Nuclear analogs of β-lactam antibiotics. Synthesis of 6,6-disubstituted acylaminopenems[1]

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The preparation of 6α-methyl-2-methyl-6β-phenoxyacetamidopenem-3-carboxylate, 6α-methoxy-2-methyl-6β-phenoxyacetamidopenem-3-carboxylate, and 6α-methoxy-2-methyl-6β-phenylmalonylamidopenem-3-carboxylate from penicillin V and 6-aminopenicillanic acid is described. These penems have been isolated and characterized as their sodium or potassium salt. The chemical stability of the above compounds was determined as their half-life in aqueous buffer. In this way, it was found that the 6α-methyl analog was more stable than the parent 6-monosubstituted acylaminopenem while the remaining analogs were of comparable stability.

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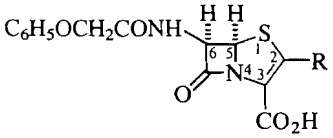
On décrit la préparation du méthyl-6α méthyl-2 phénoxyacétamido-6β pénemcarboxylate-3, du méthoxy-6α méthyl-2 phénoxyacétamido-6β pénemcarboxylate-3 et du méthoxy-6α méthyl-2 phénylmalonylamido-6β carboxylate-3 à partir de la pénicilline V et de l'acide amino-6 pénicillanique. Ces pénems ont été isolés et caractérisés sous forme de sels de sodium ou de potassium. La demi-vie de ces produits dans un tampon aqueux indique leur stabilité chimique. On a trouvé, de cette façon, que l'analogue méthyl-6α est plus stable que l'acylaminopénem monosubstitué en position 6 tandis que les deux autres analogues ont une stabilité comparable.

The first penems to be synthesized by Woodward and co-workers (1) were acylaminopenem-3-carboxylic acids of the type **1** (R = H, Me, Ph). These compounds were found to be quite unstable and had little antibacterial activity. Since the 6-unsubstituted penems **2***a* (2) and especially the penems **2***b* (3) having the 6-hydroxyethyl substitution of thienamicin (4) were chemically more stable and had a more interesting spectrum of biological activity, little attention has been given to the preparation of 6-acylamino penems. It has been shown that the introduction of a substituent, especially a methoxyl group, at the 6 or 7 position of, respectively, a penicillin or a cephalosporin results in an improvement in the chemical and enzymatic stability (3*b*). To see what effect a 6-substituent would have on the stability and activity of a 6-acylamino penem, we undertook the synthesis of penems **3***a* and **3***b*. As well, the effects of different acyl groups in the 6-acylamino side chain (**3***c*) were examined. When we initiated this study, none of these products had been reported in the literature. Recently, though, the preparation of the protected 6α-methoxy-2-methyl-6β-phenoxyacetamido penem-3-carboxylate **16** has been described (5). However, in this case, the corresponding deprotected penem could not be obtained. We were able to prepare and characterize the deprotected 6,6-disubstituted penems **3***a*, **3***b*, and **3***c*, using Woodward's approach (1) for the preparation of 6-acylamino penems from penicillin V.



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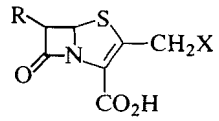
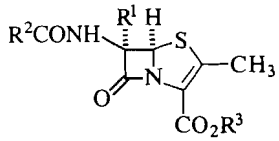


2 *a*, R = H
b, R = CH_3CHOH (*trans R*)



3 *a*, $R^1 = CH_3$, $R^2 = C_6H_5OCH_2$, R^3 = Na or K
b, $R^1 = OCH_3$, $R^2 = C_6H_5OCH_2$, R^3 = Na
c, $R^1 = OCH_3$, $R^2 = C_6H_5CHCO_2Na$, R^3 = Na

The first compound to be prepared by the above mentioned approach was the 6α-methyl-2-methyl-6β-phenoxyacetamido-penem-3-carboxylate **3***a*. In the case of penicillin, the introduction of an α-methyl group had a marked effect on the chemical stability of the β-lactam ring (6). The rate of the basic hydrolysis of 6-methyl-penicillin V methyl ester is four times slower than the unsubstituted compound.

The presence of the α-methyl group did not introduce a major problem, since the configuration at positions 5 and 6 of the penicillin nucleus is the same in the penem. The introduction of a 6α-alkyl substituent via a Schiff base is a well-documented process in penicillin chemistry (6, 7) and we used this approach. First, *N*-benzylidene-6-aminopenicillanic acid **4***a* (7*a*) was protected as its methyl ester **4***b* by treatment with diazomethane. Then, to introduce the 6-methyl group, we found Bohme's procedure (6) (potassium *tert*-butoxide, methyl iodide) to be the most satisfactory. Removal of the benzylidene group from **4***c* by exchange with 2,4-DNPH·TSOH in ethanol (7*c*) followed by acylation with phenoxyacetyl chloride gave the acylated compound **5***a* in a 59% yield from **5***c*. This compares favorably with the results of Dolfini and co-workers (6) who reported a 23% yield of acylated material by direct acylation of the Schiff base. The next step required oxidation of the sulfur of the thiazolidine ring and subsequent opening of this ring. Oxidation of **5***a* with *m*-chloroperbenzoic acid gave in high yield (90%) the two isomeric sulfoxides **5***b* and **5***c* (ratio 76:24 respectively) and these were separated by chromatography. Based on previous proton nmr studies (8) of penicillin "*R*" and "*S*" sulfoxides, the major isomer **5***b* was assigned the *S* stereochemistry and

[1]Work presented at the 67th Annual CIC Conference held in Montreal, June 3–6, 1984.

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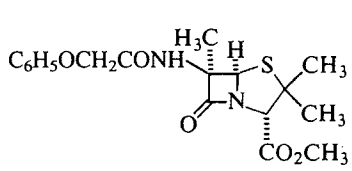
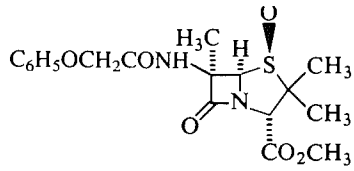
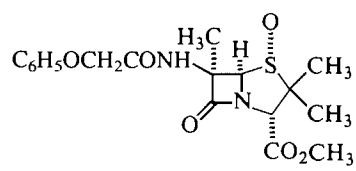
TABLE 1. ^{1}H magnetic resonance of the sulfoxides **5***b* and **5***c* (60 MHz, $CDCl_3$, chemical shift values in ppm)



5*a*

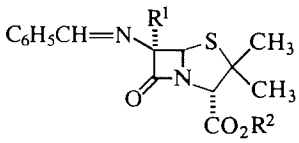


5*b* *S*

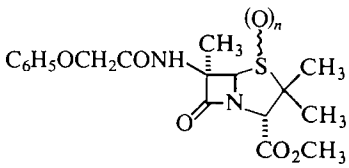


5*c* *R*

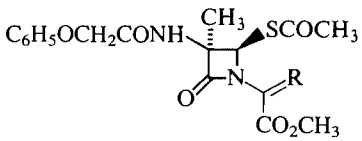
CH_3-2	1.45 and 1.48	1.25 and 1.70	1.30 and 1.66
H-3	4.41	4.63	4.53
H-5	5.43	4.83	4.56
CH_3-6	1.85	1.91	1.80
CH_2	4.5	4.51	4.53
C_6H_5	6.7–7.4	6.8–7.5	6.8–7.5
CO_2CH_3	3.78	3.85	3.83



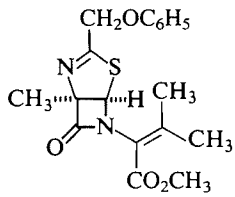
4 *a*, $R^1 = R^2 = H$
b, $R^1 = H$, $R^2 = CH_3$
c, $R^1 = R^2 = CH_3$



5 *a*, $n = 0$
b, $n = 1$ β-sulfoxide *S*
c, $n = 1$ α-sulfoxide *R*



6 *a*, R = =C(CH3)2
b, R = O
c, R = $P(C_6H_5)_3$



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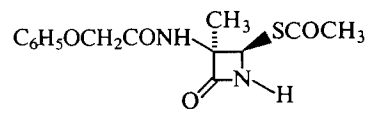
the minor, more polar, isomer **5***c* the *R* stereochemistry. Specifically, a downfield shift for the proton at position 3 due to a "*syn*-axial" effect (8*c*) is observed in the case of *S* isomer **5***b* (Table 1). Also, as has been noted by Barton for the 6-monosubstituted sulfoxides, the H-5 proton in both 6-disubstituted sulfoxides shows an upfield shift that is greater in the case of the *R* isomer. The latter upfield shift was attributed to shielding brought about by a *trans* orientation of the H-5 proton with respect to the lone pair of the sulfur atom.

We found that the two isomeric sulfoxides, **5***b* and **5***c*, behaved differently when subjected to ring-opening conditions (acetic anhydride, trimethylphosphite (9)). The major *S* isomer **5***b* reacted more slowly (105°C, 10 h) than the *R* isomer **5***c* and gave, after isomerization of the butenoate double bond with triethylamine, the thioester **6***a* in less than 30% yield. The main product isolated from this reaction was the thiazoline **7**. However, when the *R* sulfoxide **5***c* was subjected to the same conditions, the rearrangement was complete in 2 h and **6***a* was obtained in a 45% yield after isomerization. In this case, the thiazoline **7** was formed in trace amounts only.

