31. Synthesis of a Masked *p*-Quinone Methide *β*-Lactam as an Active Metabolite of Nocardicins

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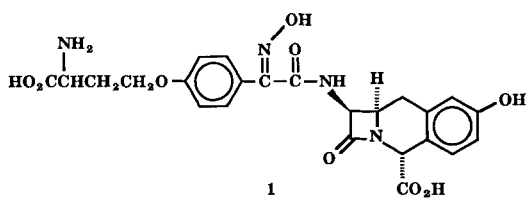
Nocardicin A analogues **30**, **34**, and **38** as well as the highly strained quinone methide **43** were synthesized. *β*-Lactam **34** was found biologically active against several *Gram*-negative microorganisms *in vitro*; pyridinium *N*-oxide derivative **38** possessed activity against *Gram*-positive *S. aureus* bacterium. Masked *p*-quinone methide *β*-lactam **43** exhibited significant antimicrobial activity *in vitro*. A mechanism involving an oxidation *in vivo* is proposed for the unprecedented biological properties of nocardicins.

Introduction. – Nocardicins are the only monocyclic azetidinones with significant antibacterial activity [1]. They are more active against *Gram*-negative than *Gram*-positive microorganisms *in vivo* [2]. Considerable evidence exists indicating that their primary mechanism of action is different from that of the classical *β*-lactam antibiotics [3]; the relatively unstrained *β*-lactam in nocardicin makes it comparatively stable towards nucleophilic attack. When additional ring strain is placed on nocardicin (**3**), the resultant analogues, *e.g.* **1** and **2**, do not exhibit greater potency nor a broader spectrum of antimicrobial activities [4] [5]. We speculated that the monocyclic, nonclassical *β*-lac-



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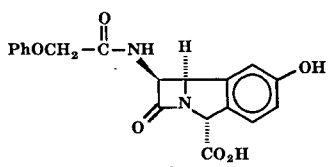

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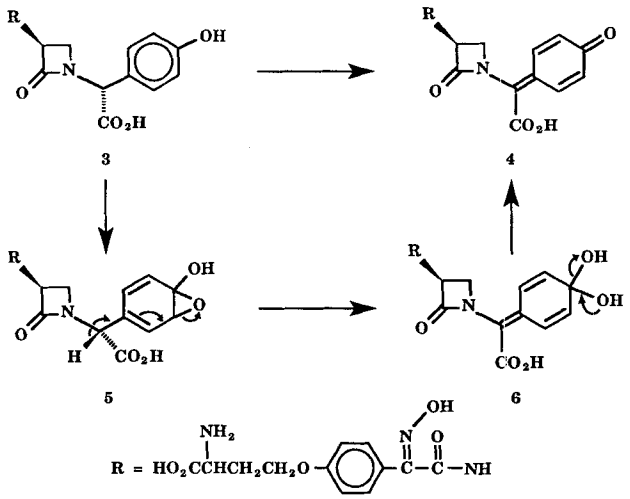
tams in this series could be readily recognized and oxidized by an oxidative enzyme *in vivo* to give the corresponding highly strained quinone methide metabolites (*i.e.* **4**, *Scheme 1*). Those metabolites may inhibit the cell-wall synthesis of bacteria. We also considered an alternative mechanism for their mode of action in biological systems, in which epoxidation of the phenolic moiety of nocardicins takes place *in vivo* (*e.g.* **5**) followed by their conversion to the corresponding cyclohexadienylidenes (*e.g.* **6**).

Herein we report our synthetic efforts on the preparation of dehydroxynocardicin A **30** and the quinone methide derivative **44**. Furthermore, we investigated the importance

Scheme 1



of the phenolic OH group of nocardicin A by preparing its phosphonate derivative **34** and pyridinium *N*-oxide analogue **38**. These two compounds were found biologically active.

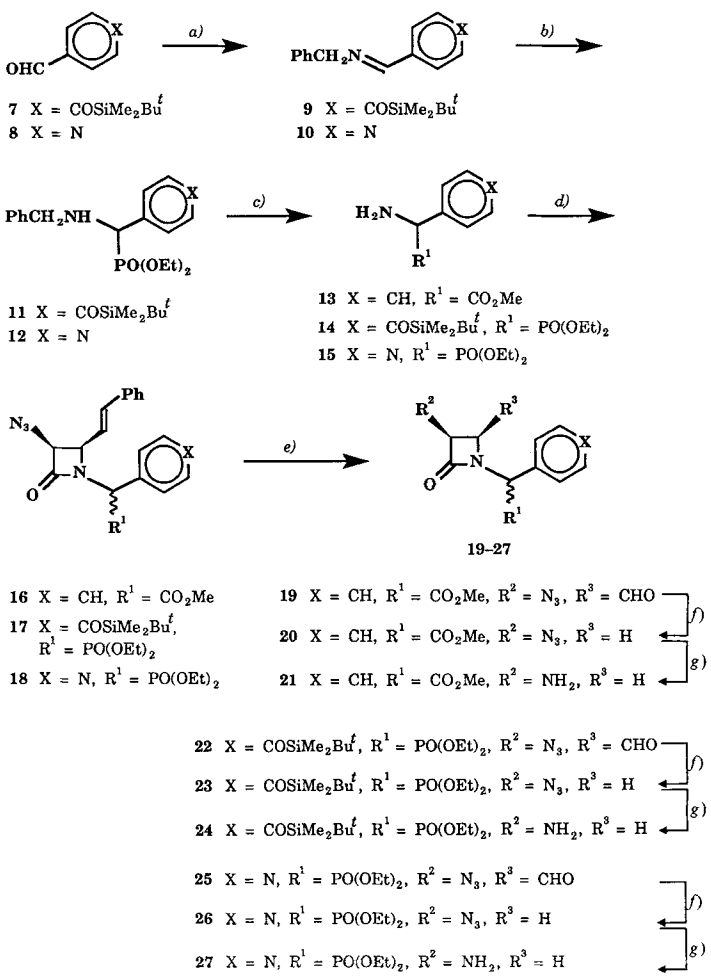
Results and Discussion. – We synthesized β-lactams **30**, **34**, and **38** from methyl (*RS*)-phenylglycinate (**13**) [10] as well as aminophosphonate precursors **14** and **15** [6], respectively. Thus, 4-[(*tert*-butyl)dimethylsilyloxy]benzaldehyde (**7**) and pyridine-4-carbaldehyde (**8**) were converted to their respective *Schiff* bases **9** (95%) and **10** (98%) by use of benzylamine in benzene (*Scheme 2*). Addition of diethyl phosphite to **9** or **10** at 80° afforded compounds **11** (98%) and **12** (99%), respectively. Ready removal of the benzyl group from **11** and **12** by catalytic reduction [7] afforded the corresponding aminophosphonates **14** and **15** in excellent yields. Reactions of **13**, **14**, or **15** with cinnamaldehyde gave the corresponding *Schiff* bases, which upon treatment with azidoacetyl chloride and Et_3N afforded the β-lactams **16** (80%), **17** (85%), and **18** (80%), respectively (stereoisomer mixtures). These β-lactams possessed *cis*-configuration, as determined by ^{1}H-NMR spectrometry (J(H–C(3),H–C(4)) = 5.0 Hz) [8]. Individual ozonolysis of **16**, **17**, and **18**, followed by Me_2S treatment, gave the expected aldehydes **19** (90%), **22** (95%), and **25** (90%), respectively. Decarbonylation of **19**, **22**, and **25** with tris(triphenylphosphine)-rhodium chloride [9] afforded compounds **20** (36%), **23** (20%), and **26** (28%). Conversions of **20** → **21**, **23** → **24**, and **26** → **27** were achieved in 95–98% yields with H_2 at 35–40 psi and Pd/C in MeOH. We then acylated amines **21**, **24**, and **27** with the protected glyoxylic acid of the nocardicin side chain in the presence of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ) to afford the corresponding amides **28** (90%), **31** (85%), and **35** (80%), respectively [10].

