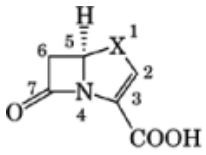
Kirk-Othmer Encyclopedia of Chemical Technology.

CARBAPENEMS AND PENEMS

1. Carbapenems and Penems

In the period up to 1970 most β-lactam research was concerned with the penicillin and cephalosporin group of antibiotics (1). Since that time, however, a wide variety of new mono- and bicyclic β-lactam structures have been described. The carbapenems, characterized by the presence of the bicyclic ring systems (**1**, X = CH_2) originated from natural sources; the penem ring (**1**, X = S) and its derivatives are the products of the chemical synthetic approach to new antibiotics. The chemical names are: 7-oxo-(*R*)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid [78854-41-8], $C_7H_7NO_3$, and 7-oxo-(*R*)-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid [69126-94-9], $C_6H_5NO_3S$, respectively.



(**1**)

2. Carbapenems

During the screening of soil samples for inhibitors of peptidoglycan biosynthesis, thienamycin (**2**), shown in Table 1, and other related derivatives were isolated from the microorganism *Streptomyces cattleya* (2). At the same time, while screening for natural inhibitors of β-lactamases, a group of interrelated metabolites known as the olivanic acids, obtained from *Streptomyces olivaceus*, was found (3). The first three compounds isolated were the sulfated derivatives having structures (**3**) and (**4**); subsequently, several nonsulfated analogues were also isolated (4). Thienamycin has the (*R*)-configuration at the C-8 hydroxy group with a trans-arrangement of protons on the β-lactam ring. In the olivanic acids the stereo-chemistry is 8(*S*)-with a cis-substituted β-lactam in the sulfated series, and both *cis*- and *trans*-β-lactams in the case of the C-8 hydroxy compounds. These compounds represented a completely new family of β-lactam structures based on the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid ring system, and which are now generally referred to as the 1-carbadethiapen-2-em or simply 1-carbapenem family of antibiotics.

Subsequently, other structural variations were reported encompassing compounds such as PS-5 (**5**) (5), carpetimycin A (**6**) (6), asparenomycin A (**7**) (7), and pluracidomycin A (**8**) (8), from a wide variety of streptomycete strains. Following these structures the simplest member of the series, having the completely unsubstituted nucleus, (**1**, X = CH_2), was isolated from bacterial strains of *Serratia* and *Erwinia* (9). All other natural

products reported have substituents at both the C-6 and C-2 positions of the bicyclic ring system. Differences in the nature and stereochemistry of these substituents has provided a wide variety of structures, and over forty variations have been reported and comprehensively listed (10).

Table 1. Carbapenems

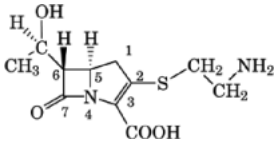
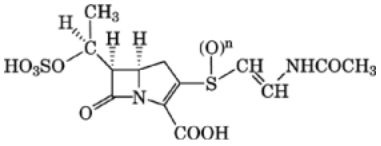
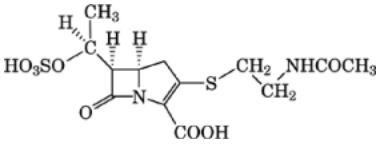
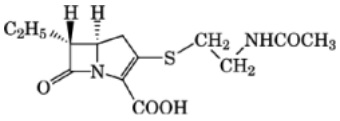
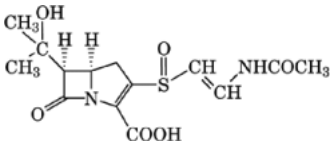
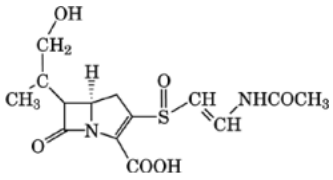
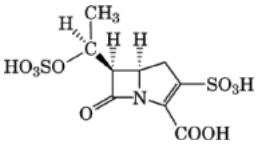
Name	CAS Registry Number	Molecular formula	Structure number	Structure
thienamycin	[59995-64-1]	$C_{11}H_{16}N_2O_4S$	(**2**)	
MM 4450MM 13902	[12795-21-0][57459-82-2]	$C_{13}H_{16}N_2O_9S_2C_{13}H_{16}N_2O_8S_2$	(**3**, n = 1)(**3**, n = 0)	
MM 17880	[61036-81-5]	$C_{13}H_{18}N_2O_8S_2$	(**4**)	
PS–5	[67007-29-8]	$C_{13}H_{18}N_2O_4S$	(**5**)	
carpetimycin A	[77209-15-5]	$C_{14}H_{18}N_2O_6S$	(**6**)	

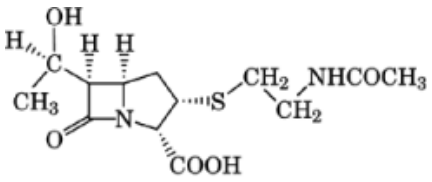
Table 1. ***Continued***

Name	CAS Registry Number	Molecular formula	Structure number	Structure
asparenomycin A	[76466-24-5]	$C_{14}H_{16}N_2O_6S$	(**7**)	
pluracidomycin A	[82138-64-5]	$C_9H_{11}NO_{10}S_2$	(**8**)	

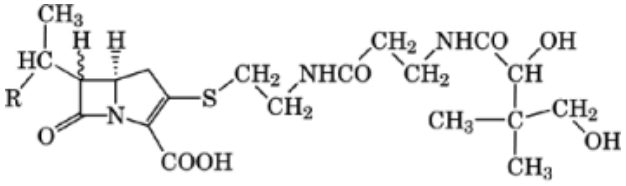
2.1. Occurrence, Fermentation, and Biosynthesis

Although a large number of *Streptomyces* species have been shown to produce carbapenems, only *S. cattleya* (2) and *S. penemfaciens* (11) have been reported to give thienamycin (**2**). Generally the antibiotics occur as a mixture of analogues or isomers and are often co-produced with penicillin N and cephamycin C. Yields are low compared to other β-lactams produced by streptomycetes, and titres are of the order of 1–20 μg/mL despite, in many cases, a great deal of effort on the optimization of the media and fermentation conditions. The rather poor stability of the compounds also contributes to a low recovery in the isolation procedures. The fermentation and isolation processes for thienamycin and the olivanic acids has been reviewed in some detail (12).

Early studies on the biosynthesis of thienamycin (**2**) indicated that the pyrroline ring was derived from glutamic acid (13, 14). Further reports demonstrated that the C-6 and C-7 atoms of the β-lactam ring are acetate derived, that the C-2 cysteaminyl side chain is from cysteine, and the two carbon atoms of the hydroxyethyl side chain originate from methionine (15). The incorporation of glutamate into the parent ring system (**1**, X = CH_2) has also bee reported (16); in this study bacterial production of various isomers of the saturated carbapenam ring structure was observed including one isomer having stereochemistry opposite to that of thienamycin at the C-5 position. Some streptomycete carbapenem producers have also been found to produce structures in which the pyrroline ring is reduced as in (**9**) (17). The microbiological interconversion of a number of the olivanic acids has been demonstrated (4), as well as the role of carbapenems, such as (**10**, R = H, OH, or OSO_3H) possessing a pantothenyl side chain, as early precursors of other carbapenem antibiotics (18). The possible biosynthetic pathways leading to both carbapenem and carbapenam ring structures have been discussed in some detail (14, 16, 18).



(**9**)



(**10**)

2.2. Properties

Thienamycin is isolated as a colorless, hygroscopic, zwitterionic solid, although the majority of carbapenems have been obtained as sodium salts and, in the case of the sulfated olivanic acids, as disodium salts (12). Concentrated aqueous solutions of the carbapenems are generally unstable, particularly at low pH. All the substituted natural products have characteristic uv absorption properties that are often used in assay procedures. The ir frequency of the β-lactam carbonyl is in the range $1760 - 1790\ \mathrm{cm}^{-1}$.

2.3. Structure Determinations

The structural elucidation of the early carbapenems, thienamycin, and the olivanic acids, followed a fairly similar sequence making use of both spectroscopic and degradation studies (19–22). Infrared absorption spectra suggested the presence of a β-lactam ring ($\nu_{\max} 1765\ \mathrm{cm}^{-1}$) and in the case of thienamycin (**2**) a trans-arrangement of β-lactam protons was indicated by the small coupling constant ($J_{5,6} < 3$ Hz) for the β-lactam hydrogens in the nmr. For the sulfated olivanic acids, (**3**) and (**4**), the coupling constant ($J_{5,6} \approx 6$ Hz) indicated the more familiar *cis*-β-lactam stereochemistry found in the penicillins and cephalosporins. One key reaction in confirming the structure of MM 13902 (**3**, $n = 0$) is shown in Figure 1**a**. The rearrangement of the monomethyl ester 1 produced the pyrrole 1; subsequent esterification followed by elimination of the sulfate residue gave a mixture of isomers 1 (20). Elimination of the sulfate moiety of the diester 1 gave solely the (*E*)-isomer of the ethylidene derivative 1 indicating a stereospecific $(E)_2$ elimination from which it was possible to assign the configuration at C-8 as (*S*). The (*E*)-geometry of the C-2 acetamidoethenyl substituent was clearly apparent from the coupling constant ($J = 14$ Hz) of the double bond protons.

In the case of thienamycin (Fig. 1**b**) the absolute stereochemistry at C-5 was unambiguously determined from the ene-lactam 1. The resultant (*R*)-aspartic acid 1 demonstrated that the absolute stereochemistry at C-5 of thienamycin is (*R*), corresponding to that found in the C-5 position of both penicillins and cephalosporins. Confirmation of the stereochemical assignments in both thienamycin (**2**) and the olivanic acid MM 13902 (**3**, $n = 0$) has been confirmed by x-ray crystallography (19, 21, 22). The structural determination of the nonsulfated derivatives from *S. olivaceus* (23), PS-5 (**5**) (5), the carpetimycins (6), and the asparenomycins (7) followed a similar pattern.

