Circular Dichroism of Monocyclic β-Lactams

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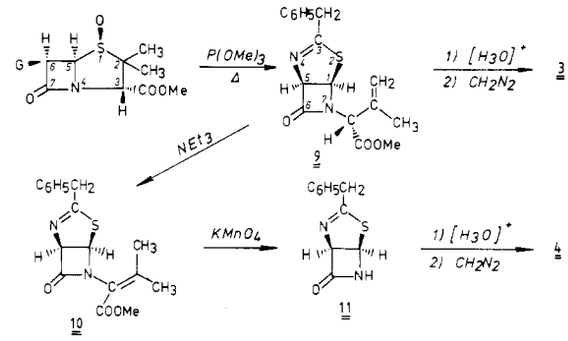
The circular dichroism of a series of polysubstituted monocyclic β-lactams of known absolute configuration was measured. The compounds were prepared from the appropriate penicillanates by cleavage of the thiazolidine ring. All β-lactams showed a n → π* Cotton effect centered at about 225 nm. The sign of this Cotton effect is discussed in terms of the Ogura lactam rule.

During a study of the circular dichroism (CD) of penicillanates[1] we found that little information was available concerning the CD of β-lactams. Only the ellipticities of some alkyl or aryl-substituted β-lactams have been published.[2] It seemed interesting to determine the CD curves of β-lactams **1–8** containing other substituents (Table I).

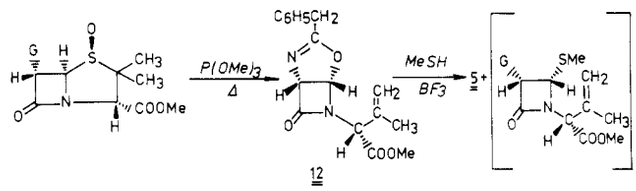
Compounds **1** and **2** were obtained respectively from penicillin G and its 6-epimer by Raney–Nickel desulfurization,[3] followed by esterification of the free carboxyl group with diazomethane. The 4-(methylthio)azetidin-2-ones **3–8** were prepared from their corresponding penicillanates by a reaction sequence involving primarily 1–2 bond cleavage of the penam nucleus according to the method employed by Cooper.[4] Treatment of the methyl ester of penicillin G (*S*)-sulfoxide with trimethyl phosphite in refluxing benzene yielded the fused thiazoline–azetidinone **9** as the principal reaction product[5] (Scheme I). Ring opening of the thiazoline ring by acid hydrolysis[6] and esterification of the resulting sulfhydryl group with diazomethane afforded the *cis*-azetidinone **3** as a crystalline compound from ether–pentane. Similarly, the *N*-nonsubstituted β-lactam **4** was obtained from thiazoline **11**, which was prepared from **9** by base-catalyzed isomerization[4,5] of the β,γ-olefinic bond to the α,β position (**10**) followed by mild oxidation[7] with potassium permanganate in slightly alkaline medium (Scheme I). The oxidative removal of the residue on the lactam nitrogen was performed on the fused thiazoline rather than on the monocyclic lactam, since it was found[8] that the latter transformation was accompanied by substantial oxidation at the methylmercapto group.

Base-catalyzed epimerization at the 3 position of **3** seemed to be the most straightforward route for preparing the *trans*-azetidinone **5.** This method, which has been used successfully for the analogous C-6 epimerization of 6-substituted penicillanates, failed, however, when applied to monocyclic lactams such as **3.** Instead, the α proton of the butenoate moiety was removed preferentially, resulting, as already mentioned, in a shift of the double bond from the β,γ to the α,β position with respect to the carboxylate group. Likewise, treatment of the *N*-unsubstituted derivative **4** with triethylamine or with bis(trimethylsilyl)acetamide and 1,5-diazabicyclo[4.3.0]non-5-ene proved to be unsuccessful in effecting isomerization of the asymmetric centers. The *trans*-azetidinone **5** was then synthetized starting from the 6-epimer of penicillin G (*S*)-sulfoxide methyl ester by reaction with trimethyl phosphite, as described for the natural isomer (Scheme II). In this case, however, no thiazoline was obtained from the reaction mixture, but a compound was isolated (38% after silica gel chromatography), which was shown by NMR and mass spectroscopy to possess the oxazoline–azetidinone structure **12.** The value of the coupling constant of the azetidinone protons in the NMR spectrum (J = 3 Hz) did not allow a definite conclusion concerning the cis–trans stereochemistry of the fused ring derivative, but from mechanistic and geometrical considerations a β,β-cis configuration of the β-lactam protons seemed justifiable. Treatment of this derivative (**12**) with methanethiol, in the presence of boron trifluoride,[9] yielded a mixture (as shown by NMR) of two isomeric 4-methylthio-substituted azetidinones. From this, the 3*S*,4*R*-isomer **5** was the major component, and could be partially separated by crystallization from ether. The minor constituent which was not isolated in a pure state most probably had the 3*S*,4*S* or cis configuration.