To increase the proportion of the *R* sulfoxide **5***c* in the oxidation of **5***a*, different oxidizing agents were examined (Table 2). When sodium periodate was used, the ratio of *R* to *S* was lowered to 17:83. However, when the oxidation was conducted with ozone in a mixture of acetone and water (10), the *R* sulfoxide **5***c* predominated (ratio *R*:*S* > 95:5 by ^{1}Hmr). Steric effects direct the approach of the ozone molecule, and the α-methyl group seems to enhance this effect.

The butenoate **6***a* was then cleaved with ozone and the resulting alkoxalyl derivative **6***b* treated with methanol to give the azetidinone **8** in a 50% yield from **6***a*. The phosphorane **6***c* was obtained using Woodward's original procedure. Reaction of **8** with *p*-nitrobenzyl glyoxylate afforded a diastereomeric mixture of hemiaminals **9***a*, which, upon successive treatment with thionyl chloride and triphenyl phosphine, gave the phosphorane **6***c* in a 45% overall yield from **8**. Upon being heated in toluene at 100°C for 48 h, the phosphorane **6***c* was smoothly converted to the penem **10** in a 72% yield after chromatography.



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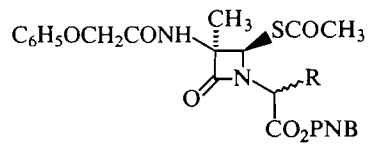
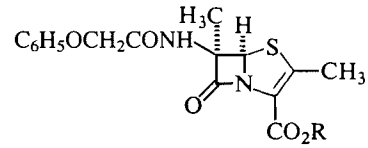
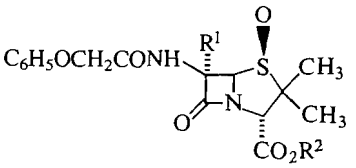


9 *a*, R = OH
b, R = Cl

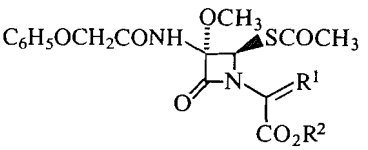


10 R = PNB
3*a* R = Na, K

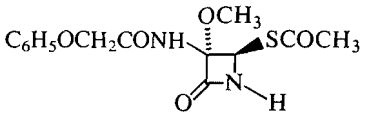
Hydrogenolysis of the *p*-nitrobenzyl ester in a two-phase system consisting of ether, tetrahydrofuran, and an aqueous phosphate buffer gave the penem as the salt **3***a* (40% yield after purification by reversed phase column chromatography). No attempt has been made to prepare the carboxylic acid. The ultraviolet spectrum of **3***a* possesses the characteristic absorption of



11 *a*, R^1 = H, R^2 = CH_3
b, R^1 = OCH_3, R^2 = CH_3
c, R^1 = H, R^2 = PNB
d, R^1 = OCH_3, R^2 = PNB



12 *a*, R^1 = $=C(CH_3)_2$, R^2 = CH_3
b, R^1 = $=C(CH_3)_2$, R^2 = PNB
c, R^1 = O, R^2 = CH_3
d, R^1 = O, R^2 = PNB
e, R^1 = $P(C_6H_5)_3$, R^2 = PNB



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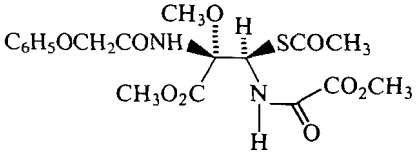

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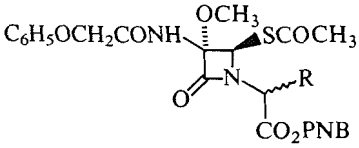
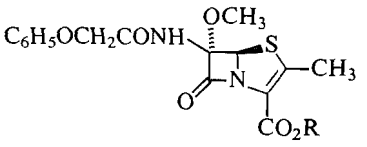


15 *a*, R = OH
b, R = Cl



16 R = PNB
3*b* R = Na

PNB = *p*-nitrobenzyl

TABLE 2. Stereochemistry of the oxidation of **5***a* in **5***b* and **5***c*

Oxidizing agent	Ratio **5***b* (*S*):**5***c* (*R*)
m-Chloroperbenzoic acid	76:24
$NaIO_4$	83:17
O_3	<5 : >95

penems at 297 nm, and the absorption of 1770 cm^{-1} in the infrared spectrum is characteristic of a strained β-lactam.

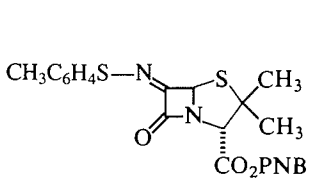
The 6-methoxy penem **3***b* was obtained by a route similar to that described for the 6-methyl penem. Numerous methods for the introduction of a 6β or a 7β methoxy substituent into, respectively, a penicillin or a cephalosporin have been described (11). In this case, the 6-methoxy penicillins **11***a* and **11***c* were chosen as starting materials. The two 6β-methoxy sulfoxides **11***b* (42%) and **11***d* (12) (71%), were readily obtained via the procedure of Koppel and Koehler (13). Opening of the thiazoline ring of **11***b* and **11***d* followed by isomerization under basic conditions gave the two azetidinones **12***a* (60%) and **12***b* (55%). These were then treated with ozone to give the respective alkoxalyl derivatives, **12***c*, (97%) and **12***d* (85%). Methanolysis of the alkoxalyl derivative **12***c* under neutral conditions gave only traces of the desired azetidinone **13**. The major product that was obtained was the ring-opened product **14**. Even methanolysis at −20°C in the presence of a catalytic amount of triethylamine resulted in opening of the β-lactam ring. However, in the presence of aqueous acid (THF, 1 N HCl), **12***c* was slowly converted to the azetidinone **13** (40% completion after 8 h; evaluated by ^{1}Hmr) and the latter could be isolated in a 36% yield.

A more convenient route to the hemiaminal **15***a* was by the direct reduction of the alkoxalyl **12***c* with diborane (1). Treatment of **15***a* with thionyl chloride and pyridine followed by triphenylphosphine and 2,6-lutidine gave the phosphorane **12***e* in 12% overall yield from **12***b*. Cyclization of **12***e* was effected by heating in toluene to give the crystalline penem **16** in a 55% yield. Hydrogenolysis of the *p*-nitrobenzyl ester **16** was conducted as before to give the deprotected penem **3***b* (61%). This material was purified by chromatography on reversed phase silica gel and the lyophilized, amorphous product showed reasonable stability at room temperature. Its ultraviolet (297 nm) and infrared (1759 cm^{-1}) spectra are consistent with the proposed structure.

We were also interested in the effect produced by varying the acylamino substituents of those penems. The combination of a methoxyl group with an α-carboxythienyl-acetamido group (as in temocillin) or various arylmalonylamino groups at position 6 of penicillins results in compounds that have very interesting antibacterial activity (11*a*, pp. 326–364; 14). However, because the thienyl moiety was not compatible with the ozonolysis step in our synthetic scheme, we undertook the preparation of the 6α-methoxy-6-phenylmalonylamidopenem **3***c*.

Our first approach to the preparation of **3***c* was to take advantage of the various intermediates that had been generated in the synthesis of the phenoxyacetamido penem **3***b*. Direct cleavage of the acylamino side chain followed by introduction of the desired acyl group was not examined because racemization problems at position 7 were encountered when this was attempted in the case of the cephamycins (15). The possibility of trans-acylation was examined. However, attempts to convert **12***b* into its diacylated derivative by treatment of this material with an acid chloride in presence of an acid scavenger (16) were not successful. Accordingly, introduction of the phenylmalonyl group at an earlier stage of the synthesis was examined.

The possible introduction of the desired acyl side chain via a sulfenimine intermediate as described by Gordon *et al.* (17) was then examined. Indeed, reaction of the sulfenimine **17** with triphenylphosphine and mercuric acetate in methanol followed by acylation with phenylmalonyl chloride mono-*p*-nitrobenzyl ester gave **18** (63%). Oxidation of **18** with *m*-chloroperbenzoic acid gave the two isomeric sulfoxides **19***a* and **19***b* in a 19:9 ratio (93%). The two sulfoxides were also a mixture of epimers at the malonyl center.



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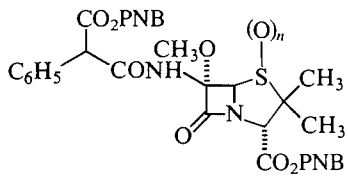
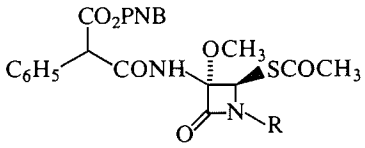


18 $n = 0$
19 *a*, $n = 1$, α-sulfoxide
b, $n = 1$, β-sulfoxide



20 *a*, R = $COCO_2PNB$
b, R = H
c, R = $CHOHCO_2PNB$

The oxalimide **20***a* and the azetidinone **20***b* could be obtained in a similar manner to that described for the preparation of the phenoxyacetamido derivative **13**. However, all subsequent attempts to obtain the phosphorane analog of **12***e* were unsuccessful. That is, reduction of the oxalimide **20***a* to **20***c* ($NaBH_4$–AcOH (18), since diborane reduction did not work in this case), followed by reaction with thionyl chloride and triphenylphosphine, only resulted in the formation of decomposition products no longer containing a β-lactam ring. Furthermore, the hemiaminal **20***c* could not be obtained by reaction of **20***b* with *p*-nitrobenzyl glyoxylate due to the instability of the β-lactam ring under the reaction conditions.

We then turned to examining alternative methods for the preparation of the penem nucleus. After considering the available methods (19), Betty's procedure involving 1,5 ring closure (20) of the penem by nucleophilic attack of sulfur at C-4 of an azetidinone was considered most promising. This method required the specific formation of the 4α-chloroazetidinone **24**, which should then be closed to the penem having the correct stereochemistry at position 5.

