Synthesis of (2*RS*, 5*RS*, 6*SR*)-3-Methoxycarbonyl-7-oxo-6-phenoxyacetamido-1-azabicyclo[3.2.0]hept-3-ene-2-carboxylic Acid

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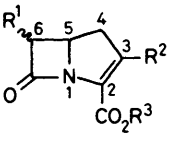
Addition of the mixed anhydride derived from azidoacetic acid and trifluoroacetic anhydride to benzyl 2-(*N*-cinnamylideneamino)-3,3-dimethylacrylate (19) in the presence of triethylamine afforded (3*RS*, 4*SR*)-3-azido-1-(1-benzyloxycarbonyl-2-methylprop-1-enyl)-4-styrylazetidin-2-one (20), which was converted into (3*RS*, 4*SR*)-1-(1-benzyloxycarbonyl-2-methoxycarbonyl-2-triphenylphosphoranylidene-ethyl)-3-phenoxyacetamido-4-styrylazetidin-2-one (29) and (3*RS*, 4*RS*)-1-(1-benzyloxycarbonyl-2-methoxycarbonyl-2-triphenylphosphoranylidene-ethyl)-4-dimethoxymethyl-3-phenoxyacetamidoazetidin-2-one (30). Ozonolysis of compound (29) in the presence of trifluoroacetic acid gave (2*RS*, 5*RS*, 6*SR*)-benzyl 3-methoxycarbonyl-7-oxo-6-phenoxyacteamido-1-azabicyclo[3.2.0]hept-3-ene-2-carboxylate (31). The ester (31) was also prepared by trifluoroacetic acid treatment of the phosphorane (30).

Hydrogenation of compound (31) over 10% Pd–C afforded (2*RS*, 5*RS*, 6*SR*)-3-methoxycarbonyl-7-oxo-6-phenoxyacetamido-1-azabicyclo[3.2.0]hept-3-ene-2-carboxylic acid (35), which was antibacterially active.

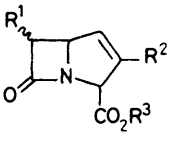
THE 7-oxo-1-azabicyclo[3.2.0]hept-2-ene ring system is present in a number of recently isolated natural products,[1] all of which are potent antibacterials. The total synthesis of such compounds (1) has therefore become of major importance, and several successful routes have been devised.[2] In comparison with their Δ^2-counterparts, 1-azabicyclohept-3-enes (2) have been only of peripheral interest. The Merck thienamycin synthesis[3] used 1-azabicyclohept-3-enes (2) as precursors of 1-azabicyclohept-2-enes (1), and derivatives unsubstituted at C-6 were prepared in these laboratories some time ago.[4] Although the antibacterial activity in the corresponding free acids was extremely low, it was significant that these analogues appeared to be chemically more stable than their Δ^2-counterparts. It was therefore surmised that 1-azabicyclohept-3-enes incorporating a 6-acylamino-group might be biologically active, since such a functionality ought to impart greater chemical reactivity to the β-lactam. Ratcliffe[5] has proposed similar arguments to explain the instability of 6-amido-1-azabicyclohept-2-enes. He suggests that the substituent further enhances the reactivity of the already sensitive β-lactam unit and causes self-destruction of the ring system.

An intramolecular Wittig reaction, utilising intermediates of type (4), has been employed by various groups[6] to construct the 2,3-double bond of 1-azabicyclohept-2-enes. Thus our intended strategy involved first the synthesis of a precursor of type (5), with a 4-alkenyl substituent as the latent carbonyl functionality, and secondly, an ozonolysis–cyclisation sequence to generate the required ring system. An identical approach has very recently been reported by Stoodley.[7] Durst[8] and Hirai[9] have also prepared similar compounds *via* intramolecular phosphonate and aldol reactions, respectively. The salt (3) was devoid of antibacterial activity.[7]

To test the intended methodology, a model series of reactions was performed on racemic 4-vinylazetidin-2-one (6).[10] Although the route essentially duplicates that published by Stoodley, in our case both possible isomers of the final product were isolated. Thus condensation of compound (6) with benzyl glyoxylate in refluxing benzene afforded the benzyloxycarbonyl derivative (7), which was converted into the chloride (8) by

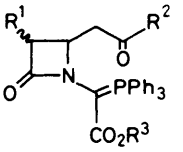


(1)



(2)

(3) $R^1 = H, R^2 = CO_2Et$, $R^3 = Na$



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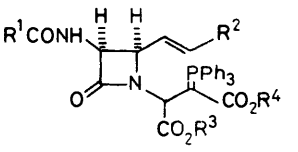
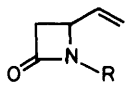


(5)

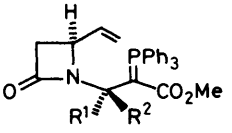
reaction with thionyl chloride. Treatment of compound (8) with methoxycarbonylmethylenetriphenylphosphorane (2 mol equiv.)[11] in dry methylene dichloride (MDC) for 24 h at room temperature provided the isomers (9) and (10), which were separated by chromatography.

The epimer (9), which has the natural penicillin stereochemistry at C-2, was ozonised in ethyl acetate at −76 °C in the presence of trifluoroacetic acid.[12] Reduction of the ozonide, followed by regeneration of the phosphorane moiety with base, led to the aldehyde (11) which immediately cyclised to give the desired bicyclic system (13) in 64% yield. In contrast, a similar sequence on compound (10) gave the isolable aldehyde (12). Cyclisation did not occur spontaneously in this case, but occurred on heating in ethyl acetate at 50 °C for 9 h, giving the bicyclo-compound (14). The stereochemistry at C-2 in these

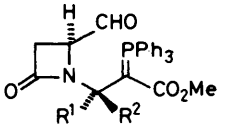
azabicyclo[3.2.0]hept-3-enes was assigned from the relative chemical shifts of the C-2 proton,[13] and was confirmed by the observation that compound (14) could be converted into its isomer (13) by base catalysis using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). There was no evidence for the formation of the Δ^2-isomer, as has been found previously.[7,9]



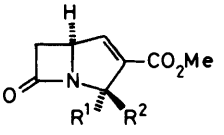
(6) R = H
(7) R = CHOH·CO_2CH_2Ph
(8) R = CHCl·CO_2CH_2Ph



