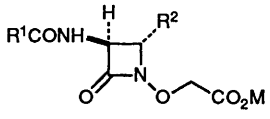
Synthesis and Reactions of 4-Acetoxy-1-oxyazetidin-2-ones

Andrew Sheppard and Marvin J. Miller*
Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556, USA

A general synthesis of 4-acetoxy-1-oxyazetidin-2-ones is described. Reaction of these compounds with certain nucleophiles caused β-lactam cleavage rather than displacement of the acetoxy group, as occurs with the simpler compound 4-acetoxyazetidin-2-one.

The oxamazins (**1**) are totally synthetic monocyclic β-lactam antibiotics, first prepared in our laboratories several years ago.[1] The bactericidal activity of the oxamazins (**1**) can be attributed to the presence of the electron-withdrawing oxygen substituent at N-1, which tends to sensitise the β-lactam ring towards nucleophilic cleavage. Similarly the activity of the naturally occurring monobactams, *e.g.* (**2**), has been explained by the presence of the sulphonate group at N-1.[2] To improve the biological activity of the oxamazins, we sought to incorporate the N-1 oxygen substituent of the oxamazins into a bicyclic structure (**3**): the majority of useful β-lactam antibiotics have a bicyclic structure in which the β-lactam ring is fused to either a five- (*e.g.*, penicillins (**4**), penems (**5**), carbapenems (**6**)] or six-membered ring [*e.g.*, cephalosporins (**7**), oxacephems (**8**), carbacephems (**9**)]. We reasoned that a compound (**10**), having an acetoxy group as a leaving group at C-4 of the β-lactam ring, might be a useful precursor for introduction of a side-chain suitable for eventual elaboration to bicycle (**3**). The simpler 4-acetoxyazetidin-2-one (**11**) readily undergoes displacement of the acetoxy group with a wide variety of carbon, nitrogen, oxygen, sulphur, and phosphorus nucleophiles;[3] indeed, so useful is substrate (**11**) that it is one of only a handful of commercially available β-lactams.† We now report a simple general synthesis of 1-alkyloxy- and 1-acyloxy-azetidin-2-ones (**10**) and also some reactions of compounds (**10**) with nucleophiles.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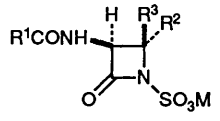
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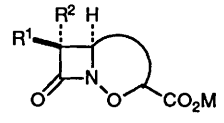
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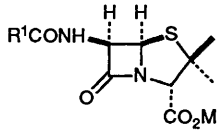
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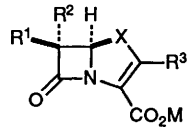
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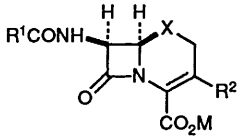
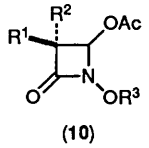
(6) X = CH_2


(7) X = S
(8) X = O
(9) X = CH_2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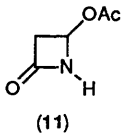
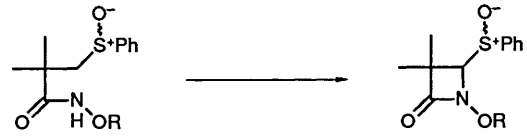
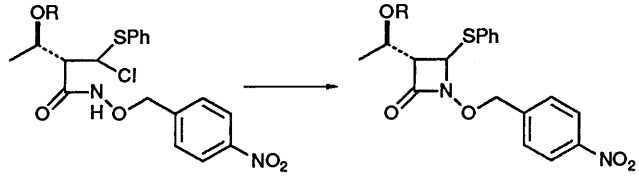

(11)

Discussion

Although there have been many C-4 carbon-substituted 1-oxyazetidin-2-ones reported in the literature,[1] examples having a heteroatom at the C-4 position are much less common. Thus, oxidation of 1-hydroxyazetidines (**12**) with lead tetra-acetate (LTA) gave the 1,4-bis(acetoxy) compounds (**13**),[4] while Pummerer-type reaction of sulphoxide (**14**)[5] or base treatment of α-chloro sulphide (**15**)[6] gave β-lactams (**16**) and (**17**) respectively. To form our 4-acetoxy-1-oxyazetidin-2-ones (**10**),

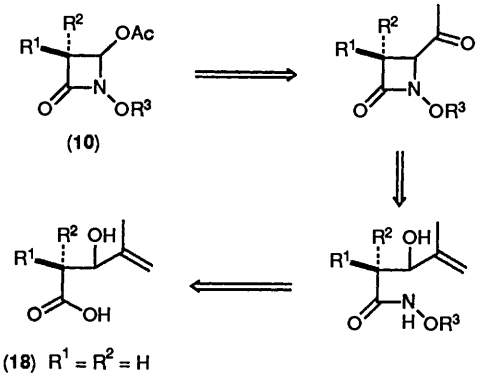

(12) (13)


(14) (16)


(15) (17)

we required a milder, more general method than that for formation of the similar compound (**13**), compatible with a variety of side-chains R^1 and R^2. After much experimentation and exploration of a variety of routes, a synthesis of compounds (**10**) based on the retrosynthesis outlined in Scheme 1 was adopted, in which the oxygen atom at C-4 was introduced by Baeyer–Villiger reaction of a ketone.[7] Another key step in the synthesis was formation of the β-lactam ring by our highly efficient intramolecular Mitsunobu-type reaction of a β-

† The 1988–1989 catalogue price for 4-acetoxyazetidin-2-one was $60.80 for 5 g (Aldrich Chemical Co., Milwaukee, WI).

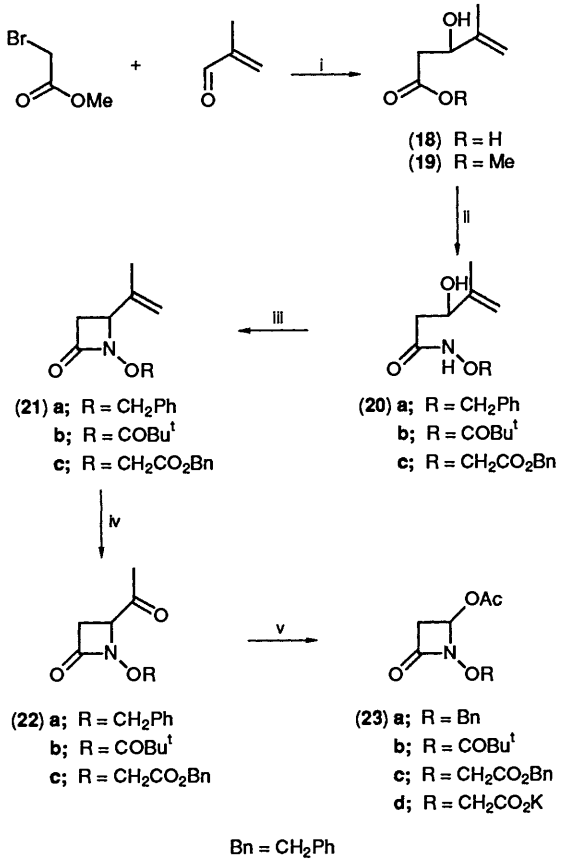


Scheme 1. Retrosynthesis of 4-acetoxy-1-oxyazetidin-2-ones (**10**).