Hydrolysis of diastereoisomeric racemates **28** with NaOH in aqueous MeOH and subsequent removal of the *tert*-butoxycarbonyl group by use of CF_3CO_2H gave **29** in 65% overall yield. On the other hand, removal of the silyl group in **31** with Bu_4NF in THF gave **32** in 98% yield. Dealkylation of **32** afforded **33** (20%) by use of Me_3SiBr in CH_2Cl_2 [11].

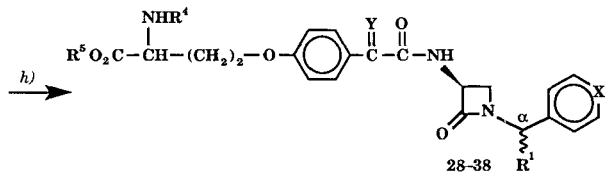
Oxidation of **35** with 3-chloroperbenzoic acid yielded the corresponding pyridinium *N*-oxide **36** (90%). Reaction of **36** with Me_3SiBr in CH_2Cl_2 afforded **37** in 15% yield. We then treated **29**, **33**, and **37** with $NH_2OH \cdot HCl$ in H_2O under neutral conditions [10] and purified the products by ion-exchange chromatography to give the corresponding nocardicin-A analogues **30** (70%), **34** (65%), and **38** (50%), respectively.

The quinone-methide derivative **44** was prepared from β-lactam **39** [12] by ozonolysis which gave aldehyde **40** in 98% yield (*Scheme 3*). Decarbonylation of **40** by use of tris(triphenylphosphine)rhodium chloride [9] yielded **41** (55%), which was allowed to react with 4,4-dimethoxycyclohexa-2,5-dien-1-one in the presence of NaH in THF to produce the desired masked *p*-quinone methide **42** in 45% yield. We then removed the *t*-Bu group from **42** by using CF_3CO_2H and a trace amount of Bu_4NClO_4 in CH_2Cl_2 to

Scheme 2



Scheme 2 (cont.)



28–38

28 X = CH, Y = O, R^1 = CO_2Me, R^4 = CO_2Bu^t, R^5 = Me

29 X = CH, Y = O, R^1 = CO_2H, R^4 = H, R^5 = H

30 X = CH, Y = NOH (*cis*), R^1 = CO_2H, R^4 = H, R^5 = H

31 X = $COSiMe_2Bu^t$, Y = O, R^1 = $PO(OEt)_2$, R^4 = CO_2Bu^t, R^5 = Me

32 X = COH, Y = O, R^1 = $PO(OEt)_2$, R^4 = CO_2Bu^t, R^5 = Me

33 X = COH, Y = O, R^1 = $PO(OH)_2$, R^4 = H, R^5 = H

34 X = COH, Y = NOH (*cis*), R^1 = $PO(OH)_2$, R^4 = H, R^5 = H

35 X = N, Y = O, R^1 = $PO(OEt)_2$, R^4 = CO_2Bu^t, R^5 = Me

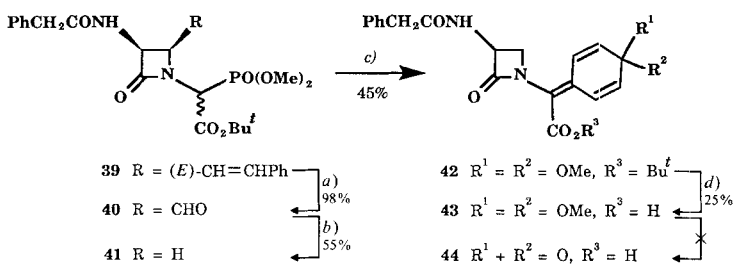
36 X = NO, Y = O, R^1 = $PO(OEt)_2$, R^4 = CO_2Bu^t, R^5 = Me

37 X = NO, Y = O, R^1 = $PO(OH)_2$, R^4 = H, R^5 = H

38 X = NO, Y = NOH (*cis*), R^1 = $PO(OH)_2$, R^4 = H, R^5 = H

a) $PhCH_2NH_2$, PhH; 95% (**9**), 98% (**10**). *b*) $(EtO)_2POH$, 80°; 98% (**11**), 99% (**12**). *c*) $PdCl_2$/cyclohexene; 90% (**14**), 95% (**15**). *d*) 1. (*E*)-PhCH=CHCHO; 2. N_3CH_2COCl/Et_3N, −20°; 80% (**16**), 85% (**17**), 80% (**18**). *e*) 1. O_3; 2. Me_2S, CH_2Cl_2; 90% (**19**), 95% (**22**), 90% (**25**). *f*) $[RhCl(Ph_3P)_3]$; 36% (**20**), 20% (**23**), 28% (**26**). *g*) Pd/C, H_2, MeOH; 95% (**21**), 95% (**24**), 98% (**27**). *h*) (*RS*)-$MeO_2CCH(NHCO_2Bu^t)CH_2CH_2OC_6H_4COCO_2H$/EEDQ, CH_2Cl_2; 90% (**28**), 85% (**31**), 80% (**35**). *i*) 1. NaOH; 2. CF_3CO_2H; 65%. *j*) NH_2OH; 70% (**30**), 65% (**34**), 50% (**38**). *k*) Bu_4NF, THF, 0°; 98%. *l*) Me_3SiBr, CH_2Cl_2, 25°; 20% (**33**), 15% (**37**). *m*) 3-$ClC_6H_4CO_3H$; 90%.

Scheme 3



39 R = (*E*)-CH=CHPh

40 R = CHO

41 R = H

42 R^1 = R^2 = OMe, R^3 = Bu^t

43 R^1 = R^2 = OMe, R^3 = H

44 R^1 + R^2 = O, R^3 = H

a) 1. O_3, CH_2Cl_2; 2. Me_2S. *b*) $[RhCl(Ph_3P)_3]$, benzene. *c*) 4,4-Dimethoxycyclohexa-2,5-dien-1-one, THF, NaH. *d*) CF_3CO_2H, Bu_4NClO_4, CH_2Cl_2.

give the corresponding carboxylic acid **43** (25%). All attempts to convert **43** to quinone methide **44** failed and resulted in the destruction of the β-lactam ring.

Biological Activity. – We tested the biological activities of nocardicin-A analogues **30**, **34**, **38**, and **43** as well as of carbenicillin *in vitro* against five pathogenic microorganisms up to a level of 800 μg/ml. The results are summarized in the *Table*.

Table. *Minimal Inhibitory Concentrations* [μg/ml]

	S. aureus FDA-209P	*S. lutea* PCI-1001	*P. vulgaris* IAM-1025	*P. mirabilis* 1432-75	*P. aeruginosa* 1101-75
30	[a])	[a])	[a])	[a])	[a])
34	[a])	38.56	21.34	15.63	18.79
38	48.75	[a])	[a])	[a])	[a])
43	176.80	4.65	1.87	0.86	6.25
Carbenicillin	0.56	0.42	0.25	0.78	70.36
Nocardicin A[b])	800	6.25	1.56–3.13	1.56	12.50

[a]) Not active up to 800 μg/ml. [b]) Data taken from [1] and [3].

