N-AZAMONOBACTAMS

1. THE SYNTHESIS OF SOME 3-SUBSTITUTED *N*-AZAMONOBACTAM DERIVATIVES

WILLIAM V. CURRAN, ADMA A. ROSS and VING J. LEE

Medical Research Division, American Cyanamid Company,
Pearl River, New York 10965, U.S.A.

(Received for publication April 12, 1988)

Ring closure of the *N*-(*tert*-butyloxycarbonyl)-L-serine 2-(diphenylmethylene)hydrazide (**10a**) and the corresponding L-threonine derivative (**10b**) gave good yields of the β-lactams **11a** and **11b**. Catalytic hydrogenation afforded the corresponding *N*-amino β-lactams **12a** and **12b**. These compounds were then further transformed into 3-(*S*)-[[(2-amino-4-thiazolyl)-(*Z*)-(methoxyimino)acetyl]amino-2-oxo-1-azetidinyl]sulfamic acid analogs **18**, **23**, and **30a** and **30b**. None of these compounds exhibited any interesting biological activity.

The discovery of the monocyclic β-lactam antibiotics containing a sulfonic acid moiety on the ring nitrogen,[1,2] *e.g.* sulfazecin **1**, has prompted a considerable amount of synthetic effort due to the fact that none of the naturally occurring antibiotics were sufficiently active.[3]

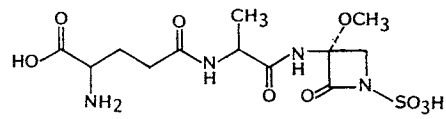
Thus far two drugs have been developed in this area, namely, aztreonam (**2**)[4] and carumonam (**3**).[5]

In addition the sulfonic acid group has been replaced with other activating groups such as **4b**~**4e**.[6,7] Herein we describe the synthesis of the *N*-aza derivatives (**4f**).

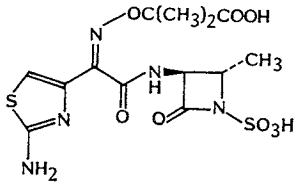
Results and Discussion

The impetus for this work was a report by TAYLOR *et al.*[8] who showed that the treatment of the chlorohydrazide **5** with sodium hydride resulted in a good yield of the β-lactam **6** and a minor amount of the zwitterion **7**. This result coupled with the elegant β-lactam synthesis developed by MILLER *et al.*,[9] starting from the simple amino acids L-serine and L-threonine led to the synthetic effort described in this report.

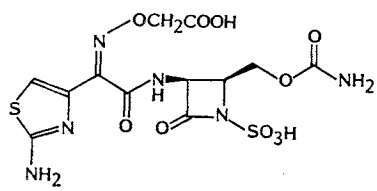
The reaction of *tert*-butyloxycarbonyl-L-serine (**8a**) with benzophenone hydrazone **9** in the presence of ethyl 1,2-dihydro-2-ethoxy-1-quinolinecarboxylate (EEDQ) afforded the hydrazide derivative **10a** which readily underwent



1

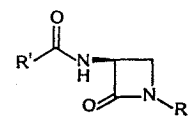


2

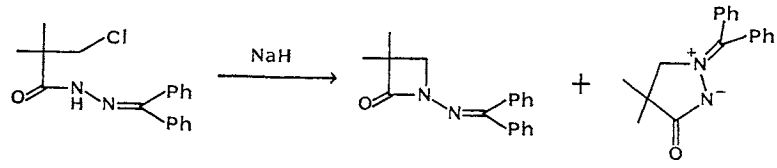


3

ring-closure under Mitsunobo conditions using diethyl azodicarboxylate and triphenylphosphine to give the β-lactam **11a** in good yield.† Catalytic hydrogenation in a Parr apparatus produced the *N*-amino compound **12a**. Starting from *tert*-butyloxycarbonyl-L-threonine (**8b**) the corresponding 4-α-methyl derivative **11b** was obtained by the same series of reactions.

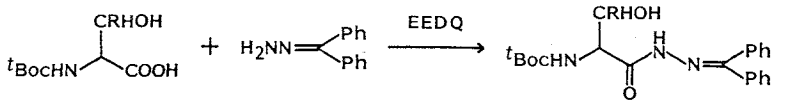


4a R=SO_3H
4b R=OSO_3H
4c R=PO_3H_2
4d R=OPO_3H_2
4e R=SSO_3H
4f R=$NHSO_3H$

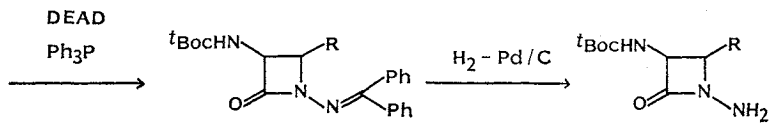


5 **6** **7**

Scheme 1.

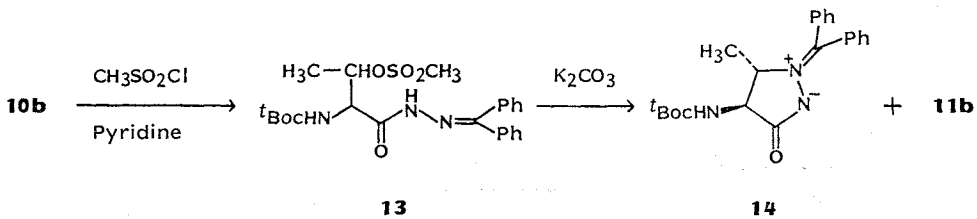


8 **9** **10**



11 **12**

a R = H
b R = CH_3



13 **14**

^{t}BOC=*tert*-Butoxycarbonyl

† A similar ring-closure starting from benzyloxycarbonyl-L-serine to give the corresponding azetidinone in 30% yield has been reported. See ref 10.

When the hydrazide derivative **10b** was converted to the mesylate **13** and refluxed in acetone in the presence of potassium carbonate the pyrazolidinium ylide **14** was isolated as the main product. The structure of this compound was assigned on the basis of the physical properties reported for compound **7**.[8] TLC of the filtrate from this compound indicated the presence of the β-lactam **11b** (Scheme 1).

