(dd, 1 H, J = 2, 4 Hz), 5.40 (b, 1 H), 5.30 (dd, 2 H, J = 14 Hz), 5.17 (s, 2 H), 3.82 (dd, 1 H, J = 4, 16 Hz), 3.47 (dd, 1 H, J = 2, 16 Hz), 3.24 (q, 2 H, J = 7 Hz), 2.90 (m, 2 H), 1.80 (quintet, 2 H, J = 7 Hz). Anal. Calcd for $C_{24}H_{22}N_4O_9S$ (542.52): C, 53.13; H, 4.09; N, 10.33; S, 5.91. Found: C, 53.03; H, 4.22; N, 10.40; S, 5.58.

12, R = Methyl. The corresponding ester **11** (R = methyl), 700 mg (2.18 mmol), was dissolved in 42 mL of ethyl acetate. To this solution 28 mL of a 0.2 *m* aqueous sodium bicarbonate solution and 1 g of palladium on charcoal (10%) catalyst were added. The mixture was stirred vigorously for 90 min in a hydrogen atmosphere and the catalyst removed by filtration over Hyflo. The filter aid was washed once with bicarbonate solution and three times with ethyl acetate. Washings and filtrate were combined, the phases were separated, and the aqueous one was washed with methylene chloride. Acidification with 5% aqueous citric acid and four extractions with methylene chloride yielded after drying over sodium sulfate and evaporation in vacuo 184 mg of the crude product (45%). Crystallization from ether–acetone gave the pure product: mp 140–167 °C dec; UV 302 nm (ϵ 6050) and 260 (3930); IR (KBr) 3.4, 3.6, 3.95, 5.62, 6.0, 6.37, 7.0, 7.6, 7.85, 8.15 μ; NMR (Me_2SO-d_6) δ 5.65 (dd, 1 H), 3.3–3.9 (m, 2 H), 2.28 (s, 3 H); MS M 185, 168, 157, 144, 143. Anal. Calcd for $C_7H_7NO_3S$ (185.2): C, 45.40; H, 3.81; N, 7.56. Found: C, 45.40; H, 3.88; N, 7.64.

R = *n*-Pentyl. The corresponding ester **11** (800 mg, 2.1 mmol) was dissolved in 48 mL of ethyl acetate and 32 mL of a 0.2 *m* sodium bicarbonate solution. Hydrogenation was effected as described for **12**, R = methyl, using 1.60 g of the same catalyst. **12** (160 mg, 28%) was obtained following the workup procedure given for **12**, R = methyl: mp 99–100 °C, recrystallized from ether–petroleum ether; UV 307 nm (ϵ 5320) and 257 (3710); IR 2.75–4.25, 5.60, 5.97, 6.40, 7.05, 7.70, 8.25, 8.32 μ; NMR δ 9.20 (b, 1 H), 5.63 (dd, 1 H, J = 2, 4 Hz), 3.80 (q, 1 H, J = 4, 16 Hz), 3.46 (q, 1 H, J = 2, 16 Hz), 2.83 (m, 2 H), 1.1–1.8 (m, 6 H), 0.89 (t, 3 H). Anal. Calcd for $C_{11}H_{15}NO_3S$ (241.31): C, 54.75; H, 6.27; N, 5.81; S, 13.29. Found: C, 54.23; H, 6.40; N, 5.84; S, 12.72.

R = Phenyl. The corresponding ester **11** (200 mg, 0.52 mmol) was hydrogenated as above, using 12 mL of ethyl acetate, 8 mL of the bicarbonate solution, and 350 mg of the catalyst. There resulted 44 mg (37%) of product, recrystallized from acetone–ether: mp 127–128 °C; UV 323 nm (ϵ 7310), 246 sh (9570), 235 (10 470); IR (KBr) 3.50, 5.60, 6.00, 6.45, 6.72, 6.97, 7.67, 7.85, 8.27, 9.65, 11.05, 13.95 μ; NMR δ 7.42 (m, 5 H), 5.78 (dd, 1 H, J = 2, 4 Hz), 3.88 (q, 1 H, J = 4, 16 Hz), 3.60 (q, 1 H, J = 2, 16 Hz). Anal. Calcd for $C_{12}H_9NO_3S$ (247.27): C, 58.29; H, 3.67; N, 5.66; S, 12.97. Found: C, 58.52; H, 3.82; N, 5.64; S, 12.75.

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The Penems, a New Class of β-Lactam Antibiotics. 3. Synthesis of Optically Active 2-Methyl-(5*R*)-penem-3-carboxylic Acid

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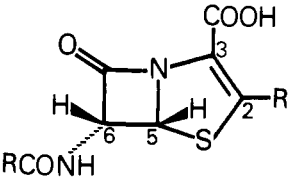
Received April 16, 1979

Abstract: 2-Methyl-(5*R*)-penem-3-carboxylic acid (**3**) has been synthesized from the natural 6(*R*)-amino-(5*R*)-penicillanic acid as an optically active representative of the novel group of 6-unsubstituted penems. It proved to be the biologically active component of the previously reported, racemic, 2-methylpenem-3-carboxylic acid. The general necessity of a 5*R*(6*R*) configuration for the biological activity of bicyclic β-lactam antibiotics is briefly discussed.

In the preceding paper of this series,[1] a second generation of penem-3-carboxylic acids **2**, lacking the 6-acylamino substituent of the previously reported penems **1**,[2] has been described.

Acids **2** proved to be substantially more stable than their predecessors **1**, and they displayed activity against a remarkably broad spectrum of bacteria including both Gram-positive and Gram-negative microorganisms. Since all the tested acids



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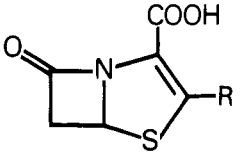

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† Deceased July 8, 1979.