In contrast with the notable antimicrobial property of nocardicin A and its phosphonate derivative **34**, dehydroxy derivative **30** did not exhibit any biological activity. These results indicate that the phenolic OH group plays an important role in biological activity of nocardicins. Pronounced antimicrobial effect resulting from β-lactam **43** indicates the possibility of oxidation of the phenolic moiety in nocardicins to the corresponding quinone methide metabolites. This process could be responsible for their remarkable antibacterial effect *in vivo* (see *Scheme 1*). Our postulation was further supported by the lack of activity of pyridinium *N*-oxide **38** against *Gram*-negative microorganisms. On the other hand, we found that β-lactam **38** exhibited moderate activity against *Gram*-positive *S. aureus* bacterium.

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Experimental Part

General. Chemicals were purchased from *Fluka Chemical Co.* Solvents were of reagent grade unless otherwise specified. Column chromatography (CC): short column of silica gel *60 Merck* (230–400 mesh) were packed in glass columns (∅ 2 or 3 cm) by use of 25 g of silica gel/g of crude mixture. TLC: *Merck* silica gel *60 F 254* anal. sheets. M.p.: *Büchi 510*. UV Spectra: *Cary 118* spectrophotometer; λ_{max} in nm (ε). IR Spectra: *Beckman IR 8* spectrophotometer; in cm^{-1}. ^{1}H-NMR Spectra: *Bruker-WH-90*; δ in ppm rel. to Me_4Si, *J* in Hz. Elemental analyses were performed by *Midwest Microlab. Ltd.*

N-{{*4-[(*tert*-Butyl)dimethylsilyloxy]phenyl*}*methylidene*}*benzylamine* (**9**). To a soln. of **7** (2.36 g, 10.0 mmol) in benzene (250 ml) was added benzylamine (1.17 g, 10.9 mmol). The soln. was heated at reflux (*Dean-Stark* trap) and H_2O removed (*ca.* 7 h). Then it was cooled, and $MgSO_4$ was added. After 1 h, the mixture was filtered and the filtrate evaporated. CC (silica gel, CCl_4): 3.10 g (95%) of **9**. Oil. IR (CH_2Cl_2): 1645 (C=N). ^{1}H-NMR ($CDCl_3$): 0.13 (*s*, Me_2Si); 1.06 (*s*, Me_3C); 4.85 (*s*, CH_2); 6.99, 7.54 (*AA'BB'*, *J* = 9.0, C_6H_4); 7.25 (*s*, C_6H_5); 7.45 (*s*, HC=N). Anal. calc. for $C_{20}H_{27}NOSi$ (325.53): C 73.79, H 8.36, N 4.30; found: C 73.70, H 8.29, N 4.38.

N-[(Pyridin-4-yl)methylidene]benzylamine (**10**). As described for **9**, **10** was obtained from **8** in 98% yield. IR (CH_2Cl_2): 1655 (C=N). ^{1}H-NMR ($CDCl_3$): 4.98 (*s*, CH_2); 7.30 (*s*, C_6H_5); 7.45, 8.56 (*AA'BB'*, *J* = 6.0, C_5H_4N); 7.59 (*s*, HC=N). Anal. calc. for $C_{13}H_{12}N_2$ (196.25): C 79.56, H 6.16, N 14.27; found: C 79.47, H 6.20, N 14.30.

*(±)-Diethyl {(Benzylamino){4-[(*tert*-butyl)dimethylsilyloxy]phenyl}methyl}phosphonate* (**11**). To **9** (3.25 g, 9.98 mmol) was added diethyl phosphite (1.40 g, 12.0 mmol) at 80°. After 1 h stirring, the reaction was complete. CC (silica gel, CH_2Cl_2/$CHCl_3$ 1:1) gave 4.54 g (98%) of **11**. Oil. IR (CH_2Cl_2): 3370 (NH). ^{1}H-NMR ($CDCl_3$): 0.10 (*s*, Me_2Si); 1.98 (*s*, Me_3C); 1.04–1.45 (2*t*, 2 MeC); 2.95 (br., NH); 3.57–4.17 (*m*, 2 CH_2O); 4.18 (br. *s*, CH_2N); 4.25 (*d*, *J* = 20.0, CHP); 6.80, 7.33 (*AA'BB'*, *J* = 8.5, C_6H_4); 7.15 (*s*, C_6H_5). Anal. calc. for $C_{24}H_{38}NO_4PSi$ (463.63): C 62.18, H 8.26, N 3.02; found: C 62.20, H 8.19, N 3.11.

Compound **11** was dissolved in Et_2O, and dry HCl gas was bubbled into the soln. After 5 min, the solvent was evaporated to give **11**·HCl (100%) as a foam.

(±)-Diethyl [(Benzylamino)(pyridin-4-yl)methyl]phosphonate (**12**). As described for **11**, **12** was prepared from **10** in 99% yield. IR (CH_2Cl_2): 3360–3380 (NH). ^{1}H-NMR ($CDCl_3$): 1.02–1.43 (2*t*, 2 Me); 3.01 (br., NH); 3.58–4.20 (*m*, 2 CH_2O, CH_2N); 4.51 (*d*, *J* = 18.0, CHP); 7.20 (*s*, C_6H_5); 7.30–8.45 (*AA'BB'*, *J* = 8.5, C_6H_4). Anal. calc. for $C_{17}H_{23}N_2O_3P$ (334.36): C 61.07, H 6.93, N 8.38; found: C 61.10, H 6.99, N 8.42.

Conversion of **12** to **12**·HCl (100%) was achieved by use of HCl gas in Et_2O.

*(±)-Diethyl {(Amino){4-[(*tert*-butyl)dimethylsilyloxy]phenyl}methyl}phosphonate* (**14**). Compound **11**·HCl (464 mg, 1.00 mmol) was dissolved in EtOH (40 ml) upon heating at reflux. Cyclohexene (25 ml) and $PdCl_2$ (300 mg) were added; refluxing was continued for 15 h. The mixture was filtered and the filtrate treated with NH_3 gas and evaporated. The residue was chromatographed (silica gel, AcOEt): **14** (336 mg, 90%). Oil. IR (CH_2Cl_2): 3340–3450 (NH_2). ^{1}H-NMR ($CDCl_3$): 0.11 (*s*, Me_2Si); 1.01 (*s*, Me_3C); 1.03–1.51 (2*t*, 2 Me); 3.08 (br., NH_2); 3.50–4.21 (*m*, 2 CH_2O); 4.35 (br., CHP); 6.82, 7.36 (*AA'BB'*, *J* = 9.0, C_6H_4). Anal. calc. for $C_{17}H_{32}NO_4PSi$ (373.51): C 54.67, H 8.64, N 3.75; found: C 54.57, H 8.59, N 3.83.

(±)-Diethyl [Amino(pyridin-4-yl)methyl]phosphonate (**15**) was prepared from **12**·HCl in 95% yield as described for **14**. IR (CH_2Cl_2): 3400–3350 (NH_2), 1580 (py). ^{1}H-NMR ($CDCl_3$/D_2O): 1.01–1.49 (2*t*, 2 Me); 3.69–4.22 (*m*, 2 CH_2O); 4.50 (*d*, *J* = 18.5, CHP); 7.33, 8.50 (*AA'BB'*, *J* = 6.3, C_5H_4N). Anal. calc. for $C_{10}H_{17}N_2O_3P$ (244.23): C 49.18, H 7.02, N 11.47; found: C 40.22, H 7.12, N 11.57.

