Synthesis of Novel β-Lactamase Inhibitors from Clavulanic Acid. Preparation and Chemical Reactions of (5*R*)-3-Vinyl-4-oxa-1-azabicyclo-[3.2.0]hept-2-en-7-one

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Three methods for the preparation of (5*R*)-3-vinyl-4-oxa-1-azabicyclo[3.2.0]hept-2-en-7-one (2) have been developed; the most convenient method involves the reaction of clavulanic acid with *NN*-dimethylformamide dimethyl acetal. Hydrogenation of the diene (2) gave three products: (3*S*,5*R*)-3-ethyl-4-oxa-1-azabicyclo-[3.2.0]heptan-7-one and (*E*)- and (*Z*)-(5*R*)-3-ethylidene-4-oxa-1-azabicyclo[3.2.0]heptan-7-one. Reaction of the diene (2) with methanol gave 4-methoxy-1-(2-oxobut-3-enyl)azetidin-2-one and 2-hydroxy-3-methoxy-3-vinyl-4-oxa-1-azabicyclo[3.2.0]heptan-7-one and with both acetic acid and thiophenol, it gave products derived from reaction at the β-lactam moiety.

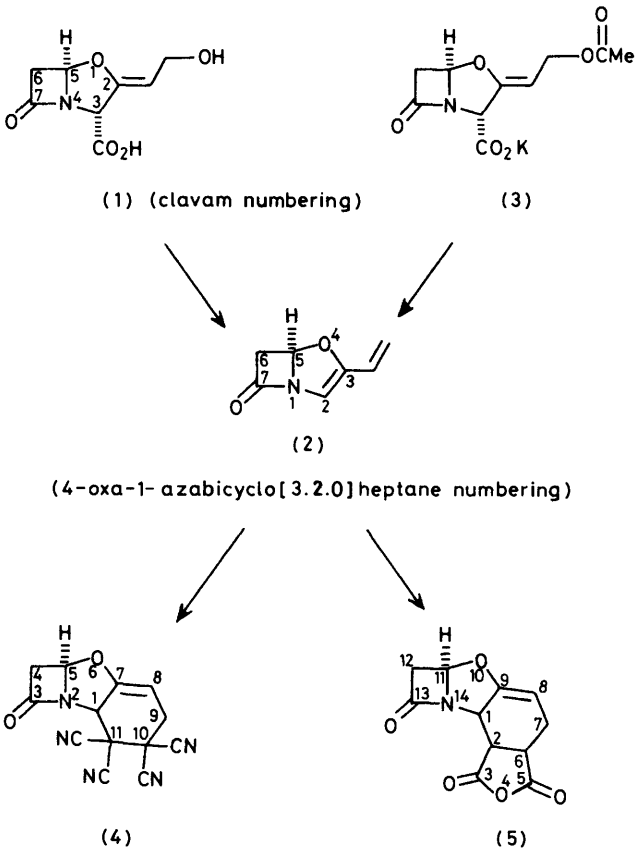
Thiophenol and oxygen reacted with the diene (2) to give a single 1,4-addition product, (*Z*)-(2*S*,5*R*)-3-(2-hydroxyethylidene)-2-phenylthio-4-oxa-1-azabicyclo[3.2.0]heptan-7-one and with thiophenol in the presence of a free-radical initiator, it gave three 1,4-addition products: (*Z*)-(5*R*)-3-(2-phenylthioethylidene)-4-oxa-1-azabicyclo[3.2.0]heptan-7-one and (*E*)- and (*Z*)-(2*S*,5*R*)-3-ethylidene-2-phenylthio-4-oxa-1-azabicyclo[3.2.0]-heptan-7-one.

Tetracyanoethylene, maleic anhydride, diethyl azodicarboxylate, singlet oxygen, acrylaldehyde, and nitrosobenzene all reacted with the diene (2) to give Diels–Alder adducts. With benzyl acrylate, (2) gives three adducts: benzyl (1*S*,5*R*,11*S*)-3-oxo-6-oxa-2-azatricyclo[5.4.0.0^{2,5}]undec-7-ene-11-carboxylate and benzyl(1*S*,5*R*,10*R*)- and (1*S*,5*R*,10*S*)-3-oxo-6-oxa-2-azatricyclo[5.4.0.0^{2,5}]undec-7-ene-10-carboxylate. Some of the above 1,4-addition products and Diels–Alder adducts were found to be β-lactamase inhibitors.

Following the discovery of the natural β-lactamase inhibitor clavulanic acid (1),[1] a number of analogues lacking the C-3 carboxy-group were prepared by total synthesis.[2] Since many of these were found to be quite active as β-lactamase inhibitors,[2,3] interest was aroused in finding preparative methods for similar analogues starting from clavulanic acid. One such method, the dehydrative decarboxylation of the acid (1) to give the conjugated diene (2), has already been reported.[4] We now describe some of the chemical reactions which the diene (2) will undergo and, in particular, we show how compound (2) has been used to prepare some novel analogues of clavulanic acid.

For the preparation of the diene (2) the most convenient method, and the one which we have used routinely, involved the reaction of the acid (1) with *NN*-dimethylformamide dimethyl acetal [5] in tetrahydrofuran (THF) at room temperature. This gives a solution of the diene in *ca.* 80% yield; if all or most of the solvent is removed from this solution then the diene appears to polymerise quite rapidly. The diene was characterised by its spectral properties and by the formation of the crystalline Diels–Alder adducts (4) and (5).

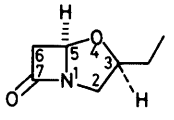
There are two other methods which we have found to give the diene (2) but these have proved to be less convenient for further preparative work. Firstly, the acid (1) can be converted into the diene (2) by reaction with triphenylphosphine and diethyl azodicarboxylate [6] in THF. This gives a solution containing the diene (2), triphenylphosphine oxide, and 1,2-bis(ethoxycarbonyl)-hydrazine. The diene cannot be readily isolated from this mixture, but after addition of maleic anhydride the adduct (5) was obtained in 60% yield. Secondly, the diene (2) can be obtained from fragmentation of the 9-*O*-



acyl derivatives [7] of clavulanic acid. For example, after a solution of the potassium salt (3) in aqueous THF had been heated at 40 °C for 3 h, the diene could be detected in the solution using thin layer chromatography (t.l.c.).

Extraction of the diene (2) into ethyl acetate, followed by addition of tetracyanoethylene to this solution, gave the adduct (4) in 15% yield.

In attempting to convert compound (2) into the desired C-3 decarboxy-analogues of (1), one of the first reactions to be investigated was catalytic hydrogenation. Thus, hydrogenation of the diene (2) in THF over 10% palladium–charcoal gave a mixture of products from which the tetrahydro-derivative (6) (27% yield) and a mixture of the desired dihydro-derivatives (7) and (8) were isolated by chromatography on silica gel. Compounds (7) (28%) and (8) (12%) were then separated by preparative high performance liquid chromatography (h.p.l.c.). The stereochemical assignment for compound (6) was based on the chemical shift separation (0.24 p.p.m.) of its two C-2 protons; * this separation would have been expected [8] to be much greater (*ca.* 1.0—1.4 p.p.m.) if compound (6) had had the alternative relative stereochemistry. The stereochemistries for the two dihydro-derivatives followed from the relative chemical shifts of their vinyl protons. In methyl clavulanate the vinyl proton (δ 4.97 †) absorbs at higher field than that in methyl isoclavulanate [9] (δ 5.38), and in the major dihydro-product the vinyl proton (δ 4.30) absorbs at higher field than that in the minor dihydro-product (δ 4.85). So, to the major isomer we assigned structure (7) in which the double-bond geometry is the same as in methyl clavulanate.