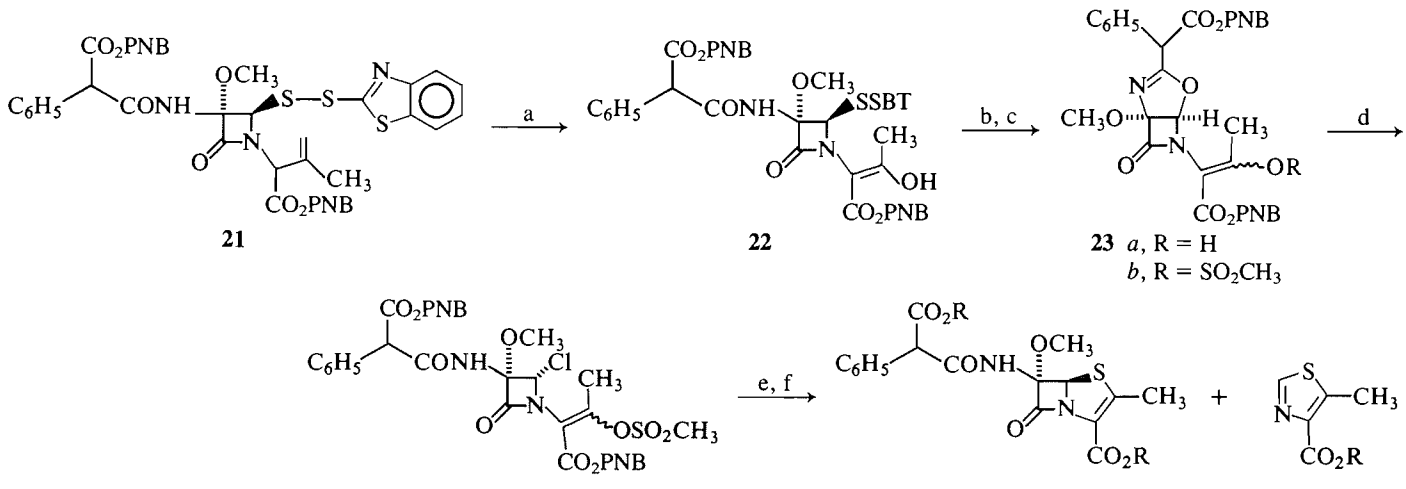
Heating the mixture of sulfoxides **19***a* and **19***b* with 2-mercaptobenzothiazole gave the disulfide **21** (Scheme 1). Ozonolysis of the terminal olefin gave the enol **22**, which was then treated with triphenylphosphine to form the oxazoline **23***a*. This product was more easily purified as the mesylate **23***b*, which was obtained in a 39% overall yield from **19**. Ring opening of the oxazoline with hydrochloric acid gave only one product, the α-chloroazetidinone **24** in 48% yield. Attack by the chloride ion on the less encumbered α face of the oxazoline results in the formation of the α-chloro isomer.

Reaction of this chloroazetidinone **24** with hydrogen sulfide and triethylamine gave the penem **25** in a low yield (25%). This penem, like most of the intermediates in this sequence, was relatively unstable on silica gel and was obtained contaminated with the degradation product, the thiazole **26***a*. Simultaneous deprotection of both ester groups by hydrogenolysis gave the penem **3***c* as its sodium salt (30% yield after chromatography on reversed phase silica gel). This product was also contaminated by the thiazole **26***b* (ratio of penem to thiazole, 75:25 by ^{1}Hmr). The malonyl penem was more unstable than the two that had been previously prepared and, even as a dry powder, underwent decomposition over the period of a few days. The carbonyl frequency of the β-lactam is at 1765 cm^{-1} and the proton nmr indicated a 1:1 mixture of epimers at the malonyl side chain.

The half-life in a pH 7.4 buffer solution at 37°C of the penems prepared above is a good indication of their chemical stability (3*a*). The parent 6-monosubstituted acylaminopenem **1** (R = CH_3) prepared by Woodward has a half-life of 1.5 h under these conditions. The 6α-methoxypenems **3***b* and **3***c* were comparable, having half-lives of 1.2 and 1.6 h respectively. Introduction of a 6α-methoxy group did not seem to have much of an effect on the stability of the penem. However, the 6α-methyl group did, since the 6α-methylpenem **3***a* had a half-life of 12 h under these conditions. This greater stability is also reflected in the ease with which this compound could be synthesized relative to the α-methoxy analogs. In vivo, all three penems **3***a*, **3***b*, and **3***c* showed only weak activity against Gram-positive and Gram-negative strains of bacteria.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are not corrected. The ultraviolet spectra were recorded



21 22 23 *a*, R = H; *b*, R = SO_2CH_3 24 25 R = PNB; 3*c* R = Na 26 *a*, R = PNB; *b*, R = Na

(a) O_3; Me_2S; (b) $P(Ph)_3$; (c) CH_3SO_2Cl; (d) HCl; (e) H_2S, Et_3N; (f) H_2, Pd/C

SCHEME 1

on a Pye Unicam SP8-100 uv/vis spectrophotometer. The infrared spectra were recorded on a Perkin–Elmer 267 grating infrared spectrophotometer. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter. The ^{1}H nuclear magnetic resonance spectra were taken with either a Varian EM-360 (60 MHz) or a Varian CFT-20 (80 MHz) nmr spectrometer. Tetramethylsilane was employed as the internal standard and chemical shifts were reported in parts per million (δ) relative to the internal standard. Tetrahydrofuran was freshly distilled from lithium aluminum hydride. Solvents were reagent grade and had been stored over molecular sieves (4Å) before use. *p*-Nitrobenzyl glyoxylate (21) was prepared from di-*p*-nitrobenzyl fumarate by ozonolysis (CH_2Cl_2, −78°C) followed by reduction with dimethyl sulfide (22). *p*-Nitrobenzyl 6-phenoxyacetamidopenicillanate-1-β-oxide **11***c* was obtained by esterification of the potassium salt of penicillin V with *p*-nitrobenzyl bromide followed by oxidation with *m*-chloroperbenzoic acid by a method similar to the one described by Baldwin and Abraham and co-workers (27). Column chromatography was carried out on silica gel (230–400 mesh, Merck) or on reversed phase silica gel (μ-Bondapak C_{18}, 55–105 μm, Waters) for the penem salts **3***a*, **3***b*, and **3***c*. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois, U.S.A. The half-lives of the penems **3***a*, **3***b*, and **3***c* were determined by uv at 37°C for 10^{-4} M solutions using the method of Woodward (3*a*).

Methyl N-*benzylidene-6-aminopenicillanate (***4**b*) (7*b*)*

A suspension of *N*-benzylidene-6-aminopenicillanic acid (**4***a*) (7*a*) (108.0 g, 0.375 mol) in ether (2.1 L) was cooled to 5°C and treated dropwise with a cold solution of diazomethane (18 g, 0.43 mol, prepared from Diazald, Aldrich Chemical Co.) in ether (1.5 L). The solution obtained was then concentrated under vacuum and the residual solid was triturated with cold hexanes to give 102.7 g (86%) of the title material **4***b* as a white solid; ir (Nujol) ν_{max}: 1760 (C=O β-lactam), 1740 (CO ester), and 1635 (C=N) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 1.51 and 1.68 (2s, 2 × 3H, CH_3-2), 3.85 (s, 2H, CO_2CH_3-3), 4.43 (s, 1H, H-3), 5.37 (dd, J = 2 Hz, J = 4 Hz, 1H, H-6), 5.63 (d, J = 4 Hz, H-5), 7.3–7.9 (m, 5H, aromatic), and 8.65 (d, J = 2 Hz, 1H, CH=N) ppm.

Methyl N-*benzylidene-6-amino-6α-methylpenicillanate (***4**c*) (6)*

A solution of methyl *N*-benzylidene-6-aminopenicillanate (**4***b*) (102.5 g, 0.32 mol) in dry 1,2-dimethoxyethane (1.4 L) was cooled to −40°C and treated with iodomethane (320 mL). Potassium *tert*-butoxide (36.3 g, 0.32 mol) was then added in portions over 5 min and the mixture was stirred at −40°C for 2 h. The red solution was then diluted with CH_2Cl_2 (2 L) and washed several times with water and brine. The organic phase was dried ($MgSO_4$) and evaporated to give 106 g (100%) of an oil, which solidified upon standing. This material was used as such for the next step: ir (Nujol) ν_{max}: 1765 (C=O β-lactam), 1750 (C=O ester), and 1635 (C=N) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 1.43 and 1.52 (2s, 2 × 3H, CH_3-2), 1.78 (s, 3H, CH_3-6), 3.77 (s, 3H, CO_2CH_3-3), 4.30 (s, 1H, H-3), 5.3 (s, 1H, H-5), 7.2–7.8 (m, 5H, aromatic), and 8.63 (s, 1H, CH=N) ppm.