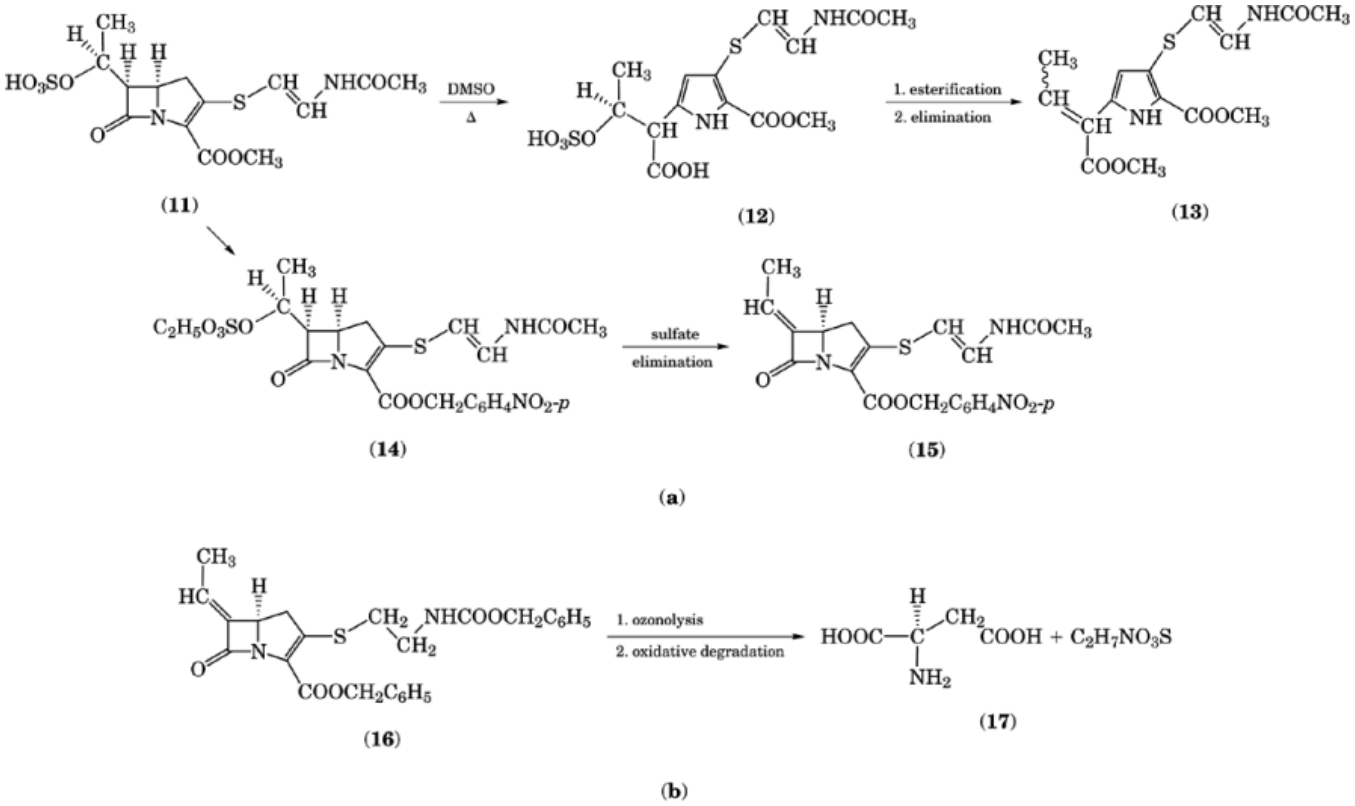
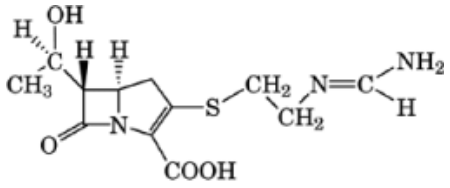


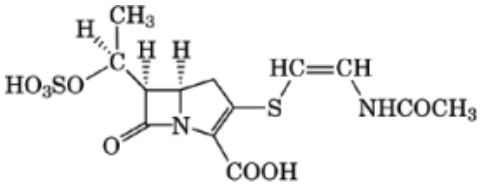
Fig. 1. Reaction sequences for steps in the structure determination of (**a**) MM 13902 (**3**, $_{n=0}$) and (**b**) thienamycin (**2**).

2.4. Reactions

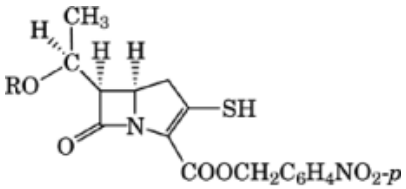
Although carbapenems are extremely sensitive to many reaction conditions, a wide variety of chemical modifications have been carried out. Many derivatives of the amino, hydroxy, and carboxy group of thienamycin (**2**) have been prepared primarily to study structure–activity relationships (24). The most interesting class of *N*-derivatives are the amidines which are usually obtained in good yield by reaction of thienamycin with an imidate ester at pH 8.3. Introduction of this basic but less nucleophilic moiety maintains or improves the potency of the natural material while greatly increasing the chemical stability. Thus *N*-formimidoyl thienamycin [64221-86-9] (MK 0787) (**18**), $C_{12}H_{17}N_3O_4S$, (25) was chosen for clinical evaluation and development. Another reaction of thienamycin involves isomerization to the chemically stable, but biologically inactive, Δ-1 isomer (26). Reductive removal of the cysteaminyl side chain has also been reported (27).



(**18**)



(19)



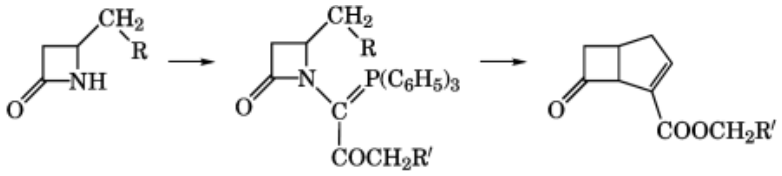
(20)

In the olivanic acid series of carbapenems the (*E*)-acetamidoethenyl grouping can be isomerized to the (*Z*)-isomer (**19**) (22) and reaction with hypobromous acid provides a bromohydrin that fragments to give a thiol of type (**20**) when R = H, SO_3H, or $COCH_3$. The thiol is not isolated but can react to provide new alkyl or alkenyl C-2 substituents (28). In the case of the nonsulfated olivanic acids, inversion of the stereochemistry at the 8(*S*)-hydroxyl group by way of a Mitsunobu reaction affords an entry to the 8(*R*)-thienamycin series (29). An alternative method for introducing new sulfur substituents makes use of a displacement reaction of a carbapenem (*S*)-oxide with a thiol (30). Microbial deacylation of the acylamino group in PS-5 (**5**) has been used to obtain the aminoethyl analogue (31).

2.5. Synthesis

One consequence of the discovery of the carbapenem natural products has been the development of new synthetic methods, the impetus for which was provided by the exceptional antibacterial potential of the compounds coupled with the extremely poor fermentation yields. Only chemical synthesis could provide the quantities of MK 0787 (**18**) necessary for clinical trials and commercial production.

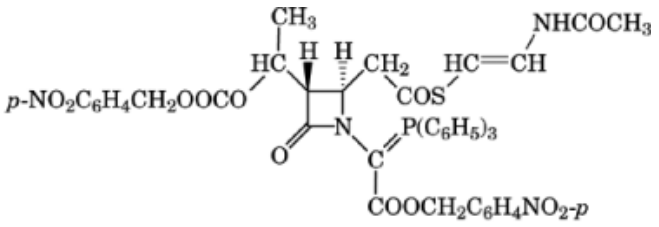
The racemic form of the unsubstituted nucleus (**1**, X = CH_2) was synthesized by several groups (32–34) prior to the disclosure of the natural material. One reaction path involved an azetidinone (**21**) where R = CH_2OH or $CH{=}CH_2$ converted to the corresponding phosphorane (**22**) where R′ = *o*-NO_2-C_6H_4 when R = CH_2OH and R′ = $COCH_3$ when R=CH=CH_2.



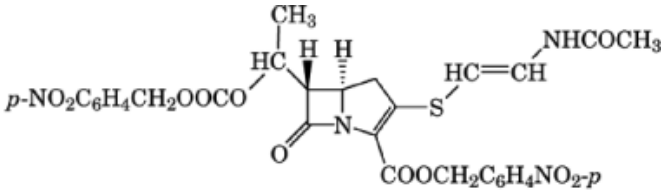
(21) (22) (23)

>Cyclization by way of the aldehyde (**22**, R = CHO) provides the appropriate ester of the bicyclic nucleus (**23**), which on deprotection gives an unstable sodium salt. Formation of the [2,3] double bond by this intramolecular Wittig procedure has been widely used for both analogue and natural product synthesis (35).

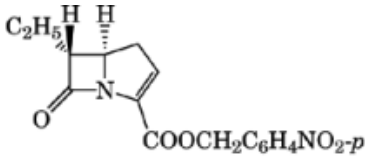
Cyclization is achievable even using a thiol ester such as (**24**) which leads to the protected olivanic acid MM 22383 [74819-56-0] (**25**), $C_{28}H_{26}N_4O_{11}S$ (36). Addition of thiols to the double bond of phosphorane-derived derivatives lacking a C-2 substituent (**26**) has been used for the synthesis of PS-5 (**5**) (37).



(**24**)

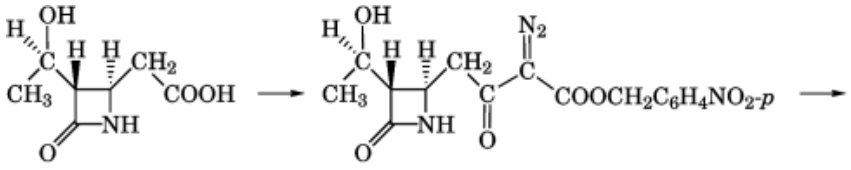


(**25**)

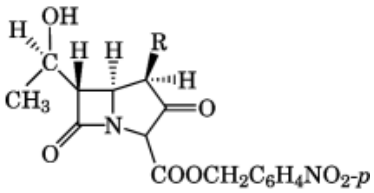


(**26**)

A synthetic approach that involves the [3,4] bond formation using a carbene insertion reaction has been highly successful and is illustrated by the enantioselective synthesis of (+)-thienamycin starting from L-aspartic acid [56-84-8], $C_4H_7NO_4$ (38). Over several steps the acid is converted to a protected form of the azetidinone (**27**) having all three contiguous chiral centers with the correct stereochemistry. Progression to the diazoketone (**28**) and cyclization using a catalytic amount of rhodium acetate provides the bicyclic ester (**29**, R = H) in high yield. Introduction of the cysteaminyl side via an activated enol derivative of (**29**) and deprotection gives (+)-thienamycin;

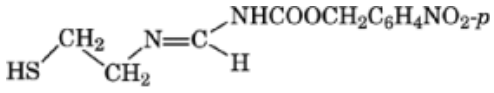


(27) (28)

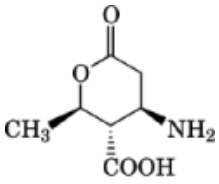


(29)

using the amidine side chain (**30**) MK 0787 (**18**) is directly accessible (39).

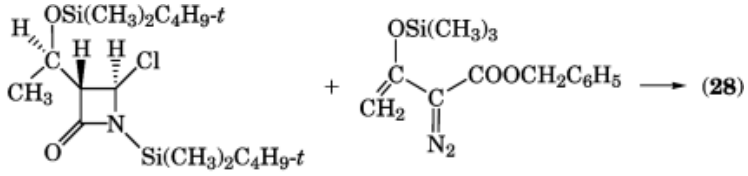


(30)



(31)

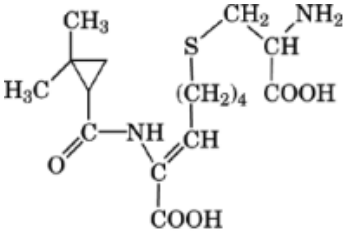
A second method makes use of the lactone (**31**) from acetone dicarboxylate (40) and for which a synthesis from (−)-carvone has been reported (41). Displacement of chlorine from the 6-aminopenicillanic acid (6-APA) derived β-lactam (**32**) by (**33**) illustrates yet another approach to the diazoketone (**28**) (42).



