[Chem. Pharm. Bull. 35(10)3985—3994(1987)]

Enantioselective Synthesis of Monocyclic β-Lactams Related to Nocardicins *via* a [2+2] Cycloaddition Reaction

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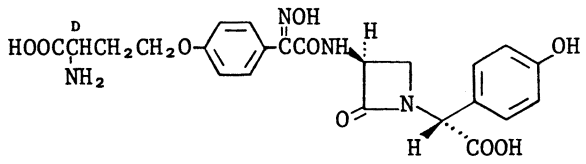
(Received December 24, 1986)

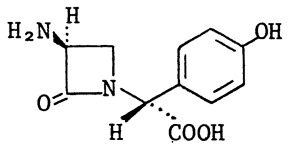
Monocyclic β-lactams related to nocardicins were enantioselectively synthesized from phthalimidoacetyl chloride and hexahydro-1,3,5-triazines (**4**) *via* a [2+2] cycloaddition reaction. The preparation and biological activity of some typical acyl derivatives are also described.

Keywords——stereochemistry; ketene–imine cycloaddition; 3-aminonocardicinic acid; nocardicin; antibacterial activity; structure–activity relationship

Nocardicins, represented by nocardicin A (**1**), are a group of naturally occurring monocyclic β-lactam antibiotics. They show chemical and biological parallels to penicillins and cephalosporins[1,2] in respect of having (*R*)-carboxyl and (*S*)-acylamino groups and being inhibitors of bacteria cell-wall biosynthesis. In the preceding paper, we reported the preparation of 3-aminonocardicinic acid (3-ANA, **2**), the basic framework of this group of antibiotics, and the synthesis of some semisynthetic nocardicins by acylation of 3-ANA.[3] As a continuation of this series of investigations, we subsequently focused on modifications of the *p*-hydroxyphenyl group in the 3-ANA structure. In a previous communication,[4] we reported a versatile synthetic method for 3-ANA. Herein we present a full account of the work and an application to the synthesis of other analogous compounds.



1



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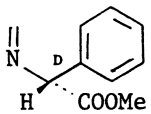

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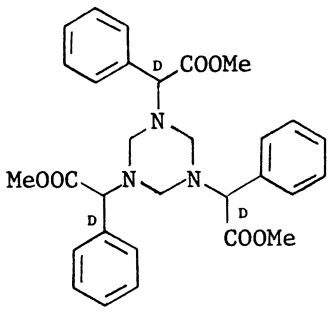
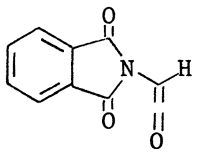


4a



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Our synthesis of β-lactams of the nocardicin type can be conceptually classified as a [2+2] cycloaddition reaction between ketenes and imines,[5] which is the best known procedure in β-lactam synthesis. The synthesis of nocardicins by this cycloaddition approach requires preparation of the appropriate formaldimine precursors (*e.g.*, **3**), which usually exist as trimers, hexahydro-*s*-triazines (*e.g.*, **4a**).[6] We conjectured that the monomeric precursors might be regenerated *in situ* by treatment of the trimers with a Lewis acid and, on reaction with ketenes, could afford the corresponding β-lactams. Thus, hexahydro-*s*-triazine **4a**, prepared from methyl phenylglycinate by the known procedure,[7] was treated with $BF_3 \cdot OEt_2$ in CH_2Cl_2 at room temperature and the mixture was added to a cooled (−78 °C) solution of phthalimidoacetyl chloride and pyridine in CH_2Cl_2. The temperature was then raised to 0 °C. The reaction seemed to proceed at temperatures near 0 °C. The usual work-up gave, after a short silica gel column chromatography, a 3 : 1 mixture of β-lactams **6** and **7** in good yield. A

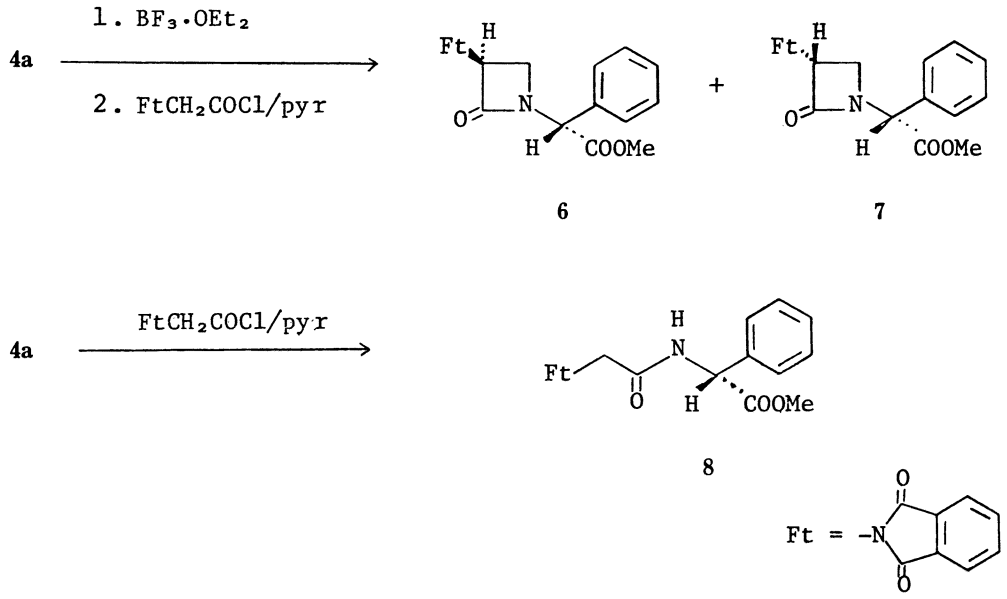


Chart 1

more careful chromatography yielded the major product **6** in 35% yield, while the minor product **7** was isolated from the mother liquor by high performance liquid chromatography (HPLC) in low yield.

The configurations of the phthalimido (Ft) groups in these products were assigned on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) spectral data in comparison with those of nocardicins. In the major product **6**, the 4β proton, which appeared at a higher field (δ 3.46) than the 4α proton (δ 3.94) in agreement with the data on nocardicins,[8] was *trans*-coupled (J = 3 Hz) to the 3α proton (δ 5.48). In the minor product **7**, on the other hand, the corresponding 4β proton, which also appeared at a higher field (δ 3.60) than the 4α proton (δ 4.10), was *cis*-coupled (J = 5 Hz) to the 3β proton (δ 5.34). The structures of these major and minor products were thus assigned as **6** and **7**, respectively.