*Methyl 6α-methyl-6-phenoxyacetamidopenicillanate (***5**a)*

A mixture of *p*-toluenesulfonic acid monohydrate (61.4 g, 0.32 mol) and finely ground 2,4-dinitrophenylhydrazine (75.8 g, containing 20% water) in anhydrous EtOH (1.4 L) was stirred at 22°C for 30 min. Then a solution of **4***c* (106.0 g, 0.32 mol) in EtOH (1 L) was added and the heterogenous mixture was stirred for 50 min. The solid formed was filtered and washed with EtOH. The filtrate and the washings were concentrated under vacuum to give a solid. Trituration with ether and filtration gave 127.7 g of the intermediate methyl 6α-methyl-6β-aminopenicillanate *p*-toluenesulfonate salt. The salt was dissolved in CH_2Cl_2 (1.4 L), cooled to 0°C, and treated successively with a solution of phenoxyacetyl chloride (60.5 g, 0.355 mol) in CH_2Cl_2 (0.5 L) and a solution of KH_2PO_4 (155 g) in cold water (1.4 L). The mixture was stirred vigorously for 30 min at 5°C, treated with pyridine (29 mL), and stirred for another 15 min. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with cold HCl (0.1 N), saturated $NaHCO_3$, and then brine. After drying (Na_2SO_4), evaporation of the solvent gave an oil, which was purified by filtration through a short pad of silica gel (500 g) followed by high-pressure liquid chromatography (hplc, Waters Associates Prep LC/system 500 using PrepPak-500/silica cartridges, elution CH_2Cl_2:EtOAc, 9:1). The title compound **5***a* was obtained as a pale yellow foam: 71.6 g (59%) (lit. (6) 23% by direct acylation of the Schiff base). The spectral data were in accordance with those already described.

*Methyl 6α-methyl-6-phenoxyacetamidopenicillanate-1β- and -1α-oxide (***5**b and **5**c)*

Method A: Oxidation with m-*chloroperbenzoic acid*

A solution of methyl 6α-methyl-6-phenoxyacetamidopenicillanate **5***a* (2.30 g, 6.1 mmol) in CH_2Cl_2 (30 mL) was cooled in an ice–water bath and treated dropwise with a solution of *m*-chloroperbenzoic acid (1.23 g of 85%, 6.1 mmol) in CH_2Cl_2 (15 mL). After 30 min at 5°C, the mixture was washed successively with cold 5% $NaHCO_3$, brine, and then dried ($MgSO_4$). The oil obtained after evaporation of the solvent was chromatographed on silica gel (100 g) using a mixture of toluene and ethyl acetate (gradient 8:2 to ethyl acetate). The β-sulfoxide **5***b* eluted first and was obtained as a white foam: 1.60 g (68%); $[\alpha]_D^{25}$ +284° (*c* 1.0, $CHCl_3$); ir (film) ν_{max}: 3300 (NH), 1780 (C=O β-lactam), 1750 (C=O ester), 1665 and 1520 (amide), and 1050 (S—O) cm^{-1}.

The more polar α-sulfoxide **5***c* was obtained as a solid, which was recrystallized from a mixture of ethyl acetate and hexanes to give 0.50 g (21%) of a white solid: mp 109–110°C; $[\alpha]_D^{25}$ +155° (*c* 1.0, $CHCl_3$); ir (KBr) ν_{max}: 3400 (NH), 1790 (C=O β-lactam), 1750 (C=O ester), 1670 and 1520 (amide), and 1050 (S—O) cm^{-1}. *Anal.* calcd. for $C_{18}H_{22}N_2O_6S$: C 54.81, H 5.62, N 7.10, S 8.13; found: C 54.63, H 5.57, N 7.55, S 8.10.

Method B: Oxidation with sodium metaperiodate

A solution of **5***a* (0.115 g, 0.3 mmol) in MeOH (1 mL) was cooled in an ice–water bath and treated with a solution of $NaIO_4$ (0.064 g, 0.30 mmol) in water (0.2 mL). The resulting mixture was slowly warmed up to 22°C and stirred for 18 h. The precipitate that formed was filtered and washed with MeOH. Evaporation of the filtrate gave the sulfoxide as a foam. The ^{1}Hmr of the crude product indicated that an 83:17 mixture of β- and α-sulfoxides had been obtained.

Method C: Oxidation with ozone

A solution of **5***a* (71.6 g, 0.189 mol) in a mixture of acetone–water (1:1, 1 L) was cooled to 0–5°C and treated with a stream of ozone until the starting material disappeared (tlc). The solution was then flushed with N_2 and extracted with CH_2Cl_2 (1 L). The aqueous phase was extracted twice with CH_2Cl_2 (100 mL) and then the combined organic phases washed successively with 3% aqueous sodium thiosulfate and brine. After drying (Na_2SO_4), evaporation of the solvent gave a solid that was triturated with hexanes to give 61.0 g (82%) of the α-sulfoxide **5***c*. The β-sulfoxide was not detected by ^{1}Hmr (60 MHz).

*Methyl α-(4*R*-acetylthio-3*R*-methyl-3-phenoxyacetamido-2-azetidinon-1-yl)-β-methylcrotonate* **6**a)*

A. By rearrangement of the α-sulfoxide **5**c*

A solution of methyl 6α-methyl-6-phenoxyacetamidopenicillanate 1α-oxide **5***c* (10.0 g, 25.4 mmol) in toluene (250 mL) was treated with acetic anhydride (20 mL, 0.21 mol) and trimethyl phosphite (9.25 g, 74.5 mmol) and then heated at 85°C for 3 h. The solvent and excess reagents were evaporated *in vacuo* and the last traces of reagents removed by coevaporation with toluene. The residual oil was diluted with ethyl acetate (100 mL), washed with water, cold 5% $NaHCO_3$, and brine, and dried ($MgSO_4$). The solution was concentrated to approximately 20 mL, cooled in an ice–water bath, and then treated with triethylamine (0.8 mL, 5.7 mmol). After 4 h at 0–5°C, the reaction mixture was diluted with ethyl acetate (100 mL), washed with cold 5% aqueous AcOH, 5% $NaHCO_3$, and brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed on silica gel (400 g) using a mixture of CH_2Cl_2 and ethyl acetate (4:1) as eluent. The title material **6***a* was obtained as a clear oil: 4.80 g (45%); ir (film) ν_{max}: 1775 (C=O β-lactam), 1720 (sh C=O ester), 1690 (C=O amide and thioester), and 1520 (amide) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 1.76 (s, 3H, CH_3-3 of azetidinone), 2.16, 2.23, and 2.26

(3s, 3 × 3H, CH_3 of crotonate and $SCOCH_3$-4 of azetidinone), 3.81 (s, 3H, CO_2CH_3), 4.5 (s, 2H, CH_2 of phenoxyacetyl), 5.66 (s, 1H, H-4 of azetidinone), and 6.7–7.5 (m, 6H, aromatic and NH) ppm.

B. By rearrangement of the β-sulfoxide **5**b

A solution of the β-sulfoxide **5***b* (0.175 g, 0.44 mmol) in toluene (1.5 mL) was treated with trimethyl phosphite (0.15 mL) and acetic anhydride (0.27 mL) and heated at 105°C for 10 h. After work-up and isomerization as above, chromatography on silica gel gave 0.080 g (43%) of thiazoline **7** as an oil and 0.055 g (30%) of the thioester **6***a*. Thiazoline **7**: ir (film) ν_{max}: 1700 (C=O β-lactam), 1715 (C=O ester), 1650 and 1595 cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 1.56, 1.73, and 2.16 (3s, 3 × 3H, CH_3 of crotonate and CH_3-3 of azetidinone), 3.70 (s, 3H, CO_2CH_3), 4.7 (s, 2H, CH_2 of phenoxyacetyl), 5.70 (s, 1H, H-4 of azetidinone), and 6.8–7.3 (m, 5H, aromatic) ppm.

N-*Methoxalyl-4*R-*acetylthio-3*R-*methyl-3-phenoxyacetamido-2-azetidinone* **6**b

A solution of methyl α-(4*R*-acetylthio-3*R*-methyl-3-phenoxyacetamido-2-azetidinon-1-yl)-β-methylcrotonate **6***a* (4.20 g, 10.0 mmol) in a mixture of CH_2Cl_2 (100 mL) and MeOH (25 mL) was cooled to −25°C and treated with ozone until a light blue color persisted. The reaction mixture was then flushed with N_2, treated with methyl sulfide (2.5 mL), and allowed to warm up to 22°C. The mixture was diluted with CH_2Cl_2 (100 mL), washed successively with 3% aqueous sodium bisulfite and brine, and dried ($MgSO_4$). Evaporation of the solvent gave 4.0 g of the crude *N*-methoxalylazetidinone **6***b* as white foam. This product was used as such for the next step: ir (film) ν_{max}: 1815 and 1750 (C=O), 1700 (br, C=O ester, amide and thioester), and 1520 (C=O amide) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 1.80 (s, 3H, CH_3-3), 2.33 (s, 3H, $SCOCH_3$-4), 3.93 (s, 3H, CO_2CH_3), 4.56 (s, 2H, CH_2 of phenoxyacetyl), 5.80 (s, 1H, H-4), and 6.8–7.4 (m, 6H, NH and aromatic) ppm.

