EtOH to which 2 mL of a 10 N NaOH solution was added. After 2 h at 80 °C (oil bath) TLC indicated complete conversion of the 3′-configuration. The solution was cooled, neutralized, and evaporated and the residue was dissolved in 100 mL of $CHCl_3$ which was washed twice again with a $NaHCO_3$ solution. After drying of the organic phase and subsequent evaporation, the residue was purified on 40 g of silica gel ($CHCl_3$–MeOH 98:2) yielding 1.69 (3.25 mmol, 81%) of the title compound **23**: UV (MeOH) λ_{max} 230 and 266 nm; ^1H NMR ($CDCl_3$) δ 1.96–2.21 (m, H-2′), 2.35–2.72 (m, H-2″), 3.56 (m, H-5′, H-5″), 3.78 (s, OCH_3), 3.98 (m, H-4′), 4.41 (m, H-3′), 6.18 (d, J = 7.5 Hz, H-1′), 6.84 (d), 7.18–7.51 (m) (trityl), 7.98 (d, 6.6 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 40.6 (C-2′), 55.1 (OCH_3), 61.5 (C-5′), 70.6 (C-3′), 83.0 (C-4′), 85.3 (C-1′), 87.3 (Ph_3C), 125.5 (C-6, J = 35.4 Hz), 140.0 (C-5, J = 229.2 Hz), 149.0 (C-2), 157.0 (C-4, J = 26.9 Hz) ppm.

3′-Fluoro-2′,3′-dideoxy-5-fluorouridine (24). The foam **23** obtained from the previous preparation (1.64 g, 3.16 mmol) was dissolved in 50 mL of dichloromethane–THF (9:1).[31] After cooling on an ice bath, 850 μL (6 mmol) of DAST was added and the reaction was left at room temperature for 2 h. The mixture was poured into 100 mL of a saturated $NaHCO_3$ solution and extracted twice with 100 mL of $CHCl_3$. The organic phase was washed once more with $NaHCO_3$, dried, and evaporated. The residue was treated with 75 mL of 80% acetic acid for 30 min at 60 °C. Evaporation and coevaporation with toluene yielded an oil which proved difficult to purify. Therefore the residue was acylated with 40 mL of pyridine–acetic anhydride (3:1) for 1 h at room temperature. The mixture was evaporated and purified by column chromatography ($CHCl_3$–MeOH 99:1) yielding 442 mg (1.52 mmol, 48%) of acylated **24**. Treatment with 50 mL of methanol saturated with ammonia for 5 h at ambient temperature and chromatographic purification yielded 280 mg (1.12 mmol, 35%) of the title compound **24**, which was crystallized from acetone–hexane: mp 171–172 °C; UV (MeOH) λ_{max} 268 nm (ϵ 8500); MS m/e 248 (M^+), 131 (B + 2H), 130 (B + H), 119 (S, 100); ^1H NMR (DMSO-d_6) δ 1.85–2.63 (m, H-2′, H-2″), 3.64 (d, J = 3.5 Hz, H-5′, H-5″), 4.19 (dt, $J_{4',F}$ = 26.8 Hz, H-4′), 5.30 (dm, $J_{3',F}$ = 52.7 Hz, H-3′), 6.19 (dt, J = 7 Hz, H-1′), 8.17 (d, J = 7.2 Hz, H-6), 11.98 (br s, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 37.8 (C-2′, J = 20.7 Hz), 61.1 (C-5′, J = 12.3 Hz), 85.0 (C-1′), 85.5 (C-4′, J =24.4 Hz), 95.2 (C-3′, J = 173.3 Hz), 124.8 (C-6, J = 34.2 Hz), 140.5 (C-5, J = 232 Hz), 149.3 (C-2), 157.3 (C-4, J = 26.8 Hz) ppm. Anal. ($C_9H_{10}F_2N_2O_4$) C, H, N.

1-(2-Fluoro-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)thymine (26). A solution of 515 mg (1 mmol) of 1-[3-deoxy-5-*O*-(monomethoxytrityl)-β-D-*threo*-pentofuranosyl]thymine[14] (**25**) in 20 mL of dichloroethane was cooled on an ice bath. Under stirring, 0.3 mL (2.1 mmol) of DAST was added and the reaction was left at room temperature for 2 h, when TLC ($CHCl_3$–MeOH 95:5) indicated complete reaction. The mixture was poured into 50 mL of a saturated $NaHCO_3$ solution and stirred for 10 min. The product was extracted with 50 mL of $CHCl_3$ (2×) and the organic phase was washed once more with $NaHCO_3$. After evaporation, the residue was treated with 50 mL of 80% acetic acid for 45 min at 60 °C. Evaporation followed by coevaporation with toluene and chromatographic purification yielded 140 mg (0.57 mmol, 57%) of **26**, which crystallized from acetone–hexane: mp 186–187 °C; UV (MeOH) λ_{max} 266 nm (ϵ 9450); MS m/e 244 (M^+), 126 (B + H, 100), 119 (S); ^1H NMR (DMSO-d_6) δ 1.75 (s, CH_3), 1.85–2.55 (m, H-3′, H-3″), 3.43–3.97 (m, H-5′, H-5″), 4.30 (m, H-4′), 5.21 (t, J = 5.0 Hz, 5′-OH), 5.29 (dm, $J_{2',F}$ = 51.9 Hz, H-2′), 5.88 (d, $J_{1',F}$ = 17.5 Hz, H-1′), 7.83 (s, H-6), 11.31 (s, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 12.4 (CH_3), 31.6 (C-3′, J = 19.5 Hz), 60.8 (C-5′), 81.4 (C-4′), 89.8 (C-1′, J = 36.6 Hz), 97.2 (C-2′, J = 178.2 Hz), 109.1 (C-5), 136.2 (C-6), 150.4 (C-2), 164.1 (C-4) ppm. Anal. ($C_{10}H_{13}FN_2O_4$) C, H, N.