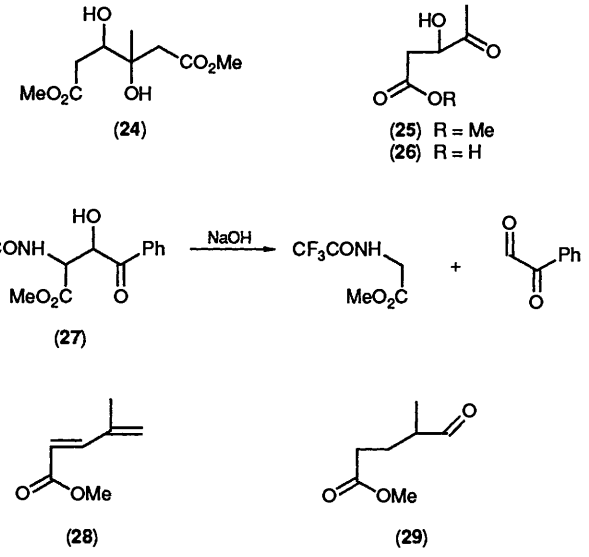
hydroxy hydroxamate.[1] In this paper we report only our results involving a simple example of compound (**10**), having $R^1 = R^2 = H$. However, this route to substrates (**10**) is generally applicable: our results for more complex examples of structure (**10**; $R^1 \neq R^2 \neq H$) will be reported later.

3-Hydroxy-4-methylpent-4-enoic acid (**18**), the starting material for the synthesis of compounds (**10**), was easily prepared on a multigram scale by Reformatsky reaction of methyl bromoacetate and 2-methylprop-2-enol (methacrolein) followed by base hydrolysis of the resulting ester (**19**) (Scheme 2).[8,9] Methacrolein, in which the alkene group can be considered to be a masked ketone moiety, was used in the Reformatsky reaction rather than the 'free' ketone methyl glyoxal MeCOCHO since it was thought that, in the latter case, a side-reaction might occur leading to the 'double Reformatsky' product (**24**). A further problem might be a retro-aldol reaction of the Reformatsky product (**25**) on base hydrolysis to give acid (**26**).* Notable in the formation of compound (**19**) is the fact that no dehydration to give diene (**28**) or Michael addition to give (**29**) occurred.

Acid (**18**) underwent a smooth carbodi-imide-mediated coupling reaction with either *O*-benzylhydroxylamine or *O*-pivaloylhydroxylamine hydrochloride to give the hydroxamates (**20a**) and (**20b**), respectively.[10] While the benzyl compound (**20a**) was stable, compound (**20b**) proved to be difficult to work with and awkward to purify since the pivaloyloxy group was partially hydrolysed on silica gel chromatography. *Rapid* short-path chromatography was usually the most efficient way to purify the *O*-pivaloyl compounds, but, because of their lability, yields for these species throughout this sequence were lower than for the corresponding reactions to form the *O*-benzyl analogues.



Scheme 2. *Reagents and conditions:* i, (a) Zn, C_6H_6, heat; (b) NaOH, aq. THF, heat; ii, NH_2OR [$Cl^- NH_3OCOBu^t$, for (**20b**)], WSC, aq. THF, pH 4–5; iii, DEAD, PPh_3, THF [for (**27a,c**)] or PPh_3, CCl_4, Et_3N, MeCN [for (**20b**)]; iv, O_3, CH_2Cl_2, −78 °C; then Me_2S −78 °C to room temp.; v, MCPBA, CH_2Cl_2, room temp. or heat.



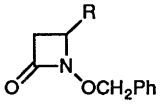
Cyclisation of compound (**20a**) to β-lactam (**21a**) was readily accomplished by Mitsunobu-type reaction with diethyl azodicarboxylate (DEAD) and triphenyl phosphine in tetrahydrofuran (THF).[1] The by-products in this reaction, diethyl hydrazodicarboxylate and triphenylphosphine oxide, could largely be removed by repeatedly dissolving the crude product in diethyl ether, cooling, and filtration. By this procedure, purification of the filtrate containing the β-lactam product was greatly facilitated, reducing the chromatography essentially to a simple filtration. β-Lactam (**21b**) could also be prepared by this reaction but, owing to the lability of the *O*-pivaloyl group, as mentioned above, we preferred to use different conditions for the cyclisation, namely triphenylphosphine and carbon tetrachloride–triethylamine.[11] The by-products in this reaction, triethylammonium chloride and triphenylphosphine oxide, could be removed by aqueous work-up (in the former case) followed by diethyl ether–cooling–filtration procedure to remove the latter. Any remaining triphenylphosphine oxide could be removed by *rapid* filtration through silica gel.

Ozonolysis of both lactams (**21a**) and (**21b**) followed by

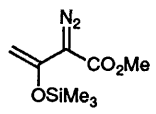
* We observed partial retro-aldol reaction of (**27**) on attempted hydrolysis to the free amino acid with base (M. J. Miller and A. Sheppard, unpublished results).

treatment of the ozonide with dimethyl sulphide *in situ* gave the corresponding ketones (**22a**) and (**22b**). Baeyer–Villiger reaction of the latter compounds with excess of *m*-chloroperoxybenzoic acid (MCPBA) gave the required 4-acetoxy-1-oxyazetidin-2-ones (**23a**) and (**23b**).

Having prepared compounds (**23a**) and (**23b**) we tried several reactions to displace the 4-acetoxy group: these studies were mainly carried out using the 1-benzyloxy compound (**23a**) due to its greater stability and ease of handling compared with the 1-pivaloyloxy species (**23b**). Thus, compound (**23a**) was treated with potassium methyl malonate[12] [aq. THF, acetone, or dimethylformamide (DMF); room temperature or heat] in the hope of producing the azetidinyl malonate (**30**). Disappointingly, only starting material was recovered. A similar lack of success was observed on treatment of compound (**23a**) with sodium toluene-*p*-sulphinate[3a] (DMF; room temperature):



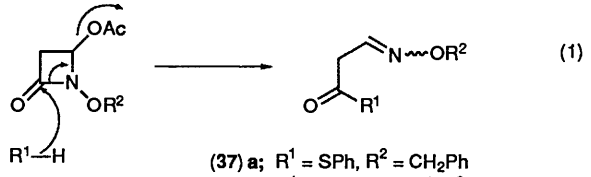
(**30**) R = $O_2CCH_2CO_2Me$
(**31**) R = SO_2Ph
(**33**) R = F
(**34**) R = $CH_2CN_2CO_2Me$
(**35**) R = SPh
(**36**) R = $SCH_2CO_2Bu^t$



(**32**)

only starting material was recovered instead of the hoped for sulphone (**31**). By contrast, reaction of compound (**23a**) with tetrabutylammonium fluoride (THF; 0 °C) or silyl enol ether (**32**)[13] [$ZnCl_2$, ZnI_2 BF_3·OEt_2, or trimethylsilyl trifluoromethanesulphonate (TMSOTf) in CH_2Cl_2] caused decomposition: neither starting material (**23a**) nor desired products (**33**) or (**34**), respectively, were recovered.

