119. 2-Oxocephems and 2-Acetylpenems – Selective Formation in an Intramolecular *Wittig* Reaction

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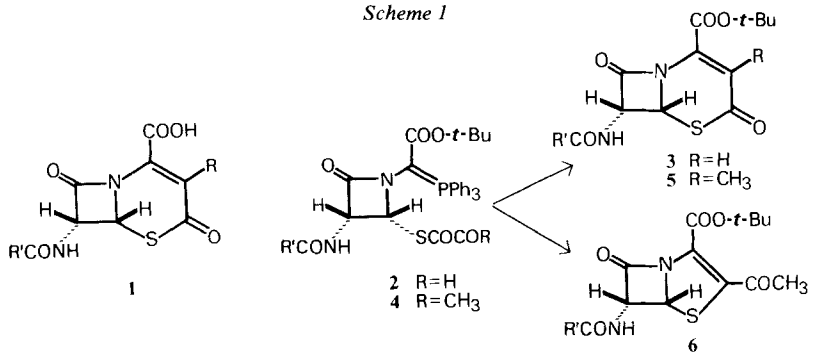
Summary

Selective formation – in intramolecular *Wittig* condensations – of the 2-oxocephem-4-carboxylate **8a** and of the 2-acetylpenem-3-carboxylate **9**, respectively, was observed as a consequence of different carbonyl reactivities in two homologous α-oxoacylthio groupings. Free, racemic and 7-unsubstituted 2-oxocephem-4-carboxylic acid (**10**) was prepared from **8a** for biological testing. Attempts to prepare the free 2-acetylpenem-3-carboxylic acid from **9** failed, probably due to the high lability of the β-lactam system.

In our recently published synthesis of 7-acylamino-2-oxocephem-4-carboxylic acids **1** [1] [2], a characteristic difference was observed in the behaviour of the glyoxyloylthio and the pyruvoylthio substituents, respectively, in the intramolecular *Wittig* condensations by which the novel bicyclic β-lactam system of **1** was formed. With the glyoxyloylthio phosphorane **2**, the formation of the six-membered unsaturated thiolactone ring of **3** was straightforward due to the high reactivity of the formyl group. On the other hand, the *S*-ester carbonyl group of the pyruvoylthio phosphorane **4** competed successfully in the *Wittig* reaction with the ketonic

Scheme 1



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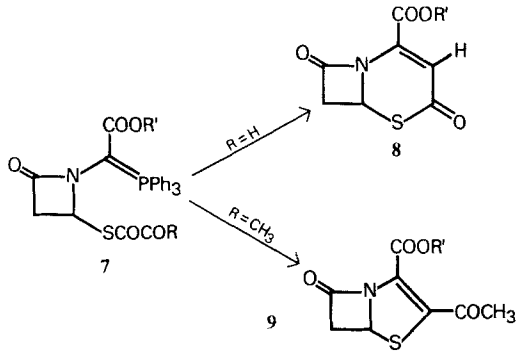
carbonyl group, and both the 2-oxocephems **5** and the 2-acetylpenems **6** resulted, the cyclization to the five-membered penem system being predominant.

An interesting effect of the acylamino substituent on the course of the cyclization of the pyruvoylthio phosphoranes **4** was further realized: Bulky acylamino groups, such as the phthalimido group, substantially suppressed the formation of the penems **6** by making the close *S*-ester carbonyl group sterically less accessible, so that mainly 2-oxocephems **5** resulted.

As far as the latter steric effect is concerned, it is conceivable that even less voluminous acylamino side-chains, such as the phenoxyacetamido group, exerted some steric hindrance on the *S*-ester carbonyl of the phosphorane intermediate **4** and that *omitting* the acylamino substituent might further enhance the formation of 2-acetylpenems in the *Wittig* condensation.

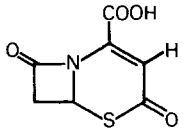
All this considered we thought it well possible to selectively prepare either of two different, simple β-lactam derivatives we were interested in, *i.e.* the parent 2-oxocephem **8** and the 6-unsubstituted 2-acetylpenem **9**, using in both cases the same synthetic scheme, but changing only the α-oxoacylthio group of the phosphorane intermediate **7**.

Scheme 2



Synthesis of racemic 2-oxocephem-4-carboxylic acid (10). – The 7-acylamino-2-oxocephem-4-carboxylic acids **1** (R = H) recently prepared in our and in other laboratories [1–4] proved very labile and of low antibacterial activity.