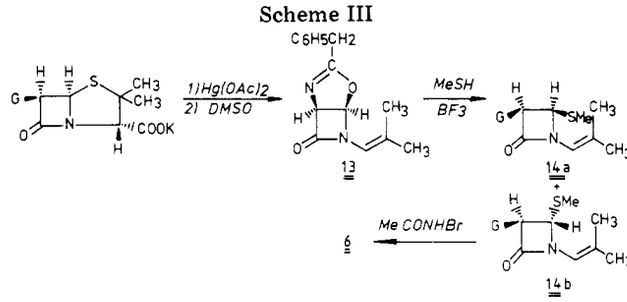
Scheme I



Scheme II



Scheme III



The *trans*-substituted β-lactam **6,** having the 3*R*,4*S* configuration, was prepared (Scheme III) from *cis*-oxazoline **13**[10] by reaction with methanethiol and boron trifluoride.[9] This was followed by separation of the resulting cis and trans derivatives by LC and oxidative removal of the *N*-methylpropenyl substituent of the trans isomer **14b** with *N*-bromoacetamide in aqueous acetone. It should be noted that a similar conversion[9] of the cis isomer **14a** yielded the cis β-lactam **4**

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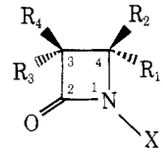
Table I. Structure and Circular Dichroism ($\Delta\epsilon$) of β-Lactams[c]



	registry no.	R_1	R_2	R_3	R_4	X	$\Delta\epsilon^a$ (λ)
1	67478-86-8	H	H	H	G	X_1	−3.0 (221)
2	67478-87-9	H	H	G	H	X_1	+2.1 (222)
3	67478-88-0	H	SMe	H	G	X_2	−10.6 (223)
4	42334-32-7	H	SMe	H	G	H	−5.8 (225)
5	67528-28-3	H	SMe	G	H	X_2	−3.6 (230)
6	55870-62-7	SMe	H	H	G	H	+4.2 (227)
7	67478-89-1	H	SMe	H	Cl	X_2	−4.8[b] (234)
8	67528-29-4	H	SMe	Cl	H	X_2	−7.6 (234)

[a] In MeOH solution at 20 °C; the molar ellipticity [Θ], expressed in units of deg cm² (dmol)⁻¹, can be obtained by multiplying $\Delta\epsilon$ by 3300. [b] The value of $\Delta\epsilon$ for this unstable compound may be questionable. [c] X_1 = D-CH(COOMe)CH(CH₃)₂; X_2 = D-CH(COOMe)-C(CH₃)=CH₂; G = NHCOCH₂C₆H₅.

which we prepared by a different reaction sequence (Scheme I).

The 3-chloro-4-methylthioazetidin-2-ones **7** and **8** were obtained by refluxing respectively methyl 6β- and 6α-chloropenicillanate (*S*)- sulfoxide[8] in benzene in the presence of trimethyl phosphite.

