05 g).

IR ($CDCl_3$) cm^{-1} 1793 (β-lactam, C=O), 1751 (C=O), 1576 (penem, C=C); ^1H NMR ($CDCl_3$, ppm) 5.80 (2H, m), 5.25 (1H, d), 4.60 (2H, dd), 4.1 (1H, m), 3.87 (3H, s), 2.90 (2H, m), 2.1 (3H, s), 1.25 (9H, s).

General Procedure for the Preparation of the Azetidinones **12a ~ 12d**

(3*R*,4*R*)-3-(2-Oxo-propyl)-4-[(4-bromo-2-chloro-6-methyl)phenyloxyacetyl]thio-azetidin-2-one (**12a**)

A solution of the oxalimide **7i** (2.14 g) in EtOAc - MeOH - H_2O (1 : 8 : 1) (250 ml) was stirred overnight at room temperature. The solvent was concentrated *in vacuo* and the residue was dissolved in EtOAc and washed with brine. The separated organic layer was dried over Na_2SO_4 and, after evaporation of the solvent *in vacuo*, the crude material was purified by flash column chromatography (cyclohexane - EtOAc, 7 : 3) to give the title compound **12a** (0.8 g).

IR ($CDCl_3$) cm^{-1} 3416 (NH), 1780 (β-lactam, C=O), 1718, 1751 (C=O); ^1H NMR ($CDCl_3$, ppm) 7.38 (1H, d), 7.25 (1H, d), 6.26 (1H, s), 5.58 (1H, d), 4.56 (2H, s), 4.1 (1H, m), 2.95 (2H, m), 2.30 (3H, s), 2.22 (3H, s).

General Procedure for the Preparation of the Oxalimides **13a ~ 13d**

(3*R*,4*R*)-3-(2-Oxo-propyl)-4-[(4-bromo-2-chloro-6-methyl)phenyloxyacetyl]thio-1-[1-(allyloxycarbonyl)-1-oxo]-azetidin-2-one (**13a**)

To a stirred solution of the azetidinone **12a** (0.6 g) in CH_2Cl_2 (25 ml) at 0°C were added potassium carbonate (0.42 g), allyloxalylchloride (0.38 g) and triethylamine (0.4 ml). After 30 minutes the solution was washed with brine and the solvent was concentrated *in vacuo* to give the crude oxalimide **13a** (0.8 g).

General Procedure for the Preparation of Penems **14a ~ 14d**

Allyl (5*R*,6*R*)-6-(2-Oxo-propyl)-3-([4-bromo-2-chloro-6-methyl)phenyloxymethyl]-7-oxo-4-thia-1-azabicyclo-[3.2.0]ept-2-ene-2-carboxylate (**14a**)

To a stirred solution of the oxalimide **13a** (0.8 g) in xylene (25 ml) was added triethylphosphite (1.1 ml) and the reaction mixture was heated at 140°C for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified by flash column chromatography (cyclohexane - EtOAc, 9 : 1) to give the title compound **14a** (0.13 g).

IR ($CDCl_3$) cm^{-1} 1794 (β-lactam, C=O), 1717, 1650 (C=O), 1580 (allyl, aromatic, C=C), 1576 (penem, C=C); ^1H NMR ($CDCl_3$, ppm) 7.36 (1H, d), 7.28 (1H, d), 5.95 (1H, d), 5.80 (1H, m), 5.30 (2H, m), 5.10 (2H, dd), 4.70 (2H, m), 4.15 (1H, m), 3.20 (2H, m), 2.30 (3H, s), 2.24 (3H, s).

General Procedure for the Preparation of 6-β-Alkylcarbonylmethylene Penems Potassium Salt **15a ~ 15d**

Potassium (5*R*,6*R*)-3-(4-Bromo-2-chloro-6-methyl)-phenyloxymethyl)-6-(3,3-dimethyl-2-oxo-butyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]ept-2-ene-2-carboxylate (**15a**)

To a stirred solution of the penem **14a** (0.1 g) in THF - EtOAc (1 : 1) (10 ml) were added triphenylphosphine (0.0063 g), tetrakis(triphenylphosphine)palladium(0) (0.0083 g) and a 0.5 M solution of potassium 2-ethylhexanoate in EtOAc (0.5 ml). After one hour the solvent was concentrated *in vacuo*. The residue was dissolved in water and purified by column chromatography (Lichoprep Rp-18; elution with H_2O then MeCN - H_2O, 9 : 1) to obtain, after lyophilization, the title penem **15a** (0.029 g).