The mechanism of the β-lactam formation in the above reaction can be explained as follows. In the presence of BF_3, the trimer **4a** might be transformed to some extent to the monomer **3**, as expected, while phthalimidoacetyl chloride might be converted to the ketene **5** in the presence of pyridine. The ketene **5** would undergo cycloaddition to the imine **3** to give the β-lactams **6** and **7**. The requirement for BF_3 in this reaction was shown by the following

observation. When the trimer **4a** was directly reacted with phthalimidoacetyl chloride–pyridine in the absence of $BF_3 \cdot OEt_2$, only the acyl derivative **8** of methyl phenylglycinate was obtained. The enantioselectivity in the above reaction would be governed by the substituents of both reactants. It is thought that the cycloaddition reaction of ketenes and imines proceeds *via* a HOMO (ketenophile)/LUMO (ketene) interaction. In our case, overlap between the π-orbitals of the formaldimine **3** and those of the phthaliminoketene **5** might be as shown in Chart 2. The phenylglycyl moiety of **3** would be situated so as to be away from the oxygen of **5**

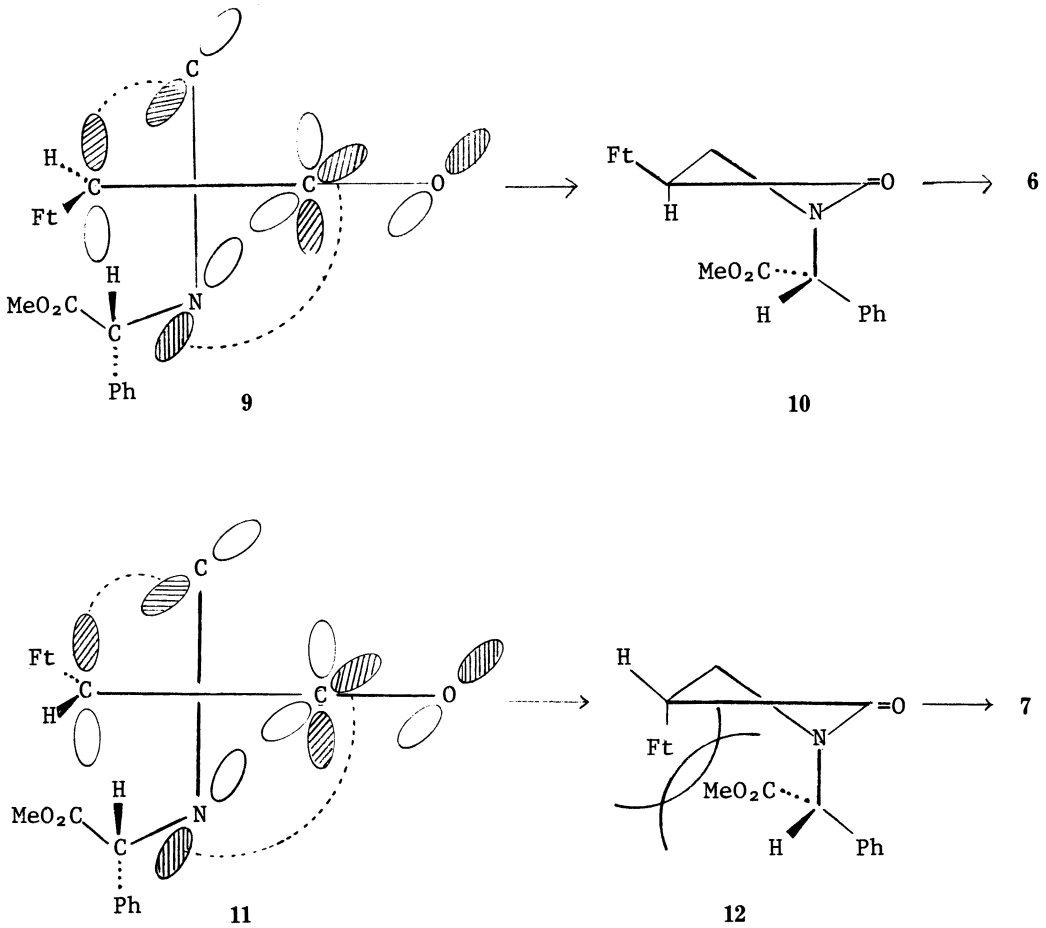


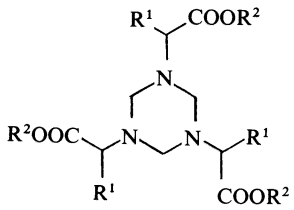
Chart 2

due to their steric (or electronic) repulsion and, further, the phenyl (Ph) group of the phenylglycyl moiety would be oriented apart from the Ft group of **5**. When **5** develops an overlap to **3** as shown in **9**, the Ft group is allowed to take an *exo* configuration in the intermediate **10**. On the other hand, overlap of **5** to **3** as shown in **11** compels the Ft group to adopt an *endo* configuration in the intermediate **12**. It is therefore clear that, on comparison of **10** and **12**, the steric interaction of the Ft group and the phenylglycyl moiety is less in **10** than **12**. The major product **6** would thus be favorably formed *via* the intermediate **10**.

In order to ascertain the stereochemical outcome in the above reaction, we examined the reaction using other ketenes and ketenophiles under the same conditions as those used for the above reaction. The results are summarized in Tables I and II. When azidoacetyl chloride was

used in place of phthalimidoacetyl chloride and allowed to react with **4a** (entry **2**), the β-lactams **13a** and **14a** were obtained in a ratio of 3:2. The poorer stereoselectivity in this reaction is ascribed to the smaller bulk of the azido group as compared with the Ft group. On the other hand, the trimer **4b** derived from α-naphthylglycine (having the naphthyl group, with a larger steric interaction than the Ph group), when reacted with phthalimidoacetyl chloride (entry **3**), gave a product with greater stereoselectivity (10:1 of **13b** and **14b**). These results support the above mechanistic considerations. The reactions of phthalimidoacetyl chloride

TABLE I. Structures of **4**, **13** and **14**



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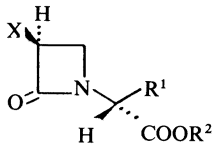
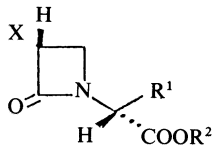


13



14

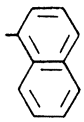
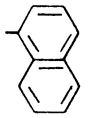
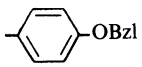
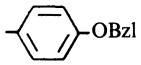
4	R^1	R^2	**13, 14**	R^1	R^2	X
4b		Me	**13a**, **14a**		Me	N_3
4c		Me	**13b**, **14b**		Me	Ft
4d		Me	**13c**, **14c**		Me	Ft
4e		Me	**13d**, **14d**		Me	Ft
4f	H	Bzl	**13e**, **14e**		Me	Ft
			13f, **14f**	H	Bzl	Ft