(9) $R^1 = CO_2CH_2Ph$, $R^2 = H$
(10) $R^1 = H$, $R^2 = CO_2CH_2Ph$

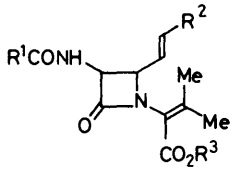


(11) $R^1 = CO_2CH_2Ph$, $R^2 = H$
(12) $R^1 = H$, $R^2 = CO_2CH_2Ph$



(13) $R^1 = CO_2CH_2Ph$, $R^2 = H$
(14) $R^1 = H$, $R^2 = CO_2CH_2Ph$

The established methodology was now extended to the synthesis of 6-acylamino-derivatives. The initial target was the preparation of a monocyclic β-lactam of type (15), analogous to the seco-penicillins that have been used by us in previous syntheses. From our earlier work [14] it was considered that, if the C-4 double bond could be protected, complete removal of the *N*-substituent by oxidation with potassium permanganate ought to be possible. Regeneration of the unsaturation should then provide an azetidinone of type (16). Alternatively



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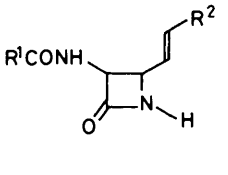
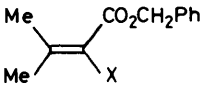


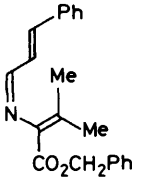
(16)

a more attractive proposition would be to attempt to utilise the isopropylideneacetate side-chain as a direct precursor of the desired carbinol moiety. Although both strategies were successful, the latter proved to be more convenient and gave better yields, and will therefore be described first.

Cinnamylidene Schiff bases have been widely used for the synthesis of β-lactams *via* the acid chloride–imine cycloaddition process.[15] Low temperature nitration of benzyl 3,3-dimethylacrylate afforded the nitro-acrylate (17), which was reduced [16] to the corresponding amine (18); condensation of this amine with cinnamaldehyde then afforded the required Schiff base (19). Treatment of crude compound (19), in MDC containing triethylamine, with the mixed anhydride derived from azidoacetic acid and trifluoroacetic anhydride [17] gave (3*RS*, 4*SR*)-3-azido-1-(1-benzyloxycarbonyl-2-methylprop-1-enyl 4-styrylazetidin-2-one (20) in 65% yield. No *trans*-isomer could be detected. Triethylamine–hydrogen sulphide reduction [18] of the azido-group, followed by acylation with phenoxyacetyl chloride, afforded the crystalline amide (21). The styryl double bond was conveniently protected as the dibromide (22) by reaction with bromine at 0 °C. A crystalline by-product was



(17) $X = NO_2$
(18) $X = NH_2$



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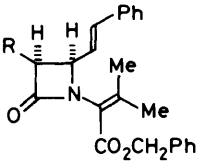
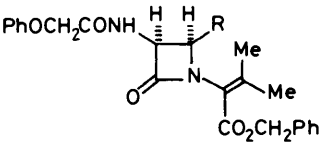
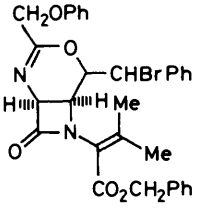
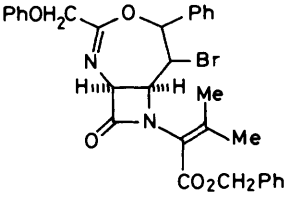


(20) $R = N_3$
(21) R = NHCO·CH_2OPh



(22) R = CHBr·CHBrPh
(23) $R = CH(OMe)_2$



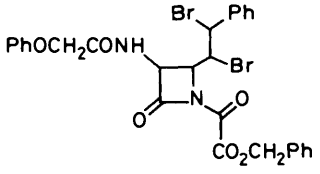


(24) (25)

also isolated from larger scale brominations. The i.r. spectrum of the material showed that the side-chain amide hydrogen had been lost, and a peak at 1 645 cm^{-1} indicated that a C=N group was present. Further confirmation was provided by the n.m.r. spectrum in which the proton α to the β-lactam carbonyl group appeared as a doublet and not the expected double doublet. Elemental analysis showed that the product was formally derived from the dibromo-derivative (22) by loss of hydrogen bromide. Structures (24) and (25) are consistent with these data, but an unequivocal assignment could not be made.

Ozonolysis of compound (22) in MDC at −20 °C gave the expected oxamide (26), which was reduced *in situ* by the addition of acetic acid and activated zinc dust to give the desired α-hydroxy-ester functionality. Concomitant debromination occurred and the product isolated was the alcohol (27), which was obtained as a mixture of epimers. Similar methodology has been recently published by the Shionogi group.[19]

Chlorination of compound (27), followed by treatment of the product with methoxycarbonylmethylenetriphenylphosphorane, gave the phosphorane (29) as an inseparable mixture of isomers. The established ozonolysis and cyclisation sequence then provided the bicyclic ester (31), the intermediate aldehyde (33) rapidly cyclising during the work-up procedure. As in the unsubstituted series, the precursor of the isomer without the natural penicillin stereochemistry at C-2 did not cyclise at room temperature, allowing the isolation of the aldehyde (34). When compound (34) was heated in refluxing ethyl acetate for 9 h, the 1-azabicyclohept-3-ene (32) was obtained in good yield.



