18. 2-Oxocephems. II. – Synthesis of 2-Oxocephalexin from Hetacillin

by **Ivan Ernest**

Woodward Research Institute, CH-4002 Basel, Switzerland

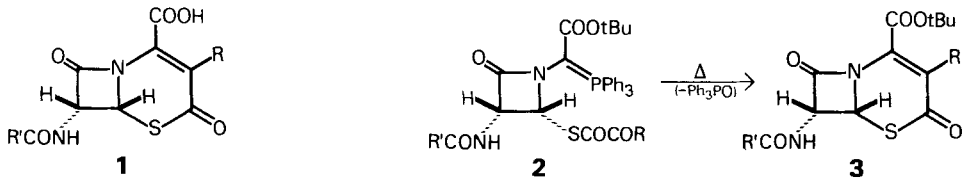
(16.X.79)

Summary

2-Oxocephalexin **4**, a very labile representative of the novel group of 2-oxocephem-4-carboxylic acids, has been synthesized from hetacillin.

Recently, two different syntheses of (7*R*)-7-acylamino-2-oxocephem-4-carboxylic acids **1** have been developed independently in the *Bristol Laboratories* [1] and in our Institute [2].

Scheme 1

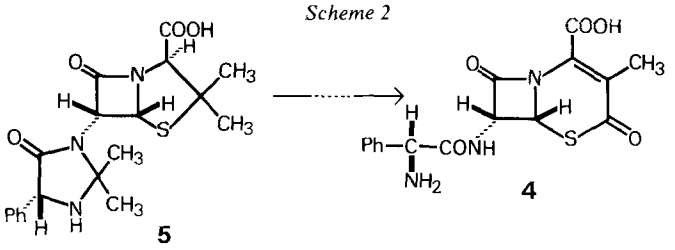


In our synthesis of the novel labile acids **1**, the bicyclic system was formed by an intramolecular *Wittig* condensation of the phosphoranes **2** prepared in several steps from penicillins.

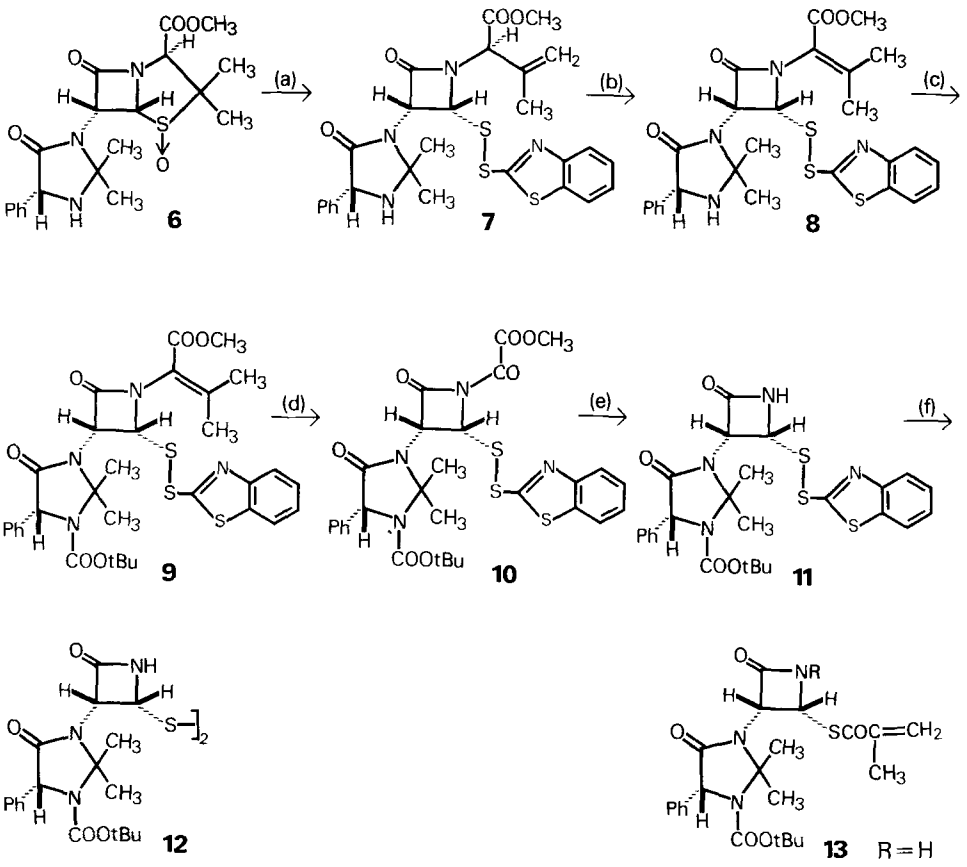
Whereas the formation of the 3-unsubstituted esters **3** (R = H) by this reaction was straightforward, a complication emerged in the synthesis of the 3-methyl homologs (**3**, $R = CH_3$), where a concomitant cyclization of the pyruvylthio phosphoranes **2** ($R = CH_3$) to the isomeric five-membered ring, 2-acetylpenems was observed. To suppress this undesired direction of the *Wittig* reaction, a bulky substituent had to be temporarily introduced on the 7-acylamino group. However, before finding a more general solution to this problem [2], we thought that the voluminous polysubstituted imidazolidonyl group of hetacillin might exert such steric control over the cyclization step as well as provide a biologically interesting 7-substituent for the final 2-oxocephem acid. When we tried to realize this idea, a deviation from the general scheme of our 2-oxocephem synthesis became unavoidable; therefore, the synthesis of 2-oxocephalexin **4** from hetacillin **5** is now described separately.

0018-019X/80/1/0201-13$01.00/0

Scheme 2



Scheme 3



a) 2-Mercaptobenzothiazole, benzene, reflux; 56–61%.
b) Et_3N, CH_2Cl_2, RT.: 98%.
c) $(BOC)_2O$, iPr_2NEt, dioxane, 50°; 89%.
d) O_3, MeOH, −20°; 72–81%.
e) MeOH, H_2O, THF, RT.: 86–92%.
f) $NaBH_4$ or Et_4NBH_4, DMF etc.

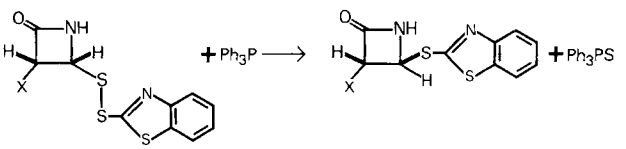
The key-intermediate of our synthetic plan for **4** was the azetidinone **13** in which the methacryloylthio substituent represented a synthetic equivalent of the pyruvoylthio group needed later in the cyclization step. A major reason for the above-mentioned deviation was the unforeseen tendency of the disulfide **11**, prepared from hetacillin (**5**) in seven easy steps (**5**–**11**) *(Scheme 3)*, to form, under the influence of hydride reagents, the very stable symmetrical disulfide **12** which resisted all attempts to reduce its S–S bond. Thus, a direct substitution, by reductive acylation, of the benzothiazolylmercapto grouping in **11** by the methacryloyl group failed and an alternative approach to **13** had to be devised.

In contrast to the disulfide **11**, its precursor **9** proved a suitable intermediate for the introduction of the methacryloyl group. With triphenylphosphine in methylene chloride in the presence of water, the S–S bond of **9** was slowly but cleanly reduced and the 4-mercaptoazetidinone thus formed could be acylated *in situ* (after removal of the aqueous phase) with an excess of methacryloyl chloride to give the thioester **14** (74%) *(Scheme 4)*[1]).

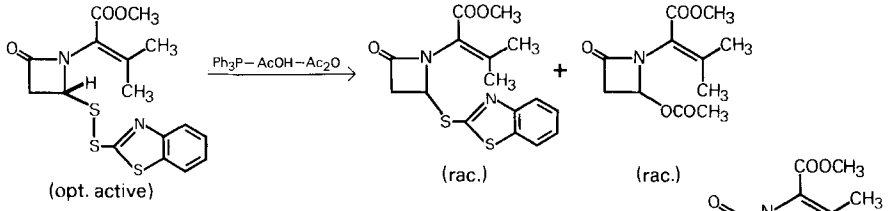
In analogy to our previous work on 2-oxocephems, the substituent on the β-lactam nitrogen of **14** was next to be oxidatively removed. For that purpose, however, the methacryloyl group had first to be temporarily protected[2]). This was achieved by a *Michael* type addition of *p*-toluenesulfinic acid affording approximately a 1:1 mixture of the epimeric sulfones **15** (85%). Low temperature ozonization of the latter, followed by methanolysis of the *N*-methoxalyl intermediate **16**, gave then the *N*-unsubstituted sulfones **17** (77% over the last two steps).