*(±)-Methyl 2-{*cis*-3-Azido-2-oxo-4-[(*E*)-2-phenylethenyl]azetidin-1-yl}-2-phenylacetates* (diastereoisomer mixture; **16**). To a soln. of **13** (1.65 g, 10.0 mmol) in CH_2Cl_2 (120 ml) was added (*E*)-3-phenylprop-2-enal (1.32 g, 10.0 mmol). The soln. was heated to reflux, and CH_2Cl_2 was stilled slowly with the constant addition of CH_2Cl_2 to maintain the same volume of liquid. After H_2O in the mixture had been removed (*ca.* 10 h), the remaining soln. was cooled and $MgSO_4$ added. The mixture was filtered. To the filtrate was added Et_3N (2.02 g, 20.0 mmol) and then azidoacetyl chloride (1.20 g, 10.0 mmol), dropwise at −20°. After stirring at −20° for 1 h, the soln. was washed with H_2O, dried ($MgSO_4$), and evaporated. The crude product was purified by CC (silica gel, CH_2Cl_2): **16** (2.90 g, 80%) as an oily mixture of diastereoisomers. IR (CH_2Cl_2): 2100 (N_3), 1760 (β-lactam), 1740 (ester). ^{1}H-NMR ($CDCl_3$): 3.98, 3.81 (2*s*, Me); 4.21–4.39 (*m*, H–C(4)); 4.73, 4.82 (2*d*, *J* = 5.0, H–C(3)); 5.50, 5.62 (2*s*, $CHCO_2$); 6.53 (*m*, CH=CH); 6.78–7.71 (*m*, 2 C_6H_5). MS: 334 ([*M* − N_2]$^+$). Anal. calc. for $C_{20}H_{13}N_4O_3$ (362.39): C 66.29, H 5.01, N 15.46; found: C 66.36, H 4.93, N 15.49.

*(±)-Diethyl {{*cis*-3-Azido-2-oxo-4-[(*E*)-2-phenylethenyl]azetidin-1-yl}{4-[(*tert*-butyl)dimethylsilyloxy]-phenyl}methyl}phosphonates* (diastereoisomer mixture; **17**) were obtained from **14** in 85% yield as described for **16**. IR (CH_2Cl_2): 2100 (N_3), 1755 (β-lactam). ^{1}H-NMR ($CDCl_3$): 0.12 (2*s*, Me_2Si); 0.99 (*s*, Me_3C); 1.11–1.48 (2*t*, 2 Me); 3.80–4.48 (*m*, 2 CH_2O); 4.45 (br., H–C(4)); 4.98 (*d*, *J* = 20.0, CHP); 5.09 (br. *d*, *J* = 5.0, H–C(3)); 6.40 (*dd*, *J* = 6.5, 16.0, PhCH=C*H*); 6.63 (*d*, *J* = 16.0, PhC*H*=CH); 6.85–7.52 (*m*, C_6H_4, C_6H_5). Anal. calc. for $C_{28}H_{39}N_4O_5PSi$ (570.71): C 58.93, H 6.89, N 9.82; found: C 58.88, H 6.78, N 9.80.

*(±)-Diethyl {{*cis*-3-Azido-2-oxo-4-[(*E*)-2-phenylethenyl]azetidin-1-yl}(pyridin-4-yl)methyl}phosphonates* (diastereoisomer mixture; **18**) were prepared from **15** in 80% yield as described for **16**. IR (CH_2Cl_2): 2100 (N_3), 1758 (β-lactam). ^{1}H-NMR ($CDCl_3$): 1.08–1.50 (2*t*, 2 Me); 3.88–4.50 (2 br. *q*, 2 CH_2O); 4.78 (*dd*, *J* = 5.0, 7.0, H–C(4)); 5.30 (*d*, *J* = 20.0, CHP); 5.49 (*d*, *J* = 5.0, H–C(3)); 6.51 (*dd*, *J* = 7.0, 16.0, PhCH=C*H*); 6.73 (*d*, *J* = 16.0, PhC*H*=CH); 7.25 (*s*, C_6H_5); 7.33, 8.51 (*AA'BB'*, *J* = 6.0, C_6H_5N). Anal. calc. for $C_{21}H_{24}N_5O_4P$ (441.43): C 57.14, H 5.48, N 15.87; found: C 57.19, H 5.51, N 15.93.

*(±)-Methyl 2-(*cis*-3-Azido-2-formyl-4-oxoazetidin-1-yl)-2-phenylacetates* (diastereoisomer mixture; **19**). Ozone was passed through a soln. of **16** (3.70 g, 10.2 mmol) in CH_2Cl_2 (100 ml) at −78° for 2 h. After the soln. was purged with N_2, Me_2S (1.86 g, 30.0 mmol) was added and the soln. allowed to warm up to 25° within 1.5 h. The solvent was removed and the residue purified by CC (silica gel, CH_2Cl_2): **19** (2.60 g, 90%). Oil. IR ($CHCl_3$): 2100 (N_3), 1773 (β-lactam), 1740 (ester), 1720 (aldehyde). ^{1}H-NMR ($CDCl_3$): 3.79, 3.81 (2*s*, Me); 4.65–4.84 (*m*, H–C(3),

H–C(4)); 5.55 (br. *s*, $CHCO_2$); 7.20 (*s*, C_6H_5); 9.65 (*d*, *J* = 1.5, CHO). Anal. calc. for $C_{13}H_{12}N_4O_4$ (288.26): C 54.17, H 4.20, N 19.44; found: C 54.20, H 4.19, N 19.60.

(±)-Methyl 2-(3-Azido-2-oxoazetidin-1-yl)-2-phenylacetates (diastereoisomer mixture; **20**). $[RhCl(Ph_3P)_3]$ (4.66 g, 5.06 mmol) was added to **19** (1.44 g, 5.00 mmol) in O_2-free benzene (100 ml). The mixture was heated at reflux under Ar for 2 h, then cooled, filtered, and evaporated and the residue chromatographed (silica gel, CH_2Cl_2): 0.46 g (36%) of **20**. Oil. IR (CH_2Cl_2): 2100 (N_3), 1758 (β-lactam), 1743 (ester). ^{1}H-NMR ($CDCl_3$): 3.21 (*dd*, *J* = 2.0, 6.6, H_β–C(4)); 3.71 (*s*, Me); 3.99 (*dd*, *J* = 5.0, 6.6, H_α–C(4)); 4.75 (*m*, H–C(3)); 5.50 (*s*, $CHCO_2$); 7.10 (*s*, C_6H_5). Anal. calc. for $C_{12}H_{12}N_4O_3$ (260.25): C 55.38, H 4.65, N 21.53; found: C 55.41, H 4.79, N 21.59.

(±)-Methyl 2-(3-Amino-2-oxoazetidin-1-yl)-2-phenylacetates (diastereoisomer mixture; **21**). To a soln. of **20** (2.69 g, 10.3 mmol) in MeOH (70 ml) was added Pd/C (400 mg), and the mixture was hydrogenated at 35–40 psi and 25° for 1.5 h. The soln. was then filtered and evaporated and the residue chromatographed (silica gel, $CHCl_3$): 2.22 g (95%) of **21**. Foam. IR (CH_2Cl_2): 3350–3400 (NH_2), 1760–1750 (β-lactam, ester). ^{1}H-NMR ($CDCl_3$): 3.16 (br., NH_2, exchange with D_2O); 3.27 (*dd*, *J* = 2.1, 6.6, H_β–C(4)); 3.63 (*s*, Me); 4.02 (*dd*, *J* = 5.0, 6.6, H_α–C(4)); 4.49 (*m*, H–C(3)); 5.37, 5.38 (2*s*, $CHCO_2$); 7.15 (*s*, C_6H_5). Anal. calc. for $C_{12}H_{14}N_2O_3$ (234.26): C 61.53, H 6.02, N 11.96; found: C 61.63, H 6.05, N 11.85.