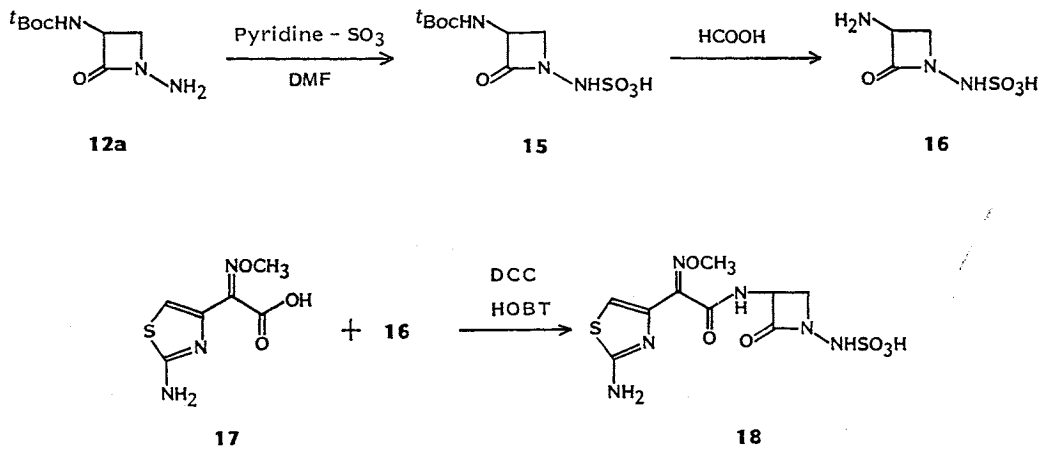
The reaction of *N*-amino derivative **12a** with pyridine sulfur trioxide complex in dimethylformamide afforded the sulfamate **15** which was isolated as the tetrabutylammonium salt. Removal of the *tert*-butoxycarbonyl protecting group with formic acid gave the amino sulfamic acid **16** which was condensed with the activated ester of 2-(2-amino-4-thiazolyl)-2-(*Z*)-methoxyiminoacetic acid **17**, prepared *in situ* by reaction with dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in dimethylformamide, to give the desired β-lactam **18** (Scheme 2). This compound did not exhibit any interesting biological activity as shown by the *in vitro* spectrum. After the completion of this work a patent appeared describing the synthesis of compound **18** by a somewhat different route.[11]

At the same time we were interested in the effect of an alkyl group on the biological activity of these compounds, therefore we synthesized the *N*-propyl analog **23**. Reaction of compound **12a** with propanal gave the Schiff base **19** which was reduced to compound **20** using hydrogen in the presence of rhodium on alumina. Treating compound **20** with sulfur dioxide - pyridine complex gave the sulfamic acid **21** which was deblocked with formic acid to produce compound **22**. Acylation of this derivative with the activated ester of compound **17** as described above afforded the *N*-propyl-β-lactam **23** (Scheme 3). Unfortunately this product was also essentially inactive in the *in vitro* antibacterial spectrum assay.

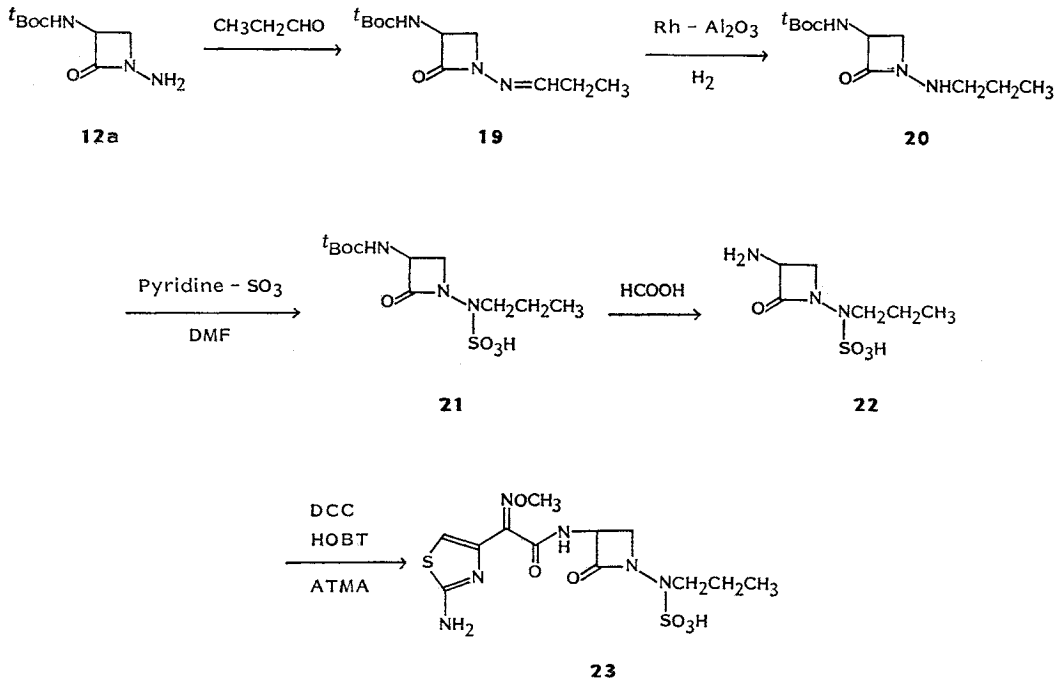
At this juncture in the problem a molecular orbital study of the monobactam system was undertaken. Using a CNDO program, the transition state energies were calculated for a variety of substituents on the β-lactam nitrogen.[12] The results of this work suggested that derivatives with electron withdrawing substituents on the exocyclic nitrogen of our system such as trifluoroethyl and hexafluoroisopropyl could possess interesting biological activity. This stimulated the synthesis of these compounds.

The starting material for this synthesis was compound **12b**. Reaction of compound **12b** with

Scheme 2.



Scheme 3.



