The Penems, a New Class of β-Lactam Antibiotics: 6-Acylaminopenem-3-carboxylic Acids[1]

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Abstract: Using penicillin V as starting material, a general synthetic route for compounds 1 with the novel, unsaturated, *penem* skeleton has been established. Compounds 1 represent a new class of β-lactam antibiotics whose molecules combine structural features, important for biological activity, of both penicillins and cephalosporins.

One of the most striking features of the chemistry of β-lactam antibiotics is the unusual reactivity of their β-lactam system toward nucleophilic agents. Whereas, for example, simple β-lactams are not easily hydrolyzed, the penicillin β-lactam ring is cleaved very readily. The same is true to a lesser extent of the azetidinone unit of cephalosporins.

The available evidence is suggestive of a correlation between biological activity on the one hand and chemical reactivity of the β-lactam system on the other, and, although no simple quantitative relationship of these two features is obvious today, the search for structures with reactive β-lactam rings has proved to be useful in designing new biologically active derivatives.

For the high reactivity of the β-lactam system in *penicillins*, a rationalization has been given in terms of a lessened stabilization of the amide linkage by diminution of the usual delocalization of the unshared electron pair of nitrogen into the adjacent carbonyl group.[2] Fusion of the four- with the five-membered ring in these compounds results in a pyramidal geometry of the β-lactam nitrogen[3] and thus in a distortion of the parallelism of the orbitals necessary for such an interaction.

In *cephalosporins*, on the other hand, the increased reactivity seems to be associated with the presence and the particular (Δ³) location of the double bond in the annelated six-membered ring. A conjugative interaction of the unshared electron pair on nitrogen with the double bond, competitive with the usual stabilization of the amide C–N bond, is possible; consequently the C–N bond is cleaved more readily as compared to the case in which the double bond is not present in that position.

To combine both the structural elements which appeared to be associated with the biological activity of penicillins and cephalosporins, i.e., the five-membered annelated ring *and* the conjugated double bond, in one single structure such as 1 appeared to us a logical extension of the above-mentioned considerations, as well as a special synthetic challenge. In this article the successful realization of the synthesis of compounds of the type 1 with the novel bicyclic *penem* system is described.

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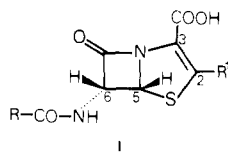
For the synthesis of 2-substituted 6-phenoxyacetamidopenem-3-carboxylic acids (1, R = $C_6H_5OCH_2$) and their esters, penicillin V served as an inexpensive, optically active starting material. The first goal was to transform penicillin V into the 4-acylthio-3-phenoxyacetamido-2-azetidinones 5, the key intermediates of our synthetic scheme.[4]

In the course of our synthetic work on penems, several paths were developed for the preparation of compounds 5 of which that shown in the scheme (2 → 5) is probably the most convenient.
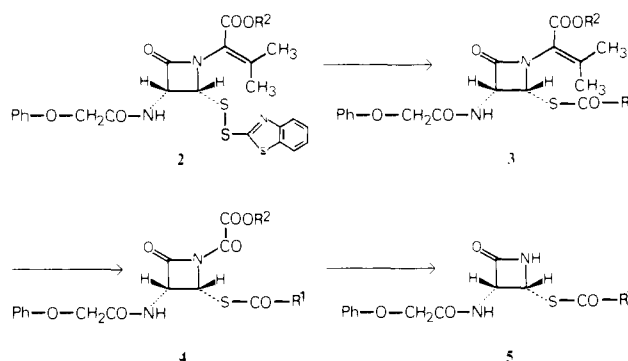

Making use of the excellent procedure established by Kamiya et al.,[7] esters of penicillin V S-oxide were first transformed by heating with 2-mercaptobenzthiazole and then treating with base (Et₃N, CH₂Cl₂) into benzthiazolyl disulfides 2, in high yields.

Reductive acylation of the disulfides 2 by triphenylphosphine in acetic anhydride–acetic acid with subsequent addition of pyridine afforded the 4-acetylthioazetidinones 3 (R¹ = Me; R² = p-nitrobenzyl = p-NB) and 3 (R¹ = Me; R² = Me) in yields of 84 and 88%, respectively. A modification of this procedure in which 2 (R² = Me) in methylene chloride was treated with triphenylphosphine and excess of benzoyl chloride while being swirled with aqueous sodium hydroxide gave the benzoylthio compound 3 (R¹ = Ph; R² = Me) (56%). Alternatively, a procedure consisting of reduction of compounds 2 with sodium borohydride in dimethylformamide and subsequent acylation in the same medium with an appropriate acyl halide or anhydride was also used for the preparation of compounds 3 (R¹ = Me; R² = Me) (62%); R¹ = p-C₆H₄NO₂; R² = Me (63%)).

As shown in the scheme, the removal of the unsaturated substituent of compounds 3 was realized in two distinct steps. Low-temperature ozonolysis of 3 (in methanol and methyl or ethyl acetate) gave the alkoxalyl derivatives 4, often crystallizing directly from the ozonization mixtures, in excellent yields. Mild methanolysis of these compounds in dilute, neutral, methanolic solutions then accomplished the transformation to the N-substituted azetidinones 5 (yields 60–70%).[8]

Except for the carbon atom C3 of the five-membered ring and the carboxylic group, the compounds 5 possess all elements needed for the construction of the penem acids 1, in proper functionalities and stereochemistry. To provide the missing two-carbon unit in a form suitable for the final ring closure, a three-step procedure developed some time ago in another

connection in our laboratories[9] and since then repeatedly used in syntheses of various analogues of cephalosporins was adopted here (scheme, **5 → 9**).

COOR^2

5

6

7

8
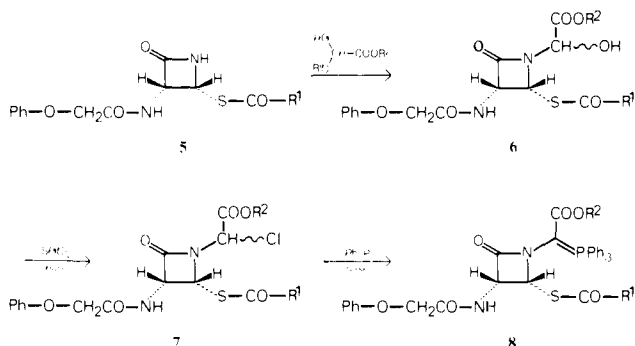
Reaction of **5** with glyoxylic esters, preferably in the form of their hydrates or hemiacetals, and in the presence of activated molecular sieves, led to diastereomeric mixtures of hemiaminals **6** which in turn were transformed by thionyl chloride in dioxane, together with a polymeric tertiary base to bind the liberated hydrogen chloride, into the diastereomeric chlorides **7**. When the latter, rather unstable, intermediates were mildly heated in toluene with triphenylphosphine and the polymeric base, phosphoranes **8** were formed in yields of 45–60% over the three steps.

An interesting simplification in the preparation of the phosphoranes **8** was made possible by diborane reduction of the alkoxalyl intermediates **4** to hemiaminals **6**. In this way, through choice of the proper ester of penicillin as starting material, the synthetic route to phosphoranes **8** could be shortened by one step and two more carbon atoms of the penicillin skeleton could be utilized. In several cases, however, the longer way via compounds **5** proved more practical.

4

6
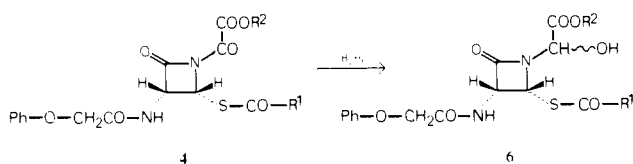
With compounds **8** in hand, we hoped to bring about an intramolecular Wittig condensation between their phosphorane function and the carbonyl group of the acylthio substituent; this reaction was to form the missing thiazoline ring and thus accomplish the synthesis of the desired penem system.[10]

8

9
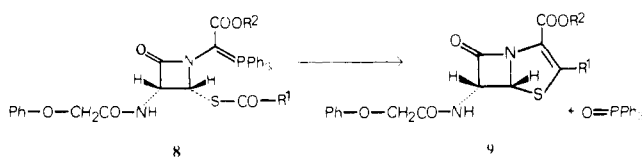
In fact, when phosphoranes **8** in dilute solutions in toluene were heated at 70–100 °C, formation of triphenylphosphine oxide and a less polar product was observed in most cases, and it was gratifying to isolate and identify the new compound in each case as one of the penem-3-carboxylates **9**.

The cyclization, however, did not proceed always with the same ease and a great sensitivity to both steric and polar effects became obvious. Whereas, e.g., the acetylthioazetidinonyl-phosphorane **8** (R^1 = Me; R^2 = *t*-Bu) needed only 10 h at 70 °C for complete conversion to 2-methylpenem-3-carboxylate **9** (R^1 = Me; R^2 = *t*-Bu),[13] the conversion of the isobutyrylthio compound **8** (R^1 = *i*-Pr; R^2 = *t*-Bu), after 5 days at 80 °C, was only about 10% and a mere 6% of the penem ester **9** (R^1 = *i*-Pr; R^2 - *t*-Bu) could in fact be isolated after 6 days at 80 °C and another 2 days at 100 °C. On the other hand, the electron-withdrawing *p*-nitrophenyl group in **8** (R^1 = *p*-NO$_2$C$_6$H$_4$; R^2 = *t*-Bu) increased the reactivity of the thioester carbonyl and

the intramolecular Wittig reaction was completed in 17 h even at the mild temperature of 55 °C, giving the corresponding penem ester **9** (R^1 = *p*-NO$_2$C$_6$H$_4$; R^2 = *t*-Bu) in a yield of 90%.

Even more amazing was the influence, on the rate of the cyclization reaction, of the character of the ester group in the phosphorane part of the compound **8**. With the methyl ester **8** (R^1 = Me; R^2 = Me), the reaction was slower (46 h at 80 °C) than with the above-mentioned *tert*-butyl ester (10 h at 70 °C) and slower still with the *p*-nitrobenzyl ester **8** (R^1 = Me; R^2 = *p*-NB) in which case 4.5 days at 80 °C was necessary for a practical conversion to **9** (R^1 = Me; R^2 = *p*-NB) (70% isolated). The strongly electron-withdrawing trichloroethyl group in **8** (R^1 = Me; R^2 = CH$_2$CCl$_3$) slowed the cyclization reaction beyond practical limits: about 10% conversion was estimated after 1 day at 80 °C, another 1 day at 90 °C, and still another 1 day at 100 °C. A similar retarding effect was observed with the *β*-cyanoethyl ester **8** (R^1 = Me; R^2 = CH$_2$CH$_2$CN).[14]

Using the same principle, i.e., a final intramolecular Wittig condensation, the 2-unsubstituted penem-3-carboxylates **9** (R^1 = H; R^2 = Me, *t*-Bu, and *p*-NB, respectively) were also prepared. However, for the synthesis of the corresponding phosphorane precursors **8** (R^1 = H), a modification of the described general scheme was necessary.

Applying the two-step procedure for removal of the N substituent mentioned earlier in this paper, i.e., ozonization followed by methanolysis, to compound **2** (R^2 = *p*-NB), the nicely crystalline intermediate **11** was first prepared (via the isolated, also crystalline, alkoxalyl derivative **10**) in overall yield of 59%.

COOR^2

2

III

11
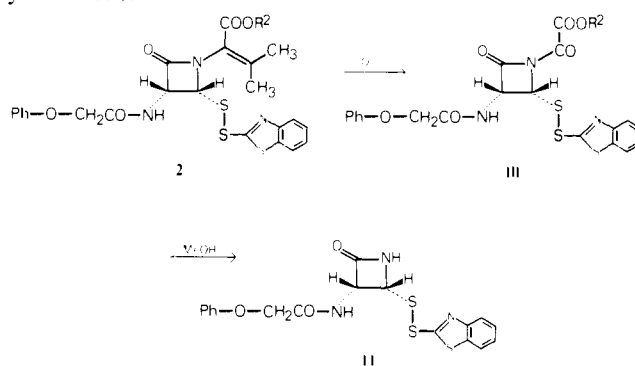
Reaction of **11** with ethyl triphenylphosphoranylidene pyruvate (in glyme, at ambient temperature) resulted in cleavage of the S–S bond and formation of the new phosphorane **12** (90%).[15]

11

12
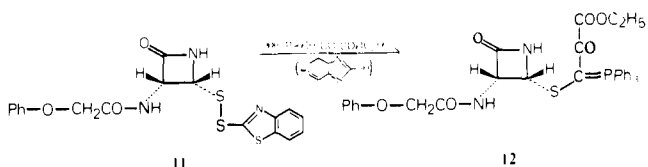
Reduction with sodium borohydride in an acidic medium (in a mixture of formic, acetic, and propionic acids) smoothly converted the phosphorane **12** into the crystalline azetidinonylthioacrylate **13** (79%).[16]

13

14
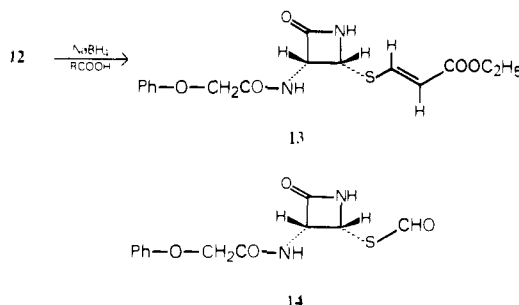
An initial plan was to ozonize **13** to the formylthioazetidinone **14** and then to build up the phosphorane grouping on the β-lactam nitrogen as with the other, aforementioned compounds of this type (i.e., **5**). In fact, however, ozonization of **13** was not as clean-cut as expected and the crude **14** proved too unstable to be purified and used for further transformations. Therefore the sequence of steps was changed and the phosphorane esters **15** were first prepared from **13** in the usual three operations in overall yields of 52, 70, and 56% for the methyl, *tert*-butyl, and *p*-nitrobenzyl ester, respectively.