In the similarly labile penems, omitting the acylamino side-chain substantially increased both the stability and biological activity [5] [6]. Thus, the question as to what antimicrobial activity the parent acid **10** would display was of great interest[2]).



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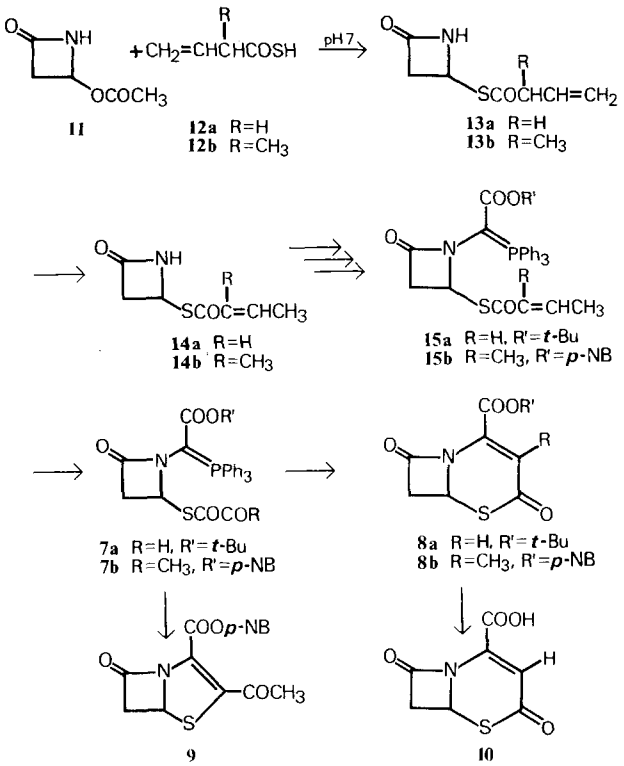
[2]) In a paper of 1979, *Ebbinghaus et al.* [4] describe among other 2-oxocephem derivatives benzhydryl 3-methyl-2-oxocephem-4-carboxylate; however, they do not mention a cleavage of this ester, obtained in a very low yield, to the free acid.

An exchange reaction *(Scheme 3)* between racemic 4-acetoxy-2-azetidinone (**11**) [7] and the sodium salt of *α*-vinyl-thioacetic *S*-acid (**12a**) in aqueous dioxane afforded 4-vinylacetylthio-2-azetidinone (**13a**; 49%) which was easily isomerized, by a 1% solution of triethylamine in methylene chloride, to an about 6:1 mixture of 4-crotonoylthio-2-azetidinone, m.p. 43.5–45°, and its *cis* double bond stereoisomer, m.p. 63–63.5° (both **14a**; 94%). Both compounds could be separated by silica gel chromatography, however, for the purpose of our synthesis, the configuration at the double bond was of no importance and the isomeric mixture was used in the next step[3]).

In a three-step procedure developed in these laboratories [8], a stabilized phosphorane grouping was next built up on the azetidinone N-atom (**14a** → **15a**; 52% over three steps). Transformation of the crotonoylthio substituent of **15a** into the glyoxyloylthio grouping necessary for the intramolecular *Wittig* reaction was achieved by low-temperature ozonization of **15a** in methylene chloride in the presence of

Scheme 3



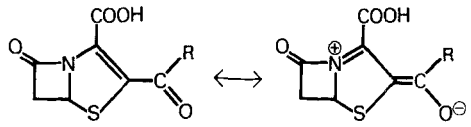
[3]) The described indirect way to **14a** *via* the vinylacetylthio derivative **13a** was necessary, since *α,β*-unsaturated thiocarboxylic *S*-acids, such as thiocrotonic *S*-acid, are not known compounds.

trifluoroacetic acid (to protect the phosphorane grouping). Subsequent reduction of the peroxidic material (Me_2S) and washing with aqueous $NaHCO_3$-solution liberated the phosphorane **7a** which spontaneously cyclized to the desired *t*-butyl 2-oxocephem-4-carboxylate (**8a**; 60% from **14a**, m.p. 80–81°).

Finally, treatment of the ester **8a** with trifluoroacetic acid afforded the free, racemic 2-oxocephem-4-carboxylic acid (**10**; 47%, m.p. 149–150°) (dec.).

The novel acid **10** proved substantially more stable than the known 7-acylamino substituted 2-oxocephem-4-carboxylic acids **1**. The half-life of **10** in an aqueous buffer solution of pH 6.0 at 37° was 13–15 h (UV. evidence) as compared to $t/2 = 80$ min at 22° for the corresponding 7-phenoxyacetamido acid [1]. Unfortunately, this increase of the stability was not paralleled by a similar increase of the antibacterial activity; on the contrary, in a simple agar plate diffusion test, the acid **10** was found only marginally active against *Staphylococcus aureus* and practically inactive against several representative *Gram*-negative strains.