---

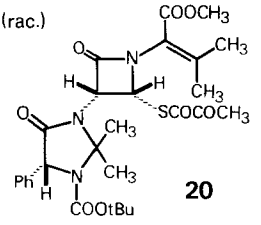
[1]) For *N*-unsubstituted azetidinonyl disulfides of type **11**, the triphenylphosphine/water reduction method is unsuitable. Instead of triphenylphosphine oxide and the two mercaptans, such substrates form triphenylphosphine sulfide and a 4-benzothiazolylmercaptoazetidinone with inverted configuration at C(4) [3].



A similar result, *i.e.* formation of triphenylphosphine sulfide and a benzothiazolylmercapto-azetidinone, was observed with an *N*-protected, but 3-unsubstituted azetidinonyl disulfide [4].

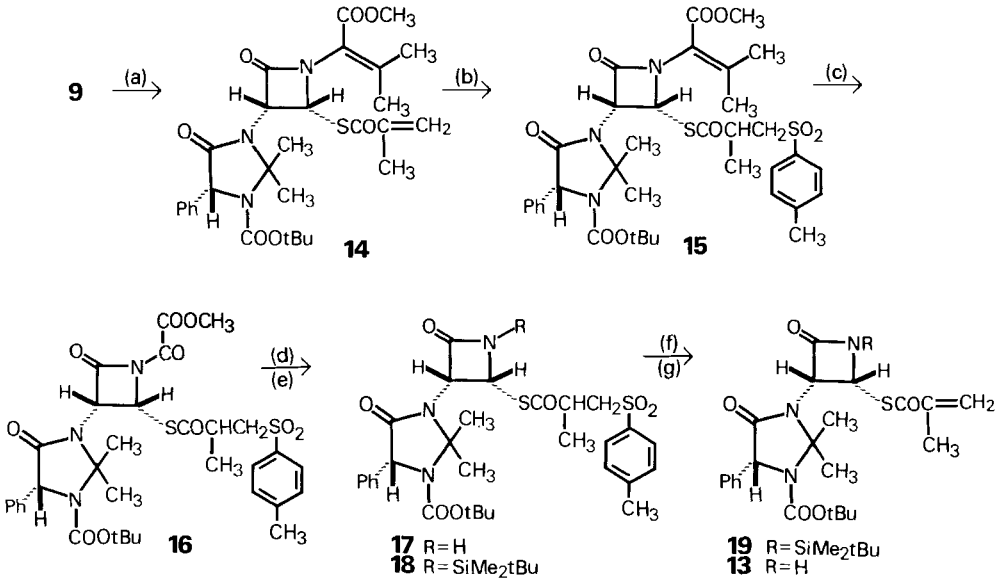


[2]) In a small-scale experiment with one equivalent of ozone (in methanol at $-60°$), the double bond of the methacryloyl group of **14** was attacked preferentially giving the following pyruvoylthio azetidinone **20**.



20

Scheme 4

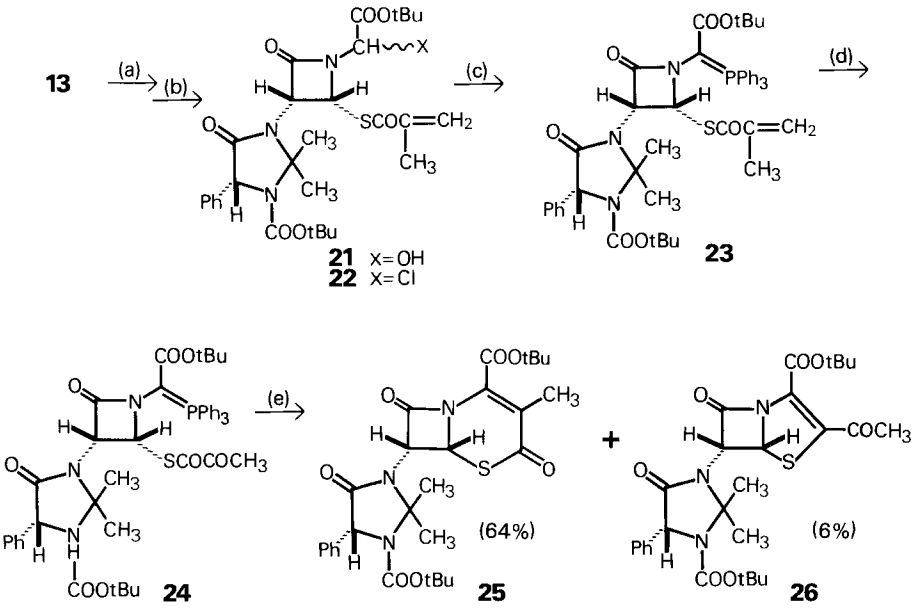


a) Ph_3P, H_2O, CH_2Cl_2, 0°; $CH_2{=}C(CH_3)COCl$, pyridine, CH_2Cl_2, RT.; 74%.
b) $C_7H_7SO_2K$, AcOH, H_2O, THF, RT.; 85%.
c) O_3, MeOH, –30°.
d) MeOH, H_2O, THF, RT.; 77% from **15**.
e) $Me_2tBuSiCl$, Et_3N, DMF, RT.
f) Et_3N, DMF, RT.; 87% over two steps.
g) HCl, H_2O, MeCN, RT.; 69%.

A model experiment with the sulfones **15** showed that a regeneration of the methacryloyl group by a base-catalyzed elimination of toluenesulfinic acid was possible. Unfortunately, the *N*-unsubstituted sulfones **17** proved much less stable toward bases than **15** leading, *e.g.* with triethylamine in methylene chloride at RT., to β-lactam-free products. When, however, the epimeric mixture **17** was first treated (in dimethylformamide) with dimethyl-*t*-butylchlorosilane and triethylamine and the *N*-silylated sulfones **18** thus formed were allowed to stand in dimethylformamide (and still in the presence of some of the chlorosilane) with triethylamine, the *N*-silylated methacryloylthio azetidinone **19** was finally isolated (87% from **17**). Desilylation of **19** with a dilute solution of hydrogen chloride in aqueous acetonitrile then provided the longed-for intermediate **13** (69%).

From this point, the synthesis of the 2-oxocephem system followed the general scheme already described. In a three-step procedure [5], a stabilized phosphorane grouping was built up on the β-lactam N-atom of **13** (**13**→**21**→**22**→**23**) and the resulting methacryloylthio phosphorane **23** (63% from **13**) was ozonized in acidic medium (to protect the ozone-sensitive phosphorane group by protonation) to give the pyruvoylthio phosphorane **24** *(Scheme 5)*.

Scheme 5



a) $(HO)_2CHCOOtBu$, toluene, DMF, molecular sieves, RT.
b) $SOCl_2$, polymeric base, dioxane, RT.
c) Ph_3P, polymeric base, dioxane, 50°; 63% over three steps.
d) O_3, CH_2Cl_2, TFA, −25°; Me_2S; CH_2Cl_2 – aq. $NaHCO_3$.
e) toluene, 60°; 64% of **25** and 6% of **26**.

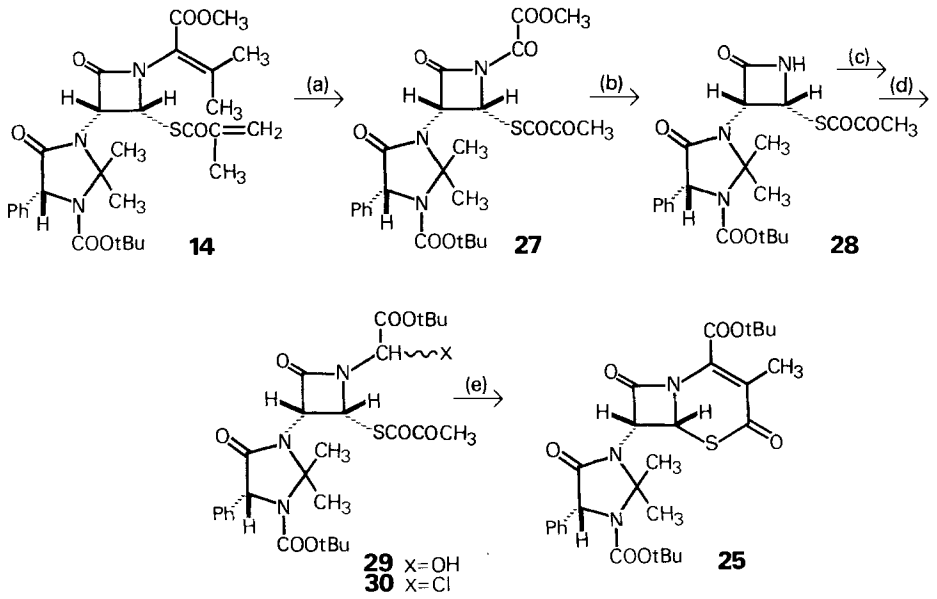
On heating the crude pyruvoylthio phosphorane **24** in toluene at 60°, only one major product was slowly formed along with triphenylphosphine oxide and, after 9 h, the desired *t*-butyl 2-oxocephem-4-carboxylate **25** was isolated (64% from **23**); only a small amount (~6%) of the five-membered isomer **26** could be detected.