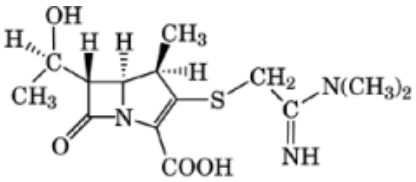
(32) (33)

Formal syntheses of thienamycin (**2**) from precursors such as carbohydrates (43–45), amino acids (46, 47), isoxazolidines (48), and tricarbonyliron lactam complexes (49) have also been reported. Many other methods for carbapenem synthesis have been widely reviewed (10, 50–52).

In addition to variable chemical stability the carbapenems are susceptible to β-lactam cleavage by a dehydropeptidase enzyme (DHP-I) located on the brush borders of the kidney (53). Clinically, MK 0787 (**18**) is used with an inhibitor of this enzyme, cilastatin [78852-98-9] (MK 0791) (**34**), $C_{16}H_{26}N_2O_5S$, which has a dramatic effect not only on the urinary recovery of the drug, but also reduces any nephrotoxic potential (52) (see Enzyme inhibition).

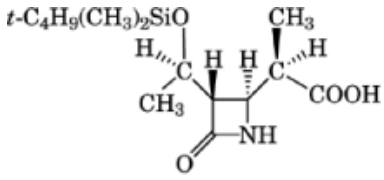


(**34**)

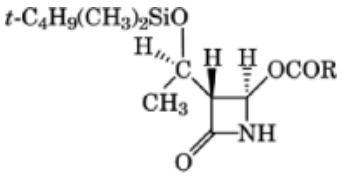


(**35**)

The disclosure that the 1β-methylcarbapenem [90822-26-7] (**35**), $C_{14}H_{21}N_3O_4S$, exhibits greatly increased chemical and enzymatic stability over MK 0787 (**18**) (54), while retaining the antibacterial potency of thienamycin (2), has caused attention to be focused on methods leading to structural analogues. The synthesis of (**35**) was by alkylation of (**27**) and elaboration via the ketoester (**29**, R = CH_3), but little stereocontrol was attainable by this procedure. Many newer approaches use the acid (**36**) derived by diastereoselective displacement at C-4 using the chiral 4-acycloxy β-lactams (**37**, R = CH_3 or C_6H_5) (55, 56). Examples make use of the tin or the boron enolates producing (**36**) in yields of 72–79% with a ratio of β:α isomers ranging from 24:1 to 60:1 (57–59).

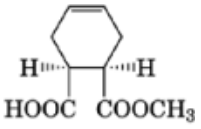


(**36**)

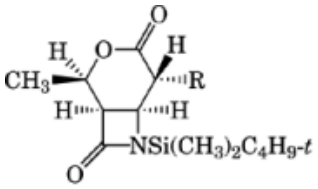


(**37**)

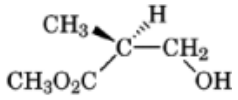
Other approaches to (**36**) make use of (**37**, R = CH_3) and reaction with a tributylstannyl allene (60) or 3-siloxypentadiene (61). A chemicoenzymatic synthesis for both thienamycin (**2**) and 1β-methyl analogues starts from the chiral monoester (**38**), derived by enzymatic hydrolysis of the dimethyl ester, and proceeding by way of the β-lactam (**39**, R = H or CH_3) (62, 63). (*S*)-Methyl-3-hydroxy-2-methylpropanoate [80657-57-4] (**40**), $C_5H_{10}O_3$, has also been used as starting material for (**36**) (64), whereas 1,3-dipolar cycloaddition of a chiral nitrone with a crotonate ester affords the oxazolidine (**41**) which again can be converted to a suitable β-lactam precursor (65).



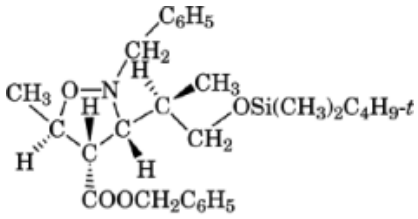
(**38**)



(**39**)

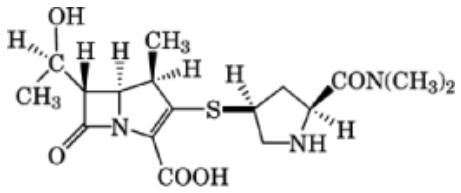


(**40**)

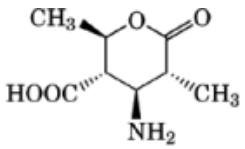


(**41**)

A number of highly potent DHP-I stable 1β-methylcarbapenems having a variety of C-2 substituents have now been described (60, 66–69) including SM 7338 [96036-03-2] (**42**), $C_{17}H_{25}N_3O_5S$. An acylamino compound (66) and a 1β-methoxy analogue (70) provide other variations. The pyrrolidine substituted 1β-methylcarbapenem SM 7338 (**42**) is being developed as a broad-spectrum parenteral antibiotic under the name meropenem; the synthesis of (**42**) is by way of the lactone (**43**) derived by a novel Diels-Alder approach to dihydropyran precursors of (**43**) (71).



(42)



(43)

2.6. Biological Properties

Thienamycin, the olivanic acids, and the majority of carbapenems are highly active broad-spectrum antibiotics having good stability to β-lactamases. Of the natural products thienamycin (**2**) is the most potent having a spectrum of activity encompassing both aerobic and anaerobic gram-positive and gram-negative bacteria including *Pseudomonas* species (72). The latter activity is attributed to the presence of the basic cysteaminyl substituent at C-2. All of the *N*-acylated derivatives have much reduced antipseudomonal activity (24).

The sulfated compounds MM 13902 (**3**, $n = 0$) and MM 17880 (**4**) are also broad-spectrum agents, but not as potent as thienamycin and all lack any significant activity against *Pseudomonas* (73). Many carbapenems are excellent inhibitors of isolated β-lactamases, particularly the olivanic acid sulfoxide MM 4550 (**3**, $n = 1$) (3). The possible mechanism of action of the carbapenems as inhibitors of β-lactamases has been discussed in some detail (74). Other carbapenems such as PS-5 (**5**) (75), the carpetimycins (76), asparenomycins (77), and pluracidomycins (8) are all highly active as antibiotics or β-lactamase inhibitors. The parent nucleus itself (**1**, X = CH_2) is intrinsically active, but chemically unstable (9).

Unlike the classical penicillins and cephalosporins, a rigid adherence to the cis-stereochemistry around the β-lactam ring is not necessary for biological activity as both trans-isomers such as (**2**), and cis-isomers (**3**, $n = 1$) are active. The hydroxy olivanic acids are not as potent as the sulfates, although in this case the cis-β-lactams are more active than the trans-isomers (73). Thienamycin (**2**) is the most stable to β-lactamases, a property attributed to the presence of the 8(*R*)-hydroxy group. Several synthetic examples lacking the C-6 hydroxyethyl side chain are much more susceptible to hydrolysis by β-lactamases (78). The order of antibiotic activity in the nonsulfated hydroxyethyl series appears to be trans-substituted β-lactam with 8(*R*) stereochemistry ie, thienamycin $>$ cis 8(*S*) $>$ trans 8(*R*) (25). As in the case of other β-lactam antibiotics, the carbapenems inhibit bacterial growth by interfering with peptidoglycan synthesis in the cell wall. In *E. coli* thienamycin has the greatest affinity for the penicillin binding protein PBP-2 (79); most of the newer cephalosporins bind principally to PBP-3.

The amidine derivative MK 0787 (**18**), named as imipenem, shows greatly improved solution stability as compared to thienamycin (**2**). Against some 800 isolates of gram-positive and gram-negative bacteria, imipenem (**18**) inhibited the majority of organisms at concentrations below 1 μg&solidusmL and was not hydrolyzed by plasmid mediated or chromosomal β-lactamases (80). The plasma half-life of imipenem in humans was considered satisfactory (1 h), but urinary recovery of antibiotic was extremely variable ranging from 6–40% (81) resulting from degradation by the DHP-I enzyme. This led to the development of the imipenemcilastatin combination as the clinical product (82). The urinary recovery of the combination was established consistently

at some 70% (83). The imipenem-cilastatin combination is used as a parenteral broad-spectrum antibiotic against a wide variety of bacterial infections. No other carbapenem has yet been developed as a commercial product although effort is being directed towards the DHP-I stable 1β-methyl analogues of which meropenem (**42**) would appear to be at the most advanced stage of development. This is a broad-spectrum agent similar to imipenem but with greatly enhanced stability to dehydropeptidase and should therefore not require concomitant administration of an enzyme inhibitor (69).

3. Penems

Historically, the development of penems is contemporary with that of the naturally occurring carbapenems and the direction of penem research has clearly been influenced by the structures of the closely related natural products. The origins of the two groups of compounds is, however, quite different. Unlike carbapenems, no penems have been found in nature. When first described (84, 85) they were viewed as hybrid molecules combining structural features of penicillins and cephalosporins.

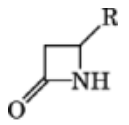
3.1. Synthesis

3.1.1. Woodward's Phosphorane Route

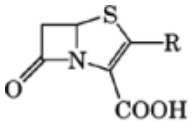
The first penem synthesis, shown in Figure 2, utilized an intramolecular Wittig reaction to form the [2,3] double bond of the thiazoline ring (84). Reductive acylation of the penicillin derived disulfide 2 gave the thioester 2. Ozonolysis of the latter provided the oxalimide 2 which on mild methanolysis gave the azetidinone 2. Well established methods were applied to convert 2 to the phosphorane 2 which underwent thermal cyclization to the penem ester 2. Catalytic hydrogenation gave the penem acid [64370-39-4] 2 which was shown to possess antibacterial activity in spite of its rather limited stability.

3.1.2. Extension of the Phosphorane Route

Ample evidence of the versatility of the phosphorane synthesis strategy is provided by the proliferation of penems that followed. Nucleophilic displacement of the acetate function of the acetoxy-azetidinone (**51**, R = $OCOCH_3$) [28562-53-0] (86) provided azetidinones where R = $SCOCH_3$, $SCSSC_2H_5$, and $SCSOC_2H_5$, which on elaboration gave the penems (**52**, R = CH_3) (87), (**52**, R = SC_2H_5) (88), (**52**, R = OC_2H_5) (89). Similar treatment of 3-substituted (or disubstituted) acetoxyazetidinones allowed the synthesis of a number of 2-substituted-6-alkyl- and 6,6-dialkylpenems (90).