Synthesis of racemic 2-acetylpenem-3-carboxylate (9). – In the synthetic studies on the penems performed in the last years in our Institute, the 2-acylpenem-3-carboxylic acids **16** were considered, among other structures, interesting candidates for synthesis. Their electron-withdrawing acyl group, conjugated to the unsaturated system of the penem bicycle, might further increase the electrophilic reactivity of the penem-β-lactam carbonyl group and thus have a positive impact on the biological activity of these compounds.



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Our experience with the intramolecular *Wittig* condensations of α-oxoacylthio phosphoranes, discussed in the introduction of this paper, let us believe that the synthesis of 2-acylpenems based on a similar scheme as used for the parent 2-oxocephem acid **10** should be possible *(Scheme 3)*. In the following, such a synthesis of the 2-acetylpenem-3-carboxylate (**9**) is described.

The preparation of the key phosphorane intermediate **7b** was carried out in a manner essentially analogous to the above procedure for the phosphorane **7a**. The exchange reaction between 4-acetoxy-2-azetidinone (**11**) and the sodium salt of α-vinyl-thiopropionic *S*-acid (**12b**) afforded in this case a mixture of the (α-vinylpropionylthio)azetidinone **13b** and of its conjugated isomer **14b** (in a ratio of 2:1). Complete isomerization of this mixture to **14b** (44% from **11**, m.p. 66–68°), was achieved using a 1% solution of triethylamine in methylene chloride.

The stabilized phosphorane grouping[4]) was next attached to the azetidinone N-atom by the usual three-step procedure to give **15b** in 36% overall yield from **14b**.

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[4]) Contrary to the 2-oxocephems, the penems are extremely acid labile. This instability excludes the use of the *t*-butyl ester for carboxylic acid protection. On the other hand, the hydrogenolytic cleavage of the *p*-nitrobenzyl esters had proved in the past [5] to be the most effective method for the preparation of free penem acids.

Low temperature ozonolysis in the presence of trifluoroacetic acid, followed by reductive work-up and treatment with aqueous $NaHCO_3$-solution gave the required pyruvoylthio phosphorane **7b**. The latter was then cyclized in refluxing methylene chloride over a period of six hours to afford *p*-nitrobenzyl 2-acetylpenem-3-carboxylate (**9**; 43% from **7b**, m.p. 128–130°). Only a trace of the alternative cyclization product, the 2-oxocephem **8b**, was observed in this ring-closure step, thus bearing out our prediction of the predominant mode of cyclization of the pyruvoylthio phosphorane **7b**.

The large effect that the electron-withdrawing acetyl group has on the reactivity of the penem system was evident from measurements of the stability of **9**. In aqueous phosphate buffer at pH 7.4 and 37°, the β-lactam ring of **9** was hydrolyzed very rapidly, with a half-life of less than 10 min. Furthermore, all attempts to cleave – by hydrogenolysis – the *p*-nitrobenzyl protecting group in order to obtain the free carboxylic acid for biological testing were unsuccessful affording only β-lactam-free material. Thus, in this simple case, the introduction of the acetyl grouping in the position 2 of the penem nucleus increased the reactivity of the β-lactam more than desired for a practical antibiotic.

The authors would like to express their warm thanks to Messrs. *R. Baudet* and *P. Felber* for the outstanding technical collaboration, to Drs. *H. Sauter, H. Fuhrer* and their colleagues (Spectroscopic Services, *Ciba-Geigy Ltd.*) for the NMR. spectra, and to Dr. *W. Padowetz* and his coworkers (Analytical Department, *Ciba-Geigy Ltd.*) for the elemental analyses. The antibacterial test was performed in the Bacterial Chemotherapy Laboratories, *Ciba-Geigy Ltd.*, under the guidance of Dr. *O. Žák;* the authors thank him and his colleagues for their collaboration.

Experimental Part

General remarks. Melting points (m.p.; *Kofler*) are uncorrected. UV. spectra: $\lambda_{max}(\varepsilon)$ in nm. IR. spectra: absorptions in μm. ^{1}H-NMR. spectra: recorded on a *Varian* HA-100D spectrometer; chemical shifts in ppm relative to tetramethylsilane (=0 ppm), coupling constants *J* in Hz. Rf Values were determined on *Merck* silica gel 60 F_{254} TLC. plates.