13

15
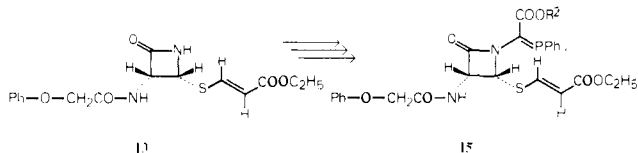
For the subsequent ozonolysis of the acrylic side chain, the ozone-sensitive phosphorane grouping in compounds **15** had first to be protected. An efficient protection was provided simply by performing the ozonization in acidic solutions (methylene chloride–trifluoroacetic acid) in which, as shown by infrared spectroscopy, the phosphoranes were present in the protonated, phosphonium form **16** which is inert to ozone. After ozone was introduced and the ozonide was reduced, neutralization of the ozonization mixtures with aqueous bicarbonate restored the phosphorane grouping and solutions of the desired precursors **18 ≡ 8** (R^1 = H) in methylene chloride were thus obtained (scheme, **15 → 18**).

15

16

17

18 ≡ 8·R^1=H
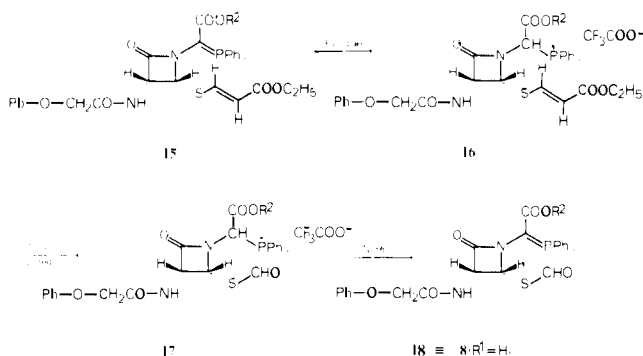
Owing to the high reactivity of the carbonyl group of the thioformate substituent, the final intramolecular Wittig reaction of compounds **18** proceeded much more readily than with the aforementioned phosphoranes **8**. With the methyl and *p*-nitrobenzyl esters, cyclization was evident even at ambient temperature and was completed by short refluxing in methylene chloride, the yields of isolated penem esters **19** (R^2 = Me) and **19** (R^2 = *p*-NB), as based on the corresponding compounds **15**, being 50 and 63%, respectively. In the *tert*-butyl ester series, the internal Wittig reaction was faster still and the penem ester **19** (R^2 = *t*-Bu) was formed within minutes after liberation of the phosphorane **18** (R^2 = *t*-Bu) from its phosphonium salt; 59% of the penem ester (based again on **15**) was isolated.


18

19 ≡ 9 (R^1=H)
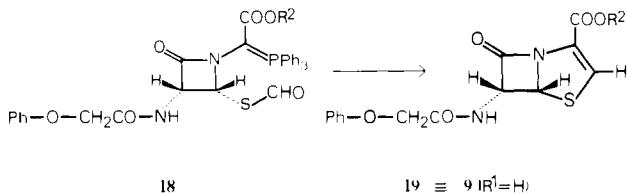
The constitution of the new penem-3-carboxylates as represented by structures **9** was firmly established by spectroscopic data and elemental analyses; only the most characteristic spectral properties of the novel penem system will be mentioned here.

The ultraviolet spectra of the penem-3-carboxylates **9** (R^1 = alkyl) and **9** (R^1 = H) display a long-wavelength maximum at about 305 and 308–310 nm, respectively, reflecting a conjugation of the sulfur atom through the carbon–carbon double bond to the carbonyl group of the ester function; this absorption, which, of course, does not appear in the spectra of penicillins or cephalosporins, is very characteristic of the new system.

A short-wavelength stretching absorption of the β-lactam carbonyl group at 5.54–5.57 μ in the infrared spectra of the compounds **9** is also very characteristic, and suggests a more strained, more reactive β-lactam system than in most penicillins.

In the 100-MHz proton magnetic resonance spectra in deuterated chloroform, the compounds **9** are characterized by a closely spaced multiplet, between δ 5.9 and 6.0, of the β-lactam ring hydrogen atoms H5 and H6. In a 360-MHz spectrum of the *p*-nitrobenzyl 2-methylpenem-3-carboxylate **9** (R^1 = Me; R^2 = *p*-NB), this multiplet was resolved to a clear doublet for H5 (δ 5.88, $J_{5,6}$ = 4.0 Hz) and a doublet of doublets for H6 (δ 5.96, $J_{5,6}$ = 4.0, $J_{6,NH}$ = 8.0 Hz); the signal of the methyl group at C2 was located at δ 2.21.

Instability to acids proved to be another—unwelcome—characteristic feature of the new penem system. Even traces of acids (HCl, trifluoroacetic acid, formic acid, etc.) induce decomposition to thiazole-4-carboxylates **20**.[17]

9

20
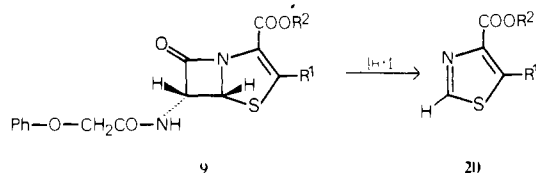
So far the synthesis of esters of penem-3-carboxylic acids **9** has been described. Our final task was to convert them to the free acids **1**, and here the acid sensitivity of the penem nucleus and the increased reactivity of its β-lactam carbonyl toward nucleophiles put serious restrictions on our choice of suitable, readily cleaved, ester precursors. The aforementioned unsatisfactory Wittig reaction of some phosphoranes **8** set further limits, making, for example, the trichloroethyl esters practically inaccessible.

A solution to the problem was found in catalytic hydrogenolysis of the *p*-nitrobenzyl esters **9** (R^2 = *p*-NB) with palladium on charcoal in a two-phase system consisting of ethyl acetate and aqueous bicarbonate. In this way, (6R)-phenoxyacetamido-(5R)-penem-3-carboxylic acid (**1a**) and (6R)-phenoxyacetamido-2-methyl-(5R)-penem-3-carboxylic acid (**1b**) were prepared as amorphous compounds of limited sta-

1a

1b
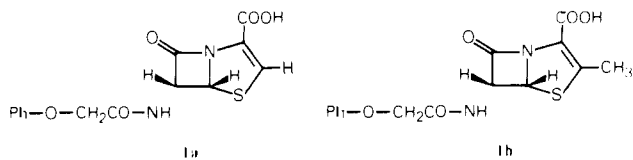
bility in yields of 20 and 55%, respectively; both acids were characterized by their UV, IR, and NMR spectra, the somewhat more stable 2-methyl-substituted acid **1b** in addition by elemental analysis. Similar hydrogenation of the 2-phenylpenem ester **9** (R^1 = Ph; R^2 = *p*-NB) afforded the corresponding penem acid only in admixture with β-lactam-free decomposition products.

Antibacterial in vitro tests on both acids **1a** and **1b** showed activities against gram-positive strains (e.g., *Staph. aureus*) and proved that biological activity *is* inherent in the new β-lactam system.

Experimental Section

Melting points (Kofler) are uncorrected. All rotations were de-

termined in CHCl$_3$, and all IR spectra in CH$_2$Cl$_2$ as solvents unless otherwise mentioned. NMR spectra were recorded (CDCl$_3$ with Me$_4$Si as internal standard) on a Varian HA-100D spectrometer; all chemical shifts are reported in δ values. Mass spectra were obtained with a Varian CH 7 spectrometer. All R_f values were determined on Merck silica gel 60 F$_{254}$ TLC plates.

Esters of Glyoxylic Acid. Methyl glyoxylate hydrate, bp 55–62 °C (35 mm), was prepared by lead tetraacetate oxidation of dimethyl tartrate in benzene (90 min at room temperature), filtration, and distillation. For the preparation of **hydrated *tert*-butyl glyoxylate** (potentially separable mixture of hydrate, mp 51-54 °C, and hemihydrate, mp 63-64 °C), the procedure described by Carpino[18] was used with minor modifications. **Trichloroethyl glyoxylate hydrate,** mp 100-104 °C, was best prepared from bis(trichloroethyl) tartrate by sodium periodate oxidation in aqueous acetic acid (1 h at room temperature), extraction with AcOEt, and crystallization from wet Et$_2$O (yield 82%). The starting bis(trichloroethyl) tartrate, mp 101.5-103.5 °C, was obtained from D-tartaric acid and excess trichloroethanol by azeotropic esterification in toluene in the presence of *p*-toluenesulfonic acid (yield 57%). **p-Nitrobenzyl glyoxylate ethylhemiacetal,** a yellowish oil crystallizing below 0 °C, was prepared from bis(*p*-nitrobenzyl) tartrate by oxidation with lead tetraacetate in benzene-dioxane, 1:1 (1 h at room temperature), filtration, evaporation in vacuo, and washing in CH$_2$Cl$_2$ containing 1% of EtOH with aqueous NaHCO$_3$ (yield 90%). Bis(*p*-nitrobenzyl) tartrate, mp 163-165 °C, was obtained in a yield of 80% by alkylation of D-tartaric acid in DMF with *p*-nitrobenzyl bromide in the presence of Et$_3$N; the ester was precipitated from the reaction mixture with water.

Disulfides 2 were prepared from the corresponding esters of penicillin V *S*-oxide by a two-step procedure established by Kamiya et al.[7] **Disulfide 2** (R^2 = Me): amorphous solid; [α]^{20}D +14 ± 1° (1%); IR 2.97, 5.63, 5.79, 5.92, 6.25, 6.60, 6.70, 6.85, 7.08, 7.25, 7.35, 8.20, 9.94 μ; NMR δ 2.11 (s, 3), 2.17 (s, 3), 3.61 (s, 3), 4.57 (s, 2), 5.28 (dd, 1), 5.58 (d, 1), 6.8-7.9 (m, 10). Anal. Calcd for C$_{24}$H$_{23}$N$_3$O$_5$S$_3$ (529.65): C, 54.43; H, 4.38; N, 7.93. Found: C, 54.70; H, 4.47; N, 7.86. **Disulfide 2** (R^2 = *p*-NB): white needles, mp 115 °C (CH$_2$Cl$_2$-Et$_2$O); [α]^{20}D −15 ± 1° (0.91%); IR 2.95, 5.63, 5.78, 5.91, 6.25, 6.56, 6.71, 7.45, 8.27, 9.95 μ; NMR δ 2.20 (s, 3), 2.23 (s, 3), 4.58 (dd, 2, J = 15 Hz), 5.04 (d, 1, J = 13 Hz), 5.17 (dd, 1, J = 5 and 7.5 Hz), 5.24 (d, 1, J = 13 Hz), 5.54 (d, 1, J = 5 Hz), 6.8-8.0 (m, 14). Anal. Calcd for C$_{30}$H$_{26}$N$_4$O$_7$S$_3$ (650.74): C, 55.37; H, 4.03; N, 8.61; S, 14.78. Found: C, 55.15; H, 4.22; N, 8.70; S, 14.53.