(**51**)



(**52**)

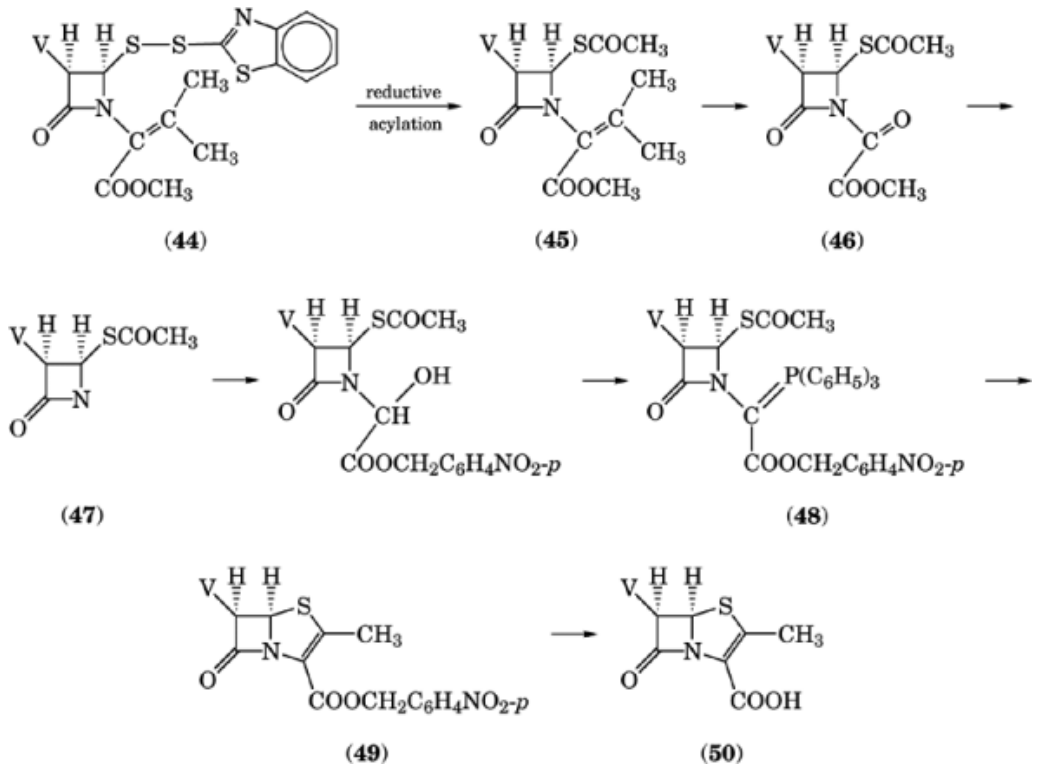
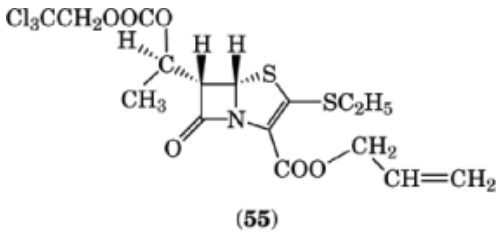


Fig. 2. Reaction scheme for the first penem synthesis where $_{V=}$ $C_6H_5OCH_2CONH$.



The naturally occurring carbapenems provided the impetus for the synthesis of the four racemates of 6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate (91). As seen in Figure 3, conversion of (3, R = $OCOCH_3$) to the *N*-protected azetidinone followed by aldol type addition gave a mixture of alcohols. Further manipulation gave the four isomers of the trithiocarbonate 3 each of which was progressed separately to the corresponding penems 3 by means of the phosphorane route. During the thermal cyclization each product gives rise to a second isomer by virtue of a novel epimerization at C-5; eg, thermolysis of the rel-5(*R*)-, 6(*S*)-, 8(*R*)-isomer [76431-42-0] gives 3 which could be shown to be the rel-5(*R*)-, 6(*R*)-, 8(*S*)-isomer [80575-20-8]. Double deprotection of 3 gave the corresponding penem salts 3.

A useful modification of the phosphorane route (92) allowed the synthesis of a wide range of penems from common advanced intermediates. Cleavage of tritylthioazetidinones of the type (**57**) when R = H, $CH_2OCOCH_2C_6H_4NO_2$-*p*, etc, using silver nitrate–methanol afforded the silver mercaptides (**58**) which on

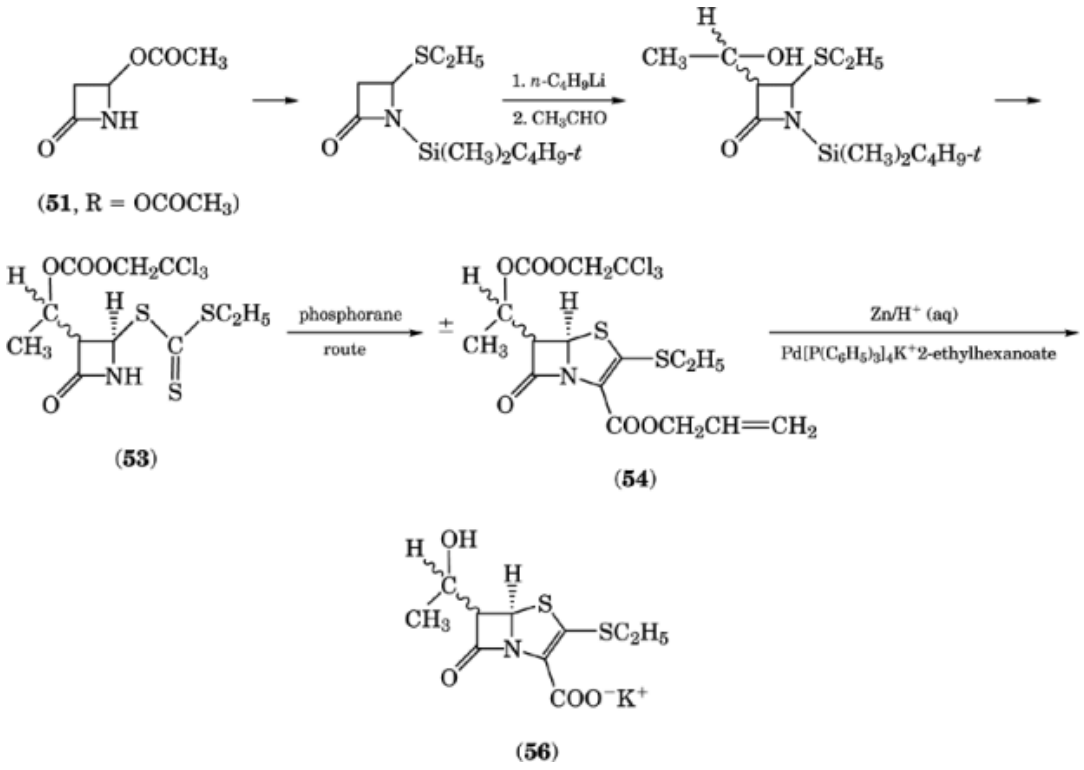
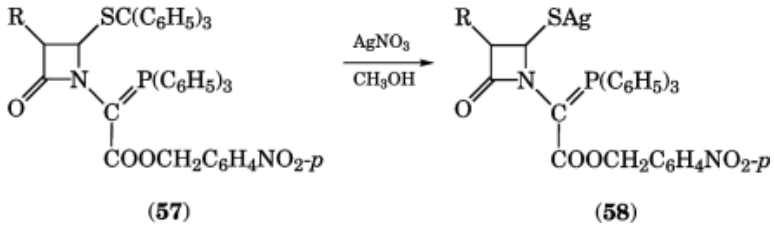


Fig. 3. Reaction scheme for the synthesis of the 6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylates (92).

acylation–cyclization gave a wide range of penems in which the 2-substituent was linked through carbon or sulfur.



In common with the naturally occurring carbapenem thienamycin (**2**), the introduction of the *trans*-6-[1-(*R*)-hydroxyethyl] group had a profound effect on the biological properties of the penems. This, together with an indication from an early study (93) that, as with other β-lactams, the 5(*R*)-enantiomer was solely responsible for antibacterial activity, provided impetus for the development of methods for the synthesis of chiral penems.

The stereochemical outcome of aldol reactions of 6,6-dibromopenicillanates was described in 1977 (94) making 6-aminopenicillanic acid [551-16-6] (6-APA), $_8H_{12}N_2O_3S$, an attractive starting material for the synthesis of chiral 6-(1-hydroxyethyl)penems (Fig. 4). Metal-halogen exchange on 4 followed by treatment with acetaldehyde gave a mixture of isomers from which the bromohydrin 4 having a desired 8(*R*) stereochemistry could be isolated as major product. Reductive removal of the halogen atom using zinc then gave the (5(*R*)-, 6(*S*)-, 8(*R*))-penem 4. Alternatively, diazotization followed by Lewis acid catalyzed reaction using ac-