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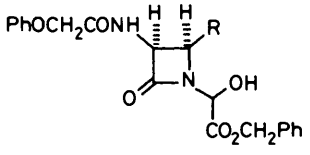
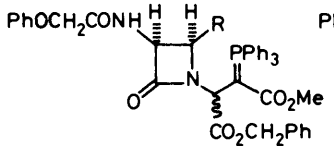
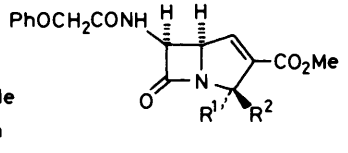


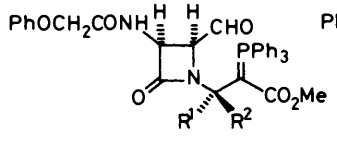
(27) R = CH=CHPh
(28) R = CH(OMe)$_2$



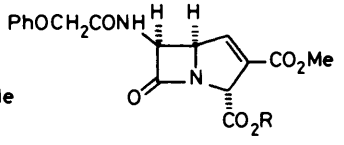
(29) R = CH=CHPh
(30) R = CH(OMe)$_2$



(31) R^1 = CO$_2$CH$_2$Ph, R^2 = H
(32) R^1 = H, R^2 = CO$_2$CH$_2$Ph



(33) R^1 = CO$_2$CH$_2$Ph, R^2 = H
(34) R^1 = H, R^2 = CO$_2$CH$_2$Ph



(35) R = H
(36) R = Me

Since the protection of the double bond of the styryl derivative (21) as the dibromide was not particularly efficient (yields 50—60%) an alternative method was investigated. When compound (21) was carefully ozonised in MDC at −76 °C, the styryl double bond was selectively cleaved. The crude product was treated with 2,2-dimethoxypropane in refluxing methanol containing a trace of toluene-*p*-sulphonic acid and gave the acetal (23) in 90% yield. The acetal was processed as described for compound (22) to provide the carbinol (28), which was converted into the phosphorane (30), an inseparable mixture of isomers, in the usual way. Deprotection of compound (30) with 95% aqueous trifluoroacetic acid, followed by work-up with base, gave the ester (31) and the phosphorane (34). The latter was converted into the bicyclic compound (32) as previously described, the total yield of both isomers being nearly quantitative. Hydrogenation of compound (31) in dioxan over 10% Pd–C for 10 min afforded the free acid (35), which showed antibacterial activity (Table) but

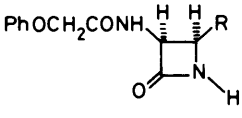
Antibacterial activity [a]

Bacterium	Bicycloheptene (35)	Penicillin V
Bacillus subtilis	1.0	0.1
Staphylococcus aureus (Oxford)	2.5	0.05
Staphylococcus aureus (Russell) [b]	>100	>100

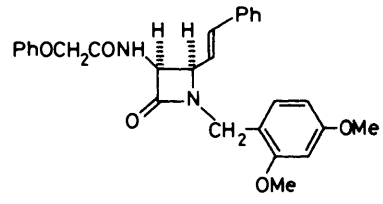
[a] The figures are the minimum inhibitory concentrations (μg ml^{-1}) required to inhibit bacterial growth after incubation on nutrient agar for 18 h. [b] Penicillinase-producing strain.

was less active than penicillin V. The authenticity of the product was confirmed by n.m.r. spectroscopy and by its conversion into the crystalline dimethyl ester (36) in high yield on treatment with diazomethane.

The original concept of completely removing the N-substituent was also examined. Oxidation of the dibromide (22) or the acetal (23) using potassium permanganate afforded the corresponding azetidin-2-ones (37) and (38) in low yield (32 and 20% respectively). The 4-styryl derivative (39) was quantitatively prepared from



(37) R = CHBr·CHBrPh
(38) R = CH(OMe)$_2$
(39) R = CH=CHPh



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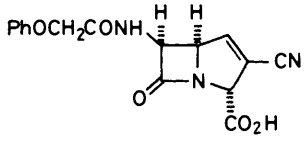

(41)

compound (37) by reaction with zinc dust in MDC containing acetic acid. While our work was in progress, Bose [20] reported that the persulphate oxidation of the dimethoxybenzyl derivative (40) gave compound (39) in 21% yield.* The availability of the azetidin-2-ones (38) and (39) meant it was possible to use different ester-protecting groups, by condensation with various glyoxylic acid esters. Although benzyl was in fact satisfactory, *p*-nitrobenzyl was employed in the synthesis of other 6-acylamino-derivatives. Details of this, as well as the extension of the synthesis to the 3-cyano-analogue (41), are available in a patent.[21]

EXPERIMENTAL

I.r. spectra were recorded for solutions in chloroform on a Perkin-Elmer 157 spectrophotometer, unless otherwise

* No spectroscopic or analytical data were quoted.

stated. U.v. spectra were determined for solutions in ethanol, with a Unicam SP 1 800 spectrometer. ^{1}H N.m.r. spectra were recorded on a Perkin-Elmer R 12a 60 MHz instrument for solutions in deuteriochloroform with tetramethylsilane as internal standard, unless otherwise stated; 80, 90, and 250 MHz spectra were obtained on Varian CFT 20, Perkin-Elmer R 32, and Brüker WM 250 instruments, respectively. Mass spectra were obtained with an AE MS 902 or a VG 7070 instrument. M.p.s were determined with a Kofler hot-stage apparatus. Preparative chromatography was carried out on columns of Merck silica gel 60 (finer than 230 mesh ASTM) using the slightly increased pressure provided by a Metcalf Hy-flo pump. Mixtures of ethyl acetate and light petroleum were used as eluant. Light petroleum refers to the fraction with b.p. 60—80 °C. Anhydrous magnesium sulphate was used for drying solutions. All the compounds are racemic.

1-[*Benzyloxycarbonyl(hydroxy)methyl*]-4-*vinylazetidin*-2-*one* (7).—4-Vinylazetidin-2-one [10] (6) (9.7 g) and benzyl glyoxylate monohydrate (36.4 g) were refluxed in benzene (300 ml) for 3 h with provision for the removal of water. The solvent was evaporated off and the residue chromatographed to give the *hydroxy-ester* (7) as a clear, viscous oil (20 g), $\nu_{max.}$ 3 300 br, 1 760, and 1 750 cm^{-1}; δ(90 MHz) 2.68 and 3.17 (2 H, AB q, *J* 15 Hz, each arm showing further coupling of 3 and 5 Hz respectively), 4.0—4.5 (2 H, m, becomes 1 H, m, on D_2O exch.), 5.0—6.2 (6 H, m), and 7.42 (5 H, m) (Found: C, 64.5; H, 5.8; N, 5.2. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.8; N, 5.4%).