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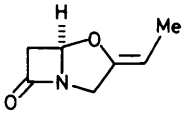

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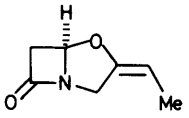

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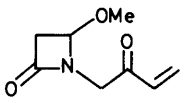

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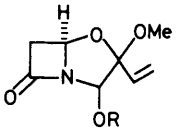
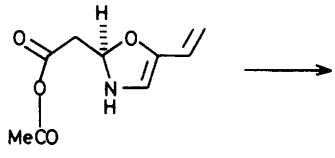


(10) R = H
(11) R = Ac

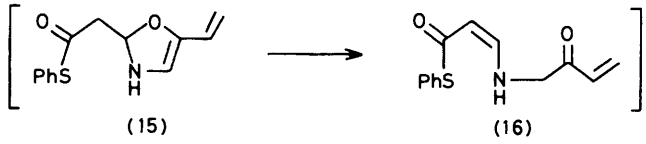
We have also investigated the reactions of the diene (2) with alcohols, carboxylic acids, and thiols. From a solution of the diene (2) in toluene–methanol kept overnight, compounds (9) (8%) and (10) (32%) were isolated by chromatography. The reaction to give (9) is analogous to the reaction of the 2-benzyloxycarbonyl derivative of (2) with methanol.[10] Compound (10) presumably arises from reaction of the diene with atmospheric oxygen and then methanol. The same compound was also obtained, in 20% yield, by reaction of the diene (2) with *m*-chloroperbenzoic acid in methanol–THF. With acetyl chloride and pyridine, the alcohol (10) gave the crystalline acetate (11); the n.m.r. spectrum of this derivative confirmed the position of the hydroxy-group in compound (10). The stereochemistry of the alcohol (10) is unknown.

When the diene (2) was treated with acetic acid in THF an acidic product was formed which, without isolation, was methylated using diazomethane. This gave the methyl ester (14) (27%) as the only isolated product. We propose that the ester is produced by way of reaction of acetic acid with the β-lactam group to give the mixed anhydride (12) which internally acetylates the secondary amino-group to form the acid (13), methylation of which then gives the methyl ester (14).



(12)

(13) R = H
(14) R = Me



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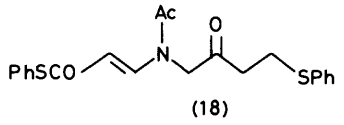


(18)

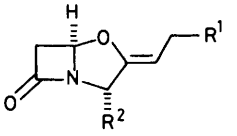
Thiols also appear to react with compound (2) by initially attacking the β-lactam group. For example, thiophenol reacted with (2) in THF to give the thiol ester (17) as a mixture of double-bond isomers in 52% yield. The isomers could not be separated by chromatography on silica gel since, as was shown using t.l.c., they were interconverted on this adsorbent. When the mixture of isomers (17) was acetylated using acetyl chloride and 2,6-lutidine, a single compound (18) was obtained in 70% yield. We propose that thiophenol initially reacts with the β-lactam group in compound (2) to give the thiol ester (15). Opening of the oxazoline ring then gives the

* Systematic numbering, as given for compounds (2) and (6), is used for the diene (2) and compounds derived therefrom; non-systematic, clavam numbering (ref. 8) is used for compound (1).

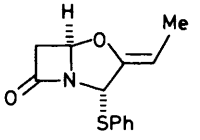
† Chemical shifts are relative to internal Me_4Si for solutions in $CDCl_3$.

unsaturated ketone (16) which adds a second molecule of thiophenol to give the observed product (17).

Of more interest, as far as preparing C-3 decarboxy-analogues of (1) was concerned, were the reactions of compound (2) with thiols under free-radical conditions.[11] Thiophenol and oxygen reacted with the diene (2) in the presence of triethylamine to give a single 1,4-addition product (19) in low yield. Acetylation of (19) gave the acetate (20), and the n.m.r. spectrum of this derivative confirmed the position of the hydroxy-group in (19). If it is assumed that the thiyl radical adds to the less hindered side of the diene (2), then the stereochemistry at C-2 will be as indicated in structure (19). The assigned double-bond geometry for compound (19) was based on the fact that the chemical shift of the vinyl proton (δ 4.89) is close to that of the corresponding proton in methyl clavulanate. As will be shown later, replacing CO_2R at C-3 of compound (1) by SPh is not expected to have much effect on this chemical shift.



(19) R^1 = OH, R^2 = SPh
(20) R^1 = OAc, R^2 = SPh
(21) R^1 = SPh, R^2 = H
(22) R^1 = SO_2Ph, R^2 = H



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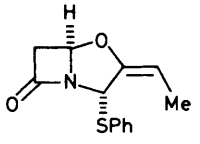
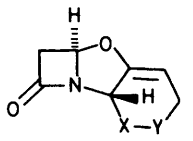


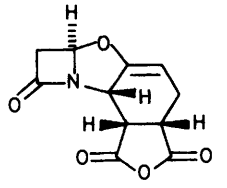
(24)

The diene (2) was also allowed to react with thiophenol in the presence of the free-radical initiator α,α′-azobisisobutyronitrile in THF at 50 °C. This gave three 1,4-addition products. Compound (21) (19%) was obtained pure by chromatography, but the other two products, (23) (49%) and (24) (11%), could not be separated from one another. The double-bond geometry assigned to compound (21) was based on the relatively high chemical shift of its vinyl proton (δ 4.44). Oxidation of the sulphide (21) using *m*-chloroperbenzoic acid (2 mol equiv.) gave the crystalline sulphone (22). For compounds (23) and (24) the stereochemistry at C-2 follows from the assumption that the thiyl radical has added to the less hindered face of the diene (2). The respective double-bond geometries follow from the relative chemical shifts of the vinyl protons [δ 4.65 for (23) and 4.96 for (24)]. The vinyl proton chemical shift for (23) is close to those for esters of 9-deoxyclavulanic acid[12] and this, as mentioned earlier, had a bearing on our assignment of the double-bond geometry in compound (19).

A number of Diels–Alder reactions involving the diene (2) have also been studied. The reactions with tetracyanoethylene or maleic anhydride, both of which give a single adduct in high yield, have been mentioned already. If it is assumed that these additions occur on the less hindered face of the diene and, in the case of maleic anhydride, that *endo*-addition occurs,[13] then stereostructures (25) and (26) respectively, can be assigned to these adducts. Diethyl azodicarboxylate also adds to (2) to give a single product, (27), as does singlet oxygen [to give compound (28)].



(25) X = Y = $C(CN)_2$
(27) X = Y = NCO_2Et
(28) X = Y = O
(29) X = O, Y = NPh



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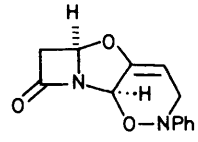


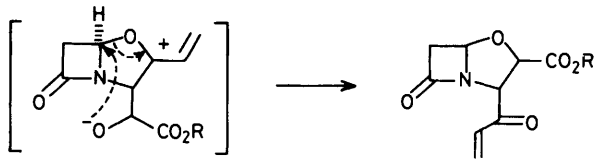
(30)

Nitrosobenzene, on the other hand, reacted with the diene (2) to give two crystalline adducts. The n.m.r. spectra of these adducts suggested that they were both derived by addition of the oxygen of nitrosobenzene to the C-2 position of the diene. Therefore, structures (29) and (30) are proposed for these products, although it is not possible to say which product has which structure.

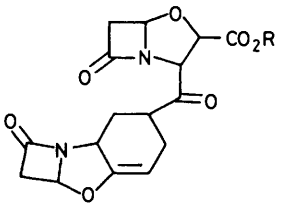
p-Nitrobenzyl glyoxylate failed to give the expected Diels–Alder adduct on reaction with compound (2). Two products were isolated by chromatography, and to these we have assigned structures (32) * and (33) on the basis of their spectral properties. The mechanism by which these compounds are formed is not immediately obvious. One possibility is that the glyoxylate, being a highly polarised dienophile, adds to the diene (2) to give a zwitterionic intermediate (31), and this then rearranges to (32). Addition of a second molecule of diene to the activated double bond in (32) would then give compound (33).

Acrylaldehyde reacted with (2) to give, after chromatography, a single addition product. This adduct was crystalline and an *X*-ray crystallographic analysis has established its stereostructure as (34).[14] Oxidation of this aldehyde with oxygen in the presence of 5% platinum–charcoal and sodium hydrogen carbonate in aqueous THF gave the corresponding sodium carboxylate, which with benzyl bromide in hexamethylphosphoramide gave the benzyl ester (37).

* Compound (32) appears to be a single diastereoisomer; the stereochemistry is unknown. The isolated material had a low optical rotation, and it is not known whether (32) is a single enantiomer or whether it is partially racemised. Likewise, little can be said regarding the stereochemistry of compound (33).