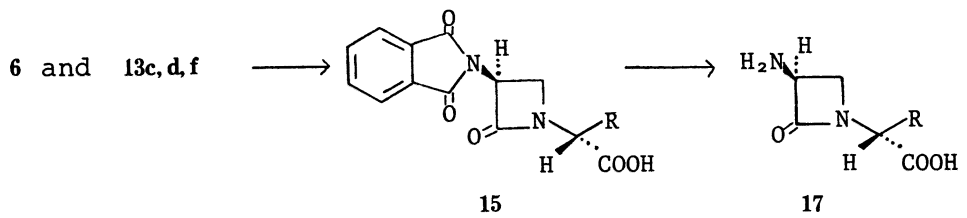
TABLE II. Product Yields and Ratios (See Text)

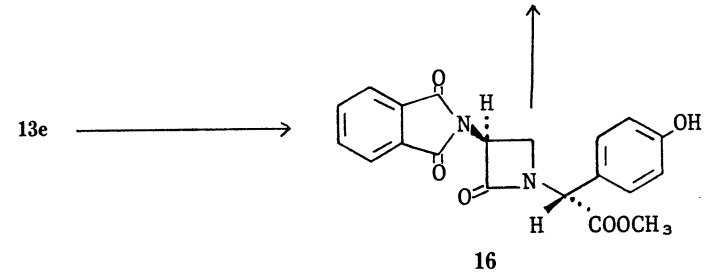
Entry	Compounds	Total yield (%) of **6** (**13**) and **7** (**14**)	Ratio of **6** (**13**) and **7** (**14**)[a]
1	**6** and **7**	80	3:1
2	**13a** and **14a**	42	3:2
3	**13b** and **14b**	51	10:1
4	**13c** and **14c**	65	7:2
5	**13d** and **14d**	39	4:1
6	**13e** and **14e**	87	3:1
7	**13f** and **14f**	35	—

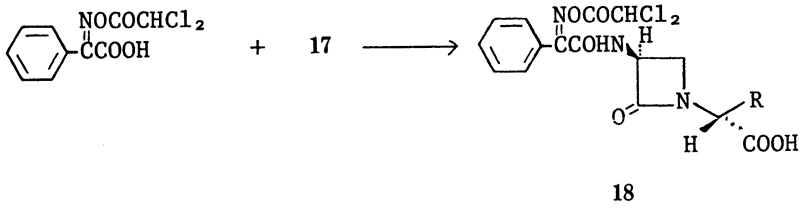
a) The ratios of **6** (**13**) and **7** (**14**) were calculated by measuring the integration values of their methyl signals in the ^{1}H-NMR spectrum.

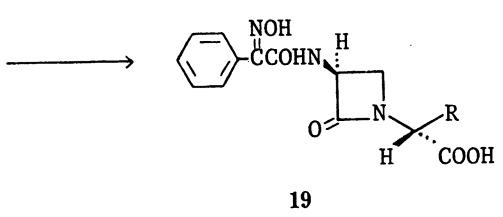
with the trimers **4c**—**e**, derived from 2-thienylglycine, 2-furylglycine, and (*p*-hydroxyphenyl)glycine having a similar steric bulk to phenylglycine, gave products with practically the same stereoselectivity as in the case of **4a** (entries **4**, **5**, and **6**).

With these results in hand, we turned to removal of the protecting groups in the *β*-







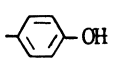


A : R = 

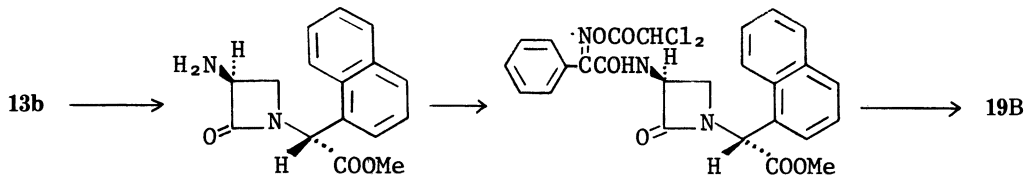
B : R =  *(dl)*

C : R = 

D : R =  *(dl)*

E : R = 

lactams **6** and **13** and acylation of the resulting amino acids **17**. According to the procedures reported in our previous report,[8] **6** was first subjected to demethylation using LiI in pyridine[9] to give the corresponding acid **15A**, which was then treated with dimethylaminopropylamine in MeOH to yield the amino acid **17A**. Similarly, **13c** and **13d** were converted to **17C** and **17D**, respectively. Conversion of **13e** *via* **15E** to 3-ANA (**17E**) was reported previously. Acylation of the resulting amino acids **17A**, C, D and E with 2-phenyl-2-(2,2-dichloroacetoxyimino) acetic acid by the acid chloride procedure using PCl_5, followed by removal of the dichloroacetyl protecting group in the products **18A**, C, D and E, provided the compounds **19A**, C, D and E. The derivative **19B** was prepared *via* an alternative route. Thus, the Ft group of **13b** (*dl*-mixture) was first removed in a similar manner and the resulting amine **20** was acylated to give **21**. Deprotection of **21** by hydrolysis with NaOH gave the derivative **19B** as a *dl*-mixture.



20 **21**

Chart 3

Antibacterial activity of **19A**, B, C, D, and E was examined by the agar dilution method and the results are summarized in Table III. All the derivatives except the naphthyl compound **19B** were active against both gram-negative and -positive bacteria. It is noteworthy that **19A** and **19C** were more active than the parent *p*-hydroxyphenyl compound **19E** against *Escherichia coli* and *Staphylococcus aureus*. The thienyl compound **19C** was the most active against all the bacteria except *Proteus vulgaris*.

TABLE III. Minimum Inhibitory Concentrations of Nocardicins[a]

Compounds	Organism					
	Pseudomonas aeruginosa 10490	*Escherichia coli* NIHJ, JC-2	*Escherichia coli* 114[b]	*Proteus vulgaris*	*Staphylococcus aureus*	*Bacillus subtilis*
19A	1.25	2.5	0.3	5	0.075	0.6
19B	>10	>10	>10	>10	0.6	>10
19C	0.15	2.5	0.15	>10	0.0375	0.15
19D	2.5	10	1.25	>10	0.6	1.25
19E	0.6	10	0.6	2.5	0.6	2.5

a) Agar dilution method (mg/ml). *b*) A mutant strain of *E. coli* NIHJ: sensitive to β-lactam antibiotics.