Methyl α-((3R)-Phenoxyacetamido-(4R)-acetylthio-2-azetidinon-1-yl)-β-methylcrotonate (3, R^1 = Me; R^2 = Me). A. Triphenylphosphine Method. To a solution of 530 mg (1 mmol) of the disulfide **2** (R^2 = Me) in 4.5 mL of acetic anhydride and 1.5 mL of acetic acid, stirred at −20 °C under N$_2$, 262 mg (1 mmol) of triphenylphosphine was added in several portions during 20 min. After another 15 min at −20 °, 3 mL of pyridine was introduced and stirring was continued for 3 h at room temperature. Evaporation in vacuo and chromatography of the residue on 50 g of Merck silica gel deactivated with 10% of H$_2$O afforded 358 mg (88%) of **3** (R^1 = Me; R^2 = Me) which was eluted in several fractions with a 4:1 mixture of toluene and ethyl acetate. Amorphous solid: [α]^{20}D + 7 ± 1° (1.15%); IR 2.97, 5.65, 5.75 (sh), 5.85, 6.10, 6.27, 6.60, 6.73, 8.15 μ; NMR δ 2.03 (s, 3), 2.22 (s, 3), 2.24 (s, 3), 3.77 (s, 3), 4.54 (s, 2), 5.38 (dd, 1, J = 5 and 8 Hz), 5.94 (d, 1, J = 5 Hz), 6.8-7.4 (m, 6). Anal. Calcd for C$_{19}$H$_{22}$N$_2$O$_6$S (406.45): C, 56.15; H, 5.46; N, 6.89; S, 7.89; O, 23.62. Found: C, 56.21; H, 5.52; N, 6.77; S, 7.75; O, 23.38. Data agree with those published by Lattrell.[19]

B. NaBH$_4$ Method. A solution of 3.65 g (6.89 mmol) of **2** (R^2 = Me) in 70 mL of DMF was dropwise added during 10 min to a freshly prepared solution of 380 mg (~10 mmol) of NaBH$_4$ in 50 mL of DMF while the mixture was stirred at −20 °C. After another 5 min at −20 °C, 25 mL of pyridine and 15 mL of acetic anhydride were added and stirring was continued for 1 h at 0 °C. Then, at −20 °C, 25 mL of acetyl bromide was introduced and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with 1.6 L of benzene and washed several times with water, aqueous NaHCO$_3$, and again with water. Evaporation of the organic part and chromatography of the residue (200 g of deactivated Merck silica gel) gave 1.74 g (62%) of **3** (R^1 = Me; R^2 = Me) with the above-mentioned properties.

p-Nitrobenzyl α-((3R)-Phenoxyacetamido-(4R)-acetylthio-2-azetidinon-1-yl)-β-methylcrotonate (3, R^1 = Me; R^2 = p-NB). Method A. Disulfide **2** (R^2 = *p*-NB) (5.5 g, 8.45 mmol) in 50 mL of acetic anhydride and 17 mL of acetic acid was reduced at −20 °C by adding, in portions, a total of 2.22 g (8.46 mmol) of triphenylphosphine. After

75 min at −20 °C, 34 mL of pyridine was added and the resulting solution was stirred at 0 °C for 3 h. Evaporation in vacuo and chromatography (420 g of Merck silica gel) afforded 3.74 g (84%) of **3** (R^1 = Me; R^2 = *p*-NB) which was eluted from the column with toluene-ethyl acetate, 4:1. Amorphous solid: [α]^{20}D −25 ± 1° (0.929%); R_f 0.45 (benzene-AcOEt, 1:1); IR 2.95, 5.62, 5.80 (sh), 5.89, 6.15, 6.25, 6.31, 6.45, 6.97, 7.08, 7.18, 7.32, 7.43 μ; NMR δ 2.09 (s, 3), 2.24 (s, 3), 2.25 (s, 3), 4.54 (s, 3), 5.29 (s, 2), 5.25 (dd, 1, J = 5 and 9 Hz), 5.94 (d, 1, J = 5 Hz), 8.21 (d, 1, J = 9 Hz), 6.8-7.4 (m, 5), 7.5-8.3 (m, 4). Anal. Calcd for C$_{25}$H$_{25}$N$_3$O$_8$S (527.54): C, 56.91; H, 4.77; N, 7.96; S, 6.07; O, 24.26. Found: C, 57.10; H, 4.80; N, 7.85; S, 6.01; O, 24.33.

Method B. Disulfide **2** (R^2 = *p*-NB) (897 mg, 1.38 mmol) in 14 mL of DMF was added at −20 °C to a solution of 76 mg (2 mmol) of NaBH$_4$ in 10 mL of DMF. After 15 min, 7 mL of acetyl bromide was introduced and stirring continued at 0 °C for 1 h. Washing in benzene (350 mL) with several 100-mL portions of water, evaporation of the solvent, and chromatography resulted in 322 mg (44.3%) of **3** (R^1 = Me; R^2 = *p*-NB).

Methyl α-((3R)-Phenoxyacetamido-(4R)-isobutyrylthio-2-azetidinon-1-yl)-β-methylcrotonate (3, R^1 = *i*-Pr; R^2 = Me). Refluxing 3.8 g (10 mmol) of penicillin V *S*-oxide methyl ester, mp 122-125 °C,[20] in 120 mL of benzene with 20 g of isobutyric anhydride and 5 mL of trimethyl phosphite for a period of 12 h afforded, on evaporation of volatile components in vacuo and chromatography of the residue (120 g of Merck silica gel), 2.33 g (53.7%) of methyl (3-phenoxyacetamido-4-isobutyrylthioazetidin-2-on-1-yl)isopropenylacetate (eluted with benzene-AcOEt, 7:1) as an amorphous solid; R_f 0.43 (benzene-AcOEt, 1:1); IR 2.97, 5.63, 5.74, 5.91, 6.24, 6.28, 6.60, 6.71, 6.97, 7.27, 7.35, 7.53 μ; NMR δ 1.15 (d, 6, J = 7 Hz), 1.92 (d, 3, J = 0.8 Hz), 2.67 (m, 1, J = 7 Hz), 3.80 (s, 3), 4.56 (s, 2), 4.82 (s, 1), 4.99 (s, 1), 5.09 (d, 1, J = 0.8 Hz), 5.57 (dd, 1, J = 5 and 8 Hz), 6.00 (d, 1, J = 5 Hz), 6.8-7.1 (m, 3), 7.2-7.4 (m, 3).

A solution of 2.2 g of the latter product in 25 mL of CH$_2$Cl$_2$ containing 0.7 mL of Et$_3$N was allowed to stand at room temperature for 1.5 h. Washing in CH$_2$Cl$_2$ with 1 N aqueous HCl and with brine, evaporation of the solvent, and chromatography (Merck silica gel, benzene-AcOEt, 4:1) gave 1.63 g (74%) of **3** (R^1 = *i*-Pr; R^2 = Me) as an amorphous solid: R_f 0.38 (benzene-AcOEt, 1:1); [α]^{20}D +5 ± 1° (1.1%); IR 2.97, 5.64, 5.81, 5.91, 6.15, 6.25, 6.29, 6.60, 6.71, 6.97, 7.24, 7.34 μ; NMR δ 1.13 (d, 6, J = 7 Hz), 2.05 (s, 3), 2.24 (s, 3), 2.67 (m, 1, J = 7 Hz), 3.79 (s, 3), 4.56 (s, 2), 5.45 (dd, 1, J = 5 and 8 Hz), 5.93 (d, 1, J = 5 Hz), 6.9-7.1 (m, 3), 7.2-7.4 (m, 3). Anal. Calcd for C$_{21}$H$_{26}$N$_2$O$_6$S (434.51): C, 58.04; H, 6.03; N, 6.44. Found: C, 57.81; H, 6.10; N, 6.35.

Methyl α-((3R)-Phenoxyacetamido-(4R)-benzoylthio-2-azetidinon-1-yl)-β-methylcrotonate (3, R^1 = Ph; R^2 = Me). To a solution of 3.18 g (6 mmol) of the disulfide **2** (R^2 = Me) and 1.1 mL (~9.5 mmol) of benzoyl chloride in 95 mL of methylene chloride, 1.65 g (6.3 mmol) of triphenylphosphine was added while the mixture was swirled in an ice-water bath with 150 mL of 0.1 N aqueous KOH. After 20 and 30 min, two 0.3-mL portions of benzoyl chloride were added. Finally, after a total of 45 min, the reaction mixture was stirred for 20 min without cooling. The organic layer was separated, dried (Na$_2$SO$_4$), and evaporated and the residue was chromatographed (200 g of Merck silica gel deactivated with 10% of H$_2$O). After several fractions with toluene and toluene-AcOEt, 9:1, 1.56 g (55.5 %) of the benzoylthio derivative **3** (R^1 = Ph; R^2 = Me) was eluted with toluene-AcOEt, 4:1. White needles: mp 130-130.5 °C (MeOH-Et$_2$O); R_f 0.38 (toluene-AcOEt, 1:1); [α]^{20}D +27 ± 1° (1.09%); IR 2.97, 5.64, 5.77, 5.92, 6.00, 6.27, 6.61, 6.72, 6.98, 7.10, 7.24, 7.34, 8.17, 8.30, 8.56, 9.03, 9.27, 9.43, 11.07 μ; NMR δ 2.08 (s, 3), 2.23 (s, 3), 3.82 (s, 3), 4.56 (s, 2), 5.50 (dd, 1, J = 5.2 and 9 Hz), 6.18 (d, 1, J = 5.2 Hz), 6.8-7.9 (m, 11). Anal. Calcd for C$_{24}$H$_{24}$N$_2$O$_6$S (468.52): C, 61.53; H, 5.16; N, 5.98; O, 20.49; S, 6.84. Found: C, 61.62; H, 5.18; N, 6.33; O, 20.46; S, 6.74.

Methyl α-((3R)-Phenoxyacetamido-(4R)-p-nitrobenzoylthio-2-azetidinon-1-yl)-β-methylcrotonate (3, R^1 = *p*-NO$_2$C$_6$H$_4$; R^2 = Me). To a stirred solution of the disulfide **2** (R^2 = Me) (106 mg, 0.2 mmol) in 5 mL of DMF, a solution of 10 mg of NaBH$_4$ in 1 mL of DMF was added at −20 °C. After 30 min at −20 °C, 207 mg (1.2 mmol) of *p*-nitrobenzoyl chloride in 0.5 mL of DMF was introduced and the resulting reaction mixture was stirred at room temperature for 40 min. Benzene was then added and some insoluble material was removed by filtration. Washing the filtrate several times with water, evaporation of the solvent, and chromatography of the residue (5 g of Merck silica gel, toluene-AcOEt, 7:1 and 3:1) afforded 65 mg (63%) of **3** (R^1

= p-NO$_2$C$_6$H$_4$; R^2 = Me). White needles: mp 132–134 °C; [α]^{20}D +38 ± 1 ° (1%); IR 2.97, 5.65, 5.80, 5.95, 6.55, 7.40, 11.8 μ; NMR δ 2.08 (s, 3), 2.22 (s, 3), 3.81 (s, 3), 4.55 (s, 2), 5.47 (dd, 1, J = 5 and 8 Hz), 6.21 (d, 1, J = 5 Hz), 6.8–7.4 (m, 6), 7.9–8.3 (m, 4). Anal. Calcd for C$_{24}$H$_{23}$N$_3$O$_8$S (529.65): C, 54.43; H, 4.38; N, 7.93. Found: C, 54.24; H, 4.80; N, 8.01.

N-**Methoxalyl-(3***R***)-phenoxyacetamido-(4***R***)-acetylthio-2-azeti-dinone (4, R^1 = Me; R^2 = Me).** Into a solution of 13.14 g (32.33 mmol) of **3** (R^1 = Me; R^2 = Me) in 350 mL of methanol, an excess of ozone was introduced at −20 °C for 5.5 h at the rate of 0.33 mmol/min. **4** (R^1 = Me; R^2 = Me) separated in white crystals from the ozonization mixture and was collected and washed on a filter with MeOH, 8.93 g (72.6%). Concentration of the filtrate under reduced pressure afforded another 0.8 g (6.5%) of **4** (R^1 = Me; R^2 = Me) of the same quality. White needles: mp 145 °C; [α]^{20}D −13 ± 1 ° (1.38%); IR 2.97, 5.48, 5.60, 5.87, 6.25, 6.60, 6.70, 7.32 μ; NMR δ 2.27 (s, 3), 3.92 (s, 3), 4.58 (s, 2), 5.60 (dd, 1, J = 6.2 and 8.5 Hz), 5.95 (d, 1, J = 6.2 Hz), 6.8–7.4 (m, 6). Anal. Calcd for C$_{16}$H$_{16}$N$_2$O$_7$S (380.37): C, 50.52; H, 4.24; N, 7.37; S, 8.43; O, 29.44. Found: C, 50.68; H, 4.25; N, 7.23; S, 8.49; O, 29.54.

N-*p*-**Nitrobenzoxalyl-(3***R***)-phenoxyacetamido-(4***R***)-acetylthio-2-azetidinone (4, R^1 = Me; R^2 = *p*-NB).** A solution of 1.82 g (3.45 mmol) of **3** (R^1 = Me; R^2 = p-NB) in 150 mL of methyl acetate was ozonized at −78 °C by introducing an excess of O$_3$ at a rate of 0.1 mmol/min for a period of 60 min. Excess O$_3$ was removed in a stream of N$_2$, and the reaction solution was washed with ice-cold 5% aqueous NaHSO$_3$ and with brine (aqueous washings were reextracted with some AcOMe) and evaporated in vacuo to give 1.56 g (90%) of crystalline **4** (R^1 = Me; R^2 = p-NB). White needles: mp 154–156 °C (CH$_2$Cl$_2$-Et$_2$O); [α]^{20}D −13 ± 1° (0.98%); IR 2.95, 5.48, 5.69, 5.87, 6.25, 6.58, 6.71, 6.95–7.08, 7.25, 7.45 μ; NMR δ 2.24 (s, 3), 4.56 (s, 2), 5.38 (s, 2), 5.52 (dd, 1, J = 6.5 and 8.5 Hz), 5.95 (d, 1, J = 6.5 Hz), 6.8–7.4 (m, 6), 7.5–8.3 (m, 4). Anal. Calcd for C$_{22}$H$_{19}$N$_3$O$_9$S (501.47): C, 52.69; H, 3.79; N, 8.38; O, 28.74. Found: C, 52.41; H, 3.86; N, 8.26; O, 29.01.