12a 19 20 21 22 23

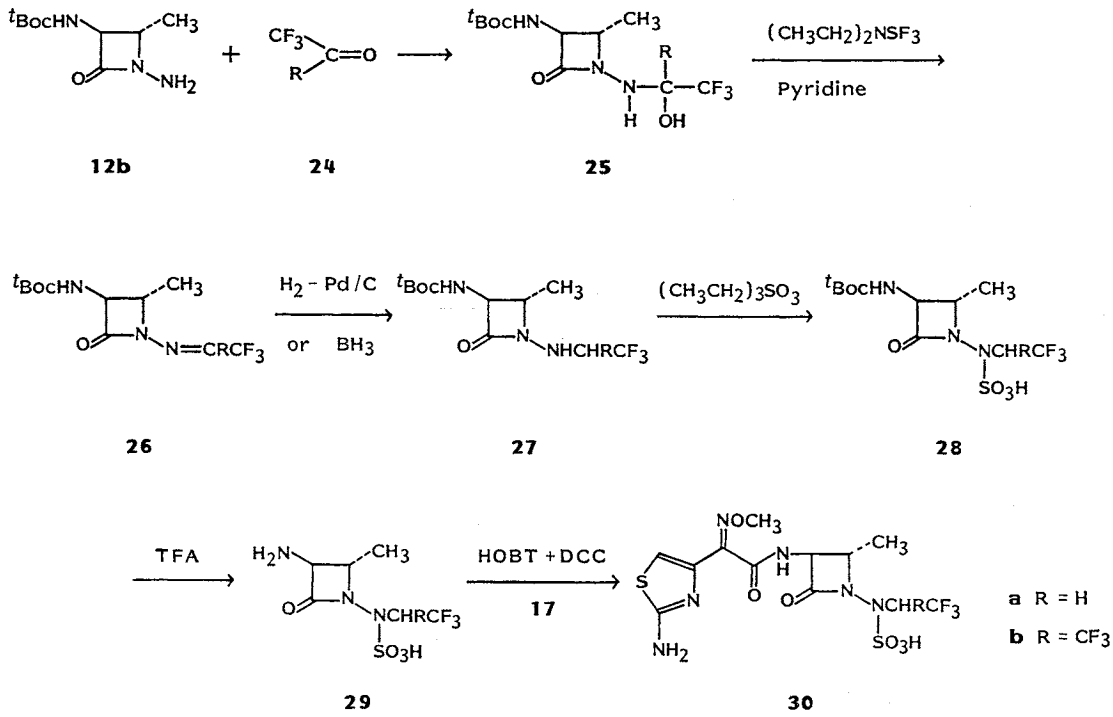
either trifluoroacetaldehyde (**24a**) or the corresponding acetal afforded the aminal derivative **25a** which was converted to the imine **26a** by treatment with diethylaminosulfur trifluoride and pyridine or phosphorus pentachloride and triethylamine. Treatment of compound **26a** by catalytic hydrogenation using palladium on carbon or 1 M borane in tetrahydrofuran solution produced the trifluoroethyl compound **27a**. Sulfonation of this compound using the pyridine - sulfur dioxide complex resulted in conversion to the sulfamic acid derivative **28a**. Deblocking of this compound using trifluoroacetic acid gave the amino derivative **29a** which was acylated with the aminothiazole side chain by the usual method to afford the desired (*S*)-2-methyl-(*S*)-[3-[[(2-amino-4-thiazolyl)-(*Z*)-(2-methoxyimino)acetyl]-amino]-4-oxo-1-azetidinyl]-2,2,2-trifluoroethylsulfamic acid (**30a**).

The reaction of the β-lactam derivative **12b** with hexafluoroacetone (**24b**) gave the aminal **25b** which was treated in a manner similar to that described above to afford compound **27b**. Sulfonation of this derivative with pyridine - sulfur dioxide complex gave a poor conversion to the sulfamic acid **28b**. In this case the use of triethylamine - sulfur dioxide complex gave a much better yield. Deblocking and conversion to the aminothiazole derivative **30b** proceeded as above (Scheme 4).

Unfortunately neither the trifluoroethyl compoundn **30a** nor the hexafluoroisopropyl derivative **30b** possessed any interesting *in vitro* antibacterial activity. In addition compound **30b** was tested *in vivo*, using mice versus *Escherichia coli*, and again no activity was observed.

A discussion of the heteroatom-activated monobactam derivatives has recently been described by BOYD *et al.*[18] Possible reasons for the lack of activity of the sulfur and nitrogen isosteres (**4e** and **4f**) compared to the oxygen analogs (**4b**) include differences in electronegativity of the heteroatom attached to the β-lactam nitrogen, IR carbonyl frequencies, chemical stabilities, and goodness of fit of the β-lactam on the active site of the penicillin binding proteins. This work provides further docu-

Scheme 4.



mentation to the fact that the *N*-aza-monobactams (represented by the general formula **4f**) do not exhibit any interesting biological activity. This is despite the fact that the putting a trifluoroethyl or hexafluoroisopropyl groups (compounds **30a** and **30b**) on the nitrogen atom appended to the β-lactam must have the effect of increasing the electronegativity at this center. In addition compound **30b** exhibited a carbonyl stretching frequency at 1780 cm^{-1} which is well within the range of other active β-lactams. This feature is well known to be a necessary but by itself insufficient criterion for biological activity. This seems to implicate the "goodness of fit" consideration as a possible explanation for the lack of biological activity of these compounds.

Experimental

General Comments

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All column chromatographic purifications were accomplished on Silica gel 60 (E. Merck, 230~400 mesh) with the appropriate solvent gradients. TLC was done on commercial silica gel plates (Analtech) containing calcium sulfate binder and fluorescent indicator. MP's were determined in open Pyrex capillary tubes on a Meltemp melting point apparatus and are uncorrected. IR spectra were recorded with either a Perkin-Elmer Model 1310 or a Nicolet Model 7199 recording IR spectrophotometer. ^1H NMR spectra were determined with either a Varian EM-390 (90 MHz) or Nicolet NT-300WB (300 MHz) spectrometer in appropriate deuterated solvents and are expressed in ppm downfield from TMS (internal standard). Significant ^1H NMR data are tabulated in order: Multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad), number of protons, coupling constant(s) in Hz, and assignments.

N-(*tert*-Butyloxycarbonyl)-L-serine-2-(diphenylmethylene)hydrazide (**10a**)

A solution of 20.0 g (0.10 mol) of *tert*-butyloxycarbonyl-L-serine, 19.6 g, (0.10 mol) of benzophenone hydrazone, and 24.7 g (0.10 mol) of EEDQ in 250 ml of methylene chloride was stirred at room temperature overnight. The solution was extracted with 100-ml portions of 1 N HCl, water, saturated sodium bicarbonate solution, water, and brine, then dried over magnesium sulfate. The solvent was evaporated at reduced pressure and the resulting syrup was dissolved in EtOAc and crystallized by the addition of hexane to afford 24.5 g (64%) of product, mp 150.0~152.5°C.

