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γ-LACTAM ANALOGUES OF PENICILLANIC AND CARBAPENICILLANIC ACIDS

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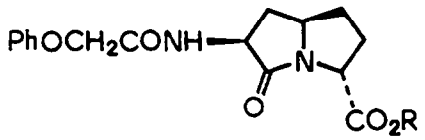
Abstract - Synthesis and biological activity of γ-lactam analogues of penicillanic and carboapenicillanic acids, and the sodium periodate mediated rearrangement of pyrrolidine-2,3-diones are described. 1,3-Dipolar addition of cyclic nitrone (6) and methyl acrylate afforded the bicyclic adducts (7a) and (7b). Reductive cleavage of the N-O bond and subsequent cyclisation of a regioisomer (11a) gave the γ-lactams (12a) and (12b) in a ratio of 85 : 15. They are transformed to the carbapenam analogues (1)-(4). Their stereochemistry was assigned according to the X-ray structure of the γ-lactam (12b). Benzyl 6-oxopenicillanate (20) was directly transformed to the γ-lactam analogue (5) via a novel ring expansion. These synthetic analogues did not show antibiotic activity or β-lactamase inhibition. Treatment of pyrrolidine-2,3-diones (25a) and (25b) with sodium periodate gave ring contracted β-lactams (26a) and (26b) respectively. Similar treatment of (27) followed by diazomethane afforded an unexpected spiro epoxide.

Synthesis of γ-Lactam Analogues. It has been well established that β-lactam antibiotics exhibit their biological activity by acylating several specific proteins, the penicillin binding proteins, to inhibit the cross-linking of the bacterial cell wall.[1] According to the hypothesis of Tipper and Strominger such activity is attributed to the structural similarity between penicillin and the D-alanyl-D-alanine terminus of the peptidoglycan strands.[2] However, the minimum structural features believed to be essential for antimicrobial activity have undergone considerable revision since the discovery of the nontraditional β-lactam antibiotics such as thienamycin,[3] clavulanic acid,[4] nocardicin,[5] and more recently, the monobactams.[6] It now appears that the minimum structural requirement for biological activity is a suitably activated β-lactam ring. There has been no systematic study on the effect of substituting the β-lactam ring with γ-lactam. In order to explore the possibility that biologically active compounds devoid of β-lactam moiety could be obtained via synthesis, we now prepared the fused γ-lactams (1)-(5).[7] Although the synthesis of γ-lactams analogues of penicillin was reported[8] in 1949, the present work is the first synthesis of stereochemically well-defined γ-lactams related to penicillins.



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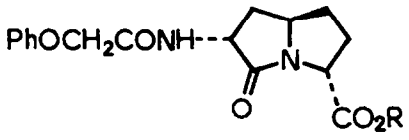

(2a) R = Me
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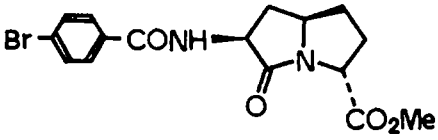

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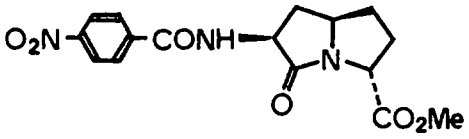

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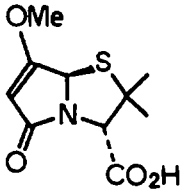
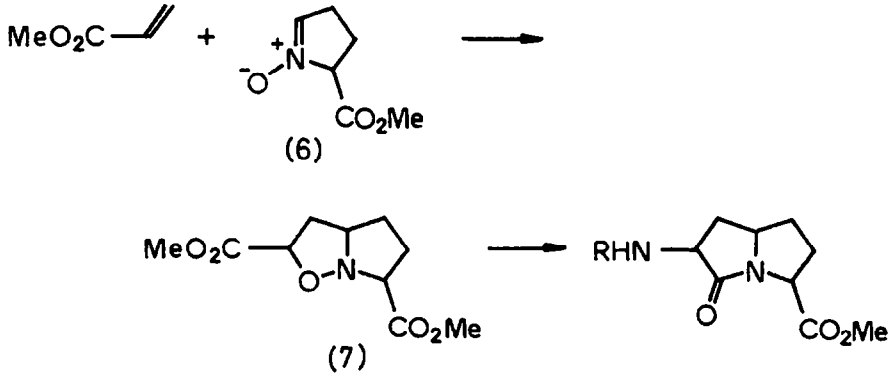


(5)

As cyclic nitrone (6) was recognised in the partial structure of carbapenicillanic acid, 1,3-dipolar addition of methyl acrylate and (6) was considered to provide an efficient methodology for the construction of fused γ-lactam system, as shown in Scheme 1.[9] Correct regiochemistry of the cycloaddition is essential and the resulting key adduct (7) could be transformed to γ-lactam via reductive ring-opening and subsequent cyclisation.



Scheme 1

The starting nitrone (6) was synthesised as follows. Methyl nitroacetate[10] was reacted with acrolein in the presence of sodium methoxide to give the Michael adduct (8), which was directly converted to the corresponding acetals [(9a), 14.4% and (9b), 44% yields]. Reduction of nitro group of (9a) and (9b) was effected with aluminium amalgam in wet ether under neutral conditions and the hydroxylamines (10a) and (10b) were obtained in 95% and 60% yields respectively. Although (10a) gave the nitrone (6) only in a low yield presumably due to the drastic condition required for the deprotection of the ethylene acetal, the dimethyl acetal (10b) was smoothly deprotected with 1N HCl at room temperature to afford the nitrone (6) quantitatively.

The nitrone (6) was then allowed to react with methyl acrylate in dichloromethane at 25°C. An inseparable mixture of isomers of 2-oxa-1-azabicyclo[3.3.0]octane, (7a) and (7b), was obtained. The mixture was directly subjected to the reduction with Raney nickel, affording a mixture of amino-alcohols (11a) and (11b). Refluxing this misture in methanol effected cyclisation of a regioisomer (11a) and the desired γ-lactam (12) was obtained in 14% overall yield based on the nitrone (6). It was shown by ^{1}H n.m.r. spectroscopy that this was a mixture of 7α- and 7β- isomers (12a) and (12b), respectively, in a ratio of 85 : 15. The isomeric alcohols could be separated by careful chromatography, and the structure of the minor isomer (12b), including the stereochemistry, was unequivocally established by X-ray crystallography to be (2R*, 5R*, 7S*)-7-hydroxy-8-oxo-1-azabicyclo[3.3.0]octane-2-carboxylate (Figure 1). Oxidation of the mixture of the alcohols gave a single ketone (22), as will be described later, showing that the alcohols were epimeric at C(7) and the stereochemistry of the major isomer (12a) was assigned to be (2R*, 5R*, 7R*).

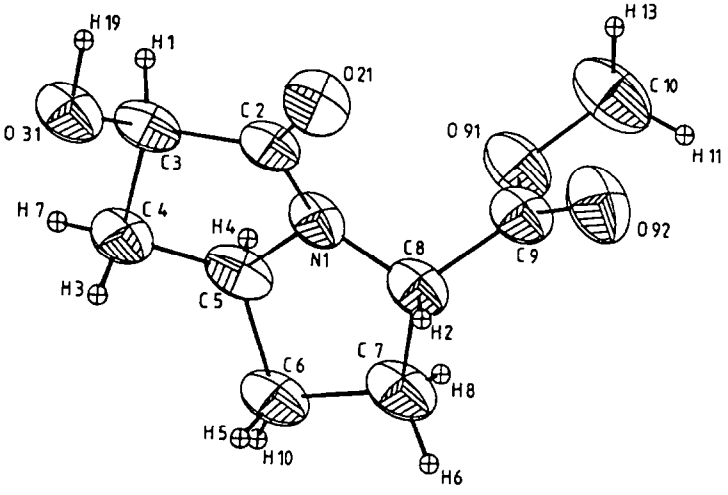
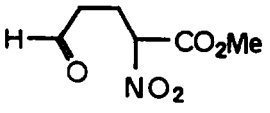


Figure 1. Molecular structure of the compound (12b).

Although both isomers of γ-lactam were successfully separated, determination of the regio-selectivity of the cycloaddition was precluded by the very complex n.m.r. of the inseparable adducts (7a) and (7b). On the other hand, when diethyl methylenemalonate (13)[11] was used in the cycloaddition with the nitrone (6), the two regioisomer formed (14a) and (14b), were separated and readily distinguished by their n.m.r. spectra. Surprisingly, the 4,4-disubstituted product (14b) was the major product of this reaction [(14a) : (14b) = 1 : 2.25]. This regiochemistry could be explained by the ionic mechanism involving the attack of the nitrone oxygen on the double bond of the methylenemalonate. Similar regioselectivity was found in the cycloaddition of diethyl methylenemalonate (13) and N-benzylidenemethylamine N-oxide (15).[12] The 5,5- and 4,4-disubstituted isomers (16a) and (16b) were formed in a 1 : 3 ratio.

