Synthesis of Novel Fused β-Lactams by Intramolecular 1,3-Dipolar Cycloadditions. Part 10.[1] The 9-Oxo-6-thia-1,3-diazabicyclo[5.2.0]nonene, 8-Oxo-5-thia-1,3-diazabicyclo[4.2.0]octene, and 8-Oxo-5-oxa-1,3-diazabicyclo[4.2.0]octene Ring Systems

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4-Acetoxyazetidin-2-one (**6**) has been converted into (*E*)- and (*Z*)-1-[azido(t-butoxycarbonyl)methyl]-[2-(ethoxycarbonyl)vinylthio]azetidin-2-one (**10**) and (**13**). Thermolysis of either geometrical isomer in refluxing xylene afforded t-butyl (2*RS*,6*RS*)-4-ethoxycarbonylmethyl-8-oxo-5-thia-1,3-diaza-bicyclo[4.2.0]oct-3-ene-2-carboxylate (**17**) and both C-2 epimers of 5-ethoxycarbonyl-9-oxo-6-thia-1,3-diazabicyclo[5.2.0]non-4-ene-2-carboxylate (**14**) and (**15**).

The penicillin-derived (3*S*,4*S*)-4-acetoxy-3-phenoxyacetamidoazetidin-2-one (**22**) has been used to prepare (1*RS*,3*S*,4*R*)-1-[azido(benzyloxycarbonyl)methyl]-4-prop-1-enyloxy-3-phenoxyacetamido-azetidin-2-one (**27**), which when heated in refluxing toluene gave benzyl (2*S*,6*R*,7*S*)-4-ethyl-8-oxo-7-phenoxy-acetamido-5-oxa-1,3-diazabicyclo[4.2.0]oct-3-ene-2-carboxylate (**29**). The corresponding free acid (**30**) was antibacterially inactive.

The synthesis of the 1,3-diazabicyclo[4.2.0]octene ring system, *via* intramolecular cycloaddition of a suitably functionalised olefinic azide, has recently been reported.[1,2] The 4-allyl derivative (**1**) gave the imine (**3**), whereas the α,β-unsaturated ester (**2**) afforded the enamine (**4**). We now report further novel products derived from thermolysis of azides substituted at C-4 of the azetidinone ring by mercaptoacrylate or vinyl ether moieties.

The sodium salt (**5**) of ethyl β-mercaptoacrylate, prepared by treatment of ethyl propiolate with sodium hydrosulphide, was treated with 4-acetoxyazetidin-2-one (**6**)[3] using the procedure described by Woodward[4] for the synthesis of the *cis*-methyl ester (**7**). The separable crystalline products (**8**) and (**11**) were individually condensed with an excess of t-butyl glyoxylate in refluxing benzene, to provide the respective hydroxy amides (**9**) and (**12**), each being a mixture of diastereoisomers. Successive treatment of (**9**) or (**12**) with thionyl chloride and sodium azide gave the corresponding azides (**10**) or (**13**) (ratio of diastereoisomers *ca.* 1:1 in each case).

Although the α,β-unsaturated ester (**2**) was cyclised by a 5.5 h period under reflux in toluene,[1,2] it was considered that replacement of carbon by sulphur would deactivate the double bond, and would therefore necessitate more forcing conditions for the cycloaddition. Indeed when either (**10**) or (**13**) was refluxed in toluene for 5 h very little change was observed. Xylene proved more effective. Thus, the azide (**10**) or (**13**) was heated under reflux in dry degassed xylene under argon for 2 h. Purification of the crude product on Florisil gave starting material and three new substances. The two most polar compounds isolated (total yield *ca.* 7%), were both crystalline, and on the basis of their spectroscopic properties they were considered to be diastereoisomeric. The highly resolution enhanced 250 MHz [1]H n.m.r. spectrum of the major (5%) diastereoisomer clearly indicated that the material was the fused seven-membered ring system (**14**) and not the expected 3-aza-cepham (**16**). The olefinic proton appeared at δ 7.75 and showed significant coupling (*J* 7.3 Hz) to the enamine NH. In the six-membered enamine system (**4**), the olefinic proton displayed only fine coupling (*J* 1.7 Hz) to the NH and was character-istically high field at δ 4.7.[1] In each diastereoisomer (**14**) or (**15**), 2-H was coupled to the enamine NH (*J* 6.2 and 4.2 Hz
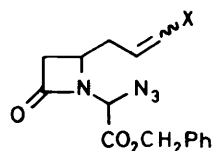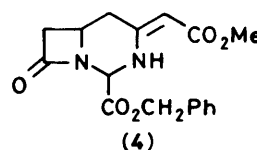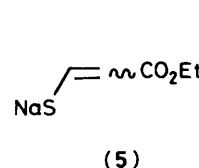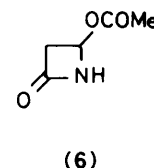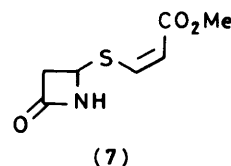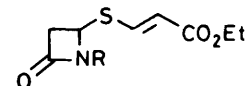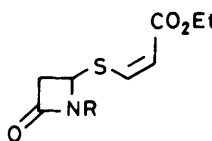