(4RS)-1-[(1RS)- *and* (1SR)-1-*Benzyloxycarbonyl*-2-*methoxycarbonyl*-2-*triphenylphosphoranylidene-ethyl*]-4-*vinylazetidin*-2-*one* (9) *and* (10).—A solution of the carbinol (7) (392 mg) in dry tetrahydrofuran (THF) (10 ml) was cooled to −20 °C and treated with 2,6-dimethylpyridine (0.26 ml) followed, during 5—10 min, by thionyl chloride (0.17 ml) in THF (3 ml). The precipitate was removed and the filtrate evaporated to leave 1-[benzyloxycarbonyl(chloro)methyl]-4-vinylazetidin-2-one (8) as a gum. This compound was dissolved in dry MDC (20 ml) and treated under argon with methoxycarbonylmethylenetriphenylphosphorane (1.1 g). After 24 h at room temperature, the solvent was evaporated off and the residue chromatographed. The less polar isomer (9) was isolated as a white, amorphous solid (518 mg), $\lambda_{max.}$ 270 nm (ε 4 170); $\nu_{max.}$ 1 740, 1 730, 1 630, and 1 620 cm^{-1}. Further elution of the column provided the more polar isomer (10) as an amorphous solid (330 mg), $\lambda_{max.}$ 269 nm (ε 4 360); $\nu_{max.}$ 1 745, 1 740, 1 640, and 1 610 cm^{-1}.

(2RS, 5SR)-*Benzyl* 3-*Methoxycarbonyl*-7-*oxo*-1-*azabicyclo*-[3.2.0]*hept*-3-*ene*-2-*carboxylate* (13).—The phosphorane (9) (786 mg) was dissolved in ethyl acetate (21 ml) and trifluoroacetic acid (1.05 ml) added. After 5 min, the solution was cooled to −76 °C and treated with ozone in oxygen until it became pale blue. The excess of ozone was removed by passing argon through the solution for 20 min. Triphenylphosphine (356 mg) in ethyl acetate (3 ml) was then added and the mixture warmed to 0 °C. After 20 min at 0 °C saturated aqueous sodium hydrogen carbonate was added with vigorous stirring. The organic layer was separated, washed with brine, dried, and evaporated. Chromatography provided the 1-*azabicyclohept*-3-*ene* (13) as a white, crystalline solid (261 mg), m.p. 79—80 °C (ethyl acetate–light petroleum); $\nu_{max.}$ (Nujol) 1 775, 1 730sh, 1 725, and 1 625 cm^{-1}; δ(90 MHz) 2.96 and 3.47 (2 H, AB q, *J* 16 Hz, each arm showing further coupling of 3 and 6 Hz respectively), 3.67 (3 H, s), 4.65 (1 H, m), 5.18 (2 H, s), 5.36 (1 H, dd, *J* 1.5 and 3 Hz), 7.10 (1 H, dd, *J* 1.5 and 1.5 Hz), and 7.33 (5 H, s) (Found: C, 63.9; H, 5.1; N, 4.8. $C_{16}H_{15}NO_5$ requires C, 63.8; H, 5.0; N, 4.7%).

(2RS, 5RS)-*Benzyl* 3-*Methoxycarbonyl*-7-*oxo*-1-*azabicyclo*-[3.2.0]*hept*-3-*ene*-2-*carboxylate* (14).—The phosphorane (10) (387 mg) was ozonised in ethyl acetate (10 ml) as described for its isomer (9). The initial product was the aldehyde (12). The dried ethyl acetate solution (50 ml) containing compound (12) was refluxed under argon for 9 h. The solvent was evaporated off and the residue chromatographed to provide the 1-*azabicyclohept*-3-*ene* (14) as an oil (63 mg), $\nu_{max.}$ 1 778, 1 735, 1 730, and 1 625 cm^{-1}; δ (80 MHz) 3.08 and 3.43 (2 H, AB q, *J* 16 Hz, higher field arm showing further coupling of 4 Hz and lower field arm further coupling of 1.5 and 6 Hz), 3.63 (3 H, s), 4.50 (1 H, m), 4.73 (1 H, m), 5.14 and 5.27 (2 H, AB q, *J* 12 Hz), 7.05 (1 H, dd, *J ca.* 1.5 and 1.5 Hz), and 7.30 (5 H, s) (Found: M^+, 301.0929. $C_{16}H_{15}NO_5$ requires *M*, 301.0950).

Conversion of the (2RS, 5RS)-*Compound* (14) *into its* (2RS, 5SR)-*Isomer*.—The 1-azabicyclohept-3-ene (14) (7 mg) was dissolved in chloroform (0.5 ml) and DBU (2 mg) added. After 1 h at room temperature t.l.c. showed that no starting material remained. Chromatography afforded the isomer (13) (5 mg), identical in all respects with the authentic material.

Benzyl 3,3-*Dimethyl*-2-*nitroacrylate* (17).—Benzyl 3,3-dimethylacrylate (80 g) was added dropwise to a well-stirred mixture of fuming nitric acid (157 ml; 95%) and water (34 ml) at −20 °C during 1 h. After 2 h at −20 °C followed by warming to 0 °C for 2 h, the reaction mixture was poured into ice (800 ml) and extracted with chloroform (3 × 200 ml). The combined organic extracts were washed successively with water (3 × 200 ml), saturated aqueous sodium hydrogen carbonate (2 × 350 ml), and brine (2 × 200 ml), dried and evaporated. Chromatography gave the product (17) as an oil (36 g), $\nu_{max.}$ (film) 1 715, 1 650, 1 530, and 1 370 cm^{-1}; δ 1.98 (3 H, s), 2.23 (3 H, s), 5.20 (2 H, s), and 7.40 (5 H, m) (Found: C, 61.2; H, 5.7; N, 6.0. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.5; N, 6.0%).

Further elution of the column provided ring-nitrated material which was not further investigated.

Benzyl 2-(N-*Cinnamylideneamino*)-3,3-*dimethylacrylate* (19).—Benzyl 3,3-dimethyl-2-nitroacrylate (17) (17.2 g) was converted into benzyl 2-amino-3,3-dimethylacrylate (18) (12.2 g) using the same conditions as for the corresponding methyl ester,[16] $\nu_{max.}$ 1 710, 1 690, and 1 640 cm^{-1}; δ(90 MHz) 1.70 (3 H, s), 2.05 (3 H, s), 2.8—3.7 (2 H, m, exch. D_2O), 5.17 (2 H, s), and 7.31 (5 H, s). The crude product (18) (80% pure by n.m.r. spectroscopy) in dry MDC (50 ml) was vigorously stirred with *trans*-cinnamaldehyde (7.72 g) and anhydrous magnesium sulphate (7 g) for 17 h. The mixture was filtered and the solvent evaporated off to give the Schiff base (19) as a red gum (19.7 g), $\lambda_{max.}$ 297 nm (ε 27 600); $\nu_{max.}$ 1 710, 1 665, and 1 625 cm^{-1}; δ(90 MHz) 1.91 (3 H, s), 2.00 (3 H, s), 5.26 (2 H, s), 6.5—7.6 (7 H, m), and 7.75 (1 H, d, *J* 7 Hz). The crude material was used directly without purification.