*(±)-Diethyl {(*cis*-3-Azido-2-formyl-4-oxoazetidin-1-yl){4-[(*tert*-butyl)dimethylsilyloxy]phenyl}methyl}-phosphonates* (diastereoisomer mixture; **22**) were obtained from **17** in 95% yield as described for **19**. IR (CH_2Cl_2): 2110 (N_3), 1770 (β-lactam), 1720 (aldehyde). ^{1}H-NMR ($CDCl_3$): 0.10 (2*s*, Me_2Si); 1.03 (2*s*, Me_3C); 1.18–1.50 (2*t*, 2 Me); 3.86–4.44 (*m*, 2 CH_2O); 4.86–5.01 (*m*, H–C(3), H–C(4), CHP); 7.00–7.49 (*AA'BB'*, *J* = 8.5, C_6H_4); 9.56 (*d*, *J* = 1.8, CHO). Anal. calc. for $C_{21}H_{33}N_4O_6PSi$ (496.58): C 50.79, H 6.70, N 11.28; found: C 50.83, H 6.79, N 11.17.

*(±)-Diethyl {(3-Azido-2-oxoazetidin-1-yl){4-[(*tert*-butyl)dimethylsilyloxy]phenyl}methyl}phosphonates* (diastereoisomer mixture; **23**) were prepared from **22** in 20% yield as described for **20**. IR (CH_2Cl_2): 2100 (N_3), 1752 (β-lactam). ^{1}H-NMR ($CDCl_3$): 0.12 (2*s*, Me_2Si); 1.01 (*s*, Me_3C); 1.22–1.45 (2*t*, 2 Me); 3.19 (*dd*, *J* = 2.0, 6.5, H_β–C(4)); 3.86–4.45 (*m*, 2 CH_2O, H_α–C(4)); 4.78 (*d*, *J* = 20.0, CHP); 4.89 (*dd*, *J* = 2.0, 5.0, H–C(3)); 6.82, 7.34 (*AA'BB'*, *J* = 8.9, C_6H_4). Anal. calc. for $C_{20}H_{33}N_4O_5PSi$ (468.57): C 51.27, H 7.10, N 11.96; found: C 51.31, H 7.18, N 12.03.

*(±)-Diethyl {(3-Amino-2-oxoazetidin-1-yl){4-[(*tert*-butyl)dimethylsilyloxy]phenyl}methyl}phosphonates* (diastereoisomer mixture; **24**) were prepared from **23** in 95% yield as described for **21** (EtOH instead of MeOH). IR (CH_2Cl_2): 3350–3410 (NH_2), 1750 (β-lactam). ^{1}H-NMR ($CDCl_3$): 0.11 (*s*, Me_2Si); 1.02 (*s*, Me_3C); 1.25–1.50 (2*t*, 2 Me); 3.20 (br., NH_2); 3.28 (*dd*, *J* = 2.1, 6.0, H_β–C(4)); 3.84–4.51 (*m*, 2 CH_2O, H_α–C(4), H–C(3)); 4.79 (*d*, *J* = 19.5, CHP); 6.81, 7.34 (*AA'BB'*, *J* = 8.5, C_6H_4). Anal. calc. for $C_{20}H_{35}N_2O_5PSi$ (442.57): C 54.28, H 7.97, N 6.33; found: C 54.35, H 8.05, N 6.44.

*(±)-Diethyl [(*cis*-3-Azido-2-formyl-4-oxoazetidin-1-yl)(pyridin-4-yl)methyl]phosphonates* (diastereoisomer mixture; **25**) were prepared from **18** in 90% yield as described for **19**. IR (CH_2Cl_2): 2100 (N_3), 1770 (β-lactam), 1722 (aldehyde). ^{1}H-NMR ($CDCl_3$): 1.10–1.58 (2*t*, 2 Me); 3.89–4.48 (*m*, 2 CH_2O); 4.76–5.58 (*m*, H–C(3), H–C(4), CHP); 7.32, 8.65 (*AA'BB'*, *J* = 5.8, C_5H_4N); 9.60 (*d*, *J* = 1.5, CHO). Anal. calc. for $C_{14}H_{18}N_5O_5P$ (367.30): C 45.78, H 4.94, N 19.07; found: C 45.73, H 4.89, N 19.10.

(±)-Diethyl [(3-Azido-2-oxoazetidin-1-yl)(pyridin-4-yl)methyl]phosphonates (diastereoisomer mixture; **26**) were obtained from **25** in 28% yield as described for **20**. IR (CH_2Cl_2): 2100 (N_3), 1756 (β-lactam). ^{1}H-NMR ($CDCl_3$): 1.12–1.40 (2*t*, 2 Me); 3.20 (*dd*, *J* = 2.0, 6.5, H_β–C(4)); 3.80–4.46 (*m*, 2 CH_2O, H_α–C(4)); 5.05 (*d*, *J* = 20.0, CHP); 5.18 (*dd*, *J* = 2.0, 5.0, H–C(3)); 7.30, 8.50 (*AA'BB'*, *J* = 6.2, C_5H_4N). Anal. calc. for $C_{13}H_{18}N_5O_4P$ (339.29): C 46.02, H 5.35, N 20.64; found: C 45.98, H 5.39, N 20.58.

(±)-Diethyl [(3-Amino-2-oxoazetidin-1-yl)(pyridin-4-yl)methyl]phosphonates (diastereoisomer mixture; **27**) were obtained from **26** in 98% yield as described for **21**. IR (CH_2Cl_2): 3350–3400 (NH_2), 1756 (β-lactam). ^{1}H-NMR ($CDCl_3$): 1.18–1.49 (2*t*, 2 Me); 3.30 (br., NH_2); 3.23 (*dd*, *J* = 2.1, 6.5, H_β–C(4)); 3.82–4.40 (*m*, 2 CH_2O, H_α–C(4), H–C(3)); 5.16 (*d*, *J* = 20.0, CHP); 7.26, 8.49 (*AA'BB'*, *J* = 6.1, C_5H_4N). Anal. calc. for $C_{13}H_{20}N_3O_4P$ (313.30): C 49.84, H 6.43, N 13.41; found: C 49.73, H 6.39, N 13.52.

*(±)-Methyl 3-{{{4-{3-[(*tert*-Butoxy)carbonylamino]-3-(methoxycarbonyl)propoxy}phenyl}glyoxyl}-amino}-2-oxo-α-phenylazetidine-1-acetates* (diastereoisomer mixture; **28**). To a CH_2Cl_2 (35 ml) soln. containing **21** (1.17 g, 4.99 mmol) and {4-{3-[(*tert*-butoxy)carbonylamino]-3-(methoxycarbonyl)propoxy}phenyl}glyoxylic acid (0.20 g, 0.52 mmol) was added ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ; 0.13 g, 0.52 mmol), and the mixture was stirred at 25° for 17 h. The soln. was washed with 5% aq. HCl soln. (30 ml) and 5% aq. $NaHCO_3$ soln. (40 ml), dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (silica gel, CH_2Cl_2 and then $CHCl_3$): 2.68 g (90%) of **28**. Foam. IR (CH_2Cl_2): 3200–3340 (NH), 1746–1760 (esters, β-lactam), 1717 (Boc), 1670–1685 (amide, ketone). ^{1}H-NMR ($CDCl_3$): 1.41 (*s*, Me_3C); 2.15–2.42 (*m*, CH_2); 3.18 (*dd*, *J* = 2.0, 6.5, H_β–C(4)); 3.72, 3.77 (2*s*, 2 Me); 4.05 (*m*, $O_2CCHNCO_2$, H_α–C(4)); 4.52 (*t*, *J* = 6.0, CH_2O); 5.28 (*m*, H–C(3)); 5.78

(*s*, $CHCO_2$); 6.72 (br., 2 NH); 6.90 (*s*, C_6H_5); 7.52, 8.30 (*AA'BB'*, *J* = 8.0, C_6H_4). Anal. calc. for $C_{30}H_{35}N_3O_{10}$ (597.63): C 60.29, H 5.90, N 7.03; found: C 60.38, H 5.73, N 7.12.

