Synthesis of Novel Fused β-Lactams by Intramolecular 1,3-Dipolar Cycloadditions. Part 9.[1] Preparation of the 7-Oxo-1,3-diazabicyclo[3.2.0]-heptane-2-carboxylate and 8-Oxo-1,3-diazabicyclo[4.2.0]octane-2-carboxylate Ring Systems

Clive L. Branch* and Michael J. Pearson
Beecham Pharmaceuticals Research Division, Brockham Park, Betchworth, Surrey, RH3 7AJ

4-Vinylazetidin-2-one (**24**) has been converted into 1-[1-azido-1-benzyloxycarbonylmethyl]-4-vinylazetidin-2-one (**27**) and 1-[1-azido-1-benzyloxycarbonylmethyl]-4-(2-methoxycarbonylvinyl)-azetidin-2-one (**43**) which on thermolysis in toluene gave (2*RS*,5*RS*)-benzyl 4-methyl-7-oxo-1,3-diazabicyclo[3.2.0]hept-3-ene-2-carboxylate (**12**) and (2*RS*,5*RS*)-benzyl 4-methoxycarbonylmethylene-7-oxo-1,3-diazabicyclo[3.2.0]heptane-2-carboxylate (**39**) respectively. The double bond geometry in (**39**) was confirmed by *X*-ray crystallography. Ozonolysis of (**39**) gave (2*RS*,5*RS*)-benzyl 4,7-dioxo-1,3-diazabicyclo[3.2.0]heptane-2-carboxylate (**44**). An identical sequence on 4-allylazetidin-2-one (**30**) gave the corresponding homologous bicyclic derivatives (**16**), (**51**), and (**54**). A similar strategy has been utilised to synthesize the analogous bicyclic C(6)-acylamino-derivatives (**103**), (**65**), and (**62**), and bicyclic C(7)-acylamino-derivatives (**106**), (**76**), and (**78**) from the appropriate monocyclic azetidinones.

(3*RS*,4*SR*)-3-Azido-1-[4-methoxymethoxyphenyl]-4-styrylazetidin-2-one (**68**) was transformed into (3*RS*,4*SR*)-4-(2-methoxycarbonylethenyl)-1-[4-methoxymethoxyphenyl]-3-phenoxyacetamidoazetidin-2-one (**71**). Ceric ammonium nitrate-mediated removal of the *N*-protecting group from (**71**) then afforded the corresponding azetidinone (**72**). The conversion of the azide (**68**) into (3*RS*,4*SR*)-1-(4-methoxymethoxyphenyl)-4-(2-nitroethyl)-3-phenoxyacetamidoazetidin-2-one (**98**) is described. Elaboration of the 4-nitroethyl moiety in (**98**) to a 4-(3-methoxycarbonylprop-2-enyl) functionality was accomplished *via* an ozonolysis procedure. Subsequent *N*-deblocking gave the azetidinone (**81**). (3*RS*,4*SR*)-3-Phenoxyacetamido-4-vinylazetidin-2-one (**118**) was obtained by sequential catalytic semi-hydrogenation and *N*-deprotection of (3*RS*,4*SR*)-4-ethynyl-1-(4-methoxymethoxyphenyl)-3-phenoxyacetamidoazetidin-2-one (**108**).

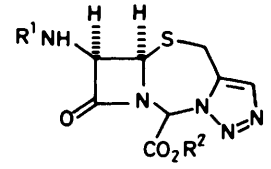
The total synthesis of (3*RS*,4*SR*)-4-(3-hydroxypropyl)-1-(4-methoxymethoxyphenyl)-3-phenoxyacetamidoazetidin-2-one (**113**) starting from azidoacetic acid, prop-3-ynol, and 4-methoxymethoxyaniline is described. A mesylation–selenenylation sequence on (**113**) afforded the corresponding 4-allylazetidinone (**111**) which was *N*-deprotected to give (3*RS*,4*SR*)-4-allyl-3-phenoxyacetamidoazetidin-2-one (**121**). The conversion of (**51**) to the Δ^2 derivative (**58**) was accomplished using electrophilic bromination–dehydrobromination but hydrogenolysis of (**58**) caused rapid β-lactam cleavage. The acids, derived by hydrogenolysis of the corresponding benzyl esters, were devoid of antibacterial activity except for (**75**), (**77**), and (**80**) which possessed weak Gram-positive activity.

The intramolecular cycloaddition reaction between an acetylene and an azido-group has been used to prepare the tricyclic triazole (**1**) from the azetidinone (**2**).[2] We were interested in extending the synthetic strategy to the preparation of novel bicyclic β-lactams such as aza-penems and aza-cephems.[3] At the outset of our study, few fused β-lactams containing additional nitrogen atoms had been reported.[4] Gleason[5] has subsequently described the 3-aza-1-dethiaceph-1-em (**3**) and Aratani[6] the 3-azacephalosporin (**4**). The Bristol investigators[7] have extended their nuclear modification programme to the preparation of further aza-cephems of type (**5**), whilst more recently Stoodley[8] has synthesized the novel structure (**6**) containing two additional nitrogen atoms in the fused six-membered ring. Preparation of the bicyclo[5.2.0]nonane ring system (**7**) by thermolysis of a 2β-azidodeacetoxycephalosporanate has been described[9] and Streith has utilised a [2 + 2]-cycloaddition process to prepare various 5-aza-1,3-nonamdiene derivatives of type (**8**).[10] Alper[11] and Nagakura[12] have prepared 1-aza-penems (**9**) and (**10**) respectively, both lacking a carboxy group and the latter has also synthesized the 3-aza-penem (**12**) and 3-aza-cephem (**16**)[12] using an identical approach to our own. The Hoechst group have recently reported the synthesis of aza-penems (**19**)[13] by desulphurisation of 2-aza-1-thia-cephems and the isomeric system (**11**)[14] by total synthesis.

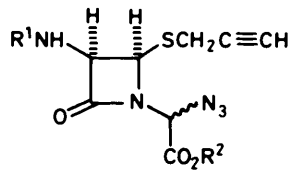
It was hoped that by analogy with the acetylenic azide (**2**) intramolecular cycloaddition of olefinic azides of type (**20**) would afford the corresponding triazolines (**21**) (see Scheme 1). Since thermal elimination of nitrogen from 1,2,3-triazolines is well documented,[15] thermolysis of the triazoline (**21**) might be expected to give both the bicyclic β-lactam (**22**) and the tricyclic β-lactam (**23**).

Although a C-6(7)-acylamino substituent was considered essential for antimicrobial activity, the proposed synthetic approach was investigated using a series of model experiments on non-acylamino derivatives. The racemic 4-vinyl- and 4-allylazetidinones (**24**)† and (**30**) were chosen as suitable starting materials.[16] An essentially identical route to the imines (**12**) and (**16**) has subsequently been described by Nagakura,[12] but in contrast, we have found that (**12**) and (**16**) are stable crystalline compounds. The corresponding acids (**13**) and (**17**) have also

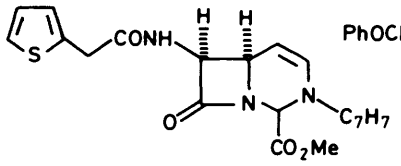
† All synthetic compounds are racemic mixtures, but only one enantiomer is depicted for convenience.



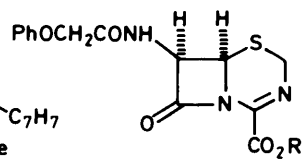
(1)



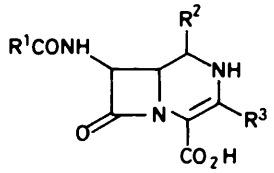
(2)



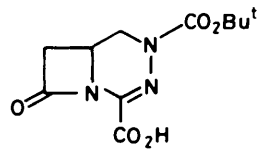
(3)



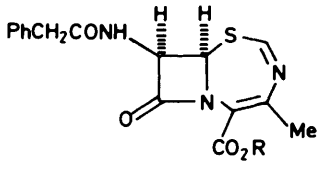
(4)



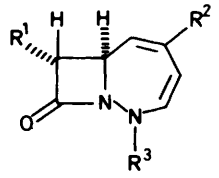
(5)



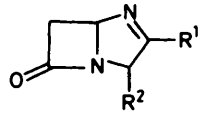
(6)



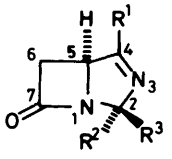
(7)



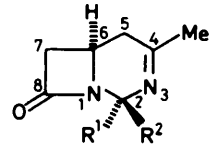
(8)



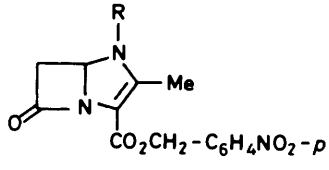
(9) R^1 = *p*-Me-C_6H_4-, R^2 = H
(10) R^1 = Me, R^2 = H
(11) R^1 = SMe, R^2 = CO_2R



(12) R^1 = Me, R^2 = CO_2CH_2Ph, R^3 = H
(13) R^1 = Me, R^2 = CO_2H, R^3 = H
(14) R^1 = Me, R^2 = H, R^3 = CO_2CH_2Ph
(15) R^1 = H, R^2 = CO_2CH_2Ph, R^3 = H



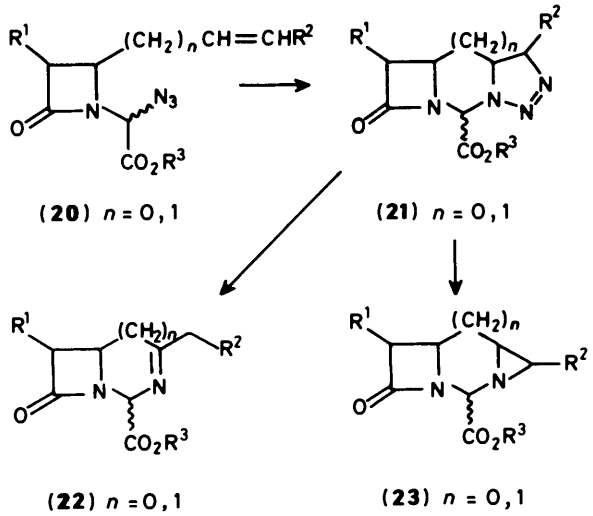
(16) R^1 = CO_2CH_2Ph, R^2 = H
(17) R^1 = CO_2H, R^2 = H
(18) R^1 = H, R^2 = CO_2CH_2Ph



(19)

been prepared and the methodolgy extended to other related aza-ring systems (*vide infra*).

Thus 4-vinylazetidinone (**24**) was condensed with benzyl glyoxylate in refluxing benzene to give the glycolate (**25**).[17] Treatment of (**25**) with thionyl chloride afforded the chloride (**26**) which on reaction with sodium azide in dimethylformamide provided the required olefinic-azide (**27**)[2] as an inseparable mixture of diastereoisomers. Thermolysis of (**27**) in dilute toluene solution (1 mg ml^{-1}) for 31 h gave two products which were separated by silica gel chromatography. These proved to be the desired aza-penems (**12**) and (**14**), signals in the n.m.r. spectrum at δ 2.20 and 2.18 being assignable to the olefinic

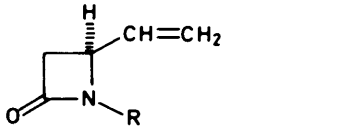


Scheme 1.

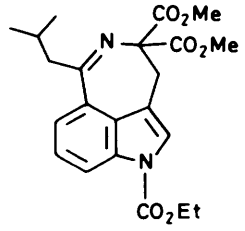
6α-proton: long range W-coupling of this type has been observed previously.[6,20]

Although attempted hydrogenolysis of the ester (**14**) caused decomposition, the C-2 epimer (**12**) having the 'natural' stereochemistry as found in penicillin was readily converted into the acid (**13**) which was devoid of antibacterial activity. By analogy with the carbapenems,[21] it was surmised that the Δ^2-aza-penem (**35**; R = H) would have a more reactive β-lactam carbonyl than its Δ^3-counterpart (**13**) and thus might possess bioactivity. However, whilst brief treatment of (**14**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) produced the epimeric imine (**12**), prolonged exposure failed to provide the ester (**35**; R = CH_2Ph). Use of other bases, such as potassium t-butoxide, produced no evidence for the formation of (**35**; R = CH_2Ph) and an excess of reagent or extended reaction times resulted in degradation.

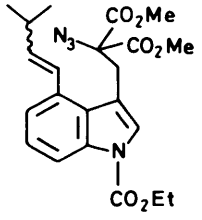
The availability of the azide (**27**) prompted a brief attempt to synthesize the imine (**15**) using an intramolecular aza-Wittig cyclisation. Ozonolysis of (**27**) followed by work-up with triphenylphosphine (2 molar equivalents) was expected to generate the imine (**15**) *via* the intermediacy of the phosphinimine (**37**), but in the event, the approach was unsuccessful.



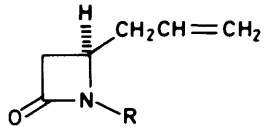
(**24**) R = H
(**25**) R = $CH(OH)CO_2CH_2Ph$
(**26**) R = $CH(Cl)CO_2CH_2Ph$
(**27**) R = $CH(N_3)CO_2CH_2Ph$



(**28**)



(**29**)

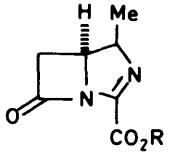


(**30**) R = H
(**31**) R = $CH(OH)CO_2CH_2Ph$
(**32**) R = $CH(Cl)CO_2CH_2Ph$
(**33**) R = $CH(N_3)CO_2CH_2Ph$
(**34**) R = $SiMe_2Bu^t$

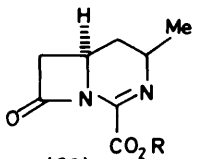
methyl group in each isomer. None of the highly strained aziridine (**23**; $n = 0$; $R^1 = R^2 = H$, $R^3 = CH_2Ph$) was isolated. Similarly, none of the presumed intermediate 1,2,3-triazolines (**21**; $n = 0$; $R^1 = R^2 = H$, $R^3 = CH_2Ph$) were observed, indicative of facile loss of nitrogen under the reaction conditions. Indeed, very recently the clavicipitic acid precursor (**28**) has been isolated directly from thermolysis of the azide (**29**).[18] The absence of any aziridine in this case was partly attributed to strain associated with generating a three-membered ring fused to a fairly constrained seven-membered ring.

The assignment of C-2 stereochemistry was made on the basis of the relative C-2 proton chemical shifts[19] and selective n.m.r. decoupling experiments. The 2β-proton (δ 5.95) in (**12**) was coupled to the C-4 methyl (J 1 Hz) and the C-5 proton (J 3 Hz), but in the epimeric (**14**) the 2α-proton (δ 5.23), in addition to being coupled to the C-4 methyl and C-5 proton by J 2 and 3 Hz respectively, showed further fine coupling of J 1.5 Hz to the

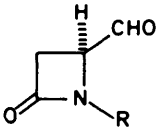
Repetition of the same sequence starting from 4-allylazetidinone (**30**) provided the homologous aza-cephem (**16**), *via* the glycolate (**31**), chloride (**32**), and azide (**33**). The latter was obtained as a mixture of diastereoisomers and complete disappearance of the azide absorption in the i.r. spectrum [$\nu_{max.}$ ($CHCl_3$) 2 115 cm^{-1}] occurred after (**33**) in dilute toluene solution had been gently heated under reflux for 7 h. Broad singlets of δ 5.72 and 5.45 in the n.m.r. spectrum of the crude product were assignable to the C-2 methine protons of the expected aza-cephems (**16**) and (**18**). However, the epimer (**18**) with the 'unnatural' penicillin stereochemistry could not be isolated by chromatography or selective crystallisation. Purification of the crude material by rapid silica gel chromatography gave only the natural epimer (**16**) in 15% yield. The presence of (**18**) was further substantiated by DBU treatment of the crude reaction in dichloromethane at −20 °C. Clean and rapid conversion of the imine (**18**) into (**16**) was evident from the disappearance of the 2α-proton signal at δ 5.45 in the n.m.r.

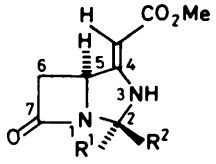


(35)



(36)



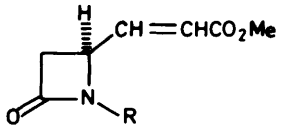


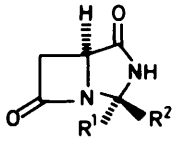
(37) R = CH(N = PPh$_3$)CO$_2$CH$_2$Ph
(38) R = CH(OH)CO$_2$CH$_2$Ph

(39) R^1 = CO$_2$CH$_2$Ph, R^2 = H
(40) R^1 = H, R^2 = CO$_2$CH$_2$Ph

spectrum, a corresponding enhancement of the 2β-proton at δ 5.72 being observed. Subsequent chromatography gave the imine (**16**) in 30% yield. Removal of the benzyl protecting group in (**16**) provided the antibacterially inactive acid (**17**), which interestingly had a surprisingly low β-lactam carbonyl frequency at 1 735 cm^{-1} in the i.r. spectrum (Nujol). Attempted isomerisation of (**16**) to the derivative (**36**) was unsuccessful.

The effect of introducing an electron-withdrawing substituent into the double bond was next examined. α,β-Unsaturated esters, being more reactive dipolarophiles, react readily with an azide moiety, giving Δ^2-1,2,3-triazolines, which have been reported to undergo thermal elimination of nitrogen to give an enamine product.[22] It was expected, therefore, that the novel vinylogous urethane (**39**) might be derived by thermolysis of the appropriate acrylic azide (**43**). Accordingly the α-hydroxy ester (**25**) was ozonised and the resulting aldehyde (**38**) treated *in situ* with methyl (triphenylphosphoranylidene)acetate to provide





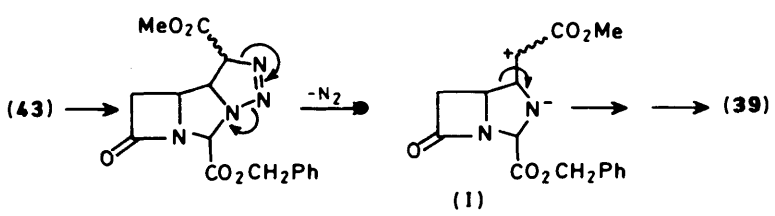
(41) R = CH(OH)CO$_2$CH$_2$Ph
(42) R = CH(Cl)CO$_2$CH$_2$Ph
(43) R = CH(N$_3$)CO$_2$CH$_2$Ph

(44) R^1 = CO$_2$CH$_2$Ph, R^2 = H
(45) R^1 = H, R^2 = CO$_2$CH$_2$Ph
(46) R^1 = CO$_2$Na, R^2 = H

the di-ester (**41**), as an inseparable mixture of *E*- and *Z*-isomers. Application of the standard thionyl chloride–sodium azide sequence then gave the corresponding azide (**43**) *via* the chloride (**42**). As expected, intramolecular cycloaddition of (**43**) in refluxing toluene proceeded more rapidly (23 h) than with the unactivated double bond to afford the enamines (**39**) (24%) and (**40**) (15%). The products were unstable to silica gel but could be purified by rapid Florisil chromatography and crystallisation. The structures were confirmed by the following considerations. The n.m.r. spectra clearly showed these compounds to be epimeric, with the C-2 methine protons appearing at δ 5.54 and 5.02 and the stereochemical assignment was made by analogy to the previously discussed aza-penems. Each compound possessed a lowfield exchangeable NH at δ *ca.* 8.1 and a singlet at δ *ca.* 4.7 for an olefinic proton. These chemical shifts and an intense u.v. absorption at *ca.* 270 nm (ε *ca.* 20 000) were totally consistent with an enamine structure.

Chemical confirmation was provided by the conversion of the vinylogous urethane (**39**) into the amide (**44**) on ozonolysis in ethyl acetate at −76 °C, followed by reductive work-up of the intermediate ozonide. In contrast to (**39**) the amide (**44**) displayed no significant u.v. absorption above 210 nm. Similarly, the enamine (**40**) gave the corresponding amide (**45**).