Synthesis of α-vinyl-thioacetic S-acid (**12a**). A solution of 24 g (0.23 mol) of vinylacetyl chloride, b.p. 93–95°/740 Torr (prepared from vinylacetic acid *(Fluka)* and 1.05 mol-equiv. of $SOCl_2$; 2.5 h at RT., 2.5 h at 50°) in 120 ml of dry CH_2Cl_2 was added dropwise, at −15° within 30 min, to a sat. H_2S-solution in 18.4 ml of pyridine and 240 ml of CH_2Cl_2 while introducing a stream of H_2S into the mixture. Stirring and H_2S-introduction was continued at −15° for 2.5 h. Excess H_2S was removed in a stream of N_2, the residual solution was washed with 2N H_2SO_4 and with sat. NaCl-solution, dried over anh. Na_2SO_4, and the solvent was evaporated under reduced pressure to afford 18.5 g (79%) of **12a** as a colorless oil; it was used in the next step (see below) without any further purification, Rf (toluene/ethyl acetate 1:1) 0.79. – IR. (CH_2Cl_2): 3.25–3.47, 5.81 br., 6.11, 7.18, 7.69–8.06, 9.01, 9.65, 10.15, 12.04. – ^{1}H-NMR. ($CDCl_3$): 3.52 (*d*×*d*, *J*=6.4 and 1, 2 H); 5.34 (*m*, 2 H); 5.94 (*m*, 1 H).

Synthesis of 4-vinylacetylthio-2-azetidinone (**13a**). Crude **12a** (3.06 g; about 30 mmol) was dissolved in 30 ml of ice-cold aq. 1N NaOH (under N_2), the strongly alkaline solution was adjusted to pH 7 with few drops of acetic acid, and filtered through paper to remove several oily droplets. The clear solution of the sodium salt thus obtained was added dropwise within 15 min to a solution of 2.6 g (20.13 mmol) of 4-acetoxy-2-azetidinone [7] in 10 ml of dioxane (freshly filtered through Alox) while stirring under N_2 in an ice-water bath. Stirring and cooling was continued for 3 h with occasional re-adjustment to pH 7 by adding more 1N NaOH. The product was extracted into CH_2Cl_2 and the extract washed with sat. NaCl-solution. Evaporation of the solvent *i.v.* afforded 2.95 g of an oil which was chromatographed on 200 g of *Merck* silica gel (deactivated by 10% of

water). With toluene/ethyl acetate 4:1, 1.45 g (48.7%) of pure, oily **13a** were eluted followed by 360 mg of unconsumed 4-acetoxy-2-azetidinone. Rf (toluene/ethyl acetate 1:1) of **13a** 0.35. – IR. (CH_2Cl_2): 2.94, 5.62, 5.92, 6.10, 6.94–7.16, 7.46, 7.78–8.08, 8.62, 8.93, 9.17. – ^{1}H-NMR. ($CDCl_3$): 2.95 (*m*, 1 H); 3.32 (*m*, 2 H); 3.44 (*m*, 1 H); 5.21 (*m*, 2 H); 5.30 (br. *s*, 1 H); 5.86 (*m*, 1 H); 6.76 (br., 1 H).

$C_7H_9NO_2S$	Calc.	C 49.11	H 5.30	N 8.18	O 18.69	S 18.73%
(171.21)	Found	„ 49.23	„ 5.33	„ 8.12	„ 18.57	„ 18.71%

Synthesis of 4-crotonoylthio-2-azetidinone (trans-**14a**). A solution of 1.24 g (7.24 mmol) of **13a** and of 1.4 ml of triethylamine in 130 ml of CH_2Cl_2 was allowed to stand at RT. for 45 min. The progress of isomerization was followed by IR. The resulting mixture was diluted with more CH_2Cl_2 and washed subsequently with 5% aq. solution of citric acid and sat. NaCl-solution. The product obtained by evaporation of the solvent *i.v.* was chromatographed on 90 g of *Merck* silica gel (deactivated by 10% of water). With toluene/ethyl acetate 5:1, both isomers of **14a** were eluted (1.16 g; 94%); *4-isocrotonoylthio-2-azetidinone* (*cis*-**14a**) the minor component, was eluted first whereas *trans*-**14a** was concentrated in the later chromatographic fractions. For characterization, fractions containing pure *cis*- and pure *trans*-**14a**, resp., were used. For the next steps of the synthesis, all remaining fractions were combined. Pure *trans*-**14a** formed white crystals, m.p. 43.5–45° (CH_2Cl_2/ether), Rf (toluene/ethyl acetate 1:1) 0.29. – IR. (CH_2Cl_2): 2.95, 5.62, 6.02, 6.13, 6.94–7.14, 7.46, 7.81–8.13, 8.62, 8.97, 9.26, 9.57, 10.25, 10.42, 11.24, 12.34. – ^{1}H-NMR. ($CDCl_3$): 1.91 ($d\times d$, J=7 and 2, 2 H); 2.97 ($d\times d\times d$, J=15, 2 and 1, 1 H); 3.45 ($d\times d\times d$, J=15, 5 and 1.8, 1 H); 5.25 ($d\times d$, J=5 and 2); 6.10 ($d\times d$, J=15.5 and 2, 1 H); 6.64 (br. *m*, 1 H); 6.93 (*m*, J=15.5, 7 and ?, 1 H).