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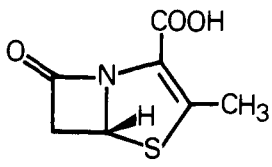
2 were racemic, the question as to which enantiomer was responsible for the biological activity (or whether both enantiomers were active) was of the utmost importance. To answer it, we chose the biologically highly active, racemic 2-methylpenem-3-carboxylic acid as a typical representative of compounds 2 and decided to synthesize its 5*R* enantiomer 3 from the natural, optically active 6(*R*)-amino-(5*R*)-penicillanic acid (4). This synthesis of 3, and the results of antibacterial testing of 3 as compared to the biological activity of the racemate, is the subject of this paper.



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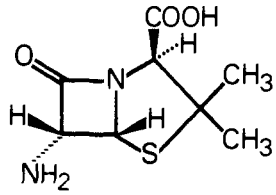

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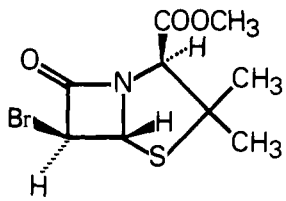
Using a procedure based upon that described by Clayton,[3] 6-aminopenicillanic acid (4) was converted, by diazotization in the presence of hydrobromic acid, into 6(*S*)-bromo-(5*R*)-penicillanic acid, which was isolated—after esterification with diazomethane—as the crystalline methyl ester 5[3-5] (~48%). Hydrogenation of the bromo ester 5 in aqueous dioxane with 5% palladium on barium carbonate afforded crystalline methyl (5*R*)-penicillanate (6)[3,4] in yields of 66-72%.[6]



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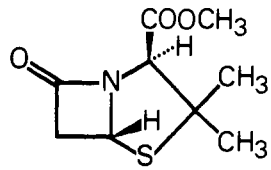
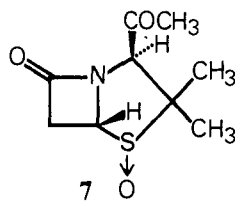


6

Methyl (5*R*)-penicillanate (6) was next oxidized with *m*-chloroperbenzoic acid to an oily *S*-oxide 7 which in turn was heated in boiling toluene with 2-mercaptobenzthiazole. In this procedure, originally established by Kamiya et al.[7] for penicillin *S*-oxide esters, the sulfenic acid formed from 7 at elevated temperature was intercepted by reaction with the mercaptan, giving the disulfide 8. The latter was transformed, by double-bond isomerization, catalyzed by triethylamine, to the conjugated ester disulfide 9; the yield of 9 over the three steps was about 80%.



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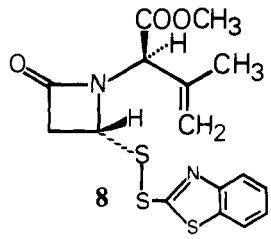

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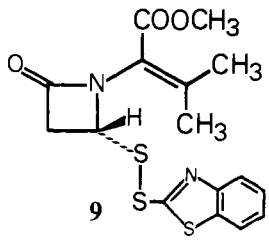
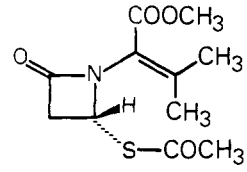


9

When the disulfide 9 was reduced with zinc dust in a mixture of acetic acid and acetic anhydride, the crystalline, optically pure, acetylthio derivative 10 was isolated in yields of 52-55%; the "dimeric" compound 11 was a byproduct in this reductive acylation.[8]



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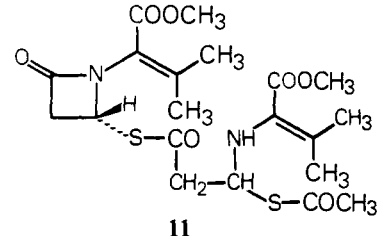
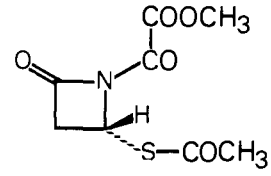


11

To remove the unsaturated substituent on the nitrogen atom of the acetylthioazetidinone 10, a two-step procedure used before in the synthesis of the corresponding intermediates for penem acids 1[2] was applied. Compound 10 was ozonized (in methanol at −20 °C) and the sensitive methoxalyl derivative 12 thus formed was subjected to mild (room temperature) methanolysis. In this way, 4(*R*)-acetylthio-2-azetidinone (13) was obtained in a yield of 84% over the two steps as an oil (crystallizing below 0 °C) identical in all respects except its optical activity ($[\alpha]^{20}_D$ +359 ± 1° in chloroform) with the intermediate in the total synthesis of racemic 2-methylpenem-3-carboxylic acid.



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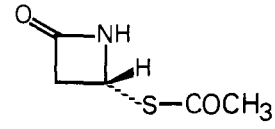
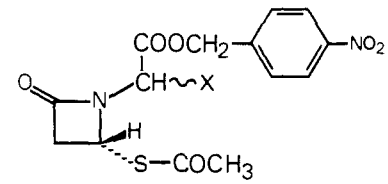
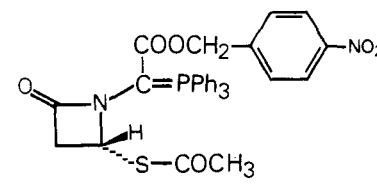


13

From this point, our synthesis of the optically active acid 3 parallels that of its racemic form. In three steps including reaction of 13 with *p*-nitrobenzyl glyoxylate ethyl hemiacetal, conversion of the resulting epimeric hemiaminals 14 to the corresponding chlorides 15, and, finally, heating the latter intermediates with triphenylphosphine, a triphenylphosphoranylideneacetate grouping was built up on the nitrogen atom of the azetidinone ring and the optically active phosphorane 16 was prepared (in a yield of 44% over the three steps).