Anal Calcd for $C_{21}H_{25}N_3O_4$: C 65.78, H 6.57, N 10.96.
Found: C 65.39, H 6.80, N 10.58.

tert-Butyl (*S*)-[1-[(Diphenylmethylene)amino]-2-oxo-3-azetidinyl]carbamate (**11a**)

A solution of diethyl azodicarboxylate (7.9 ml, 0.05 mol) in 50 ml of THF was added to a stirred solution of *N*-(*tert*-butyloxycarbonyl)-L-serine-2-(diphenylmethylene)hydrazide (**10a**) (19.5 g, 0.05 mol) and triphenylphosphin (9.6 g, 0.05 mol) in 250 ml of THF. The mixture was stirred and heated at 55°C for 6 hours. The resulting solution was evaporated to dryness at reduced pressure and dissolved in 50 ml of EtOAc and chilled. The crystalline product was filtered and discarded (diethyl hydrazinoacetate). The filtrate was evaporated to dryness and the residue was chromatographed on silica gel using EtOAc - hexane (1 : 1) as the eluent to afford 12.0 g (66%) of the desired product: MP 167~170°C; IR (KBr) 1775 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.38 (9H, s, $(CH_3)_3C$), 2.85 (1H, dd, J=3 and 6 Hz, 4-H_β), 3.25 (1H, t, J=6 and 6 Hz, 4-H_α), 4.70 (1H, m, 3-H_α), 5.25 (1H, d, NH), 7.40 (10H, m, aromatic protons).

Anal Calcd for $C_{21}H_{23}O_3N_3$: C 69.02, H 6.32, N 11.50.
Found: C 68.73, H 6.57, N 11.41.

N-(*tert*-Butyloxycarbonyl)-L-threonine-2-(diphenylmethylene)hydrazide (**10b**)

This compound was prepared as described above for compound **10a** using *N*-(*tert*-butoxycarbonyl)-L-threonine in place of the serine analog: MP 123~126°C; IR (KBr) cm^{-1} 1680, 1715 (C=O).

Anal Calcd for $C_{22}H_{27}N_3O_4$: C 66.48, H 6.85, N 10.57.
Found: C 66.57, H 6.88, N 10.98.

tert-Butyl (*S*)-[1-[(Diphenylmethylene)amino]-2-(*S*)-methyl-4-oxo-3-azetidinyl]carbamate (**11b**)

This compound was prepared as described for compound **11a** from **10b** using the Mitsunobo reaction to give a white crystalline product (68%); IR (KBr) 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (3H, d, CH_3), 1.45 (9H, s, $(CH_3)_3C$), 3.35 (1H, m, 2-H_β), 4.20 (1H, m, 3-H_β), 7.50 (10H, m, aromatic protons).

Anal Calcd for $C_{22}H_{25}N_3O_3$: C 69.64, H 6.64, N 11.07.
Found: C 69.90, H 6.54, N 11.13.

tert-Butyl (*S*)-(1-Amino-2-oxo-3-azetidinyl)carbamate (**12a**)

tert-Butyl [1-[(diphenylmethylene)amino-2-oxo-3-azetidinyl]carbamate (**11a**) (2.1 g) was dissolved in 100 ml of ethyl alcohol and 50 ml of EtOAc and 0.5 g of 10% palladium on carbon was added. The mixture was hydrogenated in a Parr apparatus at 2.1 kg/cm^2 for 24 hours. The mixture was then filtered through Celite and evaporated to dryness. The residue was crystallized from EtOAc to give 0.75 g of product: MP 165~168°C; IR (KBr) 1750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.45 (9H, s, $(CH_3)_3C$), 3.25 (1H, dd), 3.50 (1H, t), 4.50 (1H, m), 7.55 (1H, d, NH).

Anal Calcd for $C_8H_{15}N_3O_3$: C 47.75, H 7.51, N 20.88.
Found: C 47.44, H 7.27, N 20.54.

tert-Butyl [1-Amino-2-(*S*)-methyl-4-oxo-3-(*S*)-azetidinyl]carbamate (**12b**)

Prepared as compound **12a** from the diphenylmethyleneamino derivative **11b** (72% yield): IR (KBr) 1750 cm^{-1} (β-lactam C=O); ^1H NMR ($CDCl_3$) δ 1.40 (3H, d, CH_3), 1.50 (9H, s, $(CH_3)_3C$), 3.40 (1H, dd, 2-H_β), 5.35 (1H, d, 3-H_α).

Anal Calcd for $C_9H_{17}N_3O_3$: C 50.22, H 7.96, N 19.52.
Found: C 50.00, H 7.77, N 19.76.

Trans-4-(*S*)-[(*tert*-butoxycarbonyl)amino]-1-(diphenylmethylene)-5-(*S*)-methyl-3-oxo-pyrazolidinium Inner Salt (**14**)

A solution of *N*-(*tert*-butyloxycarbonyl)-L-threonine 2-(diphenylmethylene)hydrazide (**10b**) (2.75 g, 6.92 mmol) and methanesulfonyl chloride (0.58 ml, 7.5 mmol) in 15 ml of pyridine was stirred in an ice bath for 1.0 hour. An additional 0.3 ml of methanesulfonyl chloride was added and stirred for an additional 2.0 hours in the cold. The mixture was diluted with EtOAc (100 ml) and washed with two 75-ml portions of cold 1 N HCl, two aliquots of brine and dried over magnesium sulfate. The solvent was evaporated at reduced pressure and the oily residue was dissolved in 100 ml of dry acetone and 4.0 g of powdered potassium carbonate was added. The reaction mixture was stirred and refluxed for 4.5 hours, cooled and filtered through diatomaceous earth. The filtrate was diluted with EtOAc (150 ml) and extracted with 100 ml of 0.5 N HCl, half saturated sodium bicarbonate (100 ml) and brine then dried over magnesium sulfate. Evaporation of the solvent gave an oil which was crystallized from EtOAc - hexane; yield 1.12 g (43%): MP 185~188°C; IR (KBr) cm^{-1} 2975, 1680; ^1H NMR (DMSO-d_6) δ 1.18 (3H, d, CH_3), 1.40 (9H, s, $(CH_3)_3C$), 3.85 (1H, dd, 5-H_β), 4.50 (1H, dd, 4-H_α), 7.50 (10H, m, aromatic protons); UV λ_{max}^{MeOH} nm (ε) 246 (12,314), 235 (19,154).

Anal Calcd for $C_{22}H_{25}N_3O_3$: C 69.64, H 6.64, N 11.07.
Found: C 69.71, H 6.53, N 10.70.

TLC of the filtrate from this product indicated the presence of the β-lactam derivative **11b**.

Tetrabutylammonium [3-(*S*)-[[(*tert*-Butyloxy)carbonyl]amino]-2-oxo-1-azetidinyl]sulfamate (**15**)

A solution of *tert*-butyl compound **12a** (2.3 g, 11.4 mmol) and sulfur trioxide pyridine complex (1.8 g, 11.4 mmol) in 50 ml of DMF was stirred at room temperature overnight. The mixture was poured into 300 ml of 0.5 M potassium dihydrogen phosphate and extracted with two 200-ml of methylene chloride. Tetrabutylammonium bisulfate (3.9 g, 11.4 mmol) was added to the aqueous solution and the solution was extracted with three 200-ml portions of methylene chloride. The extracts were dried over magnesium sulfate and evaporated to a colorless oil which was used without further treatment.