The γ-lactams (12a) and (12b) were converted to the carbapenam analogues as follows. For the introduction of nitrogen functional group on the lactam ring the epimeric mixture of (12a) and (12b) was treated with toluene-p-sulphonyl chloride in pyridine to give the readily separable toluene-p-sulphonates (17a) and (17b) in 62% and 13% yields respectively. Displacement of the 7α-isomer (17a) with azide ion (NaN_3, dimethylformamide, 25°C) cleanly inverted the stereochemistry at C(7), affording a single azide (18b) in 86% yield. In a similar fashion 7β-toluene-p-sulphonate (17b) gave the α-azide (18a) with Walden inversion at 86% yield. The azide (18b) was hydrogenated with 10% palladium on charcoal to the crude amine (19b) which was directly acylated with phenoxy-acetyl chloride in pyridine affording the amine (1a) in 81% yield from (18b). Likewise 7α-phenoxyacetamide (2a) was obtained in 80% overall yield from (18a). Deprotection of the methyl esters (1a) and (2a) was achieved by saponification (K_2CO_3, MeOH, H_2O) to give the potassium salts



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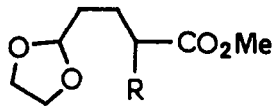
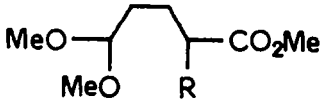


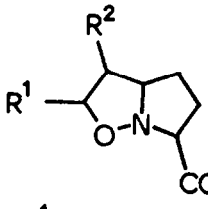
(9a) R = NO_2

(10a) R = NHOH



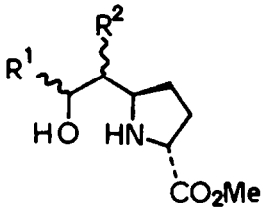
(9b) R = NO_2

(10b) R = NHOH



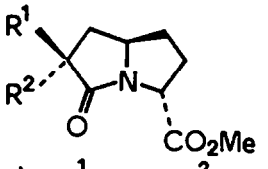
(7a) R^1 = CO_2Me, R^2 = H

(7b) R^1 = H, R^2 = CO_2Me



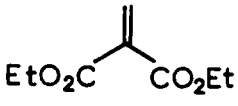
(11a) R^1 = CO_2Me, R^2 = H

(11b) R^1 = H, R^2 = CO_2Me



(12a) R^1 = H, R^2 = OH

(12b) R^1 = OH, R^2 = H



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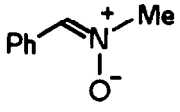

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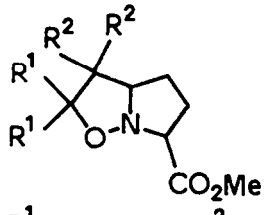
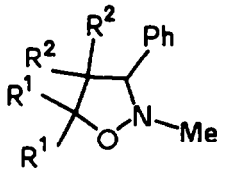


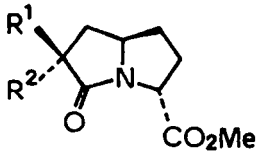
(14a) R^1 = CO_2Et, R^2 = H

(14b) R^1 = H, R^2 = CO_2Et



(16a) R^1 = CO_2Et, R^2 = H

(16b) R^1 = H, R^2 = CO_2Et



(17a) R^1 = H, R^2 = p-$MeC_6H_4SO_3$

(17b) R^1 = p-$MeC_6H_4SO_3$, R^2 = H

(18a) R^1 = H, R^2 = N_3

(18b) R^1 = N_3, R^2 = H

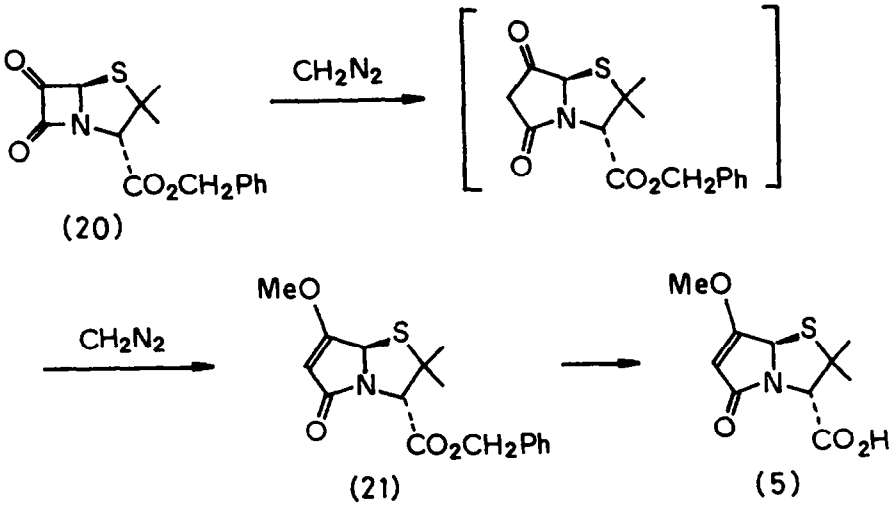
(19a) R^1 = H, R^2 = NH_2

(19b) R^1 = NH_2, R^2 = H

(1b) and (2b) in 73% and 92% yields, respectively. 7β-(4-Bromobenzamido)- and 7β-(4-nitrobenzamido)-derivatives (3) and (4) were similarly prepared in 67% and 54% yields.

Synthesis of the penicillanic acid analogue (5) was straightforward beased on a completely different approach. The γ-lactam (5) was obtained via a novel ring expansion involving a C(6)-C(7) rearrangement of the β-lactam nucleus.[13] Thus, benzyl 6-oxopenicillanate (20)[14] was treated with an excess of diazomethane in ether to give the ring expanded product (21) in 50% overall yield after chromatography (Scheme 2). It should be noted that spiro epoxide, an anticipated side-

product, was not obtained in this reaction. Sponification of the benzyl ester followed by acidification and crystallisation gave the free acid (5) in 52% yield.



Scheme 2

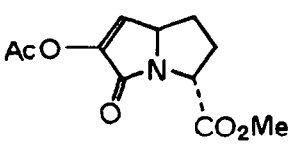
γ-Lactam analogues (1b), (2b) and (5) thus obtained were tested for antibiotic activity (Bacillus subtilis ATCC 6633 and Escherichia coli supersensitive strain No. 21/30) and β-lactamase inhibition (Bacillus cereus β-lactamase II and Klebsiella aerogenes BRL 1003) and were shown to be inactive.

Periodate-Mediated Rearrangement of Pyrrolidine-2,3-diones. The present 1,3-dipolar addition strategy furnished highly functionalised γ-lactams with well-defined stereochemistry. It was considered that the γ-lactam approach could be extended to β-lactam chemistry by means of ring contraction. Particularly interesting is the periodate-induced rearrangement of pyrrolidine-2,3-diones to β-lactams reported by Rapoport and his co-workers.[15] Considering that this reaction affords a trans β-lactam possessing a carboxyl group at C(3), a potential precursor for thienamycin synthesis, we now examined the further possibilities of this reaction.

For the preparation of bicyclic pyrrolidine-2,3-dione system oxidation of the hydroxylactams (12a) and (12b) was first examined. Whereas oxidation of (12) with dimethylsulphoxide and acetic anhydride[16] gave the enol acetate (23) in 76% yield, attempted deacetylation of (23) under basic conditions gave polymeric material. On the other hand Moffatt condition with 0.5 equivalent of dichloroacetic acid[17] resulted in the formation of the desired pyrrolidine-2,3-dione derivative (22) as a single product in 50-60% yield. [This result confirmed the stereochemistry at C(7) of (12a) and (12b), as described.] However, treatment of (22) with sodium periodate under the condition reported[15] gave a complex mixture.

Accordingly, the rearrangement of monocyclic system was next investigated. Thus, the pyrrolidine-2,3-diones (25a) and (25b) were prepared by the decarboxylation of the corresponding esters (24a) and (24b), which were synthesised by a modification of the procedure of Southwick et al.[18] They were treated with sodium periodate under the standard condition (pH 6.7 at 25°C) followed by Diazomethane, the expected β-lactams (26a) and (26b) were obtained in about 30% yields.