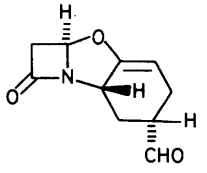
(31) R = *p*-nitrobenzyl (32) R = *p*-nitrobenzyl



(33) R = *p*-nitrobenzyl

Benzyl acrylate also reacted with the diene (2) and gave three addition products which were separated by chromatography. To the least abundant product (3%), structure (35) was assigned on the basis of its spectral properties. Again, the stereochemical assignment at C-1 was based on the assumption that addition has occurred on the less hindered face of the diene. The spin–spin coupling (J 4.5 Hz) between the protons at C-1 and C-11, together with a study of molecule models, suggested that these protons are disposed *cis* with respect to the six-membered ring. Thus, the stereochemistry depicted in (35) was assigned to this product. The other two products were deduced to have structures (37) (11%) and (39) (8%), the more abundant of these being identical with the benzyl ester derived from the acrylaldehyde addition product. The stereochemistry of compound (39) was not deduced directly, but followed from the elucidation of the stereochemistry of the corresponding methyl ester (40).

Similarly, the reaction of compound (2) with methyl acrylate gave methyl esters (36), (38), and (40), by analogy with the three benzyl esters obtained with benzyl acrylate. The stereochemistry of compound (40) was determined as follows. Firstly, n.m.r. studies involving double-resonance experiments and lanthanide-induced shifts * established that the protons at C-1 and C-10 were *trans* orientated with respect to the six-membered ring [the relevant coupling-constant data are summarised in the Table]. This established that in compound (40) either C-1 or C-10, *but not both*, differs in absolute configuration from the corresponding centres in the isomer (38). Secondly, oxidation of compound (38) using a mixture of selenium dioxide and t-butyl hydroperoxide [15] gave the azetidinone (41) which was purified by column chromatography and preparative h.p.l.c. Stereochemically, the overall result of this conversion has been to remove the asymmetry which originally existed at C-1. Similarly, the ester (42) was prepared from compound (40). These azetidinones (41) and (42) were shown to be non-identical by their different specific rotations and by small differences in their 250 MHz n.m.r. spectra. We therefore concluded that the isomeric esters (38) and (40) have different configurations at C-10, and hence the same configuration at C-1. The stereochemistry for (40) was thus established.



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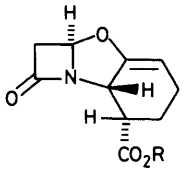
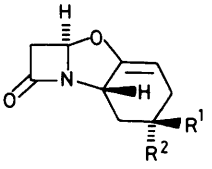
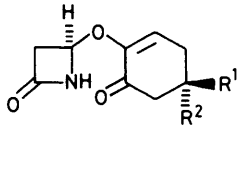


(35) R = CH_2Ph
(36) R = Me



(37) R^1 = H, R^2 = CO_2CH_2Ph
(38) R^1 = H, R^2 = CO_2Me
(39) R^1 = CO_2CH_2Ph, R^2 = H
(40) R^1 = CO_2Me, R^2 = H



(41) R^1 = H, R^2 = CO_2Me
(42) R^1 = CO_2Me, R^2 = H

First-order coupling constants for the methyl esters (38) and (40) in $CDCl_3$ at 90 MHz

Compound	Coupling constants (Hz)					
	$J_{1,8}$	$J_{1,11\alpha}$	$J_{1,11\beta}$	$J_{11\alpha,11\beta}$	$J_{11\alpha,10}$	$J_{11\beta,10}$
(38)	2	12	4.5	12	12	3
(40)	2	11	5	11	6	12

Several of the compounds which we have described were found to be β-lactamase inhibitors. Notably, the 1,4-addition products (7), (8), and (21) [and (22)], which are all unsubstituted at C-2, were found to inhibit a range of β-lactamase enzymes and were able to enhance synergistically the antibacterial activity of ampicillin against certain β-lactamase-producing bacteria. Perhaps more interesting was the discovery that the tricyclic adducts (34), (37), (38), (39), and (40) were also β-lactamase inhibitors. These compounds were also able to enhance synergistically the activity of ampicillin against a range of β-lactamase-producing bacteria. For example, when the ester (40) at a concentration of 1.0 μg ml^{-1} was combined with ampicillin it reduced the minimum inhibitory concentration of ampicillin from

* $Eu([^2H_9]fod)_3$ (A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, 1973, **73**, 553) was added in increments of 0.1 mol equiv., up to a total of 1.0 mol equiv., to a solution of the compound under study in $CDCl_3$ with Me_4Si as internal reference.

500 μg ml^{-1} to 6.25 μg ml^{-1} against a β-lactamase-producing strain of *Staphylococcus aureus*.[16]

EXPERIMENTAL

M.p.s were determined using a Kofler hot-stage apparatus. Except where stated otherwise, i.r. spectra and specific rotations were recorded for solutions in chloroform, and ^{1}H n.m.r. spectra were recorded at 90 MHz for solutions in $CDCl_3$ with Me_4Si as internal standard. U.v. spectra were recorded for solutions in ethanol. Mass spectra were determined using either an A.E.I. MS9 instrument or a V.G. Micromass 70-70F instrument. The 250 MHz ^{1}H n.m.r. spectra for compounds (41) and (42) were recorded using a Bruker WM250 instrument. Merck silica gel 60 was used for column chromatography with ethyl acetate–light petroleum as eluant. Light petroleum refers to the fraction boiling in the range 60—80 °C. THF was purified by refluxing with lithium aluminium hydride and then distilling. Ether is diethyl ether. Solutions were dried using magnesium sulphate unless otherwise stated and solvents were removed by evaporation under reduced pressure using a rotary evaporator with bath temperature below 30 °C.

General Procedure for Preparing a Solution of 3-*Vinyl*-4-*oxa*-1-*azabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (2).—Solutions of clavulanic acid (1) (600 mg) in THF (5 ml) and *NN*-dimethylformamide dimethyl acetal (400 mg) in THF (5 ml) were added dropwise and simultaneously to THF (20 ml) which was being stirred rapidly. After the addition was complete (5 min), the mixture was stirred for a further 3 min, decolourised using charcoal, and filtered. The charcoal was washed with THF (10 ml) and the washings and filtrate were then concentrated to 10 ml under reduced pressure to give a solution of the diene (2) in THF.

If a solution of the diene in some other solvent was required then all the THF was removed from the above solution, and the residue was rapidly weighed and redissolved in the desired solvent. The diene had the following spectral properties: $\lambda_{max.}$ 277.5 nm; $\nu_{max.}$ 1 797, 1 670, and 1 640 cm^{-1}; δ 3.36 (1 H, d, *J* 17 Hz), 3.63 (1 H, dd, *J* 17 and 2 Hz), 5.22 (1 H, dd, *J* 10.5 and 1 Hz), 5.49 (1 H, dd, *J* 16 and 1 Hz), 5.80br. (2 H, s), and 6.10 (1 H, dd, *J* 16 and 10.5 Hz).

Preparation of the Diene (2) *using Triphenylphosphine and Diethyl Azodicarboxylate*.—Clavulanic acid (300 mg) and triphenylphosphine (400 mg) were dissolved in THF (5 ml) and the solution was stirred under dry nitrogen while a solution of diethyl azodicarboxylate (260 mg) in THF (2 ml) was added dropwise during 2 min. The mixture was stirred for a further 30 min and then cooled in an ice-water bath. A mixture of ether and n-pentane (1 : 2; 20 ml) was added and the mixture was filtered. The filtrate was diluted with benzene (10 ml) and was then concentrated to 5 ml. The diene (2) was detected in the solution (t.l.c.).

4,10-*Dioxa*-14-*azatetracyclo*[7.5.0.0^{2,6}.0^{11,14}]*tetradec*-8-*ene*-3,5,13-*trione* (5).—To the solution from the above experiment, maleic anhydride (150 mg) was added and the mixture was kept for 18 h. The solvent was removed and the resulting gum was chromatographed to give the *anhydride* (5) as crystals (170 mg), m.p. 148—150° C. Recrystallisation from ethyl acetate–light petroleum gave rods, m.p. 157—159 °C; $[\alpha]_D^{20}$ +404° (*c* 0.75); $\nu_{max.}$ 1 800sh, 1 785, 1 740, and 1 690 cm^{-1}; δ 2.30 (1 H, m), 2.73 (1 H, ddd, *J* 15, 7, and 1 Hz), 3.02 (1 H, d, *J* 16 Hz), 3.25—3.75 (3 H, complex m), 4.42 (1 H, m), 5.13 (1 H, m), and 5.45 (1 H, d, *J* 2 Hz) (Found: C, 56.2; H, 3.7; N, 5.9. $C_{11}H_9NO_5$ requires C, 56.2; H, 3.85; N, 5.95%).