Experimental

Melting points were measured on a Thomas–Hoover apparatus and are uncorrected. Infrared (IR) and ^{1}H-NMR spectra were recorded using a Hitachi 260-10 spectrophotometer and a JEOL·Ps-100 spectrometer, respectively. Optical rotations were measured on a JASCO automatic polarimeter.

Minimum inhibitory concentrations (MIC's) of the nocardicin analogues were determined by the agar dilution method. One loopful of an overnight culture of each test organism in Trypticase broth (about 10^8 viable cells/ml) was

streaked on heart infusion agar containing graded concentrations of drugs and incubated at 37 °C for 8 h.

Trimethyl [αR,α'R,α''R]-α,α',α''-Triphenylhexahydro-1,3,5-triazine-1,3,5-triacetate (4a)——Methyl D-phenylglycinate hydrochloride (24.2 g) was dissolved in H_2O (100 ml) and benzene (250 ml) was added. To this mixture, 1 N NaOH (120 ml) was added dropwise under ice-cooling and then a 37% aqueous solution of formaldehyde (9.9 ml) was added. The mixture was stirred for 2 h at the same temperature and the organic layer was separated, washed with H_2O, and dried over $MgSO_4$. The solvent was evaporated off to give a residue, which was crystallized from diisopropyl ether to give **4a** as white needles (18.5 g, 86.5%): mp 148—155 °C. IR (Nujol): 1730 cm^{-1} (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.49 (9H, s, $COOCH_3$), 3.51 (6H, s, NCH_2N), 4.50 (3H, s, ArCHCOO), 6.90—7.42 (15H, m, ArH). *Anal.* Calcd for $C_{30}H_{33}N_3O_6$: C, 67.78; H, 6.23; N, 7.91. Found: C, 67.99; H, 6.10; N, 7.83.

The following compounds were prepared by reacting the corresponding amine derivatives with formaldehyde in substantially the same manner as described above.

Trimethyl α,α',α''-Tri(1-naphthyl)hexahydro-1,3,5-triazine-1,3,5-triacetate (**4b**): Yield 96.5%, oil. MS *m/z* 681 (M^+). IR (film): 1735 (ester C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.28 (9H, s, $COOCH_3$), 3.82 (6H, s, NCH_2N), 5.16 (3H, s, ArCHCOO), 7.03—7.83 (21H, m, ArH).

Trimethyl [αR,α'R,α''R]-α,α',α''-Tri(2-thienyl)hexahydro-1,3,5-triazine-1,3,5-triacetate (**4c**): Yield 92.9%, mp 131—134 °C. IR (Nujol): 1739 (ester C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.69 (9H, s, $COOCH_3$), 3.78 (6H, s, NCH_2N), 4.89 (3H, s, ArCHCOO), 6.80—7.43 (9H, m, ArH). *Anal.* Calcd for $C_{24}H_{27}N_3O_6S_3$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.11; H, 4.92; N, 7.57.

Trimethyl α,α',α''-Tri(2-furyl)hexahydro-1,3,5-triazine-1,3,5-triacetate (**4d**): Yield 83.5%, oil. MS *m/z* 501 (M^+). IR (film): 1740 (ester C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.50—3.80 (15H, m, $COOCH_3$ and NCH_2N overlapping), 7.32 (9H, m, ArH).

Trimethyl [αR,α'R,α''R]-α,α',α''-Tri(4-benzyloxyphenyl)hexahydro-1,3,5-triazine-1,3,5-triacetate (**4e**): Yield 58.0%, mp 141—145 °C. IR (Nujol): 1725 (ester C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.58 (15H, s, $COOCH_3$ and NCH_2N overlapping), 4.50 (3H, s, ArCHCOO), 5.04 (6H, s, CH_2Ph), 6.80 (6H, d, *J*=9 Hz, ArH), 7.29 (6H, d, *J*=9 Hz, ArH), 7.40 (15H, s, ArH). *Anal.* Calcd for $C_{51}H_{51}N_3O_9$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.83; H, 5.96; N, 4.98.

Tribenzyl Hexahydro-1,3,5-triazine-1,3,5-triacetate (**4f**): Yield 39.5%, oil. MS *m/z* 531 (M^+). IR (film): 1740 (ester C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.44 (6H, s, NCH_2COO), 3.69 (6H, s, NCH_2N), 5.10 (6H, s, CH_2Ph), 7.40 (15H, s, ArH).

Methyl (3S,αR)-2-(2-Oxo-3-phthalimido-1-azetidinyl)-2-phenylacetate (6)——A solution of pyridine (0.96 g) in CH_2Cl_2 (4 ml) was added to a solution of phthalimidoacetyl chloride (2.68 g) in CH_2Cl_2 (40 ml) over 6 min at −30—−35 °C. After 15 min of stirring, the mixture was cooled to −78 °C and a mixture of triazine (**4a**, 1.06 g), $BF_3 \cdot OEt_2$ (0.86 g) and CH_2Cl_2 (20 ml) was added over 20 min. The whole was stirred for 2 h at the same temperature and for 1 h at 0 °C and then washed successively with H_2O, 5% HCl, 5% $NaHCO_3$, and H_2O. Drying over $MgSO_4$ and evaporation gave an oil (3:1 mixture of **6** and **7**, 3.50 g, 80.3%). These two isomers were separated by column chromatography on silica gel with $CHCl_3$. The fractions containing the major compound **6** were collected and evaporated to give an oily residue, which was crystallized from a mixture of EtOH and Et_2O to give colorless needles (**6**, 35.2%): mp 133—134 °C. $[\alpha]_D^{25}$ −253° (*c*=0.98, $CHCl_3$). IR (Nujol): 1775, 1755, 1735 (β-lactam C=O), 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.46 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.77 (3H, s, $COOCH_3$), 3.94 (1H, t, *J*=5 Hz, 4α-H), 5.48 (1H, dd, *J*=3, 5 Hz, 3α-H), 5.78 (1H, s, ArCHCOO), 7.38 (5H, s, ArH), 7.57—7.96 (4H, m, ArH). *Anal.* Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 66.11; H, 4.32; N, 7.72. The fractions containing the minor product were combined and evaporated to give a crude oil, which was further purified by HPLC using Reporasol to give **7** as crystals (47.0 mg): mp 96—98 °C. $[\alpha]_D^{25}$ 20° (*c*=0.08, MeOH). IR (Nujol): 1775—1760, 1735 (β-lactam C=O), 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (1H, t, *J*=5 Hz, 4β-H), 3.84 (3H, s, $COOCH_3$) 4.10 (1H, dd, *J*=3, 5 Hz, 4α-H), 5.34 (1H, dd, *J*=3, 5 Hz, 3β-H), 5.72 (1H, s, ArCHCOO), 7.36 (5H, s, ArH), 7.57—7.96 (4H, m, ArH). *Anal.* Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 66.01; H, 4.29; N, 7.69.