$C_7H_9NO_2S$	Calc.	C 49.11	H 5.30	N 8.18	O 18.69	S 18.73%
(171.21)	Found	„ 49.39	„ 5.18	„ 8.17	„ 18.54	„ 18.67%

In the above-mentioned chromatography, 15 mg of pure *cis*-**14a** were obtained in the first fraction with toluene/ethyl acetate 5:1, m.p. 63–63.5° (as obtained by chromatography), Rf (toluene/ethyl acetate 1:1) 0.33. – IR. (CH_2Cl_2): 2.95, 5.64, 6.02, 6.23, 6.94–7.14, 7.46, 7.81–8.15, 8.62, 9.26, 9.80, 10.05, 10.31, 10.64, 11.16, 12.24. – ^{1}H-NMR. ($CDCl_3$): 2.12 ($d\times d$?, J=6.5 and 1, 3 H); 2.96 ($d\times d\times d$, J=15, 2 and 1, 1 H); 3.47 ($d\times d\times d$, J=15, 5 and 1.5, 1 H); 5.25 ($d\times d$, J=5 and 2, 1 H); 5.98–6.30 (*m*, 2 H); 6.50 (br. *m*, 1 H).

Synthesis of 1-[1-Butoxycarbonyl(triphenylphosphoranylidene)methyl]-4-crotonoylthio-2-azetidinone **15a**. A solution of 1.02 g (5.96 mmol) of *trans*-**14a** (containing a small amount of *cis*-**14a**) and of 2.65 g (about 17.9 mmol) of hydrated *t*-butyl glyoxylate [5] in 41 ml of DMF/toluene 9:32 was stirred at RT. under N_2 with molecular sieves (Type 4 Å 1/16; *Bender & Hobein Ltd.*, Zürich), activated at 250°/0.01 Torr, for 5.5 h. Filtration, washing on the filter with DMF/toluene, and evaporation *i.v.* and finally several times with toluene in high vacuum afforded 2.0 g of an epimeric mixture of the hemiaminals (Rf (toluene/ethyl acetate 1:1) 0.33 and 0.37) still containing a small amount of *t*-butyl glyoxylate. This crude product and 8 g of diisopropylaminomethyl-polystyrene (3.5 mmol-equiv./g) [9] were stirred at RT. under N_2 in 50 ml of dioxane while 1.3 ml (about 18 mmol) of thionyl chloride in 15 ml of dioxane were added dropwise within 15 min. After another 3 h at RT., the base was filtered off, washed on the filter with dioxane, and the combined filtrates were evaporated, finally in high vacuum, to give 1.9 g of the crude, epimeric chlorides (Rf (toluene/ethyl acetate 1:1) 0.54). A solution of the chlorides and of 2.35 g (9 mmol) of triphenylphosphine in 65 ml of dioxane was stirred at 50° in the presence of 8 g of the polymeric base. After 18 h at 50° and another 6 h at 60°, the base was filtered off, washed with dioxane, and the combined filtrates were evaporated *i.v.* The syrupy crude product thus obtained (*ca.* 4.5 g) was chromatographed on 200 g of *Merck* silica gel (deactivated by 10% of water). With toluene/ethyl acetate 9:1 and 4:1, the excess of triphenylphosphine, a small amount of unconsumed chlorides, and some other, minor impurities were eluted. Phosphorane **15a** was removed from the column with toluene/ethyl acetate 3:1 (1.70 g; 52.3% from **14a**), amorphous foam, Rf (ethyl acetate) 0.33. – IR. (CH_2Cl_2): 3.25–3.50, 5.71, 6.02, 6.12, 6.17 sh, 6.76, 6.96–7.09, 7.24, 7.35, 7.81–8.06, 8.62, 9.09, 9.26, 9.66, 10.03, 10.41.