(5R)-3-*Oxo*-6-*oxa*-2-*azatricyclo*[5.4.0.0^{2,5}]*undec*-7-*ene*-10,10,11,11-*tetracarbonitrile* (4).—The diene (2) [from (1) (250 mg)] in toluene (15 ml) was treated with tetracyanoethylene (120 mg) and the solution was kept at room temperature for 1 h. The mixture was filtered and the filtrate was concentrated to 5 ml, at which stage the product started to crystallise. When crystallisation was complete the product was filtered off, washed with a little cold toluene, and dried. Recrystallisation from ethyl acetate–light petroleum gave the *adduct* (4) as pale brown rods (225 mg), m.p. 203—204 °C; $[\alpha]_D^{22}$ +268.5° (*c* 0.875, *NN*-dimethylformamide); $\nu_{max.}$ (Nujol) 1 810, 1 795, and 1 690 cm^{-1}; δ [$(CD_3)_2SO$] 3.1—3.4 (2 H, m), 3.66 (1 H, dd, *J* 17 and 3 Hz), 3.72 (1 H, ddd, *J* 18, 4, and 2 Hz), 5.18 (1 H, dd, *J* 2 and 1 Hz), and 5.52 (2 H, m) (Found: C, 58.75; H, 2.75; N, 26.4. $C_{13}H_7N_5O_2$ requires C, 58.85; H, 2.65; N, 26.4%).

Fragmentation of Potassium 9-O-*Acetylclavulanate* (3).—A solution of benzyl 9-*O*-acetylclavulanate [7] (90 mg) in THF (10 ml) was shaken with 10% palladium–charcoal (30 mg) under hydrogen at 1 atm for 20 min. The catalyst was filtered off and washed with THF. The filtrate was concentrated to 5 ml to give a solution of 9-*O*-acetylclavulanic acid, to which a solution of potassium carbonate (20 mg) in water (1 ml) was added; the mixture was then stirred at room temperature for 2 h and at 40 °C (bath temperature) for 3 h. The diene (2) was detected in the solution (t.l.c.). Ethyl acetate (30 ml) was added, THF was evaporated off, and the aqueous layer was separated. The organic phase was dried (Na_2SO_4) and then concentrated to 3 ml. Tetracyanoethylene (40 mg) was added and the solution was kept for 16 h. The solvent was removed and the residue was chromatographed to give crystals (10 mg), recrystallisation of which (ethyl acetate–light petroleum) gave the adduct (4) as rods (8 mg), m.p. 200—202 °C.

Hydrogenation of the Diene (2).—A solution of the diene (2) [from (1) (600 mg)] in THF (30 ml) was shaken with 10% palladium–charcoal (120 mg) under hydrogen at 1 atm for 2 h. The catalyst was filtered off and washed with THF. The solvent was removed from the filtrate and the residue was chromatographed to give, in order of elution, (i) a mixture of the dihydro-derivatives (7) and (8) as an oil (140 mg); and (ii) (3S,5R)-3-*ethyl*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (6) as an oil (110 mg), $[\alpha]_D^{22}$ +234.2° (*c* 1.0); $\nu_{max.}$ 1 770 cm^{-1}; δ 0.95 (3 H, t, *J* 7 Hz), 1.65 (2 H, quin., *J* 7 Hz), 2.78 (1 H, d, *J* 16 Hz), 3.08 (1 H, dd, *J* 10 and 7 Hz), 3.21 (1 H, dd, *J* 16 and 2.5 Hz), 3.32 (1 H, dd, *J* 10 and 7 Hz), 4.20 (1 H, quin., *J* 7 Hz), and 5.10 (1 H, d, d, *J* 2.5 Hz); distillation gave a mobile oil, b.p. 90 °C (bath) at 1.0 mmHg (Found: C, 59.7; H, 7.85; N, 9.75. $C_7H_{11}NO_2$ requires C, 59.55; H, 7.85; N, 9.9%).

The dihydro-derivatives were separated by h.p.l.c. using a 25 cm × 9.4 mm column of 10μ silica gel with ethyl acetate–cyclohexane (1 : 9 v/v) as eluant at a rate if 4 ml min^{-1} and u.v. detection (270 nm). [The mixture (60 mg) was dissolved in the eluting solvent (1.2 ml) and was loaded onto the column in 100 μl portions.] (Z)-(5R)-3-*Ethylidene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (7) was thus obtained as an oil (33 mg) (R_t 10 min); $[\alpha]_D^{22}$ +185.1° (*c* 1.0); $\nu_{max.}$ 1 790 and 1 702 cm^{-1}; δ 1.60 (3 H, dt, *J* 7 and 2 Hz), 2.91 (1 H, d, *J* 16 Hz), 3.35 (1 H, dd, *J* 16 and 2 Hz), 3.45br (1 H, d, *J* 16 Hz), 4.1—4.4 (2 H, complex m), and 5.39 (1 H, d, *J* 2 Hz); *m/z* 139 (M^+, 88), 111 (7), 97 (43), 96 (15), 83 (45),

82 (18), 70 (56), 68 (46), 55 (100), and 54 (52) (Found: M^+, 139.0625. $C_7H_9NO_2$ requires M, 139.0634). (E)-(5R)-3-*Ethylidene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (8) was also obtained as an oil (8 mg) (R_t 12 min); $[\alpha]_D^{22}$ +219° (*c* 1.0); $\nu_{max.}$ 1 790 and 1 705 cm^{-1}; δ 1.46br (3 H, d, *J* 6 Hz), 2.88 (1 H, d, *J* 16 Hz), 3.30 (1 H, dd, *J* 16 and 2 Hz), 3.45br (1 H, d, *J* 15 Hz), 4.30br (1 H, d, *J* 15 Hz), 4.85 (1 H, m), and 5.32 (1 H, d, *J* 2 Hz); *m/z* 139 (M^+, 58), 111 (5), 97 (28), 96 (5), 83 (40), 82 (20), 70 (35), 68 (32), 55 (100), and 54 (36) (Found: M^+, 139.0628. $C_7H_9NO_2$ requires M, 139.0634).

Reaction of the Diene (2) *with Methanol.*—A solution of the diene (2) [from (1) (200 mg)] in a mixture of toluene (5 ml) and methanol (3 ml) was stirred at room temperature for 2 d. The solvent was removed and the residue chromatographed to give 2-hydroxy-3-methoxy-3-vinyl-4-oxa-1-azabicyclo[3.2.0]heptan-7-one (10) as a gum (45 mg); $\nu_{max.}$ 3 550, 3 300, and 1 785 cm^{-1}; δ 2.67br (1 H, OH), 2.93 (1 H, dd, *J* 17 and 1.5 Hz), 3.21 (3 H, s), 3.25 (1 H, complex dd, *J* 17 and 3.5 Hz), 5.21 (1 H, s), and 5.4—5.75 (4 H, complex m). Further elution gave 4-*methoxy*-1-(2-*oxobut*-3-*enyl*)*azetidin*-2-*one* (9) as a gum (14 mg); $\nu_{max.}$ 1 760, 1 700sh, 1 690, and 1 610 cm^{-1}; δ 2.84br (1 H, d, *J* 15 Hz), 3.13 (1 H, dd, *J* 15 and 3 Hz), 3.31 (3 H, s), 3.95 (1 H, d, *J* 18 Hz), 4.45 (1 H, d, *J* 18 Hz), 5.16 (1 H, dd, *J* 3 and 1 Hz), 5.87 (1 H, dd, *J* 7.5 and 4 Hz), and 6.30 (2 H, m); *m/z* 169 (M^+, 0.6), 118 (63), 100 (20), 85 (17), and 72 (100) (Found: M^+, 169.0724. $C_8H_{11}NO_3$ requires M, 169.0739).