(±)-3-{{[4-(3-Amino-3-carboxypropoxy)phenyl]glyoxyl}amino}-2-oxo-α-phenylazetidine-1-acetic Acids (diastereoisomer mixture; **29**). To a soln. of **28** (0.60 g, 1.0 mmol) in MeOH (30 ml) was added 1% aq. NaOH soln. (10 ml) within 10 min. The mixture was stirred at 25° for 13 min and then acidified with HCl soln. to pH 3.0. MeOH was evaporated and the aq. soln. extracted with AcOEt (20 ml). The org. layer was dried ($MgSO_4$) and evaporated to give a residue, which was dissolved in CF_3CO_2H (5.0 ml) containing a trace amount of $KClO_4$. After 1 h, Et_2O (35 ml) was added to afford a white precipitate which was filtered and washed with Et_2O (3 × 15 ml). Crystallization from MeOH/Et_2O 1:1 gave 0.30 g (65%) of **29**. M.p. 205–207° (dec.). IR (nujol): 3450–2650 (CO_2H, NH, NH_2), 1750–1725 (β-lactam, acid), 1670–1662 (amide, ketone). UV (EtOH): 226 (19000), 299 (16000). ^{1}H-NMR (D_2O/$NaHCO_3$): 2.02–2.40 (*m*, CH_2); 3.16 (*dd*, *J* = 2.0, 6.5, H_β–C(4)); 3.97 (*t*, *J* = 6.0, O_2CCHND_3); 4.12 (*dd*, *J* = 5.0, 6.5, H_α–C(4)); 4.41 (*t*, *J* = 6.0, CH_2O); 5.40 (br. *m*, H–C(3)); 5.52 (*s*, $CHCO_2$); 6.98 (*s*, C_6H_5); 7.43, 8.35 (*AA'BB'*, *J* = 7.9, C_6H_4). Anal. calc. for $C_{23}H_{23}N_3O_8$ (469.46): C 58.85, H 4.94, N 8.95; found: C 58.67, H 4.79, N 9.12.

(±)-(Z)-3-{{[4-(3-Amino-3-carboxypropoxy)phenyl](hydroxyimino)acetyl}amino}-2-oxo-α-phenylazetidine-1-acetic Acids (diastereoisomer mixture; **30**). To a H_2O (20 ml) soln. containing **29** (0.50 g, 1.1 mmol) was added hydroxylamine hydrochloride (0.36 g, 5.0 mmol). Then a sat. aq. $NaHCO_3$ soln. was added dropwise until pH 7.0 was reached. After 2 h heating at 50°, the mixture was cooled and acidified to pH 3.0 with conc. aq. HCl soln. The soln. was lyophilized and the residue dissolved in H_2O (4.0 ml) and poured into a column containing resin *XAD*$_4$. All salts were removed by use of H_2O, and the product was eluted with MeOH: 0.34 g (70%) of **30**. M.p. 210–212° (dec.). IR (nujol): 3400–2500 (OH, CO_2H, NH_2, NH), 1735–1720 (β-lactam, acid), 1665 (amide). UV (EtOH/H_2O): 220 (20100), 274 (14000). UV (EtOH/0.1N NaOH): 222 (20500), 290 (12000). ^{1}H-NMR (D_2O/$NaHCO_3$): 2.20–2.46 (*m*, CH_2); 3.19 (*dd*, *J* = 2.0, 6.6, H_β–C(4)); 3.90 (*t*, *J* = 6.1, O_2CCHND_3); 4.08 (*dd*, *J* = 5.0, 6.6, H_α–C(4)); 4.35 (*t*, *J* = 6.0, CH_2O); 5.29 (*m*, H–C(3)); 5.48 (*s*, $CHCO_2$); 6.90–7.63 (*m*, C_6H_5, C_6H_4). Anal. calc. for $C_{23}H_{24}N_4O_8$ (484.47): C 57.02, H 4.99, N 11.56; found: C 57.18, H 5.05, N 11.68.

*(±)-Diethyl {{3-{{{4-{3-[(*tert*-Butoxy)carbonylamino]-3-(methoxycarbonyl)propoxy}phenyl}glyoxyl}amino}-2-oxoazetidin-1-yl}{4-[(*tert*-butyl)dimethylsilyloxy]phenyl}methyl}phosphonates* (diastereoisomer mixture; **31**) were obtained from **24** in 85% yield as described for **28**. IR (CH_2Cl_2): 3190–3336 (NH), 1750 (β-lactam), 1719 (Boc), 1670–1690 (amide, ketone). ^{1}H-NMR ($CDCl_3$): 0.10 (*s*, Me_2Si); 1.02 (*s*, Me_3CSi); 1.19–1.49 (*m*, 2 Me, Me_3C); 2.13–2.40 (*m*, CH_2); 3.19 (*dd*, *J* = 2.0, 6.5, H_β–C(4)); 3.71 (*s*, MeO); 3.80–4.33 (*m*, 2 CH_2OP, $O_2CCHNCO_2$, H_α–C(4)); 4.59 (*t*, *J* = 6.0, CH_2O); 4.82 (*d*, *J* = 20.0, CHP); 5.26 (*m*, H–C(3)); 6.80 (br., 2 NH); 6.89, 7.48, 7.49, 8.28 (2 *AA'BB'*, 2 C_6H_4). Anal. calc. for $C_{38}H_{56}N_3O_{12}PSi$ (805.94): C 56.63, H 7.00, N 5.21; found: C 56.77, H 7.12, N 5.30.

*(±)-Diethyl {{3-{{{4-{3-[(*tert*-Butoxy)carbonylamino]-3-(methoxycarbonyl)propoxy}phenyl}glyoxyl}amino}-2-oxoazetidin-1-yl}(4-hydroxyphenyl)methyl}phosphonates* (diastereosimer mixture; **32**). To a soln. of **31** (0.81 g, 1.1 mmol) in dry THF (20 ml) was added anh. Bu_4NF (0.31 g, 1.2 mmol). The mixture was stirred at 0° for 1 h and then partitioned between Et_2O (35 ml) and H_2O (30 ml). The org. layer was dried ($MgSO_4$), filtered, and evaporated. Purification by CC (silica gel, $CHCl_3$/AcOEt 2:1) gave 0.68 g (98%) of **32**. Foam. IR (CH_2Cl_2): 3150–3410 (NH, OH), 1750 (β-lactam), 1720 (Boc), 1670–1688 (amide, ketone). ^{1}H-NMR ($CDCl_3$/D_2O): 1.20–1.51 (*m*, 2 Me, Me_3C); 2.14–2.42 (*m*, CH_2); 3.20 (*dd*, *J* = 2.0, 6.5, H_β–C(4)); 3.75 (*s*, MeO); 3.80–4.42 (*m*, 2 CH_2OP, $O_2CCHNCO_2$, H_α–C(4)); 4.59 (*t*, *J* = 6.0, CH_2O); 4.79 (*d*, *J* = 20.0, CHP); 5.26 (*dd*, *J* = 2.0, 5.0, H–C(3)); 6.79, 7.30 (*AA'BB'*, *J* = 8.0, C_6H_4OD); 7.51, 8.30 (*AA'BB'*, *J* = 8.9, C_6H_4CO). Anal. calc. for $C_{32}H_{42}N_3O_{12}P$ (691.68): C 55.57, H 6.12, N 6.08; found: C 55.68, H 6.23, N 6.19.