Antiviral Test Procedures. The HTLV-III_B strain of HIV was used throughout all experiments. The virus was prepared from the culture supernatant of a persistently HTLV-III_B-infected HUT-78 cell line. The antiviral assays[38] were based on the protection of HIV-infected MT-4 cells against virus-induced cytopathogenicity. They were run in parallel with the cytotoxicity assays aimed at establishing the toxicity of the compounds for uninfected MT-4 cells.

Acknowledgment. HIV (HTLV-III_B) was a kind gift by Dr. R. C. Gallo (National Cancer Institute, Bethesda, MD). MT-4 cells were a gift from Dr. N. Yamamoto (Yamaguchi University, Yamaguchi, Japan). Arthur Van Aerschot and Rudi Pauwels are fellows of the Janssen Research Foundation. Dr. P. Herdewijn is a research associate of the Belgian "Nationaal Fonds voor Wetenschappelijk Onderzoek". This work was supported in part by the AIDS Basic Research Program of the European Community and grants from the Belgian F.G.W.O. (Fonds voor Geneeskundig Wetenschappelijk Onderzoek, Projects No. 3.0037.83, 3.0040.83, and 3.0097.87) and the Belgian G.O.A. (Geconcerteerde Onderzoeksacties, Project No. 85/90-79). We are indebted to Dr. G. Janssen for recording mass spectra, Luk Kerremans, Guy Schepers, and Ann Absillis for excellent technical assistance, and Dominique Brabants and Laurent Palmaerts for fine editorial help.

(38) Pauwels, R.; De Clercq, E.; Desmyter, J.; Balzarini, J.; Goubau, P.; Herdewijn, P.; Vanderhaeghe, H.; Vandeputte, M. *J. Virol. Methods* **1987**, *16*, 171.

N-Azamonobactams. 2. Synthesis of Some *N*-Iminoacetic Acid and *N*-Glycyl Analogues

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The synthesis of the title compounds has been accomplished. The *N*-iminoacetic acid analogues (**12a** and **12b**) containing the aminothiazole type side chain exhibited good in vitro antibacterial activity against Gram-negative organisms. The corresponding *N*-glycyl derivative (**17**) was not active.

Recently, we described the synthesis of some *N*-azamonobactam derivatives.[1] This work coupled with the published accounts of *N*-oxo derivatives (**1a**)[2] and *N*-thio (**2a**)[3] compounds prompted the synthesis of the corresponding *N*-aza analogues (**1c** and **1d**) described herein.

Chemistry

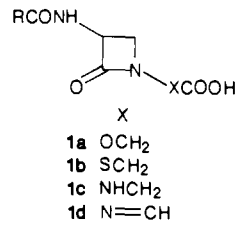
The starting materials for the synthesis of these compounds were the previously described *N*-amino derivatives

(1) Curran, W. V.; Ross, A. A.; Lee, V. J. *J. Antibiot.* **1988**, *41*, 1418.

(2) Woulfe, S. R.; Miller, M. J. *J. Med. Chem.* **1985**, *28*, 1447.

(3) Woulfe, S. R.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 3133.

0022-2623/89/1832-1749$01.50/0



2a and **-b**.[1] Reaction with benzyl glyoxylate gave the imines **3a** and **-b** which were deblocked with trifluoroacetic acid to give the amino derivatives **4a** and **-b**. Catalytic hydrogenation at atmospheric pressure afforded the debenzylated derivatives **5a** and **-b** without affecting the imine double bond. Treatment of **5b** with trifluoroacetic acid gave the imino acid **6b**.

The reaction of the amino ester derivative **4a** with phenylacetyl chloride produced the acylated product **7** which when treated with hydrogen and palladium on carbon at atmospheric pressure gave the imino acid **9**. More vigorous treatment with hydrogen using a Parr apparatus produced the amino acid **8**. X-ray crystallography of compound **9** revealed that it was the *E* isomer.[4,5] (See Scheme I.)

Compound **4a** was also acylated with the aminothiazole (ATMO) (**10**) side chain using dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. The product **11b** resisted all attempts to remove the benzyl group.[6] However, reaction of the activated ester of compound **10** with the silylated derivative (derived from **6b**) did afford the desired compound **12b**.

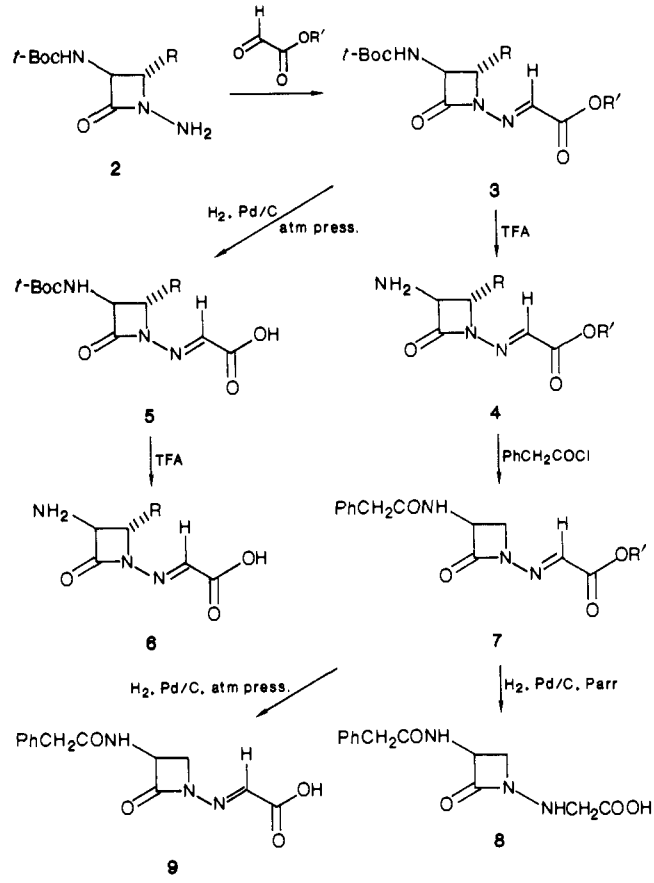
These monobactams were also prepared by using the allyl ester as the protecting group. Treatment of compound **2a** with allyl glyoxylate afforded the imine **3c** which was deblocked with trifluoroacetic acid to give compound **4c**. Condensation of this derivative with the ATMO side chain (**10**) via the activated ester gave the amide **11c**. This derivative was readily converted to the imino acid **12a** by using tetrakis(triphenylphosphine)palladium(0)[7] (Scheme II).