(1) X = H
(2) X = CO₂Me
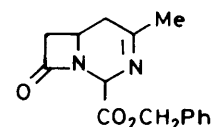
(3)

(4)

(5)

(6)

(7)

(8) R = H
(9) R = CH(OH)CO₂Buᵗ
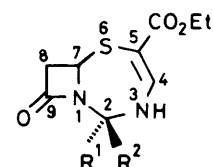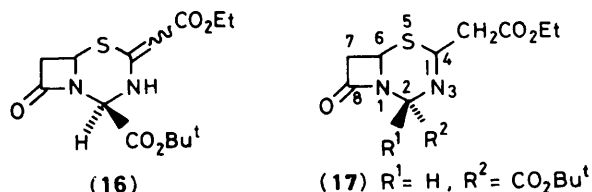(10) R = CH(N₃)CO₂Buᵗ

(11) R = H
(12) R = CH(OH)CO₂Buᵗ
(13) R = CH(N₃)CO₂Buᵗ

(14) R¹ = H, R² = CO₂Buᵗ
(15) R¹ = CO₂Buᵗ, R² = H

(16)

(17) R¹= H, R²= CO₂Buᵗ

(18)

(19) ⟶ (14) and (15)

⟶ (17)

Scheme

(20)

(21)

(22) R¹ = H, R² = OCOMe
(23) R¹ = H, R² = OCH₂CH=CH₂
(24) R¹ = OCH₂CH=CH₂, R² = H
(25) R¹ = OCH=CH(Me), R² = H

(26) X = OH
(27) X = N₃
(28) X = N = PPh₃

(29) R = CH₂Ph
(30) R = H

respectively), and additional fine coupling (J 0.7 Hz) to the olefinic proton was evident only in the case of (15). Neither diastereoisomer showed the long-range coupling between 2-H and 8-H that has been observed for some bicyclic systems.[5] Finally a comparison of the chemical shifts of 2-H in (14) (δ 5.23) and (15) (δ 5.84), led to the latter being assigned the natural penicillin stereochemistry at that centre.[6,7] N.m.r. spectroscopy showed that treatment of either (14) or (15) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in deuteriochloroform afforded the same mixture of diastereoisomers (ratio 2:1), in which (15) was predominant. Since it is well established that for penam and cepham analogues the *exo*-orientation of the carboxylate moiety represents the thermodynamically preferred situation, this result reflects the reduced steric demands of the 4,7-fused ring system.

The least polar component from the initial cycloaddition reaction was heavily contaminated with starting azide, but careful rechromatography on silica gel achieved the desired separation. Recovered azide (10) or (13) (25%) was considerably enriched in one diastereoisomer (ratio *ca.* 6:1), the cyclisation of one of the azide diastereoisomers being rendered less favourable owing to the steric interaction between the t-butoxycarbonyl group and the β-lactam carbonyl group.[7] The new product, isolated as a gum in 15% yield, was a single diastereoisomer of the 3-azacephem (17). The natural penicillin stereochemistry was assigned to C-2 because of the low chemical shift (δ 5.8) of the methine proton, which was unaltered by addition of DBU.