Another, shorter, route from the intermediate **14** to the 2-oxocephem ester **25** has also been attempted *(Scheme 6)*. An excess of ozone attacked both double bonds in **14** affording, in an excellent yield, the *N*-methoxalyl pyruvoylthio azetidinone **27**. The corresponding *N*-unsubstituted compound **28**, obtained quantitatively from **27** by mild methanolysis, was transformed into the epimeric alcohols **29** and then the chlorides **30** (50% from **28**). When a solution of the latter and triphenylphosphine in dioxane was heated at 50°, the *t*-butyl 2-oxocephem ester **25** was slowly formed, obviously *via* the phosphorane **24**. Unfortunately, simultaneous decomposition of the rather unstable chlorides **30** was also observed and only 12% of the ester **25** could be isolated from this complex reaction.

Finally, treatment of the ester **25** at room temperature with 95% aqueous formic acid removed all three protecting groups in one step and gave 2-oxocephalexin **4** (75%) as a solid containing a stoichiometric amount of formic acid.

The new acid **4**, stable enough in solutions of formic or acetic acids, proved extremely labile (much more so than the previously reported 2-oxocephem-4-

Scheme 6



a) O_3, MeOH, −75°; 93%.
b) MeOH/H_2O/THF.; ~quant.
c) $(HO)_2CHCOOtBu$, toluene, DMF, molecular sieves, RT.
d) $SOCl_2$, polymeric base, dioxane, RT.; 50% over two steps.
e) Ph_3P, polymeric base, dioxane, 50°; 12%.

carboxylic acids [2]) in aqueous solutions of pH values higher than 3. As judged by UV. spectroscopy, it was completely decomposed immediately after solution in a citrate buffer of pH 6.0, and even in a buffer of pH 3.0 (citrate-HCl), its half-life at 37° was merely about 1 h.

Not surprisingly then, practically no antibacterial activity was found for this unstable compound in an agar plate diffusion test with several *Gram*-positive and *Gram*-negative strains at pH 6.0 and 7.0.

This biological result and those previously reported [2] suggest that a direct relationship exists between the stability of the 2-oxocephem-4-carboxylic acids and their biological activity and that a general lack of stability, rather than a lack of intrinsic activity, is to blame for the disappointing results of antibacterial tests in this new group of β-lactam derivatives.

The author remembers with gratitude the stimulating interest of the late Prof. *R. B. Woodward* in the reported work. His warm thanks are further due to Mr. *P. Felber (Woodward Research Institute)* 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 co-workers (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 author thanks him and his colleagues for their collaboration.

Experimental Part

Melting points (m.p., *Kofler*) are uncorrected. ^{1}H-NMR. spectra (δ ppm, J Hz) were recorded on a Varian HA-100 D spectrometer; all chemical shifts are reported in δ values. Rf Values were determined on *Merck* silica gel 60 F_{254} TLC. plates.

Hetacillin methyl ester. To a suspension of hetacillin (**5**) (31.45 g, 80.75 mmol) in 1.2 l of CH_2Cl_2, stirred in an ice/water bath, 250 ml of a 2% solution of diazomethane in ether was slowly added and the resulting solution was stirred in the cooling bath for 30 min. Cautious evaporation under reduced pressure gave a crystalline residue which, on recrystallization from CH_2Cl_2/ether/pentane, afforded in 3 crops 28.82 g (88%) of hetacillin methyl ester, white crystals, m.p. 102° ([6] 101,5–102°); Rf (ethyl acetate) 0.31; $[\alpha]_D^{20} = +326 \pm 1°$ (0.752% in $CHCl_3$). – IR. (CH_2Cl_2): 5.60, 5.72, 5.85, 6.68, 6.87, 6.96, 7.14, 7.30, 7.69, 8.26, 8.47, 8.63, 8.84, 9.72, 10.00, 10.20 μ. – ^{1}H-NMR. ($CDCl_3$): 1.47 (*s*, 6 H); 1.52 (*s*, 3 H); 1.69 (*s*, 3 H); 2.20 (br. *s*, 1 H); 3.73 (*s*, 3 H); 4.55 (*s*, 1 H); 4.68 (br. *s*, 1 H); 4.76 (*d*, $J = 4$, 1 H); 5,59 (*d*, $J = 4$, 1 H); 7.22–7.58 (*m*, 5 H).

$C_{20}H_{25}N_3O_4S$	Calc.	C 59.53	H 6.25	N 10.41	O 15.86	S 7.95%
(403.50)	Found	,, 59.26	,, 6.38	,, 10.34	,, 16.13	,, 7.93%

Hetacillin methyl ester S-*oxide* (**6**). A solution of hetacillin methyl ester (37 g, 91.85 mmol) and 90% *m*-chloroperbenzoic acid (17.6 g, about 91.8 mmol) in 2 l of CH_2Cl_2 was allowed to stand at RT. for 90 min. Subsequent washing with aqueous $NaHCO_3$-solution and brine and evaporation of the solvent under reduced pressure afforded a solid residue which was crystallized from hot ethyl acetate (with cooling to 0°); 20.4 g of the *S*-oxide, white crystals, m.p. 136.5–137.5°, was thus obtained. Chromatography of the mother liquor residue on 1 kg of *Merck* silica gel gave, with toluene/ethyl acetate 1:1, another 10.0 g of pure *S*-oxide **6**. Yield: 30.4 g, (79%); Rf (ethyl acetate) 0.15; $[\alpha]_D^{20} = +159 \pm 1°$ (0.964% in $CHCl_3$). – IR. (CH_2Cl_2): 5.57, 5.70, 5.90, 6.69, 6.87, 6.98, 7.14, 7.29, 7.40, 8.21, 9.43, 10.20 μ. – ^{1}H-NMR. ($CDCl_3$): 1.29 (*s*, 3 H); 1.55 (*s*, 3 H); 1.60 (*s*, 3 H); 1.73 (*s*, 3 H); 2.30 (br. *s*, 1 H); 3.84 (*s*, 3 H); 4.55 (*s*, 1 H); 4.70 (*d*, $J = 4$ Hz, 1 H); 4.70 (br. *s* overlapping with the foregoing *d*, 1 H); 4.78 (*d*, $J = 4$ Hz, 1 H); 7.24–7.50 (*m*, 5 H).

$C_{20}H_{25}N_3O_5S$	Calc.	C 57.26	H 6.01	N 10.02	O 19.07	S 7.64%
(419.50)	Found	,, 57.23	,, 6.05	,, 9.96	,, 19.19	,, 7.60%

Disulfide 7. A solution of **6** (29.3 g, 69.8 mmol) and of 2-mercaptobenzothiazole (11.7 g, 70 mmol) in 800 ml of benzene was heated under reflux for 90 min[3]). Evaporation of the solvent i.V. and column chromatography of the residue on 500 g of *Merck* silica gel afforded 22.4 g (56%) of the disulfide **7** as a solid foam eluted with toluene/ethyl acetate 4:1. Rf (ethyl acetate) 0.33; $[\alpha]_D^{20} = -163 \pm 1°$ (1.465%, $CHCl_3$). – IR. (CH_2Cl_2): 5.62, 5.75, 5.89, 6.67, 6.84, 6.99, 7.09, 7.27, 7.35, 7.46, 7.63, 8.06, 8.33, 8.47, 8.62, 9.09, 9.26, 9.34, 9.90, 10.20, 10.93, 11.88 μ. – ^{1}H-NMR. ($CDCl_3$): 1.64 (*s*, 6 H); 2.04 (br. *s*, 3 H); 2.20 (br. *s*, 1 H); 3.75 (*s*, 3 H); 4.70 (*s*, 1 H); 4.75 (*d*, $J = 5$, 1 H); 5.01 (br. *s*, 1 H); 5.08 (br. *s*, 1 H); 5.18 (br. *s*, 1 H); 5.86 (*d*, $J = 5$, 1 H); 7.24–7.62 (*m*, 2 H); 7.70–7.92 (*m*, 2).