Due to the difficulties encountered with catalytic hydrogenation in the presence of the ATMO side chain, we synthesized the amino acid **17** using the allyl protecting group. Catalytic hydrogenation of the benzyl ester **3a** using a Parr apparatus produced the amino acid **13** which was converted to the allyl ester **14** by using allyl bromide and triethylamine. Deblocking using trifluoroacetic acid gave compound **15** which was acylated in the usual manner with the ATMO side chain (**10**) to give compound **16**. The reaction of this allyl ester with the palladium(0) derivative produced the desired amino acid **17** (Scheme III).

Biological Activity

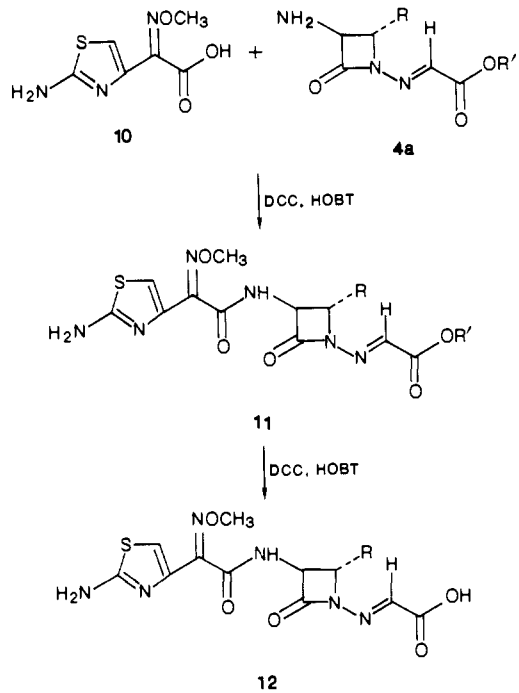
The in vitro antibacterial activity of the representative monobactam derivatives were determined against a spectrum of Gram-negative bacteria by a standard agar dilution method. Mueller–Hinton agar containing 2-fold decreasing concentrations of the compound was poured into Petri plates. The agar surfaces were inoculated with (1–5) × 10^4

Scheme I[a]



[a] **a**: R = H; R′ = benzyl. **b**: R = CH_3; R′ = benzyl. **c**: R = H; R′ = allyl.

Scheme II[a]



[a] **a**: R = H; R′ = benzyl. **b**: R = CH_3; R′ = benzyl. **c**: R = H; R′ = allyl.

colony forming units of bacteria by means of a Steere replicating device. The lowest concentration of the monobactam derivative that inhibited growth of bacterial strain after 18 h of incubation at 35 °C was recorded as

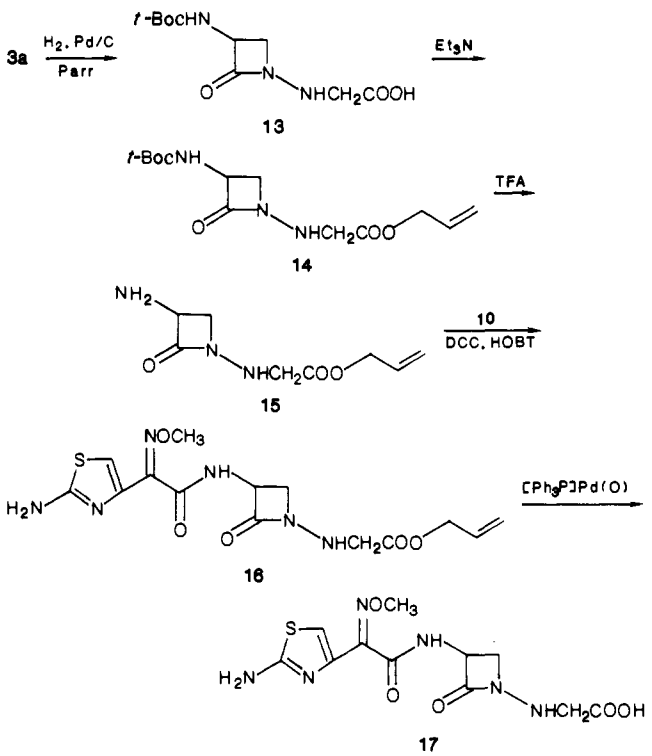
(4) This compound has also been synthesized via a slightly different route by M. R. Dick, M.S. Thesis, University of Notre Dame, Sept 1985. We thank Professor M. J. Miller for this information.
(5) The stereochemistry of all of the other imino acids described herein is not known.
(6) Other workers have experienced this same problem. See ref 2.
(7) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587.