The formation of the cycloaddition products can be rationalised in the following way. Since a zwitterionic intermediate is implicated in the decomposition of fused carbocyclic triazolines,[8] the initially formed triazoline (18) is presumed to lose nitrogen to give a dipolar episulphonium ion intermediate (19) which then collapses to the observed products (14) and (15). Classical decomposition of the triazoline (18), without intervention of sulphur, accounts for the formation of the imine (17) (see Scheme).

At about this stage in our work, Aratani[7] reported the synthesis of the acylamino derivative (20), by a different route. The structural assignments of the Japanese workers confirmed our own conclusions, and likewise to our original intention, they prepared the azacephem system (21). Unfortunately the inherent instability of the basic nucleus precluded any antibacterial activity. We were, therefore, dissuaded from continuing our own synthetic programme in this area.

Contemporaneous with the investigation already described, the series in which sulphur was replaced by oxygen was also examined. It was expected that the cycloaddition would be more facile in this case. A slightly different approach was adopted, an acylamino side-chain being incorporated throughout the synthetic sequence.

The introduction of the desired vinyl ether functionality was achieved in two steps. The azetidinone (22)[9] when warmed with prop-2-enol in benzene containing zinc acetate[9] afforded a 1:1 mixture of the *trans*- and *cis*-4-prop-2-enyloxy-3-phenoxyacetamidoazetidin-2-ones (23) and (24). These were readily separated by chromatography, and the double bond of the *cis*-isomer (24) isomerised using the Carless[10] modification of a previously reported procedure.[11] Thus, when (24) was stirred with 10% palladium–carbon under argon in dry refluxing
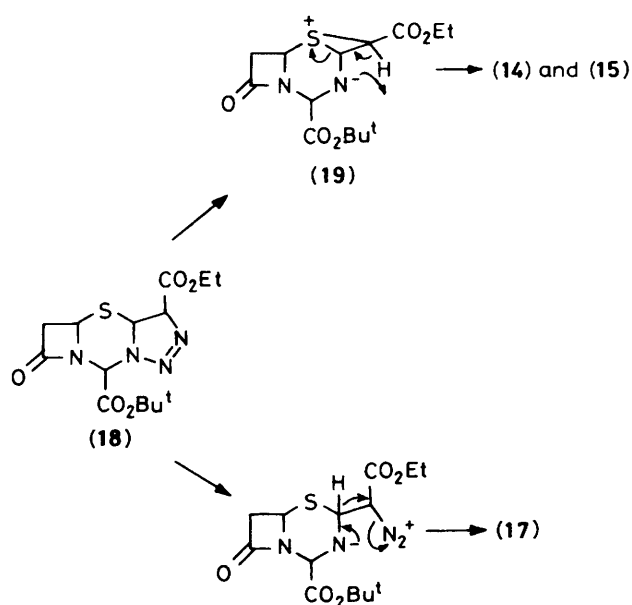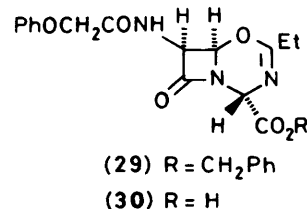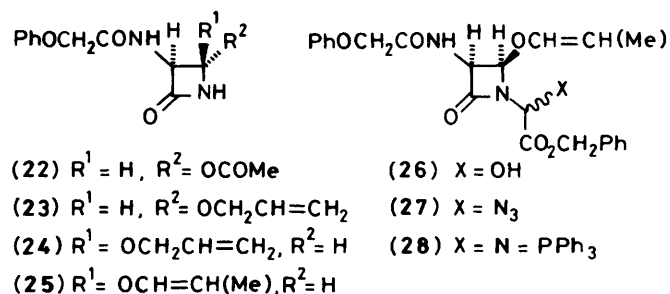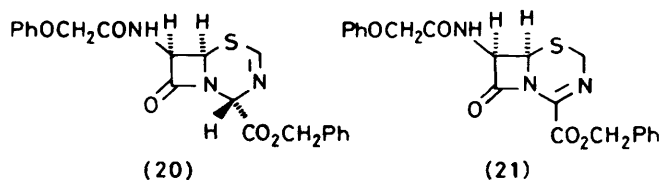
dioxane, the propenyl ether (25) was isolated as a mixture of inseparable (Z) and (E)-isomers in 77% yield (ratio 2:1). Condensation of the azetidinone (25) with benzyl glyoxylate afforded the alcohol (26) which was treated in the usual way to give the azide (27) as a 1:1 mixture of diastereoisomers. When the azide (27) was refluxed in toluene for 12 h, benzyl (2*R*, 6*R*, 7*S*)-4-ethyl-8-oxo-7-phenoxyacetamido-5-oxa-1,3-diazabicyclo[4.2.0]oct-3-ene-2-carboxylate (29) was the only new product isolated.