*4*R-*Acetylthio-3*R-*methyl-3-phenoxyacetamido-2-azetidinone* **8**

A solution of the crude *N*-methoxalyl azetidinone **6***b* (4.0 g) in a mixture of MeOH (300 mL), EtOAc (30 mL), and water (6 mL) was stirred at 22°C for 18 h. The solvent was then concentrated *in vacuo* and the residue was partitioned between EtOAc (150 mL) and water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product that was chromatographed on silica gel (75 g). Elution with toluene–EtOAc (1:2) gave 1.53 g (50%) of the azetidinone **8** as a white solid. Recrystallization from EtOAc gave white needles: mp 118–119°C; $[\alpha]_D^{22}$ −20° (*c* 1.0, $CHCl_3$); ir (KBr) ν_{max}: 3320 (NH), 1780 (C=O β-lactam), 1680 and 1660 (C=O amide and thioester), and 1520 (C=O amide) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 1.77 (s, 3H, CH_3-3), 2.32 (s, 3H, $SCOCH_3$-4), 4.54 (s, 2H, CH_2 of phenoxyacetyl), 5.41 (s, 1H, H-4), 6.1 and 6.7 (bs, 2 × 1H, NH), and 6.8–7.5 (m, 5H, aromatic) ppm. *Anal.* calcd. for $C_{14}H_{16}N_2O_4S$: C 54.53, H 5.23, N 9.08, S 10.40; found: C 54.64, H 5.21, N 9.04, S 10.11.

p-*Nitrobenzyl (4*R-*acetylthio-3*R-*methyl-3-phenoxyacetamido-2-azetidinon-1-yl)triphenylphosphoranylidene acetate* **6**c

A suspension of azetidinone **8** (1.53 g, 4.96 mmol) and *p*-nitrobenzyl glyoxylate monohydrate (1.25 g, 5.46 mmol) in CH_2Cl_2 (30 mL) was cooled to 0–5°C and treated with triethylamine (35 μL, 0.25 mmol). After 1 h, the resulting solution was diluted with CH_2Cl_2, and washed with cold 0.1 N HCl and brine. After drying ($MgSO_4$), evaporation gave 2.7 g of the crude hemiaminal **9***a* as an oil; ir (film) ν_{max}: 3300 (br), 1770 (C=O β-lactam), 1690 (C=O), and 1520 (C=O amide) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) (mixture of two diastereoisomers in a 1:1 ratio) δ: 1.69 and 1.73 (2s, 3H, CH_3-3 of azetidinone), 2.22 and 2.32 (2s, 3H, $SCOCH_3$), 4.54 (s, 2H, CH_2 of phenoxyacetyl), 5.35 (m, 2H, CH_2 of *p*-nitrobenzyl), 5.52 and 5.55 (2s, 1H, H-4 of azetidinone), 6.7 (br s, 1H, NH), and 6.9–8.3 (m, 9H, aromatic) ppm.

Thionyl chloride (0.38 mL, 5.26 mmol) was added dropwise over 5 min to a cooled (−20°C) solution of the crude hemiaminal **9***a* (2.7 g) and pyridine (0.45 mL, 5.56 mmol) in dry tetrahydrofuran (60 mL). After 15 min, the white precipitate that formed was filtered on a Celite pad and washed with benzene. The filtrate and washings were combined and concentrated *in vacuo*. The residue was rapidly purified on a silica gel pad (40 g) using a mixture of CH_2Cl_2:EtOAc, 3:1, as eluent. Evaporation gave 2.39 g (85% from **8**) of *p*-nitrobenzyl (4*R*-acetylthio-3*R*-methyl-3-phenoxyacetamido-2-azetidinon-1-yl) chloro acetate **9***b* (4:3 mixture of diastereoisomers by ^{1}Hmr) as a clear oil: ir (film) ν_{max}: 1790, 1770 (C=O), 1690 (C=O amide and thioester), and 1520 (amide) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 1.72 (s, 3H, CH_3-3 of azetidinone), 2.21 and 2.31 (2s, 3H, $SCOCH_3$), 4.55 (s, 2H, CH_2 of phenoxyacetyl), 5.32 and 5.38 (2s, 2H, CH_2 of *p*-nitrobenzyl), 5.66 and 5.77 (2s, 1H, H-4 of azetidinone), 6.16 and 6.26 (2s, 1H, H-2 of acetate), 6.6 (br s, 1H, NH), and 6.8–8.2 (br s, 1H, NH) ppm.

A solution of the epimeric chloro compounds **9***b* (0.95 g, 1.77 mmol) in dry tetrahydrofuran (50 mL) was treated with triphenylphosphine (1.0 g, 3.81 mmol) and 2,6-lutidine (0.25 mL, 2.14 mmol) and the resulting mixture was heated at 50°C under N_2 for 66 h. The solvent was then evaporated and the residue dissolved in EtOAc (200 mL). The solution was washed successively with cold 0.1 N HCl, cold 1% $NaHCO_3$, and brine, and dried ($MgSO_4$). Evaporation and chromatography of the residue on silica gel (40 g, elution with toluene:EtOAc 1:1–1:3) gave 1.20 g (88%) of the title phosphorane **6***c* as an oil: ir (film) ν_{max}: 1770 (C=O β-lactam), 1690 (br), 1620 (br), and 1520 (amide) cm^{-1}.

p-*Nitrobenzyl (5*R*) 6*R-*methyl-2-methyl-6-phenoxyacetamidopenem-3-carboxylate* ***10***

A solution of the phosphorane **6***c* (1.20 g, 1.57 mmol) in toluene (800 mL) was heated under N_2 and in the presence of a small crystal of hydroquinone, at 100°C for 48 h. The solvent was then concentrated *in vacuo* and the residue was chromatographed on silica gel (60 g). Elution with a mixture of toluene and EtOAc (85:15) gave 0.550 g (72%) of the penem **10** as a white foam: $[\alpha]_D^{25}$ +302° (*c* 1.06, $CHCl_3$); uv (EtOH) λ_{max} (ε): 307 (10 700), 274 (sh), 268 (15 000), and 262 (15 000) nm; ir (film) ν_{max}: 1787 (C=O β-lactam), 1707 (C=O ester), 1668 and 1517 (amide), and 1325 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 1.83 (s, 3H, CH_3-6), 2.35 (s, 3H, CH_3-2), 4.51 (s, 2H, CH_2 of phenoxyacetyl), 5.33 (ABq, J_{AB} = 13.6, Δν = 17.8, CH_2 of *p*-nitrobenzyl), 5.74 (s, 1H, H-5), 6.8–7.4 (m, 5H, aromatic), 7.59 (d, *J* = 8.8 Hz, 2H, H-2 of *p*-nitrobenzyl), and 8.23 ppm (d, *J* = 8.8 Hz, 2H, H-3 of *p*-nitrobenzyl). *Anal.* calcd. for $C_{23}H_{21}N_3O_7S$: C 57.14, H 4.38, N 8.69, S 6.63; found: C 56.94, H 4.60, N 8.69, S 6.50.

*(5*R*) 6*R-*Methyl-2-methyl-6-phenoxyacetamidopenem-3-carboxylic acid, sodium–potassium salt* **3**a

A solution of *p*-nitrobenzyl (5*R*) 6*R*-methyl-2-methyl-6-phenoxyacetamidopenem-3-carboxylate **10** (0.150 g, 0.31 mmol) in a mixture of tetrahydrofuran (15 mL), ether (30 mL), water (15 mL), and pH 7 phosphate buffer (20 mL of a 0.05 M solution, KH_2PO_4–NaOH) was hydrogenated over 0.3 g of 10% Pd on activated carbon in a Parr apparatus under a pressure of 45 psi (1 psi = 6.9 kPa) at room temperature for 1.5 h. The mixture was then filtered through a Celite pad, and the aqueous phase, after evaporation of traces of organic solvent *in vacuo*, was chromatographed at 0–5°C on reversed phase silica gel (2 × 18 cm). Elution with water and then a mixture of water–CH_3CN, 9:1, gave 0.053 g (48%) of the penem **3***a* as a white powder after lyophilization: $[\alpha]_D^{22}$ +321° (*c* 0.88, H_2O); uv (H_2O, pH 7.4 phosphate buffer) λ_{max} (ε based on K salt): 297 (7850), 274 (7200), 267 (7700), and 260 (7500) nm; ir (KBr) ν_{max}: 1770 (C=O β-lactam), 1675 and 1520 (amide), and 1600 (br, carboxylate) cm^{-1}; ^{1}Hmr (D_2O, 80 MHz) δ: 1.69 (s, 3H, CH_3-6), 2.19 (s, 3H, CH_3-2), 4.69 (CH_2 of phenoxyacetyl overlapping with HDO), 5.67 (s, 1H, H-5), and 6.9–7.4 ppm (m, 5H, aromatic). By uv, at 37°C, the half-life of this penem was determined to be 12 h at pH 7.4.

p-*Nitrobenzyl 6α-methoxy-6β-phenoxyacetamidopenicillanate-1-β-oxide* ***11*** d (12)

This product was obtained via a slight modification (23) of the Koppel and Koehler's method (13).

A solution of *p*-nitrobenzyl 6-phenoxyacetamidopenicillanate-1-β-oxide (**11***c*) (20.0 g, 39.8 mmol) in dry CH_2Cl_2 (300 mL) was cooled to −30°C and treated with freshly prepared *tert*-butyl hypochlorite (24).

Then lithium methoxide (43.8 mmol, prepared by dissolving lithium, 0.30 g, in MeOH, 35 mL) was added dropwise over 1 h. After another hour at −30°C, acetic acid (2.5 mL) was added and the solution was washed with 5% cold aqueous $NaHCO_3$, 5% $Na_2S_2O_3$, and brine, and dried (Na_2SO_4). Evaporation left an oil, which was chromatographed on silica gel (200 g). Elution with a mixture of toluene and EtOAc (7:3) gave 15.1 g (71%) of **11***d* as an oil: ir (film) ν_{max}: 1788 (C=O β-lactam), 1753 (C=O ester), 1688 and 1521 (amide), and 1350 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 1.13 and 1.6 (2s, 2 × 3H, CH_3-2), 3.46 (s, 3H, OCH_3-6), 4.53 (s, 2H, CH_2 of phenoxyacetyl), 4.63 (s, 1H, H-3), 5.0 (s, 1H, H-5), 5.3 (s, 2H, CH_2 of *p*-nitrobenzyl), 6.8–7.4 (m, 6H, NH and aromatic), 7.53 (d, J = 9.0 Hz, 2H, H-2 of *p*-nitrobenzyl), and 8.23 (d, J = 9.0 Hz, 2H, H-3 of *p*-nitrobenzyl) ppm.