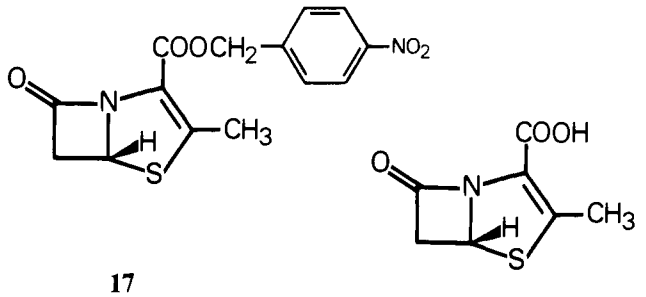
14: X = OH
15: X = Cl



16

Heating the optically active phosphorane 16—as previously in the case of the racemic form—in toluene at 90 °C (under argon and in the presence of some hydroquinone) for a period of 40 h afforded *p*-nitrobenzyl 2-methyl-(5*R*)-penem-3-carboxylate (17), which was isolated from the crude cyclization product by chromatography in a yield of 88%. It formed (from methylene chloride-ether) long, white needles different in shape and melting point (147.5-149.5 °C) from the crystals

of the corresponding racemic ester (short, rather compact needles, mp 130–132 °C from the same solvent mixture), and displaying in chloroform an $[\alpha]^{20}_D$ value of +136 ± 1°; in all other respects (UV, IR, NMR spectra, R_f, elemental analysis) there was full agreement with the corresponding properties of the previously described racemate.



17

3

Finally, two-phase hydrogenation of the *p*-nitrobenzyl ester **17** (in ethyl acetate and aqueous sodium bicarbonate) with 10% palladium on charcoal catalyst afforded the desired 2-methyl-(5*R*)-penem-3-carboxylic acid (**3**, 55%), forming (from acetone) tiny crystals with an unsharp decomposition point (142–145 °C, slow decomposition occurring above 122 °C; a similar behavior was observed with the racemic form) and showing in acetone an $[\alpha]^{20}_D$ value of +286 ± 1°; other spectral properties and elemental analysis corresponded again to those of the racemate.

In a parallel antibacterial test, with 24 Gram-positive and Gram-negative strains, the new, optically active acid **3** was twice as active as the racemic form in 20 cases while equal activity was found in the remaining 4 instances. These observations suggest strongly that the *R* isomer alone is responsible for the activity of the racemate (some of the MIC values of **3** and of the racemic acid are summarized in Table I). The close structural relationship of all penem-3-carboxylic acids **2** encourages us to assume that also with the other racemic acids of this type the 5*R* enantiomer represents the biologically active component.

In the light of the limitation of the biological activity of the synthetic penem antibiotic to the 5*R* enantiomer, taken with the fact that all known, natural, bicyclic β-lactam antibiotics are similarly oriented at the bridgehead carbon atom, it is tempting to accept the important generalization that orientation at the relevant center is of definitive significance for biological activity in this fast-growing family of compounds.

Experimental Section

Melting points (Kofler) are uncorrected. All rotations were determined in $CHCl_3$, and all IR spectra in CH_2Cl_2 as solvents unless otherwise mentioned. NMR spectra were recorded ($CDCl_3$ with Me_4Si as internal standard) on a Varian HA-100 D spectrometer; all chemical shifts are reported in δ values. Mass spectra were obtained with a Varian CH7 spectrometer. All R_f values were determined on Merck silica gel 60 F_{254} TLC plates.

Methyl 6(*S*)-Bromo-(5*R*)-penicillanate (5). A solution of 21.6 g (0.1 mol) of 6(*R*)-aminopenicillanic acid (**4**) and 52 g (~0.5 mol) of sodium bromide in 250 mL of 2.5 N H_2SO_4 was diazotized at 0–5 °C by adding dropwise (over 20 min) a solution of 10.5 g (0.15 mol) of sodium nitrite in 50 mL of water. After another 60 min at 0–5 °C and 30 min at room temperature, the acidic reaction product, which partially separated as a light-colored, sticky material, was extracted with ether and the ethereal extracts were washed with brine. Drying ($MgSO_4$) and evaporation afforded 24 g of a syrupy residue which was esterified in 100 mL of methanol and 450 mL of ether in an ice-water bath by adding a slight excess of a 2% ethereal solution of diazomethane. The residue obtained by evaporation in vacuo after 5 min was chromatographed on Merck silica gel (1 kg, deactivated by 10% of water). With toluene, small amounts of impurities were eluted in several fractions followed by 0.55 g (1.5%) of methyl 6,6-dibromopenicillanate: mp 99–101 °C (lit.[3] mp 100–101 °C); IR 5.57, 5.73, 6.97, 7.07 (sh), 7.70, 7.75–8.02, 8.25, 8.47 μ; NMR δ 1.47 (s, 3), 1.63 (s, 3), 3.80 (s, 3), 4.56 (s, 1), 5.81 (s, 1). With toluene–ethyl acetate (9:1), a total of 14.0 g (47.6%) of methyl 6(*S*)-bromopenicillanate (**5**) was eluted; mp 43 °C (as obtained by chromatography; lit.[3,4] mp 47–49 °C); IR 5.60, 5.74, 6.97, 7.07 (sh), 7.74, 7.80–8.04, 8.27, 8.48 μ; NMR δ 1.47 (s, 3), 1.62 (s, 3), 3.78 (s, 3), 4.56 (s, 1), 4.81 (d, 1, J = 1.6 Hz), 5.43 (d, 1, J = 1.6 Hz).