Initial attempts at quantitatively separating (29) from starting material (27) by silica gel chromatography were unrewarding. However, treatment of the crude reaction mixture with triphenylphosphine converted the azide (27) into the more polar phosphinimine (28), and allowed the isolation of the pure product (29). The structure and stereochemistry of (29) were assigned using the established criteria.

Hydrogenation of (29) over 10% Pd/C removed the benzyl ester to provide the free acid (30) as an amorphous solid, which was devoid of antibacterial activity. The conversion of benzyl ester (29) into the 1-oxa-3-azadethiacephalosporin ring system was not investigated since no stability advantage over the thia analogues prepared by Aratani was envisaged.

Experimental

General procedures were as in Part 1[12] and all compounds are racemic, except where indicated otherwise. 250 MHz Spectra were recorded on a Bruker WM250 instrument.

(E)- and (Z)-*Sodium 2-Ethoxycarbonylethylenethiolate* (5).— Sodium hydroxide (8.0 g) was dissolved in water (20 ml) and ethanol (400 ml) was added. The solution was cooled to 0 °C and hydrogen sulphide passed through it until it was saturated (pH of solution virtually neutral). The solution was purged with argon to remove excess of hydrogen sulphide when ethyl propiolate (19.6 g) was added in one portion. The mixture was stirred at 0 °C for 2 h, filtered, and the solid washed with ethanol and discarded. The filtrate was evaporated to dryness under reduced pressure, toluene (200 ml) was added, and the solvent evaporated. This was repeated twice more and the residue triturated with dry ether to give the sodium salt (5) as a pale yellow solid (22.2 g), which was used immediately.

(E)- and (Z)-4-(2-*Ethoxycarbonylvinylthio*)*azetidin-2-one* (8) and (11).—(We thank Dr. E. G. Brain for this preparation.) 4-Acetoxyazetidin-2-one (6) (18.4 g) was dissolved in acetone (200 ml) and the solution cooled to 0 °C. The sodium salt (5) (22 g) in water (50 ml) was added dropwise during 5 min, and then the cooling-bath was removed. After a further 30 min the acetone was evaporated off and the residue extracted with ethyl acetate (2 × 300 ml). The combined organic extracts were washed with brine, dried, and evaporated. Chromatography gave the (E)-*isomer* (8) as a gum (6.18 g) which slowly crystallised at 0 °C, m.p. 51—52 °C (ethyl acetate–hexane) (Found: C, 48.2; H, 5.7; N, 7.1; S, 15.8. $C_8H_{11}NO_3S$ requires C, 47.8; H, 5.5; N, 7.0; S, 15.9%); $\nu_{max.}$ 3 400, 3 300br, 3 000, 1 780br, and 1 590 cm^{-1}; δ_H (60 MHz) 1.3 (3 H, t, *J* 7 Hz), 2.84 and 3.1 (1 H, part of ABq, *J* 16 Hz, each arm showing further coupling of *J* ca. 1 Hz and 2 Hz, *J* ca. 1 Hz lost on D$_2$O exch), 3.41 and 3.68 (1 H, part of ABq, *J* 16 Hz, each arm showing further coupling of *J* 2 and 5 Hz, *J* 2 Hz lost on D$_2$O exch.), 4.17 (2 H, q, *J* 7 Hz), 5.05 (1 H, dd, *J* 2 and 5 Hz), 5.85 (1 H, d, *J* 16 Hz), 7.0 (1 H, br s, exch. D$_2$O), and 7.68 (1 H, d, *J* 16 Hz).