Despite these discouraging results, some further reactions were tried. Thus, attempted displacement of the acetoxy group

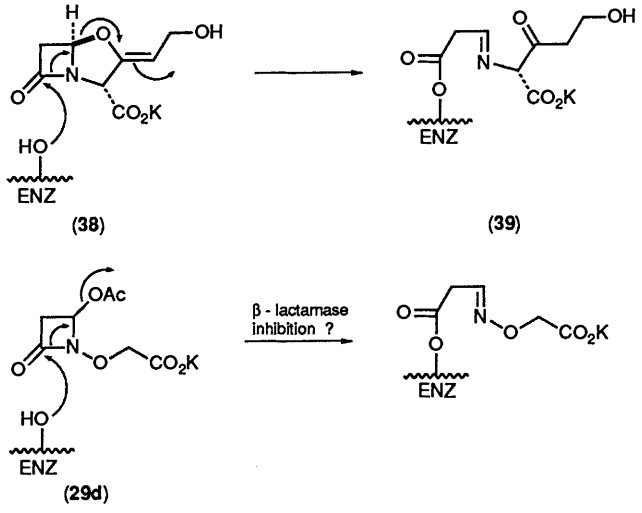


(1)

(**37**) **a**; R^1 = SPh, R^2 = CH_2Ph
b; R^1 = $SCH_2CO_2Bu^t$, R^2 = CH_2Ph
c; R^1 = NMe_2, R^2 = CH_2Ph

of substitute (**23a**) under a variety of conditions with either thiophenol or t-butyl mercaptoacetate to give the corresponding sulphides (**35**) and (**36**) gave, instead, the oximes (**37a**) and (**37b**), respectively.* Similarly, reaction of substrate (**23a**) with dimethylamine gave oxime (**37c**). It seemed that displacement of the acetoxy group *was* occurring but by an indirect route, presumably as shown in equation (1).

On the face of it exclusive formation of oximes (**37**) seemed to show that acetates (**23**) were not useful precursors for other 4-(heterosubstituted) azetidin-2-ones. However, the mechanism of β-lactam cleavage with concomitant loss of the C-4 oxy substituent led us to consider another interesting possibility. Clavulanic acid (**38**), a naturally occurring β-lactamase inhibitor, is cleaved by a β-lactamase as shown in Scheme 3.[14] A serine residue in the enzyme active site attacks the β-lactam carbonyl leading (initially) to afford loss of the 7-oxo group and formation of an imine (**39**). It struck us that there was a marked

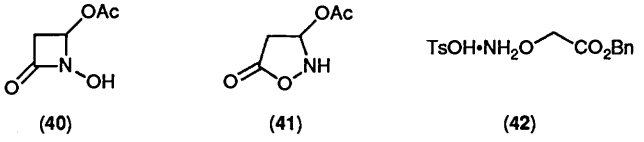


(**38**) (**39**) (**29d**)

Scheme 3.

similarity between the structure of oximes (**37**) and imine (**39**). Therefore, we reasoned that a suitably substituted derivative of 4-acetoxy compound (**23**) might also act as a β-lactamase inhibitor with a similar mechanism of action. We chose to make compound (**23d**), which has an oxyacetic acid group at N-1, as is present in the oxamazins (**1**).

The most obvious route towards substrate (**23d**) would be to remove the 1-oxy protecting group from compound (**23a**) or (**29b**) and to realkylate the resulting 4-acetoxy-1-hydroxyazetidin-2-one (**40**) with, for example, a bromoacetate.



(**40**) (**41**) (**42**)

However, under a variety of conditions hydrogenation of compound (**23a**) gave a complex mixture containing compound (**40**) and the rearrangement product (**41**),[15] while hydrolysis of compound (**23b**) with aqueous sodium carbonate was similarly unrewarding. Consequently, a synthesis of substrate (**23d**) starting from amino-oxyacetate (**42**) was carried out, using the same methodology as for the preparation of compounds (**23a,b**) (Scheme 1). Thus, tosyl salt (**42**) was coupled with acid (**18**) to give hydroxamate (**20c**), which was cyclised under Mitsunobu-type conditions to afford lactam (**21c**). Ozonolysis of the latter followed by Baeyer–Villiger reaction of the resulting ketone (**22c**) and hydrogenolysis in the presence of potassium hydrogen carbonate gave the target compound (**23d**) as the potassium salt. Unfortunately, compound (**23d**) showed no β-lactamase inhibitory activity or antibiotic activity against a variety of organisms.

Experimental

M.p.s were taken on a Thomas Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 727B

* Reinhoudt and co-workers (P. A. van Elburg, D. N. Reinhoudt, S. Harkema, and G. J. van Hummel, *Tetrahedron Lett.*, 1985, **26**, 2809) found that 1,4-diacetoxy β-lactams are cleaved similarly by alcohols and thiols to give β-oximino esters. However, we hoped that with an alkyloxy rather than an acyloxy substitutent at N-1 our 4-acetoxyazetidinone (**23a**) might be less susceptible to nucleophilic cleavage: clearly this was not the case!

spectrophotometer. NMR spectra were recorded using $CDCl_3$ as solvent, except where indicated, on a Magnachem A200 (200 MHz) or General Electric GN-300 (300 MHz) instrument). Mass spectra were recorded using the technique indicated on a Finegan-MAT 8430 machine using either the electron ionisation (EI) or chemical ionisation (Cl, isobutane as ionising gas) methods. All solvents were dried, and distilled under a nitrogen atmosphere by standard methods[16] immediately before use. Zinc dust was freshly activated before use by being washed successively with 10% aq. HCl, water, and diethyl ether and then dried at 120 °C. WSC refers to the water-soluble carbodi-imide 1-(3-dimethylaminpropyl)-3-ethylcarbodi-imide.