Thus, it was thought that γ-lactam such as (27) could be converted to carbapenem nucleus via periodate ring contraction and subsequent formation of the fused five membered ring system. To this end, δ-lactone (28) was synthesised from allylamine, 5,6-dihydro-2H-pyran-2-one (29)[19] and dimethyl oxalate in 22% yield. N,N'-Diallyloxamide was the major side product of this reaction. The compound (28) was found to exist mainly in its enol form and the enol ether (30) was formed upon treatment with excess diazomethane. Hydrolysis and decarboxylation of the lactone (28) proceeded smoothly in 1N HCl at 90-95°C, affording (27) which was subjected to the ring contraction



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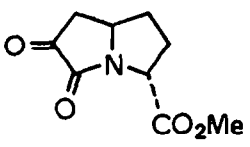

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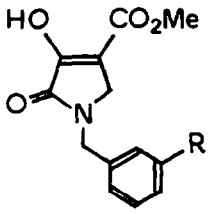

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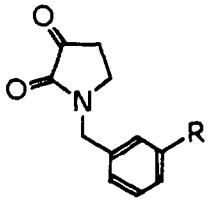
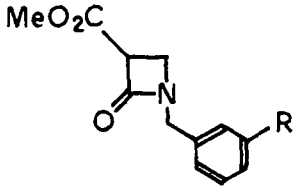
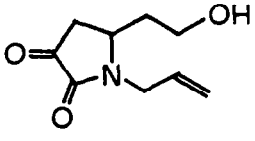
(24b) R = OMe



(25a) R = H
(25b) R = OMe



(26a) R = H
(26b) R = OMe



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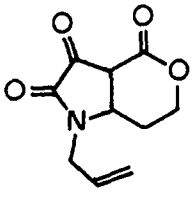

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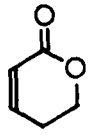

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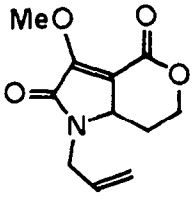

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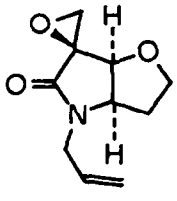
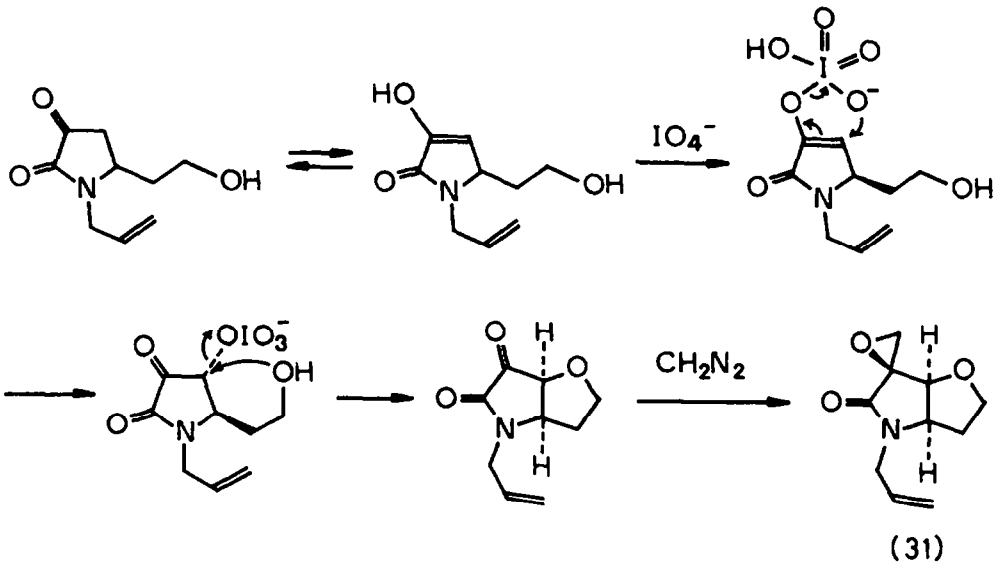


(31)

condition without further purification. The crude (27) was treated with sodium periodate at pH 6.8 and the reaction gave a multitude of products. The major product was found to be propionic acid and another substance isolated after treatment with diazomethane. The compound was assigned to the structure (31) by means of its spectral properties (i.r., ^{1}H n.m.r. and high resolution mass spectra). The presence of a spiro epoxide was proven by its ^{13}C n.m.r. spectrum. A possible mechanism of this reaction is shown in Scheme 3.



(31)

Scheme 3

EXPERIMENTAL

Melting points were taken on a Kofler hot stage or a Buchi 510 apparatus and are uncorrected. Microanalyses were performed by Dr. F. B. Strauss at this laboratory. Infrared spectra were recorded on a Perkin-Elmer Model 257 or 681 spectrometer. 90 MHz n.m.r. spectra were taken on a Hitachi Perkin-Elmer R32 spectrometer. A Bruker WH 300 n.m.r. spectrometer was employed for ^1H spectra at 300 MHz and ^{13}C spectra at 75.5 MHz. Low resolution mass spectra were obtained at 70eV on a VG Micromass ZAB-16F spectrometer. Field desorption, field ionisation and chemical ionisation mass spectra were recorded on a VG Micromass ZAB-1F spectrometer. Ultraviolet absorption spectra were recorded on a Perkin-Elmer 555 or Pye Unicam SP 800A spectrometer. Solvents and reagents were purified by standard procedures.

Methyl 4-(1,3-dioxolan-2-yl)-2-nitrobutyrate (9a). - Freshly distilled acrolein (5.6 g, 0.10 mol) was added dropwise to a stirred solution of methyl nitroacetate[10] (14.3 g, 0.12 mol) and NaOMe from 0.03 g Na) in dry MeOH (200 ml) at 0°C. Excess base was neutralised by the addition of 2N HCl (1 ml). The mixture was poured into water (400 ml) and extracted with CH_2Cl_2 (4 x 100 ml). After drying and removal of the solvent crude (8) (17.0 g) was obtained as a yellow oil. The crude product was refluxed with 1,2-ethanediol (15.0 g, 0.24 mol) in benzene (150 ml) in the presence of a catalytic amount of toluene-p-sulphinic acid for 2 h. The water formed was removed by means of a Dean-Stark apparatus. The reaction mixture was washed with water (2 x 50 ml), dried ($MgSO_4$) and concentrated to give a brown oil (24.0 g). Half of this oil (12.0 g) was chromatographed on silica gel (benzene : EtOAc = 4 : 1) yielding a slightly yellow oil (6.0 g). Vacuum distillation gave unreacted methyl nitroacetate (0.4 g, 2.8%) and (9a) as a colourless oil (3.15 g, 14.4%). B.p. 108-110°C/0.07torr.; ^1H n.m.r. (90MHz, $CDCl_3$) δ1.65-1.86(m, 2H), 2.20-2.50(m,2H), 3.80(s,3H), 3.70-4.00(m,4H), 4.90(t,J=4Hz, 1H), 5.29(dd,J=6.5,7.0Hz,1H); u.v. (95%EtOH) 205nm(ε5150), 275(ε45).

Methyl 5,5-dimethoxy-2-nitropentanoate (9b). - Methyl nitroacetate (53.5 g, 0.45 mol) was added slowly to a solution of NaOMe in MeOH (from 0.15 g Na and 500 ml MeOH) at 0°C. The light yellow solution was cooled to -30 + 5°C. Freshly distilled acrolein (16.8 g, 0.30 mol) was added with mechanical stirring maintaining the internal temperature below -20°C. The solution was stirred at -30°C for 2 h and then at 0°C for 1 h. After re-cooling to -40°C HCl gas was bubbled in until the solution was strongly acidic to moist pH paper. The solution was allowed to warm up to room temperature overnight and excess HCl was flushed out by passing in N_2 for 15 min. MeOH was removed at 25°C in vacuo to leave a yellow syrupy liquid which was taken up in CH_2Cl_2 (200 ml) and washed briefly with saturated $NaHCO_3$ (50 ml). After drying (Na_2SO_4), the solution was again concentrated in vacuo. N.m.r. spectral analysis showed that about 10% of the aldehyde was present. The crude product was re-acetalised by refluxing in a mixture of light petrol (b.p. 40-60°C, 200 ml) and MeOH (20 ml) with a catalytic amount of toluene-p-sulphonic acid until the aldehyde peak (δ9.2) disappeared in n.m.r. spectrum. The mixture was concentrated to a brown oil and distilled in vacuo to remove unreacted methyl nitroacetate (9.0 g, 17% recovery). The residue was distilled in a Kugelrohr apparatus under high vacuum to give (9b) as a light yellow oil (29.2 g, 44%). B.p. 130°C (bath)/0.05torr.; i.r.($CHCl_3$) 1760, 1570 cm^{-1}; ^1H n.m.r.(300MHz, $CDCl_3$) δ1.68-1.74(m,2H), 2.18-2.39 (m,2H), 3.32(s,3H), 3.33(s,3H), 3.83(s,3H), 4.39(t,J=5.3Hz,1H), 5.24(dd,J=5.7,9.0Hz,1H); u.v. (95%EtOH) 203nm(ε5720), 306nm(ε530); anal. calcd for $C_8H_{15}NO_6$: C43.44,H6.83,N6.33, found: C43.15, H6.46,N6.52.