$C_{31}H_{32}NO_4PS$	Calc.	C 68.24	H 5.91	N 2.57	S 5.87	P 5.68%
(545.63)	Found	„ 68.15	„ 6.02	„ 2.66	„ 5.78	„ 5.55%

Synthesis of t-*butyl 2-oxocephem-4-carboxylate* (**8a**). Into a solution of 1.02 g of **15a** in 130 ml of CH_2Cl_2 and 14 ml of trifluoroacetic acid, prepared and kept at $-30°$, a stream of O_3/O_2 was introduced at a rate of 0.1 mmol O_3/min for 20 min. After another 20 min at $-30°$, excess O_3 and O_2 were removed in a stream of N_2, 10 ml of dimethylsulfide were added and the resulting mixture was allowed to stand at -30 to $-10°$ for about 90 min. It was then diluted with more CH_2Cl_2 and shaken successively with 8% aq. $NaHCO_3$-solution and with sat. NaCl-solution. Drying over anh. Na_2SO_4 and evaporation of the organic phase under reduced pressure afforded a yellowish syrup consisting mainly of **8a** and of triphenylphosphinoxide (TLC. and IR. evidence). Chromatography on 100 g of acid-washed silica gel with toluene/ethyl acetate 9:1 afforded 290 mg (60.4%) of crystalline **8a**, m.p. 78–79°. It was recrystallized from ether/pentane: 224 mg of yellowish, rhomboid, well developed crystals, m.p. 80–81°, Rf (toluene/ethyl acetate 1:1) 0.54. – UV. (96% EtOH): 313 (6360). – IR. (CH_2Cl_2): 3.25–3.50, 5.56, 5.78, 6.06, 6.24, 7.09, 7.16, 7.30, 7.81–8.03, 8.26, 8.33, 8.62, 8.77, 9.05, 9.17, 9.43, 9.93, 10.36, 10.63, 11.90. – ^{1}H-NMR. ($CDCl_3$): 1.57 (*s*, 9 H); 3.32 (*d*×*d*, *J* = 16 and 2, 1 H); 3.78 (*d*×*d*, *J* = 16 and 5, 1 H); 5.52 (*d*×*d*, *J* = 2 and 5, 1 H); 6.26 (*s*, 1 H).

$C_{11}H_{13}NO_4S$	Calc.	C 51.75	H 5.13	N 5.49	O 25.07	S 12.56
(255.29)	Found	„ 51.75	„ 5.15	„ 5.57	„ 25.22	„ 12.69%

Synthesis of 2-oxocephem-4-carboxylic acid (**10**; *racemic*). A solution of 80 mg of racemic *t*-butyl 2-oxocephem-4-carboxylate in 4 ml of trifluoroacetic acid was allowed to stand under N_2 at 0° for 20 min and at RT. for 45 min. Evaporation under reduced pressure, finally in high vacuum, afforded a yellowish, solid foam. It was dissolved in 1 ml of acetonitrile, the solution was filtered, and the filtrate was concentrated to about 0.3 ml. The separated, slightly yellowish crystals were washed on the filter with acetonitrile/ether: 29 mg (46.5%) of **10**, m.p. 149–150° (dec.), Rf (RP plates *Antec* UP 12, H_2O/MeCN 97.5:2.5) 0.61. – UV. (96% EtOH): 312 (5750). – IR. (CH_2Cl_2/EtOH 92:8): 5.46, 5.80, 6.06, 6.23. – IR. (KBr): 2.9–4.2, 5.68, 5.79, 6.16, 6.25, 6.99, 7.14, 7.30, 7.79, 7.94, 8.16, 8.33, 8.70, 9.00, 9.12, 9.39, 10.00, 10.25, 10.63, 11.63, 12.34. – ^{1}H-NMR. (DMSO-d_6): 3.45 (*d*×*d*, *J* = 16 and 2.4, 1 H); 3.90 (*d*×*d*, *J* = 16 and 5, 1 H); 5.75 (*d*×*d*, *J* = 2.4 and 5, 1 H); 6.16 (*s*, 1 H).