Reaction of the Diene (2) *with* m-*Chloroperbenzoic Acid.*—The diene (2) [from (1) (400 mg)] in THF (8 ml) was treated with methanol (2 ml) and the mixture was stirred with ice-cooling while *m*-chloroperbenzoic acid (250 mg) was added in small portions. The mixture was then stirred for 30 min, diluted with ethyl acetate (50 ml), and washed with saturated aqueous sodium hydrogen carbonate and then with saturated brine. The organic phase was dried and the solvent was removed. Chromatography of the residue gave the alcohol (10) as a gum (55 mg), identical (i.r., n.m.r.) with the previously prepared sample.

2-*Acetoxy*-3-*methoxy*-3-*vinyl*-4-*oxa*-1-*azabicyclo*[3.2.0]-*heptan*-7-*one* (11).—The alcohol (10) (40 mg) in dry ether (3 ml) was treated with acetyl chloride (30 mg) and dry pyridine (30 mg) and the mixture was kept at room temperature with exclusion of moisture for 20 h. The mixture was diluted with ethyl acetate (30 ml), washed with water, and dried. The solvent was removed and the residue chromatographed to give the *acetate* (11) as a gum (30 mg) which crystallised from ethyl acetate–light petroleum as needles, m.p. 67.5—68 °C; $[\alpha]_D^{22}$ +34.4° (*c* 0.6); $\nu_{max.}$ 1 805 and 1 750 cm^{-1}; δ 2.00 (3 H, s), 2.99 (1 H, dd, *J* 17 and 1.5 Hz), 3.22 (3 H, s), 3.33 (1 H, dd, *J* 17 and 3 Hz), 5.3—5.7 (4 H, complex m), and 6.19 (1 H, s) (Found: C, 52.8; H, 6.0; N, 6.15. $C_{10}H_{13}NO_5$ requires C, 52.85; H, 5.75; N, 6.15%).

(2R)-3-*Acetyl*-2-*methoxycarbonylmethyl*-5-*vinyl*-4-*oxazoline* (14).—The diene (2) [from (1) (400 mg)] in THF (10 ml) was treated with acetic acid (1 ml) and the solution was kept under nitrogen for 2 d. The mixture was then treated with a slight excess of an ethereal solution of diazomethane, diluted with ethyl acetate (50 ml), washed with water, and dried. The solvent was removed and the residue was chromatographed to give the *methyl ester* (14) as a gum (85 mg), $[\alpha]_D^{22}$ +308.5° (*c* 1.0); $\lambda_{max.}$ 295 nm (ε 18 200); $\nu_{max.}$ 1 740, 1 665sh, and 1 640 cm^{-1}; δ 2.08 (3 H, s), 2.75 (1 H, dd, *J* 16 and 7 Hz), 3.05 (1 H, dd, *J* 16 and 4 Hz), 3.71 (3 H, s), 5.18 (1 H, dd, *J* 10.5 and 1 Hz), 5.46 (1 H, dd, *J* 16 and 1 Hz), 6.10 (1 H, s), 6.13 (1 H, dd, *J* 16 and 10.5 Hz), and 6.47 (1 H, dd, *J* 7 and 4 Hz); *m/z* 211 (M^+, 14), 169 (32), 138 (6), 108 (16), 96 (100), and 43 (42) (Found: M^+, 211.0829. $C_{10}H_{13}NO_4$ requires M, 211.0844).

Reaction of the Diene (2) *with Thiophenol.*—The diene (2) [from (1) (400 mg)] in THF (10 ml) was treated with thiophenol (0.25 ml) and the solution was kept under nitrogen for 4 d. The solvent was removed and the residue was chromatographed to give *E*- and *Z*-*S*-phenyl 6-oxo-8-phenylthio-4-azaoct-2-enethioate (17) as a yellow gum (290 mg); $\lambda_{max.}$ 254 (ε 6 900) and 307 nm (16 800); $\nu_{max.}$ 3 410, 3 300, 1 725, 1 620, and 1 590 cm^{-1}. The gum was dissolved in THF (5 ml), and 2,6-lutidine (110 mg) and acetyl chloride (80 mg) were added to the solution. The mixture was kept for 16 h and was then diluted with ethyl acetate (50 ml) and washed with water, dilute hydrochloric acid, dilute aqueous sodium hydrogen carbonate, and finally with saturated brine. The solution was dried, the solvent was removed, and the resulting gum was chromatographed to give S-*phenyl* (E)-4-*acetyl*-6-*oxo*-8-*phenylthio*-4-*azaoct*-2-*enethioate* (18) as a gum (220 mg); $\lambda_{max.}$ 269inf (ε 12 500) and 292 nm (23 500); $\nu_{max.}$ 1 735, 1 700, 1 675, and 1 600 cm^{-1}; δ 2.33 (3 H, s), 2.72 (2 H, t, *J* 7 Hz), 3.17 (2 H, t, *J* 7 Hz), 4.38 (2 H, s), 5.46 (1 H, d, *J* 14 Hz), 7.2—7.5 (10 H, m), and 8.00 (1 H, d, *J* 14 Hz); *m/z* 399 (M^+, 0.2), 290 (100), 248 (75), 123 (50), and 43 (25) (Found: M^+, 399.0936. $C_{21}H_{21}NO_3S_2$ requires M, 399.0952).

Reaction of the Diene (2) *with Thiophenol and Oxygen.*—A solution of the diene (2) [from (1) (400 mg)] in THF (10 ml) was stirred with ice-cooling while oxygen was bubbled through the solution. Triethylamine (30 mg) was added, followed by a solution of thiophenol (1.0 ml) in THF (10 ml), added dropwise over 1 h. After the addition was complete, stirring with passage of oxygen through the solution and ice-cooling were continued for 5 h. The solvent was then removed and the residue was chromatographed to give (*Z*)-(2*S*,5*R*)-3-(2-hydroxyethylidene)-2-phenylthio-4-oxa-1-azabicyclo[3.2.0]heptan-7-one (19) as a gum (31 mg); $[\alpha]_D^{22}$ +22.7° (*c* 1.0); $\nu_{max.}$ 3 550, 3 350, 1 790, and 1 685 cm^{-1}; δ 1.73br (1 H, s, OH), 2.93 (1 H, d, *J* 16 Hz), 3.33 (1 H, dd, *J* 16 and 3 Hz), 4.18 (2 H, d, *J* 6 Hz), 4.89 (1 H, td, *J* 6 and 1 Hz), 5.37 (1 H, d, *J* 3 Hz), 5.76 (1 H, d, *J* 1 Hz), and 7.2—7.6 (5 H, m).

(Z)-(2S,5R)-3-(2-*Acetoxyethylidene*)-2-*phenylthio*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (20).—The alcohol (19) (15 mg) in ether (2 ml) was treated with 2,6-lutidine (20 mg) and acetyl chloride (10 mg) and the mixture was kept at 4 °C for 18 h. The mixture was diluted with ethyl acetate (50 ml) and washed with water, dilute hydrochloric acid, dilute aqueous sodium hydrogen carbonate, and finally with saturated brine. The organic phase was dried and the solvent was removed. The resulting gum was chromatographed to give the *acetate* (20) as a pale yellow gum (15 mg); $\nu_{max.}$ 1 800, 1 735, and 1 700 cm^{-1}; δ 2.03 (3 H, s), 2.98 (1 H, d, *J* 16 Hz), 3.38 (1 H, dd, *J* 16 and 3 Hz), 4.65 (2 H, d, *J* 8 Hz), 4.90 (1 H, td, *J* 8 and 1 Hz), 5.39 (1 H, d, *J* 3 Hz), 5.80 (1 H, d, *J* 1 Hz), and 7.2—7.6 (5 H, m); *m/z* 305 (M^+, 2), 263 (2), 246 (12), 185 (13), 154 (56), 112 (100), and 43 (78) (Found: M^+, 305.0730. $C_{15}H_{15}NO_4S$ requires M, 305.0720).