$C_{27}H_{28}N_4O_4S_3$	Calc.	C 57.02	H 4.96	N 9.85	O 11.25	S 16.91%
(568.73)	Found	,, 56.55	,, 5.30	,, 9.89	,, 11.46	,, 16.54%

Disulfide **8**. A solution of the disulfide **7** (21.9 g, 38.5 mmol) in 340 ml of CH_2Cl_2 containing 3.4 ml of triethylamine was stirred at RT. under N_2 and the progress of the isomerization was followed by IR. spectroscopy. After 60 min, the reaction mixture was diluted with CH_2Cl_2 and the resulting solution was successively shaken with 1N aqueous HCl and with brine. Drying (Na_2SO_4) and evaporation of the solvent i.V. afforded 21.35 g (97%) of the disulfide **8** as a solid foam, used without further purification for the next step. For analysis and spectral data, a sample was chromatographed on *Merck* silica gel plates in ethyl acetate. Rf (ethyl acetate) 0.34; $[\alpha]_D^{20} = -69 \pm 1°$ (0.921%, $CHCl_3$). – IR. (CH_2Cl_2): 5.62, 5.80, 5.88, 6.15, 6.68, 6.85, 7.11, 7.23, 7.30, 7.69, 8.17, 8.62, 9.02, 9.26, 9.42, 9.94, 10.10 μ. – ^{1}H-NMR. ($CDCl_3$): 1.57 (*s*, 3 H); 1.58 (*s*, 3 H); 2.20 (*s*, 3 H); ~2.20 (br. *s*, 1 H); 2.26

---

[3]) In principle, the procedure developed by *Kamiya et al.* [7] was used.

(*s*, 3 H); 3.56 (*s*, 3 H); 4.73 (*s*, 1 H); 4.76 (*d*, $J=5$, 1 H); 5.68 (*d*, $J=5$, 1 H); 7.22–7.60 (*m*, 7 H); 7.72–7.92 (*m*, 2 H).

$C_{27}H_{28}N_4O_4S_3$	Calc.	C 57.02	H 4.96	N 9.85	O 11.25	S 16.91%
(568.73)	Found	„ 56.84	„ 4.97	„ 9.83	„ 11.25	„ 17.19%

Disulfide **9**. Disulfide **8** (5.48 g, 9.63 mmol) was heated in 135 ml of dioxane with (4.63 g, 21.2 mmol) bis-*t*-butoxycarbonyl oxide and ethyl-diisopropylamine (1.24 g, 9.64 mmol) at 50°. After 24 h, another 4.63 g of bis-*t*-butoxycarbonyl oxide was added and heating was continued for another 48 h. Evaporation of the resulting reaction mixture i.V. and chromatography of the residue on 300 g of *Merck* silica gel afforded with toluene/ethyl acetate 4:1 a total of 4.62 g of the pure *N*-Boc protected disulfide **9** as a solid foam. With toluene/ethyl acetate 1:1, 1.06 g of unchanged **8** was recovered. Yield (based on consumed **8**): 89%. – Rf (toluene/ethyl acetate 1:1) 0.41; $[\alpha]_D^{20} = -130 \pm 1°$ (0.696%, $CHCl_3$). – IR. (CH_2Cl_2): 5.62, 5.81 (sh.), 5.87, 6.15, 6.67, 6.87, 7.01, 7.19, 7.30, 7.39 (sh.), 7.46, 7.69, 8.16, 8.62, 9.09, 9.26, 9.40, 9.95, 10.10 μ. – ^{1}H-NMR. ($CDCl_3$): 1.22 (br. *s*, 9 H); 1.86 (*s*, 3 H); 2.19 (*s*, 3 H); 2.21 (*s*, 3 H); 3.55 (*s*, 3 H); 4.78 (*d*, $J=5$, 1 H); 5.12 (br. *s*, 1 H); 5.65 (*d*, $J=5$, 1 H); 7.18–7.56 (*m*, 7 H); 7.72–7.94 (*m*, 2 H).

$C_{32}H_{36}N_4O_6S_3$	Calc.	C 57.47	H 5.43	N 8.38	O 14.35	S 14.38%
(668.84)	Found	„ 57.56	„ 5.54	„ 8.37	„ 14.42	„ 14.19%

N-*Methoxalyl derivative* **10**. Into a solution of the disulfide **9** (668 mg, 1 mmol) in 20 ml of methanol, a stream of O_3 was introduced at $-20°$ at a rate of 0.1 mmol O_3/min for a period of 20 min. After another 20 min at $-20°$, the excess of O_3 was removed in a stream of N_2, the reaction mixture was concentrated i.V. to about 10 ml and diluted with CH_2Cl_2 and the resulting solution was successively washed with 3% aqueous $NaHSO_3$-solution and brine. Drying (Na_2SO_4) and evaporation of the organic part afforded 610 mg of a crude product which, on crystallization from methanol/pentane, gave 461 mg (72%) of **10**, white crystals, m.p. 164–166° (sealed capillary). In an experiment with 4.16 g of **9**, 3.25 g (81%) of crystalline **10** were obtained. – Compound **10** decomposes on *Merck* silica gel plates in toluene/ethyl acetate systems. $[\alpha]_D^{20} = -133 \pm 1°$ (0.89%, $CHCl_3$). – IR. (CH_2Cl_2): 5.46 (sh.), 5.49, 5.68, 5.86, 7.02, 7.29 (sh.), 7.35, 8.05, 8.33, 8.62, 9.15, 9.40, 9.96, 10.20 μ. – ^{1}H-NMR. ($CDCl_3$): 1.22 (*s*, 9 H); 1.82 (*s*, 3 H); 1.96 (*s*, 3 H); 3.88 (*s*, 3 H); 4.92 (*d*, $J=6$, 1 H); 5.16 (*s*, 1 H); 5.83 (*d*, $J=6$, 1 H); 7.22–7.52 (*m*, 7 H); 7.78–7.94 (*m*, 2 H).

$C_{29}H_{30}N_4O_7S_3$	Calc.	C 54.19	H 4.70	N 8.72	O 17.42	S 14.96%
(642.76)	Found	„ 54.10	„ 4.70	„ 8.80	„ 17.52	„ 15.09%

N-*Unsubstituted azetidinonyl disulfide* **11**. A solution of the *N*-methoxalyl derivative **10** (2.37 g, 3.7 mmol) in 35 ml of THF, 230 ml of methanol and 5 ml of water was allowed to stand at RT. for 17 h. Evaporation i.V., finally repeatedly with benzene, and chromatography of the residue on 70 g of *Merck* silica gel afforded, with toluene/ethyl acetate 4:1, 1.88 g (91%) of solid **11**. Crystallization of the latter material from methanol/pentane gave 1.76 g (86%) of white crystals, m.p. 149–155°, the elemental analysis of which suggested a hemihydrate of **11**; Rf (ethyl acetate) 0.45; $[\alpha]_D^{20} = -220 \pm 1°$ (1.073%, $CHCl_3$). – IR. (CH_2Cl_2): 2.96, 5.58, 5.88, 6.85 (sh.), 6.87, 7.03, 7.30, 7.36, 7.46, 8.07, 8.60, 9.15, 9.40, 9.94 μ. – ^{1}H-NMR. ($CDCl_3$): 1.22 (*s*, 9 H); 1.82 (*s*, 3 H); 1.93 (*s*, 3 H); 4.74 (*d*, $J=5$, 1 H); 5.12 (*s*, 1 H); 5.28 (*d*, $J=5$, 1 H); 7.20–7.48 (*m*, 8 H); 7.64–7.88 (*m*, 2 H).