It is worthy of note that although the azido ester (**43**) was a mixture of *E*- and *Z*-isomers, the enamine products (**39**) and (**40**) were both single geometric isomers. It is presumed that the 1,2,3-triazoline intermediate eliminates nitrogen in a non-concerted process. Therefore, the dipolar intermediate (**I**) (Scheme 2) so formed must be sufficiently long lived for carbon–carbon bond rotation to occur, giving the preferred geometric isomer. Examination of molecular models indicates the *Z*-isomer of either C-2 enamine epimer might be stabilised relative to the *E*-isomer by hydrogen bonding of the enamine NH to the oxygen of the ester carbonyl. The relative configuration of the double bond was ultimately rigorously established by a single crystal *X*-ray study on the enamine (**39**) with the 'natural' C-2 stereochemistry (see Experimental section and Figure 3) and is shown in the computer drawn Figure 1. The olefin has the predicted *Z*-configuration, and the fused five-membered ring is essentially planar presumably owing to the trigonal nature of N(6) and C(8). The C-2 ester group of (**39**) is therefore pseudo-axial as in a C-3 puckered thiazolidine [penicillin numbering; (**48**)] and the β-lactam nitrogen N(12) is very pyramidal with



Scheme 2.

Table 1.

	(39)	Sodium clavulanate (47)[a]	Potassium benzyl penicillin (48)[b]
Torsion angle (α/°)*	155.4	153.6	149.1
h/Å†	0.52	0.47	0.4

* Torsion angle (α) is defined in (**39**) by C(3)–C(16)–N(12)–C(18), (crystallographic numbering) and in (**47**) and (**48**) by C(10)–C(3)–N(4)–C(7) and C(11)–C(3)–N(4)–C(7) respectively (penicillin numbering). Clockwise rotations are positive. † *h* Is defined as the distance of the β-lactam nitrogen below the plane defined by its substituents.

[a] A. G. Brown and T. J. King, personal communication. [b] G. J. Pitt, *Acta Crystallogr.*, 1952, **5**, 770.

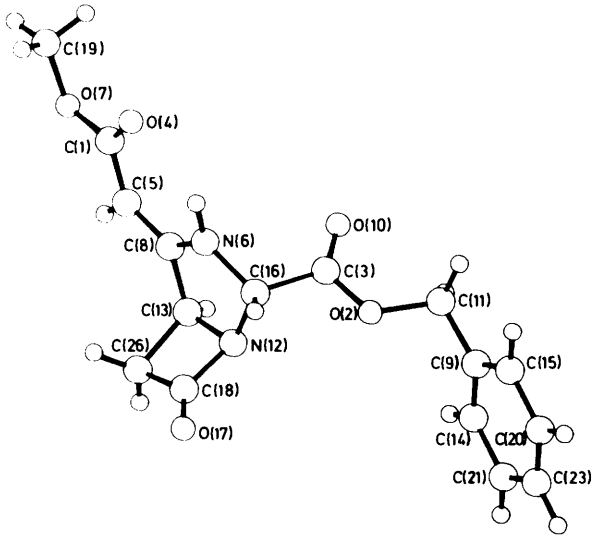


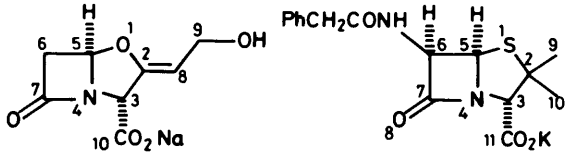
Figure 1. *X*-Ray crystal structure of (**39**) with crystallographic numbering scheme.

the nitrogen *ca.* 0.52 Å below the plane defined by its substituents (see Table 1). The sum of the bond angles around N(12) is 322.0°. Molecular modelling studies show that the ester carbonyl is well positioned for intramolecular hydrogen bonding to the enamine NH with the >C=O • • • H bond angle *ca.* 105° and the hydrogen bond *ca.* 2.26 Å.

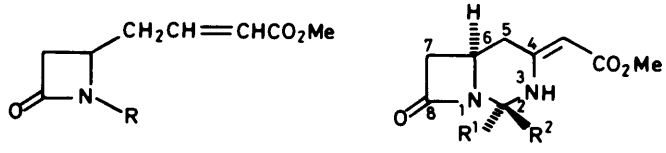
In the homologous series the glycolate (**31**) was converted into an inseparable mixture of the acrylates (**49**), which was progressed in the usual manner to the separable *E*- and *Z*-acrylic azides (**50**), each being a mixture of azide epimers. Thermal intramolecular cycloaddition of the major *E*-olefinic isomer (**50**) gave a mixture of the expected epimeric enamines (**51**) and (**52**), from which (**51**) (20%) could be crystallised. Further material (30%) as an *ca.* 1:4 mixture of (**51**) and (**52**) was obtained by Florisil chromatography of the mother liquors. The olefinic signals of (**51**) and (**52**) were discernible at δ 4.66 and 4.68 respectively, whilst a double doublet at δ 5.15 (*J* 1.7 and 4 Hz) was assignable to the 2α-proton of (**52**) and was, as expected, at higher field than the 2β-proton (δ5.53) of (**51**). Treatment of the mixture with DBU caused epimerisation of (**52**), giving the pure enamine (**51**) in 77% yield.

When the minor *Z*- olefinic isomer (**50**) was thermolysed the products were identical with those derived from the *E*-isomer (**50**). Indeed, DBU treatment of the crude product gave only the enamine (**51**). By analogy with the five-membered ring series, the double bond is assigned the *Z*-configuration. Ozonolysis of the enamine (**51**) in dichloromethane containing methanol (*ca.* 2%) at −76 °C gave the expected amide (**54**).

Catalytic hydrogenation of the amide esters (**44**) and (**54**) produced the sodium salt (**46**) and the acid (**55**) respectively. Interestingly, although the enamine ester (**51**) was readily deprotected (< 30 min) to the corresponding acid (**53**), the prolonged hydrogenolysis (80 min) necessary to cleave the benzyl group in (**39**) proceeded with partial isomerisation of the double bond presumably *via* $Pd^0\pi$-complex. The n.m.r. spectrum clearly showed that the product (**56**) was a *ca.* 1:1 mixture of *E*:*Z* isomers, pairs of signals at δ 5.53, 5.37 and δ 4.69, 4.95 being assignable to the 2β-proton and olefinic proton of each isomer respectively. The salt (**46**) and acids (**53**), (**55**), and (**56**) were all antibacterially inactive. In order to increase the potential reactivity of the β-lactam carbonyl, and hence the bioactivity, introduction of further unsaturation was investigated. Electrophilic bromination–dehydrobromination of the ester (**51**) with diethyl dibromomalonate[23] and DBU in dichloromethane at −76 °C gave the desired Δ^2-aza-cephem (**58**). As anticipated the β-lactam carbonyl stretching frequency in the i.r. spectrum ($CHCl_3$) was *ca.* 30 cm^{-1} higher, at 1 800 cm^{-1}, than in the ester (**51**). The extended chromophore was verified by the loss of both the 2β-proton and enamine NH in the n.m.r. spectrum and a marked shift to longer wavelengths in the u.v. spectrum [$\lambda_{max.}$ 315 nm (ε 14 500)]. In contrast, this procedure and other standard methods[6] for insertion of such a Δ^2-double bond were unsuccessful with the esters (**39**), (**44**), and (**54**). Unfortunately,

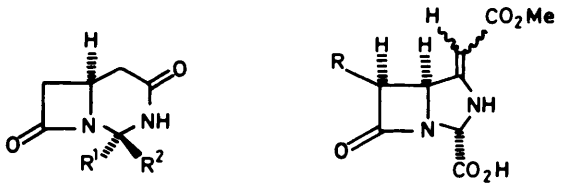


(**47**) (**48**)



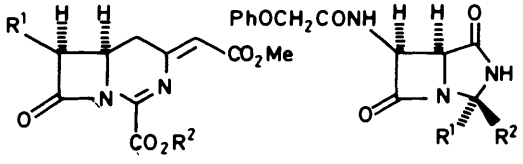
(**49**) R = $CH(OH)CO_2CH_2Ph$
(**50**) R = $CH(N_3)CO_2CH_2Ph$

(**51**) $R^1 = CO_2CH_2Ph$, $R^2 = H$
(**52**) $R^1 = H$, $R^2 = CO_2CH_2Ph$
(**53**) $R^1 = CO_2H$, $R^2 = H$

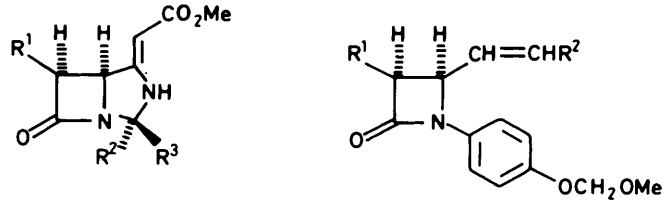


(54) $R^1 = CO_2CH_2Ph, R^2 = H$
(55) $R^1 = CO_2H, R^2 = H$
(56) R = H
(57) R = $PhOCH_2CONH$-

hydrogenolysis of the ester (**58**) caused rapid cleavage of the β-lactam and none of the acid (**59**) was observed. It must be concluded that the increased reactivity of the β-lactam carbonyl renders the ester (**58**) or the acid (**59**) unstable to the hydrogenation conditions (10% Pd–C/aqueous dioxane). A similar observation has been made in the aza-cephem[6] series where the intrinsic instability of the ester (**4**; R = CH_2Ph) prevented preparation of the corresponding acid (**4**; R = H).



(58) $R^1 = H, R^2 = CH_2Ph$
(59) $R^1 = R^2 = H$
(60) $R^1 = PhOCH_2CONH$-, $R^2 = CH_2Ph$
(61) $R^1 = CO_2H, R^2 = H$
(62) $R^1 = CO_2CH_2Ph, R^2 = H$
(63) $R^1 = H, R^2 = CO_2CH_2Ph$
(64) $R^1 = H, R^2 = CO_2H$



(65) $R^1 = PhOCH_2CONH$-, $R^2 = CO_2CH_2Ph, R^3 = H$
(66) $R^1 = N_3, R^2 = CO_2CH_2Ph, R^3 = H$
(67) $R^1 = PhOCH_2CONH$-, $R^2 = H, R^3 = CO_2CH_2Ph$
(68) $R^1 = N_3, R^2 = Ph$
(69) $R^1 = NH_2, R^2 = Ph$
(70) $R^1 = PhOCH_2CONH$-, $R^2 = Ph$
(71) $R^1 = PhOCH_2CONH$-, $R^2 = CO_2Me$

The methodology for the construction of the aza-ring systems having been established, the synthesis of the corresponding C-6(7)-acylamino analogues was undertaken. It was thought that introduction of such a substituent might improve bioactivity as a direct result of the increased chemical reactivity of the β-lactam ring. The chemical stability of the non-acylamino derivatives was taken into account in selecting the amide (**61**) and, therefore, the enamine precursor (**65**) as initial synthetic targets in this area. Fortuitously, the azetidinone (**68**) was available from other work[24] and ideally suited our requirements. Since it was envisaged that direct chemical transformation of a bicyclic β-lactam, such as (**66**) into an acylated derivative (**65**) might prove troublesome, the C-6 side-chain was introduced early in the synthetic sequence. Thus the amine (**69**), obtained by hydrogen sulphide–triethylamine reduction[25] of the azide (**68**), was acylated with phenoxyacetyl chloride to

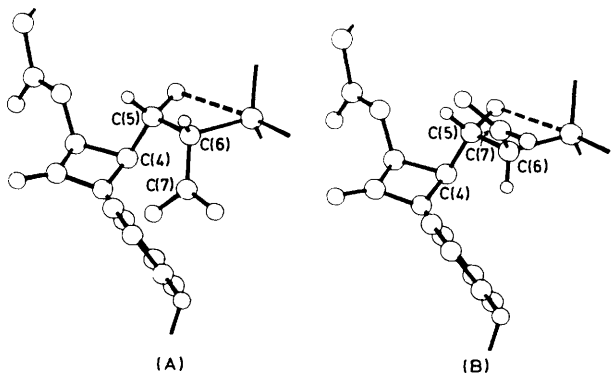


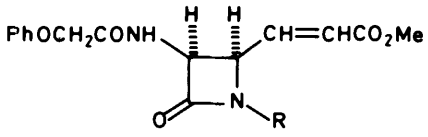
Figure 2.

provide the amide (**70**). Ozonolysis of (**70**), followed by reductive cleavage of the ozonide and reaction with methyl (triphenylphosphoranylidene)acetate afforded the expected acrylate (**71**). In contrast to the unsubstituted series, the product (**71**) was obtained as a pure *E*-isomer; none of the *Z*-isomer was detected. The presence of the 3β-acylamino substituent must force the phosphorane to approach the 4β-aldehyde from the less hindered α-face, giving the two possible betaine transition states shown in Figure 2, where the PPh_3-steric intractions are at a minimum. It is clear that the transition state (A) leading to the *Z*-isomer would have severe steric crowding between the C-7 ester carbonyl and β-lactam nitrogen aryl substituent and, therefore, is much less favourable than the alternative transition state (B), where the C-7 ester is away from the aryl substituent, giving the observed product.

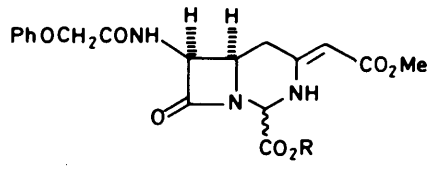
Oxidative removal of the *N*-protecting group in (**71**) with ceric ammonium nitrate[26] (CAN) gave the azetidinone (**72**) which was converted by the usual sequence into the olefinic azide (**74**) as a *ca.* 2:1 mixture of diastereoisomers. Thermolysis of (**74**) gave the desired epimeric enamines (**65**) and (**67**) in good yield. Although, as in the unsubstituted series, these products were not very stable on silica, rapid chromatography achieved partial separation giving pure (**65**) (12%) and (**67**) (14%); most of the material (39%) remained unseparated. Examination of the n.m.r. spectra of the pure products showed single olefinic protons at δ 4.71 and 4.65 respectively and in the u.v. spectrum, an intense chromophore at $\lambda_{max.}$ 275 nm (ε *ca.* 17 000) was consistent with (**65**) and (**67**). The *Z*-geometry of the double bond and C-2 stereochemistry of each epimer was assigned by analogy to the unsubstituted series.

As in the unsubstituted series, hydrogenation of (**65**) cleaved the benzyl ester with concomitant partial isomerisation of the double bond. The n.m.r. spectrum clearly showed that the product (**57**) was a *ca.* 2:1 mixture of *Z*:*E* isomers, pairs of signals at δ 5.37, 5.33 and δ 4.41, 4.94 being attributed to the 2β-proton and the olefinic proton of each isomer respectively. The material (**57**) was antibacterially inactive.

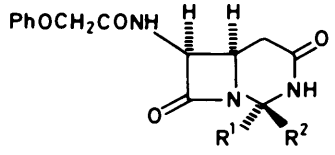
Ozonolysis, as described previously, of the total crude product from the thermolysis of azide (**74**) gave the separable amides (**62**) and (**63**) in 13 and 17% overall yield respectively. Although attempted hydrogenolysis of the amide (**63**) to give the acid (**64**) resulted in β-lactam cleavage, the amide (**62**) with the natural C-2 stereochemistry was cleanly deprotected to the antibacterially inactive acid (**61**). The synthesis of the corresponding C-(7) acylamino aza-cephems (**75**) and (**77**) was dependent on the preparation of the key intermediate (**81**). The well known ketene–imine cycloaddition procedure has been widely used for the synthesis of 4-styryl substituted *cis*-azetidinones.[27] Initially, we tried to extend the scope of this reaction to obtain *cis*-azetidinones of type (**84**). Accordingly, the replacement of



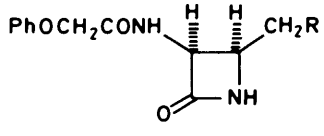
(72) R = H
(73) R = CH(OH)CO_2CH_2Ph
(74) R = CH(N_3)CO_2CH_2Ph



(75) R = H
(76) R = CH_2Ph

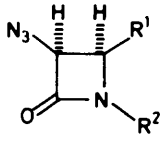


(77) $R^1 = CO_2H$, $R^2 = H$
(78) $R^1 = CO_2CH_2Ph$, $R^2 = H$
(79) $R^1 = H$, $R^2 = CO_2CH_2Ph$
(80) $R^1 = H$, $R^2 = CO_2H$

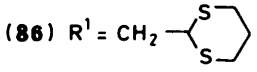


(81) R = CH=$CHCO_2Me$
(82) R = $CH(OMe)_2$

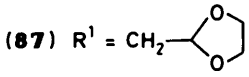
OHC·CH_2CH=CHR
(83)



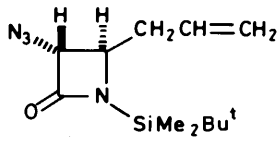
(84) $R^1 = CH_2CH$=CHR
(85) R^1 = CH=$CHCH_2R$



(86) $R^1 = CH_2$



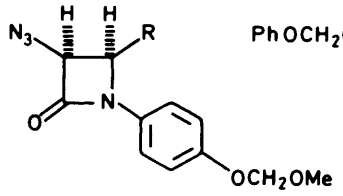
(87) $R^1 = CH_2$



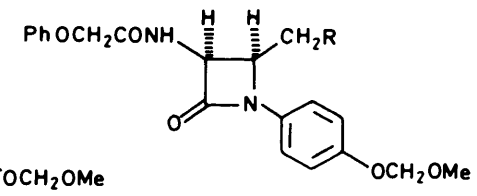
(88)

cinnamaldehyde by more appropriate aldehydes was investigated. β,γ-Unsaturated aldehydes (**83**) were prepared with difficulty (*e.g.* R = Ph[28]), but double bond isomerisation occurred in one of the subsequent steps, leading to products such as (**85**). Use of the masked aldehyde, 1,3-dithianylacetaldehyde did not provide the *cis*-3-azido-azetidinone (**86**), although more recently the corresponding 3-methoxy derivatives have been synthesized.[29] Vanderhaeghe has subsequently reported the ethylenedioxy derivative (**87**) in low yield.[30]

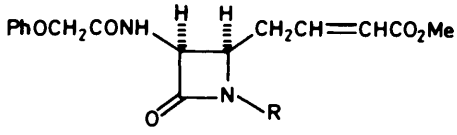
A second approach involved direct introduction of the 3-azido substituent[31] into 4-allyl-1-dimethyl-t-butylsilylazetidinone (**34**).[32] The *trans*-azetidinone (**88**) was the only observed product. Since inversion of stereochemistry at C-3 using the Merck procedure[33] had proved unrewarding in the corresponding 4-vinyl series,[1] this route was not pursued any further. The displacment of a C-4 leaving group from an azetidinone, already bearing the desired functionality at C-3, by an appropriate allyl synthon was considered an attractive alternative strategy. However, it was envisaged that the presence of a C-3 substituent might favour the formation of undesired *trans*-products. Subsequent to the completion of this programme, several procedures for the introduction of a 4-allyl substitutent into monocyclic azetidinones utilising allyl cuprates, allylsilanes, allyltin, and Grignard reagents have been reported.[34] Nevertheless, only recently has a relatively efficient process for the synthesis of *cis*-3-tritylamino-4-allylazetidinones been disclosed.[35] It was decided therefore to exploit the ready availability of the azetidinone (**68**) and attempt to transform the 4-styryl group into the required 4-allyl functionality. Initially it was thought the 4-nitroethyl derivative (**89**) would be a suitable precursor for a modified Nef reaction[36] leading to the acetal (**90**) and thence the azetidinone (**81**). Thus, ozonolysis of (**68**), followed by *in situ* reaction of the aldehyde (**91**) with nitromethane anion gave the nitro alcohol (**92**).[37] Thionyl chloride–triethylamine mediated dehydration than afforded (**93**) which was reduced with sodium borohydride to give the 4-nitroethylazetidinone (**89**). This material was readily converted into the acetal (**90**) by sequential reaction with sodium methoxide and concentrated sulphuric acid in methanol at −10 °C. As it was thought that the amide (**95**) would be more stable than the corresponding 3-azido derivative (**94**), the azide (**90**) was first reduced and acylated by the normal procedure to give (**96**) prior to elaboration of the 4-substitutent. Unexpectedly, liberation of the aldehyde (**97**) from the acetal (**96**) using a variety of conditions and subsequent reaction with methyl (triphenylphosphoranylidene)acetate gave very low yields of the olefin (**95**). The same deacetalisation–phosphorane sequence on azetidinone (**82**) obtained by CAN deprotection of (**96**), gave none of the olefin (**81**). A more viable procedure utilised the azetidinone (**98**), prepared from the corresponding azide (**89**) by