Reaction of the Diene (2) *with Thiophenol under Free-radical Conditions.*—The diene (2) [from (1) (600 mg)] in THF (10 ml) was treated, in turn, with thiophenol (0.4 ml) and α,α′-azobisisobutyronitrile (10 mg) and the mixture was heated at 50 °C under nitrogen for 2 h. The solvent was

removed and the residue was chromatographed to give a mixture of the *E*- and *Z*-isomers (23) and (24) of (2S,5R)-3-*ethylidene*-2-*phenylthio*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* as a gum (295 mg), and (Z)-(5R)-3-(2-*phenylthioethylidene*)-4-*oxa*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (21) as a gum (143 mg). The mixture of isomers (23) and (24) had $[\alpha]_D^{23}$ +50.1° (*c* 1.0); $\nu_{max.}$ 1 795 and 1 700 cm^{-1}; δ 1.64 (3 H, d, *J* 7 Hz), 2.91 (1 H, d, *J* 17 Hz), 3.30 (1 H, dd, *J* 17 and 2.5 Hz), 4.65 (0.8 H, t, *J* 7 Hz, vinyl proton of *Z*-isomer), 4.96 (0.2 H, t, *J* 7 Hz, vinyl proton of *E*-isomer), 5.38 (1 H, d, *J* 2.5 Hz), 5.74 (1 H, s), and 7.1—7.5 (5 H, m); *m/z* 247 (M^+, 6), 110 (14), 109 (17), and 96 (100) (Found: M^+, 247.0666. $C_{13}H_{13}NO_2S$ requires *M*, 247.0666). The thioether (21) had $[\alpha]_D^{23}$ +73.2° (*c* 1.0); $\nu_{max.}$ 1 793 and 1 697 cm^{-1}; δ 2.79 (1 H, d, *J* 16 Hz), 3.30 (1 H, dd, *J* 16 and 2 Hz), 3.47 (1 H, d, *J* 16 Hz), 3.58 (2 H, d, *J* 7 Hz) 4.27 (1 H, d, *J* 16 Hz), 4.44 (1 H, t, *J* 7 Hz), 5.33 (1 H, d, *J* 2 Hz), and 7.1—7.4 (5 H, m); *m/z* 247 (M^+, 6), 219 (1), 138 (20), 110 (11), 109 (13), and 96 (100) (Found: M^+, 247.0674. $C_{13}H_{13}NO_2S$ requires *M*, 247.0666).

(Z)-(5R)-3-(2-*Phenylsulphonylethylidene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (22).—A solution of the thioether (21) (125 mg) in dry dichloromethane (15 ml) was stirred and cooled in ice while a solution of *m*-chloroperbenzoic acid (180 mg) in dichloromethane (5 ml) was added dropwise during 5 min. The mixture was then stirred and cooled in ice for a further 45 min and was then diluted with ethyl acetate (100 ml). The solution was washed with saturated aqueous sodium hydrogen carbonate and then with saturated brine. The organic phase was dried and the solvent was removed. Chromatography of the residue gave the *sulphone* (22), which crystallised from ethyl acetate–light petroleum as prisms (105 mg), m.p. 145—146 °C; $[\alpha]_D^{22}$ +114.6° (*c* 1.0); $\nu_{max.}$ 1 797, 1 700, 1 320, and 1 150 cm^{-1}; δ 2.46 (1 H, d, *J* 16 Hz), 3.23 (1 H, dd, *J* 16 and 2 Hz), 3.46 (1 H, d, *J* 15 Hz), 3.84 (2 H, d, *J* 7 Hz), 4.28 (1 H, d, *J* 15 Hz), 4.43 (1 H, t, *J* 7 Hz), 5.18 (1 H, d, *J* 2 Hz), 7.35—7.65 (3 H, m), and 7.85 (2 H, dd, *J* 7 and 2 Hz) (Found: C, 55.85; H, 4.85; N, 4.9; S, 11.15. $C_{13}H_{13}NO_4S$ requires C, 55.9; H, 4.7; N, 5.0; S, 11.5%).

Diethyl (1S,5R)-3-*Oxo*-6-*oxa*-2,10,11-*triazatricyclo*[5.4.0.0^{2,5}]*undec*-7-*ene*-10,11-*dicarboxylate* (27).—The diene (2) [from (1) (600 mg)] in toluene (20 ml) was treated with diethyl azodicarboxylate (0.5 g) and the solution was kept at room temperature for 1 h. The solvent was removed and the residue was chromatographed to give the *adduct* (27) as a gum (530 mg) which crystallised from ethyl acetate–light petroleum as prisms (390 mg), m.p. 97—98 °C; $[\alpha]_D^{24}$ +251.9° (*c* 1.0); $\nu_{max.}$ 1 805 and 1 720 br cm^{-1}; *m/z* 311 (M^+, 14), 170 (100), 142 (22), 97 (50), 96 (42), and 95 (48) (Found: C, 49.85; H, 5.6; N, 13.45%; M^+, 311.1123. $C_{13}H_{17}N_3O_6$ requires C, 50.15; H, 5.5; N, 13.5; *M*, 311.1118); the peaks in the n.m.r. spectrum were very broad, suggesting that compound (27) is present in solution as slowly interconverting conformers.

(1S,5R)-6,10,11-*Trioxa*-2-*azatricyclo*[5.4.0.0^{2,5}]*undec*-7-*en*-3-*one* (28).—The diene (2) [from (1) (600 mg)] in dry dichloromethane (30 ml) containing Methylene Blue (10 mg) was irradiated with white light (800 W tungsten–halogen lamp) while oxygen was bubbled through the solution and the temperature was maintained at 10—20 °C by external cooling. After 1 h, the mixture was filtered, the filtrate was evaporated to dryness, and the resulting gum was chromatographed. The *adduct* (28) was thus obtained as rods (13 mg), m.p. 115—117 °C (ether–pentane); $[\alpha]_D^{22}$ +378.5° (*c* 1.0); $\nu_{max.}$ 1 805 and 1 705 cm^{-1}; δ 3.08 (1 H, dd' *J* 17 and 1 Hz), 3.37 (1 H, dd, *J* 17 and 3 Hz), 4.46 (1 H, dt, *J* 15 and 2 Hz), 4.83 (1 H, dt, *J* 15 and 2 Hz), 5.32 (2 H, m), and 5.72 (1 H, m) (Found: C, 49.95; H, 4.3; N, 8.05. $C_7H_7NO_4$ requires C, 49.7; H, 4.2; N, 8.3%).

(1S,5R)- and (1R,5R)-10-*Phenyl*-6,11-*dioxa*-2,10-*diazatricyclo*[5.4.0.0^{2,5}]*undec*-7-*en*-3-*one* (29) *and* (30).—The diene (2) [from (1) (600 mg)] in toluene (15 ml) was treated with nitrosobenzene (270 mg) and the mixture was kept at room temperature for 3 h. The solvent was removed and the resulting gum was chromatographed to give the two isomeric adducts (29) and (30). The *less polar isomer* (62 mg) was obtained as needles (ethyl acetate–light petroleum), m.p. 184—186 °C; $[\alpha]_D^{22}$ +367.7° (*c* 1.0); $\nu_{max.}$ 1 800 and 1 710 cm^{-1}; δ 3.05 (1 H, d, *J* 17 Hz), 3.36 (1 H, dd, *J* 17 and 3 Hz), 3.64br (1 H, d, *J* 15 Hz), 4.13br (1 H, d, *J* 15 Hz), 5.35br (2 H, s), 5.72br (1 H, s), and 6.8—7.4 (5 H, m); *m/z* 244 (M^+, 2), 147 (11), 136 (8), 107 (100), 95 (12), and 77 (31) (Found: C, 63.7; H, 5.1; N, 11.4%; M^+, 244.0844. $C_{13}H_{12}N_2O_3$ requires C, 63.95; H, 4.95; N, 11.45%; *M*, 244.0848). The *more polar isomer* (30 mg) was obtained as prisms (ethyl acetate–light petroleum), m.p. 127—128 °C; $[\alpha]_D^{22}$ +279.4° (*c* 1.0); $\nu_{max.}$ 1 800 and 1 710 cm^{-1}; δ 3.01 (1 H, d, *J* 16 Hz), 3.43 (1 H, dd, *J* 16 and 3 Hz), 3.64 (1 H, dt, *J* 15 and 2.5 Hz), 4.05 (1 H, ddd, *J* 15, 4, and 2 Hz), 5.10 (1 H, m), 5.41br (1 H, s), 5.52 (1 H, d, *J* 3 Hz), and 6.9—7.4 (5 H, m); *m/z* 244 (M^+, 0.4), 147 (14), 136 (8), 107 (100), 95 (13), and 77 (38) (Found: C, 64.0; H, 5.2; N, 11.5%; M^+, 244.0856. $C_{13}H_{12}N_2O_3$ requires C, 63.95; H, 4.95; N, 11.45%; *M*, 244.0848).