Table I. In Vitro Antibacterial Activity[a]

organism	strain	min inhibitory concn, μg/mL			
		16	12	17	aztreonam
Escherichia coli	MOR-84-20	8	2	>128	0.06
Escherichia coli	VGH-84-19	8	2	>128	0.06
Escherichia coli	CMC-84-50	4	2	>128	0.06
Escherichia coli	ATCC-25922	8	8	>128	0.06
Klebsiella pneumoniae	CMC-84-31	8	2	>128	0.03
Klebsiella pneumoniae	MOR-84-24	16	8	>128	0.06
Klebsiella pneumoniae	IO-83-5	8	4	>128	0.12
Enterobacter cloacae	VGH-84-39	16	8	>128	0.06
Enterobacter cloacae	K-84-10	8	4	>128	0.12
Enterobacter cloacae	MOR-84-30	64	32	>128	4.0
Serratia marcescens	MOR-84-41	32	4	>128	0.06
Serratia marcescens	CMC-83-74	128	16	>128	0.25
Serratia marcescens	IO-83-63	32	8	>128	0.12
Morganella morganii	VGH-84-12	64	4	>128	0.03
Morganella morganii	CMC-84-38	32	8	>128	0.015
Morganella morganii	MOR-84-45	128	16	>128	0.015
Proteus rettgeri	IO-83-21	0.5	0.12	64	0.002
Providencia stuartii	CMC-83-3	32	2	>128	0.015
Citrobacter diversus	J-82-24	16	4	>128	0.03

[a] None of the compounds described herein exhibited any activity against Gram-positive bacteria.

Scheme III



the minimal inhibitory concentration (MIC) for that strain.

The in vitro data for three acylated *N*-azamonobactams reported herein and a standard drug, namely, aztreonam, are listed on Table I. Compounds **8** and **9** were also tested but were found inactive. Thus it can be seen that only the two imino acid derivatives **12a** and **12b**, containing the ATMO side chain, exhibited any interesting antibacterial activity with the 4α-methyl analogue **12b** being the most active. Two facts emerge from this data; namely, (1) the β-lactam must be activated by the exocyclic imino double bond, and (2) the aminothiazole type side chain is necessary for biological activity to be observed. Unfortunately, the stereochemistry of this bond is not known for the two active compounds **12a** and **12b**. It is worthwhile to note that the saturated analogue **17** did not exhibit any interesting biological activity. Thus, of the three heteroatom-activated acetic acid derivatives **1a–c** only the oxygen compounds **1a** show good antibacterial activity.[8]

Experimental Section

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. Thin-layer chromatography was done on commercial silica gel plates (Analtech) containing calcium sulfate binder and fluorescent indicator. Melting points 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 infrared spectrophotometer. ^{1}H 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 parts per million (δ, ppm) downfield from tetramethylsilane (internal standard). Significant ^{1}H 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.

Benzyl (*S*)-[[3-[(*tert*-Butoxycarbonyl)amino]-2-oxo-1-azetidinyl]imino]acetate (3a). A solution of 3-[(*tert*-butoxycarbonyl)amino]-2-oxo-1-aminoazetidine (**2a**) (2.33 g, 11.57 mmol) and benzyl glyoxylate (1.90 g, 11.57 mmol) in 250 mL of toluene was refluxed for 1 h by using a water separator. The solution was then evaporated to dryness, and the residue was dissolved in methylene chloride, filtered through Magnesol, and again evaporated, and the resulting oil was triturated to a solid with ether which was collected by filtration and crystallized from acetone/hexane to give 2.12 g of product (53%): mp 128–130.5 °C; IR (KBr) 1780 cm^{-1} (β-lactam); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 3.50 (m, 1 H), 3.80 (t, 1 H), 5.25 (m, 1 H), 5.30 (s, 2 H), 7.38 (s, 5 H). Anal. ($C_{13}H_{21}N_3O_5$) C, H, N.

Benzyl [[2(*S*)-Methyl-3(*S*)-[(*tert*-butoxycarbonyl)amino]-4-oxo-1-azetidinyl]imino]acetate (3b). A solution of 4(*S*)-methyl-3(*S*)-[(*tert*-butoxycarbonyl)amino]-2-oxo-1-aminoazetidinone (**2b**) (5.34 g, 24.8 mmol) and benzyl glyoxylate (4.07 g, 24.8 mmol) in 250 mL of toluene was treated as described for compound **7a** to afford 7.31 g of product. Recrystallization from acetone/hexane gave 6.60 g (76%): mp 154.5–158 °C; IR (KBr) 1765 cm^{-1} (β-lactam C=O); ^{1}H NMR ($CDCl_3$) 1.45 (s, 9 H), 1.52 (d, 3 H, J = 8), 4.25 (m, 2 H), 5.65 (s, 2 H), 7.65 (s, 5 H), 8.25 (s,

(8) For a detailed discussion of the structural parameters related to biological activity among the heteroatom-activated β-lactams, see: Boyd, D. B.; Eigenbrot, C.; Indelicato, J. M.; Miller, M. J.; Passini, C. E.; Woulfe, S. J. *J. Med. Chem.* **1987**, *38*, 528.

(9) Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *J. Med. Chem.* **1987**, *30*, 871.

1 H). Anal. ($C_{18}H_{23}N_3O_5$) C, H, N.

Benzyl (*S*)-[(3-Amino-2-oxo-1-azetidinyl)imino]acetate Trifluoroacetate (4a). A solution of the *tert*-butoxycarbonyl compound **3a** (1.87 g, 5.38 mmol) in 20 mL of trifluoroacetic acid was allowed to stand at room temperature for 0.5 h and then evaporated to dryness at reduced pressure. The resulting oil was triturated to a solid with ether and filtered to afford 1.93 g (99%): IR (KBr) 1790 cm^{-1} (β-lactam C=O); ^1H NMR (DMSO-d_6) δ 3.53 (m, 1 H, H_{4a}), 4.05 (m, 1 H, $H_{4\beta}$), 4.65 (m, 1 H, $H_{3\alpha}$), 5.35 (s, 2 H, $PhCH_2$), 7.85 (br s, 6 H, aromatic and imino protons). Anal. ($C_{12}H_{13}N_3O_3 \cdot CF_3COOH$) C, H, N.