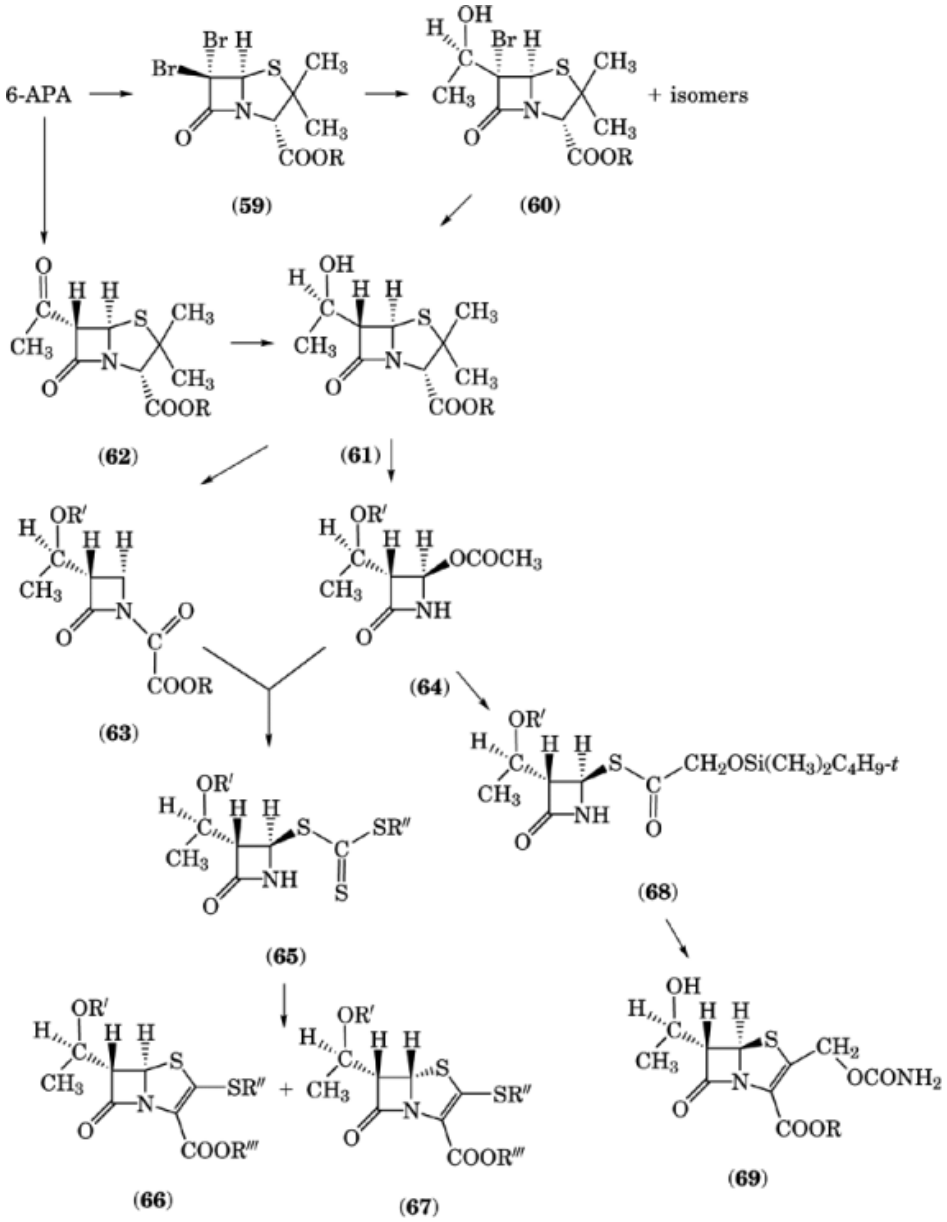


Fig. 4. Reaction scheme for the synthesis of chiral 6-(1-hydroxyethyl) penems where $_{R'=}$ H, $OCOCH_2CCl_3$, $Si(CH_3)_2C_4H_9$-*t*; $_{R''=}$ C_2H_5; and $_{R'''=}$ $CH_2CH{=}CH_2$, $CH_2C_6H_5$.

etaldehyde gave the unstable *trans*-6-acetylpenicillanate 4 which could be reduced stereoselectively to the alcohol 4 (95).

Several groups have built on this work and prepared intermediates capable of conversion to penems using the phosphorane route. In one method (96), chlorinolysis was used to prepare the chloroazetidinone 4, in another (97) the thiazolidine ring was cleaved using mercuric acetate, obtaining the acetoxyazetidinone 4 after

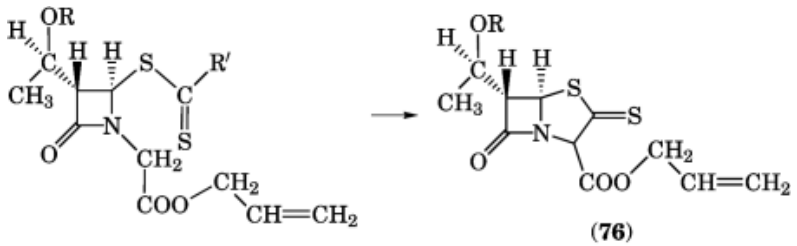
oxidative removal of the nitrogen substituent. Reaction of either 4 (96) or 4 (98) with a sodium trithiocarbonate proceeded with retention of configuration to give the azetidinones 4 from which the (5(*R*)-, 6(*S*)-, 8(*R*))-penems 4 were obtained. Some of the unwanted *cis*-5(*S*)-penems 4 were also formed during cyclization. Moreover, when either pure 4 or 4 was heated the same equilibrium mixture was obtained (96, 98), possibly involving the intermediacy of a betaine (98). The acetoxyazetidinone 4 has also been used to prepare intermediates of the type 4 for the synthesis of the Farmitalia clinical candidate FCE 22101 [84845-58-9] (4, R = Na), $C_{10}H_{12}N_2O_6SNa$ (99).

Other methods for cleavage of the thiazolidine ring of penicillanates with retention of the sulfur atom have been described. Silver assisted cleavage afforded mercaptides (100) whereas the sulfenic acids generated by the thermolysis of penicillanate sulfoxides have been intercepted by acetylenes (101–103) and mercaptans (104, 105). All these methods have provided useful intermediates for the synthesis of penems. Total synthesis starting from L-threonine [72-19-5], $C_4H_9NO_3$, (106, 107) and ethyl-3-(*S*)-hydroxybutanoate [56816-01-4], $C_6H_{12}O_3$, (108) has also been used to prepare intermediates for the preparation of penems having defined stereochemistry.

3.1.3. Alternative Methods for Formation of the Penem Ring

The reactivity of the carbonyl group in readily available oxalimides of the type 5 (Fig. 5) provides a useful alternative to the original phosphorane route. Treatment of oxalimides (5, X = O, R = CH_2OCONH_2) and (5, X = S, R = SC_2H_5) with a trialkyl phosphite at elevated temperatures gives the corresponding penems 5 (100, 109) and 5 (110, 111). In a detailed study (112) it was shown that for thiolesters (5, X = 0) carbene generation/trapping gives intermediate trialkyoxyphosphoranes 5 which then cyclize thermally. In contrast, cyclization of trithiocarbonates (5, X = S, R = SC_2H_5) does not proceed via phosphorane intermediates. Instead it has been proposed (110, 111) that the carbene generated added intramolecularly to the more reactive thiocarbonyl group to form an episulfide 5 which was then desulfurized to give the penem. The lower temperature and shorter reaction times required for cyclization of trithiocarbonates avoided the troublesome C-5 epimerization experienced with the conventional phosphorane route. The high reactivity of the oxalimide carbonyl group has also been demonstrated by the more recently reported (113) cyclization of phosphoranes of the type (5, X = $P(C_6H_5)_3$).

Although the phosphorus mediated ring closures are by far the most widely used, other methods for [2,3] bond formation have been described. Treatment of the dithiocarbamates (**75**, R = H or $Si(CH_3)_3$; R′ = ) with a strong base at low temperature gives thioxopenams (**76**) which are readily alkylated to give 2-alkylthiopenems (114).



(**75**) (**76**)

An analogous preparation of thioxopenams from dithiocarbonates (**75**, R = t-$C_4H_9(CH_3)_2Si$, R′ = OC_6H_5) has also been described (115). Additionally, an intramolecular Michael addition reaction to form the [2,3] bond has been exploited in penem synthesis to prepare FCE 22101 (**69**) (116).

Synthesis of 2-thioxopenams (**76**) has also been realized using a [sulfur, C-5] ring closure (117). Cyclization of 4-(*S*)-chloroazetidinone [88816-44-8] (**77**, R = R′ = $SCOCH_3$), $C_{19}H_{19}ClN_2O_8S_2$, using imidazole in aqueous

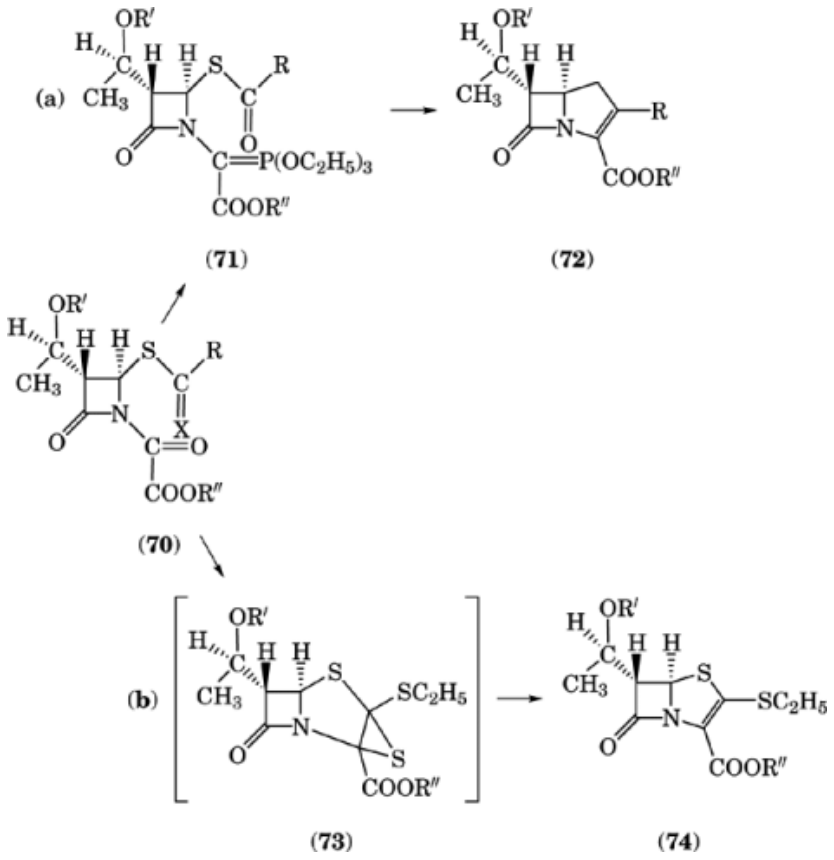
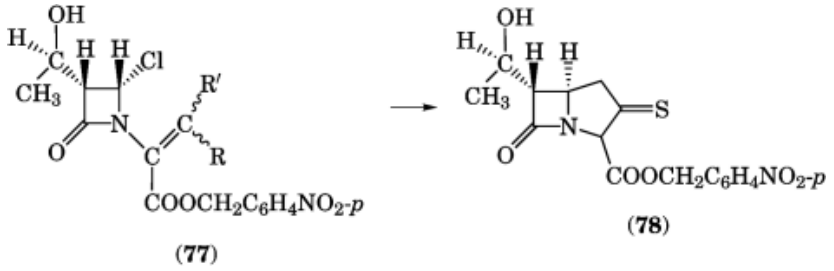


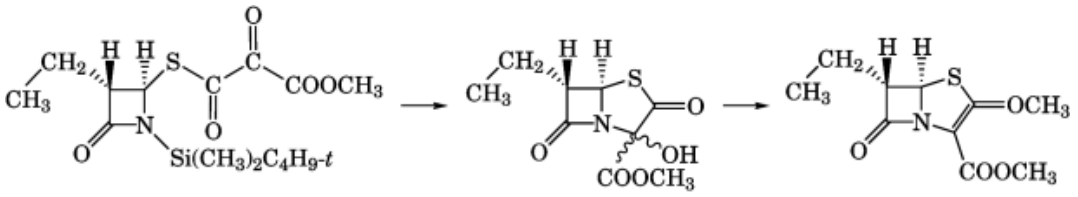
Fig. 5. An alternative method for the formation of the penem ring where $_{R'=}$ $OCOCH_2CCl_3$, $Si(CH_3)_2$, or C_4H_9-*t* and $_{R''=}$ CH_2CCl_3, or $CH_2C_6H_4NO_2$-*p*, CH_2CHCH_2; (**a**) $_{X=}$ O, $_{R=}$ CH_2OCONH_2, (**b**) $_{X=}$ S, $_{R=}$ SC_2H_5.

dioxane proceeded stereospecifically to give the 5-(*R*)-thioxopenam [83362-57-6] (**78**). Using the same approach, the azetidinone (**77**, R = —O—C$_6$H$_4$—Cl; R′ = $SCOC_4H_9$-*t*), was cyclized to the corresponding 2-aryloxypenem [85768-34-9] (118).