Methyl (5*R*)-Penicillanate (6). A solution of 882 mg (3 mmol) of methyl 6(*S*)-bromopenicillanate (**5**) in 24 mL of dioxane and 6 mL of water was hydrogenated at room temperature and atmospheric pressure on 900 mg of a 5% $Pd/BaCO_3$ catalyst. When H_2 consumption ceased (about 60 min), the catalyst was filtered off and washed on the filter with dioxane, and the combined filtrates were concentrated to 4–5 mL. Extraction with benzene, evaporation of the solvent in vacuo, and chromatography of the residue on 60 g of Merck silica gel (deactivated with 10% of H_2O) afforded, in several fractions with toluene–ethyl acetate (9:1), 464 mg (71.9%) of pure methyl (5*R*)-penicillinate (**6**): mp 52–53 °C (ether–pentane) (lit.[3,4] mp 52–53 °C); R_f 0.49 (toluene–ethyl acetate (1:1)); $[\alpha]^{20}_D$ +318 ± 1° (0.995%); IR 5.64, 5.73 μ; NMR δ 1.48 (s, 3), 1.68 (s, 3), 3.07 (dd, 1, J = 16 and 1.4 Hz), 3.58 (dd, 1, J = 16 and 4 Hz), 3.78 (s, 3), 4.48 (s, 1), 5.31 (dd, 1, J = 1.4 and 4 Hz).

In a similar experiment with 7.0 g of **5**, the yield of methyl (5*R*)-penicillanate was 3.43 g (67%). In all hydrogenations on $Pd/BaCO_3$ in aqueous dioxane, a less mobile (R_f 0.12 in toluene–ethyl acetate (1:1)) byproduct was formed and was isolated by chromatography in one case. Spectral evidence suggested methyl 2,3,4,7-tetrahydro-2,2-dimethyl-7-oxo-1,4-thiazepine-3-carboxylate (i), described before by Stoodley et al.:[6] UV (96% EtOH) λ_{max} 307 nm; IR 2.95, 3.30–3.55, 5.75, 6.15, 6.30, 6.55 (sh), 6.61, 6.85, 6.97, 7.20, 7.30, 7.39, 7.46, 7.70, 8.07, 8.25 μ; NMR δ 1.46 (s, 3), 1.53 (s, 3), 3.79 (s, 3), 4.42 (d, 1, J = 5 Hz), 5.12 (dd, 1, J = 10 and 1 Hz), 6.22 (m, 1), 6.64 (dd, 1, J = 10 and 8 Hz).

Methyl (5*R*)-Penicillanate 1-Oxide (7). To 6.5 g (30.2 mmol) of methyl penicillanate **6** in 220 mL of CH_2Cl_2, 6.14 g of 85% *m*-chloroperbenzoic acid (30.2 mmol) in 140 mL of CH_2Cl_2 was added dropwise at −15 °C. After another 2 h at −15 °C, the reaction mixture was successively washed with 3% aqueous $NaHSO_3$ and with 8% aqueous $NaHCO_3$. Drying (Na_2SO_4) and evaporation of the solvent in vacuo afforded 6.98 g (100%) of a syrupy *S*-oxide **7** contaminated only by a trace of the more mobile 1,1-dioxide. For the next step, the product was used without further purification. For analysis and spectroscopic documentation, a sample was chromatographed on a Merck silica gel plate in toluene–ethyl acetate (1:1) as a viscous oil: R_f 0.27 (toluene–ethyl acetate (1:1)); $[\alpha]^{20}_D$ +280 ± 1° (1.01%); IR 3.25–3.50, 5.61, 5.72, 6.86, 7.00, 7.10 (sh), 7.21, 7.32, 7.42, 7.81–8.01, 8.22, 8.30–8.36, 8.47, 9.21, 9.46, 9.88 (sh), 9.96 μ; NMR δ 1.23 (s, 3), 1.70 (s, 3), 3,34 (d, 2, J = 3 Hz), 3.80 (s, 3), 4.51 (s, 1), 4.97 (t, 1, J = 3 Hz); MS (40 °C) 231 (M*), 213, 189, 187, 182, 172, 154, 141, 140, 130, 114. Anal. Calcd for $C_9H_{13}NO_4S$ (231.27): C, 46.74; H, 5.67; N, 6.06; O, 27.67; S, 13.87. Found: C, 46.26; H, 5.80; N, 6.09; O, 27.73; S, 13.45.

Methyl (5*R*)-penicillanate 1,1-dioxide (contaminant of the crude 1-oxide) was prepared from the crude **7** by prolonged treatment at room temperature in CH_2Cl_2 with *m*-chloroperbenzoic acid and was

Table I. Direct Parallel Observation of Antibacterial in Vitro Activities of the Optically Active (5*R*) vs. the Racemic Form of 2-Methylpenem-3-carboxylic Acid

microorganism	MIC, μg/mL[a]	
	3 (5*R*)	racemic acid[b]
Staphylococcus aureus Smith	1	2
Staphylococcus aureus 2999 i^+ p^+	1	2
Escherichia coli $205R^+_{TEM}$	8	16
Salmonella typhimurium 277	2	4
Serratia marcescens Oberson	8	16
Klebsiella pneumoniae 327	4	8
Pseudomonas aeruginosa ATCC 12055	8	16

[a] Minimal inhibitory concentration in VST agar; inoculum ca. 10^4 cells; pH 7.4. [b] It will be noted that these independently determined activities for the racemic acid differ by no more than a factor of 2 from those reported in our previous paper.[1]

purified by plate chromatography (Merck silica gel) using toluene-ethyl acetate (1:1) as a viscous oil: R_f 0.35 (toluene-ethyl acetate (1:1)); IR 3.30-3.55, 5.56, 5.95, 6.00 (sh), 6.36, 6.48, 7.10 (sh), 7.20, 7.41, 7.58, 7.76-8.01, 8.21, 8.38, 8.46 (sh), 8.66, 8.95, 9.25, 9.95 μ; NMR δ 1.43 (s, 3), 1.63 (s, 3), 3.48 (d, 2, J = 3 Hz), 3.84 (s, 3), 4.42 (s, 1) 4.63 (t, 1, J = 3 Hz).