IR (Nujol) cm^{-1} 1755 (β-lactam, C=O), 1701, 1630 (C=O), 1589 (penem, aromatic, C=C); ^1H NMR (D_2O, ppm) 7.32 (1H, m), 7.27 (1H, m), 5.80 (1H, d), 5.09 (2H, dd), 3.10 (2H, m), 2.23 (3H, s), 2.16 (3H, s).

Pivaloyloxymethyl (2*S*,5*R*,6*S*)-3,3-Dimethyl-6-(2-methyl-allyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]eptane-2-carboxylate (**17**)

To a stirred solution of the 6-bromopenicillanate **16** (1 g) and 2-methyl-2-propenyl-tri-butyl tin (1.3 g) in toluene (40 ml) was added portionwise azoisobutyronitrile (0.1 g). The reaction mixture was heated at 100°C for 4 hours, then the solvent was concentrated *in vacuo* and the residue was dissolved in acetonitrile, washed with petroleum ether and purified by flash column chromatography (cyclohexane - EtOAc, 8 : 2) to give the title compound **17** (0.8 g).

General Procedure for the Preparation of Azetidinones **18a, 18b**

(4*R*,3*S*)-4-(Chloroacetyl)thio-3-(2-methyl-allyl)-1-[1-(pivaloyloxymethoxycarbonyl)-2-methyl-1-propenyl]-azetidin-2-one (**18a**)

To a stirred solution of phenylmercuric chloride (1 g) and DBU (0.66 ml) in acetonitrile (30 ml) at 0°C was added dropwise a solution of **17** (0.8 g) in acetonitrile (20 ml). The reaction mixture was stirred for 1 hour at room temperature, then a solution of chloroacetyl chloride (0.26 ml) in acetonitrile (20 ml) was added. After 2 hours the solvent was concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with a 5% solution of potassium hydrogencarbonate and the separated organic layer was dried over Na_2SO_4; after evaporation of the solvent *in vacuo*, the crude material was purified by flash column chromatography (cyclohexane - EtOAc, 8 : 2) to give the title compound **18a** (0.5 g).

IR ($CDCl_3$) cm^{-1} 1762 (β-lactam, ester, C=O), 1687 (C=O), 1635 (C=C); ^1H NMR ($CDCl_3$, ppm) 5.88 (2H, dd), 5.41 (1H, d), 4.84 (1H, s), 4.14 (2H, s), 3.35 (1H,

m), 2.60 (2H, m), 2.24 (3H, s), 1.98 (3H, s), 1.79 (3H, s), 1.22 (9H, s).

General Procedure for the Preparation of Oxalimides **19a, 19b**

(4*R*,3*S*)-3-(2-Oxo-propyl)-4-(chloroacetyl)thio-1-[1-(pivaloyloxymethoxycarbonyl)-1-oxo]-azetidin-2-one (**19a**)

A stirred solution of the compound **18a** (0.45 g) in dichloromethane (30 ml) at −78°C was treated with ozone for 30 minutes (flux 2 g/hour). The solution was dried over Na_2SO_4 and evaporated to give the title compound **19a**.

Pivaloyloxymethyl (5*R*,6*S*)-6-(2-Oxo-propyl)-3-(1-*N*-methyl-tetrazol-2-yl)thiomethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]ept-2-ene-2-carboxylate (**21**)

To a stirred solution of the crude mixture of the oxalimides **19a** (0.5 g) in xylene (30 ml) was added triethylphosphite (0.5 ml) and the reaction mixture was heated at 140°C for 3 hours. The solvent was concentrated *in vacuo* and the residue **20a** was dissolved in CH_2Cl_2 - H_2O (1 : 1) (50 ml). 1-*N*-methyl-5-mercapto-tetrazole sodium salt (0.12 g) and tetrabutylammonium bromide (0.06 g) were added and the reaction mixture was vigorously stirred for 2 hours. Then, the organic layer was washed with water and the separated organic layer was dried over Na_2SO_4. After evaporation of the solvent *in vacuo*, the crude material was purified by flash column chromatography (cyclohexane - EtOAc, 7 : 3) to give the title compound **21** (0.025 g).

IR ($CDCl_3$) cm^{-1} 1793 (β-lactam, C=O), 1751 (C=O), 1576 (penem, C=C); ^1H NMR ($CDCl_3$, ppm) 5.80 (2H, m), 5.25 (1H, d), 4.60 (2H, dd), 4.1 (1H, m), 3.87 (3H, s), 2.90 (2H, m), 2.10 (9H, s), 1.25 (9H, s).

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