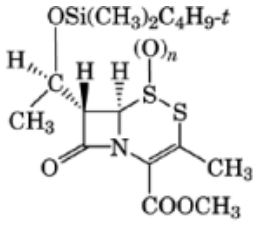
Only one successful penem synthesis involving a [nitrogen, C-3] ring closure has been described (119). Cyclization of the ketomalonate (**79**) using hydrofluoric acid-pyridine afforded the penams (**80**) which were

converted to the penem (**81**). Attempts to adapt the versatile diazoketoester-carbapenem cyclization for penem synthesis failed (120).

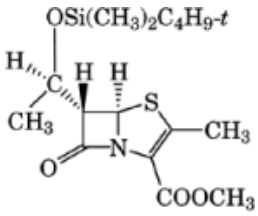


(**79**) (**80**) (**81**)

Ring contraction of 2-thiocephems has also been examined as a route to penems. Desulfurization of (**82**, $n = 0$) using triphenylphosphine gave mixtures of 5(*R*)- and 5(*S*)-penems (121). The stereochemical problem was neatly overcome by regioselective oxidation to the thiosulfonate (**82**, $n = 2$) which underwent stereospecific thermal extrusion of sulfur dioxide (122) to give the 5(*R*)-penem (**83**).



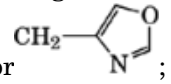
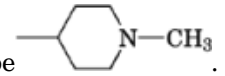
(**82**)

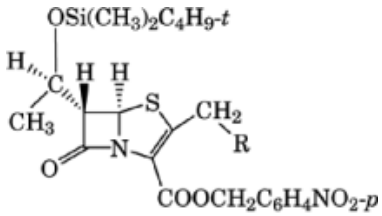


(**83**)

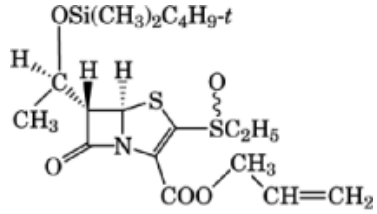
3.1.4. Modification of Intact Penems

Functional group modification has been used by a number of researchers (123–125) to synthesize a wide range of 2-substituted penems. For example, activation of the hydroxyl group of (**84**, R = OH) followed by displacement reactions provided 2-heterocyclylthiomethyl-penems (**84**, R = (*S*)-heterocyclyl) (125) and 2-(quaternary ammonio)methyl-penems (**84**, R = NR′$_3$X) (125).

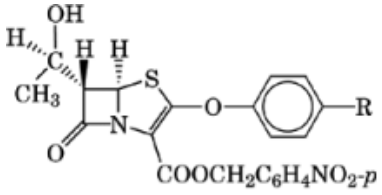
Displacement of the sulfinyl group of penems (**85**), obtained by regioselective oxidation of (5, R′ = $Si(CH_3)_2C_4H_7$-*t*, R″ = CH_2CHCH_2) (Fig. 5) using thiolates, allowed the synthesis of a range of thio-substituted penems from a common intermediate (126). A conceptually similar approach (127) enables the displacement of the phenolic leaving group in penems (**86**, R = CN) [85768-38-3] or (**86**, R = NO_2) [114707-30-1] using amines and thus provides a general route to 2-aminopenems (**87**) where R can be CH_3 or *n*-C_3H_7; R′ can be H, CH_3, $CH_2COOC_2H_5$, or  ; or both R and R′ can be  .



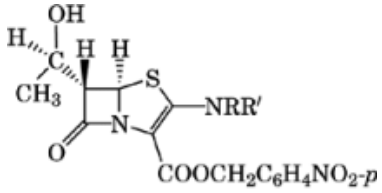
(**84**)



(**85**)

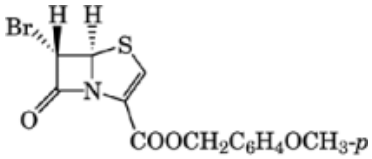


(**86**)

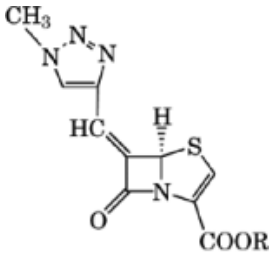


(**87**)

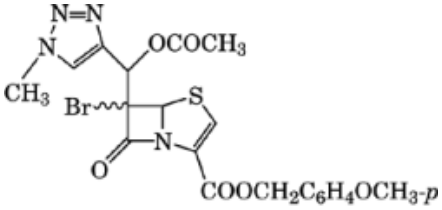
Although less researched than the 2-position, modifications at the 6-position of intact penems have been reported. Generation of the dianion of the penem (**52**, R = CH_3) using a strong base such as *n*-butyllithium or lithium diisopropylamide, followed by reaction with electrophiles yields 6-substituted 2-methylpenems in moderate yield (128). The enhanced acidity of the 6-proton in the bromopenem (**88**) [114409-16-4] has been exploited to prepare the Beecham β-lactamase inhibitor BRL 42715 [102209-75-6] (**89**, R = Na), $C_{10}H_8N_4O_3SNa$ (105). Lithium diphenylamide, a weaker base, was used to generate the anion of (**88**) which on sequential treatment with 1-methyl-1,2,3-triazole-4-carbaldehyde and acetic anhydride gives a mixture of diastereomers of the bromoacetate (**90**). Reductive elimination then provided the (*Z*)-penem (**89**, R = $CH_2C_6H_4OCH_3$-*p*) as major product which on Lewis acid mediated deprotection gave BRL 42715 (**89**, R = Na).



(88)



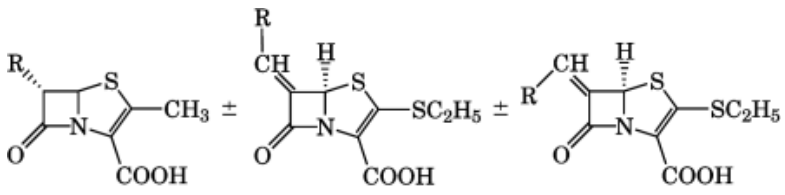
(89)



(90)

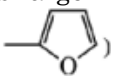
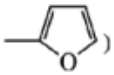
3.2. Biological Properties

In marked contrast to the antibacterially inactive penicillanic and cephalosporanic acids, 6-unsubstituted penems such as (**52**, R = CH_3) [69077-00-5] exhibit good activity against both gram-positive and gram-negative bacteria (87). The introduction of a 6β-acylamino substituent had an adverse effect on the stability of the penem nucleus, and compounds such as (50) were shown to possess only weak antibacterial properties (84, 85). Attempts to stabilize 6β-acylaminopenems by the introduction of a 6α-methoxy or 6α-methyl group was only marginally successful in the latter case and the compounds still showed only weak activity (129). A similar reduction in stability and activity was also noted for the 6α-methoxypenem (**91**, R = OCH_3) [78839-71-1], whereas the 6α-methylpenem (**91**, R = CH_3) [73660-04-5], although considerably more stable, still only exhibited modest antibacterial activity (130). 6,6-Dialkylpenems have been shown to be extremely stable but are devoid of antibacterial reactivity (130).



(91) (92) (93)

The introduction of the 1-hydroxyethyl group found in the naturally occurring carbapenems proved to be crucial for providing penems with broad-spectrum antibacterial activity and stability to β-lactamases. As with their carbapenem counterparts, biological activity showed a marked dependence on the relative stereochemistry at the three chiral centers. Evaluation of the four racemic penems 4 revealed that the *trans*-8(*R*)-isomer [76431-47-5], corresponding to thienamycin (**2**), was 20- to 30-fold more potent than the *trans*-8(*S*)-isomer [76431-46-4] whereas the two cis-penems [80629-72-7] and [80629-98-7] were of intermediate potency (131). Further structural modification at C-8 resulted in adverse effects on antibacterial activity. Removal of the C-8 methyl group resulted in loss of activity especially against β-lactamase producing bacteria (131) whereas an additional methyl group as in the 6-hydroxyisopropylpenem [79583-53-2], (**91**, R = $COH(CH_3)_2$), $C_{10}H_{13}NO_4S$, resulted in almost complete loss of activity (132). The increased bulk produced by substitution of the C-8 methyl group was also detrimental, 1-hydroxy-1-propylpenem [75940-79-3] (**91**, R = $CHOHC_2H_5$) and 1-hydroxy-2-phenylethylpenem [75940-91-9] (**91**, R = $CHOHCH_2C_6H_5$) being devoid of useful activity (132).

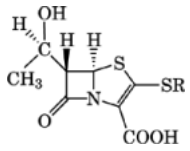
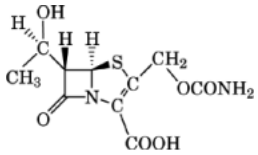
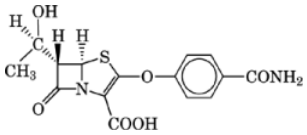
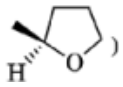
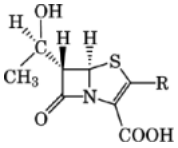
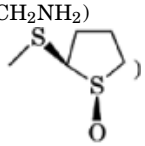
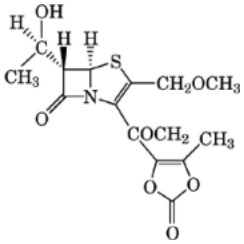
The introduction of unsaturation at [6,8] resulted in loss of all antibacterial activity except that against *staphylococcal* species. Both the (*Z*)- (**92**, R = CH_3) [81463-33-4] and the (*E*)- (**93**, R = CH_3) [81463-37-8] isomers of the 6-ethyl-idenepenem sodium salt showed potent broad spectrum β-lactamase inhibitory properties and were capable of reducing the minimum inhibitory concentration (MIC) values of sensitive β-lactams, eg, Amoxycillin, when used in combination (133). Unlike the saturated counterparts, the 6-methylenepenems were tolerant to profound changes at C-8. Improved inhibitory properties and synergism resulted from the introduction of a furan ring. However, in the case of this larger C-8 substituent, a preferred geometry for the double bond was identified and the (*Z*)-isomer (**92**, R = ) [93853-68-0] was more active than the (*E*)-isomer (**93**, R = ) (134). Structure-activity relationships for a wide range of (*Z*)-6-heterocyclylmethylenepenems have been reported (135).

With a few exceptions the 2-substituent can be seen as a means of fine-tuning the activity, pharmacokinetics, and stability properties of the penems. The great number of structural variations (98, 124, 125, 136–144) that can be accommodated without loss of the potent activity conveyed by the 6-[1-(*R*)-hydroxyethyl] group bears witness to the undemanding nature of this region of the molecule. These penems typically exhibit excellent activity against gram-positive bacteria including β-lactamase producing strains. The activity against gram-negative organisms, including those producing β-lactamase, is generally good although of a lower order. Except for compounds possessing a basic amino function in the 2-substituent (98, 144) penems are devoid of useful activity against *pseudomonas* species.