Further elution provided the (Z)-*isomer* (11) as a crystalline solid (6.24 g), m.p. 91 °C (ethyl acetate–hexane) (Found: C, 48.05; H, 5.4; N, 7.0%); $\nu_{max.}$ 3 400, 3 300br, 3 000, 1 780, 1 770, 1 690, and 1 570 cm^{-1}; δ_H (60 MHz) 1.3 (3 H, t, *J* 7 Hz), 2.85 and 3.11 (1 H, part of ABq, *J* 16 Hz, each arm showing further coupling of *J* ca. 1 and 2 Hz, *J* ca. 1 Hz lost on D$_2$O exch.), 3.37 and 3.64 (1 H, part of ABq, *J* 16 Hz, each arm showing further coupling of *J* 2 and 5 Hz, *J* 2 Hz lost on D$_2$O exch.), 4.20 (2 H, q, *J* 7 Hz), 4.93 (1 H, dd, *J* 2 and 5 Hz), 6.0 (1 H, d, *J* 10 Hz), 6.82 (1 H, br s, exch. D$_2$O), and 7.27 (1 H, d, *J* 10 Hz).

(E)- and (Z)-4-(2-*Ethoxycarbonylvinylthio*)-1-[*hydroxy(t-butoxycarbonyl)methyl*]*azetidin-2-one* (9) and (12).—t-Butyl glyoxylate monohydrate (3 g) was refluxed in benzene (15 ml)

for 0.5 h with provision for the removal of water. The azetidinone (8) (250 mg) was added and the mixture refluxed for 1½ h. The solvent was evaporated and the residue chromatographed to give the *alcohol* (9) as a thick oil (521 mg) (Found: M^+, 331.1083. $C_{14}H_{21}NO_6S$ requires M, 331.1090); $\nu_{max.}$ 3 510 br, 1 780, 1 735, 1 710, and 1 595 cm^{-1}. The n.m.r. spectrum (90 MHz) showed singlets (after D$_2$O exch.) at δ 5.0 and 5.42 for the C*H*OH protons of the two isomers (ratio ca. 1:1).

In the same way the azetidinone (11) (3.03 g) was converted into the alcohol (12), which was isolated as a viscous gum (4.6 g), $\nu_{max.}$ 3 510br, 1 775, 1 735, 1 710, and 1 590 cm^{-1}. The n.m.r. spectrum (90 MHz) showed singlets (after D$_2$O exch.) at δ 4.95 and 5.37 for the C*H*OH protons of the two isomers (ratio ca. 1:1) [Found: MNH$_4^+$, m/z (c.i.) 349. $C_{14}H_{21}NO_6S$ requires M, 331].

(E)- and (Z)-1-[*Azido(t-butoxycarbonyl)methyl*]-4-(2-*ethoxycarbonylvinylthio*)*azetidin-2-one* (10) and (13).—The alcohol (9) (662 mg) was dissolved in dry tetrahydrofuran (20 ml) at −15 °C and 2,6-lutidine (267 mg) was added, followed dropwise by thionyl chloride (297 mg) in tetrahydrofuran (2 ml) over 15 min. The mixture was filtered and the filtrate evaporated; the residue was dissolved in toluene and the solution evaporated. The crude product was dissolved in dry *N,N*-dimethylformamide (15 ml) and powdered sodium azide (145 mg) added. The mixture was vigorously stirred for 10 min and then poured into ethyl acetate. The solution was washed with dilute hydrochloric acid and brine, dried, and evaporated. Chromatography gave the azide (10) as a mixture of isomers (600 mg), $\nu_{max.}$ 2 125, 1 780, 1 745, 1 695, and 1 580 cm^{-1}. The n.m.r. spectrum (90 MHz) showed singlets at δ 5.28 and 5.32 for the C*H*N$_3$ protons of the two isomers (ratio ca. 1:1) [Found: MNH$_4^+$, m/z (c.i.) 374. $C_{14}H_{20}N_4O_6S$ requires M, 356].