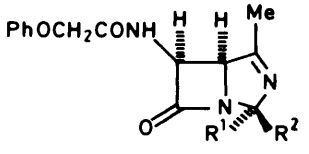
(89) R = $-(CH_2)_2NO_2$
(90) R = $-CH_2CH(OMe)_2$
(91) R = CHO
(92) R = $CH(OH)CH_2NO_2$
(93) R = $CH{=}CHNO_2$
(94) R = $CH_2CH{=}CHCO_2Me$



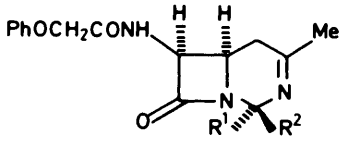
(95) R = $CH{=}CHCO_2Me$
(96) R = $CH(OMe)_2$
(97) R = CHO
(98) R = CH_2NO_2
(99) R = $CH{=}\overset{+}{N}(O^-)ONa$



(100) R = $CH(OH)CO_2CH_2Ph$
(101) R = $CH(N_3)CO_2CH_2Ph$



(102) $R^1 = CO_2H, R^2 = H$
(103) $R^1 = CO_2CH_2Ph, R^2 = H$
(104) $R^1 = H, R^2 = CO_2CH_2Ph$



(105) $R^1 = CO_2H, R^2 = H$
(106) $R^1 = CO_2CH_2Ph, R^2 = H$
(107) $R^1 = H, R^2 = CO_2CH_2Ph$

reduction and acylation. An acetal intermediate was avoided by converting the 4-nitroethyl azetidinone (**98**) into the olefin (**95**) directly *via* the aldehyde (**97**). Unfortunately, standard Nef conditions were of no synthetic utility with azetidinones of this type and more recent modified procedures using sodium methoxide-impregnated silica gel[38] or hydrogen peroxide–potassium carbonate[39] were equally unrewarding. However, careful ozonolysis of the nitronate salt (**99**)[40] provided the aldehyde (**97**) which was then treated *in situ* with methyl (triphenylphosphoranylidene)acetate to afford the olefin (**95**) in acceptable yield (*ca.* 40%). In contrast to the preparation of (**71**), the olefin (**95**) was a mixture of *E*- and *Z*-isomers (*ca.* 2:1 *E*:*Z*). The additional methylene is presumed to provide greater rotational freedom with a consequential reduction in steric interaction between the methoxycarbonyl and aryl moieties making both transition states possible (*cf.* Figure 2).

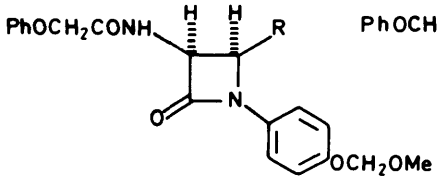
The azetidinone (**81**), obtained by CAN oxidation of (**95**), was progressed to the azido olefin (**101**) in the usual way. Thermolysis in refluxing toluene for 4 h then provided the required enamine (**76**) in 72% yield. N.m.r. analysis confirmed (**76**) to be a single *Z*-geometric isomer but a mixture of C-2 epimers (*ca.* 2:1 2α-H:2β-H). The olefinic signals appeared at δ 4.65 and 4.61 and the 2α-proton (δ 5.11) showed characteristic long range coupling, *J* 1.5 Hz to the 7α-proton. Treatment of the mixture with DBU did not give complete conversion into the pure natural C-2 epimer. An equilibrium mixture of (**76**) (*ca.* 3:2, 2β-proton:2α-proton) resulted, and more forcing conditions caused decomposition. Ozonolysis of the mixture of enamine epimers (**76**) followed by work-up with tris-*p*-methoxyphenylphosphine provided the separable amides (**78**) and (**79**). Application of the usual criteria allowed definitive stereochemical assignments to be made. In the case of the unnatural C-2 epimer (**79**), the C-2 proton appeared as a broad singlet at δ 5.16, but irradiation studies revealed the long range coupling (*J* 1.3 Hz) to the 7α-proton. Catalytic hydrogenation of (**76**) (*ca.* 3:2 2β-H:2α-H) gave the corresponding acid (**75**) as a mixture of epimers which displayed weak antibacterial activity (see Table 2). Despite the known instability of N-3-isoazacephem (**59**) and the expectation that a 7-acylamino substituent would further enhance the reactivity of the β-lactam to nucleophilic attack, the introduction of a Δ^3 double bond into ester (**76**) was investigated. In this case, we were unable to even isolate the ester precursor (**60**), extensive degradation taking place.

Standard deprotection of esters (**78**) and (**79**) afforded the acids (**77**) and (**80**). Although the degree of antibacterial activity was mediocre (see Table 2), the more active epimer possessed

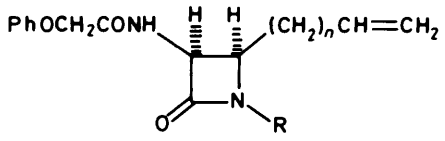
Table 2. Antibacterial activity of 7-phenoxyacetamido-8-oxo-1,3-diazabicyclo[4.2.0]octane-2-carboxylic acids

Organism	(75)	(77)	(80)
B. subtilis	125	200	25
Strep. pneumoniae CN33	16		
Staph. aureus (Oxford)		100	25
Staph. aureus (Russell)*		>200	200

* A β-lactamase-producing strain.



(108) R = -C≡CH
(109) R = -CH=CH$_2$
(110) R = Et
(111) R = CH$_2$CH=CH$_2$
(112) R = C≡CCH$_2$OH
(113) R = (CH$_2$)$_2$CH$_2$OH
(114) R = C≡CCH$_2$OSiPh$_2$Bu^t
(115) R = (CH$_2$)$_2$CH$_2$OSO$_2$Me
(116) R = (CH$_2$)$_2$CH$_2$Se(O)C$_6$H$_4$NO$_2$-*o*
(117) R = (CH$_2$)$_2$CH$_2$SeC$_6$H$_4$NO$_2$-*o*

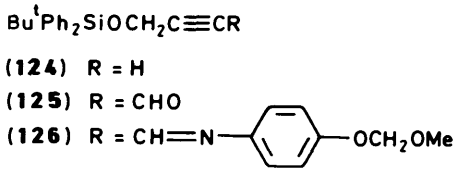


n = 0
(118) R = H
(119) R = CH(OH)CO$_2$CH$_2$Ph
(120) R = CH(N$_3$)CO$_2$CH$_2$Ph
n = 1
(121) R = H
(122) R = CH(OH)CO$_2$CH$_2$Ph
(123) R = CH(N$_3$)CO$_2$CH$_2$Ph

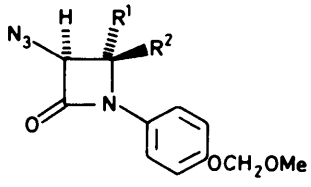
the unnatural stereochemistry at C-2. This observation has precedent in the 8-oxo-3-oxa-1-azabicyclo[4.2.0]octane-2-carboxylic acid series, previously reported by Gleason.[37]

The remaining synthetic target compounds were the C-6(7)-acylamino isoazapenem (**102**) and isoazacephem (**105**). Preparation of the former proved relatively straightforward from the available azetidinone (**108**).[24] Although catalytic semihydrogenation of (**108**) over 10% Pd–$BaSO_4$ or 5% Pd–$CaCO_3$ resulted in complete reduction to the 4-ethylazetidinone (**110**), use of 10% Pd–$BaSO_4$ in dioxane–pyridine[41] produced the required olefin (**109**). The standard *N*-deblocking–refunctionalisation sequence then provided the azide (**120**), which was heated in refluxing toluene solution for 34 h to give the expected imines (**103**) and (**104**). As in the unsubstituted series, selective n.m.r. decoupling experiments confirmed that the 2β-proton (**103**) (δ 6.14) and the 2α-proton (**104**) (δ 5.42) were coupled to both the 4-methyl and 5-proton. In addition the latter 2α-proton showed further fine coupling (*J* 1.2 Hz) to the 6α-proton. Catalytic hydrogenolysis of the ester (**103**) gave the antibacterially inactive acid (**102**) but similar treatment of (**104**) caused decomposition.

In principle, the intermediate (**111**) necessary for the azacephem counterpart (**105**) was available from methylene ylide reaction of the nitronate salt-derived aldehyde (**97**). However, we envisaged a potentially shorter route utilising the acetylenic azetidinone (**112**). Complete reduction of the triple bond followed by a formal dehydration of the resultant alcohol (**113**) should then provide the desired functionalisation. Thus, propyn-3-ol, protected as the t-butyl dimethylsilyl ether (**124**) was lithiated (butyl-lithium–THF at −25 °C) and treated with ethyl orthoformate to give the aldehyde (**125**).[42] The imine (**126**), obtained by condensation of the aldehyde (**125**) with *p*-methoxymethoxyaniline,[26] was converted by standard 'ketene–imine' methodology[43] into the *cis*-azetidinone (**127**). In addition, some *trans*-isomer (**128**) was isolated. Routine reduction–acylation of the azide (**127**) and fluoride-mediated deprotection of the thus derived amide (**114**) gave the acetylenic alcohol (**112**). Although catalytic hydrogenation proceeded to the saturated alcohol (**113**), β-elimination *via* the mesylate (**115**) using a variety of bases was unsuccessful; none of the desired olefin (**111**) was observed, even when 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene,[44] a powerful mesylate chelating agent, was employed. Consequently, the mesylate (**115**) was converted into the selenoxide (**116**) which decomposed slowly at ambient temperature to the olefin (**111**) in *ca.* 40% yield. The mesylate (**115**) was always recovered (*ca.* 50%), showing the inefficient conversion into the selenide (**117**). The olefin (**111**) was next progressed to the azide (**123**) and thermolysis in toluene for 7 h gave the expected imines (**106**) (22%) and (**107**) (7%). The latter could not be completely purified because of instability to chromatography. Hydrogenolysis of the ester (**106**) gave the antibacterially inactive acid (**105**).



(124) R = H
(125) R = CHO
(126) R = CH=N–C$_6$H$_4$–OCH$_2$OMe



(127) R^1 = H, R^2 = C≡CCH$_2$OSiPh$_2$Bu^t
(128) R^1 = C≡CCH$_2$OSiPh$_2$Bu^t, R^2 = H

Experimental

General procedures were as in Part I[20] except where indicated otherwise. 250 MHz and 80 MHz Spectra were recorded on a Bruker WM 250 and a Varian CFT-20 instrument respectively. Mass spectra were determined with either an A.E.I. MS9 or VG 70-70F machine and accurate mass measurements of molecular ions were carried out on compounds shown to be homogeneous by t.l.c. In general, the free acids described in the following experiments were not obtained analytically pure and gave no definite mass spectral data. However, most gave the expected

n.m.r., and i.r. data. The azides were generally too labile for full analytical characterisation and were used immediately after isolation. All the compounds are racemic.

1-[*Azido*(*benzyloxycarbonyl*)*methyl*]-4-*vinylazetidin*-2-*one* (**27**).—1-[Benzyloxycarbonyl(hydroxy)methyl]-4-vinylazetidin-2-one[17] (**25**) (2.36 g) in dry tetrahydrofuran (THF) (30 ml) containing 2,6-dimethylpyridine (1.58 ml) was cooled to −20 °C and thionyl chloride (0.97 ml) in dry THF (4 ml) was added dropwise over 10 min. The reaction mixture was filtered and the filtrate evaporated under reduced pressure. The residue was taken up in dry toluene and the solution re-evaporated; this was repeated. The resulting oil was dried *in vacuo* for 1 h to give the chloride (**26**) which was dissolved in dry dimethylformamide (DMF) (30 ml) and treated with finely powdered sodium azide (0.65 g). After vigorous stirring at room temperature for 1 h the reaction mixture was diluted with ethyl acetate, and washed successively with dilute brine, dilute hydrochloric acid, dilute aqueous sodium hydrogen carbonate, brine, and dried and evaporated. Chromatography of the residue gave the *azide* (**27**), an oil (2.26 g, 87%), as an inseparable mixture of isomers (Found: C, 58.6; H, 5.1; N, 19.5. $C_{14}H_{14}N_4O_3$ requires C, 58.7; H, 4.9; N, 19.6%); $\nu_{max.}$ 2 230 and 1 760 cm^{-1}; δ_H (60 MHz) 2.77 and 3.27 (2 H, ABq, *J* 15 Hz; higher field arm showing further coupling *J* 3 Hz; lower field arm showing further coupling *J* 5 and 2 Hz), 4.1—4.5 (1 H, m), 5.0—6.1 (6 H, m), and 7.38 (5 H, s).

(2RS,5RS)- *and* (2RS,5SR)-*Benzyl* 4-*Methyl*-7-*oxo*-1,3-*diazabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**12**) *and* (**14**).—The azide (**27**) (460 mg) was refluxed in dry, degassed toluene (500 ml) for 31 h and then the solution was cooled and evaporated. Chromatography of the residue gave the imine (**12**) as an oil (146 mg, 35%) (Found: C, 64.6; H, 5.7; N, 10.8. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.4; N, 10.9%); $\nu_{max.}$ 1 790, 1 750, and 1 630 cm^{-1}; $\lambda_{max.}$ 209 nm (ε 10 000 dm^3 mol^{-1} cm^{-1}); δ_H (90 MHz) 2.18 (3 H, d, *J* 1 Hz), 2.91 and 3.47 (2 H, ABq, *J* 15 Hz; higher field arm showing further coupling of *J* 3 Hz; lower field arm showing further coupling *J* 6 Hz), 4.43 (1 H, m), 5.14 (2 H, s), 5.95 (1 H, m), and 7.3 (5 H, s).

Further elution of the column gave the epimeric *imine* (**14**) as a crystalline solid (101 mg, 23%), m.p. 76—77 °C (ethyl acetate–light petroleum) (Found: C, 65.4; H, 5.7; N, 10.8%); $\nu_{max.}$(Nujol) 1 780, 1 750, and 1 630 cm^{-1}; $\lambda_{max.}$ 209 nm (ε 9 840 dm^3 mol^{-1} cm^{-1}); δ_H (90 MHz) 2.20 (3 H, d, *J* 2 Hz), 3.10 and 3.42 (2 H, ABq, *J* 16 Hz; higher field arm further coupled *J* 4 Hz; lower field arm further coupled *J* 6 and 1.5 Hz), 4.28 (1 H, m), 5.23 (3 H, m), and 7.30 (5 H, m).

(2RS,5RS)-4-*Methyl*-7-*oxo*-1,3-*diazabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylic Acid* (**13**).—The ester (**12**) (130 mg) in dry THF (15 ml) was hydrogenated over 10% Pd–C (65 mg) for 1.5 h. The catalyst was filtered off (Kieselguhr) and the filtrate evaporated. The residue was triturated with ether to give the acid (**13**) as a white solid (71 mg, 87%); $\nu_{max.}$(KBr) 3 400br, 1 765, 1 710, and 1 650 cm^{-1}; δ_H [90 MHz; $(CD_3)_2NCDO$] *inter alia* 2.19 (3 H, s), 3.14 and 3.57 (2 H, ABq, *J* 16 Hz; higher field arm further coupled *J* 3 Hz; lower field arm further coupled *J* 6 Hz), 4.4 (1 H, m), and 5.70 (1 H, m).

Conversion of the (2RS,5SR)-*Compound* (**14**) *into Its* (2RS,5RS)-*Isomer* (**12**).—The imine (**14**) (42 mg) was dissolved in dry dichloromethane (1.5 ml) and the solution was cooled to −20 °C and DBU (25 mg) in dichloromethane (0.5 ml) was then added portionwise over 50 min. After a further 50 min the reaction mixture was poured directly into a silica gel column and eluted with ethyl acetate to give the isomer (**12**) (21 mg, 50%), identical in all respects with authentic material.

4-*Allyl*-1-[*azido*(*benzyloxycarbonyl*)*methyl*]*azetidin*-2-*one* (**33**).—4-Allyl-1-[benzyloxycarbonyl(hydroxy)methyl]azetidin-2-one (**31**) (4.4 g) in dry THF (200 ml) containing 2,6-dimethylpyridine (2.72 ml) was cooled to −20 °C and thionyl chloride (1.71 ml) in dry THF (20 ml) added dropwise over 25 min. After a further 5 min the reaction mixture was filtered and the filtrate evaporated under reduced pressure. The resulting crude chloride (**32**) was immediately redissolved in dry DMF (150 ml). Powdered sodium azide (1.2 g) was then added to the vigorously stirred solution and after 5 min the mixture was poured into ethyl acetate and brine containing a few drops of 1M-hydrochloric acid. The organic layer was separated, washed with brine (×2), dried, and evaporated. Chromatography of the residue provided the azide (**33**) as a gum (3.85 g, 80%), $\nu_{max.}$(film) 2 115, 1 765br, and 1 640 cm^{-1}; δ_H (60 MHz) 2.0—3.3 (4 H, m), 3.65—4.2 (1 H, m), 4.85—6.0 (6 H, m, singlets at δ 5.45 and 5.7 were assignable to CHN_3 of the two epimers), and 7.37 (5 H, s).

(2RS,6SR)-*Benzyl* 4-*Methyl*-8-*oxo*-1,3-*diazabicyclo*[4.2.0]*oct*-3-*ene*-2-*carboxylate* (**16**).—*Method A*. The azide (**33**) (0.82 g) was refluxed in toluene (300 ml) for 7 h after which the solution was cooled and evaporated. The n.m.r. spectrum (60 MHz) of the total crude product showed signals at *ca.* δ 2.06 (3 H, s), 5.2 (2 H, s), and 5.45 (1 H, m), assignable to the unnatural imine (**18**). Chromatography of the residue gave only the *imine* (**16**) (0.11 g, 15%), m.p. 94.5—95 °C (ethyl acetate–light petroleum) (Found: C, 66.4; H, 6.1; N, 10.1. $C_{15}H_{16}N_2O_3$ requires C, 66.2; H, 5.9; N, 10.3%); $\nu_{max.}$(Nujol) 1 735 and 1 650 cm^{-1}; δ_H (90 MHz) 2.03 (3 H, s), 2.05 and 2.65 (2 H, ABq, *J* 18 Hz; higher field arm further coupled *J* 8 Hz and 3 Hz; lower field arm further coupled *J* 6 Hz), 2.55 and 3.35 (2 H, ABq, *J* 15 Hz; higher field arm further coupled *J* 4.5 Hz; lower field arm further coupled *J* 1.5 Hz), 3.45—3.65 (1 H, m), 5.15 (2 H, s), 5.72 (1 H, br s), and 7.28 (5 H, m).

Method B. The azide (**33**) (3.7 g) was refluxed in toluene (1 l) as described above and the crude total product was dissolved in dry dichloromethane (120 ml). DBU (0.182 g) in dichloromethane (20 ml) was added dropwise at −20 °C and after 1 h the solution was concentrated to *ca.* 50 ml. The reaction mixture was poured onto silica gel and chromatographed to give the required imine (**16**) (1.08 g, 30%).

(2RS,6SR)-4-*Methyl*-8-*oxo*-1,3-*diazabicyclo*[4.2.0]*oct*-3-*ene*-2-*carboxylic Acid* (**17**).—The ester (**16**) (272 mg) was hydrogenated as described for compound (**12**) to provide the acid (**17**). The product was isolated as an amorphous white solid (85 mg, 47%); $\nu_{max.}$(Nujol) 1 735 and 1 645 cm^{-1}; $\delta_H(D_2O)$ *inter alia* 2.13 (3 H, s), 2.35—3.35 (4 H, m, two overlapping ABq), 4.12 (1 H, m), and 5.06 (1 H, s).