Methyl 4-(1,3-dioxolan-2-yl)-2-hydroxyaminobutyrate (10a). - A solution of (9a) (1.40 g, 6.4

mmol) in Et_2O (8 ml) was added to a vigorously stirred suspension of aluminium amalgam (from 305 mg, 11.3 mg-atom of aluminium foil) in Et_2O (70 ml) and water (1 ml) over 15 min. When all the starting material was consumed (ca. 1 h) the mixture was filtered through celite and the solid was washed with Et_2O. The filtrate was dried ($MgSO_4$) and concentrated to give (10a) as a viscous yellow oil (1.24 g, 95%). I.r.($CHCl_3$) 3590, 3290, 1742 cm^{-1}; ^1H n.m.r.(90MHz, $CDCl_3$) δ1.70-1.85(m, 4H), 3.73(s,3H), 3.60-4.00(m,5H), 4.80-4.95(m,1H), 5.65(br s,2H).

Methyl 2-hydroxyamino-5,5-dimethoxypentanoate (10b). - Aluminium amalgam (from 4.7 g, 0.174 g-atom of aluminium foil) was suspended in a mixture of Et_2O (350 ml) and water (10 ml). One fifth of a solution of (9b) (15.9 g, 72.0 mmol) in Et_2O (30 ml) was added and the mixture was vigorously stirred. After a short induction period the Et_2O began to reflux, the rest of the solution was added dropwise at such a rate as to maintain a gentle reflux. The mixture was stirred until all the starting material was consumed, filtered through celite to remove the alumina formed and the filter cake was washed with CH_2Cl_2 (2 x 50 ml). The filtrate was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (EtOAc) to give (10b) as white crystals (9.45 g, 63%). M.p. 45-47°C(Et_2O); i.r.($CHCl_3$) 3580, 3280, 1740 cm^{-1}; ^1H n.m.r. (300MHz,$CDCl_3$) δ1.62-1.80 (m,4H), 3.32(s,6H), 3.62-3.70(m,1H), 3.78(s,3H), 4.35-4.42(m,1H), 6.62(br s,1H), 7.02(br s,1H); m.s. (chemical ionisation, NH_3) m/e 144(M^++1); anal. calcd. for $C_6H_{17}NO_5$: C46.37,H8.27,N6.76, found: C46.38,H8.29,N6.91.

5-Methoxycarbonyl-1-pyrroline 1-oxide (6), - 2N HCl (35 ml) was added slowly to a stirred suspension of (10b) (9.40 g, 45.4 mmol) in water (35 ml) at 0°C. The solid dissolved completely in 20 minutes. After stirring for a further 1.5 h solid $NaHCO_3$ was added to neutralise the acid. The solution was extracted with CH_2Cl_2 (2 x 15 ml) and the organic extract was discarded. The aqueous solution was saturated with NaCl and extracted with CH_2Cl_2 to give a yellow solid which was crystallised from $CHCl_3$ - Et_2O to give (6) as colourless needles (4.39 g, 67.6%). M.p. 93-94°C; i.r.($CHCl_3$) 1755, 1595 cm^{-1}; ^1H n.m.r. δ2.33-2.44(m, 1H), 2.52-2.61(m,1H), 2.62-2.93(m,2H), 3.84(s, 3H), 4.72-4.73(m,1H), 7.01-7.04(m,1H); m.s. m/e 143(M^+); u.v.(95%EtOH) 238nm(ε5860); high resolution m.s. calcd. for $C_6H_9NO_3$: 143.05824, found: 143.05821; anal. calcd for $C_6H_9NO_3$: C50.35, H6.34,N9.79, found: C50.31,H6.39,N9.80.

Dimethyl 2-oxa-1-azabicyclo[3.3.0]octane-3,8-dicarboxylate (7a) and dimethyl 2-oxa-1-azabicyclo[3.3.0]octane-4,8-dicarboxylate (7b). - Freshly distilled methyl acrylate (5.74 g, 66.7 mmol) was added to a solution of (6) (4.11 g, 28.7 mmol) in CH_2Cl_2 (15 ml). The solution warmed up slightly. After stirring for 2 h, the solvent and unreacted methyl acrylate were removed in vacuo. The residue was distilled under reduced pressure to give a mixture of (7a) and (7b) as a colourless oil (6.09 g, 92.5%) b.p. 135°C (bath)/0.01torr. It was used directly for the next step. The product was shown to be a mixture of regio- and stereo-isomer by its very complex ^1H n.m.r. spectrum. I.r.(neat) 2962, 1745 cm^{-1}; m.s. m/e 229(M^+); anal. calcd. for $C_{10}H_{15}NO_5$: C52.40,H.6.60,N6.11, found: C52.18,H6.52,N6.11.

Methyl (2R*, 5R*, 7R*)-7-hydroxy-8-oxo-1-azabicyclo[3.3.0]octane-2-carboxylate (12a) and methyl (2R*, 5R*, 7S*)-7-hydroxy-8-oxo-1-azabicyclo[3.3.0]octane-2-caboxylate (12b). - A distilled mixture of (7a) and (7b) (4.23 g, 18.5 mmol) was hydrogenated over Raney nickel catalyst (500 mg) at 35-40°C at a hydrogen pressure of 760 torr in MeOH (20 ml). The required amount of H_2 (437 ml at 15°C)was taken up in 36 h. The mixture was filtered through celite and the filtrate was refluxed for 2 h under N_2. The concentrated reaction mixture was flash chromatographed (10% MeOH in EtOAc) to give a colourless oil which was crystallised from toluene. The colourless crystals formed (522 mg, 14%) were shown to be a mixture of two isomers (12a) and (12b) its 300 MHz n.m.r. spectrum and melting point measurements (104-106°C and 114-115°C). Separation of the isomers was achieved by careful chromatography. The major isomer (m.p. 114-115°C, 85% of the mixture) was (12a) and the minor isomer (m.p. 104-106°C, 15% of the mixture) was (12b). (12a); i.r.($CHCl_3$) 3380(br), 1745, 1700, 1620 cm^{-1}; ^1H n.m.r. (300MHz,$CDCl_3$) δ1.21-1.41(m,1H), 1.74(br s, 1H), 1.98-2.07(m,1H), 2.10-2.24(m,2H), 2.32(ddd,J=2.2,7.1,14.2Hz,1H), 2.51-2.62(m,1H), 3.76(s,3H), 4.16-4.28(m,1H), 4.45(dd, J=2.2,7.5Hz), 4.38-4.46(m,1H); m.s. m/e 199(M^+); anal. calcd. for $C_9H_{13}NO_4$: C54.26,H6.58,N7.03, found C54.34,H6.57,N7.05. (12b); i.r.($CHCl_3$) 3360, 1742, 1690 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.30-1.56(m,1H), 1.62-1.72(m,1H), 2.06-2.31(m,2H), 2.47-2.61(m,1H), 2.83(ddd,J=5.9,8.0,13.8Hz,1H), 3.06 (br s,1H), 3.75(s,3H), 3.89-4.01(m,1H), 4.51(t,J=7.6Hz,1H), 4.69(dd,J=8.0,9.3Hz,1H); m.s. m/e 199(M^+); anal. calcd. for $C_9H_{13}NO_4$: C54.26,H6.58,N7.03, found: C54.41,H6.62,N6.85.

Diethyl 8-methoxycarbonyl-2-oxa-1-azabicyclo[3.3.0]octane-3,3-dicarboxylate (14a) and diethyl 8-methoxycarbonyl-2-oxa-1-azabicyclo[3.3.0]octane-4,4-dicarboxyliate (14b). - Diethyl methylenemalonate (13)[11] (800 mg, 4.65 mmol) was added to a solution of (6) (348 mg, 2.43 mmol) in CH_2Cl_2 (3 ml). After stirring for 45 minutes the solvent was evaporated in vacuo. The residue was separated by chromatography (hexane : EtOAc = 1 : 1) to give (14a) (220 mg, 28%) and (14b) (483 mg, 63%). (14a); I.r.(neat) 2990, 2960(sh), 2915, 1745 cm^{-1}; ^1H n.m.r. (300MHz,$CDCl_3$) 1.27(2xt,J=7Hz, 6H), 1.76-1.87(m,1H), 1.94-2.18(m,2H), 2.29-2.42(m,1H), 2.49(dd,J=6.5,13.0Hz,1H), 3.73(s,3H), 3.92-4.02(m,1H), 4.17(br t,J~7Hz,1H), 4.16-4.30(m,4H); m.s. m/e 316(M^++1), 315(M^+); high resolution m.s. calcd. for $C_{14}H_{21}NO_7$: 315.1318, found: 315.1318. (14b); I.r.(neat) 2990, 2960, 2915, 2880, 1745 cm^{-1}; ^1H n.m.r.(300MHz, $CDCl_3$) δ1.25(2xt,J=7.0Hz,6H), 1.60-1.71(m,1H), 1.94-2.12(m,2H), 2.20-2.32(m,1H), 3.75(s,3H), 3.86(dd,J=7.0,9.0Hz,1H), 4.16-4.28(m,5H), 4.39(d,J=9.7Hz,1H), 4.62(dd, J=7.5,9.0Hz,1H); m.s. m/e 316(M^++1), 315(M^+); high resolution m.s. calcd. for $C_{14}H_{21}NO_7$: 315.1318, found 315.1318.