In the same way the azetidinone (12) (1.9 g) was converted into the azide (13), which was isolated as a viscous gum (1.36 g), $\nu_{max.}$ 2 125, 1 775, 1 745, 1 695, and 1 580 cm^{-1}. The n.m.r. spectrum (90 MHz) showed singlets at δ 5.29 and 5.38 for the CHN$_3$ protons of the two isomers (ratio ca. 1:1) [Found: MNH$_4^+$ m/z (c.i.) 374].

(2RS,6SR)-*t-Butyl-4-ethoxycarbonylmethyl-8-oxo-5-thia-1,3-diazabicyclo*[4.2.0]*oct-3-ene-2-carboxylate* (17), and (2RS,6RS)-(14) and (2RS,6SR)-*t-Butyl-5-ethoxycarbonyl-9-oxo-6-thia-1,3-diazabicyclo*[5.2.0]*non-4-ene-2-carboxylate* (15).—The azide (10) (1.5 g) was refluxed under argon in dry degassed xylene (500 ml) for 2 h. The solvent was evaporated off and the residue chromatographed on Florisil (30 g). The least polar fractions which contained some starting material were rechromatographed on silica (20 g) to give the azide (10) (350 mg) enriched in one epimer (ratio CHN$_3$ δ 5.32 and 5.28, 6:1), and the *imine* (17) which was isolated as a viscous oil (245 mg) (Found: M + H$^+$, m/z 329.1177. $C_{14}H_{21}N_2O_5S$ requires M + H, m/z 329.1171); $\nu_{max.}$ 1 780, 1 740, and 1 625 cm^{-1}; δ_H (90 MHz) 1.23 (3 H, t, *J* 7 Hz), 1.47 (9 H, s), 3.03 and 3.66 (2 H, ABq, *J* 15 Hz, each arm showing further coupling of 1.5 and 4.2 Hz respectively), 3.39 (2 H, slightly broadened singlet, *J* ca. 0.7 Hz), 4.15 (2 H, q, *J* 7 Hz), 4.98 (1 H, dd, *J* 1.5 and 4.2 Hz), and 5.89 (1 H, slightly broadened singlet, *J* ca. 0.7 Hz).

Further elution of the Florisil column afforded the (2RS,6SR)-*isomer* (15) as a crystalline solid (22 mg), m.p. 186—187 °C (decomp.) (ethyl acetate–light petroleum) (Found: M^+, 328.1096. $C_{14}H_{20}N_2O_5S$ requires M, 328.1092); $\lambda_{max.}$ (2% CHCl$_3$–EtOH) 304 nm (ε 7 453 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$ 3 380, 1 775, 1 740, 1 690, and 1 600 cm^{-1}; δ_H (250 MHz, highly resolution enhanced) 1.27 (3 H, t, *J* 7.1 Hz), 1.51 (9 H, s), 3.48 and 3.56 (2 H, ABq, *J* 16 Hz, each arm showing further coupling of 4.2 and 2.55 Hz respectively), 4.17 (2 H, m), 4.96 (1 H, dd, *J*

2.55 and 4.2 Hz), 5.84 (1 H, dd, J 0.7 and 3.5 Hz), 6.10 (1 H, m, exch. D_2O), and 7.76 (1 H, dd, J 0.7 and 7.8 Hz).

The most polar fractions gave the (2RS,6RS)-*isomer* (14) as a crystalline solid (60 mg), m.p. 185—189 °C (decomp.) (ethyl acetate–light petroleum) (Found: C, 51.2; H, 6.15; N, 8.4; S, 9.3. $C_{14}H_{20}N_2O_5S$ requires C, 51.2; H, 6.10; N, 8.5; S, 9.8%); $\lambda_{max.}$ (2% $CHCl_3$–EtOH) 243 (ε 6 420 dm^3 mol^{-1} cm^{-1}) and 303 nm (7 600); $\nu_{max.}$ 3 440, 1 770, 1 760sh, 1 690, and 1 610 cm^{-1}; δ_H (250 MHz, highly resolution enhanced) 1.27 (3 H, t, J 7.1 Hz), 1.57 (9 H, s), 3.41 (2 H, m), 4.18 (2 H, m), 4.98 (1 H, dd, J 3.1 and 3.8 Hz), 5.23 (1 H, d, J 6.2 Hz), 5.57 (1 H, dd, J 6.2 and 7.3 Hz, exch. D_2O), and 7.75 (1 H, d, J 7.3 Hz).