The CD spectra of β-lactams **1–8** are represented in Figure 2. All compounds exhibit a relatively high wavelength Cotton effect centered at about 225 nm, which owing to its position, may be assigned to the n → π* transition of the cyclic amide chromophore.[11] A similar Cotton effect has also been observed by Rehling and Jensen[2] for a series of simple alkyl-substituted β-lactams. According to these authors, the sign of the amide n → π* Cotton effect could be readily predicted by the octant rule for saturated ketones. Later, Ogura et al.[12] showed that the same experimental facts may also be interpreted in terms of their lactam rule,[13] which states that the sign of the n → π* Cotton effect depends solely on classification of the compound in question into two types (A and B). However, the lactam rule seems to be much less applicable to compounds having substituents on C-3 and C-4 in trans configuration because of their unknown relative importance, and therefore Ogura[12] recommends the use of the quadrant rule of Schellman[11] in these cases. Actually, our results fit fairly well into the Ogura rule, provided the methylthio substituent on C-4 is considered as the most important one. This assumption is not unreasonable in view of the larger polarizability of the sulfur atom. In this way, we could easily explain why the CD curves for **1** and **2**, which have only one substituent (on C-3), were almost mirror images of each other, while compounds **3** (3*R*,4*R*-*cis*) and **5** (3*S*,4*R*-*trans*) and also **7** and **8** both gave a negative peak. The other cis–trans pair, however (**4** and **6**), showed a Cotton effect with opposite sign, being negative for the 4*R* isomer and positive for the 4*S* isomer. A comparison of the curves for **3** and **4** also shows that the CD pattern is not greatly affected by the substituent on the lactam nitrogen atom. In fact, this substituent having an asymmetric carbon atom, an ester group, and in some instances a β,γ double bond apparently only slightly influences the absolute value of the Cotton effect. Similarly on the basis of its circular dichroism [[Θ]$_{225}$ −22300 (methanol)] the configuration of the 4-butylthio-3-phenylacetamidoazetidin-2-one, which was obtained as a side product from the attack of butyllithium on penicillin G,[14] probably has been correctly assigned. We also find a similar [Θ] value for the methylthio analogue, i.e., our substance **4**.

For the 3-chloroazetidinones **7** and **8** we observe two Cotton effects. The peak at 233 nm may be assigned to the red-shifted n → π* transition of the β-lactam chromophore. This red shift

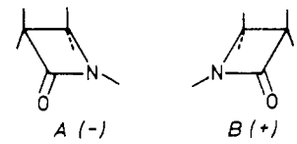


Figure 1. The Ogura lactam rule;[12] the model is arranged so that the most important substituents are above the plane of the ring.

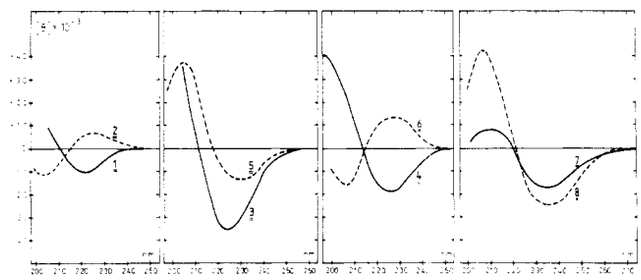


Figure 2. CD spectra of monocyclic β-lactams **1–8**, in MeOH at 20 °C.

is probably caused by orbital overlapping so as to stabilize the π* orbital in a manner analogous to that described for axially oriented α-halo ketones.[15] The 207–209-nm peak most likely is associated with the red shifted amide π → π* transition, which is not or only slightly visible in the CD spectra of the other derivatives.

Undoubtedly the 3-phenylacetamido substituent also interacts in some specific manner with the C=O orbitals of the β-lactam group. Indeed, the β-lactam compounds where this substituent is trans oriented all show a slight but measurable red shift of their CD curve with respect to the corresponding cis derivatives. Thus the beginning of a second Cotton effect (the π → π* transition), which emerges at the short wavelength end of the spectrum, becomes more visible. In this respect it may be interesting to note that, in comparing the CD spectra of natural and 6-epimeric amidopenicillanates,[1] some striking differences were observed in the spectral region between 200 and 230 nm which probably also are related to a similar red shift of the n → π*, as well as the π → π* band of the 6-epimer. An explanation of this phenomenon can be based only on orbital interaction effects, reminiscent of those that have been noted in 6-aminopenicillanic acid.[16] A detailed discussion of these effects is beyond the scope of this article. However, qualitatively one can easily visualize a mechanism where the release of steric interaction between the C-3 and the

4-methylthio substituent, in going from the cis to the trans isomer, results in a different spatial conformation of the acetamido substituent. This then is reflected in its orbital interaction with the lactam CO group.