$C_{26}H_{28}N_4O_4S_3 \cdot \frac{1}{2} H_2O$	Calc.	C 55.21	H 5.16	N 9.91	O 12.70	S 17.01%
(565.72)	Found	„ 55.19	„ 5.08	„ 9.92	„ 12.80	„ 17.10%

Symmetrical disulfide **12**. A solution of the disulfide **11** (278 mg, 0.5 mmol) and of $NaBH_4$ (46 mg, 1.2 mmol) in 11 ml of DMF was stirred at $-20°$ for 2.5 h. Methacryloyl chloride (0.3 ml, 3.1 mmol) was added and stirring was continued at 0°. After addition of another 0.12 ml of the chloride and 3 h of stirring, the reaction mixture was worked up by partition between benzene and water and washing the organic phase with aqueous $NaHCO_3$. The residue obtained by evaporation of the organic layer gave, on chromatography on *Merck* silica gel deactivated with 10% of water, 2-methacryloylthiobenzothiazole (eluted with toluene/ethyl acetate 9:1) and 177 mg (91%) of the symmetrical disulfide **12** (eluted with ethyl acetate/methanol 1:1), m.p. 203–205°; Rf (ethyl acetate)

0.04. – IR. (CH_2Cl_2): 3.05 (br.), 5.59, 5.88, 7.00, 7.31, 7.46, 8.05, 8.58, 9.13 μ. – ^{1}H-NMR. ($CDCl_3$): 1.18 (br. *s*, 18 H); 1.62 (br. *s*, 12 H); 4.70 (br. *'s'*, 2 H); 4.96 (br. *'s'*, 2 H); 5.06 (br. *s*, 2 H); 7.31 (*'s'*, 10 H); 7.76 (br. *s*, 2 H).

$C_{38}H_{48}N_6O_8S_2$	Calc.	C 58.44	H 6.20	N 10.76	S 8.21%
(780.96)	Found	„ 57.94	„ 6.37	„ 10.49	„ 7.96%

Methacryloythio derivative **14**. A solution of the disulfide **9** (6.35 g, 9.49 mmol) and of triphenylphosphine (2.75 g, 10.45 mmol) in 260 ml of CH_2Cl_2 was stirred under N_2 at 0–5° in the presence of 30 ml of water. After 88 h, the organic phase was separated, dried (Na_2SO_4) and 14 ml of pyridine followed by 9.5 ml of methacryloyl chloride were added at 0°. The resulting reaction mixture was stirred (N_2) at RT. for 4.5 h, then diluted with more CH_2Cl_2 and successively washed with water and 2% aqueous $NaHCO_3$-solution. Drying (Na_2SO_4) and evaporation of the solvent under reduced pressure gave an oily residue which was chromatographed on 350 g of *Merck* silica gel. With toluene/ethyl acetate 9:1, 2-mercaptobenzothiazole and its acylation product were first eluted. Further elution with the 9:1 solvent system and, at the end, with toluene/ethyl acetate 4:1, afforded a total of 4.03 g (74%) of the methacryloylthio derivative **14** as a solid foam. Rf (toluene/ethyl acetate 1:1) 0.45; $[a]_D^{20} = -22 \pm 1°$ (1.022%, $CHCl_3$). – IR. (CH_2Cl_2): 5.62, 5.81 (sh.), 5.84, 5.88, 6.01, 6.16, 6.79, 6.90, 7.03, 7.19, 7.32, 7.40 (sh.), 7.46 (sh.), 7.69, 8.18, 8.62, 9.17, 9.78, 10.12 μ. – ^{1}H-NMR. ($CDCl_3$): 1.15 (br. *s*, 9 H); 1.75 (*s*, 3 H); 1.80 (*s*, 3 H); 1.88 (*d*, $J = 1$, 3 H); 2.06 (*s*, 3 H); 2.18 (*s*, 3 H); 3.78 (*s*, 3 H); 4.79 (*d*, $J = 5$, 1 H); 5.60 (*d*, $J = 1$, 1 H); 5.84 (br. *s*, 1 H); 6.19 (*d*, $J = 5$, 1 H); 7.30 (*'s'*, 5 H).

$C_{29}H_{37}N_3O_7S$	Calc.	C 60.93	H 6.52	N 7.35	O 19.59	S 5.61%
(571.69)	Found	„ 60.73	„ 6.52	„ 7.25	„ 19.75	„ 5.49%

Sulfones **15**. To a solution of the methacryloylthio derivative **14** (7.72 g, 13.5 mmol) and of potassium *p*-toluenesulfinate (hemihydrate) (4.11 g, 20.2 mmol) in 200 ml of THF and 40 ml of water, 8.1 ml of a 10% solution of acetic acid in THF was added and the resulting reaction mixture was stirred at RT. under N_2. After 6 h, another 2.76 g (13.6 mmol) of the sulfinate in 70 ml of THF and another 5.4 ml of the THF solution of acetic acid were added and stirring was continued for another 15 h. After partial evaporation of THF i.V., CH_2Cl_2 was added and the resulting mixture was washed twice with water (the aqueous parts were re-extracted with CH_2Cl_2). The combined organic extracts were dried (Na_2SO_4) and evaporated i.V. to give 9.7 g of a crude product containing only very little **14**. Chromatography on 300 g of *Merck* silica gel afforded with toluene/ethyl acetate 4:1, a total of 8.32 g (85%) of pure **15** as a solid foam. Another 0.71 g of a somewhat contaminated **15** was collected in the first fractions with the 4:1 solvent system. According to ^{1}H-NMR. spectroscopy, **15** was obtained as an about 1:1 mixture of 2 epimers. Rf (toluene/ethyl acetate 1:1) 0.38. – IR. (CH_2Cl_2): 3.3–3.5, 5.61, 5.81 (sh.), 5.86, 6.15, 6.25, 6.71, 6.79, 6.90, 7.01, 7.20, 7.32, 7.40 (sh.), 7.60, 7.68, 8.16, 8.58, 8.69, 9.20, 9.39, 10.36, 12.19 μ. – ^{1}H-NMR. ($CDCl_3$): 1.18 (br. *s*, 9 H); 1.14–1.26 (2 *t*, 3 H); 1.78, 1.82, 1.85 (3 *s*, 6 H); 2.11 (*s*, 3 H); 2.20, 2.22 (2 *s*, 3 H); 2.47 (*s*, 3 H); 2.83–3.32 (*m*, 2 H); 3.38–3.80 (*m*, 1 H); 3.82 (*s*, 3 H); 4.77, 4.81 (2 *d*, $J = 5.4$, 1 H); 5.08 (br. *s*, 1 H); 6.12, 6.20 (2 *d*, $J = 5.4$, 1 H); 7.20–7.48 (*m*, 7 H); 7.65–7.81 (*m*, 2 H). – MS. (210°): 727 (*M**).

$C_{36}H_{45}N_3O_9S_2$	Calc.	C 59.40	H 6.23	N 5.77	O 19.78	S 8.81%
(727.89)	Found	„ 59.25	„ 6.26	„ 5.69	„ 19.68	„ 8.52%

N-*Methoxalyl azetidinonyl sulfones* **16**. Into a stirred solution of the sulfones **15** (8.32 g, 11.43 mmol) in 260 ml of methanol, an excess (29 mmol) of O_3 was introduced at −40° during 100 min. After another 30 min at −40°, the reaction mixture was purged with N_2, concentrated i.V. to about 50 ml volume and diluted with CH_2Cl_2. The resulting solution was washed with a 3% aqueous $NaHSO_3$-solution and with saturated brine; the aqueous parts were reextracted with CH_2Cl_2. Drying and evaporation i.V. of the combined organic parts afforded 7.93 g of **16** as a solid foam, used without any further purification in the next step. – IR. (CH_2Cl_2): 3.25–3.40, 5.49, 5.68, 5.81 (sh.), 5.87, 6.25, 6.68, 6.77, 6.87, 7.04, 7.30 (sh.), 7.35, 7.43 (sh.), 7.60, 8.06, 8.22, 8.69, 9.17, 10.38, 11.11 μ. – ^{1}H-NMR. ($CDCl_3$): 1.18 (br. *s*, 9 H); 1.14–1.26 (2 *t*, 3 H); 1.74, 1.81, 1.86 (3 *s*, 6 H); 2.45, 2.48 (2 *s*, 3 H); 2.76–3.34 (*m*, 2 H); 3.46–3.92 (*m*, 1 H); 3.91 (*s*, 3 H); 4.93, 4.98 (2 *d*, $J = 6$, 1 H); 5.16 (br. *s*, 1 H); 6.25, 6.38 (2 *d*, $J = 6$, 1 H); 7.24–7.50 (*m*, 7 H); 7.68–7.82 (*m*, 2 H).