Essentially the same yields of products were obtained on thermolysis of the azide (13) under identical conditions.

(3S,4S)-(23) *and* (3S,4R)-3-*Phenoxyacetamido-4-prop-2-enyl-oxyazetidin-2-one* (24).—The *trans*-acetate (22) (8.34 g), prop-2-enol (5.22 g), and powdered zinc acetate dihydrate (3.3 g) were stirred at 80 °C in toluene for 3 h. The mixture was filtered and the filtrate evaporated. Chromatography of the residue gave the trans-*isomer* (23) (1.4 g), m.p. 121—122 °C (ethyl acetate–light petroleum) (Found: C, 61.1; H, 5.6; N, 10.1. $C_{14}H_{16}N_2O_4$ requires C, 60.9; H, 5.8; N, 10.1%); $\nu_{max.}$ 3 350, 1 780, and 1 685 cm^{-1}; δ_H (60 MHz) 4.11 (2 H, d, J 5 Hz), 4.47 (2 H, s), 4.72 (1 H, dd, J ca. 1 and 8 Hz), 5.11 (1 H, d, J ca. 1 Hz), 5.22—6.3 (3 H, m), and 6.72—7.62 (7 H, m).

Further elution gave the cis-*isomer* (24) (1.39 g), m.p. 128—129 °C (ethyl acetate–light petroleum) (Found: C, 60.5; H, 6.0; N, 10.2%); $\nu_{max.}$ 3 350, 1 785, and 1 695 cm^{-1}; δ_H (60 MHz) 4.04 (2 H, d, J 5 Hz), 4.54 (2 H, s), 5.05—6.2 (5 H, m), and 6.76—7.54 (7 H, m).

(3S,4R)-3-*Phenoxyacetamido-4-prop-1-enyloxyazetidin-2-one* (25).—The azetidinone (24) (345 mg) was dissolved in dry dioxane (10 ml) and 10% Pd–C (89 mg) added. The mixture was refluxed under argon with vigorous stirring. After 4 h, the cooled mixture was filtered through Kieselguhr and the filtrate evaporated. Chromatography afforded the *ether* (25) as a white crystalline solid (167 mg) (Found: C, 60.9; H, 5.8; N, 10.1. $C_{14}H_{16}N_2O_4$ requires C, 60.9; H, 5.8; N, 10.1%); $\nu_{max.}$ 3 420, 1 795, and 1 690 cm^{-1}. The n.m.r. spectrum was extremely complex but clearly showed the product was a mixture of (Z)- and (E)-isomers (ratio 2:1), δ_H (250 MHz) [$CDCl_3$ + 2 drops $(CD_3)_2SO$] *inter alia* 1.53 and 1.58 (together 3 H, dd, J 1.8 and 10.8 Hz, 1.5 and 10.8 Hz, respectively), 5.49 (1 H, ddd, J ca. 1, 4, and 9.5 Hz), 6.05 and 6.13 (together 1 H, dq, J 1.5 and 6 Hz, 1.8 and 13 Hz respectively), and 8.55 and 8.59 (together 1 H, slightly broadened s).

(3S,4R)-1-[*Hydroxy(benzyloxycarbonyl)methyl*]-3-*phenoxy-acetamido-4-prop-1-enyloxyazetidin-2-one* (26).—Benzyl gly-oxylate monohydrate (189 mg) was refluxed in benzene (20 ml) for 1 h with provision for the removal of water. The azetidinone (25) (247 mg) in dioxane (3 ml) was added and the solution refluxed for a further 1 h and then cooled. Triethylamine (9 mg) was added and after 30 min the solvents were evaporated off. Chromatography gave a viscous gum (26) (358 mg), $\nu_{max.}$ 3 500, 3 420, 1 790, 1 750, and 1 690 cm^{-1}.