Research carried out in a number of laboratories has revealed several members of the penem family having biological properties worthy of further investigation. Some of these compounds are given in Table 2. Extensive studies (135) have also identified BRL 42715 [102209-75-6] (**89**, Na), $C_{10}H_7N_4O_3SNa$, as a potentially useful β-lactamase inhibitor capable of potentiating the activity of a number of clinically important β-lactam antibiotics against resistant strains (153).

In terms of activity there seems little to prevent some of these compounds finding a place in therapy, especially those such as SCH 29482, SUN 5555, and FCE 25199 which have oral absorption properties. However, as is the case for the carbapenems, some penems are extensively metabolized by human renal dehydropeptidase-I enzyme (144). Although no penem has received approval for clinical use as of this writing, expectations are high that future research and development will change that.

Table 2. Penems

Name	CAS Registry Number	Molecular formula	Structure number	Structure	Reference
SCH 29482SCH 34343	[77646-83-4][94392-37-7]	$C_{10}H_{13}NO_4S_2C_{11}H_{14}N_2O_6S_2$	(**94**, R = C_2H_5)(**94**, R = $(CH_2)_2OCONH_2$)		145146
FCE 22101FCE 22891	[84845-58-9][87238-52-6]	$C_{10}H_{12}N_2O_6SC_{13}H_{16}N_2O_8S$	(**69**, R = Na)(**69**, R = CH_2OCOCH_3)		146147
HRE 664	[109888-39-3]	$C_{15}H_{14}N_2O_6S$	(**95**)		148
SUN 5555	[106560-14-9]	$C_{12}H_{15}NO_5S$	(**96**, R = )		149
CGP 31608	[97644-04-7]	$C_9H_{12}N_2O_4S$	(**96**, R = CH_2NH_2)		150
CP 65207	[120788-07-0]	$C_{12}H_{15}NO_5S_3$	(**96**, R = )		151
FCE 25199	[120796-34-1]	$C_{15}H_{17}NO_7S$	(**97**)		152

4. Economic Aspects

Extensive carbapenem and penem antibiotic research has been ongoing since thienamycin was discovered in 1978. However, only the imipenem-cilastatin combination has become a commercial product. Launched in 1985 in the United States as a broad-spectrum hospital product under the name Primaxin,this product had

worldwide sales of some $300 million in 1988. Sales were predicted to rise to $345 million for the year ending 1989 (154).

BIBLIOGRAPHY

"Penicillin" in *ECT* 1st ed., Vol. 9, pp. 922–943, by W. E. Brown, Squibb Institute for Medical Research; "Penicillins" in *ECT* 2nd ed., Vol. 14, pp. 652–707, by Kenneth Butler, Chas. Pfizer & Co., Inc.; "Antibiotics, β-Lactams" in *ECT* 3rd ed., Vol. 2, pp. 871–919, by J. R. E. Hoover, and C. H. Nash, Smith Kline & French Laboratories.

Cited Publications

1. "Cephalosporins and Penicillins" in E. H. Flynn, ed., *Chemistry and Biology*, Academic Press, New York and London, 1972.
2. J. S. Kahan and co-workers, *J. Antibiot.* **32**, 1 (1979).
3. D. Butterworth, M. Cole, G. Hanscomb, and G. N. Rolinson, *J. Antibiot.* **32**, 287 (1979); J. D. Hood, S. J. Box, and M. S. Verall, *J. Antibiot.* **32**, 295 (1979).
4. S. J. Box, J. D. Hood, and S. R. Spear, *J. Antibiot.* **32**, 1239 (1979).
5. K. Yamamoto and co-workers, *J. Antibiot.* **33**, 796 (1980).
6. M. Nakayama and co-workers, *J. Antibiot.* **34**, 818 (1981).
7. N. Tsuji and co-workers, *J. Antibiot.* **35**, 24 (1982).
8. N. Tsuji and co-workers, *J. Antibiot.* **35**, 536 (1982).
9. W. L. Parker and co-workers, *J. Antibiot.* **35**, 653 (1982).
10. R. Southgate and S. Elson, *Fortschr. Chem. Org. Naturst.* (Progress in the Chemistry of Organic Natural Products), Springer-Verlag, New York, **47**, 1 (1985).
11. Eur. Pat. Appl. 38,534 (Apr. 15, 1981), K. Tanaka, N. Tsuji, E. Kondo, and Y. Kawamura (to Shionogi and Co., Ltd.).
12. D. Butterworth, J. D. Hood, and M. S. Verall in A. Mizrahi, ed., *Advances in Biotechnological Processes*, Vol. **1**, A. R. Liss, New York, 1982, 251–282.
13. G. Albers-Schönberg and co-workers, "Abstract 228" in *Abstracts of the 16th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1976*, American Society for Microbiology, Washington, D.C., 1976.
14. J. M. Williamson, *CRC Crit. Rev. Biotechnol.* **4**, 111 (1986).
15. J. M. Williamson and co-workers, *J. Biol. Chem.* **260**, 4637 (1985); D. R. Houk, K. Kobayashi, J. M. Williamson, and H. G. Loss, *J. Am. Chem. Soc.* **108**, 5365 (1986).
16. B. W. Bycroft in P. H. Bentley and R. Southgate, eds., *Recent Advances in the Chemistry of β-Lactam Antibiotics*, RSC Special Publication No. 70, London, 1989, 23–32.
17. T. Haneishi and co-workers, *J. Antibiot.* **36**, 1581 (1983).
18. Y. Fukagawa, M. Okabe, T. Yoshioka, and T. Ishikura in A. G. Brown and S. M. Roberts, ed., *Recent Advances in the Chemistry of β-Lactam Antibiotics*, Special Publication No. 52, London, 1985, 163–182.
19. G. Albers-Schöberg and co-workers, *J. Am. Chem. Soc.* **100**, 6491 (1978).
20. A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 523 (1977); 953 (1977).
21. A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth in G. I. Gregory, ed., *Recent Advances in Chemistry of β-Lactam Antibiotics*, RSC Special Publication No. 38, London, 1981, 255–268.
22. A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Antibiot.* **39**, 2551 (1983).
23. A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Antibiot.* **32**, 961 (1979).
24. W. J. Leanza and co-workers in Ref. 21, 240–254.
25. W. J. Leanza, K. J. Wildonger, T. W. Miller, and B. G. Christensen, *J. Med. Chem.* **22**, 1435 (1979).
26. D. H. Shih and R. W. Ratcliffe, *J. Med. Chem.* **24**, 639 (1981).
27. D. H. Shih, J. Hannah, and B. G. Christensen, *J. Am. Chem. Soc.* **100**, 8004 (1978).
28. D. F. Corbett, *J. Chem. Soc., Chem. Commun.*, 803 (1981).
29. D. F. Corbett, S. Coulton, and R. Southgate, *J. Chem. Soc. Perkin I*, 3011 (1982).
30. K. Yamamoto and co-workers, *Tetrahedron Lett.* **23**, 897 (1982).

31. Y. Fukagawa, K. Kubo, T. Ishikura, and K. Kounu, *J. Antibiot.* **33**, 543 (1980).
32. L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.* **100**, 8006 (1978).
33. J. H. Bateson and co-workers, *J. Chem. Soc. Perkin I*, 3242 (1981).
34. H. R. Pfaendler, J. R. Gosteli, R. B. Woodward, and G. Rihs, *J. Am. Chem. Soc.* **103**, 4526 (1981).
35. J. H. Bateson and co-workers in Ref. 21, 291–313.
36. R. J. Ponsford and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1085 (1980).
37. J. H. Bateson and co-workers, *J. Chem. Soc., Chem. Commun.*, 1084 (1980).
38. T. N. Salzman, R. W. Ratcliffe, B. G. Christensen, and F. A. Boufford, *J. Am. Chem. Soc.* **102**, 6161 (1980).
39. I. Shinkai and co-workers, *Tetrahedron Lett.* **23**, 4903 (1982).
40. D. G. Melillo and co-workers, *Tetrahedron Lett.* **22**, 913 (1981).
41. T. Kametani and co-workers, *J. Chem. Soc., Chem. Commun.*, 646 (1989).
42. S. Karady, J. S. Amato, R. A. Reamer, and L. M. Weinstock, *J. Am. Chem. Soc.* **103**, 6765 (1981).
43. M. Miyashita, M. N. Chida, and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.*, 1354 (1982).
44. N. Ikota, O. Yoshino, and K. Koga, *Chem. Pharm. Bull.* **30**, 1929 (1982).
45. A. Knierzinger and A. Vasella, *J. Chem. Soc., Chem. Commun.*, 9 (1985).
46. H. Maruyama, M. Shiozaki, and T. Hiraoka, *Bull. Chem. Soc. Jap.* **58**, 3264 (1985).
47. M. Shiozaki, N. Ishida, H. Maruyama, and T. Hiraoka, *Tetrahedron* **39**, 2399 (1983).
48. T. Kametani, T. Nagahara, and T. Honda, *J. Org. Chem.* **50**, 2327 (1985).
49. S. T. Hodgson, D. M. Hollinshead, and S. V. Ley, *J. Chem. Soc., Chem. Commun.*, 494 (1984).
50. T. Kametani, *Heterocycles* **17**, 463 (1982).
51. T. Nagahara and T. Kametani, *Heterocycles* **25**, 729 (1987).
52. F. M. Kahan, H. Kropp, J. G. Sundelof, and J. Birnbaum, *J. Antimicrob. Chem.*, Supplement D, **12**, 1 (1983).
53. H. Kropp, J. G. Sundelof, R. H. Hajdu, and F. M. Kahan, *Antimicrob. Agents Chemother.* **22**, 62 (1982).
54. D. H. Shih, F. Baker, L. D. Cama, and B. G. Christensen, *Heterocycles* **21**, 29 (1984).
55. A. Afonso and co-workers in Ref. 16, 295–302.
56. D. M. Tschaen and co-workers, *Tetrahedron Lett.* **29**, 2779 (1988).
57. R. Deziel and D. Faureau, *Tetrahedron Lett.* **47**, 5687 (1986).
58. F. Shirai and T. Nakai, *J. Org. Chem.* **52**, 5491 (1987).
59. T. Shibata and Y. Sugimura, *J. Antibiot.* **42**, 374 (1989).
60. J. Haruta and co-workers, *Chem. Pharm. Bull.* **37**, 2338 (1989).
61. T. J. Sowin and A. I. Meyers, *J. Org. Chem.* **53**, 4154 (1988).
62. S. Kobayashi, K. Kamijama, T. Iimori, and M. Ohno, *Tetrahedron Lett.* **25**, 2557 (1984); **29**, 1057 (1988).
63. H. Kaga, S. Kobayashi, and M. Ohno, *Tetrahedron Lett.* **30**, 113 (1989).
64. F. Shirai and T. Nakai, *Chem. Lett.*, 445 (1989).
65. M. Ihara, M. Takahashi, M. Fukumoto, and T. Kametani, *Heterocycles* **27**, 327 (1988).
66. T. N. Salzmann and co-workers in Ref. 16, 171–189.
67. S. Schmitt, T. N. Salzmann, D. M. Shih, and B. G. Christensen, *J. Antibiot.* **41**, 780 (1988).
68. C. Kim, B. Y. Luh, P. F. Misco, and M. J. Hitchcock, *J. Med. Chem.* **32**, 601 (1989).
69. P. Davey and co-workers, eds., *J. Antimicrob. Chemother.* **24**, Supplement A (1989).
70. Y. Nagao and co-workers, *J. Chem. Soc., Chem. Commun.* 821 (1989).
71. R. Bayles and co-workers in Ref. 16, 190–195.
72. H. C. Neu, *Am. J. Med.* **78** (Supplement 6A), 33 (1985).
73. M. J. Basker, R. J. Boon, and P. A. Hunter, *J. Antibiot.* **33**, 878 (1980).
74. J. R. Knowles, *Acc. Chem. Res.* **18**, 97 (1985).
75. M. Sakamoto and co-workers, *J. Antibiot.* **32**, 272 (1979).
76. F. Kobayashi and co-workers, *Antimicrob. Agents Chemother.* **21**, 536 (1982).
77. Y. Kimura and co-workers, *J. Antibiot.* **35**, 32 (1982).
78. M. J. Basker and co-workers, *J. Antibiot.* **34**, 1224 (1981).
79. B. G. Spratt, V. Jobanputra, and W. Zimmerman, *Antimicrob. Agents Chemother.* **12**, 406 (1977).
80. H. C. Neu and P. Labthavikul, *Antimicrob. Agents Chemother.* **21**, 180 (1982).
81. S. R. Norrby, B. Björnegard, F. Ferber, and K. H. Jones, *J. Antimicrob. Chemother.* (Suppl. D), **12**, 109 (1983).
82. J. Birnbaum, F. M. Kahan, H. Kropp, and J. S. MacDonald in H. C. Neu, *Am. J. Med.* **78** (Suppl. 6A), 33 (1985).