Diethyl 2-methyl-3-phenylisoxazoline-5,5-dicarboxylate (16a) and diethyl 2-methyl-3-phenyl-isoxazoline-4,4-dicarboxylate (16b). - Diethyl metylenemalonate (13) (3.0 g, 1.74 mmol) was added in small batches to a stirred solution of N-benzylidenemethylamine N-oxide (15)[12] (1.02 g, 7.5 mmol) in CH_2Cl_2(8 ml) over 20 minutes. After stirring for a further 20 minutes volatile components

were evaporated. The residue was then passed through a short column of silica gel (EtOAc : hexane = 3 : 7). A colourless oil obtained was crystallised from hexane to give (16b) (1.53 g, 66%). The mother liquor was chromatographed on silica gel (30% EtOAc in hexane) to give colourless oil (500 mg) which contained mainly (16a) and a small quantity of an unknown contaminant.(16a); i.r. (neat) 2990, 1750 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.29(t,J=7.1Hz,3H), 1.30(t,J=7.1Hz,3H), 2.66(s,3H), 3.02(A of ABX,J=9.7,12.8Hz,1H), 3.10(B of ABX,J=7.1,12.8Hz,1H), 3.68(X of ABX,m,1H), 4.26-4.37(m,4H), 7.27-7.45(m,5H): m.s. m/e 308(M^++1), 307(M^+); high resolution m.s. calcd. for $C_{16}H_{21}NO_5$: 307.1420, found 307.1417. (16b); m.p. 71-72°C; i.r.(nujol) 1750(sh), 1728 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ0.72(t,J=7.4Hz,3H), 1.26(t,J=7.4Hz,3H), 2.65(s,3H), 3.42(dq,J=7.4,10.7Hz,1H), 3.70(dq,J=7.4,10.7Hz,1H), 4.20-4.36(m,2H), 4.39(d,J=9.2Hz,1H), 4.46(br s,1H), 4.79(d,J=9.2Hz,1H), 7.26-7.32(m,3H), 7.41-7.45(m,2H): m.s. m/e 307(M^+); anal. calcd. for $C_{16}H_{12}NO_3$: C62.53,H6.89, N4.56, found: C62.73,H6.88,N4.60.

Methyl (2R*,5R*,7R*)-8-oxo-7-[(toluene-p-sulphonyl)oxyl]-1azabicyclo[3.3.0]octane-2-carboxylate (17a) and methyl (2R*,5R*,7S*)-8-oxo-7-[(toluene-p-sulphonyl)oxy]-1-azabicyclo[3.3.0]-octane-2-carboxylate (17b). - Alcohols (12a) and (12b) (85 : 15 mixture, 204 mg, 1.05 mmol) were dissolved in dry pyridine (700 µl) and cooled to 0°C. Toluene-p-sulphonyl chloride (crystallised from hexane, 240 mg, 1.26 mmol) was quickly added. After stirring for 15 minutes the solution was kept at 0°C for 24 h. The mixture was poured into ice-water (5 g), stirred for 10 minutes and extracted with CH_2Cl_2 (3 x 5 ml). The combined CH_2Cl_2 extracts were washed with 2N HCl (2 x 10 ml), saturated $NaHCO_3$ (10 ml) and brine (10 ml), dried (Na_2SO_3) and concentrated in vacuo. The residue was separated by flash chromatography (30% hexane in EtOAc) to give (17a) (62%), (17b) (13%) and intermediate mixture of the two (7%). (17a); m.p. 140-141.5°C; i.r.(nujol) 1765, 1718, 1600 cm^{-1}; ^1H n.m.r. (300MHz,$CDCl_3$) δ1.40-1.55(m,1H), 2.04-2.14(m,2H), 2.18-2.27(m,1H), 2.45(s,3H), 2.46-2.57 (m,1H), 2.97(ddd,J=6.2,8.0,14.2Hz,1H), 3.72(s,3H), 3.73-3.93(m,1H), 4.48(t,J=8.0Hz,1H), 5.31(dd, J=8.0Hz,1H), 7.35 and 7.90(para-substituted benzene,J=9.0Hz,4H); anal. calcd. for $C_{16}H_{19}NO_6S$: C54.38,H5.42,N3.96,S9.07, found: C54.30,H5.60,N3.91,S8.8. (17b); m.p. 105.5-106.5 C; i.r.(nujol) 1755, 1719, 1603 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.29-1.37(m,1H), 2.05(dt,J=15.0,7.0Hz,1H), 2.13-2.24(m,2H), 2.45(s,3H), 2.49-2.58(m,1H), 2.65(ddd,J=2.0,6.0,15.0Hz,1H), 3.73(s,3H), 4.22-4.29(m,1H), 4.33-4.38(m,1H), 4.97(dd,J=2.0,7.0Hz,1H), 7.35 and 7.84(para-substituted benzene,J=8.0Hz,4H); anal. calcd. for $C_{16}H_{19}NO_6S$: C54.38,H5.42,N3.96,S9.07, found: C54.12,H5.37,N3.94,S9.15.

Methyl (2R*,5R*,7S*)-7-azido-8-oxo-1-azabicyclo[3.3.0]octane-2-carboxylate (18b). - NaN_3 (50 mg, 0.77 mmol) was suspended in a solution of (17a) (204 mg, 0.58 mmol) in dry DMF (1.0 ml). The mixture was stirred for 18 h at room temperature then diluted with water (10 ml) and extracted with EtOAc (5 x 10 ml). The residue obtained by removal of the solvent was purified by chromatography (EtOAc) or crystallisation (CCl_4 - hexane) to give (18b) (112 mg, 86%). M.p. 74-75°C; i.r. ($CHCl_3$) 2110, 1755, 1720 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.38-1.49(m,1H), 1.54-1.65(m,1H), 2.04-2.23 (m,2H). 2.47-2.57(m,1H), 2.74(ddd,J=6.2,8.0,14.2Hz,1H), 3.73(s,3H), 3.88-3.98(m,1H), 4.45-4.54(m, 2H); anal. calcd. for $C_9H_{12}N_4O_3$: C48.21,H5.39,N24.99, found C47.98,H5.42,N25.10.

Methyl(2R*,5R*,7R*)-7-azido-8-oxo-1-azabicyclo[3.3.0]octane-2-carboxylate (18a). - In a similar manner (18a) was obtained from (17b) (36.7 mg, 0.10 mmol) and NaN_3 (14 mg, 0.20 mmol) in 86% yield, after chromatography (EtOAc), as an oil. I.r.($CHCl_3$) 2115, 1750, 1710 cm^{-1}; ^1H n.m.r. (300MHz,$CDCl_3$) δ1.25-1.38(m,1H), 1.99(distorted ddd,J=6.4,8.0,14.2Hz,1H), 2.11-2.20(m,2H), 2.24 (ddd,J=2.2,6.6,14.2Hz,1H), 2.50-2.60(m,1H), 3.75(s,3H), 4.12-4.17(m,1H), 4.19(dd,J=2.2,8.0Hz,1H), 4.41(dd,J=7.1,8.9Hz,1H); high resolution m.s. calcd. for $C_9H_{12}N_2O_3$(M-N_2): 196.0848, found: 196.0847, calcd. for $C_7H_9NO_4$(M-CO_2Me): 165.0776, found 165.0777.

Methyl (2R*,5R*,7S*)-7-amino-8-oxo-1-azabicyclo[3.3.0]octane-2-carboxylate (19b). - The azide (18b) (31 mg, 0.13 mmol) was hydrogenated over 10% Pd-C (6 mg) in MeOH (1.5 ml). After stirring for 14 h at room temperature the catalyst was filtered off and the solvent was removed. The residue was purified by flash chromatography (MeOH : EtOAc = 1 : 1) to give (19b) as a colourless oil (17.1 mg, 62%). I.r.(neat) 3375, 2960, 2880, 1745, 1700, 1605 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.36-1.49(m,2H), 1.8(br s,2H), 2.06-2.21(m,2H), 2.44-2.54(m,1H), 2.76-2.82(m,1H), 3.73(s,3H), 3.89-3.93(m,2H), 4.46(t,J=8.0Hz,1H); m.s. m/e 198(M^+); high resolution m.s. calcd. for $C_9H_{14}N_2O_3$: 198.1004, found 198.1004.