Preparation of Methyl 3-*Hydroxy*-4-*methylpent*-4-*enoate* (**19**).—A 500 ml, 3-necked flask fitted with a condenser, mechanical stirrer, and 125 ml dropping funnel was purged with nitrogen. Freshly activated zinc dust (14.1 g, 0.213 mol), and benzene (75 ml) were placed in the flask. Methyl bromoacetate (27.27 g, 0.18 mol), methacrolein (15 g, 0.21 mol, 1.2 mol equiv.), and benzene (120 ml) were placed in the dropping funnel. Nitrogen was introduced into the apparatus *via* a septum on the condenser with a septum on the dropping funnel acting as outlet. Without applied stirring, the bromide–aldehyde solution (~10 ml) was added to the zinc suspension and the mixture was *cautiously* brought to reflux. After *ca.* 10 min of gentle reflux, some foaming occurred: the heating mantle was removed and temporarily replaced by an ice–water-bath. The rest of the bromide–aldehyde solution was then added at such a rate as to maintain a gentle reflux (*ca.* 45 min required for the addition). The mixture was cooled when necessary with the ice–water bath to prevent excessive foaming. After the addition was complete *and the reaction had subsided*, the grey reaction mixture was vigorously stirred and again brought to reflux with the heating mantle. Over the course of 4 h reflux, the reaction mixture became a cloudy pale green colour and most of the zinc reacted. The reaction mixture was cooled and 10% H_2SO_4 (150 ml) was added. Ethyl acetate (100 ml) was added, the mixture was shaken well, and the two-phase system was filtered to remove unchanged zinc. The aqueous layer was then further extracted with ethyl acetate (3 × 100 ml). The combined organic layers (pale yellow) were washed with saturated brine (2 × 25 ml), dried ($MgSO_4$), filtered, and concentrated to afford a pale orange liquid (21.3 g, 83%) which, by NMR spectroscopy, was >95% pure and could be used without further purification. In another experiment, methyl bromoacetate (9.09 g, 59.4 mmol), methacrolein (5 g, 71.0 mmol), and zinc dust (4.7 g, 71.0 mmol) were allowed to react in benzene (65 ml) in the same manner as described above to give the product as a liquid (5.53 g, 65%), purified by distillation (b.p. 102–107 °C/3 mmHg); ν_{max}(film) 3 600–3 400 (OH) and 1 740 cm^{-1} (C=O); δ_H(200 MHz) 1.73 (3 H, s, MeC=C), 2.58 (2 H, distorted d, *J* 6 Hz, CH_2CO_2), 3.7 (3 H, s, CO_2Me), 4.48 (1 H, t, *J* 6 Hz, C*H*OH), and 4.86 (1 H, s) and 5.01 (1 H, s) (C=CH_2).

Preparation of 3-*Hydroxy*-4-*methylpent*-4-*enoic Acid* (**18**).[8]—Aqueous sodium hydroxide [7.0 g, 0.175 mol in water (175 ml)] was added to a solution of the ester (**19**) (8.42 g, 0.058 mol) in THF (60 ml). The brown, two-phase mixture was vigorously stirred at reflux under nitrogen for 3 h before being cooled, and extracted with diethyl ether (2 × 25 ml). The aq. layer was then acidified to pH 2 with conc. hydrochloric acid and extracted with ethyl acetate (4 × 100 ml). The combined extracts were dried ($MgSO_4$) and concentrated to give a brown oil (>95% pure by NMR). Filtration through a short (2 cm) column of flash silica (Et_2O as eluant) effected removal of most of the brown colour, leaving the product as a pale yellow, viscous gum (5.06 g, 65%), ν_{max}(film) 3 600–3 000 (OH) and 1 700 cm^{-1} (C=O); δ_H(300 MHz) 1.76 (3 H, s, MeC=C), 2.70–2.55 (2 H, m, CH_2CH), 4.51 (1 H, dd, *J* 7.5, 5.0 Hz, C*H*OH), 4.91 (1 H, ~s, C=C*H*H) and 5.05 (1 H, ~s, C=CH*H*); *m*/*z* (Cl) (*inter alia*) 131 ($MH^+ - H_2O$) and 113 (MH^+).

Preparation of N-*Benzyloxy*-3-*hydroxy*-4-*methylpent*-4-*enamide* (**20a**).—WSC (10.64 g, 2.2 mol equiv.) was added to a cloudy, pale yellow solution of acid (**18**) (3.28 g, 25.23 mmol) and *O*-benzylhydroxylamine (3.41 g, 27.75 mmol, 1.1 mol equiv.) in THF–water (100 ml of each) and the pH was adjusted (from pH 7) to pH 4. The pH was maintained at pH 4–5 during the course of the reaction by addition of 10% aq. HCl when necessary. After 1 h, the reaction mixture was extracted with ethyl acetate (50 ml), saturated with brine, and further extracted with ethyl acetate (2 × 50 ml). The combined organic layers were washed successively with 10% aq. citric acid (25 ml), 5% aq. sodium hydrogen carbonate (25 ml), and saturated brine (25 ml), dried ($MgSO_4$), filtered, and concentrated to give a pale brown solid, which was recrystallised from diethyl ether–hexanes with cooling. The product, N-*benzyloxy*-3-*hydroxy*-4-*methylpent*-4-*enamide* (**20a**), was obtained as an off-white solid (4.78 g, 81%), m.p. 66–67 °C (from Et_2O–hexanes) [Found: C, 66.2; H, 7.35; N, 5.9%; *M*(EI), 235.1212. $C_{13}H_{17}NO_3$ requires C, 66.36; H, 7.28; N, 5.95% 235.120 844]; ν_{max}(KBr) 3 500–3 100s (OH), 3 210sh s (NH), and 1 665sh s cm^{-1} (C=O); δ_H(300 MHz) 1.6 (3 H, s, MeC=C), 2.38–2.22 (2 H, m, CH_2CHOH), 4.4 (1 H, m, C*H*OH), 4.87 (2 H, s, OCH_2Ph), 4.92 (1 H, s) and 5.00 (1 H, s) (C=CH_2), 7.38 (5 H, m, Ph), and 8.57 (1 H, br s, NH); δ_C (75.5 MHz) 18.2 (q, Me), 38.8 (t, CH_2CH), 71.7 (d, CHOH), 78.1 (t, OCH_2Ph), 110.3 (s, C=CH_2), 111.3 (t, C=CH_2), 128.5 (d), 128.6 (d), 129.1 (d), and 135.2 (s) (ArC), and 145.6 (s, C=O); *m*/*z* (Cl) (*inter alia*) 236 (MH^+).

Preparation of 1-*Benzyloxy*-4-*isopropenylazetidin*-2-*one* (**21a**).—DEAD (3.52 g, 20.23 mmol) was added dropwise during 5 min to a solution of the hydroxamate (**20a**) (4.53 g, 19.27 mmol) and triphenylphosphine (TPP) (5.46 g, 20.81 mmol) in THF (200 ml) at 0 °C under nitrogen. The resulting deep orange mixture was allowed to come to room temperature during 2 h before being stirred at room temperature for a further 16 h. Concentration gave a pale orange solid. Addition of diethyl ether and cooling to −10 °C, followed by filtration of the precipitated reduced DEAD and triphenylphosphine (TPPO) gave an orange filtrate, which was concentrated. The orange gummy residue obtained was a mixture, by NMR spectroscopy, containing ~70% required β-lactam, the remainder being reduced DEAD and TPPO. The oil was chromatographed (2:1 hexanes–Et_2O) to give the title product, 1-*benzyloxy*-4-*isopropenylazetidin*-2-*one* (**21a**), as a pale yellow liquid (3.2648 g, 78%), ν_{max}(film) 1 770s cm^{-1} (β-lactam C=O); δ_H(300 MHz) 1.60 (3 H, ~dd, *J* 1, 1 Hz, C=CMe), 2.39 (1 H, dd, *J* 13.8, 2.4 Hz, *trans*-C*H*HCH), 2.69 (1 H, dd, *J* 13.8, 5.4 Hz, *cis*-CH*H*CH), 3.90 (1 H, dd, *J* 5.4, 2.4 Hz, CH_2CH), 4.83–4.91 (2 H, AB system, *J* 11, 11 Hz, OCH_2Ph), 4.90 (1 H, m) and 4.92 (1 H, m) (C=CH_2), and 7.28–7.34 (5 H, m, Ph); δ_C(75.5 MHz) 16.3 (q, Me), 37.3 (t, CH_2CH), 62.2 (d, CH_2CH), 77.7 (t, OCH_2Ph), 110.3 (s, C=CH_2), 115.9 (t, C=CH_2), 128.5 (d), 128.8 (d), 128.9 (d), and 135.2 (s) (ArC), and 140.6 (s, C=O); *m*/*z* (Cl) (*inter alia*) 218 (MH^+) [Found: (EI) M^+, 217.110 10. $C_{13}H_{15}NO_2$ requires *M*, 217.110 279].