83. S. R. Norrby and co-workers, *Antimicrob. Agents Chemother.* **23**, 300 (1983).
84. R. B. Woodward in J. Elks, ed., *Recent Advances in the Chemistry of β-Lactam Antibiotics*, The Chemical Society, 1977, 167–180.
85. I. Ernest and co-workers, *J. Am. Chem. Soc.* **100**, 8214 (1978).
86. K. Claues, D. Grimm, and G. Prossel, *Justus Liebigs Ann. Chem.*, 539 (1974).
87. M. Lang and co-workers, *Am. Chem. Soc.* **101**, 6296 (1979).
88. M. Lang, K. Prasad, J. Gosteli, and R. B. Woodward, *Helv. Chim. Acta* **63**, 1093 (1980).
89. Brit. Pat. 2,042,508A (1980), E. G. Brain (to Beecham Group, Ltd.).
90. Eur. Pat. 0,000,258 (1978), J. Gosteli, I. Ernest, M. Lang, and R. B. Woodward.
91. S. W. McCombie, *Tetrahedron Lett.* **22**, 3489 (1981).
92. U.S. Pat. 4,272,437 (1981), M. Ménard and A. Martel (to Bristol-Myers).
93. H. R. Pfaendler, J. Gosteli, and R. B. Woodward, *J. Am. Chem. Soc.* **101**, 6306 (1979).
94. F. DiNinno, T. R. Beattie, and B. G. Christensen, *J. Org. Chem.* **42**, 2960 (1977).
95. S. Karady, J. S. Amato, R. A. Reamer, and L. M. Weinstock, *J. Am. Chem. Soc.* **103**, 6765 (1981).
96. V. M. Girijavallabhan and co-workers, *Tetrahedron Lett.* **22**, 3485 (1981).
97. A. Yoshida and co-workers, *Chem. Pharm. Bull.* **29**, 2899 (1981).
98. T. Hayashi and co-workers, *Chem. Pharm. Bull.* **29**, 3158 (1981).
99. G. Franceschi and co-workers, *J. Antibiot.* **36**, 938 (1983).
100. M. Alpegiani and co-workers, *J. Am. Chem. Soc.* **107**, 6398 (1985).
101. M. Foglio and co-workers, *Heterocycles* **20**, 1491 (1983).
102. M. Foglio, G. Franceschi, C. Scarafile, and P. Zini, *Heterocycles* **16**, 1919 (1981).
103. M. Foglio, C. Battistini, F. Zarini, and G. Franceschi, *Heterocycles* **19**, 485 (1982).
104. M. Alpegiani and co-workers, *Tetrahedron Lett.* **24**, 1627 (1983).
105. N. F. Osborne and co-workers, *J. Chem. Soc., Chem. Commun.*, 371 (1989).
106. H. Yanagisawa, A. Ando, M. Shiozaki, and T. Hiraoki, *Tetrahedron Lett.* **24**, 1037 (1983).
107. S. Chackalamannil and co-workers, *J. Org. Chem.* **53**, 450 (1988).
108. G. I. Georg, J. Kant, and H. S. Gill, *J. Am. Chem. Soc.* **109**, 1129 (1987).
109. C. Battistini, C. Scarafile, M. Foglio, and G. Franceschi, *Tetrahedron Lett.* **25**, 2395 (1984).
110. A. Afonso and co-workers, *J. Am. Chem. Soc.* **104**, 6138 (1982).
111. A. Yoshida and co-workers, *Chem. Pharm. Bull.* **31**, 768 (1983).
112. E. Perrone and co-workers, *Tetrahedron Lett.* **25**, 2399 (1984).
113. A. J. Baker and M. J. Jenkins in Ref. 16, 259–272.
114. V. M. Girijavallabhan, A. K. Ganguly, P. Pinto, and R. Versace, *J. Chem. Soc., Chem. Commun.*, 908 (1983).
115. W. J. Leanza and co-workers, *Tetrahedron* **39**, 2505 (1983).
116. S. Hanessian, A. Bedeschi, C. Battistini, and N. Mongilli, *J. Am. Chem. Soc.* **107**, 1438 (1985).
117. N. Daniels, G. Johnson, and B. C. Ross, *J. Chem. Soc., Chem. Commun.*, 1006 (1983).
118. M. D. Cooke, K. W. Moore, B. C. Ross, and S. E. Turner, *J. Chem. Soc., Chem. Commun.*, 1005 (1983).
119. H. H. Wasserman and W. T. Han, *J. Am. Chem. Soc.* **107**, 1444 (1985).
120. J. Marchand-Brynaert, L. Ghosez, and E. Cossement, *Tetrahedron Lett.* **21**, 3085 (1980).
121. E. Perrone and co-workers, *Tetrahedron Lett.* **24**, 1631 (1983).
122. E. Perrone and co-workers, *J. Org. Chem.* **51**, 3413 (1986).
123. S. Oida and co-workers, *Chem. Pharm. Bull.* **28**, 3258 (1980).
124. G. Franceschi and co-workers, *J. Antibiot.* **37**, 685 (1984).
125. E. Perrone and co-workers, *J. Antibiot.* **39**, 1351 (1986).
126. F. DiNinno, D. A. Muthard, R. W. Ratcliffe, and B. G. Christensen, *Tetrahedron Lett.* **23**, 3535 (1982).
127. A. J. Baker, M. R. Teall, and G. Johnson, *Tetrahedron Lett.* **28**, 2283 (1987).
128. Y. Ueda and co-workers, *Can. J. Chem.* **60**, 904 (1982).
129. J. Banville, P. La Pointe, B. Belleau, and M. Ménard, *Can. J. Chem.* **66**, 1390 (1988).
130. J. Gosteli, W. Holick, M. Land, and R. B. Woodward in Ref. 21, 359–367.
131. S. W. McCombie and co-workers, *21st Interscience Conference on Antimicrobial Agents and Chemotherapy*, Abstract 830, Chicago, 1981, American Society for Microbiology, Washington, D.C., 1981.
132. Brit. Pat. Appl. 2,042,515 A (Sept. 24, 1980), M. Ménard and A. Martel (to Bristol-Myers).

133. M. J. Basker and N. F. Osborne, *J. Antibiot.* **43**, 70 (1990).
134. N. J. P. Broom, K. Coleman, P. A. Hunter, and N. F. Osborne, *J. Antibiot.* **43**, 76 (1990).
135. N. J. P. Broom and co-workers in Ref. 16, 247–258.
136. V. M. Girijavallabhan and co-workers, *J. Antibiot.* **39**, 1182 (1986).
137. V. M. Girijavallabhan and co-workers, *J. Antibiot.* **39**, 1187 (1985).
138. G. Emmer and co-workers, *J. Antibiot.* **38**, 1371 (1985).
139. M. Lang and co-workers, *J. Antibiot.* **40**, 217 (1987).
140. H. G. Capraro and co-workers, *J. Antibiot.* **41**, 759 (1988).
141. M. Ishiguro and co-workers, *J. Antibiot.* **41**, 1685 (1988).
142. M. Alpegiani, E. Perrone, and G. Franceschi, *Heterocycles* **27**, 49 (1988).
143. M. Alpegiani and co-workers, *Heterocycles* **27**, 1329 (1988).
144. O. Zak and co-workers, *J. Clin. Pharmacol.* **28**, 128 (1988).
145. I. Phillips, R. Wise, and H. C. Neu, eds., *J. Antimicrob. Chemother.* **9** (Suppl. C) (1982).
146. R. Wise and I. Phillips, eds., *J. Antimicrob. Chemother.* **15** (Suppl. C) (1985).
147. D. Reeves, D. Speller, R. Spencer, and P. J. Daly, eds., *J. Antimicrob. Chemother.* **23** (Suppl. C) (1989).
148. G. Seibert and co-workers, *J. Antibiot.* **40**, 660 (1987); N. Kesel and co-workers, *J. Antibiot.* **40**, 1184 (1987).
149. T. Nishino and co-workers, *J. Antibiot.* **42**, 977 (1989).
150. *26th Interscience Conference on Antimicrobial Agents and Chemotherapy*, Abstracts 630–645, New Orleans, 1986, American Society for Microbiology, Washington, D.C., 1986.
151. T. Gootz and co-workers, *Antimicrob. Agents Chemother.* **33**, 1160 (1989).
152. *29th Interscience Conference on Antimicrobial Agents and Chemotherapy*, Abstracts 85–87, Houston, 1989, American Society for Microbiology, Washington, D.C., 1989.
153. K. Coleman, D. R. J. Griffin, J. W. J. Page, and P. A. Upshon, *Antimicrob. Agents Chemother.* **33**, 1580 (1989).
154. *Scrip Review Issue*, 1989, p. 12.

General Reference

155. R. W. Ratcliffe and G. Albers-Schönberg, "The Chemistry of Thienamycin and Other Carbapenem Antibitotics" and I. Ernest, "The Penems" in R. B. Morin and M. Gorman, eds., *Chemistry and Biology of β-Lactam Antibiotics*, Academic Press, New York, 1982, Chapts. 4 and 5.

ROBERT SOUTHGATE
NEAL F. OSBORNE
SmithKline Beecham Pharmaceuticals (UK)

Related Articles

Antibiotics, survey; Cephalosporins