Experimental Section

Melting points were taken with a Büchi-Tottoli apparatus and were uncorrected. TLC was performed on silica gel F-254 plates (Merck) using the following mobile phases: I, Me_2CO–HOAc, 95:5; II, C_6H_6–Me_2CO, 80:20. All rotations were determined on a Thorn-NPL automatic polarimeter Type 243. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer, mass spectra on an AEI MS-12 apparatus, and NMR spectra on a Hitachi Perkin-Elmer R 24 apparatus with tetramethylsilane as internal standard. Circular dichroism measurements were made at 20 °C with a Cary 61 spectropolarimeter. The cell compartment was continually purged with dry purified nitrogen. A slit width setting was chosen for constant SBW of 2 nm, a time constant of 10 s and a low scanning speed (6 nm/min) were used. Measurements were made in quartz cells of 0.1-cm path length, for concentrations ranging from 0.1 to 0.2 mg/mL. The CD spectra were expressed in terms of molar ellipticity [Θ] in deg cm^2 $(dmol)^{-1}$, defined by $[\Theta] = \Theta M/10lc$, where Θ is the measured ellipticity in degrees, l is the path length in centimeters, c is the concentration in gram per milliliter, and M is the molecular weight.

(3*S*)-1-[(1′*R*)-1′-Methoxycarbonyl-2′-methylpropyl]-3-phenylacetamidoazetidin-2-one (*1*) or Desthiobenzylpenicillin Methyl Ester. Hydrogenolysis of 9.0 g of sodium benzylpenicillin with 54 g of Raney–Nickel, as described in "Chemistry of Penicillin",[3] gave 3.7 g of desthiobenzylpenicillin: mp 95–100 °C; TLC (system I) R_f 0.74; IR (KBr) 3330, 1658, 1540 (CONH), 1735 (β-lactam), 1630 cm^{-1} (COOH); NMR ($CDCl_3$–Me_2SO-d_6 10:1) δ 1.02 (d, J = 6.5 Hz, two CH_3), 1.80–2.50 (m, 2′-H), 3.44 (dd, J = 2.5 and 5.5 Hz, 4β-H), 3.56 (s, $C_6H_5CH_2$), 3.90 (t, J = 5.5 Hz, 4α-H), 4.15 (d, J = 7.5 Hz, 1′-H), 4.70–5.00 (m, 3-H), 5.62 (s, COOH), 7.25 (s, C_6H_5), and 7.95 (d, J = 8 Hz, CONH). Concentration of the mother liquor yielded 160 mg of phenylacetyl-L-alanyl-D-valine: mp 203–205 °C; TLC (system I) R_f 0.83. To a solution of 200 mg of desthiobenzylpenicillin in 10 mL of acetone was added diazomethane in ether until a persistent color was observed. After evaporation of the solvent, the residue was taken up in ether, yielding 152 mg (73%) of crystalline (3*S*)-1-[(1′*R*)-1′-methoxycarbonyl-2′-methylpropyl]-3-phenylacetamidoazetidin-2-one (**1**): mp 115–116 °C (lit.[3] mp 107–108 °C); $[\alpha]^{22}_D$ +14° (*c* 0.5, acetone); TLC (system II) R_f 0.25; *m/e* 259 ($M^+ - COOCH_3$); IR (KBr) 3260, 1642, 1555 (CONH), 1770 (β-lactam), 1730, 1205 (ester), 740, 695 cm^{-1} (phenyl). The NMR spectrum ($CDCl_3$) of **1** was in complete agreement with reported values.[17]