Methyl (2R*,5R*,7S*)-8-oxo-7-phenoxyacetamido-1-azabicyclo[3.3.0]octane-2-carboxylate (1a). - The crude amine (19b) obtained by the hydrogenation of (18b) (49 mg, 0.218 mmol) was stirred in a solution of phenoxyacetyl chloride (32 mg, 0.24 mmol) and pyridine (100 µl, 14.4 mmol) at 0°C for 45 minutes. The solution was diluted with CH_2Cl_2 (4 ml), washed with 2N HCl (2 ml), aq $NaHCO_3$(2 ml) and brine (3 ml), dried (Na_2SO_4) and concentrate in vacuo. The residue was purified by chromatography (EtOAc) to give (1a) as a colourless oil [59 mg, 81% from (18b)]. I.r.(neat) 3320, 3070(w), 2990, 2960, 1750, 1720, 1685, 1603, 1592 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.44-1.54(m,1H), 1.58-1.69 (m,1H), 2.06-2.25(m,2H), 2.45-2.55(m,1H), 3.04(ddd,J=6.2,8.0,14.2Hz,1H), 3.74(s,3H), 3.97-4.07(m,1H), 4.49(s,2H), 4.49(t,J=7.5Hz,1H), 4.87(ddd,J=6.2,8.0,11.5Hz,1H), 6.89-7.03(m,3H), 7.25(br d,J~6Hz,1H), 7.26-7.33(m,2H); ^{13}C n.m.r.(75.5Hz, $CDCl_3$) δ31.5(t), 32.1(t), 37.5(t), 52.5(q), 54.2(d), 55.0(d), 58.2(d), 67.2(t), 114.7(d), 122.1(d), 129.7(d), 157.1(s), 168.6(s), 171.1(s), 171.7(s); m.s. m/e 332(M^+); high resolution m.s. calcd. for $C_{17}H_{20}N_2O_5$: 332.1372, found 332.1372.

Potassium (2R*,5R*,7S*)-8-oxo-7-phenoxacetamido-1-azabicyclo[3.3.0]octane-2-carboxylate (1b). - A solution of (1a) (29 mg, 0.087 mmol) and K_2CO_3 (6.0 mg, 0.044 mmol) in MeOH (0.5 ml) and water (1 ml) was stirred for 24 h. MeOH was removed in vacuo. The residue was diluted with water (2 ml) and extracted with CH_2Cl_2 (3 x 4 ml) to recover unreacted (1a) (8 mg, 27%). The aqueous solution was freeze-dried to give (1b) as a colourless foam (23 mg, 73%). ^1H n.m.r.(300MHz,D_2O) δ1.37-1.51 (m,1H), 1.75-1.87(m,1H), 1.93-2.07(m,1H), 2.56-2.67(m,1H), 2.73(ddd,J=6.2,8.4,14.6Hz,1H), 3.93-4.04 (m,1H), 4.22(t,J=8.40Hz,1H), 4.64(br s,2H), 4.97(dd,J=8.4,11.1Hz), 7.01(br d,J=8Hz,2H), 7.08(t,

J=7.5Hz,1H), 7.40(br t,J=8Hz,2H); m.s.(desorption chemical ionisation, NH_3) m/e(M^+-K^+-CO_2-1).

Methyl (2R*,5R*,7R*)-8-oxo-7-phenoxacetamido-1-azabicyclo[3.3.0]octane-2-carboxylate (2a). - The azide (18a) (10 mg, 0.045 mmol) was hydrogenated in MeOH (1 ml) over 10% Pd-C (3 mg) for 8 h. Removal of the catalyst and the solvent gave the corresponding (19a) as a colourless oil (9 mg, 100%). The crude amine (19a) was dissolved in CH_2Cl_2(0.5 ml) and pyridine (20 µl), phenoxyacetyl chloride (6.5 µl, 8.0 mg) was added at 0°C. The solution was stirred for 30 minutes at 0°C. A colourless oil obtained on normal work-up was purified by preparative t.l.c. (EtOAc) to give (2a) as a colourless oil (11.9 mg, 80%). I.r.($CHCl_3$) 3420, 1750, 1700(br), 1604, 1594 cm^{-1}; ^1H n.m.r. (300MHz,$CDCl_3$) δ1.26-1.41(m,1H), 2.06-2.14(m,2H), 2.22(ddd,J=5.8,7.5,14.2Hz,1H), 2.41(ddd,J=4.4, 9.3,14.2Hz,1H), 2.51-2.61(m,1H), 3.76(s,3H), 4.40-4.10(m,1H), 4.50(dd,J=6.6,8.9Hz,1H), 4.53(s,2H), 4.73(ddd,J=5.8.7.0,9.3Hz,1H), 6.91-7.05(m,3H), 7.22(br d,J~7Hz,1H), 7.29-7.36(m,2H); m.s.(in beam electron impact) m/e 332(M^+); high resolution m.s. calcd. for $C_{17}H_{20}N_2O_5$: 332.1372, found 332.1372.

Potassium (2R*,5R*,7R*)-8-oxo-7-phenoxyacetamido-1-azabicyclo[3.3.0]octane-2-carboxylate (2b). - The methyl ester (2a) (8.9 mg, 0.027 mmol) was sponified with aqueous K_2CO_3 (0.49 M, 27 µl, 0.0134 mmol) in MeOH (0.25 ml) for 24 h. Usual work-up gave (2b) as a colourless foam (9.3 mg, 92%). ^1H n.m.r.(300MHz, D_2O) δ1.27-1.38(m,1H), 1.93-2.04(m,3H), 2.07-2.19(m,1H), 2.48-2.57(m,1H), 3.95-4.04(m,1H), 4.27(br t, J~8Hz,1H), 4.51(AB,2H), ca.4.7(signal partially hidden under D_2O peak), 6.85-6.96(m,3H), 7.20-7.26(m,2H).

Methyl (2R*,5R*,7S*)-7-(4-bromobenzamido)-8-oxo-1-azabicyclo[3.3.0]octane-2-carboxylate (3). - Crude (19b) (25mg, 0.126 mmol) was dissolved in CH_2Cl_2 (1 ml) and pyridine (20 µl, 0.247 mmol) and 4-bromobenzoyl chloride (29 mg, 0.131 mmol) was added successively at 0°C. After stirring for 30 minutes the mixture was diluted with CH_2Cl_2(4 ml) and washed successively with 2N HCl (4 ml), saturated $NaHCO_3$ (4 ml) and water (4 ml), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative t.l.c. (EtOAc) to give (3) (30.9 mg, 67%). I.r.($CHCl_3$) 3420, 1750, 1710, 1665, 1594 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.52-1.63(m,1H), 1.83(ddd,J=8.8,11.5,14.2Hz,1H), 2.09-2.27(m,2H), 2.52-2.62(m,1H), 3.03(ddd,J=6.2,8.0,14.2Hz,1H), 3.76(s,3H), 4.00-4.10(m,1H), 4.50 (br t,J~8Hz), 4.85(ddd,J=6,8.0,11.1Hz,1H), 7.45-7.49(m,2H), 7.53(br d,J=6.2Hz,1H), 7.58-7.63(m,2H); m.s. m/e 382 and 380(M^+); high resolution m.s. calcd. for $C_{16}H_{17}{}^{79}BrN_2O_4$: 380.0372, found 380.0375.

Methyl(2R*,5R*,7S*)-7-(4-nitrobenzamido)-8-oxo-1-azabicyclo[3.3.0]octane-2-carboxylate (4). - The compound prepared in a similar manner to (3) from (19b) (24.2 mg, 0.122 mmol) and 4-nitrobenzoyl chloride (24.0 mg, 0.129 mmol) in 54% yield. M.p. 205-207°C(CH_2Cl_2/Et_2O); i.r.(nujol) 3302, 1770, 1690, 1670, 1609 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.50-1.62(m,1H), 1.68-1.79(m,1H), 2.15-2.34 (m,2H), 2.53-2.64(m,1H), 3.19(ddd,J=5.7,7.5,13.7Hz,1H), 3.78(s,3H), 4.06-4.17(m,1H), 4.53(t,J=7.5Hz, 1H), 4.90(br ddd,J=5.0,7.5,11.5Hz,1H), 7.13(br d,J~5Hz,1H), 7.96 and 8.27(para-substituted benzene, J=9Hz,4H); m.s. m/e 347(M^+); high resolution m.s. calcd. for $C_{16}H_{17}N_3O_6$: 347.1117, found 347.1119; anal. calcd. for $C_{16}H_{17}N_3O_6$: C55.33,H4.93,N12.10, found: C55.39,H5.04,N12.18.

Benzyl (2R*,5R*)-6-methoxy-3,3-dimethyl-8-oxo-4-thia-1-azabicyclo[3.3.0]oct-6-ene-2-carboxylate (21). - Benzyl 6-oxopenicillanate (20)[14] (600 mg, 1.97 mmol) was dissolved in Et_2O (30 ml) and treated with a large excess of CH_2N_2 in Et_2O at 0°C. The solution was stirred for 4 h at 0°C and then 14 h at room temperature. The solution was concentrate in vacuo and the residue was purified by flash chromatography (Et_2O) to give (21) as a colourless oil (325 mg, 50%). M.p. 118-119°C(EtOAc-light petroleum); i.r.($CHCl_3$) 1740, 1700, 1620 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.40 (s,3H), 1.47(s,3H), 3.87(s,3H), 4.76(s,1H), 5.05(s,1H), 5.21(ABq,J=12Hz,1H), 5.23(ABq,J=12Hz,1H), 5.74(s,1H), 7.39-7.41(m,5H); high resolution m.s. calcd. for $C_{17}H_{19}NO_4S$: 333.1035, found 333.1034.