(3RS, 4SR)-3-*Azido*-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*styrylazetidin*-2-*one* (20). Azidoacetic acid (9.36 g) was dissolved in dry MDC (80 ml) at 0 °C under argon and trifluoroacetic anhydride (13.05 ml) added dropwise during 10 min. After 15 min, triethylamine (12.99 ml) in MDC (20 ml) was carefully added dropwise during 15 min and stirring at 0 °C continued for a further 45 min. The solu-

tion was transferred under argon to a dropping funnel, cooled to −76 °C, and added during 1 h to a mixture of the Schiff base (19) (19.7 g) and triethylamine (12.99 ml) in MDC (160 ml) at 0 °C. After a further 1 h at 0 °C, the solution was diluted with MDC, washed successively with water, dilute aqueous sodium hydrogen carbonate, and brine, dried, and evaporated. Chromatography of the residue afforded the product (20) (12.55 g) as a pale red-orange gum, $\lambda_{max.}$ 256 nm (ε 23 400); $\nu_{max.}$ 2 115, 1 760, and 1 720 cm^{-1}; δ (80 MHz) 1.98 (3 H, s), 2.21 (3 H, s), 4.63 (1 H, dd, *J* 7 and 10 Hz), 5.08 and 5.32 (2 H, AB q, *J* 15 Hz), 6.11 (1 H, dd, *J* 10 and 20 Hz), 6.48 (1 H, d, *J* 20 Hz), 7.29 (5 H, s), and 7.37 (5 H, s) (Found: C, 68.4; H, 5.5; N, 14.0. $C_{23}H_{22}N_4O_3$ requires C, 68.7; H, 5.5; N, 13.9%).

(3RS, 4SR)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*phenoxyacetamido*-4-*styrylazetidin*-2-*one* (21).—To the β-lactam (20) (6.38 g) in dry MDC (125 ml) at 0 °C was added triethylamine (2.45 ml). Hydrogen sulphide was bubbled through the mixture for 5 min and the resulting dark solution left at 0 °C for 1.5 h. The solvent was then removed under reduced pressure and the residue re-evaporated (× 3) from MDC to afford an orange solid. Without further purification, the solid was dissolved in dry MDC (60 ml) at −20 °C and triethylamine (2.45 ml) added, followed by dropwise addition of phenoxyacetyl chloride (2.45 ml) in MDC (5 ml) during 10 min. The solvent was evaporated off and the residue taken up in ethyl acetate, washed successively with water, dilute aqueous sodium hydrogen carbonate, and brine, dried and evaporated. Chromatography provided the product (21) as a white, crystalline solid (5.48 g), m.p. 107—108 °C (ethyl acetate–light petroleum), $\nu_{max.}$ 258 nm (ε 23 200); $\nu_{max.}$ 3 245, 1 755, 1 690, 1 650sh, and 1 630sh cm^{-1}; δ(90 MHz) 2.05 (3 H, s), 2.18 (3 H, s), 4.44 (2 H, s), 4.67 (1 H, dd, *J* 5 and 8 Hz), 5.08 and 5.27 (2 H, AB q, *J* 12 Hz), 5.20 (1 H, dd, *J* 5 and 8 Hz), 6.04 (1 H, dd, *J* 8 and 16 Hz), 6.47 (1 H, d, *J* 16 Hz), 6.7—7.5 (10 H, m), and 7.63 (1 H, d, *J* 8 Hz exch. D_2O) (Found: C, 72.7; H, 5.9; N, 5.4. $C_{31}H_{30}N_2O_5$ requires C, 72.9; H, 5.9; N, 5.5%).

(3RS, 4RS)-1-(*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(1,2-*dibromo*-2-*phenylethyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (22).—The lactam (21) (2 g) was dissolved in MDC (40 ml) at 0 °C and bromine (0.25 ml) in MDC (3 ml) added dropwise during 15 min. After an additional 10 min the reaction was diluted with MDC (30 ml) and washed with 5% aqueous sodium thiosulphate solution. The organic layer was separated, washed successively with brine, water, and brine, dried and evaporated. Chromatography afforded the dibromide (22) as an amorphous solid (1.49 g), $\nu_{max.}$ 3 400 1 765, 1 715sh, 1 690, and 1 630sh cm^{-1}. The product was clearly a mixture of isomers, in the ratio *ca.* 2 : 1, and the ^1H n.m.r. spectrum showed *inter alia* δ(90 MHz) 2.0, 2.17, 2.23 (all s, together 6 H), 4.52 (2 H, s), 5.22 (2 H, s), and 5.5—5.8 (1 H, m, becomes 2 d, at 5.52 and 5.69, each *J* 6 Hz, on D_2O exch.) (Found: C, 55.6; H, 4.4; Br, 23.7; N, 4.2. $C_{31}H_{30}Br_2N_2O_5$ requires C, 55.5; H, 4.5; Br, 23.9; N, 4.2%).

In larger scale experiments another product was also isolated by crystallisation from column fractions containing compound (22). The material has been assigned structure (24) or (25). For example, bromination of the azetidinone (21) (8 g) as above afforded the dibromide (22) (4.93 g) and the crystalline compound (720 mg), m.p. 185 °C (ethyl acetate–light petroleum); $\nu_{max.}$ (Nujol) 1 778, 1 720, 1 685, and 1 645 cm^{-1}; δ(90 MHz) 1.99 (3 H, s), 2.22 (3 H, s), 3.71 (1 H, dd, *J* 5 and 10 Hz), 4.82 (1 H, dd, *J* 4 and 5 Hz), 4.92 (1 H, d, *J* 10 Hz) (the last two signals partially obscure an AB q due to the $=NCH_2$ moiety), 5.14 and 5.32 (2 H, AB q, *J* 12 Hz), 5.60 (1 H, d, *J* 4 Hz), and 6.8—7.5 (15 H, m) (Found: C, 63.1; H, 4.9; Br, 13.3; N, 5.0. $C_{31}H_{29}BrN_2O_5$ requires C, 63.2; H, 4.8; Br, 13.6; N, 4.8%).