Preparation of 4-*Acetyl*-1-*benzyloxyazetidin*-2-*one* (**22a**).—Ozone was bubbled through a solution of the alkene (**21a**) (0.65 g, 3.01 mmol) in methylene dichloride (60 ml) at −78 °C for 10 min, after which time the reaction mixture had become deep blue. After being stirred for a further 10 min without loss of colour, the mixture was treated with bubbling O_2 for 15 min to displace excess of O_3. Dimethyl sulphide (0.94 g, 15.06 mmol)

was added and the pale yellow reaction mixture was allowed to come to room temperature during 1 h before being stirred for a further 10 h. The reaction mixture was concentrated to afford a yellow gum, which was purified by flash chromatography (2″ length of silica; Et_2O–hexanes 3:1) to give the product, 4-*acetyl*-1-*benzyloxyazetidin*-2-*one* (**22a**) (0.488 g, 74%), as a gum (Found: C, 65.8; H, 6.1; N, 6.3. $C_{12}H_{13}NO_3$ requires C, 65.74; H, 5.98; N, 6.39%); ν_{max}(film) 1 780s (β-lactam C=O) and 1 720s cm^{-1} (ketone C=O); δ_H(300 MHz) 2.15 (3 H, COMe), 2.59 (1 H, dd, *J* 13.8, 2.8 Hz, *trans*-C*H*HCH), 2.92 (1 H, dd, *J* 13.8, 6.1 Hz, *cis*-CH*H*CN), 4.00 (1 H, dd, *J* 6.1, 2.8 Hz, CH_2CH), 5.04 (2 H, AB system, *J* 11.1, 11.1 Hz, OCH_2Ph), and 7.39 (5 H, m, Ph); δ_C(75.5 MHz) 26.1 (q, COMe), 36.5 (t, CH_2CH), 62.9 (d, CH_2CH), 78.6 (t, OCH_2Ph), 128.7 (s), 129.1 (d), 129.2 (d), and 134.8 (s) (ArC), 163.1 (s, β-lactam C=O), and 204.1 (s, ketone C=O); *m*/*z* (Cl) (*inter alia*) 220 (MH^+).

Preparation of 4-*Acetoxy*-1-*benzyloxyazetidin*-2-*one* (**23a**).—MCPBA (1.54 g, 8.91 mmol) was added to a solution of ketone (**22a**) (0.4881 g, 2.23 mmol) in methylene dichloride (45 ml) at room temperature under nitrogen. After the mixture had been stirred for 18 h, ethyl acetate (100 ml) was added and the solution was washed successively with 10% aq. sodium sulphite (3 × 10 ml), saturated aq. sodium hydrogen carbonate (3 × 10 ml), and saturated brine (10 ml), dried ($MgSO_4$), filtered, and concentrated to afford a waxy, pale brown solid. Recrystallisation from diethyl ether–hexanes gave the product, 4-*acetoxy*-1-*benzyloxyazetidin*-2-*one* (**23a**) (0.372 g, 71%), as a waxy, white solid, m.p. 50–51 °C; ν_{max}(KBr) 1 795 (β-lactam C=O) and 1 755 cm^{-1} (ester C=O); δ_H(300 MHz) 1.95 (3 H, AcO), 2.59 (1 H, dd, *J* 14.3, 1.5 Hz, *trans*-C*H*HCH), 2.92 (1 H, dd, *J* 14.3, 4.4 Hz, *cis*-CH*H*CH), 4.90 (2 H, AB system, *J* 11.1, 11.1 Hz, OCH_2Ph), 5.95 (1 H, dd, *J* 4.4, 1.5 Hz, CH_2CH), and 7.34 (5 H, m, Ph); δ_C(75.5 MHz) 20.7 (q, O_2CMe), 39.6 (t, CH_2CH), 78.6 (t, OCH_2Ph), 78.9 (d, CH_2CH), 128.5 (d), 129.0 (d), 129.3 (d), and 134.7 (s) (ArC), 162.3 (s, C=O), and 169.8 (s, C=O); *m*/*z* (CI) (*inter alia*) 236 (MH^+) [Found: (EI) M^+, 235.0840. $C_{12}H_{13}NO_4$ requires *M*, 235.084 459].

Preparation of O-*Pivaloyl* 3-*Hydroxy*-4-*methylpent*-4-*enohydroxamate* (**20b**).—A solution of WSC (3.34 g, 17.43 mmol, 2.2 mol equiv.), carboxylic acid (**18**) (1.03 g, 7.92 mmol), and *O*-pivaloylhydroxylamine hydrochloride (1.46 g, 9.51 mmol) in THF–water (30 ml of each) was adjusted to pH 4–5 (from pH 2) with 1M-aq. NaOH. The pale pink-orange solution was stirred at room temperature for 45 min with occasional addition of 1M-aq. NaOH to maintain pH between 4 and 5. The reaction mixture was then extracted with ethyl acetate (3 × 30 ml) and the combined extracts were washed successively with 10% aq. citric acid (10 ml), 5% aq. sodium hydrogen carbonate (10 ml), and saturated brine (10 ml), dried ($MgSO_4$), filtered, and concentrated to afford a pale yellow gum, which was >95% pure by NMR analysis (1.217 g, 67%). The product *O*-pivaloyl 3-hydroxy-4-methylpent-4-enohydroxamate (**20b**), could be further purified (with significant loss) by rapid filtration through silica gel with diethyl ether as the eluant. However, the crude material was suitable for the next step of the synthesis, and showed ν_{max}(film) 3 700–3 300s (OH), 3 400–3 100s (NH), 1 780s (acyl hydroxamate C=O), 1 670s cm^{-1} (amide C=O); δ_H(300 MHz) 1.30 (9 H, s, Bu^t), 1.74 (3 H, s, MeC=C), 2.48–2.5 (2 H, m, CH_2CHOH), 4.47 (1 H, ~t, *J* 6.12 Hz, C*H*OH), 4.88 (1 H, ~s) and 5.04 (1 H, ~s) ($C=CH_2$), and 9.7 (1 H, br s, NH); δ_C(75.5 MHz) 18.2 (q, *Me*C=C), 27.0 (q, C(*Me*$_3$), 38.3 (t, CH_2CH), 39.4 (s, CMe_3), 71.6 (d, CHOH), 110.4 (s, $C=CH_2$), 111.7 (t, $C=CH_2$), and 145.4 (s, C=O); *m*/*z* (CI) (*inter alia*) 230 (MH^+).