Methyl [4(*R*)-(2'-Benzthiazolyldithio)-2-azetidinon-1-yl]isopropenylacetate (8). A solution of 685 mg (2.96 mmol) of the crude *S*-oxide **7** and 500 mg (~1 equiv) of 2-mercaptobenzthiazole in 30 mL of toluene was refluxed under N_2 for 2.5 h. Evaporation in vacuo and chromatography on 60 g of Merck silica gel afforded, after several fractions (toluene) containing some minor impurities, 980 mg (87%) of the disulfide **8** which was eluted with toluene-ethyl acetate (9:1) as a viscous oil: R_f 0.47 (toluene-ethyl acetate (1:1)); $[\alpha]^{20}_D$ −392 ± 1° (0.78%); IR 3.20-3.50, 5.66, 5.75, 5.97-6.05, 6.75 (sh), 6.84, 7.03, 7.28, 7.53, 7.60 (sh), 7.65 (sh), 8.10, 8.35, 8.50, 8.89, 9.25, 9.81, 9.93 μ; NMR δ 1.92 (d, 3, J = 1.4 Hz), 3.22 (dd, 1, J = 16 and 2.2 Hz), 3.48 (dd, 1, J = 16 and 5 Hz), 3.71 (s, 3), 4.84 (s, 1), 5.04 (s, 1), 5.17 (d, 1, J = 1.4 Hz), 5.34 (dd, 1, J = 2.2 and 5 Hz), 7.20-7.52 (m, 2), 7.68-7.90 (m, 2); MS (110 °C) 381 (M + 1), 257, 214, 182, 167, 154, 140, 113. Anal. Calcd for $C_{16}H_{16}N_2O_3S_3$ (380.50): C, 50.51; H, 4.24; N, 7.36; O, 12.61; S, 25.28. Found: C, 50.15; H, 4.31; N, 7.41; O, 12.81; S, 25.44.

In a large-scale experiment with 7 g of the sulfoxide **7** the crude disulfide **8** as obtained by evaporation of toluene from the reaction mixture was pure enough to be used in the next step without any purification.

Methyl α-[4(*R*)-(2'-Benzthiazolyldithio)-2-azetidinon-1-yl]-β-methylcrotonate (9). Disulfide **8** (14.8 g, 38.9 mmol) was allowed to stand at room temperature in 500 mL of CH_2Cl_2 containing 5 mL of triethylamine. The progress of the isomerization was followed in short intervals by IR. After 90 min, the reaction mixture was washed with 5% aqueous citric acid, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on 600 g of Merck silica gel deactivated by 10% of H_2O. Some minor impurities were removed with toluene and toluene-ethyl acetate (19:1), followed, with toluene-ethyl acetate (9:1), by 13.7 g (92.6%) of the isomerization product **9** which crystallized on standing in a refrigerator: mp 63-66 °C (ether-pentane); R_f 0.44 (toluene-ethyl acetate (1:1)); $[\alpha]^{20}_D$ −153 ± 1° (0.92%); IR 3.35-3.60, 5.66, 5.81, 5.87 (sh), 5.93 (sh), 6.15, 6.85, 7.04, 7.26, 7.36, 7.65 (sh), 7.73, 8.17, 8.90, 9.26, 9.92, 10.25 μ; NMR δ 1.92 (s, 3), 2.10 (s, 3), 3.16 (dd, 1, J = 16 and 3 Hz), 3.42 (dd, 1, J = 16 and 5 Hz), 3.72 (s, 3), 5.41 (dd, 1, J = 3 and 5 Hz), 7.16-7.52 (m, 2), 7.70-7.92 (m, 2); MS (110 °C) 380 (M*), 349, 332, 316, 315, 214, 199, 182, 167, 154, 140, 112. Anal. Calcd for $C_{16}H_{16}N_2O_3S_3$ (380.50): C, 50.51; H, 4.24; N, 7.36, O, 12,61; S, 25.28. Found: C, 50.75; H, 4.35; N, 7.38; O, 12.92; S, 25.22.

Methyl α-(4(*R*)-Acetylthio-2-azetidinon-1-yl)-β-methylcrotonate (10). To a solution of 1.14 g (~3 mmol) of the disulfide **9** in 9 mL of acetic anhydride and 15 mL of acetic acid, stirred under N_2 in an ice-water bath, a total of 3 g of zinc dust was added in several portions during 1 h. After another 1 h of stirring at room temperature, the metal was filtered off and the filtrate was evaporated in vacuo. The residue thus obtained was washed in CH_2Cl_2 with 25% aqueous NH_4Cl and with 8% aqueous $NaHCO_3$ (the aqueous parts were reextracted with CH_2Cl_2). The crude product obtained by evaporation of the combined organic parts was chromatographed on 150 g of Merck silica gel (deactivated by 10% of H_2O). After several fractions with toluene and toluene-ethyl acetate (19:1) which were discarded, 400 mg (51.9%) of the crystalline acetylthioazetidinone **10** was slowly eluted with the latter solvent system as white needles: mp 81-82 °C (ether-pentane); R_f 0.40 (toluene-ethyl acetate (1:1)); $[\alpha]^{20}_D$ +149 ± 1° (1.01%); IR 3.30-3.55, 5.66, 5.81, 5.89, 6.15, 7.00, 7.25, 7.35, 7.72, 8.15, 8.22 (sh), 8.35 (sh), 8.86, 9.15, 9.26, 9.42, 9.95, 10.17, 10.50 (broad), 10.80 μ; NMR δ 1.93 (s, 3), 2.21 (s, 3), 2.31 (s, 3), 3.03 (dd, 1, J = 16 and 3 Hz), 3.51 (dd, 1, J = 16 and 5 Hz), 3.81 (s, 3), 5.67 (dd, 1, J = 3 and 5 Hz); MS 257 (M*), 225, 215, 214, 198, 182, 155, 140, 112. Anal. Calcd for $C_{11}H_{15}NO_4S$ (257.30): C, 51.35; H, 5.88; N, 5.44; S, 12.46. Found: C, 51.50; H, 5.94; N, 5.61, S, 12.70.