(*S*)-(3-Amino-2-oxo-1-azetidinyl)sulfamic Acid (**16**)

The tetrabutylammonium compound (**15**) (5.5 g, 10.5 mmol) and 50 ml of formic acid (95~97%) was stirred at room temperature for 1.0 hour. The resulting white crystalline solid was filtered, washed with methylene chloride and dried *in vacuo* to give 1.25 g of product: IR (KBr) 1765 cm^{-1} (β-lactam C=O); ^1H NMR (DMSO-d_6) δ 3.30 (1H, dd, J=3 and 6 Hz, 4-H_β), 3.60 (1H, dd, J=6 and 6 Hz, 4-H_α), 4.30 (1H, dd, J=3 and 6 Hz, 3-H_α).

Anal Calcd for $C_3H_7O_4N_3S$: C 19.89, H 3.89, N 23.19, S 17.70.
Found: C 20.20, H 3.77, N 23.00, S 16.82.

[3-(*S*)-[[(2-Amino-4-thiazolyl)-(*Z*)-(methoxyimino)acetyl]amino]-2-oxo-1-azetidinyl]sulfamic Acid (**18**)

A solution of 2-(2-amino-4-thiazolyl)-(*Z*)-methoximinoacetic acid (**17**) (456 mg, 2 mmol), dicyclohexylcarbodiimide (412 mg, 2 mmol) and 1-hydroxybenzotriazole (306 mg, 2 mmol) in 6 ml of dimethylformamide was stirred at room temperature for 10 minutes then added to a mixture of compound **16** and triethylamine (0.28 ml, 2 mmol) in a solution of 4 ml of DMF and 2 ml of water. The mixture was stirred at room temperature overnight then poured into 50 ml of 0.5 M potassium dihydrogen phosphate and extracted with three 25-ml portions of methylene chloride. The aqueous portion deposited crystals on standing at room temperature overnight which were collected and dried to afford 340 mg of the desired product: IR (KBr) 1775 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.85 (1H, dd, 3H), 3.96 (3H, s, CH_3O), 4.14 (1H, dd, 3H), 5.18 (1H, dd, 4H), 6.98 (1H, s, thiadiazole H).

Anal Calcd for $C_9H_{12}N_6O_6S_2$: C 29.67, H 3.32, N 23.07, S 17.60.
Found: C 29.39, H 3.36, N 22.96, S 17.58.

1-(Propylideneamino)-3-[(*tert*-butoxycarbonyl)amino]-2-azetidinone (**19**)

Propionaldehyde (1.8 ml, 25 mmol) was added to the 1-amino compound **12a** (1.05 g, 5.0 mmol) in 45 ml methylene chloride. After having stirred overnight the solvent was removed under vacuum

and 25 ml ether was added. The solution was evaporated to 10 ml, chilled and filtered to give 870 mg (72%) of white crystals: MP 119~120°C; IR (KBr) 1780 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 1.07 (3H, t, J=7 Hz, CH_3CH_2), 1.42 (9H, s, $(CH_3)_3C$), 2.31 (2H, m, CH_2CH_3), 3.37 (2H, m, 4-H_β), 3.82 (1H, t, J=5 Hz, 4-H_α), 4.6 (1H, m, 3-H), 7.28 (1H, t, J=5 Hz, =CH).

Anal Calcd for $C_{11}H_{19}N_3O_3$: C 54.75, H 7.94, N 17.42.
Found: C 54.53, H 8.32, N 17.34.

1-Propylamino-3-(*S*)-(*tert*-butoxycarbonyl)aminoazetidinone (**20**)

1-(Propylideneamino)-3-(*S*)-[(*tert*-butoxycarbonyl)amino]azetidinone (**19**) (2.0 g, 8.2 mmol) in 25 ml ethanol with 200 mg 5% rhodium on alumina was hydrogenated with a Parr apparatus for 42 hours. Catalyst was filtered off, solvent removed under vacuum, and the residue crystallized using EtOAc - hexane to give 1.7 g (85%) of a white, crystalline solid: MP 110°C; IR (KBr) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, J=6 Hz, CH_3), 1.43 (9H, s, $(CH_3)_3C$), ~1.45 (4H, m, CH_2CH_3), 2.88 (4H, t, J=6 Hz, CH_2N), 3.34 (1H, m, 4-H_β), 3.64 (1H, m, 4-H_α), 4.58 (1H, m, 3-H), 5.45 (1H, br d, NH).

Anal Calcd for $C_{11}H_{21}N_3O_3$: C 54.30, H 8.70, N 17.27.
Found: C 53.85, H 8.64, N 17.28.

Tetrabutylammonium (*S*)-[3-[(*tert*-Butoxycarbonyl)amino]-2-oxo-1-azetidinyl]propyl Sulfamate (**21**)

This compound was prepared as described for compound **15a** from *tert*-butyl 1-*N*-propylamino-2-oxo-3-(*S*)-azetidinylcarbamate (1.22 g, 5.0 mmol) and sulfur trioxide - pyridine complex (2.4 g, 15 mmol) to afford 3.0 g of a colorless oil which was used without further treatment.

(*S*)-(3-Amino-2-oxo-1-azetidinyl)propylsulfamic Acid (**22**)

The tetrabutylammonium compound (**21**) (3.0 g) described above was added to 20 ml of formic acid (95~97%) and allowed to stand at room temperature for 3 hours then evaporated to dryness at reduced pressure (bath temperature 28°C). The residue was stirred in methylene chloride, chilled and filtered; yield 506 mg: IR (KBr) 1780 cm^{-1}.