N-**Methoxalyl-(3***R***)-phenoxyacetamido-(4***R***)-isobutyrylthio-2-azetidinone (4, R^1 = *i*-Pr; R^2 = Me).** A stream of ozone was introduced at a rate of 0.33 mmol/min for 32 min into a solution of 1.41 g (3.24 mmol) of **3** (R^1 = *i*-Pr; R^2 = Me) in 30 mL of methanol at −20 °C. After another 2 h at −20 °C, the precipitated crystals of **4** (R^1 = *i*-Pr; R^2 = Me) were collected and washed on a filter with some MeOH. Another crystalline crop was obtained on concentration and further ozonization of the mother liquor. A total of 886 mg (66.8%) of **4** (R^1 = *i*-Pr; R^2 = Me) was thus obtained as white needles: mp 112–114 °C (MeOH); [α]^{20}D −51 ± 1° (1.02%); IR 2.97, 5.49, 5.70, 5.86, 6.25, 6.60, 6.70, 6.95, 7.32, 8.20 μ; NMR δ 1.16 (d, 6, J = 7 Hz), 2.7 (m, 1, J = 7 Hz), 3.92 (s, 3), 4.56 (s, 2), 5.63 (dd, 1, J = 5.4 and 9 Hz), 5.95 (d, 1, J = 5.4 Hz), 6.85–7.1 (m, 3), 7.2–7.45 (m, 3). Anal. Calcd for C$_{18}$H$_{20}$N$_2$O$_7$S (408.43): C, 52.93; H, 4.93; N, 6.85; O, 27.42; S, 7.85. Found: C, 52.70; H, 4.90; N, 6.65; O, 27.66; S, 7.95.

N-**Methoxalyl-(3***R***)-phenoxyacetamido-(4***R***)-benzoylthio-2-azetidinone (4, R^1 = Ph; R^2 = Me).** Ozonization of 1.475 g (3.15 mmol) of **3** (R^1 = Ph; R^2 = Me) in 50 mL of methanol at −25 °C and workup as described above for **4** (R^1 = Me; R^2 = Me) afforded, in two crops, a total of 1.12 g (80.6%) of **4** (R^1 = Ph; R^2 = Me) as white needles: mp 151–152 °C (AcOEt-Et$_2$O); [α]^{20}D +15 ± 1° (0.89%); IR 2.97, 5.49, 5.65, 5.89, 6.26, 6.61, 6.70, 6.97, 7.07, 7.31, 7.52, 8.11, 8.28, 8.51 μ; NMR δ 3.90 (s, 3), 4.53 (s, 2), 5.68 (dd, 1, J = 6.2 and 9 Hz), 6.16 (d, 1, J = 6.2 Hz), 6.7–7.9 (m, 11 H). Anal. Calcd for C$_{21}$H$_{18}$N$_2$O$_7$S (442.44): C, 57.01; H, 4.10; N, 6.33; O, 25.31; S, 7.25. Found: C, 56.83; H, 4.17; N, 6.43; O, 25.41; S, 7.09.

N-**Methoxalyl-(3***R***)-phenoxyacetamido-(4***R***)-*p*-nitrobenzoyl-thio-2-azetidinone (4, R^1 = *p*-NO$_2$C$_6$H$_4$; R^2 = Me).** Into a solution of 1.8 g of **3** (R^1 = p-NO$_2$C$_6$H$_4$; R^2 = Me) in 20 mL of ethyl acetate, ozone was introduced at −20 °C for 45 min at a rate of 0.33 mmol/min. Washing with 40 mL of 10% aqueous sodium bisulfite and twofold washing with 25 mL of 10% brine gave, after drying with sodium sulfate and evaporation in vacuo, the title compound. White crystals: mp 133 °C (MeOH); unstable on Merck analytical TLC silica gel plates; [α]^{20}D +33 ± 1° (1%); IR 2.97, 5.5, 5.7, 6.55, 7.45, 11.8 μ; NMR (acetone-d_6) 3.86 (s, 3), 4.63 (s, 2), 5.71 (dd, 1, J = 6.5 and 8 Hz), 6.54 (d, 1, J = 6.5 Hz), 6.8–7.3 (m, 5), 8.1–8.6 (m, 4), 8.57 (d, 1, J = 8 Hz). Anal. Calcd for C$_{21}$H$_{17}$N$_3$O$_9$S (487.44): C, 51.75; H, 3.52; N, 8.62. Found: C, 51.44; H, 3.82; N, 8.56.

(3***R***)-**Phenoxyacetamido-(4***R***)-acetylthio-2-azetidinone (5, R^1 = Me). A.** Crude *N*-*p*-nitrobenzoxalyl derivative **4** (R^1 = Me; R^2 = *p*-NB) as obtained by ozonization of 2.78 g of **3** (R^1 = Me; R^2 =

p-NB) was allowed to stand at room temperature in 55 mL of methyl acetate, 500 mL of methanol, and 11 mL of water. Evaporation in vacuo after 18 h and chromatography (300 g of Merck silica gel) gave methyl p-nitrobenzyl oxalate (eluted with benzene-AcOEt, 4:1) and 1.20 g of a material which was eluted with benzene-AcOEt, 1:1. Crystallization of the latter from CH$_2$Cl$_2$-Et$_2$O afforded 1.03 g (66.4% over two steps) of **5** (R^1 = Me) as white needles: mp 137.5–138 °C (lit.^{5} mp 138–141 °C); R_f 0.20 (benzene-AcOEt, 1:1); [α]^{20}D +98 ± 1° (1.16%); IR 2.96, 5.61, 5.92, 6.27, 6.60, 6.71, 6.97, 7.08 μ; NMR δ 2.30 (s, 3), 4.56 (s, 2), 5.53–5.71 (m, 2, J = 5 and 1 Hz), 7.32–7.44 (d?, 1), 6.8–7.0 (m, 3), 7.1–7.4 (m, 2). Anal. Calcd for C$_{13}$H$_{14}$N$_2$O$_4$S (294.33): C, 53.05; H, 4.79; N, 9.51; O, 21.74; S, 10.84. Found: C, 53.18; H, 4.84; N, 9.66; O, 22.00; S, 11.01.

B. Crude methoxalyl azetidinone **4** (R^1 = Me; R^2 = Me) as prepared by ozonization of 1 mmol of **3** (R^1 = Me; R^2 = Me) was methanolyzed at room temperature in 200 mL of methanol, 10 mL of acetone, and 4 mL of water. Evaporation in vacuo after 15 h and crystallization of the residue from AcOEt-benzene gave 150 mg (51% over two steps) of **5** (R^1 = Me), mp 137–138 °C. Another 58 mg (20%) of **5** (R^1 = Me) was obtained by chromatography of the mother liquor on Merck silica gel (toluene-AcOEt, 2:1). In the preceding fractions with toluene-AcOEt, 3:1, 44 mg of the β-lactam-free byproduct i (R^1 = Me; R^2 = Me) was isolated as an oil: IR 2.97, 5.74 (sh), 5.80 (sh), 5.85–5.95, 6.26, 6.55–6.73, 6.98 μ; NMR δ 2.30 (s, 3), 3.77 (s, 3), 3.86 (s, 3), 4.53 (s, 2), 5.12 (dd, 1, J = 5 and 8.5 Hz), 5.93 (dd, 1, J = 5 and 9 Hz), 6.8–7.4 (m, 5), 7.67 (d, 1, J = 8.5 Hz), 8.30 (d, 1, J = 9 Hz).

(3***R***)-**Phenoxyacetamido-(4***R***)-isobutyrylthio-2-azetidinone (5, R^1 = *i*-Pr).** A solution of 650 mg (1.59 mmol) of **4** (R^1 = *i*-Pr; R^2 = Me) in 13 mL of methyl acetate, 100 mL of methanol, and 13 mL of water was allowed to stand at room temperature for 2.5 h. Partial evaporation of the solvents and subsequent partition between CH$_2$Cl$_2$ and water afforded a crude product which was chromatographed on 30 g of Merck silica gel. With benzene-AcOEt, 4:1, 330 mg of **5** (R^1 = *i*-Pr) contaminated by a more mobile, β-lactam-free byproduct, probably i (R^1 = *i*-Pr; R^2 = Me), was eluted. Crystallization from CH$_2$Cl$_2$-Et$_2$O gave, in two crops, 295 mg (57.5%) of pure **5** (R^1 = *i*-Pr): mp 109–111 °C; R_f 0.26 (benzene-AcOEt, 1:1); [α]^{20}D +57 ± 1° (1.11%); IR 2.97, 5.61, 5.92, 6.25, 6.60, 6.70, 6.97, 7.08, 8.10 μ; NMR δ 1.14 (d, 6, J = 7 Hz), 2.67 (m, 1), 4.52 (s, 2), 5.49 (d, 1, J = 5 Hz), 5.63 (dd, 1, J = 5 and 8 Hz), 5.78 (d, 1, J = 8 Hz), 6.8–7.1 (m, 3), 7.2–7.4 (m, 2). Anal. Calcd for C$_{15}$H$_{18}$N$_2$O$_4$S (322.38): C, 55.89; H, 5.63; N, 8.69; O, 19.85; S, 9.95. Found: C, 55.79; H, 5.58; N, 8.73; O, 19.88; S, 9.71.

(3***R***)-**Phenoxyacetamido-(4***R***)-benzoylthio-2-azetidinone (5, R^1 = Ph).** Compound **4** (R^1 = Ph; R^2 = Me) (1.15 g, 2.6 mmol) was allowed to stand at room temperature in 30 mL of methyl acetate, 90 mL of methanol, and 2 mL of water. Evaporation in vacuo after 17 h and crystallization of the residue from CH$_2$Cl$_2$-Et$_2$O afforded 435 mg of crystalline **5** (R^1 = Ph), mp 160–162 °C. The material of the mother liquor was chromatographed on 70 g of Merck silica gel (deactivated with 10% of H$_2$O). With toluene-AcOEt, 2:1, 240 mg (∼19%) of the β-lactam-free byproduct i (R^1 = Ph; R^2 = Me) was first eluted. From the following fractions with the same solvent system, another 85 mg of **5** (R^1 = Ph) was obtained after crystallization from CH$_2$Cl$_2$-Et$_2$O. Thus, a total of 520 mg (56%) of **5** (R^1 = Ph) was isolated). White needles: mp 160–162 °C; R_f 0.20 (toluene-AcOEt, 1:1); [α]^{20}D +141 ± 1° (1.07%); IR 2.97, 5.60, 5.92, 6.00, 6.26, 6.59, 6.72, 6.97, 8.15, 8.28, 8.52, 9.26, 9.42 μ; NMR δ 4.56 (s, 2), 5.66–5.82 (m, 2), 6.8–7.9 (m, 12). Anal. Calcd for C$_{18}$H$_{16}$N$_2$O$_4$S (356.40): C, 60.66; H, 4.53; N, 7.86; O, 17.96; S, 9.00. Found: C, 60.56; H, 4.55; N, 7.87; O, 18.10; S, 9.00.

Compound i (R^1 = Ph; R^2 = Me): amorphous; R_f 0.28 (toluene-AcOEt, 1:1); IR 2.98, 5.70, 5.74, 5.84, 5.92, 6.26, 6.61, 6.70, 6.98, 7.08, 8.10, 8.29 μ; NMR δ 3.80 (s, 3), 3.86 (s, 3), 4.57 (s, 2), 5.24 (dd, 1, J = 5 and 9 Hz), 6.17 (dd, 1, J = 5 and 9 Hz), 6.8–7.9 (m, 11), 8.45 (d, 1, J = 9 Hz).

(3***R***)-**Phenoxyacetamido-(4***R***)-(*p*-nitrobenzoylthio)-2-azetidinone (5, R^1 = *p*-NO$_2$C$_6$H$_4$).** A solution of the crude methoxalyl derivative **4** (R^1 = p-NO$_2$C$_6$H$_4$; R^2 = Me) (487 mg, 1 mmol) in 1 mL of ethyl acetate was diluted with 20 mL of methanol containing 0.4 mL of H$_2$O and the resulting suspension was stirred overnight at room temperature. Evaporation in vacuo of the solution thus formed and crystallization of the residue from AcOEt-benzene afforded 240 mg (61%) of **5** (R^1 = p-NO$_2$C$_6$H$_4$). Another 30 mg (7.5%) of **5** (R^1 = p-NO$_2$C$_6$H$_4$) was obtained by chromatography of the mother liquor residue on Merck silica gel (CH$_2$Cl$_2$-AcOEt, 4:1). White needles: mp

159 °C (AcOEt); R_f 0.16 (toluene-AcOEt, 1:1); $[\alpha]^{20}{}_D$ +126 ± 1° (1%); IR (KBr) 5.65, 6.0, 6.55, 7.4, 11.8 μ; NMR (acetone-d_6) 4.56 (s, 3), 5.65 (dd, 1, J = 5 and 9 Hz), 5.86 (d, 1, J = 5 Hz), 6.8-7.3 (m, 5), 8.0-8.4 (m, 5). Anal. Calcd for $C_{18}H_{15}N_3O_6S$ (401.39): C, 53.86; H, 3.77; N, 10.47; S, 7.99. Found: C, 53.70; H, 3.76; N, 10.36; S, 7.94.

tert-Butyl ((3R)-Phenoxyacetamido-(4R)-acetylthio-2-azetidinon-1-yl)triphenylphosphoranylideneacetate (8, R^1 = Me; R^2 = *t*-Bu). A solution of 294 mg (1 mmol) of 5 (R^1 = Me) and of 0.5 g (~3.1 mmol) of *tert*-butyl glyoxylate hydrate in 10 mL of toluene and 2.5 mL of DMF was stirred at room temperature (N_2) in the presence of molecular sieves (3 Å; activated at 250 °C (0.01 Torr)). Filtration after 1 h and repeated evaporation with toluene under high vacuum afforded 450 mg of a crude mixture of both epimers of 6 (R^1 = Me; R^2 = *t*-Bu) contaminated by a small amount of the glyoxylate reagent.