The following compounds were prepared by reacting the corresponding perhydro-1,3,5-triazines with acyl chlorides in substantially the same manner as described aobve.

Methyl (3R,αR)- and (3S,αR)-2-(3-Azido-2-oxo-1-azetidinyl)-2-phenylacetate (**13a**, **14a**): Yield 42.0%. Major product (**13a**, 13.4%): oil. MS *m/z* 232 (M^+ −28). IR (film): 2100 (N_3), 1765 (β-lactam C=O), 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.93 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.73 (3H, s, $COOCH_3$), 3.86 (1H, t, *J*=5 Hz, 4α-H), 4.63 (1H, dd, *J*=3, 5 Hz, 3α-H), 5.56 (1H, s, ArCHCOO), 7.28 (5H, s, ArH). Minor product (**14a**, trace): oil. MS *m/z* 232 (M^+ −28). IR (film): 2100 (N_3), 1760 (β-lactam C=O), 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.26—3.76 (2H, m, 4α, 4β-H overlapping), 3.80 (3H, s, $COOCH_3$), 4.50 (1H, dd, *J*=3, 5 Hz, 3β-H), 5.60 (1H, s, ArCHCOO), 7.33 (5H, s, ArH).

Methyl 2-(1-Naphthyl)-2-(2-oxo-3-phthalimido-1-azetidinyl)acetate (**13b**, **14b**): Yield 51.3%. Major product (**13b**, 43.3%): mp 192 °C. IR (Nujol): 1780, 1750, 1740 (β-lactam C=O), 1742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.16 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.80 (3H, s, $COOCH_3$), 3.89 (1H, t, *J*=5 Hz, 4α-H), 5.50 (1H, dd, *J*=3, 5 Hz, 3α-H), 6.45 (1H, s, ArCHCOO), 7.30—8.30 (7H, m, ArH). *Anal.* Calcd for $C_{24}H_{18}N_2O_5$: C, 69.56; H, 4.38; N, 6.76. Found: C, 69.84; H, 4.35; N, 6.68. The minor isomer was not isolated.

Methyl (3R,αS)- and (3S,αS)-2-(2-Oxo-3-phthalimido-1-azetidinyl)-2-(2-thienyl)acetate (**13c**, **14c**): Yield 65.2%.

Major product (**13c**, 32.1%): mp 167—170 °C. $[\alpha]_D^{25}$ −116° (c=0.38, $CHCl_3$). IR (Nujol): 1765, 1735 (β-lactam C=O), 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.62 (1H, dd, J=3, 5 Hz, 4β-H), 3.81 (3H, s, $COOCH_3$), 3.96 (1H, t, J=5 Hz, 4α-H), 5.52 (1H, dd, J=3, 5 Hz, 3α-H), 5.98 (1H, s, ArCHCOO), 6.90—7.42 (3H, m, ArH), 7.75 (4H, m, ArH). *Anal.* Calcd for $C_{18}H_{14}N_2O_5S$: C, 58.38; H, 3.81; N, 7.56. Found: C, 58.21; H, 3.99; N, 7.57. Minor product (**14c**, trace): mp 152—154.5 °C. $[\alpha]_D^{25}$ −10° (c=0.40, $CHCl_3$). IR (Nujol): 1770, 1735 (β-lactam C=O), 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.73 (1H, t, J=5 Hz, 4β-H), 3.88 (3H, s, $COOCH_3$), 4.09 (1H, dd, J=3, 5 Hz, 4α-H), 5.38 (1H, dd, J=3, 5 Hz, 3β-H), 5.98 (1H, s, ArCHCOO), 6.92—7.42 (3H, m, ArH), 7.78 (4H, m, ArH). *Anal.* Calcd for $C_{18}H_{14}N_2O_5S$: C, 58.38; H, 3.81; N, 7.56. Found: C, 58.27; H, 3.92; N, 7.44.

Methyl 2-(2-Furyl)-2-(2-oxo-3-phthalimido-1-azetidinyl)acetate (**13d**, **14d**): Yield 39.2%. Major product (**13d**, 17.5%): mp 176—178 °C. IR (Nujol): 1760, 1730 (β-lactam C=O), 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.64 (1H, dd, J=3, 5 Hz, 4β-H), 3.80 (3H, s, $COOCH_3$), 4.02 (1H, t, J=5 Hz, 4α-H), 5.52 (1H, dd, J=3, 5 Hz, 3α-H), 5.84 (1H, s, ArCHCOO), 6.64 (1H, m, ArH), 7.47 (1H, d, J=3 Hz, ArH), 7.77 (4H, m, ArH). *Anal.* Calcd for $C_{18}H_{14}N_2O_6$: C, 61.01; H, 3.98; N, 7.71. Found: C, 61.22; H, 3.91; N, 7.91. The minor isomer was not isolated.

Methyl (3*R*,α*R*)- and (3*S*,α*R*)-2-(2-Oxo-3-phthalimido-1-azetidinyl)-2-(4-benzyloxyphenyl)acetate (**13e**, **14e**): Yield 87.2%. Major product (**13e**, 40.4%): oil. MS m/z 470 (M^+). IR (film): 1780, 1760, 1740 (β-lactam C=O), 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.42 (1H, dd, J=3, 5 Hz, 4β-H), 3.78 (3H, s, $COOCH_3$), 3.90 (1H, t, J=5 Hz, 4α-H), 5.04 (2H, s, CH_2Ph), 5.46 (1H, dd, J=3, 5 Hz, 3α-H), 5.72 (1H, s, ArCHCOO), 7.00 (2H, d, J=9 Hz, ArH), 7.33 (2H, d, J=9 Hz, ArH), 7.37 (5H, s, ArH), 7.70 (4H, m, ArH). Minor product (**14e**, trace): oil. MS m/z 470 (M^+). IR (film): 1775, 1760, 1735 (β-lactam C=O), 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.66 (1H, t, J=5 Hz, 4β-H), 3.78 (3H, s, $COOCH_3$), 4.06 (1H, dd, J=3, 5 Hz, 4α-H), 4.97 (2H, s, CH_2Ph), 5.32 (1H, dd, J=3, 5 Hz, 3β-H), 5.65 (1H, s, ArCHCOO), 6.98 (2H, d, J=9 Hz, ArH), 7.35 (2H, d, J=9 Hz, ArH), 7.37 (5H, s, ArH), 7.70 (4H, m, ArH).