1-[*Benzyloxycarbonyl*(*hydroxy*)*methyl*]-4-[2-*methoxycarbonylvinyl*]*azetidin*-2-*one* (**41**).—A solution of the α-hydroxy ester (**25**) (2.8 g) in ethyl acetate (50 ml) was ozonised at −76 °C until a pale blue colour persisted. The solution was purged with argon for 45 min and then a solution of triphenylphosphine (3.09 g) in ethyl acetate (25 ml), pre-cooled to −76 °C, was added. The mixture was stirred for a further 1 h after which methyl (triphenylphosphoranylidene)acetate (7.88 g) was added. The solution was allowed to warm to room temperature over 1 h, and then evaporated. Chromatography gave the acrylate (**41**), as an oil (2.46 g, 72%) which was an inseparable mixture of isomers (Found: C, 59.7; H, 5.5; N, 4.2. $C_{16}H_{17}NO_6$ requires C, 60.2; H, 5.3; N, 4.4%); $\nu_{max.}$ 3 500br, 1 770, 1 750, 1 710sh, and 1 660 cm^{-1}; δ_H (90 MHz) 2.5—2.9 (1 H, m), 3.0—3.4 (1 H, m), 3.65 (3 H, s), 4.2 (0.5 H, m), 4.35 (1.5 H, m, collapses to 0.5 H, m, on exch.), 5.0—5.3 (3 H, m), 5.97 (1 H, m), 6.83 (1 H, m), and 7.27 (5 H, s).

1-[*Azido(benzyloxycarbonyl)methyl*]-4-(2-*methoxycarbonylvinyl*)*azetidin*-2-*one* (**43**).—The α-hydroxy ester (**41**) (2.17 g) was treated as described for compound (**25**) to give the *azide* (**43**). The product, a colourless oil, was an inseparable mixture of isomers (1.83 g, 78%) (Found: C, 55.8; H, 4.8; N, 16.3. $C_{16}H_{16}N_4O_5$ requires C, 55.8; H, 4.7; N, 16.3%); $\nu_{max.}$ 2 250, 1 770, 1 760sh, 1 710, and 1 665 cm^{-1}; δ_H (90 MHz) 2.6—3.0 (1 H, m), 3.1—3.5 (1 H, m), 3.7 (3 H, s), 4.0—4.5 (1 H, m), 5.1—5.5 (3 H, m), 5.93 (1 H, m), 6.8 (1 H, m), and 7.30 (5 H, m).

(2RS,5RS)- *and* (2RS,5SR)-*Benzyl* 4-*Methoxycarbonylmethylene*-7-*oxo*-1,3-*diazabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**39**) *and* (**40**).—The azide (**43**) (1.7 g) was refluxed in toluene (1.7 l) for 24 h. The cooled solution was evaporated to leave an oil, from which on drying *in vacuo* a white solid crystallised. Trituration with ether and recrystallisation from ethyl acetate–light petroleum gave the *enamine* (**39**) (0.27 g, 17%), m.p. 154.5—156 °C (Found: C, 60.9; H, 5.3; N, 8.7; M^+, 316.1113. $C_{16}H_{16}N_2O_5$ requires C, 60.8; H, 5.1; N, 8.9%; *M*, 316.1167); $\nu_{max.}$(Nujol) 3 390, 1 797, 1 740, 1 667, and 1 638 cm^{-1}; $\lambda_{max.}$ 275 nm (ε 18 100 dm^3 mol^{-1} cm^{-1}); δ_H (90 MHz) 3.01 and 3.64 (2 H, ABq, *J* 16 Hz; higher field arm further coupled, *J* 3 Hz; lower field arm further coupled, *J* 6 Hz), 3.64 (3 H, s), 4.49 (1 H, dd, *J* 6 and 3 Hz), 4.77 (1 H, s), 5.13 (2 H, s), 5.54 (1 H, s), 7.29 (5 H, s), and 8.16 (1 H, s, exch.).

Chromatography of the mother liquors on Florisil afforded a further quantity of the *enamine* (**39**) (0.11 g, 7%) and the epimeric *enamine* (**40**) (0.24 g, 15%), m.p. 137—139.5 °C (ethyl acetate–light petroleum) (Found: C, 61.0; H, 5.2; N, 8.7%); $\nu_{max.}$(Nujol) 3 375, 1 785, 1 770, 1 755, 1 665, and 1 630 cm^{-1}; $\lambda_{max.}$ 274 nm (ε 20 450 dm^3 mol^{-1} cm^{-1}); δ_H (90 MHz) 3.04 and 3.55 (2 H, ABq, *J* 16 Hz; higher field arm further coupled *J* 3 Hz; lower field arm further coupled, *J* 6 Hz), 3.62 (3 H, s), 4.40 (1 H, m), 4.71 (1 H, s), 5.02 (1 H, s), 5.23 (2 H, s), 7.33 (5 H, s), and 8.17 (1 H, s, exch.).

(2RS,5RS)-*Benzyl* 4,7-*Dioxo*-1,3-*diazabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**44**).—A solution of the enamine (**39**) (60 mg) in ethyl acetate (5 ml) was ozonised at −76 °C until a pale blue colour persisted. After purging the solution with argon for 30 min, tris(*p*-methoxyphenyl)phosphine (130 mg) was added in ethyl acetate (2 ml), pre-cooled to −76 °C. The solvent was evaporated off after a further 30 min and the residue chromatographed to give the *amide* (**44**) as an amorphous solid (32 mg, 65%) (Found: C, 60.0; H, 4.5; N, 11.1. $C_{13}H_{12}N_2O_4$ requires C, 60.0; H, 4.6; N, 10.8%); $\nu_{max.}$ 3 425, 1 802, 1 750, and 1 725 cm^{-1}; δ_H (90 MHz) 3.16 and 3.57 (2 H, ABq, *J* 17 Hz; higher field arm further coupled *J* 4 Hz; lower field arm further coupled *J* 6 Hz), 3.94 (1 H, dd, *J* 4 and 6 Hz), 5.22 (2 H, s), 5.42 (1 H, s), 7.18 (1 H, s), and 7.27 (5 H, s).

(2RS,5SR)-*Benzyl* 4,7-*Dioxo*-1,3-*diazabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**45**).—A solution of the enamine (**40**) (122 mg) was ozonised as described for compound (**39**) except that decomposition of the ozonide was achieved using dimethyl sulphide (72 mg) overnight at room temperature. Chromatography gave the *amide* (**45**) (34 mg, 34%), m.p. 154.5—155.5 °C (ethyl acetate–light petroleum) (Found: C, 59.7; H, 4.7; N, 10.5. $C_{13}H_{12}N_2O_4$ requires C, 60.0; H, 4.6; N, 10.8%); $\nu_{max.}$(Nujol) 3 200br, 1 785, 1 780, 1 753, and 1 730 cm^{-1}; δ_H (90 MHz) 3.23 and 3.51 (2 H, ABq, *J* 16 Hz; higher field arm further coupled, *J* 4 Hz; lower field arm further coupled, *J* 6 Hz), 3.95 (1 H, m), 5.07 (1 H, s), 5.22 (2 H, s), 7.22 (1 H, s), and 7.30 (5 H, s).

1-[*Benzyloxycarbonyl(hydroxy)methyl*]-4-(3-*methoxycarbonylprop*-2-*enyl*)*azetidin*-2-*one* (**49**).—The α-hydroxy ester (**31**) (1.1 g) was converted into the acrylate (**49**) as described for compound (**25**). The product, isolated as an oil, was an inseparable mixture of four isomers (0.87 g, 67%) (Found: C, 60.6; H, 5.9; N, 4.3. $C_{17}H_{19}NO_4$ requires C, 61.3; H, 5.7; N, 4.2%); $\nu_{max.}$(film) 3 500, 1 740br, 1 720sh, and 1 655 cm^{-1}; δ_H (90 MHz) *inter alia* 2.2—3.3 (4 H, m), 3.73 (3 H, s) (latter signal obscures 1 H, m), 4.13 (1 H, br s, exch.), 5.28 and 5.31 (2 H, two s), 5.5 (1 H, br s, becomes two s at δ 5.4 and 5.45 on exch.), 6.0 (1 H, br s), 6.5—7.1 (1 H, m), and 7.42 (5 H, s).

1-[*Azido(benzyloxycarbonyl)methyl*]-4-(3-*methoxycarbonylprop*-2-*enyl*)*azetidin*-2-*one* (**50**).—The α-hydroxy ester (**49**) (1.78 g) was treated as described for compound (**31**) to give the azide (**50**). Chromatography of the crude product afforded the separable olefinic isomers, each of which consisted of two azide epimers: *Z-isomer*, gum (0.28 g, 15%); $\nu_{max.}$(film) 2 115, 1 760br, 1 720, and 1 648 cm^{-1}; δ_H (60 MHz) *inter alia* 2.52—3.4 (4 H, m), 3.72 (3 H, s), 3.83—4.28 (1 H, m), 5.28 (2 H, s), 5.45—6.3 (3 H, m), and 7.4 (5 H, s); *E-isomer*, gum (1.3 g, 68%); $\nu_{max.}$(film) 2 110, 1 760br, 1 718, and 1 655 cm^{-1}; δ_H (60 MHz) *inter alia* 2.15—3.37 (4 H, m), 3.7 (3 H, s), 3.75—4.21 (1 H, m), 5.23 (2 H, s), 5.5—5.93 (2 H, two s and one br s), 6.43—7.15 (1 H, m), and 7.37 (5 H, m).

(2RS,6SR)-*Benzyl* 4-*Methoxycarbonylmethylene*-8-*oxo*-1,3-*diazabicyclo*[4.2.0]*octane*-2-*carboxylate* (**51**).—*Method A.* The azide (**50**; *E*-olefinic isomer) (2.0 g) was refluxed in toluene solution (500 ml), under argon, for 5.5 h. The solution was cooled and the solvent evaporated off to leave an oily residue which on drying *in vacuo* gave a white solid. Recrystallisation from ethyl acetate–light petroleum afforded the pure *enamine* (**52**) (0.44 g, 20%), m.p. 149—150 °C (ethyl acetate–light petroleum) (Found: C, 61.7; H, 5.6; N, 8.2. $C_{17}H_{18}N_2O_5$ requires C, 61.9; H, 5.5; N, 8.5%); $\nu_{max.}$(Nujol) 3 280, 1 770, 1 750, 1 630, and 1 615 cm^{-1}; $\lambda_{max.}$ 283 nm (ε 18 700 dm^3 mol^{-1} cm^{-1}); δ_H (90 MHz) 2.35 (1 H, higher field arm of ABq, *J* 16 Hz; further coupled, *J* 9 and *ca.* 2 Hz), 2.55—2.90 (2 H, m), 3.38 (1 H, lower field arm of ABq, *J* 16 Hz, further coupled *J* 5 Hz), 3.6 (3 H, s), 3.7 (1 H, m), 4.66 (1 H, d, *J ca.* 2 Hz), 5.22 (2 H, AA′), 5.52 (1 H, d, *J ca.* 2 Hz), 7.3 (5 H, s), and 9.18 (1 H, br s, exch.).

Chromatography of the mother liquors on Florisil gave a 1:4 mixture of (**51**) and the enamine (**52**) (635 mg, 30%); δ_H (250 MHz) *inter alia* 3.22 (1 H, lower field arm of ABq, *J* 16 Hz; further coupled *J* 6 Hz and 1.7 Hz), 4.68 (1 H, d, *J ca.* 1 Hz), 5.15 (1 H, dd, *J* 4 and 1.7 Hz), 5.24 (2 H, s), and 9.10 (1 H, br s, exch.). Treatment of this material in dry dichloromethane (10 ml) with DBU (250 mg) for 10 min at room temperature, followed by chromatography of the total product on Florisil gave the enamine (**51**) (465 mg, 73%).

Method B. The azide (**50**; *Z*-olefinic isomer) (277 mg) was converted into a mixture of enamines (**51**) and (**52**) (94 mg) identical in all respects to that described in Method A. The total crude product (94 mg) was treated with DBU as described above to give the enamine (**51**) (65 mg, 25%).

(2RS,6SR)-*Benzyl* 4,8-*Dioxo*-1,3-*diazabicyclo*[4.2.0]*octane*-2-*carboxylate* (**54**).—A solution of the enamine (**51**) (370 mg) in dry dichloromethane (25 ml) containing dry methanol (2 ml) was ozonised as described for compound (**40**) except that dimethyl sulphide (20 drops) was added at −30 °C for 1 h. Chromatography gave the *amide* (**54**) (267 mg, 86%), m.p. 141—142 °C (ethyl acetate–light petroleum) (Found: C, 61.3; H, 5.3; N, 9.9. $C_{14}H_{14}N_2O_4$ requires C, 61.3; H, 5.1; N, 10.2%); $\nu_{max.}$(Nujol) 3 280, 1 760, 1 740, 1 670, and 1 625 cm^{-1}; δ_H (250 MHz) 2.39 and 2.86 (2 H, ABq, *J* 17.2 Hz; higher field arm further coupled, *J* 8.6 Hz; lower field arm further coupled, *J* 5.6 Hz), 2.74 and 3.44 (2 H, ABq, *J* 15.5 Hz; higher field arm further coupled, *J* 1.7 Hz; lower field arm further coupled, *J* 4.7 Hz), 3.86—3.96 (1 H, dddd, *J* 8.6, 5.6, 4.7, and 1.7 Hz), 5.24 (2 H, s), 5.61 (1 H, br s), 7.02 (1 H, br s), and 7.31 (5 H, s).

(2RS,5RS)-*Sodium* 4,7-*Dioxo*-1,3-*diazabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**46**).—The ester (**44**) (44 mg) in dioxane (12 ml) and water (3 ml) was hydrogenated over 10% Pd–C (26 mg) for 30 min. Sodium hydrogen carbonate (17 mg) in water (0.15 ml) was added and the reaction mixture filtered through Kieselguhr. The filtrate was then concentrated to *ca.* 6 ml and partitioned with ethyl acetate. The aqueous layer was separated and evaporated. The residue was taken up in ethanol and the solution re-evaporated. This was repeated with toluene. The residual solid was dried *in vacuo* and then triturated with ether to give the sodium salt (**46**) (35 mg, 92%); $\nu_{max.}$(KBr) 3 400br, 1 775, 1 695, and 1 620 cm^{-1}; δ_H (80 MHz; D_2O) *inter alia* 3.24 and 3.65 (2 H, ABq, *J* 13 Hz; higher field arm further coupled, *J* 4 Hz; lower field arm further coupled, *J* 6.5 Hz), 4.14 (1 H, dd, *J* 6.5 and 4 Hz), and 5.33 (1 H, s).

(2RS,6SR)-4,8-*Dioxo*-1,3-*diazabicyclo*[4.2.0]*octane*-2-*carboxylic Acid* (**55**).—The ester (**54**) (70 mg) in dioxane (5 ml) was hydrogenated over 10% Pd–C (40 mg) for 35 min. Isolation of the product (**55**), as described for compound (**13**), gave a white solid (43 mg, 85%); $\nu_{max.}$(KBr) 3 400, 3 285, 1 760, 1 735, and 1 630 cm^{-1}; δ_H (250 MHz; D_2O) 2.42 and 2.63 (2 H, ABq, *J* 17 Hz; each part showing further coupling, *J* 9 and 5.8 Hz, respectively), 2.68 and 3.26 (2 H, ABq, *J* 16 Hz; each part showing further coupling *J* 1.5 and 4.7 Hz respectively), 3.79 (1 H, m), and 5.46 (1 H, s).

(2SR,5RS)-4-*Methoxycarbonylmethylene*-7-*oxo*-1,3-*diazabicyclo*[3.2.0]*heptane*-2-*carboxylic Acid* (**56**).—The ester (**39**) (100 mg) in dioxane (5 ml) was hydrogenated over 10% Pd–C (50 mg) for 80 min as described for compound (**12**). The product (**56**), a white amorphous solid (30 mg, 42%) was a *ca.* 1:1 mixture of *E*:*Z* olefinic isomers; $\nu_{max.}$(KBr) 3 400br, 1 750br, 1 660, and 1 620 cm^{-1}; $\lambda_{max.}$(MeCN) 272 nm (ε 12 990 dm^3 mol^{-1} cm^{-1}); δ_H [250 Mz; $(CD_3)_2SO$] *inter alia* 2.97 and 3.86 (1 H, ABq, *J* 17 Hz; higher field arm further coupled, *J* 3 Hz; lower field arm further coupled, *J* 6 Hz), 3.08 and 3.78 (1 H, ABq, *J* 17 Hz; higher field arm further coupled, *J ca.* 2.5 Hz; lower field arm further coupled, *J ca.* 7 Hz), 3.51 and 3.56 (together 3 H, two s), 4.55 (0.5 H, m), 4.69 (0.5 H, br s), 4.73 (0.5 H, m), 4.95 (0.5 H, d, *J ca.* 2 Hz), 5.33 and 5.37 (together 1 H, two s), and 8.55 (1 H, m).

(2RS,6SR)-4-*Methoxycarbonylmethylene*-8-*oxo*-1,3-*diazabicyclo*[4.2.0]*octane*-2-*carboxylic Acid* (**53**).—The ester (**51**) (100 mg) in dioxane (10 ml) was hydrogenated over 10% Pd–C (50 mg) for 30 min. The mixture was filtered through Kieselguhr, the filtrate evaporated, and the residue redissolved in dioxane containing some water (0.5 ml); the solution was then refiltered. The filtrate was evaporated, toluene added to the residue, and the process repeated. The product was triturated with ether to give the acid (**53**) as a pale yellow solid (62 mg, 82%); $\nu_{max.}$(KBr) 3 430br, 1 740, 1 710sh, 1 650, and 1 610sh cm^{-1}; $\lambda_{max.}$ 282 nm (ε 13 445 dm^3 mol^{-1} cm^{-1}); δ_H [250 MHz; $(CD_3)_2SO$] *inter alia* 2.36—2.90 (4 H, m), 3.2—3.5 (1 H, m), 3.54 (3 H, s), 4.55 (1 H, s), 5.48 (1 H, s), and 9.40 (1 H, s).

Benzyl 4-*Methoxycarbonylmethylene*-8-*oxo*-1,3-*diazabicyclo*-[4.2.0]*oct*-2-*ene*-2-*carboxylate* (**58**).—A solution of the ester (**51**) (110 mg) in dry dichloromethane (3 ml) was cooled to −76 °C under argon and diethyl dibromomalonate (106 mg) added, followed by DBU (100 mg). After 1 h further diethyl dibromomalonate (106 mg) was added and stirring continued for 1.5 h. Acetic acid (2 drops) was added and the reaction mixture immediately chromatographed to give the *ester* (**58**) (40 mg, 35%), m.p. 137—138 °C (ethyl acetate–light petroleum) (Found: C, 62.0; H, 5.0; N, 8.5. $C_{17}H_{16}N_2O_5$ requires C, 62.2; H, 4.9; N, 8.5%); $\nu_{max.}$(KBr) 1 800, 1 740, 1 710, and 1 640 cm^{-1}; $\lambda_{max.}$ 315 nm (ε_m 14 500 dm^3 mol^{-1} cm^{-1}); δ_H (80 MHz) 1.75—2.2 (1 H, m), 2.85 and 3.05 (1 H, 2 × d, *J* 3.5 Hz), 3.25—3.95 (2 H, m), 3.75 (3 H, s), 4.3—4.65 (1 H, 2 × d, *J* 5 Hz) (the latter signal obscures a broad one proton multiplet due to 6-H), 5.3 and 5.46 (2 H, ABq, *J* 16 Hz), 6.24 (1 H, d, *J* 2 Hz), and 7.2—7.55 (5 H, m).