Methyl 6α-methoxy-6β-phenoxyacetamidopenicillanate-1β-oxide ***11****b* (12)

Starting with methyl 6-phenoxyacetamidopenicillanate **11***a* (25) (3.80 g, 10.0 mmol) and using the same procedure as was used to prepare **11***d*, we obtained 1.73 g (42%) of **11***b* as an oil: ir (film) ν_{max}: 1788 (C=O β-lactam), 1755 (C=O ester), 1690 and 1510 (amide) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 1.23 and 1.66 (2s, 2 × 3H, CH_3-2), 3.5 (s, 3H, OCH_3-6), 3.83 (s, 3H, CO_2CH_3-3), 4.58 (s, 2H, CH_2 of phenoxyacetyl), 4.60 (s, 1H, H-3), 5.0 (s, 1H, H-5), and 6.7–7.6 (m, 6H, NH and aromatic) ppm.

p-*Nitrobenzyl α-(4*R*-acetylthio-3*S*-methoxy-3-phenoxyacetamido-2-azetidinon-1-yl)-β-methylcrotonate* ***12****b*

A solution of sulfoxide **11***d* (15.0 g, 28.0 mmol) in toluene (250 mL) was treated with trimethyl phosphite (12.4 g, 0.1 mol) and acetic anhydride (26.7 mL, 0.28 mol) at 96°C for 24 h. Work-up as for **6***a* followed by isomerization (EtOAc 50 mL, Et_3N 0.8 mL, 3 h) and chromatography gave 8.69 g (55%) of **12***b* as a syrup: $[\alpha]_D^{22}$ +20° (*c* 1.14, $CHCl_3$); ir (film) ν_{max}: 1780 (C=O β-lactam), 1715 (sh, C=O ester), 1695 and 1520 (amide), and 1345 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 2.16 and 2.3 (2s, 3H and 6H, CH_3 of crotonate and $SCOCH_3$), 3.5 (s, 3H, OCH_3-3), 4.53 (s, 2H, CH_2 of phenoxyacetyl), 5.30 (s, 2H, CH_2 of *p*-nitrobenzyl), 5.93 (s, 1H, H-4), 6.8–7.4 (m, 6H, NH and aromatic), 7.56 (d, J = 9.0 Hz, 2H, H-2 and *p*-nitrobenzyl), and 8.20 (d, J = 9.0 Hz, 2H, H-3 of *p*-nitrobenzyl) ppm.

*Methyl α-(4*R*-acetylthio-3*S*-methoxy-3-phenoxyacetamido-2-azetidinon-1-yl)-β-methylcrotonate* ***12****a*

Using the same procedure described above for **12***b*, 10.3 g (72.1 mmol) of **11***b* gave 6.59 g (60%) of **12***a* as an oil: $[\alpha]_D^{20}$ +55° (*c* 1.08, $CHCl_3$); ir (film) ν_{max}: 1772 (C=O β-lactam), 1715 (sh C=O ester), 1700 and 1520 (amide) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 2.15, 2.26 and 2.3 (3s, 3 × 3H, CH_3 of crotonate and $SCOCH_3$), 3.6 and 3.76 (2s, 2 × 3H, OCH_3-3 and CO_2CH_3), 4.53 (s, 2H, CH_2 of *p*-nitrobenzyl), 6.0 (s, 1H, H-4), and 6.8–7.5 (6H, NH and aromatic) ppm. *Anal.* calcd. for $C_{20}H_{24}N_2O_7S$: C 55.03, H 5.54, N 6.42, S 7.34; found: C 54.85, H 5.47, N 6.25, S 6.86.

N-p-*Nitrobenzoxalyl 4*R*-acetylthio-3*S*-methoxy-3-phenoxyacetamido-2-azetidinone* ***12****d*

Ozonolysis of 2.60 g (4.66 mmol) of **12***h* in a mixture of CH_2Cl_2 (80 mL) and MeOH (10 mL) at −20°C and work-up as described above for **6***b* gave 2.40 g (97%) of **12***d* as a clear oil; $[\alpha]_D^{23}$ +17° (*c* 0.98, $CHCl_3$); ir (film) ν_{max}: 1822 and 1760 (C=O β-lactam, oxalyl), 1710 (br, C=O ester, amide), 1525 (amide), and 1350 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 2.36 (s, 3H, $SCOCH_3$), 3.6 (s, 3H, OCH_3-3), 4.60 (s, 2H, CH_2 of phenoxyacetyl), 5.40 (s, 2H, CH_2 of *p*-nitrobenzyl), 6.0 (1H, s, H-4), 7.0–7.6 (m, 6H, NH and aromatic), 7.56 (d, J = 8.8 Hz, 2H, H-2 of *p*-nitrobenzyl), and 8.4 (d, J = 8.8 Hz, H-3 of *p*-nitrobenzyl) ppm.

N-*Methoxalyl 4*R*-acetylthio-3*S*-methoxy-3-phenoxyacetamido-2-azetidinone* ***12****c*

Ozonolysis of 0.736 g (1.68 mmol) of the crotonate **12***a* at −20°C in methanol (25 mL) and work-up as described above for **6***b* gave 0.602 g (85%) of **12***c as a clear oil: ir (film)* ν_{max}: 1820 and 1755 (C=O β-lactam and oxalyl), 1710 (br, C=O ester, amide, and thioester), and 1510 (sh, amide) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 2.37 (s, 3H, $SCOCH_3$), 3.63 (s, 3H, OCH_3-3), 3.96 (s, 3H, CO_2CH_3), 4.63 (s, 2H, CH_2 of phenoxyacetyl), 6.03 (s, 1H, H-4), and 6.8–7.6 (m, 6H, NH and aromatic) ppm.

*4*R*-Acetylthio-3*S*-methoxy-3-phenoxyacetamido-2-azetidinone* ***13***

A solution of *N*-methoxalyl 4*R*-acetylthio-3*S*-methoxy-3-phenoxyacetamido-2-azetidinone **12***c* (0.677 g, 1.85 mmol) in tetrahydrofuran (10 mL) was treated with 1 M aqueous HCl (2 mL) and stirred at 22°C for 8 h. The reaction mixture was diluted with EtOAc, washed with brine, and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue on silica gel (20 g, elution toluene–EtOAc 1:1) gave 0.180 g (36%) of the title azetidinone **13** as a solid. Recrystallization from a mixture of ether and hexanes gave white needles: mp 123–124°C (lit. (*5a*) mp 136–139°C); ir (KBr) ν_{max}: 3260 (NH), 1778 (C=O β-lactam), and 1681 (amide) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.34 (s, 3H, $SCOCH_3$), 3.58 (s, 3H, OCH_3-3), 4.58 (s, 2H, CH_2 of phenoxyacetyl), 5.58 (s, 1H, H-4), 6.3 (br, 1H, NH), and 6.8–7.4 (m, 5H, aromatic) ppm. *Anal.* calcd. for $C_{14}H_{16}N_2O_5S$: C 51.84, H 4.97, N 8.63, S 9.88; found: C 51.44, H 4.96, N 8.39, S 9.58.

p-*Nitrobenzyl (4*R*-acetylthio-3*S*-methoxy-3-phenoxyacetamido-2-azetidinon-1-yl)triphenylphosphoranylidene acetate* ***12****e*

A solution of *N*-*p*-nitrobenzoxalyl 4*R*-acetylthio-3*S*-methoxy-3-phenoxyacetamido-2-azetidinone **12***d* (2.40 g, 4.52 mmol) in tetrahydrofuran (40 mL) was cooled to 0–5°C and treated with 6.8 mL (6.8 mmol) of a 1 M solution of B_2H_6 in tetrahydrofuran (Aldrich Chemical Co.). After 1 h, the reaction mixture was quenched by addition of aqueous NH_4Cl solution (20 mL) and extracted with CH_2Cl_2. After drying (Na_2SO_4), evaporation gave 2.09 g of crude hemiaminal **15***a* as an oil. This product was unstable on silica gel and was used as is for the next step: ir (film) ν_{max}: 1760 (C=O β-lactam), 1700 (C=O) and 1520 (amide) cm^{-1}.

Thionyl chloride (0.27 mL, 3.74 mmol) was added dropwise over 5 min to a cooled (−27°C) solution of the crude hemiaminal **15***a* and pyridine (0.30 mL, 3.74 mL) in dry tetrahydrofuran (40 mL). After 15 min, the solid that formed was filtered through a Celite pad and washed with tetrahydrofuran (20 mL). The combined filtrates were concentrated *in vacuo* and chromatographed on silica gel (30 g). Elution with a mixture of CH_2Cl_2 and ethyl acetate (8:2) gave 0.71 g (34% from **12***d*) of *p*-nitrobenzyl (*4R*-acetylthio-3*S*-methoxy-3-phenoxyacetamido-2-azetidinon-1-yl) chloro acetate **15***b* as a clear oil. The ^{1}Hmr indicated a 2:1 mixture of diastereoisomers: ir (film) ν_{max}: 1794 (C=O β-lactam), 1766 (C=O ester), 1700 (C=O thioester and amide), and 1526 (amide) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 2.23 and 2.3 (2s, 3H, $SCOCH_3$), 3.56 (s, 3H, OCH_3-3), 4.56 (s, 2H, CH_2 of phenoxyacetyl), 5.33 and 5.36 (2s, 2H, CH_2 of *p*-nitrobenzyl), 5.86 and 5.93 (2s, 1H, H-4 of azetidinone), 6.13 and 6.16 (2s, 1H, H-2 of acetate), 6.7–7.3 (m, 6H, aromatic and NH), 7.52 (d, J = 8.5 Hz, 2H, H-2 of *p*-nitrobenzyl), and 8.20 (d, J = 8.5 Hz, 2H, H-3 of *p*-nitrobenzyl) ppm.