Benzyl 2-(2-Oxo-3-phthalimido-1-azetidinyl)acetate (13f)——A solution of pyridine (0.48 g) in CH_2Cl_2 (5 ml) was added to a solution of phthalimidoacetyl chloride (1.34 g) in CH_2Cl_2 (15 ml) over 10 min at −30°——35 °C.

A solution of tribenzyl 1,3,5-triazine-1,3,5(2*H*,4*H*,6*H*)-triacetate (**4f**, 0.531 g) and $BF_3 \cdot OEt_2$ (0.43 g) in CH_2Cl_2 (15 ml) was then added dropwise at −15 °C over 15 min, and the whole was stirred for 2 h at the same temperature and then for 1 h under ice-cooling. The reaction mixture was washed with 10% HCl, 5% $NaHCO_3$, and H_2O, dried over $MgSO_4$ and evaporated to give a residue (1.4 g), which was subjected to column chromatography on silica gel. Elution was carried out with $CHCl_3$ and the fractions containing the target compound were collected. The solvent was removed to give an oil, which was crystallized from Et_2O to give **13f** as colorless crystals (0.375 g, 35.4%): mp 129—135 °C (dec.). IR (Nujol): 1780, 1750, 1730 (β-lactam C=O), 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.81—3.94 (2H, m, 4α-H, 4β-H overlapping), 5.08 and 5.36 (2H, ABq, J=18 Hz, NCH_2COO), 5.19 (2H, s, $COOCH_2Ph$), 5.52 (1H, dd, J=3, 5 Hz, 3α-H), 7.68—7.92 (9H, m, ArH). *Anal.* Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.94; H, 4.34; N, 7.66

Reaction of Perhydro-1,3,5-triazine with Phthalimidoacetyl Chloride in the Absence of BF_3——A solution of pyridine (0.48 g) in CH_2Cl_2 (2 ml) was added to a solution of phthalimidoacetyl chloride (1.34 g) in CH_2Cl_2 (20 ml) over 5 min at −30——35 °C. After 15 min, the mixture was cooled to −78 °C and a solution of the triazine (**4a**, 0.50 g) in CH_2Cl_2 (10 ml) was added over 20 min. The mixture was stirred for 2 h at the same temperature and for 1 h at 0 °C. After removal of the solvent, the residue was dissolved in AcOEt and this solution was washed with H_2O, 5% HCl, and 5% $NaHCO_3$. Drying over $MgSO_4$ and evaporation gave a residue, which was crystallized from EtOH to give **8** as colorless needles (0.64 g, 62.2%): mp 262—263 °C. IR (Nujol): 3400, 1775, 1740, 1725, 1670 (amide C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.62 (3H, s, $COOCH_3$), 4.35 (2H, s, NCH_2CON), 5.48 (1H, d, J=8 Hz, ArCHCOO), 7.40 (5H, s, ArH), 7.93 (4H, m, ArH), 9.23 (1H, d, J=8 Hz, CONH). *Anal.* Calcd for $C_{19}H_{16}N_2O_5$: C, 64.76; H, 4.58; N, 7.95. Found: C, 65.01; H, 4.61; N, 7.78.

Methyl (3*S*,α*R*)-2-(2-Oxo-3-phthalimido-1-azetidinyl)-2-(4-hydroxyphenyl)acetate (16)——A mixture of methyl (3*R*,α*R*)- and (3*S*,α*R*)-2-(2-oxo-3-phthalimido-1-azetidinyl)-2-(4-benzyloxyphenyl)acetate (**13e**, 0.27 g) in EtOH (20 ml) and 10% Pd–C (0.10 g) was shaken with H_2 under atmospheric pressure until the absorption ceased. After the catalyst had been filtered off, the filtrate was evaporated to give an oil, which was crystallized from ether to give **16** as colorless needles (0.11 g, 60.0%): mp 203—204 °C (dec.). $[\alpha]_D^{25}$ −238° (c=0.025, MeOH). IR (Nujol): 1780, 1740 (β-lactam C=O), 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.47 (1H, dd, J=3, 5 Hz, 4β-H), 3.80 (3H, s, $COOCH_3$), 3.95 (1H, t, J=5 Hz, 4α-H), 4.89 (1H, dd, J=3, 5 Hz, 3α-H), 5.71 (1H, s, ArCHCOO), 6.80 (2H, d, J=8 Hz, ArH), 7.20 (2H, d, J=8 Hz, ArH), 7.75 (4H, m, ArH). *Anal.* Calcd for $C_{20}H_{16}N_2O_6$: C, 63.15; H, 4.24; N, 7.37. Found: C, 63.18; H, 4.11; N, 7.31.

(3*S*,α*R*)-2-(2-Oxo-3-phthalimido-1-azetidinyl)-2-phenylacetic Acid (15A)——Anhydrous LiI (0.42 g) was added to a solution of methyl 2-(2-oxo-3-phthalimido-1-azetidinyl)-2-phenylacetate (**6**, 0.36 g) in dry pyridine (5 ml), and the mixture was refluxed for 2 h. After cooling, the reaction mixture was poured into a mixture of ice-water and AcOEt. The organic layer was separated, washed with 5% HCl and H_2O, dried over $MgSO_4$, and evaporated to give an oil, which was crystallized from AcOEt to give **15A** as colorless needles (0.26 g, 74.0%): mp 191.5 °C (dec.). $[\alpha]_D^{25}$ −244° (c=1.01, acetone). IR (Nujol): 1780, 1720 (β-lactam C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.54 (1H, dd, J=3, 5 Hz, 4β-H), 3.94 (1H, t, J=5 Hz, 4α-H), 5.48 (1H, dd, J=3, 5 Hz, 3α-H), 5.68 (1H, s, ArCHCOO), 7.45 (5H, s, ArH), 7.84 (4H, s, ArH). *Anal.* Calcd for $C_{19}H_{14}N_2O_5$: C, 65.13; H, 4.02; N, 8.00. Found: C, 65.04; H, 4.21; N, 7.98.

The following compounds were prepared by reacting the corresponding β-lactam esters with LiI in substantially the same manner as described above.