(*S*)-[3-[[(2-Amino-4-thiazolyl)-(*Z*)-(methoxyimino)acetyl]amino]-2-oxo-1-azetidinyl]propylsulfamic Acid (**23**)

A mixture of 2-(2-amino-4-thiazolyl)-(*Z*)-methoxyiminoacetic acid (**17**) (228 mg, 1.0 mmol), dicyclohexylcarbodiimide (206 mg, 1.0 mmol), and 1-hydroxybenzotriazole (153 mg, 1.0 mmol) in dimethylformamide (6 ml) was stirred at room temperature for 15 minutes. To this was added a solution of (*S*)-(3-amino-2-oxo-1-azetidinyl)propylsulfamic acid (**22**) (223 mg, 1.0 mmol) and triethylamine (0.2 ml) in DMF (4 ml) and the reaction mixture was stirred overnight at room temperature then filtered. The filtrate was diluted with 25 ml of water, adjusted to pH 3 with 1 N HCl and added to a column of XAD-2. The column was eluted with water and MeOH. The progress of the column was monitored by TLC and the product was isolated from the MeOH fractions. Further purification by preparative TLC on silica gel using EtOAc - propanol - water (10 : 6 : 4) gave the desired compound as a glass: IR (KBr) 1760 cm^{-1} (β-lactam C=O); ^1H NMR (DMSO-d_6) δ 1.85 (3H, t, CH_3), 1.65 (2H, m, CH_2), 3.92 (3H, s, CH_3O), 4.52 (2H, t, CH_2N), 5.00 (1H, m, 3-H), 6.80 (1H, s, thiazole H), 7.50 (2H, s, NH_2), 9.35 (1H, d, NH).

1-[(2,2,2-Trifluoro-1-hydroxyethyl)amino]-3-(*S*)-[(*tert*-butoxycarbonyl)amino]-4-(*S*)-methyl-2-azetidinone (**25a**)

A solution of 215 mg (1.0 mmol) of 1-amino-3-(*S*)-(*tert*-butoxycarbonyl)amino-2-(*S*)-methylazetidinone (**12b**) and 0.6 ml (5.0 mmol) trifluoroacetaldehyde hydrate in 15 ml methylene chloride was stirred for 42 hours with 3A molecular sieves. The solution was evaporated to a solid which was washed with 1.5 ml cold methylene chloride to give 240 mg (80%) of a white crystalline solid: MP 137.5~139°C; IR (KBr) 1730 cm^{-1} (C=O); ^1H NMR (CD_3COCD_3) δ 1.39 (3H, d, J=6 Hz, CH_3), 1.42 (9H, s, $(CH_3)_3C$), 3.85 (1H, m, 4-H_β), 4.08 (1H, m, 3-H), 4.91 (1H, m, $CHOHCF_3$), 5.70 (1H,

br d, J=7 Hz, OH), 5.99 (1H, d, J=6 Hz, N*H*CH), 6.60 (1H, d, J=8 Hz, NHC).

Anal Calcd for $C_{11}H_{18}F_3N_3O_4$: C 42.18, H 5.79, N 13.40, F 18.20.
Found: C 42.19, H 5.70, N 13.26, F 17.93.

1-[[2,2,2-Trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]amino]-3-(*S*)-[(*tert*-butoxycarbonyl)amino]-4-(*S*)-methyl-2-azetidinone (**25b**)

A solution of 4.28 g (0.02 mol) of 1-amino-3-(*S*)-(*tert*-butoxycarbonylamino)-2-(*S*)-methylazetidinone (**12b**) and 7.04 g (0.044 mol) hexafluoroacetone sesquihydrate in 64 ml THF was stirred over the weekend with 16 g 3A molecular sieves. The sieves were filtered off and the filtrate evaporated and pumped for 1 hour. Hexane was added to a total volume of 40 ml and the flask was stored 3 hours in the freezer. The sticky solid was filtered off and pumped overnight to give 6.5 g (86%) of dry while crystals: MP 126~128°C; IR (KBr) 1773 cm^{-1} (β-lactam C=O); ^1H NMR ($CDCl_3$) δ 1.43 (3H, d, J=7 Hz, 2-CH_3), 1.45 (9H, s, $(CH_3)_3C$), 3.91 (1H, m, 2-H_β), 4.06 (1H, br d, J=7 Hz, 3-H_α), 5.06 (1H, d, NHC), 5.21 (s), 5.4~6.9 (2H, OHNH); ^{13}C NMR (DMSO-d_6) δ 15.3 (s, 4-CH_3), 27.9 (s, $(CH_3)_3C$), 60.45, 61.28 (C-4 and C-3), 78.4 (s, CH_3CO), 154.6 (s, OCN), 165.4 (s, β-lactam C=O).

Anal Calcd for $C_{12}H_{17}N_3O_4F_6$: C 37.80, H 4.48, N 11.02, F 29.90.
Found: C 37.42, H 4.26, N 11.04, F 29.58.

1-[(2,2,2-Trifluoroethylidene)amino]-3-(*S*)-[(*tert*-butoxycarbonyl)amino]-4-(*S*)-methyl-2-azetidinone (**26a**)

Diethylaminosulfur trifluoride (DAST, 0.5 g, 38 ml, 3.1 mmol) was added to 2 ml of methylene chloride and chilled to −40°C. A slurry of 0.8 g (2.6 mmol) of 1-(2,2,2-trifluoro-1-hydroxyethyl)-amino-3-(*tert*-butoxycarbonyl)amino-4-methylazetidinone (**25a**) in 8 ml methylene chloride was added in portions. The mixture was stirred at −40°C until solution occurred and then poured over ice. The methylene chloride layer was washed with water, saturated brine, dried over magnesium sulfate and evaporated. Recrystallization from EtOAc - hexane yielded 0.70 mg, (91%) white crystals: MP 142.5~144.0°C; IR (KBr) 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (9H, s, $(CH_3)_3C$), 2.54 (3H, d, CH_3), 3.9~4.4 (2H, m, 4-H and 3-H), 5.28 (1H, d, J=8 Hz, NH), 8.24 (1H, q, J=4.5 Hz, =CHC).

Anal Calcd for $C_{11}H_{16}F_3N_3O_3$: C 44.75, H 5.46, N 14.23, F 19.30.
Found: C 44.61, H 5.19, N 14.10, F 18.91.

1-[[2,2,2-Trifluoro-1-(trifluoromethyl)ethylidene]amino]-3-(*S*)-[(*tert*-butoxycarbonyl)amino]-4-(*S*)-methyl-2-azetidinone (**26b**)

DAST (3.5 ml, 0.026 mmol) was added to a solution of 8.4 g (0.022 mmol) of 1-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethylamino]-3-(*S*)-(*tert*-butoxycarbonyl)amino-2-(*S*)-methylazetidinone (**25b**) in 45 ml methylene chloride at −50°C. After solution occurred, the reaction was allowed to come to room temperature over 30 minutes and placed in a 35°C bath for 30 minutes. Ice water was added and the product was extracted into EtOAc. The EtOAc layer was washed with water and brine, dried over magnesium sulfate, evaporated and purified by chromatography on silica gel using hexane - EtOAc (2 : 1) to give 7.0 g (88%) of a crystalline solid: MP 87~89°C; IR (KBr) 1798 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.44 (9H, s, $(CH_3)_3C$), 1.57 (3H, d, J=5 Hz, 4-CH_3), 4.34 (1H, m, 4-H), 4.42 (1H, m, 3-H), 5.41 (1H, d, J=6 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 17.2 (s, CH_3), 28.2 (s, $(CH_3)_3C$), 63.2, 63.5 (C-4 and C-3), 81.3 (CO), 116.6, 118.8 (q, J=281.2 Hz, $=C(CF_3)_2$), 154.9 (s, OC=O), 163.6 (s, NC=O).