(3RS,4SR)-1-(4-*Methoxymethoxyphenyl*)-3-*phenoxyacetamido*-4-*styrylazetidin*-2-*one* (**70**).—To the β-lactam (**68**) (3.5 g) in dry dichloromethane (100 ml) at 0 °C was added triethylamine (1.1 g). Hydrogen sulphide was bubbled through the mixture for 5 min and the resulting dark solution left at 0 °C for 1 h. The solvent was then removed under reduced pressure and the residue re-evaporated (× 3) from dichloromethane to afford a pale yellow solid. Without further purification, the crude amine (**69**) was dissolved in dry dichloromethane (100 ml) at −10 °C and triethylamine (1.1 g) added, followed by dropwise addition of phenoxyacetyl chloride (1.87 g) in dichloromethane (10 ml) over 10 min. The solution was washed with water, dried, and evaporated. Trituration of the residue with ethyl acetate gave the *amide* (**70**) as a solid (4 g, 87%). Chromatography of the mother liquors gave further material (0.4 g, 8%), m.p. 186—187 °C (ethyl acetate–light petroleum) (Found: C, 70.8; H, 5.8; N, 5.7. $C_{27}H_{26}N_2O_5$ requires C, 70.7; H, 5.7; N, 6.1%); $\nu_{max.}$(Nujol) 3 265, 1 755, 1 670, and 1 510 cm^{-1}; δ_H [90 MHz; $(CD_3)_2SO$] 3.32 (3 H, s), 4.52 (2 H, s), 5.0 (1 H, dd, *J* 9 and 5.5 Hz), 5.11 (2 H, s), 5.48 (1 H, dd, *J* 9.5 and 5.5 Hz), 6.41 (1 H, dd, *J* 16 and 9 Hz), 6.7—7.5 (15 H, m), and 8.98 (1 H, d, *J* 9.5 Hz).

(3RS,4SR)-4-[(E)-2-*Methoxycarbonylvinyl*]-1-(4-*methoxymethoxyphenyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**71**).—The lactam (**70**) (4 g) in dichloromethane (250 ml) was converted, as described for compound (**25**), into the *olefin* (**71**) (2 g, 62%), m.p. 178—179 °C (ethyl acetate–light petroleum) (Found: C, 62.7; H, 5.4; N, 6.2. $C_{23}H_{24}N_2O_7$ requires C, 62.7; H, 5.5; N, 6.4%); $\nu_{max.}$(Nujol) 3 400, 1 758, 1 725, 1 685, and 1 515 cm^{-1}; δ_H (90 MHz) 3.43 (3 H, s), 3.67 (3 H, s), 4.47 (2 H, s), 4.9 (1 H, m, *J ca.* 6, 5.5, and *ca.* 0.5 Hz), 5.1 (2 H, s), 5.52 (1 H, dd, *J* 8 and 5.5 Hz), 6.06 (1 H, dd, *J* 16 and *ca.* 0.5 Hz), and 6.7—7.5 (11 H, m).

(3RS,4SR)-4-[(E)-2-*Methoxycarbonylvinyl*]-3-*phenoxyacetamidoazetidin*-2-*one* (**72**).—The azetidinone (**71**) (1.699 g) was dissolved in THF (60 ml) and the solution cooled to 0 °C. Ceric ammonium nitrate (10.6 g) in water (10 ml) was added dropwise over 10 min. After a further 10 min solid sodium sulphite was added to discharge the orange-red colour, and the mixture poured into ethyl acetate–brine. After filtration through Kieselguhr the organic layer was separated, washed with brine, dried, and evaporated. Chromatography of the residue gave the *azetidinone* (**72**) (0.59 g, 66%), m.p. 147—148 °C (ethyl acetate–light petroleum) (Found: C, 58.9; H, 5.3; N, 9.1. $C_{15}H_{16}N_2O_5$ requires C, 59.2; H, 5.3; N, 9.2%); $\nu_{max.}$(Nujol) 3 380, 3 330, 1 785, 1 700, 1 680, and 1 660 cm^{-1}; δ_H [250 MHz; $(CD_3)_2SO$] 3.72 (3 H, s), 4.46 (1 H, ddd, *J* 6, 5, and *ca.* 1 Hz), 4.48 (2 H, s), 5.32 (1 H, ddd, *J* 8, 5, and *ca.* 1 Hz), 6.04 (1 H, dd, *J* 15 and 1 Hz), 6.91 (1 H, dd, *J* 15 and 6 Hz), 6.9—7.0 and 7.2—7.3 (5 H, 2 × m), 8.41 (1 H, br s), and 8.59 (1 H, d, *J* 8 Hz).

(3RS,4SR)-1-[*Benzyloxycarbonyl*(*hydroxy*)*methyl*]-4-(2-*methoxycarbonylvinyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**73**).—Benzyl glyoxylate (994 mg) was refluxed in benzene (25 ml) for 30 min with provision for the removal of water. The solution was cooled, the β-lactam (**72**) (475 mg) added in dioxane (4 ml), and refluxing continued for a further 14 h. The solution was evaporated and the residue chromatographed to give the α-hydroxy ester (**73**) as a 1:1 mixture of isomers (643 mg, 88%); $\nu_{max.}$ 3 500, 3 410, 3 320, 1 780, 1 750, 1 730, and 1 690 cm^{-1}; δ_H (250 MHz) 3.68 and 3.71 (together 3 H, 2 × s), 4.36—4.55 (3 H, m, 1 H, exch.), 4.79 (1 H, ddd, *J* 8, 5, and *ca.* 1 Hz), 5.09 and 5.18 (1 H, ABq of one isomer, *J* 12 Hz), 5.13 and 5.22 (1 H,

ABq of other isomer, *J* 12 Hz), 5.33 (0.5 H, broad signal becomes sharp singlet on exch.), 5.54 (0.5 H, d, *J* 6 Hz, collapses to s on exch.), 5.28 (0.5 H, dd, *J* 8.5 and 5.5 Hz), 5.34 (0.5 H, dd, *J* 8.5 and 5.5 Hz), 6.02 (0.5 H, dd, *J* 15.5 and *ca.* 1 Hz), 6.15 (0.5 H, dd, *J* 15.5 and *ca.* 1 Hz), and 6.7—7.5 (12 H, m).

(3RS,4SR)-1-[*Azido*(*benzyloxycarbonyl*)*methyl*]-4-(2-*methoxycarbonylvinyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**74**).—The α-hydroxy ester (**73**) (1.589 g) was treated as described for compound (**31**) to give the azide (**74**). The product was isolated as a *ca.* 2:1 mixture of isomers (1.6 g, 95%); $\nu_{max.}$ 3 410, 2 120, 1 780, 1 755, 1 730, and 1 690 cm^{-1}; δ_H (250 MHz) 3.71 (3 H, s), 4.42 and 4.5 (0.67 H, ABq of one isomer, *J* 15 Hz), 4.44 and 4.51 (1.33 H, ABq of other isomer, *J* 15.5 Hz), 4.68 (0.33 H, ddd, *J* 8, 5, and *ca.* 1 Hz), 4.73 (0.67 H, ddd, *J* 8, 5, and *ca.* 1 Hz), 5.14 and 5.26 (1.33 H, ABq of one isomer, *J* 12 Hz), 5.23 and 5.31 (0.67 H, ABq of other isomer), 5.4 (0.67 H, s), 5.42 (0.33 H, dd, *J* 8 and 5 Hz), 5.49 (0.67 H, dd, *J* 8 and 5 Hz), 5.66 (0.33 H, s), 6.04 (0.33 H, dd, *J* 15 and *ca.* 1 Hz), 6.09 (0.67 H, dd, *J* 15 and *ca.* 1 Hz), and 6.75—7.4 (12 H, m).

(2RS,5RS,6RS)- *and* (2RS,5SR,6SR)-*Benzyl* 4-*Methoxycarbonylmethylene*-7-*oxo*-6-*phenoxyacetamido*-1,3-*diazabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**65**) *and* (**67**).—The azide (**74**) (482 mg) was refluxed in toluene for 25 h as described for compound (**27**) to give the *enamine* (**65**) (54 mg, 12%), m.p. 131—132 °C (decomp.) (ethyl acetate–hexane) (Found: C, 61.9; H, 5.0; N, 8.8. $C_{24}H_{23}N_3O_7$ requires C, 61.9; H, 4.9; N, 9.0%); $\nu_{max.}$ 3 400, 3 350, 1 807, 1 750, 1 690sh, 1 680, and 1 612 cm^{-1}; $\lambda_{max.}$ 275 nm (ε 16 600 dm^3 mol^{-1} cm^{-1}); δ_H (250 MHz) 3.69 (3 H, s), 4.49 and 4.58 (2 H, ABq, *J* 15 Hz), 4.71 (1 H, d, *J* 1 Hz), 4.79 (1 H, dd, *J* 6 and 1 Hz), 5.20 (2 H, s), 5.66 (1 H, s), 5.83 (1 H, dd, *J* 9 and 6 Hz), 6.85—7.4 (11 H, m), and 8.23 (1 H, br s).

Further elution of the column gave the epimeric *enamine* (**67**) (70 mg, 14%) as an amorphous solid (Found: M^+, 465.1547. $C_{24}H_{23}N_3O_7$ requires *M*, 465.1536); $\nu_{max.}$ 3 400, 3 350, 1 807, 1 758, 1 690sh, 1 680, and 1 630 cm^{-1}; $\lambda_{max.}$ 274 nm (ε 17 700 dm^3 mol^{-1} cm^{-1}); δ_H (250 MHz) 3.78 (3 H, s), 4.49 and 4.57 (2 H, ABq, *J* 15 Hz), 4.65 (1 H, d, *J* 1 Hz), 4.72 (1 H, ddd, *J* 6, 1, and *ca.* 0.5 Hz), 5.13 (1 H, d, *J ca.* 0.5 Hz), 5.31 (2 H, s), 5.84 (1 H, dd, *J* 9 and 6 Hz), 6.85—7.5 (11 H, m), and 8.25 (1 H, br s). The bulk of the material (177 mg, 39%) was isolated as a mixture of enamines (**65**) and (**67**).

(2RS,5RS,6RS)-4-*Methoxycarbonylmethylene*-7-*oxo*-6-*phenoxyacetamido*-1,3-*diazabicyclo*[3.2.0]*heptane*-2-*carboxylic Acid* (**57**).—The ester (**65**) (40 mg) in dioxane (10 ml) was hydrogenated over 10% Pd–C (20 mg) for 90 min as described for compound (**12**). The product (**57**), a white solid (30 mg; 75%) was a *ca.* 2:1 mixture of *Z*:*E* olefinic isomers; $\nu_{max.}$(KBr) 3 360, 1 800, 1 740, 1 675, and 1 620 cm^{-1}; $\lambda_{max.}$ 276 nm (ε 16 630 dm^3 mol^{-1} cm^{-1}); δ_H [250 MHz; $(CD_3)_2SO$] *inter alia* 3.42 and 3.59 (together 3 H, 2 × s), 4.36 and 4.44 (0.67 H, ABq, *J* 14.2 Hz), 4.51 and 4.58 (1.33 H, ABq, *J* 15 Hz), 4.41 (0.67 H, s), 4.7 (0.67 H, d, *J* 5.8 Hz), 4.94 (0.33 H, d, *J* 1 Hz), 5.01 (0.33 H, dd, *J* 6.2 Hz and *ca.* 1 Hz), 5.33 (0.33 H, s), 5.37 (0.67 H, s), 5.61 (0.67 H, dd, *J* 8.4 and 5.8 Hz), 5.68 (0.33 H, dd, *J* 8.4 and 6.2 Hz), 6.8—7.0 and 7.2—7.35 (5 H, 2 × m), 8.5 (1 H, m), and 8.84 (1 H, d, *J* 8.4 Hz) (the carboxylic OH was not clearly visible).

(2RS,5RS,6RS)- *and* (2RS,5SR,6SR)-*Benzyl* 4,7-*Dioxo*-6-*phenoxyacetamido*-1,3-*diazabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**62**) *and* (**63**).—A crude mixture of the enamines (**65**) and (**67**) (1.32 g) as a foam obtained from azide (**74**) (1.6 g), was dissolved in ethyl acetate (100 ml), and ozonised as described for compound (**51**) to give, after chromatography, the *amide* (**62**) (177 mg, 13%), m.p. 158—159 °C (decomp.) (ethyl acetate–hexane) (Found: C, 61.5; H, 4.7; N, 10.2. $C_{21}H_{19}N_3O_6$ requires C, 61.6; H, 4.6; N, 10.3%); $\nu_{max.}$(Nujol) 3 250, 1 810, 1 750, 1 725, and 1 650 cm^{-1}; δ_H (250 MHz) 4.12 (1 H, dd, *J* 6.3 Hz), 4.5 (2 H, s), 5.22 (2 H, AA′), 5.35 (1 H, dd, *J* 8.22 and 6.3 Hz), 5.53 (1 H, s), 6.9—7.03 (3 H, m), 7.25—7.4 (7 H, m), 8.41 (1 H, d, *J* 8.22 Hz), and 8.79 (1 H, br s).

Further elution of the column gave the epimeric *amide* (**63**) (225 mg, 17%), m.p. *ca.* 140 °C (decomp.) (ethyl acetate–hexane) (Found: C, 61.4; H, 4.8; N, 10.2%; M^+ 409.1233); $\nu_{max.}$(Nujol) 3 375, 1 810, 1 750, and 1 690 cm^{-1}; δ_H (250 MHz) 4.17 (1 H, dd, *J* 6.3 and 1.6 Hz), 4.52 (2 H, s), 5.23 (1 H, d, *J* 1.6 Hz), 5.27 (2 H, AA′), 5.52 (1 H, dd, *J* 7.8 and 6.3 Hz), 6.9—7.05 (3 H, m), 7.25—7.5 (7 H, m), 8.11 (1 H, d, *J* 7.8 Hz), and 8.95 (1 H, s).

(2RS,5RS,6RS)-4,7-*Dioxo*-6-*phenoxyacetamido*-1,3-*diazabicyclo*[3.2.0]*heptane*-2-*carboxylic Acid* (**61**).—The ester (**62**) (46 mg) in dioxane (10 ml) was hydrogenated over 10% Pd–C (23 mg) for 80 min as described for compound (**12**). The product (**61**) was isolated as a white solid (35 mg, 100%); $\nu_{max.}$(KBr) 3 360, 1 800, 1 770, and 1 680br cm^{-1}; δ_H [250 MHz; $(CD_3)_2SO$] 4.2 (1 H, d, *J* 6.3 Hz), 4.52 (2 H, s), 4.6 (1 H, br s), 5.47 (1 H, dd, *J* 8.6 and 6.3 Hz), 5.5 (1 H, s), 6.9—7.05 (3 H, m), 7.25—7.35 (2 H, m), 7.91 (1 H, d, *J* 8.6 Hz), and 8.44 (1 H, s).

(3RS,4RS)-4-*Allyl*-3-*azido*-1-*dimethyl*-*t*-*butylsilylazetidin*-2-*one* (**88**).—Di-isopropylamine (3.33 g) in dry THF (75 ml) was cooled to 0 °C and butyl-lithium (1.6M-solution in hexane; 20.4 ml) added. After 10 min the solution was cooled to −76 °C and the β-lactam (**34**) (6.7 g)[32] in THF (40 ml) added dropwise during 30 min, followed by stirring at −76 °C for a further 2 h. Tosyl azide (6.54 g) in dry THF (30 ml) was then added dropwise over 10 min and after 45 min trimethylsilyl chloride (7.14 g) was added in THF (40 ml). After a further 30 min the reaction mixture was neutralised with acetic acid in THF, the solvent evaporated off, and the residue partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (300 g) using 2% ethyl acetate–hexane (*ca.* 3 l) to elute toluene-*p*-sulphonamide. Elution with 5% ethyl acetate–hexane (*ca.* 1 l) then gave the product (**89**) as a thick oil (2.7 g, 42%) (Found: $M + H^{\neg +}$ 267.1660; $C_{12}H_{22}N_4OSi + H$ requires *M*, 267.1641); $\nu_{max.}$ 2 125, 1 740, and 1 640 cm^{-1}; δ_H (90 MHz) *inter alia* 0.26 (3 H, s), 0.28 (3 H, s), 0.98 (9 H, s), 1.8—2.97 (2 H, m), 3.37—3.7 (1 H, m), 4.19 (1 H, d *J* 2 Hz), and 5.0—6.2 (3 H, m).

Further elution with 10% ethyl acetate–hexane (1 l) gave starting material (**34**) (1.3 g, 19%).

(3RS,4RS)-3-*Azido*-4-(1-*hydroxy*-2-*nitroethyl*)-1-(4-*methoxymethoxyphenyl*)*azetidin*-2-*one* (**92**).—The β-lactam (**68**) (14 g) in dry dichloromethane (400 ml) was ozonised at −76 °C until a pale blue colour persisted. The solution was purged with argon for 15 min, after which the reaction mixture was warmed to room temperature over 1 h and the solvent evaporated off. The residue was immediately dissolved in nitromethane (120 ml) and triethylamine (12.32 ml) added with cooling. After 2.5 h at room temperature, the solution was evaporated, the residue dissolved in toluene, and the solution re-evaporated. The process was repeated and the residue chromatographed to give the *alcohol* (**92**) as an oil (12.44 g, 94%) (Found: C, 46.1; H, 4.7; N, 20.6. $C_{13}H_{15}N_5O_6$ requires C, 46.3; H, 4.5; N, 20.8%); $\nu_{max.}$ 3 350, 2 120, 1 755, 1 555, and 1 505 cm^{-1}; δ_H (90 MHz) 3.41 (4 H, s, reduces to 3 H on exch.), 4.3—4.85 (4 H, m), 4.91 (1 H, d, *J* 5 Hz), 5.10 (2 H, s), and 6.9—7.5 (4 H, m).

(3RS,4SR)-3-*Azido*-1-(4-*methoxymethoxyphenyl*)-4-(2-*nitrovinyl*)*azetidin*-2-*one* (**93**).—The alcohol (**92**) (12.44 g) in dry THF (125 ml) was cooled to −20 °C and triethylamine (7.7 ml) added, followed by thionyl chloride (3.96 ml) in THF (10 ml)

dropwise over 10 min. After a further 10 min more triethylamine (7.77 ml) in THF (20 ml) was added dropwise over 5 min, the reaction mixture warmed to 5 °C over 45 min, and then filtered through Kieselguhr. The filter cake was washed well with toluene, and the filtrate evaporated. The residue was chromatographed to give the *olefin* (**93**) (10.37 g, 88%) (Found: C, 49.0; H, 4.3; N, 21.9%; M^+, 319.0907. $C_{13}H_{13}N_5O_5$ requires C, 48.9; H, 4.1; N, 21.9%; *M*, 319.0916); $\nu_{max.}$ 2 120, 1 770, 1 530, and 1 510 cm^{-1}; δ_H (90 MHz) 3.44 (3 H, s), 4.93 (1 H, dd, *J* 5 and 4 Hz), 5.1 (1 H, d, *J* 5 Hz), 5.12 (2 H, s), and 6.95—7.40 (6 H, m).

(3RS,4SR)-3-*Azido*-1-(4-*methoxymethoxyphenyl*)-4-(2-*nitroethyl*)*azetidin*-2-*one* (**89**).—Sodium borohydride (2.57 g) in water (20 ml) was added to a solution of the olefin (**93**) (21.7 g) in THF (400 ml) at −20 °C. After 10 min, glacial acetic acid (3.89 ml) was added and after a further 10 min the reaction mixture was diluted with ethyl acetate–dilute aqueous sodium hydrogen carbonate. The organic phase was separated, washed with brine, dried, and evaporated. Chromatography gave the *nitroalkane* (**89**) (19.11 g, 87%), m.p. 54—56 °C [ethyl acetate–light petroleum (b.p. 40—60 °C)] (Found: C, 48.8; H, 4.8; N, 22.1%; M^+, 321.1071. $C_{13}H_{15}N_5O_5$ requires C, 48.6; H, 4.7; N, 21.8%; *M*, 321.1073); $\nu_{max.}$ 2 120, 1 755, 1 555, and 1 510 cm^{-1}; δ_H (90 MHz) 2.1—3.0 (2 H, complex m), 3.44 (3 H, s), 4.2—4.6 (3 H, m), 4.92 (1 H, d, *J* 5 Hz), 5.13 (2 H, s), and 6.95—7.40 (4 H, m).