(3S,4R)-1-[*Azido(benzyloxycarbonyl)methyl*]-3-*phenoxyacet-amido-4-prop-1-enyloxyazetidin-2-one* (27).—The hydroxy ester (26) (352 mg) was converted into the azide (27) as described for

(9). The product (27) was a viscous gum (292 mg), $\nu_{max.}$ 3 415, 2 120, 1 790, 1 755, 1 690, and 1 675 cm^{-1}.

(2S,6R,7S)-*Benzyl-4-Ethyl-8-oxo-7-phenoxyacetamido-5-oxa-1,3-diazabicyclo*-[4.2.0]*oct-3-ene-2-carboxylate* (29).—The azide (27) (207 mg) was refluxed in dry toluene (200 ml) under argon for 12 h. The solvent was evaporated off and the residue chromatographed to give an inseparable mixture of starting material (27) and the product (29). The material (95 mg) was dissolved in dichloromethane and triphenylphosphine (10 mg) added. After 30 min the solvent was evaporated off and chromatography afforded the pure *product* (29) as an amorphous solid (64 mg) (Found: M^+, 437.1586. $C_{23}H_{23}N_3O_6$ requires M, 437.1587); $[\alpha]_D^{20}$ + 105.5 (c 2.24 in $CHCl_3$); $\lambda_{max.}$ 262 (ε 1 150 dm^3 mol^{-1} cm^{-1}), 268 (1 430), and 275 nm (1 080); (250 MHz) 1.09 (3 H, t, J 7.5 Hz), 2.22 (2 H, q, J 7.5 Hz), 4.56 (2 H, s), 5.20 and 5.25 (2 H, ABq, J 12 Hz), 5.48 (1 H, slightly broadened s), 5.54 (1 H, d, J ca. 3 Hz), 5.66 (1 H, dd, J ca. 3 and 9 Hz), 6.9—7.1 (3 H, m), and 7.25—7.4 (8 H, m).

(2S,6R,7S)-4-*Ethyl-8-oxo-7-phenoxyacetamido-5-oxa*-1,3-*diazabi-cyclo*[4.2.0]*oct-3-ene-2-carboxylic Acid* (30).—The ester (29) (25 mg) was hydrogenated over 10% Pd–C (11 mg) in dioxane (7 ml) for 2 h. The catalyst was removed by filtration through Kieselguhr and the filtrate evaporated. Trituration of the residue with ether afforded the acid (30) as a white amorphous solid (15 mg), $\lambda_{max.}$ 268 (ε 3 183 dm^3 mol^{-1} cm^{-1}) and 275 nm (3 342); $\nu_{max.}$(KBr) 3 400, 1 785, 1 745, and 1 660 cm^{-1}; δ_H (250 MHz) [$(CD_3)_2SO$] 0.98 (3 H, t, J 7.5 Hz), 2.25 (2 H, q, J 7.5 Hz), 4.56 (2 H, s), 4.76 (1 H, s), 5.24 (1 H, dd, J 4 and 9 Hz), 6.12 (1 H, d, J 4 Hz), 6.85—7.05 (3 H, m), 7.2—7.4 (2 H, m), and 8.79 (1 H, d, J 9 Hz).

References

1 Part 9, C. L. Branch and M. J. Pearson, *J. Chem.. Soc., Perkin Trans. 1*, preceding paper.
2 C. L. Branch and M. J. Pearson, *J. Chem. Soc., Chem. Commun.*, 1981, 946.
3 K. Clauss, D. Grimm, and G. Prossel, *Justus Liebigs Ann. Chem.*, 1974, 539.
4 H. R. Pfaendler, J. Gosteli, and R. B. Woodward, *J. Am. Chem. Soc.*, 1979, **101**, 6306.
5 M. D. Bachi, F. Frolow, and C. Hoornaert, *J. Org. Chem.*, 1983, **48**, 1841.
6 R. G. Alexander and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1977, 405.
7 M. Aratani and M. Hashimoto, *J. Am. Chem. Soc.*, 1980, **102**, 6171.
8 A. Padwa, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 123, and references cited therein.
9 C. L. Branch and M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2268.
10 H. A. J. Carless and D. J. Heywood, *J. Chem. Soc., Chem. Commun.*, 1980, 980.
11 R. Boss and R. Scheffold, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 558.
12 D. Davies and M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2539.