Reaction of the Diene (2) *with* p-*Nitrobenzyl Glyoxylate*.—The diene (2) [from (1) (1.1 g)] in benzene (20 ml) was treated with *p*-nitrobenzyl glyoxylate monohydrate (1.3 g) and the mixture was refluxed for 2 h with azeotropic removal of water. The mixture was cooled, diluted with ethyl acetate (100 ml), and washed with water and then with saturated brine. The organic phase was dried and the solvent was removed. Chromatography of the resulting gum gave p-*nitrobenzyl*-2-*acryloyl*-7-*oxo*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptan*-3-*carboxylate* (32) as a gum (70 mg); $[\alpha]_D^{20}$ +9.6° (*c* 1.0); $\nu_{max.}$ 1 795, 1 750, 1 700, and 1 670 cm^{-1}; δ 3.18 (1 H, d, *J* 16 Hz), 3.41 (1 H, dd, *J* 16 and 2 Hz), 5.01 (1 H, d, *J* 3 Hz), 5.30 (3 H, s), 5.48br (1 H, s), 6.00 (1 H, dd, *J* 8 and 4 Hz), 6.53 (1 H, d, *J* 4 Hz), 6.56 (1 H, d, *J* 8 Hz), 7.53 (2 H, d, *J* 8 Hz), and 8.24 (2 H, d, *J* 8 Hz); INDOR experiments showed that the proton at δ 5.01 was coupled to one of the protons at δ 5.30 and that the proton at δ 6.00 was coupled to the protons at δ 6.53 and 6.56; *m/z* 346 (M^+, 2), 318 (6), 305 (7), 291 (40), 210 (8), 154 (27), 136 (85), and 55 (100) (Found: M^+, 346.0814. $C_{16}H_{14}N_2O_7$ requires *M*, 346.0800) and p-*nitrobenzyl* (5R)-7-*oxo*-2-(3-*oxo*-6-*oxa*-2-*azatricyclo*[5.4.0.0^{2,5}]*undec*-7-*en*-10-*ylcarbonyl*)-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-3-*carboxylate* (33) as a gum (70 mg); $[\alpha]_D^{20}$ +96.7° (*c* 1.0); $\nu_{max.}$ 1 790, 1 750sh, 1 720, and 1 700sh cm^{-1}; δ 1.56 (1 H, ddd, *J* 17, 11, and 6 Hz), 1.95—2.50 (4 H, complex m), 2.95 (1 H, d, *J* 17 Hz), 3.10—3.55 (4 H, complex m), 4.0—4.3 (1 H, m), 4.85 (1 H, t, *J* 4 Hz), 5.10—5.30 (2 H, m), 5.28 (2 H, s), 5.47br (1 H, s), 7.52 (2 H, d, *J* 8 Hz), and 8.23 (2 H, d, *J* 8 Hz); *m/z* 483 (M^+, 7), 441 (38), 261 (46), 192 (31), 164 (40), and 136 (100) (Found: M^+, 483.1298. $C_{23}H_{21}N_3O_9$ requires *M*, 483.1276).

(1S,5R,10S)-3-*Oxo*-6-*oxa*-2-*azatricyclo*[5.4.0.0^{2,5}]*undec*-7-*ene*-10-*carbaldehyde* (34).—The diene (2) (340 mg) and hydroquinone (100 mg) were dissolved in acrylaldehyde (15 ml) and the solution was stirred at 50 °C (bath) under dry

nitrogen for 3.5 h. The acrylaldehyde was removed under reduced pressure and the residue was chromatographed to give the *aldehyde* (34) as crystals (97 mg). Recrystallisation from ethyl acetate–light petroleum gave prisms, m.p. 94—95 °C; $[\alpha]_D^{22}$ +337.5° (*c* 1.0); $\nu_{max.}$ 2 800, 1 785, 1 720, and 1 700 cm^{-1}; δ 1.39 (1 H, q, *J* 12 Hz), 2.2—2.8 (4 H, complex m), 2.95 (1 H, d, *J* 16 Hz), 3.32 (1 H, dd, *J* 16 and 2.5 Hz), 4.18 (1 H, ddd, *J* 12, 4, and 2 Hz), 5.15 (2 H, m), and 9.60 (1 H, s); *m/z* 193 (M^+, 0.5), 151 (0.5), 122 (2), 120 (1), 119 (12), 99 (27), 95 (55), 67 (42), and 55 (100) (Found: C, 61.9; H, 5.9; N, 7.0%; M^+, 193.0743. $C_{10}H_{11}NO_3$ requires C, 62.15; H, 5.75; N, 7.25%; *M*, 193.0739).

Benzyl (1S,5R,10S)-3-*Oxo*-6-*oxa*-2-*azatricyclo*[5.4.0.$0^{2,5}$]-*undec*-7-*ene*-10-*carboxylate* (37).—The aldehyde (34) (90 mg) and sodium hydrogen carbonate (40 mg) were dissolved in a mixture of THF (6 ml) and water (3 ml). 5% Platinum–charcoal (90 mg) was added to the solution which was then stirred while oxygen was bubbled through it at 50 °C for 2 h and then at 23 °C for 16 h. The catalyst was filtered off and washed with water. The THF was evaporated off from the combined washings and filtrate. The aqueous residue was washed once with ether and freeze-dried to give the sodium salt as a pale brown amorphous powder (75 mg); $\nu_{max.}$ (KBr) 1 772, 1 695, 1 560, and 1 400 cm^{-1}.

The sodium salt (20 mg) was dissolved in dry hexamethylphosphoramide (3 ml) and benzyl bromide (30 mg) was added to the solution. The mixture was kept at room temperature for 18 h and then diluted with ethyl acetate (50 ml) and washed three times with water (20 ml portions). The solution was dried, the solvent was evaporated off, and the residue was chromatographed to give the *benzyl ester* (37) as a pale yellow gum (9 mg); $[\alpha]_D^{22}$ +237° (*c* 0.9); $\nu_{max.}$ 1 780, 1 730, and 1 710sh cm^{-1}; δ 1.56 (1 H, q, *J* 11.5 Hz), 2.1—3.0 (5 H, complex m), 3.24 (1 H, dd, *J* 15 and 2 Hz), 4.09 (1 H, ddd, *J* 11.5, 5, and 2 Hz), 5.08 (4 H, s, with overlapping m), and 7.27 (5 H, s); *m/z* 299 (M^+, 0.1), 271 (10), 257(8), 208 (9), 166 (9), 139 (8), and 91 (100) (Found: M^+, 299.1156. $C_{17}H_{17}NO_4$ requires *M*, 299.1157).

Reaction of the Diene (2) *with Benzyl Acrylate*.—The diene (2) [from (1) (600 mg)] and hydroquinone (50 mg) were dissolved in benzyl acrylate (7 ml) and the solution was heated at 80 °C (bath) for 1.5 h. Most of the benzyl acrylate was removed at 100 °C and 0.5 mmHg and the residue was chromatographed to give *benzyl* (1S,5R,11S)-3-*oxo*-6-*oxa*-2-*azatricyclo*[5.4.0.$0^{2,5}$]*undec*-7-*ene*-11-*carboxylate* (35) as prisms (20 mg), m.p. 79—80 °C (ethyl acetate–light petroleum); $[\alpha]_D^{22}$ +217.4° (*c* 1.0); $\nu_{max.}$ 1 785, 1 730, and 1 710 cm^{-1}; δ 1.70—2.40 (4 H, complex m), 2.86 (1 H, d, *J* 16 Hz), 3.1—3.35 (2 H, complex m), 4.24br (1 H, dd, *J* 4.5 and 2 Hz), 5.00 (1 H, m), 5.07 (2 H, s), 5.20 (1 H, d, *J* 2 Hz), and 7.27 (5 H, s) (Found: C, 68.2· H, 5.65; N, 4.55. $C_{17}H_{17}NO_4$ requires C, 68.2; H, 5.7; N, 4.7%); further elution gave the benzyl ester (37) (80 mg); $[\alpha]_D^{22}$ +239.1° (*c* 1.0), and with spectral properties as described above, and *benzyl* (1S,5R,10R)-3-*oxo*-6-*oxa*-2-*azatricyclo*[5.4.0.$0^{2,5}$]*undec*-7-*ene*-10-*carboxylate* (39) as a gum (55 mg); $[\alpha]_D^{22}$ +172.2° (*c* 1.0); $\nu_{max.}$ 1 785, 1 725, and 1 705 cm^{-1}; δ 1.55 (1 H, td, *J* 11.5 and 6 Hz), 2.0—3.0 (5 H, complex m), 3.23 (1 H, dd, *J* 16 and 2 Hz), 4.08 (1 H, ddd, *J* 11.5, 5, and 2 Hz), 5.10 (4 H, s, with overlapping m), and 7.28 (5 H, s); *m/z* 299 (M^+, 0.2), 271 (18), 257 (8), 208 (14), 166 (12), 139 (10), and 91 (100) (Found: M^+, 299.1161. $C_{17}H_{17}NO_4$ requires *M*, 299.1157).