Further elution of the column, finally with toluene-ethyl acetate (1:1), afforded 87 mg (12.3%) of an amorphous byproduct whose IR, NMR, and mass spectra suggested the "dimeric" structure **11:** R_f 0.12 (toluene-ethyl acetate (1:1)); IR 2.97, 3.43, 5.68, 5.81, 5.92, 6.13, 6.74, 7.00, 7.06 (sh), 7.25, 7.35, 7.70, 8.20, 8.90, 9.24 μ; NMR δ 1.84 (s, 3), 2.02 (s, 3), 2.17 (s, 3), 2.27 (s, 3), 2.34 (s, 3), 2.85 (d, 2, J = 7 Hz), 2.92 (dd, 1, J = 15 and 2.5 Hz), 3.46 (dd, 1, J = 15 and 5.6 Hz), 3.73 (s, 3), 3.79 (s, 3), 4.94 (t, 1, J = 7 Hz), 5.34 (dd, 1, J = 2.5 and 5.6 Hz), 6.94 (broad s, 1); MS (160 °C) 473, 472 (M*), 441, 397, 274, 268, 258, 242, 216, 214, 182.

When the disulfide **9** (380 mg, 1 mmol) in 4.5 mL of acetic anhydride and 1.5 mL of acetic acid was stirred with 262 mg (1 mmol) of triphenylphosphine, first for 30 min at −20 °C and finally, after adding 3 mL of pyridine, for 3 h at room temperature, the resulting reaction mixture was evaporated in vacuo, and the residue was chromatographed (30 g of Merck silica gel with 10% of H_2O), the following products were isolated: (a) 169 mg (57.5%) of triphenylphosphine sulfide; (b) 33 mg (9.5%) of methyl α-[4-(2'-benzthiazolylmercapto)-2-azetidinon-1-yl]-β-methylcrotonate (v) [mp 138 °C; R_f 0.54 (toluene-ethyl acetate (1:1)); IR 5.67, 5.82, 5.91 (sh), 7.06, 7.26, 7.36, 8.18, 8.30 (sh), 9.27, 10.05 μ; NMR δ 1.98 (s, 3), 2.15 (s, 3), 3.18 (dd, 1, J = 15 and 3 Hz), 3.66 (dd, 1, J = 15 and 5 Hz), 3.83 (s, 3), 6.12 (dd, 1, J = 3 and 5 Hz), 7.20-7.50 (m, 2), 7.68-7.90 (m, 2); addition of the optically active shift reagent $Eu(TFC)_3$ to the NMR probe caused doubling of all signals suggesting the presence of both enantiomers in an approximate ratio of 2:3; MS (80 °C) 348 (M*), 317, 277, 220, 192, 182, 167, 140]; (c) ~10 mg of an impure sample of the acetylthio compound **10;** (d) 115 mg (47.7%) of (racemic) methyl α-(4-acetoxy-2-azetidinon-1-yl)-β-methylcrotonate (iv) [oil; R_f 0.43 (toluene-ethyl acetate (1:1)); $[\alpha]^{20}_D$ −1 ± 1° (1.57%); IR 5.64, 5.73, 5.81, 6.14, 7.25, 7.33 (sh), 8.18, 8.30 (sh), 9.23, 9.58 μ; NMR δ 1.98 (s, 3), 2.08 (s, 3), 2.24 (s, 3), 3.00 (d, 1, J = 15 and 2 Hz), 3.34 (dd, 1, J = 15 and 4 Hz), 3.78 (s, 3), 6.20 (dd, 1, J = 2 and 4 Hz); MS (20 °C) 241 (M*), 199, 182, 181, 168, 167, 140, 68, 43.

***N*-Methoxalyl-4(*R*)-acetylthio-2-azetidinone (12).** A stream of O_3/O_2 (0.33 mmol O_3/min) was introduced at −20 °C into a solution of 2.47 g (9.6 mmol) of compound **10** in 50 mL of methanol for a period of 2 h. After another 1 h at −20 °C, the reaction mixture was concentrated under reduced pressure to about 20 mL, diluted with CH_2Cl_2, and briefly shaken with two 100-mL portions of cold, 3% aqueous $NaHSO_3$; the aqueous washings were reextracted with CH_2Cl_2. Drying (Na_2SO_4) and evaporation in vacuo of the combined organic parts afforded 2.2 g (~100%) of a crude, oily methoxalyl compound **12** of a very good quality; it was used in the next step without any purification. For analysis and spectroscopic characterization, a sample was chromatographed on Merck silica gel deactivated with 10% of H_2O (elution with toluene-ethyl acetate (9:1)) as a viscous oil, streaks on Merck silica gel plates in toluene-ethyl acetate systems: $[\alpha]^{20}_D$ −46 ± 1° (0.90%); IR 3.30-3.42, 5.52, 5.70, 5.83 (sh), 5.86, 6.98, 7.08 (sh), 7.40, 8.07, 8.19, 8.30 (sh), 8.46 (sh), 8.90, 9.22, 9.52, 9.91, 10.30, 10.53 μ; NMR δ 2.43 (s, 3), 3.30 (dd, 1, J = 17 and 4 Hz), 3.83 (dd, 1, J = 17 and 6 Hz), 3.96 (s, 3), 5.77 (dd, 1, J = 4 and 6 Hz). Anal. Calcd for $C_8H_9NO_5S$ (231.22): C, 41.56; H, 3.93; N, 6.06; O, 34.60; S, 13.87. Found: C, 41.62; H, 4.06; N, 6.41; O, 34.54; S, 14.09.