A solution of the chloro acetate **15***b* (0.70 g, 1.27 mmol) in tetrahydrofuran (45 mL) was treated with triphenylphosphine (1.04 g, 3.96 mmol) and 2,6-lutidine (0.112 g, 1.04 mmol) and heated under N_2 at 53°C for 48 h. The solvent was evaporated *in vacuo*, the residue dissolved in CH_2Cl_2, washed with cold 0.1 N aqueous HCl, cold 1% aqueous $NaHCO_3$, and brine. After drying (Na_2SO_4), evaporation of the solvent gave a residue that was chromatographed on silica gel (2 × 14 cm). Elution with a mixture of CH_2Cl_2 and EtOAc (7:3) gave 0.361 g (36% from **15***b*) of the title phosphorane **12***e* as a gum: ir (film) ν_{max}: 1770 (C=O β-lactam), 1700 (C=O), 1625 and 1600, 1520 (amide), and 1350 (NO_2) cm^{-1}.

p-*Nitrobenzyl (5*R*) 6*S*-methoxy-2-methyl-6-phenoxyacetamidopenem-3-carboxylate* ***16***

A solution of the phosphorane **12***e* (0.360 g, 0.46 mmol) in dry toluene (200 mL) was maintained at 98°C under N_2 for 24 h. The solvent was then concentrated to ~10 mL and this was chromato-

graphed on silica gel (20 g). Elution with a mixture of toluene and EtOAc (8:23) gave 0.129 g (55%) of the title penem **16** as a white solid. Recrystallization from a mixture of CH_2Cl_2 and ether gave white cubes: mp 152–153°C (lit. (5*a*) mp 152–153°C); $[\alpha]_D^{22}$ +235° (*c* 0.44, $CHCl_3$); uv (EtOH) λ_{max} (ε): 308 (8300), 274 (sh), 268 (12 200), and 262 (sh) nm; ir (KBr) ν_{max}: 1785 (C=O β-lactam), 1704 (C=O ester), 1670 and 1513 (C=O amide), 1585, 1493, and 1323 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.33 (s, 3H, CH_3-2), 3.51 (s, 3H, OCH_3-6), 4.56 (s, 2H, CH_2 of phenoxyacetyl), 5.34 (ABq, J_{AB} = 13.6 Hz, $\Delta\nu$ = 17 Hz, CH_2 of *p*-nitrobenzyl), 5.92 (s, 1H, H-5), 6.7–7.4 (m, 5H, aromatic), 7.60 (d, *J* = 8.8 Hz, 2H, H-2 of *p*-nitrobenzyl), 7.78 (br s, 1H, NH), and 8.20 (d, *J* = 8.8 Hz, 2H, H-3 of *p*-nitrobenzyl) ppm. *Anal.* calcd. for $C_{23}H_{21}N_3O_8S$: C 55.30, H 4.24, N 8.41, S 6.42; found: C 55.36, H 4.28, N 8.36, S 6.49.

Sodium (5R) 6S-methoxy-2-methyl-6-phenoxyacetamidopenem-3-carboxylate ***3b***

A solution of *p*-nitrobenzyl (5*R*) 6*S*-methoxy-2-methyl-6-phenoxyacetamidopenem-3-carboxylate **16** (0.095 g, 0.19 mmol) in a mixture of tetrahydrofuran (5 mL), ether (15 mL), water (15 mL), pH 7.0 phosphate buffer (4 mL of a 0.5 M solution), and sodium bicarbonate (0.015 g, 0.19 mmol) was hydrogenated over 0.15 g of 10% Pd on activated carbon under 45 psi of H_2 at ~15°C for 3 h. The catalyst was removed by filtration through a Celite pad and the aqueous phase was chromatographed at 0–5°C on reversed phase silica gel (2 × 8 cm). Elution with a mixture of H_2O and CH_3CN (9:1) gave 0.045 g (61%) of the penem **3***b* as a white amorphous powder after lyophilization: $[\alpha]_D^{22}$ +150° (*c* 0.44, H_2O); uv (H_2O, pH 7.4 phosphate buffer) λ_{max} (ε): 297 (4900), 272 (5200), 265 (5700), and 259 (5700) nm; ir (KBr) ν_{max}: 1759 (C=O β-lactam), 1688 (C=O of amide), and 1620 (br, carboxylate) cm^{-1}; ^{1}Hmr (D_2O, 80 MHz) δ: 2.16 (s, 3H, CH_3-2), 3.44 (s, 3H, OCH_3-6), 4.67 (s, 2H, CH_2 of phenoxyacetyl), 5.86 (s, 1H, H-5), and 6.8–7.4 (m, 5H, aromatic) ppm. By uv, at 37°C the half-life of this penem was determined to be 1.2 h in a pH 7.4 phosphate buffer.

p-*Nitrobenzyl 6α-methoxy-6β-[α-(p-nitrobenzyloxycarbonyl)phenylacetamido]penicillanate* ***18***

A solution of *p*-nitrobenzyl 6-*p*-toluenesulfenimidopenicillanate (**17**) (13.7 g, 29.1 mmol) (17) in dry CH_2Cl_2 (500 mL) was treated at 24°C with triphenylphosphine (22.8 g, 87.0 mmol) and a solution of mercuric acetate (9.23 g, 29.0 mmol) in methanol (100 mL). After 3.5 h, the solvent was evaporaed and the residue dissolved in CH_2Cl_2 (300 mL). Propylene oxide (180 mL) and pyridine (9 mL) were added and the mixture cooled to −10°C. Then a solution of phenylmalonyl chloride mono-*p*-nitrobenzyl ester (87.6 mmol) in CH_2Cl_2 (70 mL) (prepared by mono-esterification of the commercial phenylmalonic acid with *p*-nitrobenzyl alcohol (26) to give the phenylmalonic acid mono-*p*-nitrobenzyl ester (mp 128–129°C), followed by reaction of the mono-ester (27.6 g, 87.6 mmol) in CH_2Cl_2 (70 mL) with oxalyl chloride (7.7 mL) and a drop of *N*,*N*-dimethylformamide at 22°C for 2 h and evaporation) was added dropwise over 10 min and the resulting mixture was stirred for 3 h at −10°C. The reaction mixture was filtered through a Celite pad, which was then washed with CH_2Cl_2. The filtrate and the washings were washed with cold saturated aqueous $NaHCO_3$, brine, and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was chromatographed on silica gel (200 g). Elution with a mixture of toluene and EtOAc (9:1–7:3) gave 12.6 g (63%) of the title material **18** as a clear oil. The ^{1}Hmr indicated a 1:1 mixture of diastereoisomers: ir (film) ν_{max}: 1778 (C=O β-lactam), 1750 (C=O ester), 1695 and 1520 (amide), and 1350 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 1.24, 1.28, and 1.23 (3s, 2 × 3H and 6H, CH_3-2), 3.36 and 3.38 (2s, 2 × 3H, OCH_3-6), 4.41 and 4.46 (2s, 1H, CH of malonyl), 4.67 and 4.69 (2s, 1H, H-3), 5.28 (s, 4H, CH_2 of *p*-nitrobenzyl), 5.52 and 5.54 (s, 1H, H-5), and 7.2–8.3 (m, 14H, NH and aromatic) ppm. *Anal.* calcd. for $C_{32}H_{30}N_4O_{11}S$: C 56.63, H 4.46, N 8.26, S 4.72; found: C 56.63, H 4.48, N 8.05, S 4.73.

p-*Nitrobenzyl 6α-methoxy-6β-[α-(p-nitrobenzyloxycarbonyl)phenylacetamido]penicillanate-1β- and -1α-oxide (****19****b and* ***19****a)*

m-Chloroperbenzoic acid (3.09 g, 17.9 mmol) was added in small portions over 30 min to a solution of 6α-methoxy penicillanate **18** (12.2 g, 17.9 mmol) in CH_2Cl_2 (250 mL) at −20°C. After 1 h at −20°C, the mixture was washed with cold aqueous saturated $NaHCO_3$, brine, and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was chromatographed on silica gel (300 g). Elution with a mixture of toluene and EtOAc (7:3) gave 10.65 g (85%) of the major β-oxide **19***b* as an oil: ir (film) ν_{max}: 1785 (C=O β-lactam), 1750 (C=O ester), 1680 and 1515 (amide), and 1345 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) (mixture of epimers at the malonyl side chain in 1:1 ratio) δ: 1.12 and 1.59 (2s, 2 × 3H, CH_3-2), 3.38 (s, 3H, OCH_3-6), 4.6, 4.62, 4.65, 4.75, 4.90, and 4.93 (6s, total 3H, H-3, H-5 and CH of malonyl), 5.27 and 5.32 (br s, 4H, CH_2 of *p*-nitrobenzyl), and 7.1–8.3 (m, 13H, aromatic) ppm. *Anal.* calcd. for $C_{32}H_{30}N_4O_{12}S$: C 55.33, H 4.35, N 8.05, S 4.61; found: C 55.0, H 4.24, N 7.97, S 4.61. Further elution with the same solvent system gave 1.01 g (8%) of the minor α-sulfoxide **19***a* as a solid, which was crystallized from a mixture of toluene and CH_2Cl_2: mp 160–165°C (dec); ir (KBr) ν_{max}: 1788 (C=O β-lactam), 1750 and 1740 (sh) (C=O ester), 1690 and 1520 (amide), and 1350 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) (mixture of epimers at the malonyl side chain in 1:1 ratio) δ: 1.12, 1.17, 1.20, and 1.22 (4s, 6H, CH_3-2), 3.45 and 3.50 (2s, 3H, OCH_3-6), 4.50, 4.53, 4.66, 4.71, 4.84, and 4.92 (6s, 3H, H-3, H-5 and CH of malonyl), 5.29 (br s, 4H, CH_2 of *p*-nitrobenzyl), and 7.2–8.3 (m, 13H, aromatic) ppm. *Anal.* calcd. for $C_{32}H_{30}N_4O_{12}S$: C 55.33, H 4.35, N 8.05, S 4.61; found: C 55.39, H 4.39, N 8.03, S 4.63.