Anal Calcd for $C_{12}H_{15}N_3O_3F_6$: C 39.68, H 4.16, N 11.57, F 31.38.
Found: C 39.89, H 4.08, N 11.56, F 31.07.

1-[(2,2,2-Trifluoroethyl)amino]-3-(*S*)-[(*tert*-butoxycarbonyl)amino]-4-(*S*)-methyl-2-azetidinone (**27a**)

A solution of 0.62 g (2.1 mmol) of 1-(2,2,2-trifluoroethylidene)amino-3-(*tert*-butoxycarbonyl)-amino-4-methylazetidinone (**26a**) in 6 ml of THF was cooled to −50°C. A solution of 4.5 ml of 1 M borane in THF was added over 15 minutes maintaining the temperature at −20°C. The solution was stirred at −10°C for 2.5 hours and 5 ml of MeOH was added. The solution was evaporated and MeOH was added and evaporated twice. The resulting residue was chromatographed on silica gel using EtOAc - heptane (1 : 2) to give 0.57 g of white crystals; IR (KBr) 1775 cm^{-1}; ^1H NMR ($CDCl_3$)

1.8 (3H, d, J=6 Hz, 4-CH_3), 1.45 (9H, s, $(CH_3)_3C$), 3.3~3.7 (m, 4-H_β and CH_2CF_3), 4.05 (1H, m, 3-H), 4.6 (1H, t, J=4.6 Hz, N*H*CH_2), 5.1 (1H, d, J=6.6 Hz, NHC=O).

Anal Calcd for $C_{11}H_{18}F_3N_3O_3$: C 44.44, H 6.10, N 14.13, F 19.17.
Found: C 44.29, H 5.89, N 14.05, F 18.82.

1-[[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]amino]-3-(*S*)-[(*tert*-butoxycarbonyl)amino]-4-(*S*)-methyl-2-azetidinone (**27b**)

A solution of 4.8 g (0.013 mmol) of 1-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidineamino]-3-(*S*)-(*tert*-butoxycarbonyl)amino-2-(*S*)-methylazetidinone (**26b**) in 15 ml THF was chilled in an acetone-dry ice bath. A solution of 30 ml (0.030 mmol) of 1 M borane in THF was added and the solution was stirred at ambient temperature for 90 minutes and in a 35°C water bath for 30 minutes. MeOH was added and solvent evaporated at reduced pressure three times to give an oil which was chromatographed on silica gel using hexane - EtOAc (3 : 1), yielding 4.6 g (66%) of a colorless glass: IR (KBr) 1775 cm^{-1} (β-lactam C=O).

Anal Calcd for $C_{12}H_{17}N_3O_3F_6$: C 39.46, H 4.69, N 11.50, F 31.21.
Found: C 39.70, H 5.12, N 11.24, F 30.12.

Tetrabutylammonium [3-(*S*)-[(*tert*-Butyloxycarbonyl)amino]-2-(*S*)-methyl-4-oxo-1-azetidinyl](2,2,2-trifluoroethyl)sulfamate (**28a**)

A solution of **27a** (654 mg, 2.2 mmol) and pyridine sulfur dioxide complex (1.2 g, 7.54 mmol) in 15 ml of dimethylformamide was stirred at room temperature overnight. The reaction mixture was worked up as described for compound **15** using tetrabutylammonium bisulfate (0.75 g, 2.2 mmol) to give a colorless oil which was used without further treatment.

Tetrabutylammonium [3-(*S*)-[(*tert*-Butoxycarbonyl)amino]-2-(*S*)-methyl-4-oxo-1-azetidinyl[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]sulfamate (**28b**)

A solution of the *N*-amino compound **27b** (1.60 g, 4.38 mmol) and triethylamine sulfur dioxide complex (2.5 g, 13.8 mmol) in DMF (10 ml) was heated at 75°C overnight. TLC showed the reaction was incomplete, therefore an additional 2.5 g (13.8 mmol) of triethylamine sulfur dioxide complex was added to the reaction mixture and stirred for an additional 8 hours. TLC indicated that the presence of starting material, therefore an additional 2.5 g of triethylamine - sulfur dioxide complex was added and again stirred at 75°C overnight. At this time TLC indicated the reaction was complete. On cooling the reaction mixture was diluted with 300 ml of 0.5 M potassium dihydrogen phosphate and extracted with three portions of methylene chloride (100 ml). Tetrabutylammonium sulfate (1.5 g, 4.4 mmol) was added to the aqueous which was extracted with three 100-ml portions of methylene chloride. The organic extracts were dried (magnesium sulfate) and evaporated to a syrup which was used as such for the preparation of **29b**.

[3-(*S*)-Amino-2-(*S*)-methyl-4-oxo-1-azetidinyl](2,2,2-trifluoroethyl)sulfamic Acid (**29a**)

The tetrabutylammonium sulfamate **28a** (790 mg) was dissolved in trifluoroacetic acid (10 ml) and allowed to stand at room temperature for 10 minutes, then evaporated to dryness at reduced pressure (30°C). The residue was dissolved in methylene chloride and evaporated several times to remove the trifluoroacetic acid. Finally this residue was dissolved in DMF (10 ml) and adjusted to pH 7 with 0.36 ml of triethylamine. This solution was used for the preparation of compound **30a**.

[3-(*S*)-Amino-2-(*S*)-methyl-4-oxo-1-azetidinyl]-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]sulfamic Acid (**29b**)

A solution of the tetrabutylammonium compound **28b** (2.70 g) in trifluoroacetic acid (25 ml) was allowed to stand at room temperature for 15 minutes then evaporated at reduced pressure (30°C). The residue was dissolved in methylene chloride and evaporated several times then dissolved in DMF (25 ml) and added 3.0 ml of triethylamine. This solution was used directly in the preparation of compound **30b**.