Preparation of 4-*Isopropenyl*-1-*pivaloyloxyazetidin*-2-*one* (**21b**).—TPP (0.986 g, 3.76 mmol, 1.05 mol equiv.) then triethylamine (0.399 g, 3.934 mmol) were added to a solution of the hydroxamate (**20b**) (0.820 g, 3.58 mmol) in a mixture of acetonitrile (70 ml) and carbon tetrachloride (2 ml) at room temperature under nitrogen. The reaction mixture gradually turned a deep red. After being stirred for 24 h the reaction mixture was concentrated to afford a brown solid, which was taken up in a mixture of ethyl acetate (30 ml) and saturated brine (10 ml). The organic layer was washed with a further quantity of saturated brine (10 ml), dried ($MgSO_4$), filtered, and concentrated to give a brown, gummy solid. The crude mixture of β-lactam and TPPO was dissolved in diethyl ether–hexanes (1:1), filtered, applied to a 2″/1″ (length/width) column of flash silica, and *rapidly* eluted with 1:1 diethyl ether–hexanes. The early fractions were combined and concentrated to give the product, 4-*isopropenyl*-1-*pivaloyloxyazetidin*-2-*one* (**21b**), as a yellow oil (9.496 g, 66%), ν_{max}(film) 1 805sh s [NO(C=O)Bu^t] and 1 770s cm^{-1} (β-lactam C=O); δ_H(300 MHz) 1.21 (9 H, s, Bu^t), 1.71 (3 H, s, C=CMe), 2.63 (1 H, dd, *J* 13.8, 2.8 Hz, *trans*-C*H*HCH), 3.02 (1 H, dd, *J* 13.8, 5.8 Hz, *cis*-CH*H*CH), 4.46 (1 H, dd, *J* 5.8, 2.8 Hz, CH_2CH), and 4.95 (1 H, s) and 5.05 (1 H, s) ($C=CH_2$); δ_C(75.5 MHz) 16.8 (q, Me), 26.8 (q, C*Me*$_3$), 37.8 (t, CH_2CH), 38.1 (s, CMe_3), 62.5 (d, CH_2CH), 110.3 (s, $C=CH_2$), 115.1 (t, $C=CH_2$), 140.2 (s, C=O), and 164.0 (s, C=O); *m*/*z* (CI) (*inter alia*) 212 (MH^+) [Found: (EI) M^+, 211.1209. $C_{11}H_{17}NO_3$ requires *M*, 211.120 844].

Preparation of 4-*Acetyl*-1-*pivaloyloxyazetidin*-2-*one* (**22b**).—A solution of the alkene (**21b**) (0.371 g, 1.76 mmol) in methylene dichloride (35 ml) was cooled to −78 °C before bubbling ozone was passed through the reaction mixture. After *ca.* 10 min of ozone bubbling the reaction mixture had become deep blue, indicating that excess of ozone was present—when the mixture was stirred for a further 10 min, there was no loss of colour. O_2 was bubbled through the reaction mixture for 15 min before the addition of dimethyl sulphide (0.546 g, 8.79 mmol). The reaction mixture was allowed to come to room temperature during 1 h before being stirred for a further 10 h. The reaction mixture was then concentrated to give a yellow gum which, by NMR spectroscopy, was >95% pure 4-acetyl-1-pivaloyloxyazetidin-2-one (**22b**) (0.36 g, 95% crude), ν_{max}(film) 1 810s [NO(C=O)Bu^t], 1 770s (β-lactam C=O), and 1 720s cm^{-1} (ketone C=O); δ_H(300 MHz) 1.28 (9 H, s, Bu^t), 2.29 (3 H, OAc), 2.88 (1 H, dd, *J* 14.2, 3.1 Hz, *trans*-C*H*HCH), 3.24 (1 H, dd, *J* 14.2, 6.7 Hz, *cis*-CH*H*CH), and 4.47 (1 H, dd, *J* 6.7, 3.1 Hz, CH_2CH); δ_C(75.5 MHz) 26.0 (q, CO*Me*), 26.9 (q, C*Me*$_3$), 37.0 (t, CH_2CH), 38.3 (s, CMe_3), 63.1 (d, CH_2CH), 163.1 (s, C=O), 186.5 (s, C=O), 203.8 (s, ketone C=O); *m*/*z* (CI) (*inter alia*) 214 (MH^+).

Preparation of 4-*Acetoxy*-1-*pivaloyloxyazetidin*-2-*one* (**23b**).—MCPBA (1.22 g, 7.07 mmol) was added to a solution of ketone (**22b**) (0.376 g, 1.77 mmol) in methylene dichloride (35 ml) at room temperature under nitrogen. After being stirred for 18 h, the reaction mixture was diluted with ethyl acetate (100 ml) and washed successively with 10% aq. sodium sulphite (3 × 10 ml), saturated aq. sodium hydrogen carbonate (3 × 10 ml), and saturated brine (10 ml), dried ($MgSO_4$), filtered, and concentrated to give a yellow gum, 4-acetoxy-1-pivaloyloxyazetidin-2-one (**23b**) (233 mg, 56%), ν_{max}(film) 1 815s (hydroxamate C=O), 1 775 (β-lactam C=O), and 1 730 cm^{-1} (ester C=O); δ_H(300 MHz) 1.23 (9 H, s, Bu^t), 2.06 (3 H, OAc), 2.89 (1 H, dd, *J* 14.4, 1.8 Hz, *trans*-C*H*HCH), 3.19 (1 H, dd, *J* 14.4, 4.9 Hz, *cis*-CH*H*CH), and 6.18 (1 H, dd, *J* 4.9, 1.8 Hz, CH_2CH); δ_C(75.5 MHz) 20.5 (q, O_2CMe), 26.8 (q, C*Me*$_3$), 27.0 (s, CMe_3), 39.0 (t, CH_2CH), 79.0 (d, CH_2CH), 162.1 (s, C=O), 170.2 (s, C=O), and 175.4 (s, C=O); *m*/*z* (CI) (*inter alia*) 230 (MH^+).

Reaction of Compound (**23a**) *with Dimethylamine.*—A solution of β-lactam (**23a**) (30.2 mg, 0.13 mmol) and dimethylamine (40% aq.; 22 μl, 0.193 mmol, 1.5 mol equiv.) in THF (2 ml) was refluxed for 3 h. The reaction mixture was diluted with ethyl acetate (10 ml), washed with saturated brine (5 ml), dried ($MgSO_4$), filtered, and concentrated to give 3-(*benzyloxyimino*)-N,N-*dimethylpropanamide* (**37c**) as a 5:3 mixture of geometrical isomers (15.1 mg, 53%), ν_{max}(film) 1 650 cm^{-1}; δ_H(300 MHz) (major isomer) 2.89 and 2.91 (6 H, 2 s, NMe_2), 3.35 (2 H, d, *J* 4.8 Hz, CH_2CH), 5.07 (2 H, s, OCH_2Ph), 7.11 (1 H, t, *J* 4.8 Hz, CH_2CH), and 7.28 (5 H, m, Ph); (minor diastereomer) 2.87 and 2.90 (6 H, 2 s, NMe_2), 3.20 (2 H, d, *J* 6.1 Hz, CH_2CH), 5.00 (2 H, s, OCH_2Ph), 7.11 (1 H, t, *J* 6.1 Hz, CH_2CH), and 7.56 (5 H, m, Ph); *m/z* (CI) (*inter alia*) 221 (MH^+) [Found: (EI) M^+, 220.1209. $C_{12}H_{16}N_2O_2$ requires *M*, 220.121 178].