(*S*)-[[3-[(*tert*-Butoxycarbonyl)amino]-2-oxo-1-azetidinyl]imino]acetic Acid (5a). A solution of the benzyl compound **3a** (1.0 g, 2.88 mmol) in 20 mL of THF was hydrogenated at atmospheric pressure for 3 h in the presence of 5% palladium on carbon (200 mg). The catalyst was removed by filtration, and the solution was evaporated at reduced pressure to give a foam which was crystallized from ethyl acetate/hexane to yield 650 mg (88%): mp 145–147 °C; IR (KBr) 1800 cm^{-1} (β-lactam, C=O); ^1H NMR (DMSO-d_6) δ 1.35 (s, 9 H, *tert*-butyl), 3.50 (m, 1 H,), 3.85 (dd, J = 3 and 6, 1 H), 4.62 (m, 1 H), 7.20 (s, 1 H), 7.65 (d, 1 H). Anal. ($C_{15}H_{15}N_3O_5$) C, H, N.

[[3(*S*)-[(*tert*-Butoxycarbonyl)amino]-2(*S*)-methyl-4-oxo-1-azetidinyl]imino]acetic Acid (5b). A solution of benzyl [[4(*S*)-methyl-3(*S*)-[(*tert*-butoxycarbonyl)amino]-2-oxo-1-azetidinyl]imino]acetate (**3b**) (3.0 g, 8.3 mmol) and 5% palladium on charcoal (500 mg) in 70 mL of THF was hydrogenated at atmospheric pressure for 3 h and worked up as described for compound **8a** to afford a foam: yield 2.58 g; IR (KBr) 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 [s, 9 H, $(CH_3)_3C$], 1.62 (d, 3 H, J = 8, CH_3), 4.25 (m, 2 H,), 8.75 (s, 1 H, =CH).

[[3(*S*)-Amino-4-oxo-2(*S*)-methyl-1-azetidinyl]imino]acetic Acid Trifluoroacetate (6). Prepared by the same procedure as described for compound **4a** from [[3(*S*)-[(*tert*-butoxycarbonyl)amino]2(*S*)-methyl-4-oxo-1-azetidinyl]imino]acetic acid (**5b**): mp 172–174 °C dec; IR (KBr) 1780 cm^{-1}; ^1H NMR (TFA) δ 1.80 (d, 3 H, J = 8), 4.65 (br s, 1 H, $H_{3\alpha}$), 4.80 (d, 1 H, J = 8, 4 H). Anal. ($C_6H_9N_3O_3$) C, H, N.

Benzyl (*S*)-[[2-Oxo-3-[(phenylacetyl)amino]-1-azetidinyl]imino]acetate (7). A cold solution of benzyl [(2-oxo-3-amino-1-azetidinyl)imino]acetate (**4a**) (650 mg, 1.8 mmol) and 0.5 mL (36 mmol) of triethylamine in 5 mL of THF was added to a solution of phenylacetyl chloride (0.24 mL, 1.8 mmol) in 2 mL of THF in an ice bath. The mixture was stirred in the cold for 0.5 h and at room temperature for 1.5 h and then poured into ice water. The resulting solid was collected by filtration and dissolved in ethyl acetate which was extracted with saturated sodium bicarbonate solution and brine and then dried ($MgSO_4$). Evaporation of the solvent at reduced pressure afforded a glass which was dissolved in methylene chloride and filtered through Magnesol. Elution of the Magnesol with ethyl acetate followed by evaporation of the solvent gave a solid which was recrystallized from acetone/hexane to afford 128 mg of the desired product: mp 123.5–125.5 °C. Chromatography of the methylene chloride extract on silica gel using ethyl acetate/hexane gave an additional 200 mg of product: mp 126–127.5 °C (66%); IR (KBr) 1780 cm^{-1} (β-lactam C=O) 1720 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) δ 3.62 (s, 1 H, $PhCH_2C$=O), 3.65 (dd, 1 H, J = 3.1 and 6.8, $H_{4\beta}$), 3.93 (dd, 1 H, J = 6.8 and 6.4, H_{4a}), 4.92 (m, 1 H, H_{3a}), 5.27 (s, 2 H, OCH_2Ph), 6.20 (d, 1 H, NH), 7.20–7.40 (M, 11 H, N=CH, and aromatic protons). Anal. ($C_{20}H_{19}N_3O_4$) C, H, N.

(*S*)-[[2-Oxo-3-[(phenylacetyl)amino]-1-azetidinyl]imino]acetic Acid (9). A mixture of the benzyl ester **7** (150 mg) and 5% palladium on carbon in 10 mL of THF was hydrogenated at atmospheric pressure for 3 h. The flask was flushed with nitrogen, ethanol (10 mL), methanol (5 mL), and water (5 mL) were added, and the solution was then filtered. The filtrate was evaporated to dryness, and the resulting solid was recrystallized from methylene chloride/methanol to give 71 mg (63%): mp 200.5–202.5 °C dec; IR (KBr) 1795 cm^{-1} (β-lactam C=O); ^1H NMR (DMSO-d_6) δ 3.47 (s, 2 H, $PhCH_2$), 3.60 (dd, 1 H, J = 3.1 and 6.8, $H_{4\beta}$), 3.94 (dd, 1 H, J = 6.8 and 6.4, H_{4d}), 4.85 (m, 1 H, H_{3d}), 7.11 (s, 1 H, N=CH), 7.20–7.34 (m, 5 H, aromatic protons), 8.82 (d, 1 H, J = 7.6, NH). Anal. ($C_{13}H_{13}N_3O_4$) C, H, N.

***N*-[3-[(Phenylacetyl)amino]-2-oxo-1-azetidinyl]glycine (8).** A mixture of the benzyl ester **7** (100 mg) and 10% palladium on carbon (58 mg) in 10 mL of ethanol and 10 mL of methanol was hydrogenated in a Parr apparatus at 20 lb/in.^{2} for 6 h. The reaction mixture was filtered and evaporated to give a solid: yield 60 mg (80%); IR (KBr) 1760 cm^{-1} (β-lactam C=O); ^1H NMR (DMSO-d_6 + TFA) δ 3.30 (m, 1 H, $H_{4\beta}$), 3.45 (s, 2 H, $PhCH_2$) 3.55 (s, 2 H, $NHCH_2$), 3.60 (m, 1 H, H_{4a}), 4.65 (m, 1 H, H_{3a}), 7.28 (s, 5 H, aromatic protons).