(3RS, 4SR)-1-[*Benzyloxycarbonyl*(*hydroxy*)*methyl*]-3-*phenoxyacetamido*-4-*styrylazetidin*-2-*one* (27).—The β-lactam (22) (335 mg) was dissolved in MDC (6 ml) at −20 °C and the solution ozonised until a pale blue colour persisted. The solution was purged with argon for 20 min and then allowed to warm to room temperature. Glacial acetic acid (6 ml) was added, followed immediately by freshly activated zinc dust (357 mg). After being stirred for 1 h, the mixture was filtered through Kieselguhr, the filter cake being washed well with ethyl acetate. The filtrate was washed successively with water (× 2), aqueous sodium hydrogen carbonate, and brine, dried, and evaporated. Chromatography gave the less polar isomer (27) as a crystalline solid (67 mg), m.p. 149—152 °C (ethyl acetate–hexane); $\nu_{max.}$ 3 500, 3 415, 1 770, 1 750, 1 690, and 1 655 sh cm^{-1}; δ(250 MHz) 4.25br (1 H, s exch. D_2O), 4.38 (2 H, s), 4.47 (1 H, dd, *J* 5.5 and 8 Hz), 5.27 (2 H, AA′ system), 5.4 (1 H, dd, *J* 5.5 and 9 Hz), 5.42 (1 H, s), 6.03 (1 H, dd, *J* 8 and 16 Hz), 5.53 (1 H, d, *J* 16 Hz), and 6.7—7.5 (11 H, m) (Found: C, 68.9; H, 5.5; N, 5.6. $C_{28}H_{26}N_2O_6$ requires C, 69.1; H, 5.3; N, 5.8%).

Further elution gave the more polar isomer (27) (50 mg), m.p. 150—156 °C (ethyl acetate–hexane); $\nu_{max.}$ 3 500, 3 410, 1 770, 1 750, 1 690, and 1 655 cm^{-1}; δ(250 MHz) 4.4 (2 H, s, this signal obscures a 1 H br s, exchanged by D_2O), 4.7 (1 H, dd, *J* 5.5 and 8 Hz), 4.92 and 5.14 (2 H, AB q, *J* 12 Hz), 5.42 (1 H, s), 5.45 (1 H, dd, *J* 5.5 and 9 Hz), 5.91 (1 H, dd, *J* 8 and 16 Hz), 6.68 (1 H, d, *J* 16 Hz), and 6.7—7.5 (11 H, m) (Found: C, 69.4; H, 5.5; N, 5.7%).

(3RS, 4RS)-1-(1-*Benzyloxycarbonyl*-2-*methoxycarbonyl*-2-*triphenylphosphoranylidene-ethyl*)-3-*phenoxyacetamido*-4-*styrylazetidin*-2-*one* (29).—The alcohol (27) (0.972 g) was converted into the phosphorane (29) as described for compound (7). The product (29) was isolated as an inseparable mixture of isomers, $\nu_{max.}$ (Nujol) 3 330, 1 765, 1 760, 1 732, 1 690, 1 685, and 1 638 cm^{-1} (Found: C, 72.8; H, 5.4; N, 3.5. $C_{49}H_{43}N_2O_7P$ requires C, 73.3; H, 5.4; N, 3.5%).

(3RS, 4RS)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*dimethoxymethyl*-3-*phenoxyacetamidoazetidin*-2-*one* (23).—Ozonised oxygen was bubbled through a solution of the β-lactam (21) (3.06 g) in MDC (30 ml) at −76 °C for 1.5 h, when cleavage of the 4-styryl moiety was complete (t.l.c. control). Argon was then bubbled through the solution for 20 min, triphenylphosphine (1.56 g) in a little MDC was added, and the reaction allowed to reach room temperature. After 1.5 h the solvent was removed and the residual oil immediately taken up in methanol (50 ml) and 2,2-dimethoxypropane (20 ml). The solution was refluxed for 16 h with toluene-*p*-sulphonic acid as catalyst. The reaction mixture was diluted with ethyl acetate, and washed successively with dilute aqueous sodium hydrogen carbonate and brine; it was then dried and evaporated. Chromatography provided the product (23) (2.6 g), $\nu_{max.}$ 3 420, 1 755, 1 715sh, 1 685, and 1 630 cm^{-1}; δ(90 MHz) 2.02 (3 H, s), 2.20 (3 H, s), 3.22 (6 H, s), 4.17 (1 H, dd *J* 3 and 6 Hz), 4.33 (1 H, d, *J* 3 Hz), 4.60 (2 H, s), 5.08 and 5.30 (2 H, AB q, *J* 12 Hz), 5.47 (1 H, dd, *J* 6 and 10 Hz), 6.8—7.5 (10 H, m), and 7.6 (1 H, d, *J* 10 Hz) (Found: C, 64.7; H, 6.2; N, 5.8. $C_{26}H_{30}N_2O_7$ requires C, 64.7; H, 6.2; N, 5.8%).

(3RS, 4RS)-1-[*Benzyloxycarbonyl*(*hydroxy*)*methyl*]-4-*dimethoxymethyl*-3-*phenoxyacetamidoazetidin*-2-*one* (28).—The

lactam (23) (2.4 g) was converted into the alcohol (28) as described for compound (23). Chromatography afforded the less polar isomer (28) (900 mg), $\nu_{max.}$ 3 500, 3 420, 1 780, 1 758, and 1 690 cm^{-1}; δ(250 MHz), 3.31 (3 H, s), 3.32 (3 H, s), 3.85 (1 H, dd, *J* 2.7 and 5.5 Hz), 4.24 (1 H, d, *J* 2.7 Hz), 4.26 (1 H, d, *J* 10.5 Hz, exch. D_2O), 4.47 and 4.55 (2 H, AB q, *J* 14.9 Hz), 5.19 and 5.29 (2 H, AB q, *J* 12.1 Hz), 5.52 (1 H, dd, *J* 5.5 and 10.5 Hz), 5.63 (1 H, d, *J* 10.5 Hz, becomes s on D_2O exch.), 6.85—7.4 (10 H, series of m), and 7.51 (1 H, d, *J* 10.5 Hz) (Found: C, 60.3; H, 6.0; N, 6.1. $C_{23}H_{26}N_2O_8$ requires C, 60.3; H, 5.7; N, 6.1%).