4(*R*)-Acetylthio-2-azetidinone (13). Crude *N*-methoxalylazetidinone **12** (2.2 g, 9.5 mmol) as obtained by ozonolysis of **10** was allowed to stand at room temperature in a mixture of 330 mL of methanol, 33 mL of methyl acetate, and 7 mL of water. Evaporation under reduced pressure after 43 h, finally several times with toluene, and chromatography of the residue on 100 g of Merck silica gel (deactivated with 10% of H_2O) afforded, with toluene-ethyl acetate (4:1) as eluant, 1.16 g (84%) of oily azetidinone **13:** R_f 0.29 (toluene-ethyl acetate (1:1)); $[\alpha]^{20}_D$ +359 ± 1° (0.95%); IR 2.98, 5.62, 5.91, 7.13, 7.46, 7.83-8.15, 8.62, 8.89, 10.19, 10.58, 11.05-11.15 μ; NMR δ 2.37 (s, 3), 2.95 (ddd, 1, J = 16, 2.4 and 1 Hz), 3.46 (ddd, 1, J = 16, 5, and 1 Hz), 5.24 (dd, 1, J = 2.4 and 5 Hz), 6.86 (broad s, 1); MS (20 °C) 146, 145 (M*), 117, 112, 103, 70. Anal. Calcd for $C_5H_7NO_2S$ (145.18): C, 41.36; H, 4.86; N, 9.65; O, 22.04; S, 22.08. Found: C, 41.04; H, 4.90; N, 9.50; O, 22.47; S, 21.89.

***p*-Nitrobenzyl (4(*R*)-Acetylthio-2-azetidinon-1-yl)triphenylphosphoranylideneacetate (16).** A solution of 1.28 g (8.8 mmol) of the acetylthioazetidinone **13** and of 4.7 g (18.4 mmol) of *p*-nitrobenzyl glyoxylate ethyl hemiacetal[2] in 25 mL of DMF and 100 mL of toluene was stirred for 17 h at room temperature and 1 h at 50 °C with activated molecular sieves (Type 4A 1/16, Bender + Hobein Ltd., Zürich) (N_2 atmosphere). Filtration and evaporation of the solvents in vacuo gave a syrupy residue which was chromatographed on 100 g of Merck silica gel. With toluene-ethyl acetate (9:1), the excess of *p*-nitrobenzyl glyoxylate was removed. A 4:1 mixture of the same solvents then afforded 1.41 g of the hemiaminals **14** (epimeric mixture) and 1.44 g

of the hemiaminals contaminated by ~30% of the starting azetidinone **13**. A similar treatment as described above of the latter material with 1.04 g of *p*-nitrobenzyl glyoxylate ethyl hemiacetal followed by chromatography afforded an additional 1.29 g of the hemiaminals **14**, thus raising the yield to 87%: viscous oil; R_f 0.48 (elongated spot, ethyl acetate); IR 2.89 (broad), 3.40–3.55, 5.64, 5.73, 5.91, 6.24, 6.56, 7.44, 7.62, 7.83–8.15, 8.26, 8.39, 8.80–9.30 μ. To the hemiaminals (2.73 g, 7.70 mmol) and 12 g of polymeric Hünig base (see ref 2, note 21) in 100 mL of dioxane, 2.84 g (24 mmol) of thionyl chloride in 20 mL of dioxane was added dropwise at room temperature and stirring was continued for 1.5 h. The polymeric base was filtered off and washed on the filter with dioxane, and the combined filtrates were evaporated in vacuo to give a syrupy, epimeric mixture of the chlorides **15**: R_f 0.52 (toluene–ethyl acetate (1:1)); IR 3.40–3.55, 5.59, 5.69 (sh), 5.90, 6.22, 6.56, 7.43, 7.60, 8.91, 11.43 μ. The latter material was heated at 50 °C in 120 mL of dioxane in the presence of 12 g of polymeric Hünig base with 3.14 g (~1.5 equiv) of triphenylphosphine (N_2 atmosphere) for a period of 17 h. Filtration, washing of the polymeric base on the filter with dioxane, and evaporation in vacuo of the combined filtrates gave a syrupy residue which was chromatographed on 120 g of Merck silica gel. The excess of triphenylphosphine and some mobile impurities were removed with toluene and toluene–ethyl acetate (4:1). With toluene–ethyl acetate (3:2), 2.34 g (50.77% over the last two steps, 44.2% from **13**) of the phosphorane **16** was eluted as a colorless foam; R_f 0.21 (toluene–ethyl acetate (1:1)); $[\alpha]^{20}_D$ +35 ± 1° (0.87%); IR 3.30–3.55, 5.70, 5.90, 6.05 (sh), 6.09 (sh), 6.16, 6.22 (sh), 6.57, 6.74, 6.96, 7.05 (sh), 7.20, 7.44, 7.80–8.05, 8.25, 8.40, 8.85, 9.05, 9.25 μ. Anal. Calcd for $C_{32}H_{27}N_2O_6PS$ (598.61): C, 64.21; H, 4.55; N, 4.68; P, 5.17; S, 5.36. Found: C, 64.23; H, 4.65; N, 4.89; P, 5.18; S, 5.45.