(3RS,4SR)-3-*Azido*-4-(2,2-*dimethoxyethyl*)-1-(4-*methoxymethoxyphenyl*)*azetidin*-2-*one* (**90**) *and* (3RS,4SR)-3-*Azido*-1-(4-*methoxymethoxyphenyl*)-4-*oxoethylazetidin*-2-*one* (**91**).—To the β-lactam (**89**) (160 mg) in dry methanol (5 ml) at −10 °C under argon was added sodium methoxide (0.12M-solution in methanol; 4.61 ml) dropwise during 10 min. After a further 5 min the resulting solution was added rapidly to a vigorously stirred mixture of concentrated sulphuric acid (1.8 ml) and methanol (4.8 ml) at −10 °C. After 10 min the mixture was poured into dichloromethane (40 ml) and the solution washed successively with dilute aqueous sodium phosphate (×2) and brine, and then dried and evaporated. Chromatography afforded the *acetal* (**90**) (101 mg, 60%), m.p. 63—65 °C [ethyl acetate–light petroleum (b.p. 40—60 °C)] (Found: C, 53.5; H, 6.1; N, 16.8%; M^+, 336.1457. $C_{15}H_{20}N_4O_5$ requires C, 53.6; H, 5.9; N, 16.7%; *M*, 336.1433); $\nu_{max.}$ 2 110, 1 750, and 1 510 cm^{-1}; δ_H (90 MHz) 2.14 (2 H, m), 3.37 (6 H, s), 3.43 (3 H, s), 4.39 (1 H, dt, *J* 8 and 5 Hz), 4.49 (1 H, t, *J* 5 Hz), 4.83 (1 H, d, *J* 5 Hz), 5.12 (2 H, s), and 6.95—7.40 (4 H, m).

Further elution of the column gave the aldehyde (**91**) (16 mg, 11%) (Found: M^+, 290.1027. $C_{13}H_{14}N_4O_4$ requires *M*, 290.1015); $\nu_{max.}$ 2 120, 1 755, 1 720, and 1 505 cm^{-1}; δ_H (250 MHz) 2.97 and 3.16 (2 H, ABq, *J* 18.5 Hz; higher field arm further coupled, *J* 9.7 Hz; lower field arm further coupled *J* 3.5 Hz), 3.47 (3 H, s), 4.73—4.81 (1 H, 5 lines, *J* 9.7, 5.3, and 3.5 Hz), 5.01 (1 H, d, *J* 5.3 Hz), 5.15 (2 H, s), 7.03 and 7.25 (4 H, ABq, *J* 8.8 Hz), and 9.89 (1 H, s). This product was not usually observed on larger-scale reactions.

(3RS,4SR)-4-(2,2-*Dimethoxyethyl*)-1-(4-*methoxymethoxyphenyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**96**).—The azide (**90**) (1.048 g) was reduced and acylated as described for compound (**68**) to give the *amide* (**96**) (1.28 g, 92%), m.p. 115—116 °C (ethyl acetate–light petroleum) (Found: C, 62.2; H, 6.3; N, 6.3%; M^+, 444.1868. $C_{23}H_{28}N_2O_7$ requires C, 62.2; H, 6.3; N, 6.3%; *M*, 444.1896); $\nu_{max.}$ 3 350, 1 750, 1 680, and 1 510 cm^{-1}; δ_H (90 MHz) 2.08 (1 H, dd, *J* 6 and 6 Hz), 3.28 (3 H, s), 3.31 (3 H, s), 3.45 (3 H, s), 4.2—4.6 (3 H, m), 4.56 (2 H, s), 5.13 (2 H, s), 5.58 (1 H, dd, *J* 9 and 5 Hz), 6.8—7.5 (9 H, m), and 8.01 (1 H, d, *J* 9 Hz).

(3RS,4SR)-4-(3-*Methoxycarbonylprop*-2-*enyl*)-1-(4-*methoxymethoxyphenyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**95**).—*Method 1.* The β-lactam (**98**) (1.98 g) was dissolved in dichloromethane (200 ml) under argon and sodium methoxide (1.087M-solution in methanol; 4.25 ml) added at room temperature. After 30 min the suspension was diluted with methanol (18 ml) and the resulting solution carefully ozonised at −76 °C until a pale grey colour persisted. The solution was purged with argon for 20 min, triphenylphosphine (1.32 g) in dichloromethane added, followed after 20 min by methyl (triphenylphosphorylidene)acetate (1.86 g) and the reaction was allowed to reach room temperature. After 2.5 h the solution was evaporated and the residue chromatographed to give the *olefin* (**95**) as a *ca.* 2:1 mixture of *E*:*Z* isomers (1.24 g, 41%). The *E*-isomer could be selectively crystallised from the mixture, m.p. 165—166 °C (ethyl acetate–light petroleum) (Found: C, 63.4; H, 5.7; N, 6.4. $C_{24}H_{26}N_2O_7$ requires C, 63.4; H, 5.7; N, 6.2%); $\nu_{max.}$(Nujol) 3 290, 1 740, and 1 675 cm^{-1}; δ_H (250 MHz) 2.60 (1 H, dddd, *J* 15.8, 7.5, 7.3, and 1.5 Hz), 2.74 (1 H, dddd, *J* 15.8, 7.5, 4.3, and 1.5 Hz), 3.48 (3 H, s), 3.69 (3 H, s), 4.46 (1 H, ddd, *J* 7.5, 4.8, and 4.3 Hz), 4.55 (2 H, s), 5.16 (2 H, s), 5.51 (1 H, dd, *J* 8.2 and 4.8 Hz), 5.85 (1 H, dt, *J* 15.8 and 1.5 Hz), 6.83 (1 H, ddd, *J* 15.8, 7.5, and 7.3 Hz), and 6.9—7.4 (10 H, m). The *Z*-isomer could not be isolated free of contamination with the *E*-isomer (Found: M^+, 454.1744. $C_{24}H_{26}N_2O_7$ requires *M*, 454.1739); δ_H (250 MHz) *inter alia* 3.48 (3 H, s), 3.50 (3 H, s), 4.50 (2 H, s), 5.17 (2 H, s), and 6.10 (1 H, m).

Method 2. The acetal (**96**) (18 mg) in acetone (1 ml) was treated with 5M-hydrochloric acid. After 4.5 h the reaction was diluted with ethyl acetate–dilute aqueous sodium hydrogen carbonate and the organic phase separated, washed with brine, dried, and evaporated. The residual oil was dissolved in dichloromethane containing methyl (triphenylphosphorylidene)-acetate (13 mg). After 16 h at room temperature the solution was evaporated. Chromatography gave the product (**95**) (3 mg, 15%) as a mixture of geometric isomers. This material was identical in all respects with that obtained from Method 1. The olefin (**95**) was generally used as a mixture of *E*- and *Z*-isomers.

(3RS,4SR)-4-(2,2-*Dimethoxyethyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**82**).—The β-lactam (**96**) (222 mg) was deprotected as described for compound (**71**) to give the *azetidinone* (**82**) (87 mg, 57%) (Found: C, 58.1; H, 6.7; N, 9.0. $C_{15}H_{20}N_2O_5$ requires C, 58.4; H, 6.5; N, 9.1%); $\nu_{max.}$ 3 400, 1 760, and 1 680 cm^{-1}; δ_H (90 MHz) 1.71 (2 H, m), 3.27 (3 H, s), 3.31 (3 H, s), 3.97 (1 H, ddd, *J* 8, *ca.* 7, and 5 Hz), 4.45 (1 H, dd, *J* 11 and 8 Hz), 4.52 (2 H, s), 5.33 (1 H, dd, *J* 8 and 5 Hz), 6.22 (1 H, s, exch.), and 6.8—7.5 (6 H, m). The e.i. spectrum shows no molecular ion at *m*/*z* 308, but does show a strong peak at *m*/*z* 218 due to loss of H and the 4-$CH_2CH(OMe)_2$ substituent (Found: $M - C_4H_{10}O_2^{\cdot+}$ 218.0686. $C_{11}H_{10}N_2O_3$ requires $M - C_4H_{10}O_2$, 218.0691); the c.i. spectrum shows a strong $M + H^{\cdot+}$ at 309 which is consistent with the above structure.

(3RS,4SR)-1-[4-*Methoxymethoxyphenyl*]-4-(2-*nitroethyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**98**).—The azide (**89**) (19.11 g) was reduced and acylated as described for compound (**68**) to give the *amide* (**98**) (15 g, 59%), m.p. 198—199 °C (ethyl acetate–light petroleum) (Found: C, 58.6; H, 5.2; N, 9.7. $C_{21}H_{23}N_3O_7$ requires C, 58.7; H, 5.4; N, 9.8%); $\nu_{max.}$(Nujol) 3 315, 1 758, and 1 670 cm^{-1}; δ_H (250 MHz) 2.01 (1 H, ddt, *J* 15.5, 10.0, and 5.5 Hz), 2.68 (1 H, ddt, *J* 15.5, 8.0, and 3.3 Hz), 3.47 (3 H, s), 4.35 (2 H, dd, *J* 10.0 and 8.0 Hz), 4.40 (1 H, ddd, *J* 5.5, 4.5, and 3.3 Hz), 4.59 (2 H, s), 5.14 (2 H, s), 5.35 (1 H, dd, *J* 7.0 and 4.5 Hz), 6.90—7.36 (9 H, m), and 7.40 (1 H, d, *J* 7.0 Hz).

(3RS,4SR)-4-[3-*Methoxycarbonylprop*-2-*enyl*]-3-*phenoxyacetamidoazetidin*-2-*one* (**81**).—The β-lactam (**95**) (3.82 g) in THF (100 ml) and dioxane (50 ml) was deprotected as described for compound (**71**) to give the *azetidinone* (**81**) as a *ca.* 2:1

mixture of geometic isomers (2.06 g, 77%) (Found: C, 60.4; H, 5.7; N, 8.8%; M^+, 318.1235. $C_{16}H_{18}N_2O_5$ requires C, 60.4; H, 5.7; N, 8.8%; M, 318.1340); $\nu_{max.}$(Nujol) 3 260, 3 170, 1 760, 1 730, and 1 660 cm^{-1}; δ_H (90 MHz) 2.34 (1 H, m), 2.89 (1 H, s), 3.60 and 3.73 (together 3 H, 2 × s), 3.95 (1 H, m), 4.47 (0.6 H, s), 4.51 (1.4 H, s), 5.35 (1 H, m, collapses to d, J 5 Hz on exch.), 5.82 (1 H, dt, J 14 and *ca.* 2 Hz), 6.1 (0.3 H, m), 6.56 and 6.60 (together 1 H, 2 × s, exch.), 6.78 (0.7 H, m), 6.8—7.4 (5 H, m), and 7.63 (1 H, d, J 8 Hz, exch.).

(3RS,4SR)-[*Benzyloxycarbonyl(hydroxy)methyl*]-4-(3-*methoxycarbonylprop*-2-*enyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**100**).—The azetidinone (**81**) (250 mg) was condensed with benzyl glyoxylate (357 mg) in refluxing benzene (10 ml) over 14 h as described for compound (**72**) to give the *glycolate* (**100**) (310 mg, 82%) as a mixture of isomers (Found: C, 61.7; H, 5.6; N, 5.5. $C_{25}H_{26}N_2O_8$ requires C, 62.2; H, 5.4; N, 5.8%); $\nu_{max.}$ 3 400, 3 300br, 1 770, 1 750, 1 720, 1 690, and 1 635sh cm^{-1}; δ_H (90 MHz) 2.40 (1 H, m), 2.95 (1 H, m), 3.48 and 3.49 (together 1.5 H, 2 × s), 3.62 (5 H, s), 3.8—4.2 (1 H, m), 4.41 and 4.43 (together 2 H, 2 × s), 4.65 (1 H, br s, exch.), 5.25 (4 H, m), 5.6—6.1 (1.5 H, m), 6.6—7.4 (10.5 H, m), and 7.60 (1 H, m, exch.).

(3RS,4SR)-1-[*Azido(benzyloxycarbonyl)methyl*]-4-(3-*methoxycarbonylprop*-2-*enyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**101**).—The α-hydroxy ester (**100**) (485 mg) was treated in the same way as compound (**31**) to give the azide (**101**) which was isolated as a mixture of isomers (400 mg, 81%); $\nu_{max.}$ 3 410, 2 120, 1 778, 1 760, 1 720, 1 695, and 1 630sh cm^{-1}; δ_H (90 MHz) 2.25 (1 H, m), 3.0 (1 H, m), 3.49 and 3.63 (together 3 H, s), 4.15 (1 H, m), 4.43 and 4.47 (together 2 H, 2 × s), 5.23 and 5.24 (together 2 H, 2 × s), 5.3—5.5 (2 H, m), 5.6—6.2 (1.5 H, m), and 6.7—7.5 (11.5 H, m) (Found: $M - CO^{\neg +}$, 479.1831 and $M - CO_2CH_3^{\neg +}$, 448.1363. $C_{24}H_{25}N_5O_6$ requires $M - CO^{\neg}$, 479.1962 and $C_{23}H_{22}N_5O_5$ requires $M - CO_2CH_3^{\neg}$, 448.1676).

(2RS,6SR,7RS)- *and* (2RS,6RS,7SR)-*Benzyl* 4-*Methoxycarbonylmethylene*-8-*oxo*-7-*phenoxyacetamido*-1,3-*diazabicyclo*[4.2.0]*octane*-2-*carboxylate* (**76**).—The azide (**101**) (400 mg) was refluxed in toluene (125 ml) for 4 h as described for compound (**27**) to give the enamine (**76**) as a *ca.* 2:1 mixture of epimers (390 mg, 72%) (Found: M^+, 479.1710. $C_{25}H_{25}N_3O_7$ requires M, 479.1837); $\nu_{max.}$ 3 410, 3 250, 1 780, 1 750, 1 690, 1 670, and 1 615 cm^{-1}; $\lambda_{max.}$ 281 nm (ε 16 259 dm^3 mol^{-1} cm^{-1}); δ_H (250 MHz) 2.27 and 2.48 (0.66 H, ABq, J 16 Hz; higher field arm further coupled, J 8.2 and *ca.* 1.5 Hz; lower field arm further coupled, broadened d, J 6 Hz), 2.43 and 2.60 (1.33 H, ABq, J 16 Hz; higher field arm further coupled, broadened d, J 5 Hz; lower field arm further coupled, J 8.2 and *ca.* 1.5 Hz), 3.54 and 3.55 (together 3 H, 2 × s), 4.03 (1 H, m), 4.54 (2 H, s), 4.61 (0.33 H, s), 4.65 (0.66 H, s), 5.11 (0.66 H, dd, J 3.9 and 1.5 Hz), 5.23 (0.66 H, AA′), 5.25 (1.33 H, s), 5.43 (1 H, m), 5.55 (0.33 H, d, J 2 Hz), 6.9—7.1 (4 H, m), 7.18 (1 H, d, J 8 Hz), 7.2—7.4 (6 H, m), and 9.15 (1 H, s). The enamine (**76**) (*ca.* 2:1 2α-H:2β-H) (51 mg) was dissolved in dichloromethane (1 ml) and DBU (8 mg) added at room temperature. After 40 min the reaction mixture was poured onto Florisil and chromatographed to give the enamine (**76**) (45 mg, 90%) as a *ca.* 2:3 mixture of 2α-H:2β-H epimers.

(2RS,6SR,7RS) *and* (2RS,6RS,7SR)-*Benzyl* 4,8-*Dioxo*-7-*phenoxyacetamido*-1,3-*diazabicyclo*[4.2.0]*octane*-2-*carboxylate* (**78**) *and* (**79**).—The enamine (**76**) (189 mg) was ozonised as described for compound (**39**) to give the *amide* (**78**) (51 mg, 31%), m.p. 168—169 °C (ethyl acetate–hexane) (Found: C, 61.8; H, 5.1; N, 9.7%; M^+, 423.1444. $C_{22}H_{21}N_3O_6$ requires C, 62.4; H, 5.0; N, 9.9%; M, 423.1503); $\nu_{max.}$(Nujol) 3 255, 1 785, 1 745, 1 670, and 1 650 cm^{-1}; δ_H (250 MHz) 2.36 and 2.61 (2 H, ABq, J 18 Hz; higher field arm further coupled, J 8 Hz; lower field arm further coupled, J 6 Hz), 4.24 (1 H, ddd, J 8, 6, and 4 Hz), 4.57 (2 H, s), 5.25 (2 H, s), 5.38 (1 H, dd, J 8 and 4 Hz), 5.63 (1 H, d, J 2.5 Hz), 6.23 (1 H, br s), 6.9—7.1 (3 H, m), 7.20 (1 H, d, J 8 Hz), and 7.25—7.45 (7 H, m); and the *amide* (**79**) as an amorphous solid (56 mg, 35%) (Found: M^+, 423.1432); $\nu_{max.}$ 3 400, 1 785, 1 755, and 1 680 cm^{-1}; δ_H (250 MHz) 2.49 and 2.62 (2 H, ABq, J 17 Hz; higher field arm further coupled, J 6 Hz; lower field arm further coupled, J 9 Hz), 4.17 (1 H, ddd, J 9, 6, and 4.5 Hz), 4.54 (2 H, s), 5.16 (1 H, br s, on irradiaton at δ 6.88, collapses to d, J 1.3 Hz), 5.23 and 5.28 (2 H, ABq, J 12 Hz), 5.43 (1 H, ddd, J 8, 4.5, and 1.3 Hz), 6.88 (1 H, br s), 6.9—7.1 (3 H, m), 7.2—7.5 (7 H, m), and 7.73 (1 H, d, J 8 Hz).

(2RS,6SR,7RS)- *and* (2RS,6RS,7SR)-4-*Methoxycarbonylmethylene*-8-*oxo*-7-*phenoxyacetamido*-1,3-*diazabicyclo*[4.2.0]*octane*-2-*carboxylic Acid* (**75**).—The ester (**76**) (43 mg) in dioxane (10 ml) was hydrogenated over 10% Pd–C (21 mg) for 50 min as described for compound (**12**) to give the acid (**75**) as a white solid (29 mg, 83%); $\nu_{max.}$(KBr) 3 400, 1 760, 1 710, 1 660, and 1 600 cm^{-1}; $\lambda_{max.}$ 285 nm (ε 15 374 dm^3 mol^{-1} cm^{-1}); δ_H (250 MHz) *inter alia* 3.67 (3 H, s), 4.56 (2 H, s), 4.53 and 4.56 (together 1 H, two s), 5.11 and 5.53 (together 1 H, two br s), and 9.14 (1 H, br s).

(2RS,6SR,7RS)-4,8-*Dioxo*-7-*phenoxyacetamido*-1,3-*diazabicyclo*[4.2.0]*octane*-2-*carboxylic Acid* (**77**).—The ester (**78**) (27 mg) in dioxane (10 ml) was hydrogenated over 10% Pd–C (16 mg) for 45 min as described for compound (**12**) to give the acid (**77**) as a white solid (20 mg, 94%); $\nu_{max.}$(KBr) 3 400br, 1 775, 1 660, and 1 640sh cm^{-1}; δ_H [250 MHz; $(CD_3)_2SO$] *inter alia* 2.26 and 2.47 (2 H, ABq, J 17 Hz; higher field arm further coupled, J 7 Hz; lower field arm further coupled, J 8 Hz), 4.05 (1 H, m), 4.61 (2 H, s), 5.33 (1 H, d, J 2.5 Hz, exch.), 5,42 (1 H, dd, J 8.5 and 4 Hz), 6.9—7.4 (5 H, m), 8.19 (1 H, d, J 2.5 Hz, exch.), and 9.02 (1 H, d, J 8.5 Hz).