(3*R*)-1-[(1′*R*)-1′-Methoxycarbonyl-2′-methylpropyl]-3-phenylacetamidoazetidin-2-one (*2*) or 6-Epidesthiobenzylpenicillin Methyl Ester. In a round-bottom flask, provided with a stirrer and a thermometer, 50 mL of water was warmed to 70 °C and a teaspoon of Raney–Nickel W6 (ref 20, and washed with water but not under hydrogen) was added. The flask was put in an oil bath at 160 °C and 1 g of 6-epibenzylpenicillin potassium salt[18] was added. After refluxing for 15 min, the mixture was cooled rapidly, and the nickel was filtered off and washed with water (5 × 10 mL). The combined filtrates were brought to pH 5 with hydrochloric acid and concentrated. After filtration, the solution was acidified to pH 2 and extracted three times with ethyl acetate. Evaporation of the organic layer yielded 600 mg of an oil. Chromatography on a column of silica gel and elution with dichloromethane followed by dichloromethane–ethyl acetate 70:30 yielded 332 mg of product, which according to TLC was still a mixture of two substances. The crude 6-epidesthiobenzylpenicillin was then dissolved in 10 mL of dichloromethane and a solution of diazomethane in ether was added until a persistent color was obtained. The solution was evaporated to a colorless oil, and the mixture was separated on a column of silica gel (5 g) using a gradient of dichloromethane to dichloromethane–acetone 95:5 as eluent. The eluate was examined by TLC, and from the appropriate fractions 140 mg of 6-epidesthiobenzylpenicillin methyl ester (**2**) was obtained: mp 99–100 °C; $[\alpha]_D^{22}$ +7.2° (*c* 0.5, acetone); TLC (system II) R_f 0.22; *m/e* 259 ($M^+ - COOCH_3$); IR (KBr) 3310, 1680, 1519 (CONH), 1745 (β-lactam and ester), 1212 cm^{-1} (ester); NMR ($CDCl_3$) δ 0.93 (d, J = 7 Hz, two CH_3), 1.70–2.40 (m, 2′-H), 3.40 (dd, J = 2 and 6 Hz, 4α-H), 3.54 (s, $C_6H_5CH_2$), 3.71 (s, OCH_3), 3.75 (m, 4β-H), 4.14 (d, J = 8 Hz, 1′-H), 5.03 (m, 3-H), 6.39 (br, CONH), and 7.27 (s, C_6H_5). The R_f value of phenylacetyl-D-alanyl-D-valine methyl ester, in system II, was 0.14.

(3*R*,4*R*)-1-[(1′*R*)-1′-Methoxycarbonyl-2′-methylprop-2′-enyl]-4-methylthio-3-phenylacetamidoazetidin-2-one (*3*). Treatment of penicillin G (*S*)-sulfoxide methyl ester with trimethyl phosphite in refluxing benzene was used, as described by Wolfe et al.[5] The reaction mixture was purified by column chromatography on silica gel using dichloromethane as the eluent. Crystallization from ethyl acetate yielded (1*R*,5*R*)-3-benzyl-7-[(1′*R*)-1′-methoxycarbonyl-2′-methylprop-2′-enyl]-2-sulfa-4,7-diazabicyclo[3.2.0]hept-3-en-6-one (**9**): mp 98.5–99 °C (lit.[5] mp 98–99 °C); $[\alpha]^{22}_D$ −156° (*c* 0.6, acetone); TLC (system II) R_f 0.73; *m/e* 330 (M^+); IR (KBr) 1765 (β-lactam), 1743, 1210 (ester), 1621 (C=N), 765, 706 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.69 (s, CH_3), 3.72 (s, OCH_3), 3.86 (s, $C_6H_5CH_2$), 4.82 and 4.88 (m, $=CH_2$), 5.03 (s, 1′-H), 5.91 (AB, 1-H and 5-H), and 7.27 (s, C_6H_5). Thiazoline **9** (165 mg, 0.5 mmol) was dissolved in acetone (7.5 mL) and hydrochloric acid (N, 3 mL) was then added. After storage at room temperature for 5 min, the reaction mixture was diluted with ice–water (25 mL) and extracted with dichloromethane (2 × 25 mL). The organic layer was washed with water (2 × 20 mL), dried (Na_2SO_4), and filtered. A solution of diazomethane in ether was added dropwise to the filtrate until a yellow color persisted. After 10 min at room temperature, the reaction mixture was evaporated leaving an oily product (125 mg), which was adsorbed on a column of silica gel (6 g) and eluted with dichloromethane changing to dichloromethane–acetone 90:10. The fractions containing the desired compound were collected and yielded 81 mg (45%) of (3*R*,4*R*)-1-[(1′*R*)-1′-methoxycarbonyl-2′-methylprop-2′-enyl]-4-methylthio-3-phenylacetamidoazetidin-2-one (**3**) as a foam. The compound was crystallized from ether–*n*-pentane: mp 75.5–76 °C; $[\alpha]^{20}_D$ −62° (*c* 0.5, acetone); TLC (system II) R_f 0.49; *m/e* 362 (M^+); IR (KBr) 3339, 1649, 1520 (CONH), 1766 (β-lactam), 1745, 1200 cm^{-1} (ester); NMR ($CDCl_3$) δ 1.84 (s, two CH_3), 3.62 (s, $C_6H_5CH_2$), 3.73 (s, OCH_3), 4.71 (s, 1′-H), 5.01 (d, J = 4 Hz, 4-H), 5.08 (br, $=CH_2$), 5.46 (dd, J = 4 and 8 Hz, 3-H), 6.45 (d, J = 8 Hz, CONH), and 7.29 (s, C_6H_5).