N-*Unsubstituted azetidinonyl sulfones* **17**. A solution of 7.93 g of the crude sulfones **16** in 50 ml of THF, 500 ml of methanol and 12.5 ml of water was allowed to stand overnight at RT. The resulting solution was concentrated i.V. to a volume of about 50 ml, the residual liquid was diluted with CH_2Cl_2 and washed with saturated brine. Drying (Na_2SO_4) and evaporation i.V. afforded 7.4 g of a residue which was chromatographed on 200 g of *Merck* silica gel deactivated with 10% of water. The epimeric sulfones **17** were eluted with toluene/ethyl acetate 2:1 as a solid foam. Yield: 5.45 g (77% from **15**). Rf (toluene/ethyl acetate 1:1) 0.14. – IR. (CH_2Cl_2): 2.96, 3.30–3.50, 5.59, 5.88, 6.25, 6.71, 6.80, 6.90, 7.04, 7.32, 7.38, 7.46, 7.78–8.05, 8.60 (sh.), 8.70, 9.17, 10.36 μ. – ^{1}H-NMR. ($CDCl_3$): 1.18 (br. *s*, 9 H); 1.14–1.30 (2 *t* ?, 3 H); 1.71, 1.78, 1.80 (3 *s*, 6 H); 2.45, 2.47 (2 *s*, 3 H); 2.80–3.30 (*m*, 2 H); 3.40–3.80 (*m*, 1 H); 4.72, 4.77 (2 *d* overlapping to a *t*, $J=5$, 1 H); 5.11 (br. *s*, 1 H); 5.71, 5.82 (2 *d*, $J=5$, 1 H); 6.46, 6.50 (2 br. *s*, 1 H); 7.24–7.44 (*m*, 7 H); 7.66–7.82 (*m*, 2 H).

$C_{30}H_{37}N_3O_7S_2$	Calc.	C 58.52	H 6.06	N 6.82	O 18.19	S 10.41%
(615.76)	Found	„ 58.49	„ 6.20	„ 6.80	„ 18.91	„ 9.79%

N-*(Dimethyl-*t*-butylsilyl) azetidinonyl sulfones* **18**. The sulfones **17** (8.22 g, 13.34 mmol), dimethyl-*t*-butylchlorosilane (6.89 g, 45.7 mmol) and triethylamine (4.62 g, 45.7 mmol) in 140 ml of DMF were stirred at RT. (N_2) for 2 h. TLC. (*Merck* silica gel, toluene/ethyl acetate 1:1) at the end of this period showed only **18** accompanied by a small amount of the more mobile, *N*-silylated, methacryloylthio azetidinone **19**. The reaction mixture was diluted with toluene and washed with several portions of water (the aqueous washings were re-extracted with toluene). The organic extracts were dried (Na_2SO_4) and evaporated i.V. to give 9.3 g of a crude mixture of epimeric sulfones **18** containing some **19** used without any further purification for the preparation of **19**. – Rf (toluene/ethyl acetate 1:1) 0.46. – IR. (CH_2Cl_2): 3.30–3.55, 5.67, 5.88, 6.25, 6.71, 6.89, 7.04, 7.20, 7.33, 7.41, 7.46, 7.69–8.06, 8.58, 8.69, 9.20, 9.39, 9.61, 10.42, 11.90, 12.19 μ.

$C_{36}H_{51}N_3O_7S_2Si$ (730.02) Calc. Si 3.85% Found Si 3.86%

N-*(Dimethyl-*t*-butylsilyl) methacryloylthio azetidinone* **19**. A solution of the crude sulfones **18** (9.0 g, about 12.3 mmol), dimethyl-*t*-butylchlorosilane (3.22 g, 21.5 mmol) and triethylamine (3.9 g, 38.6 mmol) of in 140 ml of DMF was allowed to stand overnight at RT. Toluene was added and the resulting solution was washed with water and a 5% aqueous solution of citric acid; all aqueous washings were re-extracted with toluene. Drying and evaporation i.V. of the combined organic parts gave 9.3 g of a residue which was chromatographed on 300 g of *Merck* silica gel. With toluene/ethyl acetate 4:1, 5.3 g of the methacryloylthio derivative **19** were eluted as a solid foam followed by 2.0 g of unchanged **18**. A similar treatment of the latter to that described above and chromatography afforded another 1.15 g of **19** thus increasing the total yield to 6.45 g (91% from **18**; 87% as based on **17**). Rf (toluene/ethyl acetate 1:1) 0.52. – IR. (CH_2Cl_2): 3.45, 3.52, 5.68, 5.81 (sh.), 5.88, 6.01, 6.15, 6.71, 6.81, 6.92, 7.04, 7.22, 7.32, 7.46, 7.73–8.06, 8.59, 9.17, 9.40, 9.58, 9.80, 10.15, 10.30, 10.63, 11.32, 11.87, 12.19 μ. – ^{1}H-NMR. ($CDCl_3$): 0.20 (*s*, 3 H); 0.24 (*s*, 3 H); 0.96 (*s*, 9 H); 1.15 (br. *s*, 9 H); 1.70 (*s*, 3 H); 1.76 (*s*, 3 H); 1.90 (*s*, 3 H); 4.74 (*d*, $J=5$, 1 H); 5.06 (br. *s*, 1 H); 5.60 (*d*, $J=1$, 1 H); 5.84 (*s*, 1 H); 5.87 (*d*, $J=5$, 1 H); 7.31 ('*s*', 5 H).

Methacryloylthio azetidinone **13**. A solution of **19** (5.3 g, 9.24 mmol) in 240 ml of acetonitrile and 80 ml of 1N aqueous HCl was stirred at RT. during 17 h. The acid was quenched with an excess of 8% aqueous $NaHCO_3$ and most acetonitrile was removed under reduced pressure. From the remaining liquid, the product was extracted into CH_2Cl_2, and the extract was washed with water. Drying (Na_2SO_4) and evaporation i.V. afforded 3.85 g of a residue which was chromatographed on 90 g of *Merck* silica gel. With toluene/ethyl acetate 4:1, a total of 2.91 g (69%) of pure **13** was eluted. It formed a solid foam. Rf (toluene/ethyl acetate 1:1) 0.21; $[\alpha]_D^{20} = -77 \pm 1°$ (1.1%, $CHCl_3$). – IR. (CH_2Cl_2): 2.96, 3.3–3.5, 5.59, 5.82 (sh.), 5.88, 6.02, 6.17, 6.70, 6.80, 6.89, 7.04, 7.19, 7.32, 7.38, 7.46, 7.85–8.06, 8.36, 8.60, 9.17, 9.39, 9.76, 10.20, 10.33, 10.63, 11.27 μ. – ^{1}H-NMR. ($CDCl_3$): 1.18 (*s*, 9 H); 1.75 (*s*, 3 H); 1.80 (*s*, 3 H); 1.89 (*s*, 3 H); 4.78 (*d*, $J=4.8$, 1 H); 5.11 (*s*, 1 H); 5.57 (*d*, $J=1.4$, 1 H); 5.80 (*s*, 1 H); 5.82 (*d*, $J=4.8$, 1 H); 6.64 (*s*, 1 H); 7.33 ('*s*', 5 H).

$C_{23}H_{29}N_3O_5S$	Calc.	C 60.11	H 6.36	N 9.14	S 6.97%
(459.56)	Found	„ 59.73	„ 6.56	„ 8.96	„ 6.59%

Compound **20** (see footnote 2). Into a solution of **14** (114.2 mg, 0.2 mmol) in 2.5 ml of methanol, one equivalent of O_3 was introduced at $-60°$. After 45 min at $-45°$ and another 75 min at $-20°$,

the reaction mixture was diluted with CH_2Cl_2 and washed with 3% aqueous $NaHSO_3$ and with brine. The residue of the organic part (110 mg) was chromatographed on *Merck* silica gel plates in toluene/ethyl acetate to give 50 mg (44%) of the pyruvoylthio derivative **20** (as a solid foam) and 36 mg of unchanged **14**. Rf (toluene/ethyl acetate 1:1) 0.40. – IR. (CH_2Cl_2): 5.62, 5.81, 5.88, 5.95 (sh.), 6.77, 6.88, 7.03, 7.20, 7.29, 7.40 (sh.), 7.46, 7.69, 8.18, 8.61, 9.12, 9.41, 11.33 μ. – ^{1}H-NMR. ($CDCl_3$): 1.18 (*s*, 9 H); 1.76 (*s*, 3 H); 1.82 (*s*, 3 H); 2.09 (*s*, 3 H); 2.21 (*s*, 3 H); 2.39 (*s*, 3 H); 3.84 (*s*, 3 H); 4.83 (*d*, J = 5.2, 1 H); 5.06 (br. *s*, 1 H); 6.08 (*d*, J = 5.2, 1 H), 7.36 ('*s*', 5 H).