(2RS,6RS,7SR)-4,8-*Dioxo*-7-*phenoxyacetamido*-1,3-*diazabicyclo*[4.2.0]*octane*-2-*carboxylate* (**80**).—The ester (**79**) (28 mg) in dioxane (12 ml) was hydrogenated over 10% Pd–C (14 mg) for 45 min as described for compound (**12**) to give the acid (**80**) as a white solid (19 mg, 86%); $\nu_{max.}$(KBr) 3 350br, 1 775, 1 660, and 1 640sh cm^{-1}.

(3RS,4SR)-4-*Ethyl*-1-(4-*methoxymethoxyphenyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**110**).—*Method 1.* The β-lactam (**108**) (51 mg) in dioxane (10 ml) was hydrogenated over 10% Pd–$BaSO_4$ (17 mg) for 1 h. The mixture was filtered through Kieselguhr, the filtrate evaporated, and the solid residue recrystallised from ethyl acetate–hexane to give the *azetidinone* (**110**) (45 mg, 88%), m.p. 160 °C (ethyl acetate–hexane) (Found: C, 65.5; H, 6.3; N, 7.2. $C_{21}H_{24}N_2O_5$ requires C, 65.6; H, 6.3; N, 7.3%); $\nu_{max.}$ 3 410, 1 745, and 1 690 cm^{-1}; δ_H (90 MHz) 0.86 (3 H, t, J 7 Hz), 1.58 (2 H, m), 3.44 (3 H, s), 4.18 (1 H, m), 4.56 (2 H, s), 5.12 (2 H, s), 5.47 (1 H, dd, J 8.5 and 5 Hz), and 6.8—7.5 (10 H, m).

Method 2. The β-lactam (**108**) (61 mg) in methanol (15 ml) was hydrogenated over 5% Pd–$CaCO_3$ (6 mg) for 30 min. The product (**110**) (54 mg, 88%) was identical with that described in Method 1.

(3RS,4SR)-1-(4-*Methoxymethoxyphenyl*)-3-*phenoxyacetamido*-4-*vinylazetidin*-2-*one* (**109**).—The β-lactam (**108**) (2.646 g) in dioxane (200 ml) containing pyridine (810 mg) was hydrogenated over 10% Pd–$BaSO_4$ (106 mg) for 1.5 h. The mixture was filtered through Kieselguhr and the filtrate evaporated. The residue was dissolved in ethyl acetate and the

solution washed successively with citric acid and brine, dried, and evaporated to give the product (**109**) (2.64 g) as an amorphous solid (Found: M^+, 382.1506. $C_{21}H_{22}N_2O_5$ requires M, 382.1526); $\nu_{max.}$ 3 420, 1 750, and 1 695 cm^{-1}; δ_H (90 MHz) *inter alia* 3.42 (3 H, s), 4.49 (2 H, s), 4.73 (1 H, m), 5.09 (2 H, s), 5.22—5.95 (4 H, m), and 6.8—7.5 (10 H, m). This material was contaminated with *ca.* 10% of the 4-ethylazetidinone (**110**) which could not be removed by chromatography or recrystallisation.

(3RS,4SR)-3-*Phenoxyacetamido*-4-*vinylazetidin*-2-*one* (**118**).—The β-lactam (**109**) (2.76 g) was deprotected as described for compound (**71**) to the azetidinone (**118**) which was obtained as a white solid (0.815 g, 46%) (Found: M^+, 246.1019. $C_{13}H_{14}N_2O_3$ requires M, 246.0096); $\nu_{max.}$(Nujol) 3 290, 3 240sh, 1 760, and 1 670 cm^{-1}; δ_H (250 MHz) *inter alia* 4.46 (1 H, ddd, *J* 6, 6, and *ca.* 1 Hz), 4.52 (2 H, s), 5.29 (1 H, ddd, *J* 10, 1, and 1 Hz), 5.34 (1 H, ddd, *J* 17, 1, and 1 Hz), 5.45 (1 H, ddd, *J* 8.5, 6, and 1 Hz), 5.71 (1 H, ddd, *J* 17, 10, and 6 Hz), 6.24 (1 H, br s), 6.85—7.35 (5 H, m), and 7.12 (1 H, d, *J* 8.5 Hz). The material was contaminated with *ca.* 5% of the corresponding 4-ethyl derivative.

(3RS,4SR)-1-[*Benzyloxycarbonyl*(*hydroxy*)*methyl*]-3-*phenoxyacetamido*-4-*vinylazetidin*-2-*one* (**119**).—Benzyl glyoxylate (730 mg) was refluxed in benzene (50 ml) for 1 h with provision for removal of water. The solution was cooled and the β-lactam (**118**) (815 mg) was added in dioxane (20 ml) and refluxing continued for a further 1 h. The solution was cooled and triethylamine (38 mg) added to it; after a further 1.5 h the mixture was evaporated and the residue chromatographed to give the glycolate (**119**) as an amorphous solid (1.11 g, 82%); $\nu_{max.}$ 3 425, 3 300br, 1 770, 1 750sh, 1 690, and 1 600 cm^{-1}.

(3RS,4SR)-1-[*Azido*(*benzyloxycarbonyl*)*methyl*]-3-*phenoxyacetamido*-4-*vinylazetidin*-2-*one* (**120**).—The glycolate (**119**) (1.1 g) was treated as described for compound (**31**) to give the azide (**120**) which was isolated as a *ca.* 3:2 mixture of isomers (1.08 g, 92%); $\nu_{max.}$ 3 415, 2 120, 1 780, 1 760sh, 1 695, and 1 680 cm^{-1}; δ_H (250 MHz) *inter alia* 4.50 (1.2 H, s), 4.51 (0.8 H, s), 4.47—4.58 (1 H, m), 5.22 (2 H, s), 5.17—5.75 (5 H, complex m; signals are discernible at δ 5.38 and 5.55 for CHN_3), and 6.85—7.4 (11 H, m).

(2RS,5RS,6RS)- *and* (2RS,5SR,6SR)-*Benzyl* 4-*Methyl*-7-*oxo*-6-*phenoxyacetamido*-1,3-*diazabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**103**) *and* (**104**).—The azide (**120**) (0.9 g) was refluxed in toluene for 34 h, as described for compound (**27**) to give the *imine* (**103**) (0.24 g, 28%), m.p. 117 °C (decomp.) (ethyl acetate–hexane) (Found: C, 65.2; H, 5.1; N, 10.1. $C_{22}H_{21}N_3O_5$ requires C, 64.9; H, 5.2; N, 10.3%); $\nu_{max.}$ 3 400, 1 805, 1 755, 1 700, and 1 630 cm^{-1}; δ_H (250 MHz) 2.06 (3 H, m), 4.56 (2 H, s), 4.81 (1 H, m, irradiation at δ 2.06 and 6.14 gives dd, *J* 5.8 and 3.2 Hz), 5.15 and 5.23 (2 H, ABq, *J* 12 Hz), 5.67 (1 H, dd, *J* 8 and 5.8 Hz), 6.14 (1 H, m, irradiation at δ 2.06 gives d, *J* 3.2 Hz), and 6.85—7.4 (11 H, m); and the epimeric *imine* (**104**) (301 mg, 36%) as an amorphous solid (Found: M^+, 407.1475. $C_{22}H_{21}N_3O_5$ requires M, 407.1386); $\nu_{max.}$ 3 400, 1 805, 1 755, 1 695, and 1 638 cm^{-1}; δ_H (250 MHz) 2.04 (3 H, m), 4.56 (2 H, s), 4.65 (1 H, m, irradiation at δ 2.04 gives dd, *J* 5.5 and 3.3 Hz), 5.27 and 5.34 (2 H, ABq, *J* 12 Hz), 5.42 (1 H, m, irradiation at δ 2.04 gives dd, *J* 3.3 and 1.2 Hz), 5.68 (1 H, ddd, *J* 8.1, 5.5, and 1.2 Hz), and 6.85—7.5 (11 H, m).

(2RS,5RS,6RS)-4-*Methyl*-7-*oxo*-6-*phenoxyacetamido*-1,3-*diazabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylic Acid* (**102**).—The ester (**103**) (68 mg) in dioxane (10 ml) was hydrogenated over 10% Pd–C (34 mg) for 2 h as described for compound (**12**) to give the acid as a white solid (48 mg, 90%); $\nu_{max.}$(KBr) 3 400br, 1 780, 1 670, and 1 600 cm^{-1}; δ [250 MHz; $(CD_3)_2SO$] *inter alia* 1.98 (3 H, s), 4.57 (2 H, s), 4.65 (1 H, m), 5.55 (1 H, dd, *J* 8 and 6 Hz), 5.75 (1 H, s), 6.8—7.0 (3 H, m), 7.2—7.4 (2 H, m), and 9.06 (1 H, d, *J* 8 Hz).

3-*Diphenyl*-t-*butylsilyloxypropyne* (**124**).—Prop-2-ynol (2.8 g, 2.91 ml) was dissolved in dry DMF (30 ml) and imidazole (3.78 g) and diphenyl-t-butylsilyl chloride (15.1 g) were added. The solution was stored at room temperature for 17 h and then partitioned between ether and water. The organic layer was separated, washed successively with very dilute hydrochloric acid (0.01M) and brine, dried, and evaporated. Chromatography afforded the *diphenyl*-t-*butylsilyl ether* (**124**) as a thick oil (13.4 g, 91%) (Found: M^+, 294.1457. $C_{19}H_{22}OSi$ requires M, 294.1439); $\nu_{max.}$ 3 320 cm^{-1}; δ_H (60 MHz) 1.07 (9 H, s), 2.34 (1 H, t, *J ca.* 2.3 Hz), 4.3 (2 H, d, *J ca.* 2.3 Hz), and 7.3—7.9 (10 H, m).

4-*Diphenyl*-t-*butylsilyloxybut*-2-*ynal* (**125**).—Butyl-lithium (1.6M-solution in hexane; 66.28 ml) was added over 10 min to a solution of the acetylene (**124**) (31.23 g) in dry THF (250 ml) under argon at −25 °C. After 10 min ethyl formate (16.15 g) in THF (20 ml) was quickly added and stirring continued for 30 min. The reaction mixture was poured into ice–water containing acetic acid (9.55 g) and extracted with ethyl acetate. The extracts were washed successively with dilute aqueous sodium hydrogen carbonate and brine, dried, and evaporated. Chromatography of the residue gave the aldehyde (**125**) as an oil (17.78 g, 52%); $\nu_{max.}$ 2 280, 2 210, and 1 680 cm^{-1}; δ_H (60 MHz) 1.08 (9 H, s), 4.5 (2 H, s), 7.3—7.85 (10 H, m), and 9.17 (1 H, s) (Found: $M - C_4H_9^{7+}$ 265.0702. $C_{16}H_{13}O_2Si$ requires $M - C_4H_9$, 265.0685).

(3RS,4RS)- *and* (3RS,4SR)-3-*Azido*-4-[3-*diphenyl*-t-*butylsilyloxyprop*-1-*ynyl*]-1-(4-*methoxymethoxyphenyl*)*azetidin*-2-*one* (**128**) *and* (**127**).—4-Methoxymethoxyaniline (5.97 g) and the aldehyde (**125**) (12.58 g) was stirred in dry dichloromethane (80 ml) containing anhydrous magnesium sulphate (3 g) for 16 h at room temperature. The mixture was filtered and the solvent evaporated off to give the Schiff base (**126**) as an oil (18 g, 100%); $\nu_{max.}$ 2 210, 1 640, 1 610, and 1 510 cm^{-1}. Azidoacetic acid (5.96 g) was dissolved in dry dichloromethane (60 ml) at 0 °C under argon and trifluoroacetic anhydride (8.27 ml) in dry dichloromethane (20 ml) added dropwise over 20 min. After 15 min triethylamine (8.22 ml) in dry dichloromethane (20 ml) was carefully added dropwise over 15 min and stirring at 0 °C continued for a further 45 min. The solution was transferred under argon to a dropping funnel cooled to −76 °C, and added over 1 h to a mixture of the Schiff base (**126**) (18 g) and triethylamine (8.2 ml) in dichloromethane (200 ml) at 0 °C. After a further 1.5 h, the solution was diluted with dichloromethane, washed successively with water, dilute aqueous sodium hydrogen carbonate, and brine, dried, and evaporated. Chromatography of the residue gave the *trans*-product (**128**) as a gum (1.47 g, 7%) (Found: M^+, 540.2187. $C_{30}H_{32}N_4O_4Si$ requires M, 540.2192); $\nu_{max.}$ 2 120, 1 765, and 1 515 cm^{-1}; δ_H (90 MHz) 1.01 (9 H, s), 3.43 (3 H, s), 4.26 (1 H, dt, *J* 3 and 2 Hz), 4.35 (2 H, d, *J* 2 Hz), obscures 4.37 (1 H, d, *J* 3 Hz), 5.12 (2 H, s), and 6.9—7.8 (14 H, m).

Further elution of the column gave the cis-*product* (**127**) as a gum (12.25 g, 58%) (Found: M^+, 540.2216); $\nu_{max.}$ 2 115, 1 760, 1 590, and 1 510 cm^{-1}; δ_H (90 MHz) 1.04 (9 H, s), 3.42 (3 H, s), 4.37 (2 H, d, *J* 2 Hz), 4.67 (1 H, d, *J* 5.5 Hz), 4.75 (1 H, dt, *J* 5.5 and 2 Hz), 5.11 (2 H, s), and 6.9—7.7 (14 H, m).

(3RS,4SR)-4-(3-*Diphenyl*-t-*butylsilyloxyprop*-1-*ynyl*)-1-(4-*methoxymethoxyphenyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**114**).—The azide (**127**) (10.78 g) was reduced and acylated as

described for compound (**68**) to afford the *amide* (**114**) (8.4 g, 65%), m.p. 73—74 °C (ethyl acetate–hexane) (Found: C, 70.0; H, 6.3; N, 4.2%; M^+, 648.2689. $C_{38}H_{40}NO_6Si$ requires C, 70.4; H, 6.2; N, 4.3%; *M*, 648.2254); $\nu_{max.}$(Nujol) 3 300, 1 775, 1 760, 1 690, 1 680, and 1 510 cm^{-1}; δ_H (250 MHz) 1.00 (9 H, s), 3.48 (3 H, s), 4.11 and 4.19 (2 H, ABq, *J* 16 Hz; each arm further coupled, *J ca.* 2 Hz), 4.49 and 4.58 (2 H, ABq, *J* 15 Hz), 4.85 (1 H, dt, *J* 6 and *ca.* 2 Hz), 5.15 (2 H, s), 5.64 (1 H, dd, *J* 10 and 6 Hz), and 6.8—7.65 (20 H, m).

(3RS,4SR)-4-(3-*Hydroxyprop*-1-*ynyl*)-1-(4-*methoxymethoxyphenyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**112**).—The β-lactam (**114**) (5.62 g) in anhydrous THF (100 ml) was stirred with tetraethylammonium fluoride dihydrate (1.43 g) for 20 min. The reaction mixture was poured into ethyl acetate, washed successively with water and brine, dried, and evaporated. Chromatography of the residue gave the *alcohol* (**112**) (3.27 g, 92%), m.p. 134—135 °C (ethyl acetate–hexane) (Found: C, 64.4; H, 5.5; N, 6.8. $C_{22}H_{22}N_2O_6$ requires C, 64.4; H, 5.4; N, 6.8%); $\nu_{max.}$(Nujol) 3 470, 3 300, 1 750, 1 680, and 1 510 cm^{-1}; δ_H (90 MHz) 1.94 (1 H, t, *J* 5 Hz, exch.), 3.43 (3 H, s), 4.1 (2 H, d, *J* 5 Hz, collapses to broadened s, on exch.), 4.66 (2 H, s), 4.85 (1 H, m, collapses to broadened d, *J* 5 Hz, on exch.), 5.1 (2 H, s), 5.61 (1 H, dd, *J* 9 and 5 Hz), and 6.8—7.6 (10 H, m).

(3RS,4SR)-4-(3-*Hydroxypropyl*)-1-(4-*methoxymethoxyphenyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**113**).—The acetylenic alcohol (**112**) (1.5 g) in dioxane (50 ml) was hydrogenated over 10% Pd–C (0.150 g) for 6.5 h. The mixture was filtered through Kieselguhr and the filtrate evaporated. The residue was recrystallised from ethyl acetate–light petroleum to give the *saturated alcohol* (**113**) (1.2 g, 80%), m.p. 158—159 °C (Found: C, 63.8; H, 6.2; N, 6.6%; M^+, 414.1782. $C_{22}H_{26}N_2O_6$ requires C, 63.8; H, 6.3; N, 6.8%; *M*, 414.1789); $\nu_{max.}$(Nujol) 3 495, 3 390, 1 730, 1 665, and 1 515 cm^{-1}; δ_H (90 MHz) 1.0—2.3 (5 H, complex m), 3.43 (3 H, s), obscures 3.51 (2 H, t, *J* 6 Hz), 4.2—4.45 (1 H, complex m), 4.53 (2 H, s), 5.11 (2 H, s), 5.43 (1 H, dd, *J* 5 and 8 Hz), and 6.8—7.6 (10 H, m).

(3RS,4SR)-4-(3-*Methylsulphonyloxypropyl*)-1-(4-*methoxymethoxyphenyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**115**).—The alcohol (**113**) (1.6 g) was dissolved in dry dichloromethane (30 ml) at 0 °C and triethylamine (0.6 ml) added, followed by dropwise addition of methanesulphonyl chloride (0.33 ml) in dichloromethane (2 ml) over 5 min. The reaction mixture was diluted with dichloromethane, washed with brine, dried, and evaporated. The residue was recrystallised from ethyl acetate–hexane to give the *mesylate* (**115**) (1.86 g, 97%), m.p. 150—151 °C (Found: C, 56.1; H, 5.6; N, 5.6; S, 6.3%; M^+ 492.1557. $C_{23}H_{28}N_2O_8S$ requires C, 56.1; H, 5.7; N, 5.7; S, 6.5%; *M*, 492.1564); $\nu_{max.}$ 3 420, 1 755, 1 690, and 1 510 cm^{-1}; δ_H (250 MHz) 1.66 (3 H, m), 2.02 (1 H, m), 2.91 (3 H, s), 3.46 (3 H, s), 4.12 (2 H, m, collapses to ABq, δ 4.09 and 4.15, *J* 11 Hz on irradiation at δ 1.66), 4.30 (1 H, m), 4.52 and 4.61 (2 H, ABq, *J* 16 Hz), 5.14 (2 H, s), 5.46 (1 H, dd, *J* 8 and 5 Hz), 6.9—7.1 (5 H, m), 7.2—7.4 (4 H, m), and 7.45 (1 H, d, *J* 8 Hz).

(3RS,4SR)-1-(4-*Methoxymethoxyphenyl*)-3-*phenoxyacetamido*-4-*prop*-2-*enylazetidin*-2-*one* (**111**).—*o*-Nitrophenyl selenocyanate (0.707 g) in anhydrous dimethoxyethane (30 ml) at 0 °C was treated with sodium borohydride (0.118 g). After 35 min methanol (2 drops) was added, followed after a further 10 min by the mesylate (**115**) (1.54 g) in anhydrous dichloromethane (30 ml); the solution was then stirred for 24 h at room temperature. After addition of dichloromethane (5 ml) to redissolve the precipitated solid, *m*-chloroperbenzoic acid (0.594 g) was added, and stirring continued for a further 2 days. The reaction mixture was evaporated, and the residue redissolved in ethyl acetate. The solution was washed successively with dilute aqueous sodium metabisulphite, dilute aqueous sodium hydrogen carbonate, and brine, dried, and evaporated. Chromatography of the residue gave the *olefin* (**111**) (0.4 g, 33%), m.p. 152—153 °C (ethyl acetate–hexane) (Found: C, 66.5; H, 6.0; N, 7.0. $C_{22}H_{24}N_2O_5$ requires C, 66.6; H, 6.1; N, 7.1%); $\nu_{max.}$ 3 420, 1 750, 1 690, and 1 515 cm^{-1}; δ_H (250 MHz) 2.57 (2 H, m), 3.48 (3 H, s), 4.42 (1 H, ddd, *J* 8, 6, and 5.5 Hz), 4.55 (2 H, AA′), 5.11 (1 H, dd, *J* 16 Hz and *ca.* 1.5 Hz; lower field arm partially obscured by s, δ 5.17), 5.14 (1 H, dd, *J* 10.5 and *ca.* 1.5 Hz; lower field arm obscured by s, δ 5.17), 5.17 (2 H, s), 5.58 (1 H, dd, *J* 9 and 5.5 Hz), 5.70 (1 H, dddd, *J* 16, 10.5, 8, and 6 Hz), and 6.9—7.4 (10 H, m). Further elution of the column gave unchanged mesylate (**115**) (0.61 g, 40%).