Reaction of the Diene (2) *with Methyl Acrylate*.—The diene (2) [from (1) (1.1 g)] and hydroquinone (20 mg) were dissolved in methyl acrylate (20 ml) and the mixture was heated at 80 °C (bath) for 3.5 h. The mixture was cooled and the methyl acrylate was evaporated off. The resulting oil was chromatographed to give three compounds: *methyl* (1S,5R,11S)-3-*oxo*-6-*oxa*-2-*azatricyclo*[5.4.0.$0^{2,5}$]*undec*-7-*ene*-11-*carboxylate* (36) as rods (27 mg), m.p. 103—104 °C (ether–light petroleum); $[\alpha]_D^{20}$ +279.0° (*c* 0.9); $\nu_{max.}$ 1 790, 1 735, and 1 710 cm^{-1}; δ 1.70—2.40 (4 H, complex m); 2.92 (1 H, d, *J* 16 Hz), 3.20 (1 H, m), 3.30 (1 H, dd, *J* 16 and 3 Hz), 3.67 (3 H, s), 4.28 (1 H, m; decoupling at δ 2.10 converted this into a dd, *J* 5 and 2.5 Hz), 5.06 (1 H, m; decoupling at δ 2.10 converted this into a d, *J* 2.5 Hz), and 5.40 (1 H, d, *J* 3 Hz) (Found: C, 59.35; H, 5.95; N, 6.25. $C_{11}H_{13}NO_4$ requires C, 59.2; H, 5.85; N, 6.25%), *methyl* (2S,5R,10S)-3-*oxo*-6-*oxa*-2-*azatricyclo*[5.4.0.$0^{2,5}$]*undec*-7-*ene*-10-*carboxylate* (38) as needles (120 mg), m.p. 83—83.5 °C (ether–light petroleum); $[\alpha]_D^{20}$ +298.8° (*c* 1.0); $\nu_{max.}$ 1 792, 1 735, and 1 710 cm^{-1}; δ 1.57 (1 H, q, *J* 12 Hz), 2.25—2.85 (4 H, complex m), 2.96 (1 H, d, *J* 16 Hz), 3.31 (1 H, dd, *J* 16 and 3 Hz), 3.69 (3 H, s), 4.14 (1 H, ddd, *J* 12, 4.5, and 2 Hz), and 5.18 (2 H, m) (Found: C, 58.95; H, 5.75; N, 6.25. $C_{11}H_{13}NO_4$ requires C, 59.2; H, 5.85; N, 6.25), and *methyl* (1S,5R,10R)-3-*oxo*-6-*oxa*-2-*azatricyclo*[5.4.0.$0^{2,5}$]*undec*-7-*ene*-10-*carboxylate* (40) as a gum (85 mg); $[\alpha]_D^{20}$ +234.5° (*c* 1.0); $\nu_{max.}$ 1 790, 1 735, and 1 710 cm^{-1}; δ 1.57 (1 H, td, *J* 11 and 6 Hz), 2.10—3.05 (5 H, complex m), 3.28 (1 H, dd, *J* 17 and 3 Hz), 3.70 (3 H, s), 4.10 (1 H, ddd, *J* 11, 5, and 2 Hz), and 5.18 (2 H, m); *m/z* 223 (M^+, 6), 195 (22), 192 (17), 182 (14), 167 (8), 164 (10), 154 (3), 122 (37), 121 (95), 95 (52), 94 (20), and 55 (100) (Found: M^+, 223.0849. $C_{11}H_{13}NO_4$ requires *M*, 223.0844).

Methyl (1S)-5-*Oxo*-4-[(2R)-4-*oxoazetidin*-2-*yloxy*]*cyclohex*-3-*enecarboxylate* (41).—Selenium dioxide (40 mg) was suspended in dichloromethane (4 ml) and t-butyl hydroperoxide (0.2 ml) was added to the mixture which was then stirred for 0.5 h. The methyl ester (38) (80 mg) was added and the mixture was refluxed for 1.5 h, cooled, diluted with ethyl acetate (50 ml), and washed with saturated aqueous sodium hydrogen carbonate and then with saturated brine. The organic phase was dried and evaporated to dryness and the residue was chromatographed to give the oxidation product as a pale yellow gum (8 mg). This was purified further by h.p.l.c. on a 25 cm × 4.6 mm column of 10μ silica gel with propan-2-ol–1,2-dichloroethane (1 : 24 v/v) as eluant at a flow rate of 3 ml/min^{-1}, and u.v. detection at 254 nm. The *γ-keto-ester* (41) was thus obtained as a gum (4 mg) (R_t 2.8 min); $[\alpha]_D^{20}$ +33.0° (*c* 0.2); $\lambda_{max.}$ 254 nm (ε 8 400); $\nu_{max.}$ 3 420, 3 250, 1 780, 1 730, 1 690, and 1 630 cm^{-1}; δ (250 MHz) 2.74 (4 H, m with peaks at δ 2.72, 2.74, 2.745, 2.77, and 2.80), 2.995 (1 H, d, *J* 15 Hz), 3.105 (1 H, pentet, *J* 7 Hz), 3.22 (1 H, ddd, *J* 15, 3, and 1.5 Hz), 3.73 (3 H, s), 5.335 (1 H, d, *J* 3 Hz), 6.11 (1 H, t, *J* 4.5 Hz), and 6.57br (1 H, NH) [double-resonance experiments showed that the proton at δ 3.22 is coupled to those at δ 5.335 and 6.57; decoupling the proton at δ 6.11 converted the multiplet at δ 2.74 into two doublets: δ 2.73 (2 H, d, *J* 7 Hz), and 2.78 (2 H, d, *J* 7 Hz)]; *m/z* 239 (M^+, 1), 170 (10), 111 (48), and 70 (100) (Found: M^+, 239.0800. $C_{11}H_{13}NO_5$ requires *M*, 239.0792).

Methyl (1R)-5-*Oxo*-4-[(2R)-4-*oxoazetidin*-2-*yloxy*]*cyclohex*-3-*enecarboxylate* (42).—The ester (40) (45 mg) was oxidised and the product was purified using exactly the same process as described in the previous experiment. The *γ-keto-ester* (42) was obtained as a gum (5 mg) (R_t 2.8 min); $[\alpha]_D^{20}$ −29.6° (*c* 0.5); $\lambda_{max.}$ 254 nm (ε 9 050); $\nu_{max.}$ 3 420, 3 250,

1 780, 1 730, 1 690, and 1 630 cm^{-1}; δ (250 MHz) 2.75 (4 H, m with peaks at δ 2.715, 2,745, 2.76, 2.77, and 2.795), 3.00 (1 H, d, *J* 15 Hz), 3.10 (1 H, pentet, *J* 7 Hz), 3.23br (1 H, d, *J* 15 Hz), 3.73 (3 H, s), 5.385 (1 H, dd, *J* 3 and 1 Hz), 6.12 (1 H, t, *J* 4.5 Hz), and 6.59br (1 H, NH) [double-resonance experiments showed that the proton at δ 5.385 is coupled to those at δ 3.00 and 3.23, and the proton at δ 6.59 is coupled to that at δ 3.23; decoupling the proton at δ 6.12 converted the multiplet at δ 2.75 into two doublets: δ 2.725 (2 H, d, *J* 7 Hz), and 2.78 (2 H, d, *J* 7 Hz)]; *m/z* (ammonia chemical ionisation) 257 ($[M + NH_4]^+$, 10), 240 ($[M + H]^+$, 100), 188 (67), 171 (16), 170 (21), and 70 (55).

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