(2R*,5R*)-6-Methoxy-3,3-dimethyl-8-oxo-4-thia-1-azabicyclo[3.3.0]oct-6-ene-2-carboxylic acid (5). - To a solution of (21) (45 mg, 0.13 mmol) in 1,4-dioxane (1 ml) was added 0.2N NaOH (1 ml). After stirring for 1 h at room temperature the mixture was extracted with Et_2O (2 x 2 ml). The aqueous layer was acidified with 1N HCl (eq.) and extracted with Et_2O (3 x 10 ml). The combined acid extracts were dried and concentrated in vacuo. The residue was recrystallised from EtOAc to give (5) as white crystals (17 mg, 52%). M.p. 188-189°C; i.r. 1730, 1700, 1625 cm^{-1}; ^1H n.m.r. (300MHz,$CDCl_3$) δ1.58(s,3H), 1.62(s,3H), 3.89(s,3H), 4.58(s,1H), 5.12(s,1H), 5.70(s,1H); anal. calcd. for $C_{10}H_{13}NO_4S$: C49.37,H5.39,N5.76, found C49.29,H5.52,N5.72.

Methyl (2R*,5R*)-7-acetoxy-8-oxo-1-azabicyclo[3.3.0]oct-6-ene-2-carboylate (23). - Acetic anhydride (1 ml) was added to a solution of recrystallised alcohols (12a) and (12b) (33 mg, 0.17 mmol) in DMSO (4 ml) at room temperature. After standing at room temperature for 48 h excess reagents were removed by Kugelrohr distillation. The residue was purified by preparative t.l.c. (EtOAc) to give (23) as a yellow oil (30 mg, 76%). I.r. ($CHCl_3$) 1775, 1742, 1712, 1645, 1625 cm^{-1}; ^1H n.m.r.(90MHz,$CDCl_3$) δ1.10-1.43(m,1H), 2.27(s,3H), 1.85-2.80(m,3H), 3.75(s,3H), 4.27-4.58(m,2H), 6.99(d,J=1.5Hz,1H); m.s. m/e 239 (M^+).

Methyl (2R*,5R*)-7,8-dioxo-1-azabicyclo[3.3.0]octane-2-carboxylate (22) - Recrystallised alcohols (12a) and (12b) (102 mg, 0.51 mmol) and N,N'-dicyclohexylcarbidiimide (DCC) (318 mg, 1.54 mmol) were dissoved in dry DMSO (0.6 ml) in a dry flask. Dry benzene (6 ml) was added and the flask was cooled to 0°C. Dichloroacetic acid (21.5 µl, 33.5 mg, 0.26 mmol) was added with stirring. The mixture was stirred at 0°C for 2 h. Excess DCC was destroyed by adding oxalic acid (330 mg) and stirring for 15 min. The solid was filtered off and washed with EtOAc (10 ml). The combined organic solutions were washed with water (2 x 10 ml), dried and concentrated. The aqueous washings were saturated with NaCl and extracted with CH_2Cl_2. The organic extracts were combined and concentrated to about 1 ml and DMSO was removed in vacuo at room temperature. The residue was taken up in EtOAc (5 ml) and left in a refrigerator overnight. Precipitate was filtered off and the filtrate was concentrated and purified by chromatography (EtOAc) to give (22) as a light

yellow oil (55.5 mg, 55%). I.r.($CHCl_3$) 1780, 1750, 1725 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.40-1.58 (m,1H), 2.07-2.21(m,1H), 2.31-2.38(m,1H), 2.43(dd,J=4.0,20.0Hz,1H), 2.63(dt,J=14.0,8.0Hz,1H), 3.03 (dd,J=7.0,20.0Hz,1H), 3.73(s,3H), 4.00-4.10(m,1H), 4.64(t,J=8.0Hz,1H); m.s. m/e 198(M^++1); high resolution m.s. calcd. for $C_9H_{11}NO_4$: 197.0688, found 197.0686.

Methyl 1-benzyl-4-hydroxy-5-oxo-3-pyrrolidine-3-carboxylate (24a) - The modified procedure of Southwick et al.[18] was adopted. Benzylamine (12.0 g, 0.112 mol) was added dropwise to a solution of methyl acrylate (9.56 g, 0.111 mol) in MeOH (50 ml). The solution was stirred for 20 minutes and kept at 25°C for 24 h. A suspension of dimethyl oxalate (13.1 g, 0.111 mol) in a solution of NaOMe in MeOH (prepared from 2.55 g, 0.111 g-atom of Na and 50 ml dry MeOH) was also prepared in a separate flask. To this suspension was added the benzylamine-acrylate mixture and the whole thing was refluxed under N_2 for 1 h. The white crystals formed were collected, dissolved in boiling water (200 ml) and then acidified with 6N HCl. The white crystals that precipitated after cooling were recrystallised from MeOH to give (24a) as colourless needles (20.0 g 73%). M.p. 182.5-184°C (lit.[18] m.p. 183-184°C); i.r.(nujol) 2500-3350, 1703, 1683, 1673 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.62(br s, exchangable, 1H), 3.83(s,3H), 3.88(s,2H), 4.69(s,2H), 7.17-7.40(m,5H); m.s. m/e 248 (M^++1), 247(M^+).

Methyl 4-hydroxy-1-(3-methoxybenzyl)-5-oxo-3-pyrroline-3-carboxylate (24b). - The compound was prepared in a similar manner to (24a) from methyl acrylate (4.30 g, 0.05 mol), 3-methoxybenzylamine (6.86 g, 0.05 mol) and dimethyl oxalate (5.90 g, 0.05 mol). The crude product was recrystallised from MeOH to give (24b) as colourless needles (8.83 g, 64%). M.p. 125.5-127.5°C; i.r.(KBr) 2800-3400, 2960, 2840, 1705, 1675, 1590 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ3.80(s,3H), 3.83(s,3H), 3.89(s, 2H), 4.65(s,2H), 6.75-6.88(m,3H), 7.23-7.30(m,1H), 8.95(br s,1H); ^{13}C n.m.r.(75.5MHz,$CDCl_3$) δ45.7(t), 46.8(t), 51.7(q), 55.2(q), 107.6(s), 113.4(d), 113.7(d), 120.3(d), 129.8(d), 137.3(s), 155.8(s), 159.9(s), 164,2(s), 164.9(s); m.s. m/e 277(M^+); anal. calcd for $C_{14}H_{15}NO_5$: C60.64,H5.45,N5.05, found: C60.91,H5.43,N5.03.

1-Benzylpyrrolidine-2,3-dione (25a). - The ester (24a) was refluxed in 20% HCl (50 ml) for 20 minutes. The brown reaction mixture was filtered to remove resinous material, cooled and extracted with CH_2Cl_2 (4 x 50 ml). The organic extracts were dried ($MgSO_4$) and concentrated to give brown crystals which were recrystallised from $CHCl_3$-cyclohexane to give (25a) as off-white needles. M.p. 97-100.5°C (lit.[18] m.p. 99-100°C); i.r.($CHCl_3$) 1770, 1715 cm^{-1}; ^1H n.m.r. (300MHz, $CDCl_3$) δ2.68(t,J=6.0Hz,2H), 3.54(t,J=6.0Hz,2H), 4.70(s,2H), 7.27-7.40(m,5H); m.s. m/e 190(M^++1), 189(M^+).

1-(3-Methoxybenzyl)pyrrolidine-2,3-dione (25b). - In a similar manner, (25b) was prepared from (24b) as a yellow oil in 80% yield. It was used directly for the next step. I.r. (neat) 3050, 2935, 2840, 1765, 1715, 1605, 1590 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ2.65(t,J=6.0Hz,2H), 3.45(t,J=6.0Hz,2H), 3.77(s,3H), 4.63(s,2H), 6.80-6.92(m,3H), 7.25-7.35(m,1H).

Oxidative ring contraction of pyrrolidine-2,3-diones by sodium periodate. General procedure.[20] - $NaIO_4$ (4 equivalents) was dissolved in 0.2 M lithium phosphate buffer and the pH was adjusted to ca. 6.6 by the addition of 2N NaOH or dilute phosphoric acid. The pyrrolidine-2,3-dione dissolved in the minimum quantity of MeOH was quickly added. The final pH was noted and the solution was stirred for the time specified. Excess periodate was destroyed by the addition of sodium sulphite while maintaining the pH around 7 by the addition of saturated K_2CO_3. Complete destruction of the periodate was indicated by a negative test with starch-iodide paper. The resulting solution was concentrated to about 20 ml, acidified to pH 2 with 6N HCl and extracted with CH_2Cl_2. The produce was then esterified with diazomethane.