Preparation of Benzyl Amino-oxyacetate Tosyl Salt (**42**).—Triethylamine (29.4 g, 0.29 mol) was added to a pale yellow solution of *N*-hydroxyphthalimide (31.6 g, 0.19 mol) and methyl bromoacetate (37.0 g, 0.24 mol) in dry DMF (250 ml) at 0 °C.[17] The reaction mixture immediately became blood red. After a few seconds, a heavy white precipitate formed and the reaction mixture faded to pale pink. After being stirred for 15 min the reaction mixture was poured onto ice (2 kg). After the ice had melted, the product was filtered off, and recrystallised from boiling absolute ethanol. Methyl phthalimido-oxyacetate was obtained as needles (37.3 g, 82%), m.p. 143–144 °C. The product was suspended in a mixture of glacial acetic acid (120 ml) and 48% aq. hydrobromic acid (180 ml) and the orange mixture was gently refluxed for 10 min. The resulting clear solution was cooled and the precipitated phthalic acid was filtered off. The filtrate was concentrated under high vacuum at ≤45 °C and the pale orange residue was extracted with diethyl ether (3 × 50 ml). The remaining pale yellow solid was dissolved in ice–water (30 ml), filtered, and concentrated to give amino-oxyacetic acid hydrobromide as a pale yellow solid, which was used without further purification (24.3 g, 89%). The amino acid salt (8.60 g, 0.05 mol) was suspended in a solution containing toluene-*p*-sulphonic acid monohydrate (19.02 g, 0.1 mol) and benzyl alcohol (16.22 g, 0.15 mol) in benzene (300 ml) in a Dean–Stark separator. After being refluxed for 5 h the clear, pale-yellow reaction mixture was cooled and concentrated to give an oily solid. Diethyl ether (250 ml) was added and the resulting solid was filtered off and washed well with more diethyl ether. Benzyl amino-oxyacetate tosyl salt (**42**) was obtained as a white powder (13.84 g, 78%), m.p. 136–137 °C; δ_H(200 MHz; D_2O; HOD at δ_H 4.80) 2.37 (3 H, s, Me), 4.73 (2 H, s, OCH_2CO_2), 5.28 (2 H, s, OCH_2Ph), 7.36 (2 H, d, *J* 7 Hz) and 7.68 (2 H, d, *J* Hz) (*p*-$MeC_6H_4SO_3$), and 7.44 (5 H, s, Ph); *m/z* (CI) (*inter alia*) 182 ($\overset{+}{N}H_3OCH_2CO_2Bn$). The free base can be regenerated if required by dissolving the tosyl salt in 5% aq. sodium hydrogen carbonate solution and extraction with methylene dichloride δ_H(300 MHz) 4.19 (2 H, s, OCH_2CO_2), 5.11 (2 H, s, CO_2CH_2Ph), 5.84 (2 H, br s, NH_2), and 7.27 (5 H, m, Ph).

Preparation of N-*Benzyloxycarbonylmethoxy*-3-*hydroxy*-4-*methylpent*-4-*enamide* (**20c**).*—WSC (6.5 g, 33.85 mmol) was added to a solution of the carboxylic acid (**18**) (2.00 g, 15.38 mmol) and tosyl salt (**42**) (5.97 g, 16.92 mmol) in THF–water (360 ml) and the pH was adjusted from 2 to 4.5 with 1M-NaOH. Further NaOH was added during 1 h to maintain the reaction mixture at this pH. The reaction mixture was then extracted with ethyl acetate (2 × 50 ml), saturated with brine, and further extracted with ethyl acetate (2 × 50 ml). The combined extracts were washed successively with 10% aq. citric acid (2 × 30 ml), 5% aq. sodium hydrogen carbonate (2 × 30 ml), water (25 ml), and saturated brine (25 ml), dried ($MgSO_4$), filtered, and concentrated to give a pale yellow gum. Chromatography (Et_2O–hexanes 1:2) gave the *hydroxamate* (**20c**) as a pale yellow gum (2.971 g, 66%), ν_{max}(film) 3 600–3 100br s (OH and NH), 1 750s (ester C=O), and 1 670s cm^{-1} (amide C=O); δ_H(200 MHz) 1.74 (3 H, s, MeC=C), 2.20–2.25 (2 H, m, CH_2CHOH), 4.40 (1 H, m, $CHOH$), 4.50 (2 H, s, OCH_2CO_2), 4.80 (1 H, s) and 5.00 (1 H, s) ($C=CH_2$), 7.40 (5 H, m, Ph), and 9.50 (1 H, br s, NH); δ_C (75.5 MHz) 18.1 (q, Me), 38.9 (t, CH_2CH), 67.0 (t, OCH_2CO_2), 71.5 (t, CO_2CH_2Ph), 72.2 (d, CHOH), 111.3 (t, $C=CH_2$), 128.4 (d), 128.5 (d), 128.6 (d), and 134.9 (s) (ArC), 145.7 (s, $C=CH_2$), 169.4 (s, C=O), and 169.4 (s, C=O); *m/z* (CI) (*inter alia*) 294 (MH^+) [Found: (EI) M^+, 293.1254. $C_{15}H_{19}NO_5$ requires *M*, 293.1263].

Preparation of Benzyl (2-*Isopropenyl*-4-*oxoazetidin*-1-*yl*)*oxyacetate* (**21c**).—DEAD (1.94 g, 11.154 mmol) was added dropwise during 10 min to a solution of the hydroxamate (**20c**) (2.971 g, 10.14 mmol) and TPP (2.93 g, 11.15 mmol) in THF (200 ml) at 0 °C under N_2. The resulting deep yellow solution was allowed to come to room temperature and was stirred for 12 h before being concentrated to give a deep orange gum. The crude product was chromatographed (Et_2O–hexanes 1:3) to give the β-lactam (**21c**) (1.917 g, 69%) as a pale yellow gum, ν_{max}(film) 1 780 (β-lactam C=O) and 1 740 cm^{-1} (ester C=O); δ_H(300 MHz) 1.71 (3 H, dd, *J* 1.0, 0.7 Hz, C=CMe), 2.49 (1 H, dd, *J* 13.9 2.6 Hz, *trans*-CHHCH), 2.84 (1 H, dd, *J* 13.9, 5.6 Hz, *cis*-CHHCH), 4.40 (1 H, dd, *J* 5.6, 2.6, 0.4 Hz, CH_2CH), 4.53 (2 H, AB system, *J* 16.3, 16.3 Hz, OCH_2CO_2), 5.03 (1 H, s) and 5.13 (1 H, s) ($C=CH_2$), 5.20 (2 H, AB system, *J* 12.1, 12.1 Hz, OCH_2Ph), and 7.36 (5 H, m, Ph); δ_C(75.5 MHz) 16.5 (q, Me), 37.6 (t, CH_2CH), 62.9 (d, CH_2CH), 67.1 (t, OCH_2CO_2), 72.4 (t, OCH_2Ph), 116.0 (t, $C=CH_2$), 128.5 (d), 128.6 (d), and 135.0 (s) (ArC), 140.6 (s, $C=CH_2$), 164.6 (s, C=O), and 168.1 (s, C=O); *m/z* (Cl) 276 (MH^+) [Found: (EI) M^+, 275.1155. $C_{15}H_{17}NO_4$ requires *M*, 275.115 759].