(3*R*,4*R*)-4-Methylthio-3-phenylacetamidoazetidin-2-one (*4*). The fused thiazoline–azetidinone **9** was isomerized with triethylamine in methanol solution as described by Wolfe et al.[5] After evaporation of the organic layer, crystals of (1*R*,5*R*)-3-benzyl-7-(1′-methoxycarbonyl-2′-methylprop-1′-enyl)-2-sulfa-4,7-diazabicyclo[3.2.0]-hept-3-en-6-one (**10**) were obtained: mp 79–80 °C; $[\alpha]^{30}_D$ +18° (*c* 0.5, acetone); TLC (system II) R_f 0.71; *m/e* 330 (M^+), 331 $(M + 1)^+$; IR (KBr) 1761 (β-lactam), 1730, 1228 (ester), 1620 (C=N), 1605 (C=C), 775, 700 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.58 (s, CH_3), 2.12 (s, CH_3), 3.76 (s, OCH_3), 3.85 (s, $C_6H_5CH_2$), 5.76 (d, J = 4 Hz, 1- or 5-H), 5.95 (d, J = 4 Hz, 5- or 1-H), and 7.22 (s, C_6H_5). Compound **10** (495 mg, 1.5 mmol) was dissolved in dry acetone (30 mL) and after cooling to 0 °C a solution of potassium permanganate (474 mg, 3 mmol) in 0.1 M phosphate buffer, pH 8 (15 mL), was added. The suspension was stirred at 0 °C for 10 min and subsequently extracted with ethyl acetate (2 × 75 mL).

The organic layer was washed with water (2 × 50 ml), dried (Na_2SO_4), and stripped to leave, after crystallization from ether–*n*-pentane, 186 mg (57%) of (1*R*,5*R*)-3-benzyl-2-sulfa-4,7-diazabicyclo[3.2.0]hept-3-en-6-one (**11**): mp 169–173 °C dec; $[\alpha]^{16}_D$ +46° (*c* 0.5, acetone); TLC (system II) R_f 0.40; *m/e* 218 (M^+); IR (KBr) 3200 (NH), 1725 (broad, β-lactam), 765, 705 cm^{-1} (phenyl); NMR ($CDCl_3$/Me_2SO-d_6 3:1) δ 3.87 (s, $C_6H_5CH_2$), 5.46 (d, J = 4 Hz, 5-H), 5.89 (m, 1-H), 7.28 (s, C_6H_5), and 8.56 (br, CONH). Compound **11** (218 mg, 1 mmol) was dissolved in acetone (15 mL) and hydrochloric acid (N, 6 ml) was added. After standing at room temperature for 10 min, the reaction mixture was diluted with water (50 mL) at 0 °C, and the suspension was extracted with dichloromethane (2 × 50 mL). The organic layer was washed with water (50 mL), dried (Na_2SO_4), and treated with a solution of diazomethane in ether until a yellow color persisted for 10 min. The solution was evaporated and the residue was crystallized from ether (10 mL) to yield 194 mg (78%) of (3*R*,4*R*)-4-methylthio-3-phenylacetamidoazetidin-2-one (**4**): mp 168–169.5 °C; $[\alpha]^{16}_D$ +32° (*c* 0.5, acetone); TLC (system II) R_f 0.23; *m/e* 250 (M^+); IR (KBr) 3290, 3190 (NH), 1782 (β-lactam), 1732, 1665, 1532 (CONH), 745, 697 cm^{-1} (phenyl); NMR ($CDCl_3$/Me_2SO-d_6 1:1) δ 2.03 (s, SCH_3), 3.63 (s, $C_6H_5CH_2$), 4.91 (br, 4-H), 5.27 (br, 3-H), 7.35 (s, C_6H_5), and 8.78 (br, two CONH). Upon addition of D_2O the signal at δ 4.91 became (d, J = 4 Hz) 5.27 (dd, J = 4 and 7 Hz) and 8.78 (d, J = 7 Hz, one CONH). According to ref 9, compound **4**, which has been prepared by a different scheme, had mp 175–177 °C (from benzene). Other physical data were in agreement with our figures.