Methyl 1-benzyl-2-oxoazetidine-3-carboxylate (26a). The compound was prepared from (25a) (500 mg, 2.65 mmol) and $NaIO_4$ (2.30 g, 10.7 mmol) in 4 h. The yield of (26a) was 30% after chromatography (EtOAc). I.r.(neat) 3030, 2960, 2900, 1770, 1735 cm^{-1}; ^1H n.m.r.(300MHz,CDC_3) δ 3.28(dd,J=5.3,5.7Hz,1H), 3.47(dd,J=2.6,5.7Hz,1H), 3.78(s,3H), 4.05(dd,J=2.6,5.3Hz,1H), 4.42(s,2H), 7.25-7.45(m,5H); m.s. m/e 219(M^+); anal. calcd for $C_{12}H_{13}NO_3$: C65.74,H5.98,N6.39, found: C65.46, H6.06,N6.36.

Methyl 1-(3-methoxybenzyl)-2-oxoazetidine-3-carboxylate (26b). - The compound was prepared from (25b) (500 mg, 2.28 mmol) and $NaIO_4$ (1.95 g, 9.13 mmol) over 4 h. Esterification of the crude acid and chromatography (20% EtOAc in CH_2Cl_2) gave (26b) as a colourless oil (198 mg, 35%). I.r.(neat) 2950, 2900, 2840, 1765, 1735, 1605, 1590 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ3.29(dd,J=5.3, 5.7Hz,1H), 3.49(dd,J=2.6,5.7Hz,1H), 3.79(s,3H), 3.81(s,3H), 4.06(dd,J=2.6,5.3Hz,1H), 4.40(distorted s,2H), 6.75-6.88(m,3H), 7.25-7.32(m,1H); ^{13}C n.m.r.(75.5MHz,$CDCl_3$) δ41.8(t), 46.3(t), 52.6(q), 53.9(d), 55.3(q), 113.5(d), 120.3(d), 130.0(d), 136.4(s), 160.1(s), 162.2(s), 167.9(s); m.s. m/e 250(M^++1), 249(M^+).

7-Allyl-3-oxa-7-azabicyclo[4.3.0]nonane-2,8,9-trione (28). - 5,6-Dihydro-2H-pyran-2-one (29)[19] (4.9 g, 0.05 mol) and allylamine (3.75 ml, 2.85 g, 0.05 mol) were dissoved in absolute EtOH (25 ml) and stored at 25°C for 24 h. The solution was added to a solution of NaOEt in EtOH (prepared from 1.15 g, 0.05g-atom Na and 50 ml EtOH) and diethyl oxalate (7.31 g, 0.05 mol). The solution was refluxed for 1 h under N_2. EtOH was removed in vacuo to give a brown solid which was dissolved in hot water (100 ml) and acidified with 6N HCl. A brown solution and a solid were obtained. This solid was collected and recrystallised from hot MeOH to give N,N'-diallyloxamide as white fluffy needles (900 mg, 11%). The brown aqueous solution was extracted with CH_2Cl_2 (4 x 60 ml). The organic extracts were dried ($MgSO_4$) and concentrated to a brown oil which solidified on standing. Recrystallisation from MeOH gave (28) as white crystals (2.26 g, 21.6%) N,N-Diallyloxamide; m.p. 154.5-155°C, i.r.($CHCl_3$) 3400, 1680, 1650, 1510 cm^{-1}; ^1H n.m.r. (300MHz,$CDCl_3$) δ3.93-3.98(m,4H),

5.16-5.28(m,4H), 5.78-5.91(m,2H), 7.36(br s,2H). (27); m.p. 175-176°C(dec.); i.r.(KBr) 2800-3200, 1725, 1690, 1665 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.62-1.76(m,1H), 2.43-2.51(m,1H), 4.01(br dd,J=6.6, 15.4Hz,1H), 4.21-4.42(m,3H), 4.60(ddd,J=1.9,4.6,12.0Hz,1H), 5.22-5.29(m,2H), 5.76-5.87(m,1H); m.s. m/e 210(M^++1), 209(M^+); u.v.(MeOH) 248nm(ε22000), 308nm(ε4700); high resolution m.s. calcd. for $C_{10}H_{11}NO_4$: 209.0688, found: 209,0688; anal. calcd. for $C_{10}H_{11}NO_4$: C57.41,H5.30,N6.70, found: C57.44, H5,35,N6.85.

7-Allyl-9-methoxy-3-oxa-7-azabicyclo[4.3.0]non-9-ene-2,8-dine(30). - A solution of CH_2N_2 in Et_2O was added to a solution of finely ground (28) (209 mg, 1.0 mmol) in CH_2Cl_2 until the solid dissolved and a yellow colour persisted. After stirring for a further 5 minutes the solvent was evaporated to leave a yellow oil which was purified by chromatography (MeOH : EtOAc = 1 : 9) to give (30) as a light yellow oil (200 mg, 89%). I.r.(neat) 3080, 2955, 2860, 1710, 1640 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.65-1.78(m,1H), 2.42-2.48(m,1H), 3.92(br dd,J=6.8,15.6Hz,1H), 4.18(dd,J=4.4, 12.0Hz,1H), 4.28-4.41(m,2H), 4.38(s,3H), 4.55(ddd,J=1.9,5.2,12.0Hz,1H), 5.21-5.27(m,2H), 5.74-5.82 (m,1H); ^{13}C n.m.r.(75.5MHz,$CDCl_3$) 29.4(t), 44.0(t), 54.7(d), 61.0(q), 66.9(t), 109.6(s), 118.6(d), 132.1(d), 153.8(s), 159.8(s), 163.9(s).

1-Allyl-5-(2-hydroxyethyl)pyrrolidine-2,3-dione(27). - A suspension of finely powdered (28) (418 mg, 2.0 mmol) in 1N HCl (2 ml) was heated to 90-95°C under N_2 for 10 minutes. The resulting solution was saturated with NaCl and extracted with CH_2Cl_2 to give (27) as a yellow oil (426 mg). I.r.(neat) 3100-3600, 2930, 1770, 1705, 1645 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.67-1.77(m,ca.2H), 2.13-2.25(m,1H), 2.63(½ split into doublets,J=19.6,2.6Hz,1H), 2.91(½AB split into doublets,J=19.6, 7.4Hz,1H), 3.72-3.85(m,3H), 4.10-4.13(m,1H), 4.57(br dd,J=15.1,4.8Hz,1H), 5.28-5.38(m,2H), 5.73-5.88(m,1H); m.s. m/e 184(M^++1), 183(M^+).

(1R*,5R*,8S*)-6-Allyl-7-oxo-2-oxa-6-azabicyclo[3.3.0]octane-8-spiro-2'-oxirane (31). - A solution of the crude (27) [from 418 mg, 2.0 mmol of (28)] in water (2 ml) was added to a solution of $NaIO_4$ (1.50 g, 7.0 mmol) in 0.2 M lithium phosphate buffer (100 ml, pH 6.8) at room temperature. The solution was stirred for 6 h and worked up as usual. The resulting solution was concentrated to 35 mol, acidified to pH 1 and extracted with EtOAc (4 x 30 ml) to give propionic acid (ca. 150 mg). The aqueous solution was further extracted with CH_2Cl_2 to give a yellow oil which was flash chromatographed (10% MeOH in EtOAc). A light yellow oil obtained (180 mg) was reacted with excess CH_2N_2 in Et_2O - CH_2Cl_2 with evolution of N_2. Purification by chromatography (EtOAc) gave (31) as a light yellow oil (30 mg, 7.7%). I.r.($CHCl_3$) 1710 cm^{-1}; ^1H n.m.r.(300MHz,$CDCl_3$) δ1.92-2.10(m,2H), 3.22(ABq,J=6.2Hz,2H), 3.61-3.87(m,2H), 3.97(ddd,J=3.2,7.1,9.3Hz,1H), 4.34-4.43(m,2H), 4.53(d,J=7.1Hz,1H), 5.24-5.31(m,2H), 5.71-5.84(m,1H); ^{13}C n.m.r.(75.5MHz,$CDCl_3$) 30.8(t), 45.2(t), 48.6(t), 59.5(d), 60.4(s), 66.6(t), 77.9(d), 119.3(t), 131.5(d), 169.1(s);m.s. m/e 196(M^++1), 195(M^+); high resolution m.s. calcd. for $C_{10}H_{13}NO_3$; 195.0895, found; 195.0895.

Crystal structure of (12b). Crystal data: $C_9H_{13}NO_4$, M = 199.21 triclinic, space group $P\bar{1}$, a = 6.637(4), b = 7.072(2), c = 11.377(4) Å, α = 77.60(3), β = 70.83(4), γ = 76.52(4)°, U = 484.9 $Å^3$, Z = 2, D_m = 1.36 gcm^{-3}. 1241 Independent reflections were measured by four circle (CAD-4) diffractometry using Mo-Kα radiation (λ = 0.71069 Å). The structure was determined by direct methods and all atomic parameters including those for H atoms were refined by the full-matrix least-square method. The final R-vale was 0.053 (R_w - 0.0693). The atomic co-ordinates have been deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

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