Further elution provided the more polar isomer (28) (1 g), $\nu_{max.}$ 3 500, 3 415, 1 780, 1 750 sh, and 1 690 cm^{-1}; δ(250 MHz) 3.22 (3 H, s), 3.35 (3 H, s), 4.05 (1 H, d, *J* 6.6 Hz), exch. D_2O), 4.15 (1 H, dd, *J* 3.9 and 5.5 Hz), 4.3 (1 H, d, *J* 3.9 Hz), 4.48 and 4.54 (2 H, AB q, *J* 15.2 Hz), 5.2 and 5.31 (2 H, AB q, *J* 12.1 Hz), 5.43 (1 H, d, *J* 6.6 Hz collapses to s on D_2O exch.), 5.51 (1 H, dd, *J* 5.5 and 9.7 Hz), 6.9—7.4 (10 H, series of m), and 7.5 (1 H, d, *J* 9.7 Hz) (Found: C, 60.2; H, 5.7; N, 6.2%).

(3RS, 4RS)-1-(1-*Benzyloxycarbonyl*-2-*methoxycarbonyl*-2-*triphenylphosphoranylidene-ethyl*)-4-*dimethoxymethyl*-3-*phenoxyacetamidoazetidin*-2-*one* (30).—The hydroxy-compound (28) (210 mg) was converted into the phosphorane (30) as described for compound (27). The product, an amorphous solid, was an inseparable mixture of isomers (153 mg), $\nu_{max.}$ 3 390, 1 755, 1 678, and 1 620 cm^{-1} (Found: C, 68.4; H, 5.5; N, 3.3. $C_{44}H_{43}N_2O_9P$ requires C, 68.2; H, 5.5; N, 3.6%).

[(2RS, 5RS, 6SR)-*Benzyl* 3-*Methoxycarbonyl*-7-*oxo*-6-*phenoxyacetamido*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (31) and (3RS, 4RS)-1-[(1SR)-1-*Benzyloxycarbonyl*-2-*methoxycarbonyl*-2-*triphenylphosphoranylidene-ethyl*]-4-*formyl*-3-*phenoxyacetamidoazetidin*-2-*one* (34).—*Method A*. The phosphorane (29) (845 mg) in ethyl acetate (25 ml) containing trifluoroacetic acid (2.5 ml) was converted into the 1-azabicyclohept-3-ene (31) as described for compound (9). The product was isolated as an amorphous solid (200 mg), $\nu_{max.}$ 3 410, 1 790, 1 735, and 1 690 cm^{-1}; δ(250 MHz) 3.65 (3 H, s), 4.50 (2 H, s), 4.98 (1 H, ddd, *J* 5.5, 3.3 and *ca.* 1.5 Hz), 5.16 (2 H, s), 5.37 (1 H, dd, *J* 3.3 and 1.8 Hz), 5.54 (1 H, dd, *J* 7 and 5.5 Hz), 6.80 (1 H, dd, *J* 1.8 and 1.5 Hz), and 6.8—7.4 (11 H, m) (Found: C, 63.7; H, 5.2; N, 5.8. $C_{24}H_{22}N_2O_7$ requires C, 64.0; H, 4.9; N, 6.2%).

Further elution provided the aldehyde (34) (280 mg) (contaminated with some triphenylphosphine oxide), $\nu_{max.}$ 3 375br, 1 760, 1 725, 1 685, and 1 615 cm^{-1}.

Method B. The phosphorane (30) (54 mg) was dissolved in 95% aqueous trifluoroacetic acid (1 ml) at room temperature and, after 3 h, the solution was evaporated, toluene added and the process repeated. The residue was taken up in ethyl acetate and the solution washed successively with aqueous sodium hydrogen carbonate and brine, dried and evaporated. Chromatography gave the required 1-azabicyclohept-3-ene (31) (13 mg) and the aldehyde (34) (35 mg) (contaminated with some triphenylphosphine oxide).

(2RS, 5SR, 6RS)-*Benzyl* 3-*Methoxycarbonyl*-7-*oxo*-6-*phenoxyacetamido*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (32).—The aldehyde (34) (289 mg) (from method A, contaminated with triphenylphosphine oxide) was gently refluxed in ethyl acetate for 5 h. The solution was cooled and evaporated to give an oil. Chromatography provided the product (32) as an amorphous, white solid (99 mg), $\nu_{max.}$ 3 410, 1 785, 1 735, and 1 690 cm^{-1}; δ(90 MHz) 3.64 (3 H, s), 4.50 (2 H, s), 4.83 (2 H, m), 5.22 (2 H, s), 5.43 (1 H, m), 6.79 (1 H, m), 7.03 (1 H, d, *J* 7 Hz), and 6.8—7.4 (10 H, m) (Found: C, 64.0; H, 5.2; N, 5.7%; M^+, 450.1425. $C_{24}H_{22}N_2O_7$ requires C, 64.0; H, 4.9; N, 6.2%; *M*, 450.1433).

The aldehyde (34) (35 mg) (from method B, contaminated with some triphenylphosphine oxide) similarly provided the product (32) (15 mg).

(2RS, 5RS, 6SR)-3-*Methoxycarbonyl*-7-*oxo*-6-*phenoxyacetamido*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylic Acid* (35).—The ester (31) (15 mg) was hydrogenated over 10% Pd–C (7 mg) in dioxan (4 ml) and water (1 ml) for 10 min. The catalyst was filtered off (Kieselguhr) and the filtrate evaporated. Ethanol was added and the solvent evaporated off to give a white solid which was dried *in vacuo*. The residue was triturated with diethyl ether to give the acid (35) (13 mg), $\nu_{max.}$ (KBr) 3 410, 1 775, 1 715, 1 675, and 1 600 cm^{-1}; δ[250 MHz; D_2O–$(CD_3)_2SO$] 3.63 (3 H, s), 4.52 (2 H, s), 4.79 (1 H, ddd, *J* 5.7, 3.5, and 1.8 Hz), 4.93 (1 H, dd, *J* 3.5 and 1.8 Hz), 5.34 (1 H, d, *J* 5.7 Hz), 6.63 (1 H, dd, *J* 1.8 and 1.8 Hz), and 6.8—7.3 (5 H, m).