Benzyl (*S*)-[[3-[[(2-Amino-4-thiazolyl)-(*Z*)-(methoxyimino)acetyl]amino]-2-oxo-1-azetidinyl]imino]acetate (11a). A mixture of 2-(2-amino-4-thiazolyl)-2(*Z*)-(methoxyimino)acetic acid (788 mg, 3.92 mmol), dicyclohexylcarbodiimide (807 mg, 3.92 mmol), and 1-hydroxybenzotriazole (600 mg, 3.92 mmol) in DMF (12 mL) was stirred at room temperature for 10 min. To this was added a solution of the trifluoroacetate salt **4a** (1.416 g, 3.92 mmol) and triethylamine (0.55 mL, 3.92 mmol) in 10 mL of DMF, and the mixture was stirred at room temperature overnight and then filtered. The filtrate was diluted with water (150 mL), and the resulting solid was filtered, dried, and recrystallized from ethyl acetate/ethanol to afford 862 mg (51%) of the desired compound: mp 204–207 °C dec; IR (KBr) 1780 cm^{-1} (β-lactam C=O) 1725 cm^{-1} (ester C=O); ^1H NMR (DMSO-d_6) δ 3.60 (dd, 1 H, J = 3.0 and 6.7, $H_{4\beta}$), 3.84 (s, 3 H, CH_3O), 4.04 (dd, 1 H, J = 6.5 and 6.45, H_{4a}) 5.02 (m, 1 H, H_{2a}) 5.28 (s, 2 H, CH_2O), 6.73 (s, 1 H, thiazole H), 7.22 (s, 2 H, NH_2), 7.29 (S, 1 H, N=CH), 7.55 (m, 5 H, aromatic protons), 9.28 (d, 1 H, J = 7.69, NH). Anal. ($C_{18}H_{18}N_6O_5S$) C, H, N.

[[3-(*S*)-[[(2-Amino-4-thiazolyl)-(*Z*)-(methoxyimino)-acetyl]amino]-2(*S*)-methyl-4-oxo-1-azetidinyl]imino]acetic Acid (12b). A mixture of 2-(2-amino-4-thiazolyl)-(*Z*)-2-(methoxyimino)acetic acid (687 mg, 3.42 mmol), dicyclohexylcarbodiimide (705 mg, 3.42 mmol), and 1-hydroxybenzotriazole (523 mg, 3.42 mmol) in DMF (18 mL) was stirred at room temperature for 20 min. To this was added a mixture of [[3-(*S*)-amino-2(*S*)-methyl-4-oxo-1-azetidinyl]imino]acetic acid trifluoroacetate (**6b**) (830 mg, 3.42 mmol), chlorotrimethylsilane (1.30 mL, 7.70 mmol), and triethylamine (1.07 mL, 7.70 mmol) in DMF (15 mL). The resulting mixture was stirred at room temperature overnight and then filtered. The filtrate was diluted with 100 mL of water and extracted with two 50-mL portions of ethyl acetate.

The aqueous extract was stirred for several hours with 50 mL of granular carbon and decanted, and the carbon was washed several times with water and then stirred for several hours with 50% aqueous acetone (pH 3). The mixture was filtered, and the filtrate was evaporated to dryness at reduced pressure. The residue was dissolved in a small amount of DMSO and precipitated by the addition of ether to give the desired product: IR (KBr) 1775 cm^{-1} (β-lactam C=O); ^1H NMR (DMSO-d_6 + TFA) δ 1.50 (d, 3 H), 4.05 (s, 3 H), 4.35 (m, 1 H), 4.65 (d, 1 H), 7.18 (s, 1 H), 7.50 (s, 1 H).

Allyl (*S*)-[[3-[(*tert*-Butoxycarbonyl)amino]-2-oxo-1-azetidinyl]imino]acetate (3c). A solution of 3(*S*)-[(*tert*-butoxycarbonyl)amino]-2-oxo-1-aminoazetidine (**2a**) (3.74 g, 18.6 mmol) and allyl glyoxylate (2.38 g, 18.6 mmol) in 125 mL of toluene was refluxed for 1 h with a water separator. The solution was then evaporated to dryness, and the residue was dissolved in methylene chloride, filtered through Magnesol, and again evaporated at reduced pressure to afford a yellow glass: yield 3.30 g (60%); M^+ (FAB) 297; IR (mull) 1795 cm^{-1} (β-lactam C=O), 1720 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) δ 1.45 [s, 9 H, $(CH_3)_3C$], 3.77 (dd, 1 H, J = 3.1 and 6.8, $H_{4\beta}$), 4.02 (dd, 1 H, J = 6.8 and 6.4, H_{4a}), 4.77 (d, 2 H, J = 5 and 9, OCH_2), 4.80 (m, 1 H, H_{3a}), 5.20 (d, 1 H, NH), 5.30 (d, 1 H, J = 10, allyl cis H), 5.38 (d, 1 H, J = 15.8, allyl trans H), 5.96 (m, 1 H, CH_2CH=), 7.44 (s, 1 H, N=CH).