Phosphorane **23**. The methacryloylthio azetidinone **13** (459 mg, 1 mmol) was stirred in 3 ml of DMF and 12 ml of toluene with *t*-butyl glyoxylate hydrate (444 mg, ~3 mmol) in the presence of activated molecular sieves (Type 4A 1/16, *Bender+Hobein* Ltd, Zürich). After 3 h at RT. the sieves were filtered off and washed on the filter with toluene. Evaporation of the combined filtrates i.V., finally repeatedly with toluene in high vacuum, gave 573 mg of the crude epimeric adducts **21** (solid foam). Rf (toluene/ethyl acetate 1:1) 0.38 (one elongated spot). – IR. (CH_2Cl_2): 2.90 (br.), 3.3–3.5, 5.62, 5.78 (sh.), 5.81 (sh.), 5.88, 6.02, 6.17, 6.79, 6.89, 7.04, 7.35, 7.41, 7.81–8.05, 8.62, 9.17, 9.77 μ.

To a solution of the above-mentioned adducts in 10 ml of dioxane, a solution of 340 mg (2.86 mmol) of thionyl chloride in 3 ml of dioxane was added and the resulting mixture was stirred at RT. (N_2) in the presence of polymeric *Hünig* base [8] (3.95 meq/g) for a period of 3 h. The base was filtered off, washed with dioxane, and the combined filtrates were evaporated i.V. to give 560 mg of a residue which was chromatographed on 10 g of *Merck* silica gel. With toluene/ethyl acetate 9:1, a total of 495 mg of pure epimeric chlorides **22** (81% from **13**) was eluted as solid foam. Rf (toluene/ethyl acetate 1:1) 0.58. – IR. (CH_2Cl_2): 3.3–3.5, 5.57, 5.75, 5.81 (sh.), 5.88, 6.02, 6.17, 6.78, 6.90, 7.04, 7.34, 7.40, 7.81–8.01, 8.72, 9.09, 9.80, 10.10 μ.

A solution of the chlorides **22** (1.16 g, 1.91 mmol), prepared as described above, and of triphenylphosphine (752 mg, 2.87 mmol) in 20 ml of dioxane was heated at 50° under N_2 in the presence of 2.6 g of polymeric *Hünig* base. After 38 h, the suspension was filtered and the base was washed with dioxane. On evaporation i.V., the combined filtrates gave 1.8 g of a residue which was chromatographed on 60 g of *Merck* silica gel. With toluene and toluene/ethyl acetate 9:1, the excess of triphenylphosphine and some minor impurities were removed. Elution with toluene/ethyl acetate 2:1 afforded 902 mg of pure phosphorane **23** and another 470 mg of **23** contaminated with triphenylphosphine oxide. Chromatography of the latter material on *Merck* preparative plates with toluene/ethyl acetate 1:1 gave another 342 mg of **23**. Total yield: 1244 mg (78% from the chlorides **22**; 63% from **13**). The phosphorane was obtained as a solid foam. Rf (toluene/ethyl acetate 1:1) 0.18. – IR. (CH_2Cl_2): 3.35–3.52, 5.65, 5.81, 5.88, 5.95 (sh.), 6.02, 6.06, 6.16, 6.21 (sh.), 6.79, 6.90, 6.97, 7.09 (sh.), 7.22, 7.35, 7.40 (sh.), 7.46 (sh.), 7.81–8.00, 8.62, 9.05, 9.80, 10.15, 10.30, 10.64, 11.23 μ.

$C_{47}H_{52}N_3O_7PS$	Calc.	C 67.69	H 6.29	N 5.04	S 3.84 P 3.71%
(833.98)	Found	„ 67.39	„ 6.17	„ 5.22	„ 3.68 „ 3.65%

t-*Butyl 7(*R*)-(2,2-dimethyl-3-*t*-butoxycarbonyl-4(*R*)-phenyl-imidazolid-5-on-1-yl)-3-methyl-2-oxo-(6*R*)-cephem-4-carboxylate* **25**. *A. From the Phosphorane* **23**. The methacryloylthio phosphorane **23** (902 mg, 1.08 mmol) was ozonized in 66 ml of CH_2Cl_2 and 6 ml of trifluoroacetic acid at −25° with an excess of O_3/O_2 which was introduced at a rate of 0.1 mmol/min for 22 min. After another 20 min at −25°, the reaction mixture was purged with N_2, 6 ml of dimethylsulfide was added, and the resulting solution was kept at −25° for 17 h. More CH_2Cl_2 was added, the acid was quenched by shaking with an excess of cold 8% aqueous $NaHCO_3$-solution, and the organic phase was washed with saturated brine; the aqueous washings were re-extracted with CH_2Cl_2. Drying (Na_2SO_4) and evaporation of the combined organic parts afforded 885 mg of the pyruvoylthio phosphorane **24**. Rf (toluene/ethyl acetate 1:1) 0.18. – IR. (CH_2Cl_2): 3.32–3.50, 5.65, 5.81, 5.89, 6.02, 6.17 (br.), 6.76, 6.91, 6.98, 7.09, 7.23, 7.35, 7.40 (sh.), 7.47 (sh.), 7.81–8.03, 8.62, 9.09 μ.

A solution of the phosphorane **24** in 25 ml of toluene was heated under N_2 at 60°. A major product Rf 0.50, and a minor one Rf 0.46 (toluene/ethyl acetate 1:1) were slowly formed along with triphenylphosphine oxide. Evaporation i.V. after 9 h, chromatography on 25 g of acid-washed silica gel with toluene/ethyl acetate 9:1, and, finally, re-chromatography of some mixed fractions on *Merck* silica gel plates (toluene/ethyl acetate 1:1) gave 385 mg (64%, based on **23**) of the 2-oxocephem ester **25** and 36 mg (~6%) of the isomeric 2-acetylpenem ester **26**. The 2-oxocephem ester **25** as obtained by chromatography formed a solid foam, but could be crystallized from ether/pentane to

give 290 mg of long, yellowish, needles decomposing between 145° and 195°; Rf (toluene/ethyl acetate 1:1) 0.50; $[\alpha]_D^{20} = -50 \pm 1°$ (0.862%, $CHCl_3$). – UV. (96% EtOH): $\lambda_{max} = 308$ nm (ε 5050) (a broad maximum probably resulting from an overlap of $\lambda_{max} = 315$ nm and $\lambda_{max} = 298$ nm). – IR. (CH_2Cl_2): 5.52, 5.78, 5.85, 6.06, 6.18, 6.67, 6.76, 6.85, 7.04, 7.14, 7.25, 7.30 (sh.), 7.42, 7.69, 8.03, 8.58, 9.09, 10.86 μ. – ^{1}H-NMR. ($CDCl_3$): 1.15 (br. *s*, 9 H); 1.52 (*s*, 9 H); 1.78 (*s*, 3 H); 1.83 (*s*, 3 H); 1.88 (*s*, 3 H); 4.95 (*d*, $J = 4.5$, 1 H); 5.08 (br. *s*, 1 H); 5.75 (*d*, $J = 4.5$, 1 H); 7.28 ('*s*', 5 H).

$C_{28}H_{35}N_3O_7S$	Calc.	C 60.31	H 6.33	N 7.53	O 20.08	S 5.75%
(557.66)	Found	„ 60.54	„ 6.54	„ 7.48	„ 20.03	„ 5.52%

The 2-acetylpenem ester **26** (a yellowish solid) was slightly contaminated with *t*-butyl 5-acetylthiazole-4-carboxylate [2] to which it decomposes on silica gel (or, very rapidly, on treatment in CH_2Cl_2 with a drop of trifluoroacetic acid). Rf (toluene/ethyl acetate 1:1) 0.46. – IR. (CH_2Cl_2): 3.3–3.5, 5.53, 5.85 (sh.), 5.88, 6.39, 6.71, 6.80, 6.94, 7.11, 7.25, 7.35, 7.46, 7.57, 8.33, 8.69, 9.17 μ. – ^{1}H-NMR. ($CDCl_3$): 1.20 (br. *s*, 9 H); 1.51 (*s*, 9 H); 1.86 (*s*, 3 H); 1.89 (*s*, 3 H); 2.02 (*s*, 3 H); 5.14 (*s*, 1 H); 5.16 (*d*, $J = 3.8$, 1 H); 5.92 (*d*, $J = 3.8$, 1 H); 7.34 ('*s*', 5 H).