Disulfide ***21***

A mixture of *p*-nitrobenzyl 6α-methoxy-6β-[α-(*p*-nitrobenzyloxycarbonyl)phenylacetamido]penicillanate-1β-oxide (**19***b*) (5.50 g, 7.99 mmol) and 2-mercaptobenzothiazole (1.34 g, 8.0 mmol) in toluene (160 mL) was heated under reflux for 5 h. The solvent was evaporated and the residual oil (6.60 g) was used as such for the next step. Attempted purification on silica gel led to isomerization of the β double bond; ir (film) ν_{max}: 1775 (C=O β-lactam), 1740 (C=O ester), 1680 and 1520 (amide), and 1345 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 1.90 (br s, 3H, CH_3 of 3-butenoate), 3.50 (br s, 3H, OCH_3), and 7.1–8.3 (m, aromatic) ppm.

Enol ***22***

A solution of the disulfide **21** (6.60 g, 7.83 mmol) in CH_2Cl_2 (120 mL) was cooled to −78°C and treated with a stream of ozone until a yellow-green solution was obtained. The mixture was then stirred at −78°C for 15 min, flushed with N_2, and treated with methyl sulfide (2 mL). The solution was allowed to warm up to 22°C and washed successively with 10% aqueous solution bisulfite (100 mL) and brine. After drying (Na_2SO_4), evaporation gave 6.0 g of the title material **22** as an oil. Since the product was strongly absorbed on silica gel, the crude material was used as such for the next step. Chromatography of a sample on silica gel (elution toluene:EtOAc 6:4) gave the title enol **22** as an oil; ir (film) ν_{max}: 3300 (OH), 1780 (C=O β-lactam), 1755 (C=O ester), 1675 and 1520 (amide), and 1345 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) (mixture of epimers ratio 1:1 at the malonyl side chain) δ: 2.32 (br s, 3H, CH_3 acetoacetate), 3.45 and 3.50 (2s, 3H, OCH_3), 4.7 and 4.75 (2s, 1H, H of malonyl), 5.1 and 5.3 (br s, CH_2 of *p*-nitrobenzyl and H-4), and 7.2–8.3 (m, aromatic) ppm.

Oxazoline ***23****b*

Triphenylphosphine (1.02 g, 3.90 mmol) was added over 15 min to a solution of the crude enol **22** (3.30 g, 3.90 mmol) in ethyl acetate (30 mL) that had been cooled to 0°C. The resulting mixture was stirred at 0°C for 30 min. Mesyl chloride (0.60 mL, 7.8 mmol) and triethylamine (1.08 mL, 7.8 mmol) were then added over 5 min. After 1.5 h at 0°C, the reaction mixture was diluted with EtOAc (300 mL), washed with brine, and dried (Na_2SO_4). Evaporation of the solvent gave a dark violet gum, which was rapidly chromatographed on silica gel (2.5 × 20 cm; this product was relatively unstable on silica gel). Elution with a mixture of CH_2Cl_2 and EtOAc 9:1 gave 1.10 g (39% from the enol **22**) of the oxazoline **23***b* as a light yellow oil: ir (film) ν_{max}: 1790 (C=O β-lactam), 1730 (C=O ester), 1675, 1605, 1520, and 1345 cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.63 (s, 3H, CH_3 of

crotonate), 3.1 and 3.16 (2s, 3H, CH_3 of mesylate), 3.58 (s, 3H, OCH_3), 5.3 (br, CH_2 of *p*-nitrobenzyl), 6.06 and 6.1 (2s, 1H, H-4), and 7.2–8.4 (m, aromatic) ppm.

Chloro azetidinone ***24***

A solution of the oxazoline **23***b* (1.10 g, 1.52 mmol) in dry CH_2Cl_2 (40 mL) was treated with a stream of dry HCl for 2.5 h. The reaction mixture was then concentrated *in vacuo* and chromatographed on silica gel (2 × 18 cm). Elution with a mixture of CH_2Cl_2 and EtOAc (9:1) gave 0.55 g (48%) of the chloro azetidinone **24** as a clear oil; $[\alpha]_D^{22}$ +30° (*c* 2.5, $CHCl_3$); ir (film) ν_{max}: 1788 (C=O β-lactam), 1730 (C=O ester), 1690 and 1520 (amide), and 1350 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) (mixture of epimers at the malonyl side chain, ratio 1:1) δ: 2.68 (s, 3H, CH_3 of crotonate), 3.15 and 3.17 (2s, 3H, CH_3 of mesylate), 3.48 and 3.51 (2s, 3H, OCH_3), 4.61 and 4.63 (2s, 1H, H of malonate), 5.27 (s, 4H, CH_2 of *p*-nitrobenzyl), 6.11 and 6.15 (2s, 1H, H-4 of azetidinone), and 7.1–8.2 (m, 14H, aromatic) ppm.

p-*Nitrobenzyl (5*R*) 6*S*-methoxy-2-methyl-6-[α-(*p*-nitrobenzyloxycarbonyl)phenylacetamido]penem-3-carboxylate* ***25***

A solution of triethylamine (0.106 mL, 0.76 mmol) in dry THF (5 mL) was cooled to −20°C and hydrogen sulfide was bubbled through the solution for 5 min. Then *N*,*N*-dimethylformamide (1 mL) and the chloroazetidinone **24** (0.290 g, 0.38 mmol) in THF (2 mL) were added and the mixture was stirred at −20°C for 30 min. The reaction mixture was then diluted with EtOAc (25 mL), washed with cold brine, and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was rapidly chromatographed on silica gel (2 × 10 cm, elution with toluene–EtOAc 85:15) to give 0.070 g (~25%) of the title penem **25** as an oil. This product was relatively unstable on silica gel and was contaminated by the thiazole **26***a* (ratio penem:thiazole = 7:3 by ^{1}Hmr); ir (film) ν_{max}: 1785 (C=O β-lactam), 1740 (C=O ester), 1700 (broad), 1520 and 1445 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) penem **25** (mixture of epimers ratio 1:1 at the malonyl side chain) δ: 2.22 and 2.29 (2s, 3H, CH_3-2), 3.39 and 3.43 (2s, 3H, OCH_3-6), 4.68 (s, 1H, H of malonyl), 5.29 (br s, CH_2 of *p*-nitrobenzyl), 5.81 and 5.83 (2s, 1H, H-5), and 7.2–8.2 (m, aromatic) ppm; thiazole **26***a* δ: 2.8 (s, CH_3), 5.47 (s, CH_2 of *p*-nitrobenzyl), and 8.8 (br s, H-2) ppm.

*Disodium (5*R*) 6*S*-2-methyl-6-(α-carboxyphenylacetamido)penem-3-carboxylate* ***3***c

A solution of the crude penem ester **25** (0.070 g, mixture of penem **25** and thiazole **26***a* in a 7:3 ratio) in a mixture of tetrahydrofuran (8 mL), ether (15 mL), pH 7.0 phosphate buffer (5 mL of a 0.05 M solution), ice (15 g), and 0.017 g (0.2 mmol) of $NaHCO_3$ was hydrogenated over 0.2 g of 10% Pd on activated carbon under 45 psi of H_2 at 15°C for 1.5 h. The reaction mixture was then filtered through a Celite pad and the aqueous phase was chromatographed on reversed phase silica gel (1.5 × 11 cm) using cold water (0–5°C) as eluent. Freeze-drying of the uv active fractions gave 0.015 g (~30%) of the title material as a white amorphous powder. By ^{1}Hmr this product contained 25% (mole ratio) of the thiazole **26***b*; uv (H_2O pH 7.4 phosphate buffer) λ_{max}: 299 (4100) and 250 (4700) nm; ir (KBr) ν_{max}: 1765 (C=O β-lactam), 1670 (amide), and 1600 (br, carboxylate) cm^{-1}; ^{1}Hmr (D_2O, 80 MHz) penem **3***c* (mixture of epimers at the malonyl side chain in a 1:1 ratio) δ: 2.13 and 2.17 (2s, 3H, CH_3-2), 3.40 and 3.54 (2s, 3H, OCH_3-6), 4.51 and 4.61 (2s, 1H, H of malonyl), 5.80 and 5.82 (2s, 1H, H-5) ppm; thiazole **26***b* δ: 2.60 (s, CH_3) and 8.61 (s, H-2) ppm.

By uv at 37°C, the half-life of this penem was determined to be 1.6 h in a pH 7.4 phosphate buffer. At 22°C the half-life increased to 6.6 h. This penem was unstable even in the dry form and decomposed at 0°C after a few days.

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