Allyl (*S*)-[(3-Amino-2-oxo-1-azetidinyl)imino]acetate Trifluoroacetate (4c). A solution of allyl (*S*)-[[3-[(*tert*-butoxycarbonyl)amino]-2-oxo-1-azetidinyl]imino]acetate (**3c**) (2.97 g, 9.76 mmol) in 40 mL of trifluoroacetic acid was stored at room temperature for 1.0 h and then evaporated to dryness at reduced pressure (35 °C). The resulting oil was triturated to a solid with ether to afford 2.01 g (67%) of the desired salt: IR (KBr) 1775 cm^{-1} (β-lactam C=O); ^1H NMR (DMSO-d_6) δ 3.72 (dd, 1 H, J = 3.1 and 6.8, $H_{4\beta}$), 4.07 (dd, 1 H, J = 6.8 and 6.0, H_{4a}), 4.66 (dd, 1 H, J = 2.8 and 6.0), 4.75 (d, 2 H, J = 5.5, OCH_2), 5.28 (d, 1 H, J = 10, allyl cis H), 5.37 (d, 1 H, J = 16.8, allyl trans H), 5.98 (m, 1 H, CH_2CH=), 7.40 (s, 1 H, N=CH), 8.90 (br s, 3 H, $^+NH_3$). Anal. ($C_8H_{11}N_3O_3 \cdot CF_3COOH$) C, H, N, F.

Allyl (*S*)-[[3-[[(2-Amino-4-thiazolyl)-(*Z*)-2-(methoxyimino)acetyl]amino]-2-oxo-1-azetidinyl]amino]acetate (11c). A mixture of 2-(2-amino-4-thiazolyl)-(*Z*)-2-(methoxyimino)acetic acid (2.0 g, 10 mmol), dicyclohexylcarbodiimide (2.06 g, 10 mmol), and 1-hydroxybenzotriazole (1.53 g, 10 mmol) in DMF (50 mL) was stirred at room temperature for 20 min. To this was added a mixture of allyl (*S*)-[(3-amino-2-oxo-1-azetidinyl)imino]acetate trifluoroacetate (**4c**) (3.12 g, 10 mmol) and triethylamine (2.08 mL, 15 mmol) in DMF (25 mL). The resulting mixture was stirred at room temperature overnight and then filtered. The filtrate was evaporated at reduced pressure (40 °C) to remove the DMF, and the residue was chromatographed on silica gel with ethyl acetate as the eluent to afford 1.56 g (41%) of product: IR (KBr) 1777 cm^{-1} (β-lactam C=O) 1719 cm^{-1} (ester C=O); ^1H NMR (DMSO-d_6) δ 3.68 (dd, 1 H, J = 3.1 and 6.8, $H_{4\beta}$), 3.85 (s, 3 H, CH_3), 4.06 (dd, 1 H, J = 6.8 and 6.4, H_{4a}), 4.74 (d, 2 H, J = 5.5, OCH_2); 5.01 (m, 1 H, H_{3a}), 5.28 (d, 1 H, J = 10), allyl cis H), 5.38 (d, 1 H, J = 16.2, allyl trans H), 5.98 (m, 1 H, $CHCH$=), 6.74 (s, 1 H, thiazole H), 7.24 (s, 2 H, NH_2), 7.28 (s, 1 H, N=C*H*), 9.31 (s, 1 H, N*H*). Anal. ($C_{14}H_{16}N_6O_5S$) C, H, N, S.

Potassium (*S*)-[[3-[[(2-Amino-4-thiazolyl)-(*Z*)-(methoxyimino)acetyl]amino]-2-oxo-1-azetidinyl]imino]acetate (12a). A mixture of allyl (*S*)-[[3-[[2-(2-amino-4-thiazolyl)-(*Z*)-2-(methoxyimino)acetyl]amino]-2-oxo-1-azetidinyl]imino]acetate (**11c**) (180 mg, 0.47 mmol), tetrakis(triphenylphosphine)palladium(0) (38 mg), triphenylphosphine (27 mg), and 1.0 mL of 0.5 M potassium 2-ethylhexanoate solution (in ethyl acetate) in 10 mL of methylene chloride and 5 mL of ethyl acetate was stirred at room temperature (nitrogen atmosphere) for 40 min. The reaction mixture was diluted with ether (20 mL), and the resulting solid was collected by filtration. The solid was dissolved in a small volume of water, treated with decolorizing carbon, filtered, and lyophilized to afford 38 mg of product: IR (KBr) 1764 cm^{-1} (β-lactam C=O); ^1H NMR (DMSO-d_6) δ 3.84 (s, 3 H, CH_3O), 3.85 (m, 2 H, H_{4a} and $H_{4\beta}$), 4.92 (m, 1 H, H_{3a}), 6.75 (s, 1 H, thiazole H), 7.00 (s, 1 H, C*H*=N), 7.22 (s, 2 H, NH_2), 9.22 (d, 1 H, J = 7.5, NH).

(*S*)-*N*-[3-[(*tert*-Butoxycarbonyl)amino]-2-oxo-1-azetidinyl]glycine (13). A solution of the benzyl ester derivative **3a** (3.0 g, 8.64 mmol) in ethanol (150 mL) was hydrogenated in a Parr apparatus in the presence of 10% palladium on carbon (1.00 g) for 18 h. The mixture was filtered, and the filtrate was evaporated to a white foam: 2.15 g (96%): IR (KBr) 1760 cm^{-1} (β-lactam C=O); ^1H NMR ($CDCl_3$) δ 1.43 [s, 9 H, $(CH_3)_3C$], 3.42 (m, 1 H, $H_{4\beta}$), 3.65 (s, 2 H, CH_2COOH), 3.76 (m, 1 H, H_{4a}), 4.66 (m, 1 H, H_{3a}). Anal. ($C_{10}H_{13}N_3O_5$) C, H, N.