(±)-{{3-{{{4-(3-Amino-3-carboxypropoxy)phenyl]glyoxyl}amino}-2-oxoazetidin-1-yl}(4-hydroxyphenyl)methyl}phosphonic Acids (diastereoisomer mixture; **33**). To a soln. of **32** (1.38 g, 1.99 mmol) in CH_2Cl_2 (30 ml) was added Me_3SiBr (3.06 g, 20.0 mmol). The mixture was stirred at 25° for 15 h, then MeOH (40 ml) and H_2O (10 ml) were added. After evaporation, the resultant precipitate was crystallized from MeOH/Et_2O 1:1: 0.20 g (20%) of **33**. M.p. 249–251° (dec.). IR (nujol): 3500–2610 (OH, CO_2H, NH_2, NH), 1747 (β-lactam), 1670–1660 (amide, ketone). UV (EtOH): 230 (20100), 299 (14500). ^{1}H-NMR (D_2O/$NaHCO_3$): 2.01–2.39 (*m*, CH_2); 3.19 (*dd*, *J* = 2.0, 6.5, H_β–C(4)); 3.99 (*t*, *J* = 6.0, O_2CCHND_3); 4.14 (*dd*, *J* = 5.0, 6.5, H_α–C(4)); 4.40 (*t*, *J* = 2.0, 5.0, H–C(3)); 6.80, 7.33 (*AA'BB'*, *J* = 8.5, C_6H_4OD); 7.41, 8.32 (*AA'BB'*, *J* = 9.0, C_6H_4CO). Anal. calc. for $C_{22}H_{24}N_3O_{10}P$ (521.42): C 50.68, H 4.64, N 8.06; found: C 50.89, H 4.40, N 8.24.

(±)-(Z)-{{3-{{{4-(3-Amino-3-carboxypropoxy)phenyl](hydroxyimino)acetyl}amino}-2-oxoazetidin-1-yl}(4-hydroxyphenyl)methyl}phosphonic Acids (diastereisomer mixture; **34**) were prepared from **33** in 65% yield as described for **30**. M.p. 230–233° (dec.). IR (nujol): 3500–2500 (OH, CO_2H, NH_2, NH), 1726 (β-lactam), 1660 (amide), 1605. UV (EtOH/H_2O): 225 (18500), 272 (15000). UV (EtOH/0.1N NaOH): 226 (20000), 291 (12500).

^{1}H-NMR (D_2O/$NaHCO_3$): 2.19–2.46 (*m*, CH_2); 3.20 (*dd*, *J* = 2.2, 7.0, H_β–C(4)); 3.90 (*t*, *J* = 6.0, O_2CCHND_3); 4.15 (*dd*, *J* = 4.5, 7.0, H_α–C(4)); 4.32 (*t*, *J* = 6.0, CH_2O); 4.44 (*d*, *J* = 19.5, CHP); 5.20 (*dd*, *J* = 2.2, 4.5, H–C(3)); 6.80–7.60 (*m*, 2 C_6H_4). Anal. calc. for $C_{22}H_{25}N_4O_{10}P$ (536.44): C 49.26, H 4.70, N 10.44; found: C 49.14, H 4.88, N 10.49.

*(±)-Diethyl {{3-{{{4-[3-[(*tert*-Butoxy)carbonylamino]-3-(methoxycarbonyl)propoxy}phenyl}glyoxyl}-amino}-2-oxoazetidin-1-yl}(pyridin-4-yl)methyl}phosphonates* (diastereoisomer mixture; **35**) were prepared from **27** in 80% yield as described for **28**. IR (CH_2Cl_2): 3185–3330 (NH), 1760 (β-lactam), 1720 (Boc), 1670–1690 (amide, ketone). ^{1}H-NMR ($CDCl_3$): 1.14–1.46 (*m*, 2 Me, Me_3C); 2.14–2.40 (*m*, CH_2); 3.17 (*dd*, *J* = 2.0, 6.5, H_β–C(4)); 3.90 (*s*, MeO); 3.80–4.33 (*m*, 2 CH_2OP, $O_2CCHNCO_2$, H_α–C(4)); 4.60 (*t*, *J* = 6.0, CH_2O); 5.20 (*d*, *J* = 20.0, CHP); 5.28 (*m*, H–C(3)); 6.80, 7.02 (2 br., 2 NH); 7.48, 7.32, 8.28, 8.50 (2 *AA'BB'*, C_6H_4, C_5H_4N). Anal. calc. for $C_{31}H_{41}N_4O_{11}P$ (676.67): C 55.03, H 6.11, N 8.28; found: C 55.14, H 6.21, N 8.16.

*(±)-Diethyl {{3-{{{4-[3-[(*tert*-Butoxy)carbonylamino]-3-(methoxycarbonyl)propoxy}phenyl}glyoxyl}-amino}-2-oxoazetidin-1-yl}(1-oxidopyridin-1-ium-4-yl)methyl}phosphonates* (diastereoisomer mixture; **36**). To a dry CH_2Cl_2 (20 ml) soln. containing 3-$ClC_6H_4CO_3H$ (516 mg, 2.99 mmol) was added **35** (677 mg, 1.00 mmol) at 0°. After the soln. had been stirred at 0° for 1 h and at 25° for 30 min, 1% $NaHCO_3$ soln. (10 ml) was added. The org. layer was dried ($MgSO_4$) and evaporated and the crude material chromatographed (silica gel, AcOEt/MeOH 9:1): 0.62 g (90%) of **36**. Foam. IR (CH_2Cl_2): 3200–3350 (NH), 1770 (β-lactam), 1720 (Boc), 1669–1690 (amide, ketone). ^{1}H-NMR ($CDCl_3$/D_2O): 1.15–1.50 (*m*, 2 Me, Me_3C); 2.15–2.40 (*m*, CH_2); 3.19 (*dd*, *J* = 2.0, 7.0, H_β–C(4)); 3.70 (*s*, MeO); 3.75–4.44 (*m*, 2 CH_2OP, $O_2CCHNCO_2$, H_α–C(4)); 4.58 (*t*, *J* = 6.0, CH_2O); 5.30 (*dd*, *J* = 2.0, 5.0, H–C(3)); 5.54 (*d*, *J* = 18.5, CHP); 7.25, 8.45 (*AA'BB'*, *J* = 5.8, C_5H_4NO); 7.50, 8.30 (*AA'BB'*, *J* = 8.5, C_6H_4). Anal. calc. for $C_{31}H_{41}N_4O_{12}P$ (692.67): C 53.76, H 5.97, N 8.09; found: C 53.89, H 5.82, N 8.16.

(±)-{{3-{{{4-(3-Amino-3-carboxypropoxy)phenyl]glyoxyl}amino}-2-oxoazetidin-1-yl}(1-oxidopyridin-1-ium-4-yl)methyl}phosphonic Acids (diastereoisomer mixture; **37**) were obtained from **36** in 15% overall yield as described for **33**. M.p. 228–230° (dec.). IR (nujol): 3450–2600 (2 OH, CO_2H, NH_2, NH), 1756 (β-lactam), 1675–1660 (amide, ketone). UV (EtOH): 229 (20000), 300 (14150). ^{1}H-NMR (D_2O): 2.02–2.40 (*m*, CH_2); 3.02 (*dd*, *J* = 2.2, 7.0, H_β–C(4)); 4.01 (*t*, *J* = 6.0, O_2CCHND_3); 4.15 (*dd*, *J* = 5.4, 7.0, H_α–C(4)); 4.42 (*t*, *J* = 6.0, CH_2O); 5.20 (*dd*, *J* = 2.2, 5.4, H–C(3)); 5.45 (*d*, *J* = 19.0, CHP); 7.20, 8.40 (*AA'BB'*, *J* = 6.0, C_5H_4NO); 7.41, 8.25 (*AA'BB'*, *J* = 6.0, C_6H_4). Anal. calc. for $C_{21}H_{23}N_4O_{10}P$ (522.41): C 48.28, H 4.44, N 10.72; found: C 48.16, H 4.26, N 10.95.