This crude product in 15 mL of dioxane was stirred at room temperature with 300 mg of thionyl chloride in the presence of polymeric Hünig base[21] (1 g, i.e., 3.4 mequiv, suspended 30 min before use in dioxane). After 3 h, the reaction mixture was filtered, the polymeric base was washed with dioxane, and the combined filtrates were evaporated in vacuo to give the crude chloride(s) 7 (R^1 = *t*-Bu).

A solution of the latter and of 393 mg (1.5 mmol) of triphenylphosphine in 15 mL of dioxane was heated under N_2 at 50 °C in the presence of 1 g of polymeric Hünig base (pretreated with dioxane). Filtration after 18 h at 50 °C, evaporation in vacuo, and chromatography of the residue (Merck silica gel) afforded 314 mg (47% over three steps) of the phosphorane 8 (R^1 = Me; R^2 = *t*-Bu) (eluted with benzene-AcOEt, 1:1). Amorphous solid: R_f 0.21 (benzene-AcOEt, 1:1); $[\alpha]^{20}{}_D$ −19 ± 1° (0.86%); IR 2.98, 5.68, 5.92, 6.11, 6.20, 6.28 (sh), 6.34 (sh), 6.60, 6.72, 6.98, 7.35 μ. Anal. Calcd for $C_{37}H_{37}N_2O_6PS$ (668.78): N, 4.18, S, 4.79. Found: N, 4.01; S, 4.67.

Methyl ((3R)-Phenoxyacetamido-(4R)-acetylthio-2-azetidinon-1-yl)triphenylphosphoranylideneacetate (8, R^1 = Me; R^2 = Me). A. From Azetidinone 5 (R^1 = Me). Azetidinone 5 (R^1 = Me) (588 mg, 2 mmol) in 20 mL of toluene and 5 mL of DMF was stirred at room temperature with 640 mg (~6 mmol) of methyl glyoxylate hydrate and with activated molecular sieves. Filtration and evaporation in vacuo after 1.5 h gave a crude mixture of the adducts 6 (R^1 = Me; R^2 = Me) which in turn was stirred in 20 mL of dioxane with 600 mg of thionyl chloride and with 2 g of polymeric Hünig base for a period of 3 h. Filtration, washing on a filter with dioxane, and evaporation of the combined filtrates in vacuo afforded the crude chlorides 7 (R^1 = Me; R^2 = Me). The latter product and 786 mg of triphenylphosphine in 30 mL of dioxane were heated at 50 °C (N_2) in the presence of 2 g of polymeric Hünig base. After 18 h, the polymeric base was filtered off, the filtrate was evaporated in vacuo, and the residue was chromatographed on 30 g of Merck silica gel. With benzene-AcOEt, 4:1, the excess of Ph_3P and some minor impurities were eluted; the phosphorane 8 (R^1 = Me; R^2 = Me) (628 mg, 50% over three steps) was removed from the column with a 1:1 mixture of the mentioned solvents. Amorphous solid: R_f 0.32 (AcOEt); $[\alpha]^{20}{}_D$ −29 ± 1° (0.77%); IR 2.96, 5.67, 5.90, 6.19, 6.25 (sh), 6.60, 6.71, 6.97 μ. Anal. Calcd for $C_{34}H_{31}N_2O_6PS$ (626.67): N, 4.47; S, 5.11. Found: N, 4.50; S, 5.33.

B. From *N*-Methoxalylazetidinone 4 (R^1 = Me; R^2 = Me). To a solution of 380 mg (1 mmol) of the *N*-methoxalylazetidinone 4 (R^1 = Me; R^2 = Me) in 10 mL of THF, 1.5 mL of a 1 M solution of B_2H_6 in THF (Aldrich) was added at 0 °C (N_2) and the resulting reaction mixture was stirred at 0 °C for 60 min. Washing in CH_2Cl_2 with 25% aqueous NH_4Cl and with water, drying over Na_2SO_4, and evaporation in vacuo gave crude hemiaminals 6 (R^1 = Me; R^2 = Me) (320 mg) which were used for the next step ($SOCl_2$/polymeric base) without any purification. The final yield of the phosphorane 8 (R^1 = Me; R^2 = Me) prepared from this material in the above described way was 35% (based on 4 (R^1 = Me; R^2 = Me)).

p-Nitrobenzyl ((3R)-Phenoxyacetamido-(4R)-acetylthio-2-azetidinon-1-yl)triphenylphosphoranylideneacetate (8, R^1 = Me; R^2 = *p*-NB). A solution of 3.53 g (12 mmol) of 5 (R^1 = Me) and of 9.18 g (~36 mmol) of *p*-nitrobenzyl glyoxylate ethylhemiacetal in 36 mL of DMF and 145 mL of toluene was stirred at room temperature with molecular sieves for 4 h. To remove excess glyoxylate, the crude product (as obtained by filtration and evaporation) was triturated with five 150-mL portions of Et_2O-pentane, 1:1. A short chromatography of the residual material on 200 g of Merck silica gel (toluene-AcOEt, 1:1) afforded 5.0 g (82%) of the hemiaminals 6 (R^1 = Me; R^2 =

p-NB) as an amorphous solid: R_f 0.25 (elongated spot, benzene-AcOEt, 1:1); IR 2.85, 2.97, 5.61, 5.72, 5.90, 6.26, 6.55, 6.70, 6.97, 7.09, 7.44 μ. The conversion of the latter product to the chlorides 7 (R^1 = Me; R^2 = *p*-NB) was achieved in 110 mL of dioxane with 3.57 g (~3 equiv) of $SOCl_2$ in the presence of 7.5 g of polymeric Hünig base (5 h at room temperature, filtration and evaporation in vacuo) Amorphous solid: R_f 0.47 and 0.52 (two spots, benzene-AcOEt, 1:1); IR 2.97, 5.60, 5.72, 5.90, 6.30, 6.55, 6.70, 6.95-7.10, 7.42 μ. A solution of the chlorides and of 3.93 g (~1.5 equiv) of Ph_3P in 150 mL of dioxane was heated at 50 °C (N_2) in the presence of 7.5 g of polymeric Hünig base for 17 h. Filtration, evaporation in vacuo, and chromatography on 250 g of Merck silica gel (deactivated with 10% of H_2O) gave 4.04 g (54.4% from 6 (R^1 = Me; R^2 = *p*-NB)) of the phosphorane 8 (R^1 = Me; R^2 = *p*-NB) which was eluted in several fractions with toluene-AcOEt, 4:1. Amorphous solid: R_f 0.20 (toluene-AcOEt, 1:1); $[\alpha]^{20}{}_D$ −12 ± 1° (1.05%); IR 2.98, 5.66, 5.90, 6.09 (sh), 6.15, 6.24, 6.57, 6.71, 6.98, 7.08 (sh), 7.44 μ. Anal. Calcd for $C_{40}H_{34}N_3O_8PS$ (747.76): C, 64.25; H, 4.58; N, 5.62; S, 4.29; P, 4.29. Found: C, 64.09; H, 4.77; N, 5.49; S, 4.00; P, 4.13.

Trichloroethyl ((3R)-Phenoxyacetamido-(4R)-acetylthio-2-azetidinon-1-yl)triphenylphosphoranylideneacetate (8, R^1 = Me; R^2 = CH_2CCl_3). The crude hemiaminals 6 (R^1 = Me; R^2 = CH_2CCl_3) were prepared from 5 (R^1 = Me) with 3 equiv of trichloroethyl glyoxylate hydrate (toluene, DMF, molecular sieves, 4 h at room temperature). Excess glyoxylate and DMF were removed by washing in toluene with water. The subsequent reactions with $SOCl_2$ and with Ph_3P were realized similarly as with the *tert*-butyl ester (see above). The phosphorane 8 (R^1 = Me; R^2 = CH_2CCl_3) as obtained by final chromatography was an amorphous solid: R_f 0.34 (benzene-AcOEt, 1:1); IR 2.98, 5.67, 5.91, 6.12, 6.27, 6.30 (sh), 6.61, 6.72, 6.98, 7.39 μ. Anal. Calcd for $C_{35}H_{30}Cl_3N_2O_6PS$ (744.03): C, 56.50; H, 4.07; Cl, 14.30; N, 3.77; P, 4.16; S, 4.31. Found: C, 57.07; H, 4.30; Cl, 14.13; N, 3.66; P, 4.09; S, 4.21.

tert-Butyl ((3R)-Phenoxyacetamido-(4R)-isobutyrylthio-2-azetidinon-1-yl)triphenylphosphoranylideneacetate (8, R^1 = *i*-Pr; R^2 *t*-Bu). This phosphorane was prepared from the isobutyrylthioazetidinone 5 (R^1 = *i*-Pr) in three steps in a similar way to the acetylthiophosphorane 8 (R^1 = Me; R^2 = *t*-Bu) (see above). It was purified by column chromatography (Merck silica gel; benzene-AcOEt, 1:1). Amorphous solid: R_f 0.25 (benzene-AcOEt, 1:1); IR 2.97, 5.65, 5.90, 6.10, 6.18, 6.25, 6.59, 6.70, 6.96, 7.33 μ. Anal. Calcd for $C_{36}H_{41}N_2O_6PS$ (696.80): C, 67.23; H, 5.93; N, 4.02; P, 4.45; S, 4.60. Found: C, 67.07; H, 5.98; N, 4.03; P, 4.40; S, 4.52.

p-Nitrobenzyl ((3R)-Phenoxyacetamido-(4R)-benzoylthio-2-azetidinon-1-yl)triphenylphosphoranylideneacetate (8, R^1 = Ph; R^2 = *p*-NB). This phosphorane was prepared from 5 (R^1 = Ph) in a similar way to the acetylthiophosphorane 8 (R^1 = Me; R^2 = *p*-NB) (see above). The epimeric chlorides 7 (R^1 = Ph; R^2 = *p*-NB) were purified by column chromatography (Merck silica gel, toluene-AcOEt, 9:1) (64.5% over two steps). Amorphous solid: R_f 0.44 and 0.50 (two spots, toluene-AcOEt, 1:1); IR 2.97, 5.58, 5.69, 5.90, 6.00, 6.26, 6.30, 6.58, 6.68, 7.46, 8.29 μ. The phosphorane 8 (R^1 = Ph; R^2 = *p*-NB) as obtained by final chromatography (Merck silica gel, toluene-AcOEt, 2:1) (71%) was amorphous: R_f 0.21 (toluene-AcOEt, 1:1); $[\alpha]^{20}{}_D$ −37 ± 1° (0.77%); IR 2.96, 5.66, 5.91, 6.00, 6.16, 6.25, 6.58, 6.70, 7.45, 8.30, 8.51, 9.04 μ. Anal. Calcd for $C_{45}H_{36}N_3O_8PS$ (809.83): C, 66.74; H, 4.48; N, 5.19; S, 3.96. Found: C, 67.16; H, 4.79; N, 5.05; S, 4.15.

tert-Butyl ((3R)-Phenoxyacetamido-(4R)-*p*-nitrobenzoylthio-2-azetidinon-1-yl)triphenylphosphoranylideneacetate (8, R^1 = *p*-$NO_2C_6H_4$; R^2 = *t*-Bu). The title compound was prepared from 5 (R^1 = *p*-$NO_2C_6H_4$) using the procedure described for 8 (R^1 = Me; R^2 = *t*-Bu). The chlorides 7 (R^1 = *p*-$NO_2C_6H_4$; R^2 = *t*-Bu) were purified by column chromatography (Merck silica gel, toluene-AcOEt, 4:1) and isolated as an epimeric mixture. Amorphous solid: IR 2.98, 5.62, 5.78, 5.93-5.98, 6.25, 6.56, 6.72, 7.35, 7.42 μ. The title phosphorane (purified by column chromatography on Merck silica gel with toluene-AcOEt, 2:1) was obtained upon reaction of chlorides 7 (R^1 = *p*-$NO_2C_6H_4$; R^2 = *t*-Bu) with 2 equiv of triphenylphosphine in a minimum amount of THF to dissolve both solid reactants (room temperature, 2 days) in 52% yield (based on 5 (R^1 = *p*-$NO_2C_6H_4$)). Amorphous solid: R_f 0.23 (toluene-AcOEt, 1:1); IR 2.97, 5.65, 5.90, 6.00, 6.10, 6.19, 6.25, 6.55, 6.71, 7.00, 7.35, 7.45 μ. Anal. Calcd for $C_{42}H_{38}N_3O_8PS$ (775.8): C, 65.02; H, 4.94; N, 5.42; S, 4.13. Found: C, 64.48; H, 5.00; N, 5.33; S, 3.74.