(3*S*,4*R*)-1-[(1′*R*)-1′-Methoxycarbonyl-2′-methylprop-2′-enyl]-4-methylthio-3-phenylacetamidoazetidin-2-one (*5*). 6-Epibenzylpenicillin (*S*)-sulfoxide methyl ester[19] (364 mg, 1 mmol) was suspended in 12 mL of benzene. After addition of 0.24 mL (2 mmol) of trimethyl phosphite, the reaction mixture was refluxed for 24 h and then evaporated to leave a yellow oil, which was purified by column chromatography on silica gel (15 g). Elution was performed with a gradient changing from dichloromethane to dichloromethane–acetone 95:5. The appropriate fractions were collected and

evaporated to yield 120 mg (38%) of a colorless oil, which was identified as (1*S*,5*R*)-3-benzyl-7-[(1′*R*)-1′-methoxycarbonyl-2′-methylprop-2′-enyl]-2-oxa-4,7-diazabicyclo[3.2.0]hept-3-en-6-one (**12**): TLC (system II) R_f 0.75; *m/e* 315, 314 (M^+); IR (CH_2Cl_2) 1781 (β-lactam), 1751, 1205 (ester), 1650 (C=N), 1605 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.74 (s, CH_3), 3.70 (s, OCH_3), 3.73 (s, $C_6H_5\mathbf{CH_2}$), 4.66 (br s, 1′-H), 5.02 (d, J = 3 Hz, 1- or 5-H), 5.11 (br, $=CH_2$), 5.78 (d, J = 3 Hz, 5- or 1-H), and 7.28 (s, C_6H_5). The oxazoline–azetidinone **12** (840 mg, 2.67 mmol) was dissolved in methanethiol (5 mL) at 0 °C and 0.25 mL of boron trifluoride etherate was added. After the pale yellow solution was stirred for 1 h, at 0 °C, the reaction mixture was diluted with dichloromethane and washed with potassium hydrogen carbonate (0.1 M, 10 mL) and water (2 × 20 mL). The residue, obtained after evaporation of the dried ($MgSO_4$) organic layer, was fractionated by chromatography on silica gel (50 g) using dichloromethane–acetone 9:1 as eluent. Fractions (3 mL) 42–61 gave a colorless oil (572 mg, 59%) of the cis and trans β-lactams (as shown by NMR) in a ratio of 1:4. Addition of ether (10 mL) to the oil afforded the *trans*-azetidinone **5** in a crystalline state (203 mg): mp 123 °C; $[\alpha]^{22}_D$ +63° (*c* 0.8, acetone); TLC (system II) R_f 0.47; *m/e* 362 (M^+); IR (KBr) 1772 (β-lactam), 1746, 1205 (ester), 1645, 1560 (CONH), 735, 691 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.91 (s, CH_3), 2.08 (s, SCH_3), 3.49 (s, $C_6H_5\mathbf{CH_2}$), 3.71 (s, OCH_3), 4.58 (s, 1′-H), 4.60 (dd, J = 2 and 8 Hz, 3-H), 4.86 (d, J = 2 Hz, 4-H), 5.05 (br, $=CH_2$), 7.03 (d, J = 8 Hz, CONH), and 7.24 (s, C_6H_5). From the filtrate, which was still a mixture of both isomers [(ratio cis:trans 1:2) with J = 4 Hz for the lactam protons of the cis isomer], no further pure material could be obtained.