***p*-Nitrobenzyl 2-Methyl-(4*R*)-penem-3-carboxylate (17).** A solution of 350 mg (0.58 mmol) of phosphorane **16** in 175 mL of dry toluene purged by argon and containing a few milligrams of hydroquinone was heated under argon at 90 °C for 40 h. Evaporation of the solvent in vacuo and chromatography of the residue on 10 g of Merck silica gel with toluene–ethyl acetate (19:1) afforded 166 mg (88.6%) of the crystalline ester **17** as white, long needles: mp 147.5–149.5 °C (CH_2Cl_2–ether); $[\alpha]^{20}_D$ +136 ± 1° (1.03%); R_f 0.54 (toluene–ethyl acetate (1:1)); λ_{max} (96% EtOH) 310 nm (ϵ 9130), 263 (11 440); IR 3.40–3.55, 5.59, 5.84, 5.95 (sh), 6.22 (sh), 6.30, 6.55, 7.15, 7.28, 7.41, 7.61, 7.69 (sh), 8.28, 8.35, 8.56, 9.10, 9.25, 9.43, 9.62, 9.84 μ; NMR δ 2.38 (s, 3), 3.46 (dd, 1, J = 16 and 2 Hz), 3.80 (dd, 1, J = 16 and 4 Hz), 5.32 (q (AB), 2, J = 14 Hz), 5.63 (dd, 1, J = 2 and 4 Hz), 7.58 ("d", 2, J = 8.5 Hz), 8.19 ("d", 2, J = 8.5 Hz); MS (110 °C) 320 (M*), 292, 279, 278, 260, 233, 187, 156, 142, 136, 127, 126, 99. Anal. Calcd for $C_{14}H_{12}N_2O_5S$ (320.32): C, 52.50; H, 3.78; N, 8.75; O, 24.98; S, 10.01. Found: C, 52.53; H, 3.85; N, 8.72; O, 25.45; S, 9.88.

2-Methyl-(4*R*)-penem-3-carboxylic Acid (3). A solution of 100 mg (0.31 mmol) of the *p*-nitrobenzyl ester **17** in 6 mL of ethyl acetate was hydrogenated at room temperature and atmospheric pressure in the presence of 140 mg of a 10% Pd on charcoal catalyst (Fluka) and 4 mL of a 0.2 M aqueous solution of $NaHCO_3$. After 30 min of vigorous stirring, another 70 mg of the catalyst was added and hydrogenation was continued for another 30 min. The catalyst was filtered off and washed on the filter with 2 mL of 0.2 M $NaHCO_3$ and with ethyl acetate and the two layers of the combined filtrates were separated. The aqueous layer was washed with CH_2Cl_2, acidified with an excess of 5% aqueous citric acid, and extracted with CH_2Cl_2. Drying and evaporation of the extract afforded 32 mg (55.3%) of the crystalline acid **3** as fine, off-white crystals (from acetone): mp 142–145 °C dec (slow decomposition above 122 °C); $[\alpha]^{20}_D$ +286 ± 1° (0.60%); λ_{max} (96% EtOH) 305 nm (ϵ 6660), 261 (3530); λ_{max} (phosphate buffer, pH 7.4) 297 nm (ϵ 6430), 258 (4800); IR (KBr) 2.85–4.30 (broad), 5.60 (sh), 5.66, 5.97 (sh), 6.04, 6.42, 7.05, 7.32, 7.64, 7.90, 8.17–8.25, 8.40 μ; NMR (acetone-d_6), δ 2.31 (s, 3), 3.39 (dd, 1, J = 16 and 2 Hz), 3.82 (dd, 1, J = 16 and 4 Hz), 5.69 (dd, 1, J = 2 and 4 Hz). Anal. Calcd for $C_7H_7NO_3S$ (185.20): C, 45.40; H, 3.81; N, 7.56; S, 17.31. Found: C, 45.50; H, 3.95; N, 7.58; S, 17.10.

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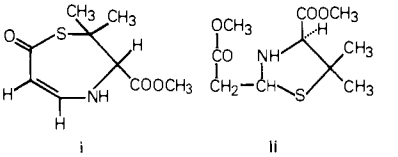
(5) In agreement with Clayton,[3] small amounts of methyl 6,6-dibromo-(5*R*)-penicillanate were also isolated by chromatography in this two-step procedure.
(6) As a byproduct, the seven-membered cyclic compound i was isolated by chromatography of the crude hydrogenation product. Stoodley et al. (J. P. Clayton, R. Southgate, B. G. Ramsay, and R. J. Stoodley, *J. Chem. Soc. C*, 2089 (1970)) obtained this compound by rearrangement of methyl (5*R*)-penicillanate with a Lewis acid. With methanol as solvent in the hydrogenation reaction, yields of methyl penicillanate **6** were lower than with aqueous dioxane and formation of another byproduct, namely, the product of methanolysis of methyl penicillanate, ii, was observed.



i ii

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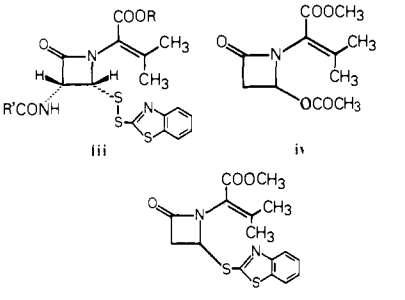
(8) Reductive acylation with triphenylphosphine in acetic acid–acetic anhydride (with subsequent addition of pyridine)—a useful procedure with 6-acylamino-substituted disulfides iii[2]—failed to give the desired acetylthio derivative **10** in a preparative yield when applied to the 6-unsubstituted disulfide **9**. Racemic 4-acetoxyacetidinone iv and partially racemized 4-benzthiazolylthioazetidinone v were formed instead in yields of 48 and 10%, respectively.



iii iv

v

Another method which has been successfully used to transform disulfides iii to the corresponding 4-acetylthioazetidinones, namely, reduction with sodium borohydride in dimethylformamide followed by acylation with acetic anhydride–pyridine and acetyl bromide (or with acetyl bromide alone),[2] led in the case of the 6-unsubstituted disulfide **9**, repeatedly, to partially racemized acetylthio derivative **10**. The presence of the undesired 5*S* enantiomer in such samples of **10** manifested itself by lower melting point and $[\alpha]_D$ values, as compared to those of the pure 5*R* enantiomer prepared by the Zn–AcOH–Ac_2O method, as well as by doubling of most signals of a ^1H NMR spectrum in $CDCl_3$ on addition of the optically active shift reagent Eu(TFC)$_3$.