tert-Butyl (6R)-Phenoxyacetamido-2-methyl-(5R)-penem-3-carboxylate (9, R^1 = Me; R^2 = *t*-Bu). Phosphorane 8 (R^1 = Me; R^2 =

t-Bu) (668 mg) in toluene (600 mL) was heated under argon at 70 °C for 10 h. Evaporation in vacuo and chromatography of the residue on 60 g of an acid-washed silica gel (Merck silica gel washed with concentrated HCl and subsequently with distilled water to neutrality) afforded, in several fractions with benzene-AcOEt, 4:1, 274 mg (70%) of the penem ester 9 (R^1 = Me; R^2 = *t*-Bu) as an amorphous solid: R_f 0.53 (benzene-AcOEt, 1:1); $[\alpha]^{20}_D$ +202 ± 1° (0.57%); UV (96% EtOH) λ_{max} 304 (ε 7800), 275 (5330), 268 (5640), 263 (5350); IR 2.98, 5.57, 5.90, 6.27, 6.60, 6.71, 6.97-7.08, 7.33 μ; NMR δ 1.52 (s, 9), 2.33 (s, 3), 4.56 (s, 2), 5.79-5.85 (m, 2, H5 and H6), 7.44 (d, 1, *J* = 8 Hz), 6.9-7.1 (m, 3), 7.2-7.4 (m, 2); MS (110 °C) *m/e* 390 (M*), 362, 334, 317, 200, 191, etc. Anal. Calcd for $C_{19}H_{22}N_2O_5S$ (390.45): C, 58.44; H, 5.68; N, 7.17; S, 8.21. Found: C, 58.47; H, 5.85; N, 7.04; S, 8.34.

When a solution of 9 (R^1 = Me; R^2 = *t*-Bu) (4.9 mg) in TFA-CH₂Cl₂, 1:4 (0.5 mL), was allowed to stand at 0 °C for 1 h and the resulting solution was partitioned between more CH₂Cl₂ and concentrated aqueous AcONa, *tert*-butyl 5-methylthiazole-4-carboxylate 20 (R^1 = Me; R^2 = *t*-Bu) (2 mg, 80%) was isolated: mp 37-38.5 °C (purified by chromatography); R_f 0.38 (benzene-AcOEt, 1:1); UV (96% EtOH) λ_{max} 236 nm; IR 5.85, 5.96 (sh), 7.01, 7.32, 7.43, 7.50, 7.84-8.00, 8.59 (sh), 8.70, 9.43; 11.70 μ; NMR δ 1.63 (s, 9), 2.76 (s, 3), 8.56 (s, 1).

Methyl (6*R*)-Phenoxyacetamido-2-methyl-(5*R*)-penem-3-carboxylate (9, R^1 = Me; R^2 = Me). Heating 42 mg of the phosphorane 8 (R^1 = Me; R^2 = Me) in 30 mL of toluene at 80 °C for 18 h resulted in only partial conversion to the penem ester 9 (R^1 = Me; R^2 = Me) of which 9 mg (39%) was isolated by chromatography on acid-washed silica gel. Amorphous solid: R_f 0.52 (AcOEt); UV (96% EtOH) λ_{max} 306, 275, 268, 262 nm; IR 2.97, 5.56, 5.85-5.90, 6.27, 6.60, 6.70, 6.97, 7.08 μ; NMR δ 2.39 (s, 3), 3.82 (s, 3), 4.57 (s, 2), 5.82-6.01 (m, 2, H5 and H6), 6.9-7.15 (m, 3), 7.22-7.55 (m, 3); MS (130 °C) *m/e* 348 (M*), 320, 317, 191, 158, 126, 107.

Extension of the reaction time to 46 h (80 °C) brought a practically complete conversion of the phosphorane and an increased yield (57%) of the penem ester, but the latter was contaminated by its decomposition product, i.e., methyl 5-methylthiazole-4-carboxylate 20 (R^1 = Me; R^2 = Me): NMR δ 2.80 (s, 3), 3.94 (s, 3), 8.57 (s, 1).

A solution of 22 mg of the penem ester 9 (R^1 = Me; R^2 = Me) and 13 mg of 85% *m*-chloroperbenzoic acid in 1.2 mL of CH₂Cl₂ was stirred at room temperature for 1.5 h, the reaction mixture was washed with 8% aqueous NaHCO₃, and the organic layer was evaporated in vacuo to give 15 mg of an oily *S*-oxide, decomposing on Merck TLC plates: IR 2.97, 5.53, 5.79, 5.93, 6.25, 6.59, 6.70, 6.97, 7.54, 7.65, 8.07-8.27, 8.54, 8.66, 9.26, 9.44, 9.68 μ; NMR δ 2.57 (s, 3), 3.90 (s, 3), 4.52 (s, 2), 4.73 (d, 1, *J* = 6 Hz), 6.26 (dd, 1, *J* = 6 and 10 Hz), 6.82-7.38 (2 m's, 5), 8.55 (d, 1, *J* = 10 Hz).

p-Nitrobenzyl (6*R*)-Phenoxyacetamido-2-methyl-(5*R*)-penem-3-carboxylate (9, R^1 = Me; R^2 = *p*-NB). A solution of 209 mg of the phosphorane 8 (R^1 = Me; R^2 = *p*-NB) in 210 mL of toluene was heated, under argon and in the presence of a small amount of hydroquinone, at 80 °C for 4.5 days. Evaporation in vacuo and chromatography of the residue on 30 g of acid-washed silica gel afforded, with toluene-AcOEt, 4:1, as eluent, 92 mg (70%) of the penem ester 9 (R^1 = Me; R^2 = *p*-NB). Amorphous solid: R_f 0.52 (benzene-AcOEt, 1:1); $[\alpha]^{20}_D$ +163 ± 1° (0.793%); UV (96% EtOH) λ_{max} 304 nm (ε 8800), 274 (11 150), 267 (12 260), 264 (12 000); IR 2.97, 5.54, 5.86-5.91, 6.30, 6.58, 6.72, 6.95, 7.08, 7.43, 7.66 μ; NMR δ 2.42 (s, 3), 4.62 (s, 2), 5.28 (d, 1, *J* = 14 Hz), 5.50 (d, 1, *J* = 14 Hz), 5.90-6.08 (m, 2, H5 and H6), 6.9-7.5 (m, 6), 7.6-7.7 (m, 2), 8.23-8.33 (m, 2). Anal. Calcd for $C_{22}H_{19}N_3O_7S$ (469.46): C, 56.28; H, 4.08; N, 8.95; O, 23.85; S, 6.83. Found: C, 56.66; H, 4.27; N, 8.73; O, 23.74; S, 6.50.

In a cyclization experiment with a sample of 8 (R^1 = Me; R^2 = *p*-NB) which was contaminated by a trace of a more mobile impurity, and using Merck instead of the acid-washed silica gel for the ultimate chromatography, 33% of *p*-nitrobenzyl 5-methylthiazole-4-carboxylate was isolated: mp 130 °C (as obtained by chromatography with benzene-AcOEt, 4:1); R_f 0.32 (benzene-AcOEt, 1:1); IR 5.82, 6.23, 6.57, 7.00, 7.25, 7.43, 7.57, 7.83-8.05, 8.45, 8.75, 9.02, 9.40, 9.85 μ; NMR δ 2.84 (s, 3), 5.51 (s, 2), 7.66 (m, 2), 8.25 (m, 2), 8.62 (s, 1).

tert-Butyl (6*R*)-Phenoxyacetamido-2-isopropyl-(5*R*)-penem-3-carboxylate (9, R^1 = *i*-Pr; R^2 = *t*-Bu). Heating 81 mg of the phosphorane 8 (R^1 = *i*-Pr; R^2 = *t*-Bu) in 40 mL of toluene under argon at 80 °C for 6 days and at 100 °C for another 2 days afforded, after evaporation in vacuo and chromatography on four Merck analytical silica gel plates (20 × 20 × 0.05 cm) in benzene-AcOEt, 1:1: (a) 2.8 mg (~6%) of the penem ester 9 (R^1 = *i*-Pr; R^2 = *t*-Bu) [R_f 0.58

(benzene-AcOEt, 1:1); IR 2.98, 5.59, 5.91, 6.26, 6.30, 6.35 (sh), 6.60, 6.70, 7.34, 8.70 μ]; (b) 6.0 mg (23%) of *tert*-butyl 5-isopropylthiazole-4-carboxylate 20 (R^1 = *i*-Pr; R^2 = *t*-Bu) [R_f 0.42 (benzene-AcOEt, 1:1); IR 5.86, 7.34, 7.49, 7.56, 8.67, 8.81 μ]; (c) 21 mg of unreacted phosphorane 8 (R^1 = *i*-Pr, R^2 = *t*-Bu); and (d) 13.2 mg (41%) of triphenylphosphine oxide.

p-Nitrobenzyl (6*R*)-Phenoxyacetamido-2-phenyl-(5*R*)-penem-3-carboxylate (9, R^1 = Ph; R^2 = *p*-NB). Phosphorane 8 (R^1 = Ph; R^2 = *p*-NB) (193 mg) in toluene (100 mL) was heated under argon (and with some hydroquinone) at 90 °C for 3.5 days. The resulting reaction mixture was washed with water, dried, and evaporated. Column chromatography on 20 g of acid-washed silica gel with toluene-AcOEt, 9:1, gave 56 mg (53% as based on consumed phosphorane) of the penem ester 9 (R^1 = Ph; R^2 = *p*-NB); 32 mg of the phosphorane 8 (R^1 = Ph; R^2 = *p*-NB) was recovered with toluene-AcOEt, 1:1. The penem ester 9 (R^1 = Ph; R^2 = *p*-NB) was obtained as an amorphous solid decomposing on Merck analytical silica gel plates: $[\alpha]^{20}_D$ +139 ± 1° (0.933%); UV (96% EtOH) λ_{max} 324 nm (ε 6500), 273 (17 530), 267 (19 400), 262 (19 600); IR 2.97, 5.55, 5.79 (sh), 5.89, 6.25, 6.30 (sh), 6.35 (sh), 6.58, 6.71, 6.96-7.10, 7.29, 7.44 μ; NMR δ 4.60 (s, 2), 5.24 (q, 2, *J* = 14 Hz), 5.97-6.11 (m, 2, H5 and H6), 6.86-8.20 (several m's, 15). Anal. Calcd for $C_{27}H_{21}N_3O_7S$ (531.54): C, 61.01; H, 3.98; N, 7.91; S, 6.03. Found: C, 60.96; H, 4.19; N, 7.83; S, 6.23.

tert-Butyl (6*R*)-Phenoxyacetamido-2-*p*-nitrophenyl-(5*R*)-penem-3-carboxylate (9, R^1 = *p*-NO₂C₆H₄; R^2 = *t*-Bu). A solution of 8 (R^1 = *p*-NO₂C₆H₄; R^2 = *t*-Bu) (77.6 mg, 0.1 mmol) in 10 mL of toluene was heated under argon at 55 °C for 17 h. Evaporation in vacuo and chromatography on acid-washed silica gel (2 g) with toluene-AcOEt, 4:1, afforded 45 mg (90%) of 9 (R^1 = *p*-NO₂C₆H₄; R^2 = *t*-Bu) as an amorphous yellow solid: it decomposes on Merck TLC silica gel plates; $[\alpha]^{20}_D$ +92 ± 1° (1%); UV (*n*-hexane) λ_{max} 262 nm (ε 16 000), 267 (16 000), 348 (5300); IR 2.97, 5.55, 5.90, 6.25, 6.60, 6.70, 7.45 μ; NMR δ 1.45 (s, 9), 4.58 (s, 2), 5.89-6.07 (m, 2, H5 and H6), 6.9-8.3 (several m's, 10). Anal. Calcd for $C_{24}H_{23}N_3O_7S$ (497.52): C, 57.94; H, 4.66; N, 8.45; S, 6.44. Found: C, 58.31; H, 4.71; N, 8.42, S, 6.12.