(3*S*,α*S*)-2-(2-Oxo-3-phthalimido-1-azetidinyl)-2-(2-thienyl)acetic Acid (**15C**): Yield 78.5%, mp 199—201 °C. $[\alpha]_D^{25}$ −192° (*c*=0.5, MeOH). IR (Nujol): 1770, 1740, 1720 (β-lactam C=O) cm^{-1}. ^{1}H-NMR ($D_2O+NaHCO_3$) δ: 3.36 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.91 (1H, t, *J*=5 Hz, 4α-H), 5.38 (1H, dd, *J*=3, 5 Hz, 3α-H), 5.73 (1H, s, ArCHCOO), 7.00—7.80 (7H, m, ArH). *Anal.* Calcd for $C_{17}H_{12}N_2O_5S$: C, 57.31; H, 3.39; N, 7.86. Found: C, 57.25; H, 3.59; N, 7.74.

(3*RS*,α*SR*)-2-(2-Oxo-3-phthalimido-1-azetidinyl)-2-(2-furyl)acetic Acid (**15D**): Yield 70.8%, mp 187—190 °C (dec.). IR (Nujol): 1780, 1730 (β-lactam C=O), 1710 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.59 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.97 (1H, t, *J*=5 Hz, 4α-H), 5.42 (1H, dd, *J*=3, 5 Hz, 3α-H), 5.76 (1H, s, ArCHCOO), 6.53 (1H, m, ArH), 6.62 (1H, d, *J*=3 Hz, ArH), 7.71 (1H, d, *J*=3 Hz, ArH), 7.86 (4H, s, ArH). *Anal.* Calcd for $C_{17}H_{12}N_2O_6$: C, 60.00; H, 3.55; N, 8.23. Found: C, 59.75; H, 3.49; N, 8.04.

(3*S*,α*R*)-2-(2-Oxo-3-phthalimido-1-azetidinyl)-2-(4-hydroxyphenyl)acetic Acid (**15E**): Yield 63.1%, mp 202—203 °C (dec.). $[\alpha]_D^{25}$ −301° (*c*=0.59, MeOH). IR (Nujol): 1780, 1740, 1720 (β-lactam C=O), 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.47 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.86 (1H, t, *J*=5 Hz, 4α-H), 5.39 (1H, dd, *J*=3, 5 Hz, 3α-H), 5.46 (1H, s, ArCHCOO), 6.88 (2H, d, *J*=8 Hz, ArH), 7.17 (4H, s, ArH), 7.26 (2H, d, *J*=8 Hz, ArH). *Anal.* Calcd for $C_{19}H_{14}N_2O_6$: C, 62.29; H, 3.85; N, 7.65. Found: C, 62.40; H, 3.88; N, 7.43.

(3*S*,α*S*)-2-(3-Amino-2-oxo-1-azetidinyl)-2-phenylacetic Acid (17A)——*N*,*N*-Dimethyl-1,3-propanediamine (0.31 g) was added to a solution of D-2-(2-oxo-3-phthalimido-1-azetidinyl)-2-phenylacetic acid (**15A**, 0.35 g) in MeOH (6 ml) and the mixture was stirred for 8 h at ambient temperature. The reaction mixture was poured into H_2O (6 ml), and Amberlite IRC-50 (about 20 ml) was added to adjust the pH to 5.8—6.0. After removal of the resin by filtration, the filtrate was evaporated to give a residue (0.19 g), which was crystallized from CH_3CN to give **17A** as needles (0.12 g, 54.0%): mp 143—147 °C (dec.). IR (Nujol): 1780 (β-lactam C=O), 1620 cm^{-1}. ^{1}H-NMR (D_2O) δ: 3.04 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.83 (1H, t, *J*=5 Hz, 4α-H), 4.35 (1H, dd, *J*=3, 5 Hz, 3α-H), 5.30 (1H, s, ArCHCOO), 7.42 (5H, s, ArH). *Anal.* Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.71; H, 5.68; N, 12.61.

The following compounds were prepared by reacting the corresponding phthaloyl β-lactams with *N*,*N*-dimethyl-1,3-propanediamine in substantially the same manner as described above.

(3*S*,α*R*)-2-(3-Amino-2-oxo-1-azetidinyl)-2-(2-thienyl)acetic Acid (**17C**): Yield 57.8%, mp 144—149 °C (dec.). IR (Nujol): 1760 (β-lactam C=O), 1745, 1620 cm^{-1}. ^{1}H-NMR (D_2O) δ: 3.13 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.92 (1H, t, *J*=5 Hz, 4α-H), 4.31 (1H, dd, *J*=3, 5 Hz, 3α-H), 5.53 (1H, s, ArCHCOO), 7.10—7.46 (3H, m, ArH). *Anal.* Calcd for $C_9H_{10}N_2O_3S\cdot 1/2H_2O$: C, 45.96; H, 4.71; N, 11.91. Found: C, 46.24; H, 4.67; N, 11.82.

(3*RS*,α*SR*)-2-(3-Amino-2-oxo-1-azetidinyl)-2-(2-furyl)acetic Acid (**17D**): Yield 20.0%, mp 185—189 °C (dec.). IR (Nujol): 1725 (β-lactam C=O), 1640 cm^{-1}. ^{1}H-NMR (D_2O) δ: 3.36 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.90 (1H, t, *J*=5 Hz, 4α-H), 5.41 (1H, s, ArCHCOO), 6.49 (2H, m, ArH), 7.37 (1H, m, ArH). *Anal.* Calcd for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.79; N, 13.33. Found: C, 51.64; H, 4.77; N, 13.15.

3-Aminonocardicinic Acid (3-ANA) (**17E**): Yield 60.4%, mp 194—199 °C (dec.). $[\alpha]_D^{25}$ −239° (*c*=1.0, 0.1 N $NaHCO_3$). IR (Nujol): 1763, (β-lactam C=O), 1742 cm^{-1}. ^{1}H-NMR ($D_2O+NaHCO_3$) δ: 2.89 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.79 (1H, t, *J*=5 Hz, 4α-H), 4.22 (1H, dd, *J*=3, 5 Hz, 3α-H), 5.26 (1H, s, ArCHCOO), 6.88 (2H, d, *J*=8 Hz, ArH), 7.26 (2H, d, *J*=8 Hz, ArH). *Anal.* Calcd for $C_{11}H_{12}N_2O_4$. C, 55.93; H, 5.11; N, 11.86. Found: C, 56.11; H, 5.00; N, 11.68.