$C_7H_5NO_4S$	Calc.	C 42.21	H 2.53	N 7.03	O 32.13	S 16.10%
(199.18)	Found	„ 42.25	„ 2.73	„ 7.48	„ 32.11	„ 15.50%

Inhibition zones (diameters, in mm) in an agar plate diffusion test with a 0.5% solution of **10** in DMSO (in parentheses: corresponding values for Penicillin V):

	pH 6.0	pH 7.0
Staphylococcus aureus SMITH 14	19 (38)	9 (32)
Staphylococcus aureus $2999_{i^+\,p^+}$	8 (10)	7 (10)
Escherichia coli 205	10 (13)	9 (13)

Synthesis of α-*vinyl-thiopropionic* S-*acid* (**12b**). A solution of 7.25 g (0.061 mol) of α-vinylpropionyl chloride [10] in 35 ml of dry CH_2Cl_2 was added dropwise, at $-15°$ within 30 min, to a sat. H_2S-solution in 4.9 ml of pyridine and 65 ml of CH_2Cl_2 while introducing a stream of H_2S into the mixture. Stirring and H_2S-introduction was continued at $-15°$ for 2.5 h. Excess H_2S was removed in a stream of N_2, the residual solution was washed with 2N H_2SO_4 and with sat. NaCl-solution, dried over anh. Na_2SO_4 and the solvent evaporated under reduced pressure to afford 6.25 g (88%) of **12b** as a pale yellow oil. – IR. (CH_2Cl_2): 2.8–4.0, 5.75, 5.91, 6.16, 6.93, 7.09, 8.9 br., 10.2, 10.8, 11.1, 12.1. – ^{1}H-NMR. ($CDCl_3$): 1.34 (*d*, *J* = 7, 3 H); 3.55 (*m*, *J* = 7 and 7, 1 H); 5.27 (*m*, 2 H); 5.94 (*m*, 1 H).

*Synthesis of 4-(*α*-methylcrotonoylthio)-2-azetidinone* (**14b**). Crude **12b** (4.36 g; about 38 mmol) was dissolved in 38 ml of ice-cold aq. 1N NaOH (under N_2). The strongly alkaline solution was adjusted to pH 7 with a few drops of acetic acid and then added dropwise (15 min) to a solution of 3.9 g (30 mmol) of 4-acetoxy-2-azetidinone [7] in 24 ml of dioxane cooled to 0°. Stirring and cooling was continued for 4 h with occasional re-adjustment to pH 7 by adding more 1N NaOH.

The product was extracted into CH_2Cl_2 and the extract washed with sat. NaCl-solution. Evaporation of the solvent *i.v.* afforded 4.8 g of the mixture **13b/14b** in a ratio of 2:1. To a solution of this crude mixture in 215 ml of CH_2Cl_2 were added 2.02 ml of triethylamine, and the solution was allowed to stand at RT. for 1 h. The resulting mixture was washed with 1N HCl and with sat. NaCl-solution. Evaporation of the solvent *i.v.* gave a yellow oil which was purified by chromatography on 200 g of silica gel using toluene/ethyl acetate 4:1 as eluant to give 2.44 g (44%) of crystalline **14b**, m.p. 66–68° (CH_2Cl_2/ether), Rf (toluene/ethyl acetate 1:1) 0.26. – IR. (CH_2Cl_2): 2.93, 5.64, 6.08, 7.46, 8.20, 10.2, 11.5. – ^{1}H-NMR. ($CDCl_3$): 1.84 (*m*, 2 H); 2.96 (*d*×*d*×*d*, *J* = 16, 2 and 1, 1 H); 3.42 (*d*×*d*×*d*, *J* = 16, 5 and 1, 1 H); 5.24 (*d*×*d*, *J* = 5 and 2, 1 H); 6.8 (*m*, 2 H).

$C_8H_{11}NO_2S$	Calc.	C 51.87	H 5.99	N 7.56	S 17.31%
(185.24)	Found	„ 51.91	„ 5.88	„ 7.64	„ 17.19%