(±)-(Z)-{{3-{{{4-(3-Amino-3-carboxypropoxy)phenyl](hydroxyimino)acetyl}amino}-2-oxoazetidin-1-yl}-(1-oxidopyridin-1-ium-4-yl)methyl}phosphonic Acids (diastereoisomer mixture; **38**) were obtained from **37** in 50% yield as described for **30**. M.p. 240–242° (dec.). IR (nujol): 3550–2400 (OH, CO_2H, NH_2, NH), 1740 (β-lactam), 1660 (amide), 1610. UV (EtOH/H_2O): 223 (17000), 270 (16500). UV (EtOH/0.1N NaOH); 223 (19000), 292 (13000). ^{1}H-NMR (D_2O): 2.17–2.42 (*m*, CH_2); 3.23 (*dd*, *J* = 2.0, 6.6, H_β–C(4)); 3.91 (*t*, *J* = 6.0, O_2CCHND_3); 4.11 (*dd*, *J* = 5.0, 6.6, H_α–C(4)); 4.35 (*t*, *J* = 6.0, CH_2O); 5.18 (*dd*, *J* = 2.0, 5.0, H–C(3)); 5.38 (*d*, *J* = 18.0, CHP); 7.26–8.45 (*m*, C_5H_4NO, C_6H_4). Anal. calc. for $C_{21}H_{24}N_5O_{10}P$ (537.43): C 46.93, H 4.50, N 13.03; found: C 46.80, H 4.71, N 12.86.

*(±)-*tert*-Butyl 2-[*cis*-2-Formyl-4-oxo-3-(phenylacetamido)azetidin-1-yl]-2-(dimethylphosphono)acetates* (diastereoisomer mixture; **40**) were prepared from **39** in 98% yield as described for **19**. IR (CH_2Cl_2): 3420 (NH), 1770 (β-lactam), 1740 (ester), 1720 (aldehyde), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 1.29, 1.34 (2*s*, Me_3C); 3.58 (br. *s*, CH_2CO); 3.78, 3.90 (2*d*, 2 Me); 4.78 (br., H–C(4)); 4.83, 5.03 (2*d*, *J* = 23.0, CHP); 5.40–5.80 (2*dd*, *J* = 5.0, 10.0, H–C(3)); 7.30 (br. *s*, NH, C_6H_5); 9.65, 9.90 (2*d*, *J* = 1.6, CHO). MS: 454 (M^+), 426 ([M – CO]$^+$). Anal. calc. for $C_{20}H_{27}N_2O_8P$ (454.42): C 52.86, H 5.99, N 6.16; found: C 52.91, H 6.01, N 6.19.

*(±)-*tert*-Butyl 2-[2-Oxo-3-(phenylacetamido)azetidin-1-yl]-2-(dimethylphosphono)acetates* (diastereoisomer mixture; **41**) were obtained from **40** in 55% yield as described for **20**. IR (CH_2Cl_2): 3410 (NH), 1769 (β-lactam), 1740 (ester), 1685 (amide). ^{1}H-NMR ($CDCl_3$): 1.32 (*s*, Me_3C); 3.13 (*dd*, *J* = 1.9, 6.5, H_β–C(4)); 3.59 (*s*, CH_2CO); 3.76, 3.89 (2*d*, 2 Me); 4.01 (*dd*, *J* = 5.0, 6.5, H_α–C(4)); 4.90 (*d*, *J* = 23.0, CHP); 4.97–5.05 (*m*, H–C(3)); 6.91 (*d*, *J* = 8.5, NH); 7.25 (*s*, C_6H_5). Anal. calc. for $C_{19}H_{27}N_2O_7P$ (426.41): C 53.52, H 6.38, N 6.57; found: C 53.60, H 6.44, N 6.63.

*(±)-*tert*-Butyl 2-[2-Oxo-3-(phenylacetamido)azetidin-1-yl]-2-(4,4-dimethoxycyclohexa-2,5-dienylidene)acetate* (**42**). To a soln. of **41** (4.26 g, 10.0 mmol) and 4,4-dimethoxycyclohexa-2,5-dien-1-one (1.54 g, 10.0 mmol) in THF (70 ml) was added NaH (240 mg, 10.0 mmol). The soln. was stirred at −20° for 1 h and at 25° for 4 h. The mixture was quenched with 3% aq. NH_4Cl soln. (25 ml) and extracted with CH_2Cl_2. The org. layer was dried ($MgSO_4$) and evaporated. Purification by CC (silica gel, CH_2Cl_2) gave 2.04 g (45%) of **42**. Oil. IR (CH_2Cl_2): 3400 (NH), 1800 (β-lactam), 1756 (ester), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 1.58 (*s*, Me_3C); 3.22 (*dd*, *J* = 2.1, 6.4, H_β–C(4)); 3.46 (br. *s*, 2 Me); 3.60 (*s*, CH_2CO); 4.16 (*dd*, *J* = 5.0, 6.4, H_α–C(4)); 5.17 (*m*, H–C(3)); 6.10, 6.24 (2*d*, *J* = 10.2,

(C*H*=CH)$_2$C(OMe)$_2$); 6.63 (br. *d*, *J* = 10.2, (CH=C*H*)$_2$C(OMe)$_2$); 7.5 (*s*, C_6H_5); 7.70 (*d*, *J* = 8.0, NH). Anal. calc. for $C_{25}H_{39}N_2O_6$ (454.53): C 66.06, H 6.65, N 6.16; found: C 66.29, H 6.50, N 6.28.

(±)-2-[2-Oxo-3-(phenylacetamido)azetidin-1-yl]-2-(4,4-dimethoxycyclohexa-2,5-dienylidene)acetic Acid (**43**). To a soln. of **42** (0.91 g, 2.0 mmol) in CH_2Cl_2/CF_3CO_2H 3:1 (12 ml) was added a trace amount of Bu_4NClO_4, and the soln. was stirred at 25° for 1 h. Purification by CC (silica gel, Et_2O) afforded 0.20 g (25%) of **43**. Pale yellow precipitate. M.p. 60° (brown), 80° (dec.). IR (CH_2Cl_2): 3100–3420 (NH, CO_2H), 1798 (β-lactam), 1713 (acid), 1670 (amide). ^{1}H-NMR ($CDCl_3/D_2O$): 3.16 (*dd*, *J* = 2.0, 6.0, H_β–C(4)); 3.38 (*s*, 2 Me); 3.61 (*s*, CH_2CO); 4.01 (*dd*, *J* = 4.5, 6.0, H_α–C(4)); 5.06 (*dd*, *J* = 2.0, 4.5, H–C(3)); 5.91, 6.02 (2*d*, *J* = 10.0, (C*H*=CH)$_2$C(OMe)$_2$); 6.49 (*d*, *J* = 10.0, (CH=C*H*)$_2$C(OMe)$_2$); 7.40 (*s*, C_6H_5). Anal. calc. for $C_{21}H_{22}N_2O_6$ (398.42): C 63.31, H 5.57, N 7.03; found: C 63.54, H 5.30, N 6.82.

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