B. From the pyruvoylthio azetidinone **28**. A solution of the pyruvoylthio azetidinone **28** (see below) (840 mg, 1.82 mmol) and of hydrated *t*-butyl glyoxylate (840 mg, ~5.67 mmol) in 4 ml of DMF and 18 ml of toluene was stirred at RT. under N_2 in the presence of activated molecular sieves. After 3 h, the sieves were filtered off, washed with toluene, and the combined filtrates were evaporated under reduced pressure, finally several times with toluene i.HV., to give a crude mixture of epimeric hemi-animals **29**. The latter were stirred in 30 ml of dioxane with thionyl chloride (0.68 g, 5.7 mmol) and with polymeric *Hünig* base (3.8 g, 3.95 meq/g) at RT. for 3 h. Filtration, washing of the polymeric base on the filter with dioxane, and evaporation i.V. of the combined filtrates gave a crude product which was chromatographed on 60 g of acid-washed silica gel. With toluene and toluene/ethyl acetate 9:1, some mobile impurities were eluted followed, by further eluting with the 9:1 and, finally, with a 4:1 solvent system, by 550 mg (49% from **28**) of the epimeric chlorides **30** as a solid foam. Rf (toluene: ethyl acetate) 0.57 and 0.53 (with slight streaking). – IR. (CH_2Cl_2): 3.32–3.50, 5.59, 5.75, 5.88, 6.71, 6.78, 6.89, 7.04, 7.18, 7.33, 7.41, 8.73, 9.11 μ. The chlorides **30** (235 mg, 0.385 mmol) were heated in 12 ml of dioxane at 50° with triphenylphosphine (151 mg, 0.58 mmol) and with polymeric *Hünig* base (0.9 g). After 50 h, the reaction mixture was filtered and evaporated i.V. and the residue chromatographed on 30 g of *Merck* silica gel. With toluene/ethyl acetate 4:1, material (82 mg) was eluted which, on re-chromatography on *Merck* analytical silica gel plates (toluene/ethyl acetate 1:1), finally afforded 25 mg (12% from **30**) of pure ester **25** identical (Rf, IR. and NMR.) with the crystalline ester as prepared by Method A.

N-Methoxalyl pyruvoylthio azetidinone **27**. Into a solution of **14** (1.12 g, 1.96 mmol) in 22 ml of methanol, a fivefold excess of O_3 was introduced at −75° within 100 min. After another 100 min at this temperature, the reaction mixture was diluted with CH_2Cl_2 and washed successively with 3% aqueous $NaHSO_3$-solution and saturated brine. Drying and evaporation i.V. of the organic part afforded 1.0 g (93%) of crude **27** of a very good quality. It proved unstable toward silica gel and was used in the next step (see **28**) without any further purification. – IR. (CH_2Cl_2): 5.49, 5.71, 5.81 (sh.), 5.88, 7.04, 7.34 (sh.), 7.38, 8.05, 8.23, 8.62, 9.17, 10.20, 11.36 μ. – ^{1}H-NMR. ($CDCl_3$): 1.16 (br. *s*, 9 H); 1.71 (*s*, 3 H); 1.76 (*s*, 3 H); 2.40 (*s*, 3 H); 3.86 (*s*, 3 H); 4.98 (*d*, $J = 6.5$, 1 H); 5.12 (br. *s*, 1 H); 6.23 (*d*, $J = 6.5$, 1 H); 7.33 ('*s*', 5 H).

N-Unsubstituted pyruvoylthio azetidinone **28**. A solution of the *N*-methoxalyl derivative **27** (1.0 g, 1.82 mmol) in 0.7 ml of THF and 7.2 ml of methanol containing 2% of water was allowed to stand overnight at RT. Evaporation i.V., finally several times with toluene i.HV., afforded 0.84 g of crude noncrystalline **28** of very good quality (NMR.) justifying direct use in the next step (see **25**, Method B). For analysis and characterization, a sample was crystallized from CH_2Cl_2/ether/pentane; m.p. 173–178°. The compound streaks on silica gel plates. $[\alpha]_D^{20} = -72 \pm 1°$ (0.513%, $CHCl_3$). – IR. (CH_2Cl_2): 2.95, 5.56, 5.78, 5.86, 5.91 (sh.), 6.67, 6.76, 6.84, 7.01, 7.30, 7.35, 7.43, 8.55, 9.09, 9.34, 11.23 μ. – ^{1}H-NMR. ($CDCl_3$): 1.18 (br. *s*, 9 H); 1.74 (*s*, 3 H); 1.78 (*s*, 3 H); 2.34 (*s*, 3 H); 4.78 (*d*, $J = 4.6$, 1 H); 5.08 (br. *s*, 1 H); 5.66 (*d*, $J = 4.6$, 1 H); 6.68 (br. *s*, 1 H); 7.34 ('*s*', 5 H).

$C_{22}H_{27}N_3O_6S$	Calc.	C 57.25	H 5.90	N 9.10	O 20.80	S 6.95%
(461.53)	Found	„ 57.07	„ 5.89	„ 9.38	„ 20.83	„ 6.81%

2-Oxocephalexin **4**. A solution of 69 mg (0.12 mmol) of the ester **25** in 2 ml of 95% formic acid was allowed to stand at RT. for 24 h. The resulting reaction mixture was evaporated i.V. and the residue was treated, at RT., with another 2 ml of 95% formic acid. Next day, the latter procedure was repeated once more. Finally, after a total of 65 h, the solid residue as obtained by evaporation i.V. was triturated with 2 small portions of CH_2Cl_2, redissolved in formic acid (98%), and thoroughly evaporated i.HV. to give 33 mg (65%) of an off-white solid analyzing for the formate of **4**. – UV. (96% EtOH with 1% HCOOH): λ_{max} = 313 nm (ε 5030), 290 nm (inflection, ε 4680); at 37°, the original maxima disappeared and a new one at 343 nm (ε 4500) was formed; t/2 (37°): ~18 min. – UV. (aqueous citrate-HCl buffer, pH 3.0): λ_{max} = 316.5 nm (ε 4300), 287.5 nm (ε 4500); at 37°, a new absorption maximum at 336 nm was developing at the expense of the original two; t/2 (37°): ~66 min. – UV. (aqueous citrate buffer, pH 6.0): only the absorption curve of a decomposition product, λ_{max} = 349 nm, was observed. – IR. (KBr): 5.62, 5.93, 6.09–6.73, 7.11, 7.40, 7.94, 8.21, 9.31, 10.10, 10.37 μ. – ^{1}H-NMR. (DCOOD): 2.10 (*s*, 3 H); 5.61 (*s*, 1 H); 6.00 (*s*, 2 H); 7.60 (*s*, 5 H).

$C_{16}H_{15}N_3O_5S \cdot HCOOH = C_{17}H_{17}N_3O_7S$ (407.40)	Calc.	C 50.11	H 4.21	N 10.32	O 27.49	S 7.87%
	Found	„ 50.10	„ 4.40	„ 10.23	„ 27.87	„ 7.48%

Inhibition zones (diameters, in nm) in an agar plate diffusion test with a 0.5% solution of **4** in DMSO (in parentheses: corresponding values for cephalexin):

	pH 6.0	pH 7.0
Staphylococcus aureus Smith 14	14 (27)	8 (27)
Staphylococcus aureus 2999i$^+$p$^+$	8 (28)	7 (26)
Escherichia coli 205	9 (20)	7 (20)

REFERENCES

[1] *C. U. Kim, P. F. Misco & D. N. McGregor,* J. medicin. Chemistry *22*, 743 (1979).

[2] *I. Ernest,* Helv. *62*, 2681 (1979).

[3] Unpublished results from *Woodward Research Institute.*

[4] *I. Ernest, J. Gosteli & R. B. Woodward,* J. Amer. chem. Soc. *101*, 6301 (1979), Note 8.

[5] *R. B. Woodward, K. Heusler, I. Ernest, K. Burri, R. J. Friary, F. Haviv, W. Oppolzer, R. Paioni, K. Syhora, R. Wenger & J. K. Whitesell,* Nouveau J. Chimie *1*, 85 (1977); *K. Heusler & R. B. Woodward,* German Offenlegungsschrift 1935970 (June 15, 1969).

[6] *D. A. Johnson & Ch. A. Panetta (Bristol-Myers),* U.S. 3198804 (Aug. 3, 1965); Chem. Abstr. *63*, 14869g (1965).

[7] *T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi & T. Oku,* Tetrahedron Letters, *1973*, 3001.

[8] See [5], Note 5.