2-[3-(2-Hydroxyimino-2-phenylacetamido)-2-oxo-1-azetidinyl]-2-phenylacetic Acid (19A)——PCl_5 (0.25 g) was added to a suspension of 2-(2,2-dichloroacetoxyimino)-2-phenylacetic acid (0.35 g) in benzene (7 ml), and the mixture was stirred for 40 min at ambient temperature. The resulting solution was evaporated to dryness to give a residue, which was dissolved in CH_2Cl_2 (5 ml). This solution was cooled to 0 °C, and the silyl ester of 2-(3-amino-2-oxo-1-azetidinyl)phenylacetic acid [prepared from **17A** (0.22 g) and *N*,*N*-bis(trimethylsily)acetamide (0.87 g) in CH_2Cl_2 (20 ml) by stirring for 30 min at ambient temperature] was added. The reaction mixture was stirred for 1 h at 0 °C, then washed with 5% HCl, and the solvent was removed by evaporation. The residue was dissolved in AcOEt and extracted with 5% $NaHCO_3$. The aqueous layer was separated, adjusted to pH 1—2 with 10% HCl and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give a residue, which was triturated with a small amount of $CHCl_3$ to give **19A** as crystals (0.11 g, 30.1%): mp 147—150 °C (dec.). IR (Nujol): 1745 (β-lactam C=O), 1700, 1665 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.28 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.39 (1H, t, *J*=5 Hz, 4α-H), 5.05 (1H, dd, *J*=3, 5 Hz, 3α-H), 5.59 (1H, s, ArCHCOO), 7.12—7.72 (10H, m, ArH). *Anal.* Calcd for $C_{19}H_{17}N_3O_5$: C, 62.12; H, 4.66; N, 11.44. Found: C, 62.31; H, 4.55; N, 11.21.

The following compounds were obtained by the reaction of the corresponding 3-amino-β-lactam derivatives and 2-(2,2-dichloroacetoxyimino)-2-phenylacetyl chloride in substantially the same manner as described above.

2-[3-(2-Hydroxyimino-2-phenylacetamido)-2-oxo-1-azetidinyl]-2-(2-thienyl)acetic Acid (**19C**): Yield 64.7%, mp 144.5—148 °C. IR (Nujol): 1755 (β-lactam C=O), 1700, 1650 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.43 (1H, dd, *J*=3, 5 Hz, 4β-H), 3.95 (1H, t, *J*=5 Hz, 4α-H), 5.71 (1H, dd, *J*=3, 5 Hz, 3α-H), 5.84 (1H, s, ArCHCOO), 6.90—7.73 (8H, m, ArH). *Anal.* Calcd for $C_{17}H_{15}N_3O_5S$: C, 54.68; H, 4.05; N, 11.25. Found: C, 54.89; H, 3.39; N, 10.98.

2-[3-(2-Hydroxyimino-2-phenylacetamido)-2-oxo-1-azetidinyl]-2-(2-furyl)acetic Acid (**19D**): Yield 41.4%, mp

142—145 °C (dec.). IR (Nujol): 1755 (β-lactam C=O), 1735, 1710, 1660 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 3.41 (1H, dd, J=3, 5 Hz, 4β-H), 3.99 (1H, t, J=5 Hz, 4α-H), 5.25 (1H, m, 3α-H), 5.71 (1H, s, ArCHCOO), 6.46 (1H, m, ArH), 6.58 (1H, d, J=3 Hz, ArH), 7.30—7.70 (6H, m, ArH), 8.26 (1H, d, J=8 Hz, CONH). *Anal.* Calcd for $C_{17}H_{15}N_3O_6$: C, 57.14; H, 4.23; N, 11.76. Found: C, 57.16; H, 4.19; N, 11.51.

2-[3-(2-Hydroxyimino-2-phenylacetamido)-2-oxo-1-azetidinyl]-2-(4-hydroxyphenyl)acetic Acid (**19E**): Yield 59.3%, mp 197—199 °C (dec.). IR (Nujol): 1730 (β-lactam C=O), 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.09 (1H, dd, J=3, 5 Hz, 4β-H), 3.78 (1H, t, J=5 Hz, 4α-H), 5.01 (1H, m, 3α-H), 5.12 (1H, s, ArCHCOO), 7.28—7.52 (9H, m, ArH). *Anal.* Calcd for $C_{19}H_{17}N_3O_6 \cdot 1/2H_2O$: C, 58.15; H, 4.62; N, 10.71. Found: C, 58.11; H, 4.77; N, 10.48.

Methyl (3*RS*,α*SR*)-2-[3-(2,2-Dichloroacetoxyimino-2-phenylacetamido)-2-oxo-1-azetidinyl]-2-(1-naphthyl)acetate (21)——*N*,*N*-Dimethyl-1,3-propanediamine (1.08 g) was added to a solution of methyl (3*RS*,α*SR*)-2-(2-oxo-3-phthalimido-1-azetidinyl)-2-(1-naphthyl)acetate (**13b**, 2.07 g) in a mixture of MeOH (30 ml) and $CHCl_3$ (40 ml), and the mixture was stirred overnight at ambient temperature. After evaporation of the reaction mixture, the residue was dissolved in AcOEt and extracted with 10% HCl. The aqueous layer was adjusted to pH 8 with $NaHCO_3$ and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated to give a residue (1.53 g), which was subjected to column chromatography on silica gel. Elution was carried out with $CHCl_3$ and the fractions containing the desired compound were collected and evaporated to give **20** as a crude oil. This product was reacted with 2-(2,2-dichloroacetoxyimino)-2-phenylacetyl chloride (1.91 g) in substantially the same manner as described above to give **21** (1.55 g, 74.3%): oil. MS m/z 431 (M^+). IR (film): 1740 (β-lactam C=O), 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.89 (1H, dd, J=3, 5 Hz, 4β-H), 3.67 (3H, s, $COOCH_3$), 3.84 (1H, t, J=5 Hz, 4α-H), 5.07 (1H, m, 3α-H), 6.32 (1H, s, ArCHCOO), 7.12—7.96 (12H, m, ArH).

2-[3-(2-Hydroxyimino-2-phenylacetamido)-2-oxo-1-azetidinyl]-2-(1-naphthyl)acetic Acid (19B)——A solution of **21**, (0.20 g) in MeOH (10 ml) was treated with 1 N NaOH (9.3 ml) under ice-cooling, and the mixture was stirred for 3 h at the same temperature. After evaporation of the mixture, the residue was dissolved in H_2O, and this solution was adjusted to pH 2 with 10% HCl and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give an oil, which was triturated with a small amount of AcOEt to give **19B** as crystals (0.14 g, 72.4%): mp 124—129 °C. IR (Nujol): 1730 (β-lactam C=O), 1675 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 3.06 (1H, dd, J=3, 5 Hz, 4β-H), 4.07 (1H, t, J=5 Hz, 4α-H), 6.35 (1H, s, ArCHCOO), 7.08—8.02 (12H, m, ArH). *Anal.* Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07. Found: C, 65.91; H, 4.55; N, 10.13.

References and Notes

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