Preparation of Benzyl (2-*Acetyl*-4-*oxoazetidin*-1-*yl*)*oxyacetate* (**22c**).—A solution of alkene (**21c**) (1.917 g, 6.97 mmol) in methylene dichloride (135 ml) at −78 °C was ozonised until the reaction mixture turned pale blue. The reaction mixture was stirred for a further 10 min, during which time the blue colour did not fade. O_2 was bubbled through the reaction mixture for 20 min to displace excess of ozone, and dimethyl sulphide (2.17 g, 34.85 mmol) was added to the pale yellow reaction mixture. The reaction mixture was allowed to come to room temperature and was then stirred for 8 h before being concentrated to afford a deep yellow gum, which was chromatographed (Et_2O–hexanes 2:3) to give the *ketone* (**22c**) as a gum (1.372 g, 73%), ν_{max}(film) 1 790 (β-lactam C=O), 1 750 (ester C=O), and 1 720 cm^{-1} (ketone C=O); δ_H(300 MHz) 2.15 (3 H, s, COMe), 2.52 (1 H, dd, *J* 13.9, 3.0 Hz, *trans*-CHHCH), 2.93 (1 H, dd, *J* 13.9, 6.3 Hz, *cis*-CHHCH), 4.50 (1 H, dd, *J* 6.3, 3.0 Hz, CH_2CH), 4.56 (2 H, s, OCH_2CO_2), 5.11 (2 H, AB system, *J* 12.1, 12.1 Hz, OCH_2Ph), and 7.31 (5 H, m, Ph); δ_C (75.5 MHz) 26.6 (q, $COMe$), 36.5 (t, CH_2CH), 63.3 (d, CH_2CH), 66.8 (t, OCH_2CO_2), 72.8 (t, OCH_2Ph), 128.4 (d), and 134.7 (s) (ArC), 163.4 (s, C=O), 168.4 (s, C=O), and 203.6 (s, C=O); *m/z* (CI) 278 (MH^+) [Found: (EI) M^+, 277.0951. $C_{14}H_{15}NO_5$ requires *M*, 277.095 024].

Preparation of Benzyl (2-*Acetoxy*-4-*oxoazetidin*-1-*yl*)*oxyacetate* (**23c**).—MCPBA (3.05 g, 17.69 mmol) was added to a solution of ketone (**22c**) in methylene dichloride (35 ml) and the reaction mixture was gently refluxed for 18 h. After cooling, the reaction mixture was diluted with methylene dichloride (35 ml) and washed successively with 5% aq. sodium hydrogen

* Benzyl (3-hydroxy-4-methylpent-4-enohydroxamato)acetate.

carbonate (2 × 30 ml), 10% aq. sodium sulphite (3 × 25 ml), 5% aq. sodium hydrogen carbonate (2 × 30 ml), and saturated brine (25 ml), dried (Na_2SO_4), filtered, and concentrated to afford a gum. Diethyl ether–hexanes (2:1; 5 ml) was added and, after filtration, the filtrate was applied to a 1″ wide/3″ long silica gel flash column. Elution with diethyl ether–hexanes 2:1 gave the *title product* (**23c**) as an oil (0.469 g, 45%), ν_{max} 1 790 (β-lactam C=O) and 1 750br cm^{-1} (ester C=O); δ_H(300 MHz) 2.01 (3 H, s, OAc), 2.61 (1 H, dd, *J* 14.5, 1.6 Hz, *trans*-C*H*HCH), 2.98 (1 H, dd, *J* 14.5, 4.6 Hz, *cis*-CH*H*CH), 4.47 (2 H, AB system, *J* 16.3, 16.3 Hz, OCH_2CO_2), 5.13 (2 H, AB system, *J* 12.1, 12.1 Hz, OCH_2Ph), 6.18 (1 H, dd, *J* 4.6, 1.6 Hz, CH_2CH), and 7.29 (5 H, m, Ph); δ_C(75.5 MHz) 20.7 (q, CO*Me*), 40.0 (t, CH_2CH), 67.1 (t, OCH_2Ph), 72.8 (t, OCH_2CO_2), 79.4 (d, CH_2CH), 128.1 (d), 128.2 (d), 128.6 (d), and 134.9 (2) (ArC), 162.5 (s, C=O), 167.7 (s, C=O), and 169.9 (s, C=O); *m/z* (CI) 294 (MH^+) [Found: (EI) ($M^+ - COCH_3$), 250.0718. $C_{12}H_{12}NO_5$ requires *m/z*, 250.0718].

Preparation of Potassium (2-*Acetoxy*-4-*oxoazetidin*-1-*yl*)-*oxyacetate* (**23d**).—Hydrogen was bubbled through a solution of β-lactam (**23c**) (42.5 mg, 0.145 mmol) and potassium hydrogen carbonate (14.4 mg, 0.144 mmol) in 95% ethanol (10 ml) containing 10% Pd/C. After 1 h the reaction mixture was filtered through a Celite pad (2 cm) in a Pasteur pipette and the filtrate was concentrated at room temperature on a rotary evaporator. Chloroform (2 × 2 ml) was added and the residue was dried *in vacuo* over P_2O_5 to give the *potassium salt* (**23d**) as a hygroscopic glass (31.1 mg, 89% crude) (Found: C, 34.8; H, 3.4; N, 5.9. $C_7H_8KNO_6$ requires C, 34.85; H, 3.34; N, 5.81%); ν_{max}(KBr) 1 790 (β-lactam C=O), 1 750 (ester C=O), and 1 615 cm^{-1} (carboxylate salt C=O); δ_H(300 MHz; D_2O; HOD at δ 4.80) 2.15 (3 H, s, OAc), 2.83 (1 H, dd, *J* 14.5 and 1.3 Hz, *trans*-C*H*HCH), 3.18 (1 H, dd, *J* 14.5, 4.3 Hz, *cis*-CH*H*CH), 4.46 (2 H, AB system, *J* 15.6, 15.6 Hz, OCH_2CO_2), and 6.35 (1 H, dd, *J* 4.3, 1.3 Hz, CH_2CH); δ_C(75.5 MHz; dioxane at δ 66.5) 20.3 (q, O_2CMe), 39.0 (t, CH_2CH), 74.2 (t, OCH_2CO_2), 80.1 (d, CH_2CH), 164.9 (s, C=O), 172.8 (s, C=O), and 173.9 (s, C=O); *m/z* (CI) (negative ion) (*inter alia*) 203 ($MH^+ - K$).

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