***N*-*p*-Nitrobenzoxalyl-(3*R*)-phenoxyacetamido-(4*R*)-(2'-benz-thiazolyldithio)-2-azetidinone (10).** Into a solution of 1.95 g (~3 mmol) of the disulfide 2 (R^2 = *p*-NB) in 150 mL of methyl acetate, a stream of O₃/O₂ was introduced at a rate of 0.1 mmol O₃/min while cooling in a dry ice-acetone bath. After 40 min of introduction and another 15 min of standing at −78 °C, excess O₃ was removed with N₂ and the ozonization mixture was washed at 0 °C with 10% aqueous NaHSO₃ and with brine (the aqueous layers were reextracted with AcOMe). Drying (Na₂SO₄) and evaporation of the combined organic parts afforded 1.7 g of crude, crystalline 10. Crystallization from hot CH₂Cl₂ gave, in several crops, 1.38 (74%) of pure 10: mp 130-131 °C; decomposes on Merck TLC silica plates; $[\alpha]^{20}_D$ +28 ± 1° (0.923%); IR 2.98, 5.49, 5.70, 5.87, 5.92 (sh), 6.25, 6.57, 6.71, 6.87, 6.96 (sh), 7.08, 7.25, 7.42 μ; NMR δ 4.75 (s, 2), 5.48 (s, 2), 5.48 (dd, 1, overlaps with the preceding signal), 5.79 (d, 1, *J* = 6 Hz), 6.9-7.1 (m, 3), 7.2-7.5 (m, 4), 7.58-7.73 (m, 2), 7.78-7.93 (m, 2), 8.15-8.29 (m, 2), 9.44 (d, 1, *J* = 8 Hz). Anal. Calcd for $C_{27}H_{20}N_4O_8S_3$ (624.65): C, 51.91; H, 3.22; N, 8.96; O, 20.48; S, 15.39. Found: C, 51.77; H, 3.37; N, 8.73; O, 20.30; S, 15.32.

(3*R*)-Phenoxyacetamido-(4*R*)-(2'-benzthiazolyldithio)-2-azetidinone (11). Crude ozonization product 10 as obtained from 1.95 g of 2 (R^2 = *p*-NB) was refluxed in 220 mL of MeOH, 30 mL of methyl acetate, and 4.4 mL of water for 20 min. The residue after evaporation of the solvents in vacuo was chromatographed on 100 g of Merck silica gel. Benzene-AcOEt, 4:1, eluted methyl *p*-nitrobenzyl oxalate; with AcOEt, 0.85 g of 11, slightly contaminated by a more mobile impurity, was collected. Triturating the latter material with Et₂O afforded 740 mg (59% over two steps) of pure, crystalline 11: mp 156-158 °C (CH₂Cl₂-MeOH); R_f 0.26 (benzene-AcOEt, 1:1); $[\alpha]^{20}_D$ +389 ± 1° (0.936%); IR 2.96, 5.59, 5.91, 6.25, 6.60, 6.70, 6.85, 6.97, 7.08, 8.12, 8.20 (sh), 8.28 (sh), 9.26, 9.45 μ; NMR (CDCl₃-CD₃OD) δ 4.58 (q, 2), 5.28 (d, 1, *J* = 4.6 Hz), 5.45 (d, 1, *J* = 4.6 Hz), 6.9-7.1 (m, 3), 7.2-7.5 (m, 4), 7.7-7.9 (m, 2). Anal. Calcd for $C_{18}H_{15}N_3O_3S_3$ (417.54): C, 51.78; H, 3.62; N, 10.06; O, 11.50; S, 23.04. Found: C, 51.62; H, 3.67; N, 9.95; O, 11.53; S, 23.17.

Ethyl ((3*R*)-Phenoxyacetamido-2-azetidinon-(4*R*)-ylthio)triphen-ylphosphoranylidenepyruvate (12). A solution of 316 mg (0.76 mmol) of the disulfide 11 and 300 mg (0.79 mmol) of ethyl triphenylphosphoranylidene pyruvate (for preparation see below) in 70 mL of glyme was allowed to stand under N₂ at room temperature for 3 days.

Evaporation in vacuo and chromatography on 20 g of Merck silica gel gave (a) 2-mercaptobenzthiazole (benzene–AcOEt, 3:1) and (b) 427 mg (90%) of the phosphorane **12** (eluted with AcOEt). The latter was obtained as an amorphous solid; R_f 0.21 (AcOEt); $[\alpha]^{20}_D$ +65 ± 1° (1.01%); IR 2.96, 5.63, 5.83 (sh), 5.91, 6.27, 6.48, 6.60 (sh), 6.72, 6.97, 7.07, 7.50, 8.36, 9.08 μ. Anal. Calcd for $C_{34}H_{31}N_2O_6PS$ (626.63): C, 65.17; H, 4.99; N, 4.47; P, 4.94; S, 5.12. Found: C, 64.73; H, 5.03; N, 4.47; P, 5.00; S, 5.53.

Ethyl Triphenylphosphoranylidenepyruvate. Equimolecular amounts of ethyl bromopyruvate and of triphenylphosphine in CH_2Cl_2 were allowed to stand at room temperatue for 1.5 h. The crude product obtained on evaporation was partitioned between pentane and water (with the help of some THF), the aqueous layer was made alkaline with excess $NaHCO_3$, and the phosphorane was extracted with CH_2Cl_2; it was contaminated by triphenylphosphine oxide. Crystallization from hot acetone afforded pure phosphorane: mp 187 °C (22–25%); IR 5.78, 5.85, 6.33, 6.40, 6.75, 6.97, 8.20, 9.05 μ. Anal. Calcd for $C_{23}H_{21}O_3P$ (376.43): C, 73.40; H, 5.63; P, 8.23. Found: C, 73.50; H, 5.50; P, 8.40.

Ethyl β-((3R)-Phenoxyacetamido-2-azetidinon-(4R)-ylthio)acrylate (13). To a solution of 4.0 g (6.38 mmol) of the phosphorane **12** in 80 mL of acetic, 40 mL of propionic, and 10 mL of formic acids, a total of 4.0 g of $NaBH_4$ was added in many portions during 25 min while stirring vigorously in an ice–water bath. Concentration in vacuo, successive washing in CH_2Cl_2 with 25% aqueous NH_4Cl and with 8% aqueous $NaHCO_3$, and evaporation gave 3.9 g of a crude product. Dry-column chromatography of the latter on 300 g of Woelm silica gel in AcOEt afforded 1.45 g (79% as based on consumed **12**) of crystalline **13** and 0.71 g of unconsumed phosphorane **12**. Acrylate **13**: mp 109–112 °C (CH_2Cl_2–Et_2O); R_f 0.44 (AcOEt); $[\alpha]^{20}_D$ −29 ± 1° (1.05%); UV (96% EtOH) λ_{max} 273 nm (ε 18 300), 269 (18 000); IR 2.95, 5.60, 5.89, 6.29, 6.60, 6.71, 6.98, 7.09, 7.35, 7.70, 7.84, 8.11, 8.29, 8.55, 9.25, 9.44, 9.70 μ; NMR δ 1.22 (t, 3, J = 7 Hz), 4.14 (q, 2, J = 7 Hz), 4.50 (s, 2), 5.27 (d, 1, J = 4.8 Hz), 5.66 (dd, 1, J = 4.8 and 9 Hz), 5.81 (d, 1, J = 15.5 Hz), 7.55 (d, 1, J = 15.5 Hz), 7.85 (d, 1, J = 9 Hz), 7.53 (broad s, 1), 6.82–7.08 (m, 3), 7.17–7.35 (m, 2). Anal. Calcd for $C_{16}H_{18}N_2O_5S$ (350.39): C, 54.84; H, 5.18; N, 8.00; O, 22.83; S, 9.14. Found: C, 54.56; H, 5.27; N, 7.87; O, 22.93; S, 9.11.

A 55-mg fraction of the cis isomer of **13** was also isolated in the above-mentioned chromatography: R_f 0.39 (AcOEt); IR 2.97, 5.60, 5.91, 6.05, 6.25, 6.34, 6.60, 6.70, 6.97, 7.08, 7.30, 7.42, 8.10, 8.20, 8.55, 9.25, 9.42 μ; NMR (acetone-d_6) 1.22 (t, 3; J = 7 Hz), 2.81 (broad s, 1), 4.14 (q, 2, J = 7 Hz), 4.58 (s, 2), 5.34 (d, 1, J = 4.8 Hz), 5.55 (ddd, 1, J = 4.8, 8 and 1 Hz), 5.89 (d, 1, J = 10 Hz), 7.28 (d, 1, J = 10 Hz), 6.88–7.04 (m, 3), 7.18–7.36 (m, 2), 8.23 (d, 1, J = 8 Hz).

tert-Butyl [(3R)-Phenoxyacetamido-(4R)-(β-ethoxycarbonyl-vinylthio)-2-azetidinon-1-yl]triphenylphosphoranylideneacetate (15, R² = t-Bu). Acrylate **13** (240 mg, 0.69 mmol) and tert-butyl glyoxylate hydrate (340 mg, ~3.3 equiv) in toluene (8 mL) and DMF (2 mL) were stirred at room temperature in the presence of activated molecular sieves for 3 h. Thorough evaporation, finally under high vacuum, gave a crude mixture of diastereomeric hemiaminals which was treated in dioxane (9 mL) at room temperature with 220 mg of thionyl chloride in the presence of polymeric Hünig base (0.8 g, 3.34 mequiv/g). The diastereomeric mixture of chlorides, obtained after 3 h by filtration and evaporation in vacuo, was heated in dioxane (14 mL) at 50 °C with 280 mg (~1.5 equiv) of triphenylphosphine and with 0.8 g of the polymeric base. After 20 h, the base was filtered off and the filtrate was concentrated in vacuo. Chromatography of the residue on 30 g of Merck silica gel afforded, with benzene–AcOEt, 1:1, 347 mg (70%, based on **13**) of the phosphorane **15** (R² = t-Bu) as an amorphous solid; R_f 0.25 (benzene–AcOEt, 1:1); IR 2.97, 5.66, 5.90, 6.14, 6.30, 6.62, 6.73, 6.99, 7.28, 7.36, 7.70–8.20, 8.63, 9.10, 10.60 μ. Anal. Calcd for $C_{40}H_{41}N_2O_7PS$ (724.92): N, 3.86; S, 4.42. Found: N, 3.82; S, 4.30.

Methyl [(3R)-Phenoxyacetamido-(4R)-(β-ethoxycarbonylvinyl-thio)-2-azetidinon-1-yl]triphenylphosphoranylideneacetate (15, R² = Me). Using methyl glyoxylate hydrate in the first step of the above-described procedure, the phosphorane **15** (R² = Me) (45 mg) was prepared from **13** (50 mg) in an overall yield of 52%. Amorphous solid: R_f 0.26 (AcOEt); IR 2.97, 5.67, 5.80 (broad), 6.10, 6.15, 6.27, 6.60, 6.70, 6.97, 7.24, 7.35, 7.70–8.15, 8.50–8.62, 9.04 μ.

p-Nitrobenzyl [(3R)-Phenoxyacetamido-(4R)-(β-ethoxycarbonyl-vinylthio)-2-azetidinon-1-yl]triphenylphosphoranylideneacetate (15, R² = p-NB). A solution of 1.32 g (3.77 mmol) of **13** and of 2.88 g (11.3 mmol) of p-nitrobenzyl glyoxylate ethylhemiacetal in 10 mL of DMF

and 40 mL of toluene was stirred at room temperature with activated molecular sieves for 3 h. The crude product obtained on filtration and evaporation was triturated with several 50-mL portions of Et_2O and, finally, chromatographed on 100 g of Merck silica gel to give, with toluene–AcOEt, 1:1, 1.37 g (65%) of a mixture of the diastereomeric hemiaminals. The latter were converted with 0.73 g of $SOCl_2$ in 30 mL of dioxane in the presence of polymeric Hünig base (2 g) (5 h at room temperature) into the corresponding crude chlorides which in turn were heated in 22 mL of dioxane at 50 °C with 0.92 g of triphenylphosphine and 2 g of the polymeric base. Filtration after 17 h, evaporation in vacuo, and chromatography on 100 g of Merck silica gel, deactivated with 10% of H_2O, afforded 1.33 g (44% over three steps) of **15** (R² = Me) (eluted with toluene–AcOEt, 4:1). Amorphous solid: R_f 0.31 (benzene–AcOEt, 1:1); $[\alpha]^{20}_D$ −37 ± 1° (0.93%); IR 2.97, 5.66, 5.90 (broad), 6.05 (sh), 6.09 (sh), 6.14, 6.25, 6.30, 6.58, 6.70, 6.98, 7.35, 7.45, 7.70, 7.75–8.0, 8.10 (broad), 8.28, 8.52–8.65, 9.05, 9.26 μ. Anal. Calcd for $C_{43}H_{38}N_3O_9PS$ (803.82): C, 64.25; H, 4.77; N, 5.23; S, 3.99; P, 3.85. Found: C, 64.23; H, 4.86; N, 5.42; S, 3.74; P, 4.19.

tert-Butyl (6R)-Phenoxyacetamido-(5R)-penem-3-carboxylate (19, R² = t-Bu). The phosphorane **15** (R² = t-Bu) (72.5 mg, 0.1 mmol) in 10 mL of CH_2Cl_2 containing 0.5 mL of trifluoroacetic acid was ozonized at −20 °C by introducing 1 equiv of O_3 during 1 min. After another 3 min at −20 °C, 0.5 mL of dimethyl sulfide was added and the reaction mixture was allowed to reach room temperature. When the KI-starch test was negative, 20 mL of CH_2Cl_2 was added and the resulting solution was successively shaken with 8% aqueous $NaHCO_3$ and with brine. Drying over Na_2SO_4 and evaporation under reduced pressure afforded 63 mg of a crude product consisting (TLC, IR) of triphenylphosphine oxide and a new, TLC-mobile component. Short chromatographic filtration on 10 g of acid-washed silica gel using benzene–AcOEt, 4:1, gave 22 mg (58.5%) of pure, crystalline **19** (R² = t-Bu): mp 99–102 °C; R_f 0.50 (benzene–AcOEt, 1:1; partial decomposition); $[\alpha]^{20}_D$ +206 ± 1° (0.74%); UV (96% EtOH) λ_{max} 308, 275, 268, 262 nm; IR 2.98, 5.54, 5.87, 6.25, 6.28 (sh), 6.40, 6.61, 6.71, 6.97, 7.07 (sh), 7.21, 7.32, 7.48, 7.62 μ; NMR δ 1.51 (s, 9), 4.56 (s, 2), 5.90–6.03 (m, 3, H5 and H6), 7.14 (s, 1, H2), 7.49 (d, 1), 6.85–7.12 (m, 3), 7.21–7.42 (m, 2); MS (110 °C) m/e 376 (M*), 320, 303, 191, 186.