Allyl (*S*)-[3-[(*tert*-Butoxycarbonyl)amino]-2-oxo-1-azetidinyl]glycinate (14). A solution of allyl bromide (1.04 mL, 10.2 mmol) in 25 mL of DMF was added dropwise to a solution of *N*-[3-[(*tert*-(butoxycarbonyl)amino]-2-oxo-1-azetidinyl]glycine (**13**) (2.39 g, 9.23 mmol) and triethylamine (1.70 mL, 10.2 mmol) in 25 mL of DMF over 30 min. The reaction mixture was stirred at room temperature overnight and then the DMF was evaporated at reduced pressure (32 °C). The residue was dissolved in 50 mL of ethyl acetate and extracted with cold solution of water, saturated sodium hydroxide, and brine. The solution was dried over magnesium sulfate and evaporated to a colorless oil, yield 1.45 g (53%). Thin-layer chromatography and spectral data showed this material was pure. For analytical data a portion was crystallized from ethyl acetate/hexane: mp 95–97 °C; IR (KBr) 1775 cm^{-1} (β-lactam C=O) and 1742 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) δ 1.44 [s, 9 H, $(CH_3)_3C$], 3.42 (dd, 1 H, J = 2.4 and 5.3, $H_{4\beta}$), 3.73 (m, 3 H, CH_2O and H_{4a}), 4.48 (dd, J = 5.2 and 10.6, H_{4a}), 4.65 (d, 2 H, J = 6.0, OCH_2CH=), 5.26 (dd, J = 11.0 and 1.3, allyl cis H), 5.30 (dd, 1 H, J = 16 and 1.4, allyl trans H), 5.92 (m, 1 H, C*H*=C). Anal. ($C_{13}H_{21}N_3O_5$) C, H, N.

Allyl (*S*)-*N*-(3-Amino-2-oxo-1-azetidinyl)glycinate Trifluoroacetate (15). A solution of the *tert*-butoxycarbonyl derivative **14** (667 mg, 2.23 mmol) in 10 mL of trifluoroacetic acid was allowed to stand at room temperature for 1 h and then evaporated at reduced pressure (30 °C). The residue was stirred in chloroform and again evaporated several times. Trituration with ether gave a white solid, yield 670 mg (96%). Anal. ($C_8H_{13}N_3O_3 \cdot CF_3COOH$) C, H, N, F.

Allyl (*S*)-*N*-[3-[[(2-Amino-4-thiazolyl)-(*Z*)-(methoxyimino)acetyl]amino]-2-oxo-1-azetidinyl]glycinate (16). A mixture of 2-(2-amino-4-thiazolyl)-2(*Z*)-(methoxyimino)acetic acid (385 mg, 1.92 mmol), dicyclohexylcarbodiimide (395 mg, 1.92 mmol), and 1-hydroxybenzotriazole (294 mg, 1.92 mmol) in 20 mL of DMF was stirred at room temperature for 0.5 h. To this was added a solution of compound **15** (600 mg, 1.92 mmol) and triethylamine (0.53 mL, 3.84 mmol) in 20 mL of DMF. The reaction mixture was stirred at room temperature overnight and filtered and most of the DMF evaporated at reduced pressure (40 °C). The residue was stirred in cold water (25 mL) and filtered. The filtrate was chilled overnight, and the resulting white crystalline product was collected by filtration and dried to give 400 mg (56%) of the desired product: IR (KBr) 1744 cm^{-1} (β-lactam C=O) and 1723 cm^{-1} (ester C=O); ^1H NMR (DMSO-d_6 + TFA) δ 2.53 (m, 2 H, CH_2C=O), 3.37 (dd, 1 H, J = 2.3 and 5.0, $H_{4\beta}$), 3.69 (m, 1 H, H_{4a}), 4.00 (5.3 H, CH_3O), 4.62 (d, 2 H, J = 5.5, OCH_2CH), 4.76 (dd, 1 H, J = 2.6 and 5.31, H_{3a}), 5.23 (dd, 1 H, J = 1.4 and 10.6, allyl cis H), 5.35 (dd, 1 H, J = 1.5 and 16.3, allyl trans H), 5.94 (m, 1 H, $CHCH$=), 7.00 (s, 1 H, thiazole H). Anal. ($C_{14}H_{18}N_6O_5S$) C, H, N, S.

Potassium (*S*)-*N*-[3-[[(2-Amino-4-thiazolyl)-(*Z*)-(methoxyimino)acetyl]amino]-2-oxo-1-azetidinyl]glycinate (17). A mixture of the allyl ester **16** (271 mg, 0.70 mmol), tetrakis(triphenylphosphine)palladium(0) (50 mg), triphenylphosphine (50 mg), and 2 mL of a 0.5 M potassium 2-ethylhexanoate solution (in ethyl acetate) in 8 mL of DMF and 4 mL of THF was stirred at room temperature overnight (nitrogen atmosphere). Ether (25 mL) was added, and the solid was collected by filtration: yield 183 mg; IR (KBr) 1758 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.50 (m, 2 H, CH_2C=O), 3.25 (m, 1 H, $H_{4\beta}$), 3.58 (m, 1 H, H_{4a}), 3.82 (s, 3 H, CH_3O), 4.68 (m, H, H_{3a}), 6.71 (s, 1 H, thiazole H), 7.26 (ns, 2 H, NH_2), 9.14 (d, 1 H, N*H*).

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Registry No. **2a**, 121142-63-0; **2b**, 121142-81-2; **3a**, 121142-64-1; **3b**, 121142-82-3; **3c**, 121142-83-4; **4a**·TFA, 121142-66-3; **4c**·TFA, 121157-67-3; **5a**, 121142-67-4; **5b**, 121142-84-5; **6b**·TFA, 121142-69-6; **7** (R′ = CH_2Ph), 121142-70-9; **8**, 121142-71-0; **9**, 121142-72-1; **10**, 65872-41-5; **11a**, 121142-73-2; **11c**, 121142-85-6; **12a** (free acid), 121142-87-8; **12a**·K, 121142-74-3; **12b**, 121142-86-7; **13**, 121142-75-4; **14**, 121142-76-5; **15**·TFA, 121142-78-7; **16**, 121142-79-8; **17** (free acid), 121142-88-9; **17**·K, 121142-80-1; $OHCCOOCH_2Ph$, 52709-42-9; $PhCH_2COCl$, 103-80-0; $BrCH_2CH$=CH_2, 106-95-6; $OHCCOOCH_2CH$=CH_2, 64370-42-9.