(2RS, 5RS, 6SR)-*Methyl* 3-*Methoxycarbonyl*-7-*oxo*-6-*phenoxyacetamido*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (36).—The acid (35) (20 mg) was dissolved in dimethyl sulphoxide (0.25 ml) and ethyl acetate (1 ml) and an excess of diazomethane in diethyl ether added. After 10 min the solution was purged with argon, washed with water, dried, and evaporated. Chromatography afforded the *dimethyl ester* (36) (17 mg), m.p. 82—85 °C (ethyl acetate–light petroleum); $\nu_{max.}$ (Nujol) 3 360, 1 790, 1 740, 1 730, 1 690, 1 660, and 1 620 cm^{-1}; δ(80 MHz) 3.76 (3 H, s), 3.79 (3 H, s), 4.54 (2 H, s), 5.01 (1 H, m, *J* 5.3, 3.5, and 1.5 Hz), 5.36 (1 H, dd, *J* 3.5 and 1.8 Hz), 5.56 (1 H, dd, *J* 7.2 and 5.3 Hz), 6.82 (1 H, dd, *J* 1.5 and 1.8 Hz), and 6.91—7.42 (6 H, m) (Found: C, 57.8; H, 4.6; N, 7.6. $C_{18}H_{18}N_2O_7$ requires C, 57.8; H, 4.8; N, 7.5%).

(3RS, 4RS)-4-(1,2-*Dibromo*-2-*phenylethyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (37).—Powdered potassium permanganate (0.177 g) was added to the β-lactam (22) (0.5 g) in *N*,*N*-dimethylformamide (DMF) (5 ml) and water (1 ml) at — 20 °C. The reaction mixture was warmed to 0 °C and, after 1 h, ethyl acetate was added and sulphur dioxide passed through the mixture. The latter was washed successively with water, dilute hydrochloric acid (0.5N), dilute aqueous sodium hydrogen carbonate, and brine, and then dried and evaporated. Chromatography gave the *azetidin*-2-*one* (37) as a white crystalline solid (0.13 g), m.p. 143—145 °C (decomp.) (ethyl acetate–light petroleum), $\nu_{max.}$ (Nujol) 3 320, 1 775, and 1 670 cm^{-1}; δ[$CDCl_3$–$(CD_3)_2SO$]; 80 MHz] 4.07 (1 H, dd, *J* 6.5 and 8.5 Hz), 4.60 (2 H, s), 4.8—5.3 (4 H, m), 6.5—7.5 (10 H, m), 8.38 (1 H, s), and 8.80 (1 H, d, *J* 8 Hz) (Found: C, 47.3; H, 3.4; Br, 33.4; N, 5.7. $C_{19}H_{18}Br_2N_2O_3$ requires C, 47.3; H, 3.7; Br, 33.2; N, 5.8%).

(3RS, 4SR)-3-*Phenoxyacetamido*-4-*styrylazetidin*-2-*one* (39).—Activated zinc dust (0.143 g) was added in one portion to the β-lactam (37) (90 mg) in MDC (10 ml) and glacial acetic acid (1 ml) at room temperature. After 10 min the mixture was filtered and the filtrate diluted with MDC and washed successively with water, aqueous sodium hydrogen carbonate, and brine; it was then dried and evaporated. The azetidin-2-one (39) was isolated as a white crystalline solid (60 mg), m.p. 181—182 °C (ethyl acetate); $\nu_{max.}$ 258 nm (ε 19 200), $\nu_{max.}$ (Nujol) 3 290, 3 225, 1 780, 1 730, and 1 680 cm^{-1}; δ[$(CD_3)_2SO$], 250 MHz] 4.43 (1 H, dd, *J* 8.2 and 5 Hz), 4.49 and 4.57 (2 H, AB q, *J* 15 Hz), 5.27 (1 H, ddd, *J* 9.2, 5, and *ca.* 0.5 Hz), 6.38 (1 H, dd, *J* 16 and 8.2 Hz), 6.65 (1 H,

d, *J* 16 Hz), 6.8—7.5 (10 H, m), 8.53 (1 H, d, *J* *ca.* 0.5 Hz, exch. D_2O), and 8.88 (1 H, d, *J* 9.2 Hz, exch. D_2O) (Found: C, 70.8; H, 5.7; N, 8.5. $C_{19}H_{18}N_2O_3$ requires C, 70.8; H, 5.6; N, 8.7%).

(3RS, 4RS)-4-*Dimethoxymethyl*-3-*phenoxyacetamidoazetidin*-2-*one* (38).—The acetal (23) (82 mg) in DMF (0.8 ml), pyridine (0.8 ml), and water (0.32 ml) at 0 °C was treated with potassium permanganate (40 mg). After 1 h the mixture was diluted with ethyl acetate and a little water, and sulphur dioxide bubbled through to give a clear solution. The organic layer was separated, washed successively with dilute hydrochloric acid (0.25N), dilute aqueous sodium hydrogen carbonate, and brine, and then dried and evaporated. Chromatography afforded the *azetidin*-2-*one* (38) as a white crystalline solid (10 mg), m.p. 136 °C (ethyl acetate–hexane); $\nu_{max.}$ 3 430, 1 780, and 1 690 cm^{-1}; δ(250 MHz), 3.36 (3 H, s), 3.43 (3 H, s), 3.98 (1 H, dd, *J* 5 and 3 Hz), 4.33 (1 H, d, *J* 3 Hz), 4.51 and 4.58 (2 H, AB q, *J* 15 Hz), 5.56 (1 H, dd, *J* 10 and 5 Hz, each part shows unresolved fine coupling, lost on D_2O exch.), 5.93br (1 H, s, exch. D_2O), 6.87—7.08 (3 H, m), 7.25—7.38 (2 H, m), and 7.5 (1 H, d, *J* 10 Hz, exch. D_2O) (Found: C, 57.2; H, 6.2; N, 9.5. $C_{14}H_{18}N_2O_5$ requires C, 57.1; H, 6.1; N, 9.5%).

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