Methyl (6R)-Phenoxyacetamido-(5R)-penem-3-carboxylate (19, R² = Me). Ozonization of 44.6 mg (0.065 mmol) of the phosphorane **15** (R² = Me) in TFA–CH_2Cl_2 at −20 °C and workup in the above-described way (see **19** (R² = t-Bu)) afforded 40 mg of a crude product consisting of triphenylphosphine oxide, the penem ester **19** (R² = Me), and the formylthiophosphorane **18** (R² = Me) (IR, TLC). To complete the ring closure reaction, the latter material in 5 mL of toluene was heated at 50 °C for 30 min. Chromatography of the residue, after evaporation of the solvent in vacuo, on a short column of acid-washed silica gel afforded, with benzene–AcOEt, 4:1, 11 mg (50.4%) of **19** (R² = Me) as an amorphous solid: R_f 0.58 (AcOEt, partial decomposition); UV (96% EtOH) λ_{max} 310, 274, 268, 262 nm; IR 2.97, 5.54, 5.81, 5.90, 6.25, 6.28 (sh), 6.39, 6.60, 6.70, 6.97, 7.47, 7.60, 8.08 (sh), 8.25 μ; NMR δ 3.82 (s, 3), 4.58 (s, 2), 5.94–6.07 (m, 2, H5 and H6), 6.86–7.14 (m, 3), 7.22–7.44 (m, 3).

p-Nitrobenzyl (6R)-Phenoxyacetamido-(5R)-penem-3-carboxylate (19, R² = p-NB). Ozonization of 275 mg (0.34 mmol) of the phosphorane **15** (R² = p-NB) in TFA–CH_2Cl_2 at −20 °C and the following workup of the ozonization mixture in the way described for **19** (R² = t-Bu) afforded ~250 mg of a crude product whose IR and TLC suggested the formylthiophosphorane **18** (R² = p-NB) with only little of the cyclization product **19** (R² = p-NB). Cyclization was effected by refluxing this material in 10 mL of CH_2Cl_2 for 1 h under N_2. Evaporation in vacuo and short chromatography on acid-washed silica gel (deactivated by 10% of H_2O) with benzene–AcOEt, 9:1, gave 98 mg (63%) of the crystalline penem ester **19** (R² = p-NB): mp 146–147 °C (CH_2Cl_2–Et_2O); R_f 0.46 (benzene–AcOEt, 1:1; partial decomposition); $[\alpha]^{20}_D$ +191 ± 1° (0.54%); UV (96% EtOH) λ_{max} 310 nm (ε 7970), 274 (11 000), 267 (12 200), 264 (12 040); IR 2.97, 5.55, 5.80, 5.90, 6.25, 6.43, 6.57, 6.70, 7.43, 7.65, 8.10–8.18, 8.29, 8.76, 9.25 μ; NMR δ 4.52 (s, 2), 5.35 (AB, 2), 5.96–6.09 (m, 2, H5 and H6), 6.86–7.12 (m, 3), 7.22–7.40 (m, 2), 7.39 (s, 1, H2), 7.50–7.62 (m, 3), 8.15–8.27 (m, 2). Anal. Calcd for $C_{21}H_{17}N_3O_7S$ (455.44): C, 55.38; H, 3.76; N, 9.23; O, 24.59; S, 7.04. Found: C, 55.30; H, 3.84; N, 9.12; O, 24.56; S, 6.78.

(6R)-Phenoxyacetamido-(5R)-penem-3-carboxylic Acid (1a). A solution of 60 mg (0.132 mmol) of the p-nitrobenzyl ester **19** (R² = p-NB) in 4.5 mL of AcOEt was vigorously stirred at room tempera-

ture in an H_2 atmosphere with 100 mg of a 10% Pd on charcoal catalyst in the presence of 2 mL of a 0.2 M aqueous solution of $NaHCO_3$. After 30 min, another 50 mg of the catalyst was added and stirring was continued for another 5 min. The catalyst was filtered off and washed on a filter with 1 mL of the $NaHCO_3$ solution and with lots of AcOEt, and the combined aqueous parts were acidified with 5 mL of 5% aqueous citric acid. Repeated extraction of the resulting solution with CH_2Cl_2 afforded 8.0 mg (19%) of the acid **1a** as an amorphous solid. The acid proved labile decomposing in both nonaqueous (CH_2Cl_2, $CDCl_3$) and aqueous ($NaHCO_3$) solutions; decomposition was observed even on storage at -25 °C. Therefore no meaningful quantitative data are available. UV (96% EtOH) λ_{max} 304, 274, 266, 260 nm; IR 2.97, 3.0–4.3 (broad), 5.55, 5.92, 6.26, 6.42 (sh), 6.45 (sh), 6.60, 6.71, 6.97–7.10, 8.10–8.20, 8.28 (sh), 8.55–8.81, 9.25, 9.44 μ; NMR δ 4.62 (s, 2), 5.95–6.10 (m, 2, H5 and H6), 6.87–7.15 (m, 3), 7.25–7.44 (m, 2), 7.45 (s, 1), 7.62 (d, 1, J = 8 Hz), 8.90 (broad s, 1).

(6R)-Phenoxyacetamido-2-methyl-(5R)-penem-3-carboxylic Acid (1b). Using the two-phase procedure described above for **1a**, 51 mg (0.109 mmol) of the p-nitrobenzyl ester **9** (R^1 = Me; R^2 = p-NB) was transformed into 20 mg (55%) of the amorphous acid **1b**; $[\alpha]^{20}_D$ +191 ± 1° (0.39%); UV (96% EtOH) λ_{max} 300 nm (ϵ 5820), 273 (4520), 266 (4900), 260 (4760); IR 2.97, 2.8–4.2 (broad), 5.55, 5.83 (sh), 5.88 (sh), 5.92, 6.25 (sh), 6.30, 6.59, 6.69, 6.95, 7.06 μ; NMR δ 2.38 (s, 3), 4.57 (s, 2), 5.82–5.98 (m, 2, H5 and H6), 6.87–7.14 (m, 3), 7.22–7.42 (m, 2), 7.54 (d, 1, J = 8 Hz), 8.35 (broad s, 1). Anal. Calcd for $C_{15}H_{14}N_2O_5S$ (334.35): C, 53.89; H, 4.22; N, 8.38. Found: C, 53.91; H, 4.68; N, 8.24.

References and Notes

(1) Some of the investigations described in this paper were presented by R.B.W. In lectures, given before the Swedish Chemical Society In Stockholm on Dec. 9, 1975, and before The Chemical Society at Cambridge on June 29, 1976. Cf. R. B. Woodward, "Recent Advances In the Chemistry of β-Lactam Antibiotics", *Chem. Soc., Spec. Publ.*, **No. 28**, 167 (1977).
(2) R. B. Woodward In "The Chemistry of Penicillin", H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N.J., 1949, p 440.
(3) (a) D. Crowfoot, C. W. Bunn, D. W. Rogers-Low, and A. Turner-Jones in ref 2, p 310; (b) R. M. Sweet In "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, p 280.
(4) One compound of this type (**5**, R^1 = Me) has been described previously by Nayler et al.,[5] as prepared from penicillin V S-oxide trichloroethyl ester via the acetylthio derivative **3** (R^1 = Me; R^2 = CH_2CCl_3),[6] by removal of the unsaturated grouping attached to the β-lactam nitrogen through oxidation by permanganate.
(5) E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, **229** (1972).
(6) L. D. Hatfield, J. Fisher, F. L. José, and R. D. G. Cooper, *Tetrahedron Lett.*, 4897 (1970).
(7) T. Kamiya, T. Terajl, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron Lett.*, 3001 (1973). See also German Offenlegungsschrift 2 230 372 (1973).

(8) (a) The described, two-step removal of the N substituent was used before In another penicillin degradation by R. D. G. Cooper and F. L. José, *J. Am. Chem. Soc.*, **94**, 1021 (1972); (b) Compounds I resulting from a "wrongside" methanolysis of the alkoxalylazetidinones **4** were isolated as minor byproducts in several cases.
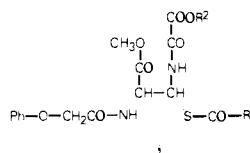
(9) R. B. Woodward, K. Heusler, I. Ernest, K. Burri, R. J. Friary, F. Haviv, W. Oppolzer, R. Paioni, K. Syhora, R. Wenger, and J. K. Whitesell, *Nouveau J. Chim.*, **1**, 85 (1977); K. Heusler and R. B. Woodward, German Offenlegungsschrift 1 935 970 (June 15, 1969). See also K. Heusler in ref 3b, p 273.
(10) Several reasons made us enter upon this crucial step of our synthesis with some trepidation. First, it was known of compounds similar to **8** that the N-azetidinonylphosphorane grouping was rather unreactive, in that *inter*molecular Wittig condensations were successful only with aldehydes.[9] *Intra*molecular condensations with ketonic[11] and even with an anhydride carbonyl group[12] could be realized only under forcing conditions. No intramolecular reaction of an ester group had been observed with compounds of this type;[12] no experience with the carbonyl group of a thioester was available. Further, there was a possibility that limited thermal stability of the penem esters **9** might severely restrict the choice of the conditions for the cyclization reaction.
(11) J. H. C. Nayler, N. F. Osborne, M. J. Pearson, and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1615 (1976); D. Bormann, *Justus Liebigs Ann. Chem.*, 1391 (1974).
(12) Unpublished results of the Woodward Research Institute.
(13) Owing to Instability Inherent In the penem esters **9** (to be discussed later) only 70% of **9** (R^1 = Me; R^2 = t-Bu) was isolated by column chromatography on acid-washed silica gel. Similar discrepancies between conversions and isolated yields were also observed in other cases.
(14) The observed retarding influence of electron-withdrawing substituents in the ester part of the phosphoranes **8** is in principle understandable—such groups help the delocalization of the partial negative charge on the carbon next to the phosphorus into the ester grouping and thus make the phosphoranes less nucleophilic. It is perhaps more surprising how significant this effect is in these reactions.
(15) Originally, it was hoped that the phosphorane **12** would serve as a more direct precursor In an alternative penem synthesis. We supposed that its ketonic carbonyl group might be attacked by the NH of the β-lactam to produce a cyclic intermediate ii—identical with the intermediate of a Wittig reaction. Elimination of triphenylphosphine oxide and formation of the penem-3-carboxylate would follow. In spite of many attempts, no such reaction could be realized. The reason for this failure may lie in the fact that the phosphorane exists largely in the zwitterionic phosphonium enolate form **12a** in which the "carbonyl" carbon atom is not electrophilic.
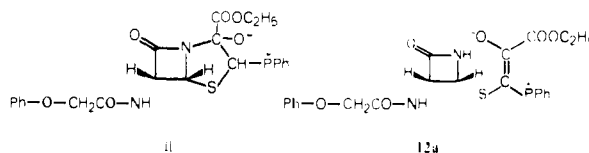
(16) Small amounts of the corresponding cis isomer of **13** were also formed In this reduction.
(17) Partial decomposition of penem esters **9** to thiazole-4-carboxylates **20** was also observed In some cyclizations of phosphoranes **8**, especially when higher temperatures and longer reaction times were used. To explain the formation of thiazole-4-carboxylates under such conditions as the reverse of a thermal [2 + 2] cycloaddition of **20** and a corresponding ketene is an attractive idea. However, the above-mentioned catalyzed process caused by a trace of acid formed In the reaction mixture cannot be excluded.
(18) L. A. Carpino, *J. Org. Chem.*, **29**, 2820 (1964).
(19) R. Lattrell, *Justus Liebigs Ann. Chem.*, 1937 (1974).
(20) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **85**, 1896 (1963).
(21) Polymeric Hünig base is prepared from highly chloromethylated polystyrene by heating with diisopropylamine In benzene–MeOH at 150 °C (autoclave) and subsequent washing with Et_3N and with MeOH. J. Schreiber and A. Eschenmoser, private communication; see also M. Roth, P. Dubs, E. Götschi, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 710 (1971) (footnote 12).