[3-(*S*)-[[(2-Amino-4-thiazolyl)-(*Z*)-(methoxyimino)acetyl]amino]-2-(*S*)-methyl-4-oxo-1-azetidinyl]-(2,2,2-trifluoroethyl)sulfamic Acid Sodium Salt (**30a**)

A mixture of 2-(2-amino-4-thiazolyl)-2-(*Z*)-methoximinoacetic acid (257 mg, 1.28 mmol), dicyclohexylcarbodiimide (264 mg, 1.28 mmol) and 1-hydroxylbenzotriazole (196 mg, 1.28 mmol) in 10 ml of DMF was stirred at room temperature for 20 minutes. To this was added a solution of the salt of compound **29a** (from the above described experiment). The mixture was stirred at room temperature, filtered and this solvent was evaporated reduced pressure (40°C). The residue was dissolved in acetone (25 ml) and diluted with ether then chilled. The resulting precipitate (475 mg) was collected by filtration and purified by preparative TLC on silica gel using EtOAc - EtOH - water (66 : 33 : 2) as the eluant to afford 192 mg of the free acid (**30a**). This product (108 mg) was converted to the sodium salt by dissolving in water (15 ml) and passing through a small column of Dowex 50 (Na^+) followed by evaporation to dryness at room temperature; yield 94 mg; IR (KBr) 1756 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 1.39 (3H, d, J=6.2 Hz, CCH_3), 3.7~4.1 (3H, m, CH_2CF_3 and 2-H_β), 3.84 (3H, s, OCH_3), 4.35 (1H, dd, J=4.7 and 7.0 Hz, 3-H_α), 6.72 (1H, s, thiadiazole H), 9.43 (1H, d, J= 7.0 Hz, NH).

[(*S*)-2-Methyl-(*S*)-3-[[(2-amino-4-thiazolyl)-(*Z*)-(methoxyimino)acetyl]amino]-4-oxo-1-azetidinyl]-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]sulfamic Acid (**30b**)

A mixture of 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetic acid, (0.80 g, 3.93 mmol), dicyclohexylcarbodiimide (0.81 g, 3.93 mmol), and 1-hydroxybenzotriazole (0.50 g, 3.93 mmol) in 25 ml of DMF was stirred at room temperature for 30 minutes. To this was added a solution of **29b** (prepared as described above) in 25 ml of DMF. The mixture was stirred at room temperature overnight then filtered. The filtrate was diluted with ether (225 ml) and the resulting insoluble oil was chromatographed on silica gel using EtOAc - EtOH - water (80 : 20 : 1) as the eluent to afford 275 mg of free acid of the desired product as a glass-like solid: IR (KBr) 1780 cm^{-1} (β-lactam C=O); ^1H NMR (DMSO-d_6) δ 1.46 (3H, d, J=5.7 Hz, CH_3), 3.82 (3H, s, CH_3O), 3.86 (1H, q, J=5.7 Hz, 2-H_β) 4.33 (1H, d, J=7 Hz, 3-H_α), 5.35 (1H, m, $CH(CF_3)_2$), 6.67 (1H, s, thiazole H), 7.18 (2H, s, NH_2), 9.37 (1H, d, J=7 Hz, NH).

Aeknowledgment

We thank Mr. E. Ross and Mr. N. Passarella for the microanalyses reported herein and Mr. George Morton for the spectral information. We also thank Mrs. Nydia Kuck, Peter Peterson and Thomas Fenton for the biological data. We are also indebted to Drs. R. E. Carhart and D. A. Dunn for the molecular orbital calculations.

References

1) Imada, A.; K. Kitano, K. Kintaka, M. Muroi & M. Asai: Sulfazecin and isosulfazecin, novel β-lactam antibiotics of bacterial origin. Nature 289: 590~591, 1981
2) Sykes, R. B.; C. M. Cimarusti, D. P. Bonner, K. Bush, D. M. Floyd, N. H. Georgopapadakou, W. H. Koster, W. C. Liu, W. L. Parker, P. A. Principe, M. L. Rathnum, W. A. Slusarchyk, W. H. Trejo & T. S. Wells: Monocyclic β-lactam antibiotics produced by bacteria. Nature 291: 489~491, 1981
3) Koster, W. H.; C. M. Cimarusti, R. B. Sykes: Monobactams. *In* Chemistry and Biology of β-Lactam Antibiotics. Vol. 3. *Eds.*, R. B. Morin & M. Gorman, pp. 339~375, Academic Press, New York, 1982
4) Loren, G.: Aztreonam. Drugs Future 8: 296~300, 1984
5) Carumonam. Annual Drug Data Report 6: 127, 1984
6) Slusarchyk, W. A.; T. Dejneka, E. M. Gordon, E. R. Weaver & W. H. Koster: Monobactams: Ring activating N-1 substituents in the monocyclic antibiotics. Heterocycles 21: 191~209, 1984
7) Woulfe, S. R. & M. J. Miller: The synthesis of substituted [[3(*S*)-(acylamino)-2-oxo-1-azetidinyl]thio]-acetic acids. J. Org. Chem. 51: 3133~3139, 1986
8) Taylor, E. C.; N. F. Haley & R. J. Clemens: Synthesis and properties of 3-oxo-1,2-diazetidinium ylides. J. Am. Chem. Soc. 103: 7743~7752, 1981
9) Mattingly, P. G.; J. F. Kerwin, Jr. & M. J. Miller: A facile synthesis of substituted *N*-hydroxy-2-

azetidinones. A biogenetic type β-lactam synthesis. J. Am. Chem. Soc. 101: 3983~3985, 1979

10) BOSE, A. K.; D. P. SAHU & M. S. MANHAS: Stereoselective chiral synthesis of *N*-aryl-α-amino-β-lactams from β-hydroxy-α-amino acids. J. Org. Chem. 46: 1229~1231, 1981

11) BREUER, H.; H. STAUB & U. D. TREUNER (Von Heyden Gmbh): Monocyclic β-lactam antibiotics. Ger. 3122795, Dec. 30, 1982

12) BOYD, D. B.; D. K. HERRON, W. H. W. LUNN & W. A. SPITZER: Parabolic relationships between antibacterial activity of cephalosporins and β-lactam reactivity predicted from molecular orbital calculations. J. Am. Chem. Soc. 102: 1812~1814, 1980

13) BOYD, D. B.; C. EIGENBROT, J. M. INDELICATO, M. J. MILLER, C. E. PASINI & S. R. WOULFE: Heteroatom-activated β-lactam antibiotics; considerations of differences in the biological activity of [[3(*S*)-(acylamino)-2-oxo-1-azetidinyl]oxy]acetic acids (oxamazins) and the corresponding sulfur analogs (thiamazins). J. Med. Chem. 30: 528~536, 1987