Synthesis of 4-(α-methylcrotonoylthio)-1-[(p-nitrobenzyloxycarbonyl)(triphenylphosphoranylidene)-methyl]-2-azetidinone (**15b**). A solution of 2.44 g (13.2 mmol) **14b** and of 7.5 g (29.4 mmol) of the ethyl hemiacetal of *p*-nitrobenzyl glyoxylate [5] in 176 ml of DMF/toluene 36:140 was stirred at RT. under N_2 with freshly activated molecular sieves for 18 h. The mixture was then filtered, and evaporated *i.v.*, and the residue triturated with ether to remove excess glyoxylate. The crude mixture of hemiaminals thus obtained was used directly in the next reaction. The crude product was dissolved in 66 ml of dry THF and cooled to −15°, and 2.25 ml (16 mmol) of triethylamine were added, followed by 1.9 g (16 mmol) of thionyl chloride in 10 ml of THF (dropwise addition within 15 min). After stirring at 0° for 1 h, the mixture was diluted with 150 ml of CH_2Cl_2, extracted with 75 ml of 1N HCl and evaporated *i.v.* to afford the crude epimeric chlorides. A solution of the chlorides and 5.24 g (20 mmol) of triphenylphosphine in 8 ml of THF was stirred at RT. under N_2 for 18 h. After dilution with 150 ml of CH_2Cl_2, washing with sat. aq. $NaHCO_3$-solution and evaporation *i.v.*, the crude product thus obtained was chromatographed on 250 g of silica gel using first toluene/ethyl acetate 9:1 to remove excess triphenylphosphine, then toluene/ethyl acetate 3:2 to elute 3.0 g (36% from **14b**) of **15b** as an amorphous foam, Rf (toluene/ethyl acetate 1:1) 0.15. – IR. (CH_2Cl_2): 3.2-3.6, 5.72, 6.07, 6.20, 6.80, 7.02, 7.47, 7.91, 8.3, 9.1, 9.3, 11.6, 12.6.

$C_{35}H_{31}N_2O_6PS$	Calc.	C 65.82	H 4.89	N 4.39	S 5.02%
(638.68)	Found	„ 66.02	„ 4.96	„ 4.44	„ 4.95%

Synthesis of p-*nitrobenzyl 2-acetylpenem-3-carboxylate* (**9**). Into a solution of 2.10 g (3.3 mmol) of **15b** in 210 ml of CH_2Cl_2 and 23 ml of trifluoroacetic acid, prepared and kept at −30°, a stream of O_3/O_2 was introduced at a rate of 0.1 mmol O_3/min for 50 min. After another 20 min at −30°, excess O_3/O_2 was removed in a stream of N_2, 16.5 ml of dimethylsulfide were added, and the resulting mixture was allowed to stand at −18° overnight. It was then diluted with more CH_2Cl_2 and shaken successively with sat. aq. $NaHCO_3$- and NaCl-solution. The organic phase was dried over Na_2SO_4, concentrated to approximately 30 ml and then heated under reflux for 6 h to effect the intramolecular *Wittig* cyclization. Evaporation of the solvent *i.v.* gave the crude product as an oil which was purified by chromatography on 90 g of silica gel using toluene/ethyl acetate 9:1 to elute 490 mg (43%) of **9**. Crystallization from CH_2Cl_2/ether gave pale yellow crystals, m.p. 128–130°, Rf (toluene/ethyl acetate 1:1) 0.44. – UV. (dioxane): 262 (12,950), 330 (4620). – IR. (CH_2Cl_2): 5.58, 5.88, 6.24, 6.61, 7.20, 7.32, 7.44, 7.64, 8.2, 8.4, 8.5, 9.2, 9.8, 10.2, 11.8. – ^{1}H-NMR. ($CDCl_3$): 2.41 (*s*, 3 H); 3.64 (*d*×*d*, *J* = 17 and 3, 1 H); 3.88 (*d*×*d*, *J* = 17 and 4, 1 H); 5.28 (*qa*, 2 H); 7.54 (*d(?)*, *J* = 9, 2 H); 8.19 (*d(?)*, *J* = 9, 2 H).

$C_{15}H_{12}N_2O_6S$	Calc.	C 51.72	H 3.47	N 8.04	S 9.21%
(348.33)	Found	„ 51.45	„ 3.48	„ 7.97	„ 8.89%

In the ^{1}H-NMR. of the crude mixture, traces of the alternative cyclization product, *p*-nitrobenzyl 3-methyl-2-oxocephem-4-carboxylate (**8b**), were detected by the characteristic [1] *s* of H_3C–C(3) at 2.06 ($CDCl_3$).

Hydrogenolysis of **9**. A solution of 174 mg (0.5 mmol) of **9** in 11.5 ml of ethyl acetate was vigorously stirred for 1 h at RT. under H_2 in the presence of 335 mg of 10% Pd/C and 7.6 ml of 0.2M aq. $NaHCO_3$. After filtering off the catalyst, the aq. phase was acidified with 5% aq. solution of citric

acid. Repeated extraction of the resulting solution with CH_2Cl_2 afforded only 9 mg of an amorphous solid lacking any β-lactam-containing material as judged by UV., IR. and NMR. measurements.

Additional attempts to deprotect the *p*-nitrobenzyl ester by hydrogenolysis under non-alkaline conditions, *e.g.* in ethyl acetate alone or in methanol, also failed to produce the required free carboxylic acid.

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