(3RS,4SR)-3-*Phenoxyacetamido*-4-*prop*-2-*enylazetidin*-2-*one* (**121**).—The β-lactam (**111**) (0.4 g) was deprotected as described for compound (**71**) to give the *azetidinone* (**121**) (0.17 g, 64%), m.p. 153—154 °C (ethyl acetate–hexane) (Found: C, 64.8; H, 6.1; N, 10.6%; M^+ 260.1145. $C_{14}H_{16}N_2O_3$ requires C, 65.1; H, 6.2; N, 10.9%; *M*, 260.1159); $\nu_{max.}$(Nujol) 3 300, 1 765, 1 755, and 1 665 cm^{-1}; δ_H (250 MHz) 2.12 and 2.33 (2 H, ABq, *J* 14.8 Hz; higher field arm further coupled, dddd, *J* 8.4, 7.8, *ca.* 1.2, and *ca.* 1.0 Hz; lower field arm further coupled, dddd, *J* 6, 4.5, *ca.* 1.6 and *ca.* 1.2 Hz), 3.95 (1 H, ddd, *J* 8.4, 5, and 4.5 Hz), 4.54 (2 H, s), 5.09 (1 H, dddd, *J* 10.5, *ca.* 1.5, *ca.* 1.2, and *ca.* 1.2 Hz), 5.12 (1 H, dddd, *J* 16.4, *ca.* 1.5, *ca.* 1.6, and *ca.* 1.0 Hz), 5.37 (1 H, ddd, *J* 8.5, 5, and 1.2 Hz), 5.72 (1 H, dddd, *J* 16.4, 10.5, 7.8, and 6 Hz), 6.23 (1 H, br s), 6.9—7.16 (3 H, m), and 7.25—7.40 (3 H, m).

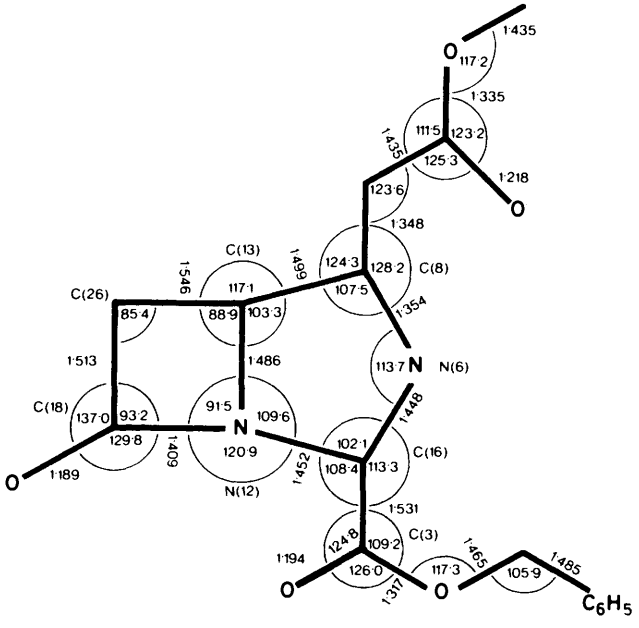
(3RS,4SR)-1-[*Benzyloxycarbonyl*(*hydroxy*)*methyl*]-3-*phenoxyacetamido*-4-*prop*-2-*enylazetidin*-2-*one* (**122**).—The azetidinone (**121**) (167 mg) was treated with benzyl glyoxylate as described for compound (**118**) to give the glycolate (**122**) as a *ca.* 1:1 mixture of isomers (249 mg, 91%); $\nu_{max.}$ 3 400br, 1 770, 1 760, 1 695, and 1 640 cm^{-1}; δ_H (250 MHz) *inter alia* 2.09—2.37 (2 H, m), 3.85 (0.5 H, ddd, *J* 6.9, *ca.* 6.5, and 5 Hz), 4.12 (0.5 H, ddd, *J* 7, *ca.* 5.5, and 5 Hz), 4.04 and 4.26 (together 1 H, d, *J* 7.5 Hz, exch.), 4.49 (2 H, s), 5.02 and 5.04 (together 1 H, dddd, *J* 16.5, *ca.* 1.5, *ca.* 1.5, and *ca.* 1.5 Hz), 5.05 and 5.06 (together 1 H, dddd, *J* 11, *ca.* 1.5, *ca.* 1.5, and *ca.* 1.5 Hz), 5.23 and 5.31 (1 H, ABq, *J* 11 Hz), 5.24 (1 H, AA′), 5.29 (0.5 H, d, *J* 7.5 Hz, collapses to s on exch.), 5.35 (0.5 H, dd, *J* 9 and 5 Hz), 5.41 (0.5 H, dd, *J* 9 and 5 Hz), 5.56 (0.5 H, d, *J* 7.5 Hz, collapses to s on exch.), 5.66 (1 H, dddd, *J* 16.5, 11, 7.5, and 6 Hz), 6.85—6.93 (2 H, m), 6.97—7.08 (1 H, m), and 7.25—7.50 (8 H, m).

(3RS,4SR)-1-[*Azido*(*benzyloxycarbonyl*)*methyl*]-3-*phenoxyacetamido*-4-*prop*-2-*enylazetidin*-2-*one* (**123**).—The α-hydroxy ester (**122**) (203 mg) was treated as described for compound (**31**) to give the azide (**123**) as a mixture of isomers (185 mg, 86%); $\nu_{max.}$ 3 420, 2 125, 1 775, 1 760, and 1 690 cm^{-1}; δ_H (250 MHz) *inter alia* 2.1—2.5 (2 H, complex m), 4.05—4.11 (1 H, m), 4.52 (2 H, AA′), 4.97—5.11 (2 H, complex m), 5.20—5.36 (2 H, m), 5.40—5.42 (1 H, m), 5.39 (0.66 H, s), 5.54—5.7 (1 H, complex m), 5.73 (0.33 H, s), and 6.9—7.4 (11 H, m).

(2RS,6SR,7RS)- *and* (2RS,6RS,7SR)-*Benzyl* 4-*Methyl*-8-*oxo*-7-*phenoxyacetamido*-1,3-*diazabicyclo*[4.2.0]*oct*-3-*ene*-2-*carboxylate* (**106**) *and* (**107**).—The azide (**123**) (175 mg) was dissolved in toluene (175 ml) under argon, and the solution was refluxed for 7 h, with a provision for removal of water. The solution was cooled, evaporated, and the residue chromatographed to give the *imine* (**106**) (38 mg, 22%) as an amorphous solid (Found: M^+, 421.1676. $C_{23}H_{23}N_3O_5$ requires *M*, 421.1627); $\nu_{max.}$ 3 420, 1 770, 1 760, 1 695, and 1 660 cm^{-1}; δ_H (250 MHz) *inter alia* 2.00 and 2.33 (2 H, ABq, *J* 19 Hz; higher field arm further coupled, *J* 8 and 3 Hz; lower field arm further

Table 3. Fractional atomic co-ordinates with standard deviation in parentheses for ester (**39**)

Atom	*x/a*	*y/b*	*z/c*
C(1)	0.344 0(3)	0.669 1(3)	0.294 9(2)
O(2)	0.245 5(2)	0.888 6(3)	0.842 7(2)
C(3)	0.234 1(3)	0.843 5(3)	0.721 1(2)
O(4)	0.447 0(2)	0.835 9(2)	0.341 7(1)
C(5)	0.251 2(3)	0.530 8(3)	0.362 2(2)
N(6)	0.361 6(2)	0.743 7(2)	0.570 0(2)
O(7)	0.303 2(2)	0.592 9(2)	0.172 0(1)
C(8)	0.264 0(3)	0.572 7(3)	0.487 0(2)
C(9)	0.150 9(3)	0.953 4(3)	1.018 2(2)
O(10)	0.157 6(2)	0.866 4(3)	0.643 0(2)
C(11)	0.153 7(3)	0.970 8(4)	0.886 5(3)
N(12)	0.234 6(2)	0.541 6(2)	0.691 2(2)
C(13)	0.169 9(3)	0.429 2(3)	0.559 2(2)
C(14)	0.050 0(3)	0.777 5(4)	1.044 1(3)
C(15)	0.250 9(3)	1.108 1(4)	1.115 9(3)
C(16)	0.329 0(2)	0.747 3(3)	0.694 5(2)
O(17)	0.393 5(3)	0.457 2(3)	0.805 5(2)
C(18)	0.302 8(3)	0.431 4(3)	0.716 4(2)
C(19)	0.388 8(3)	0.715 2(4)	0.093 6(2)
C(20)	0.252 3(4)	1.087 7(6)	1.238 2(3)
C(21)	0.052 8(4)	0.759 2(5)	1.166 7(4)
C(23)	0.154 8(5)	0.915 3(7)	1.263 3(3)
C(26)	0.222 5(4)	0.287 9(3)	0.591 3(3)



C(3)–C(16)–N(12)–C(18) 155.4°
C(16)–N(12)–C(18)–C(26) 122.4°
C(3)–C(16)–N(6)–C(8) 97.9°
C(16)–N(6)–C(8)–C(13) 10.0°
h (see Table 1) 0.52 Å

Figure 3. Bond lengths (Å) (standard deviations 0.002—0.005 Å), bond angles (°) (standard deviations 0.16—0.31°) and selected torsion angles of ester (**39**).

coupled, *J* 6 Hz), 2.04 (3 H, d *J ca.* 1.5 Hz), 4.02 (1 H, ddd, *J* 6, 8, and 4.5 Hz), 4.56 (2 H, s), 5.16 and 5.24 (2 H, ABq, *J* 13 Hz), 5.32 (1 H, dd, *J* 6 and 4.5 Hz), 5.77 (1 H, br s), 6.87—7.10 (3 H, m), and 7.2—7.45 (8 H, m).

Further elution of the column gave the epimeric imine (**107**) (24 mg, 14%) (Found: M^+, 421.1605); $\nu_{max.}$ 3 420, 1 770, 1 765, 1 690, and 1 660sh cm^{-1}; δ_H (250 MHz) *inter alia* 2.09 and 2.33 (2 H, ABq, *J* 17 Hz; higher field arm further coupled, *J* 10 and 2 Hz; lower field arm further coupled, *J* 6 and *ca.* 3 Hz), 2.09 (3 H, d, *J ca.* 2 Hz), 3.85 (1 H, ddd, *J* 10, 6, and 5 Hz), 4.56 (2 H, s), 5.2—5.35 (1 H, obscured m), 5.40 (1 H, m), and 6.9—7.5 (11 H, m). This material could not be completely purified because of instability on chromatography.

(2RS,6RS,7RS)-4-*Methyl*-8-*oxo*-7-*phenoxyacetamido*-1,3-*diazabicyclo*[4.2.0]*oct*-3-*ene*-2-*carboxylic Acid* (**105**).—The ester (**106**) (21 mg) in dioxane (10 ml) was hydrogenated over 10% Pd–C (10 mg) for 110 min as described for compound (**12**) to give the acid (**105**) as a white solid (13 mg, 79%); $\nu_{max.}$(KBr) 3 400br, 1 765, 1 710, and 1 660 cm^{-1}; δ_H [250 MHz; $(CD_3)_2SO$] *inter alia* 1.92 (3 H, d, *J ca.* 1.5 Hz), 2.26 (2 H, dd, *J* 7.5 and 7.0 Hz), 3.82 (1 H, ddd, *J* 7.5, 7.0, and 5 Hz), 4.60 (2 H, s), 5.38 (1 H, dd, *J* 9 and 5 Hz), 5.41 (1 H, br s), 6.93—7.01 and 7.28—7.40 (5 H, m), and 8.92 (1 H, d, *J* 9 Hz).

Crystal Structure Determination of Ester (**39**).—*Crystal data.* $C_{16}H_{16}N_2O_5$, M = 316.3. Triclinic, a = 10.133(3), b = 8.093(2), c = 11.056(3) Å, α = 98.43(5), β = 96.15(5), γ = 119.21(5)°, Mo-K_α, λ = 0.710 69 Å, space group $P\bar{1}$.

Data collection. Hilger-Watt Y290 diffractometer, graphite-monochromated Mo-K_α radiation. Reflections scanned for $\theta \leqslant 27.5°$; 3 455 reflections measured, giving 2 222 with $I \geqslant 3\sigma(I)$ and were used in the refinement.

Structure analysis and refinement. The structure was solved using the centrosymmetric direct methods routine of SHELX[45] which found all non-hydrogen atoms. The hydrogen atoms were located from a difference map and included in the final cycles of refinement in fixed calculated positions. All other atoms were refined anisotropically. The final R- value = 0.045. The standard deviations for bond lengths and angles were in the ranges 0.002—0.005 Å and 0.16—0.31° respectively.

Acknowledgements

We thank Dr. J. H. C. Nayler for his interest in this work, Mr. M. J. Basker for the microbiological data, Dr. J. Gower, Mr. J. W. Tyler, and Mr. A. Cutmore for the spectral data, and the late Prof. T. J. King for the *X*-ray crystallographic determination.

References

1 Part 8, M. J. Pearson and J. W. Tyler, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1927.
2 M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1977, 189.
3 Preliminary Communication: C. L. Branch and M. J. Pearson, *J. Chem. Soc., Chem Commun.*, 1981, 946; M. J. Pearson, *Tetrahedron Lett.*, 1982, **23**, 2999; C. L. Branch and M. J. Pearson, *ibid.*, 1982, **23**, 3003; C. L. Branch and M. J. Pearson, *ibid.*, 1983, **24**, 1649.
4 M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2544 and references cited therein.
5 J. G. Gleason, D. B. Bryan, and K. Holden, *Tetrahedron Lett.*, 1980, **21**, 3947.
6 M. Aratani and M. Hashimoto, *J. Am. Chem. Soc.*, 1980, **102**, 6171.
7 T. W. Doyle, J. L. Douglas, B. Belleau, T. T. Conway, C. F. Ferrari, D. E. Horning, G. Lim, B.-Y. Luh, A. Martel, M. Menard, and L. R. Mossis, *Can. J. Chem.*, 1980, **58**, 2508.
8 C. M. Pant, R. J. Stoodley, A. Whiting, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1984, 1289.
9 Y. Hoshide, Y. Hashimoto, H. Ogawa, K. Suzuki, T. Seki, and S. Tasaka, *Yakugaku Zasshi*, 1982, **102**, (9), 844.
10 R. Allman, T. Debaerdemaeker, G. Kiehl, J.-P. Luttringer, T. Tschamber, G. Wolff, and J. Streith, *Justus Leibigs Ann. Chem.*, 1983, 1361; J. Streith, T. Tschamber, and G. Wolff, *ibid.*, 1983, 1374.

11 H. Alper, C. P. Perera, and F. R. Ahmed, *J. Am. Chem. Soc.*, 1981, **103**, 1289.
12 I. Nagakura, *Heterocycles*, 1981, **16**, 1495.
13 G. Johnston and B. C. Ross, *J. Chem. Soc., Chem. Commun.*, 1981, 1269.
14 G. Johnston, P. M. Rees, and B. C. Ross, *J. Chem. Soc., Chem. Commun.*, 1984, 970.
15 A. L. Logothetis, *J. Am. Chem. Soc.*, 1965, **87**, 749.
16 J. H. Bateson, A. J. G. Baxter, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3242.
17 C. L. Branch and M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2123.
18 A. P. Kozikowski and M. N. Greco, *J. Org. Chem.*, 1984, **49**, 2310.
19 E. G. Brain, A. J. Eglington, J. H. C. Nayler, N. F. Osborne, R. Southgate, and P. Tolliday, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2479 and references cited therein.
20 D. O. Spry, *Tetrahedron Lett.*, 1973, 165; T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi, and T. Oku, *J. Am. Chem. Soc.*, 1976, **98**, 2343; D. Davies and M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2539.
21 J. H. Bateson, A. J. G. Baxter, K. H. Dickinson, R. I. Hickling, R. J. Ponsford, P. M. Roberts, T. C. Smale, and R. Southgate, 'Recent Advances in the Chemistry of β-Lactam Antibiotics,' ed. G. I. Gregory (Special Publication No. 38), Royal Society of Chemistry, London, 1981, p. 291.
22 M. T. Garcia-Lopez, G. Garcia-Munoz, and R. Madrariero, *J. Heterocycl. Chem.*, 1972, **9**, 717.
23 L. Van der Wolf and H. J. J. Pabon, *J. Royal Netherlands Chem. Soc.*, 1977, **96**, 72.
24 C. L. Branch, S. C. Finch, and M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1491.
25 T. W. Doyle, B. Belleau, B.-Y. Luh, C. F. Ferrari, and M. P. Cunningham, *Can. J. Chem.*, 1977, **55**, 468.
26 T. Fukuyama, R. K. Frank, and C. F. Jewell, Jr., *J. Am. Chem. Soc.*, 1980, **102**, 2122.
27 For a recent review see G. A. Koppel in 'The Chemistry of Heterocyclic Compounds,' ed. A. Hassner, Interscience, New York, 1983, vol. 42, Part 2, p. 219.
28 W. Oppolzer, S. Siles, R. L. Snowden, B. H. Bakker, and M. Petrzilka, *Tetrahedron Lett.*, 1979, **45**, 4391.
29 M. W. Foxton, R. C. Mearman, C. E. Newall, and P. Ward, *Tetrahedron Lett.*, 1981, **22**, 2497.
30 P. Herdewijn, P. J. Claes, and H. Vanderhaeghe, *Nouv. J. Chim.*, 1983, **7**, 691.
31 K. Kuhlein and H. Jensen, *Justus Liebigs Ann. Chem.*, 1974, 369.
32 J. H. Bateson, R. I. Hickling, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1980, 1084.
33 R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, 1974, **39**, 437.
34 P. Bevilacqua and J. L. Roberts, *Synth. Commun.*, 1983, **13**, 797 and references cited therein; K. Fujimoto, Y. Iwano, and K. Hirai, *Tetrahedron Lett.*, 1985, **1**, 89.
35 C. M. Cimarusti, D. P. Bonner, H. Breuer, H. W. Chang, A. W. Fritz, D. M. Floyd, T. P. Kissock, W. H. Koster, D. Kronenthal, F. Massa, R. H. Mueller, J. Pluscec, W. A. Slusarchyk, R. B. Sykes, M. Taylor, and E. R. Weaver, *Tetrahedron*, 1983, **39**, 2577.
36 R. M. Jacobsen, *Tetrahedron Lett.*, 1974, 3215.
37 J. G. Gleason, T. F. Buckley, K. G. Holden, D. B. Bryan, and P. Siler, *J. Am. Chem. Soc.*, 1979, **101**, 4730.
38 E. Keinan and Y. Mazur, *J. Am. Chem. Soc.*, 1977, **99**, 3861.
39 G. A. Olah, M. Aruanaghi, Y. D. Vankar, and G. K. S. Prakash, *Synthesis*, 1980, 662.
40 J. E. McMurray, J. Melton, and H. Padgett, *J. Org. Chem.*, 1974, **39**, 259.
41 S. Swaminathen, J. P. John, and S. Ramachandran, *Tetrahedron Lett.*, 1962, 729.
42 H. Haptmann and M. Mader, *Synthesis*, 1978, 307.
43 A. K. Bose, J. C. Kapur, S. D. Sharma, and M. S. Manhas, *Tetrahedron Lett.*, 1973, 2319.
44 F. Heiner, M. Soukap, and A. Eschenmoser, *Helv. Chem. Acta*, 1978, **61**, 2851.
45 The SHELX Crystal Structure Calculation System, G. M. Sheldrick, University of Cambridge.

Received 18*th September* 1985; *Paper* 5/1610