(3*R*,4*S*)-4-Methylthio-3-phenylacetamidoazetidin-2-one (*6*). The oxazoline **13** was obtained[10] from the potassium salt of penicillin G by reaction with mercury(II) acetate followed by treatment with dimethyl sulfoxide. This was reacted with methanethiol in the presence of boron trifluoride–ether as described by Corbett and Stoodley.[9] The (3*R*,4*S*)-*trans*-azetidinone **14b** was separated from the accompanying (3*R*,4*R*)-*cis*-isomer **14a** by LC on a 60 cm × 0.4 cm column of Lichrosorb 10, and eluted with dichloromethane–*n*-hexane–propanol-2 50:50:3, at a flow rate of 200 mL/h. This was then treated with *N*-bromoacetamide–triethylamine to remove the methylpropenyl substituent. After purification of the reaction mixture by chromatography on silica gel (10 g, benzene–acetone 9:1 as eluent), 16 mg (15%) of pure (3*R*,4*S*)-4-methylthio-3-phenylacetamidoazetidin-2-one (**6**) was obtained as a colorless oil. The physical constants, in particular NMR data, were in agreement with those determined on the mixture.[9]

(3*R*,4*R*)-3-Chloro-1-[(1′*R*)-1′-methoxycarbonyl-2′-methylprop-2′-enyl]-4-methylthioazetidin-2-one (*7*). To a solution of methyl 6β-chloropenicillanate (*S*)-sulfoxide[8] (80 mg, 0.3 mmol) in benzene (10 mL) was added trimethyl phosphite (0.07 mL, 0.6 mmol). The reaction mixture was heated under reflux for 18 h and then concentrated to a yellow oil. This was extracted with *n*-pentane (2 × 10 mL), and the remainder of the oil was separated on silica gel (2 g) using dichloromethane as eluent. Fractions 12 and 13 (2 mL), containing the desired compound, were evaporated to leave 10 mg (12%) of (3*R*,4*R*)-3-chloro-1-[(1′*R*)-1′-methoxycarbonyl-2′-methylprop-2′-enyl]-4-methylthioazetidin-2-one (**7**) as a colorless, unstable oil: TLC (system II) R_f 0.69; *m/e* 263 (M^+); IR (KBr) 1785 (β-lactam), 1749, 1202, 1180 cm^{-1} (ester).

(3*S*,4*R*)-3-Chloro-1-[(1′*R*)-1′-methoxycarbonyl-2′-methylprop-2′-enyl]-4-methylthioazetidin-2-one (*8*). Trimethyl phosphite (0.24 mL, 2 mmol) was added to a solution of methyl 6α-chloropenicillanate (*S*)-sulfoxide[8] (265 mg, 1 mmol) in 12 mL of benzene, and the reaction mixture was heated under reflux for 15 h. After concentration, the resulting yellow oil (284 mg) was washed with *n*-pentane (2 × 10 mL) and purified by column chromatography on silica gel (5 g) using dichloromethane as eluent. Fractions 14–17 (3 mL) were collected, and after evaporation of the solvent, 94 mg (35%) of (3*S*,4*R*)-3-chloro-1-[(1′*R*)-1′-methoxycarbonyl-2′-methylprop-2′-enyl]-4-methylthioazetidin-2-one (**8**) was obtained as a colorless oil: TLC (system II) R_f 0.69; *m/e* 263 (M^+); IR (CH_2Cl_2) 1786 (β-lactam), 1750, 1205, 1172, cm^{-1} (ester); NMR ($CDCl_3$) δ 1.90 (s, CH_3), 2.12 (s, SCH_3), 3.78 (s, OCH_3), 4.62 (s, 1′-H), 4.90 (d, J = 1.5 Hz, 3- or 4-H), 5.08 (br, $=CH_2$), and 5.19 (d, J = 1.5 Hz, 4- or 3-H).

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Registry No.—1 free acid, 4425-26-7; **2** free acid, 67478-90-4; **9**, 61990-36-1; **10**, 67529-66-2; **11**, 34103-69-0; **12**, 67478-91-5; **13**, 49841-83-0; **14a**, 54124-26-4; **14b**, 54163-93-8; sodium benzylpenicillin, 69-57-8; phenylacetyl-L-alanyl-D-valine, 21142-73-4; 6-epibenzylpenicillin K salt, 21794-94-5; penicillin G (*S*)-sulfoxide methyl ester, 24652-72-0; 6-epibenzylpenicillin (*S*)-sulfoxide methyl ester, 41536-91-8; methyl 6β-chloropenicillanate (*S*)-sulfoxide, 65039-68-1; methyl 6α-chloropenicillanate (*S*)-sulfoxide, 61657-23-6.

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