A Short and Stereoselective Synthesis of the Carbapenem Antibiotic PS-5

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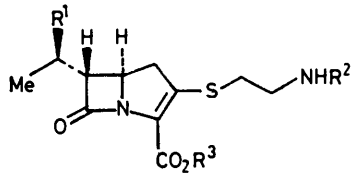
The benzyl ester (3) and *p*-nitrobenzyl ester (PNB ester) (4) of the antibiotic PS-5 and the bis-protected PS-6 (5) were stereoselectively synthesised by application of the new carbon–carbon bond formation reaction at the C-4-position of 4-acetoxy-3-ethyl- or 4-acetoxy-3-isopropyl-azetidin-2-ones [(10) or (11)].

ANTIBIOTICS PS-5 [1,2] (1) and PS-6 [3] (2) have been isolated from the fermentation broth of a soil micro-organism, *Streptomyces cremeus* subsp. *auratilis* A271(ATCC31358) and *Streptomyces fulvoridis* A933 as a new β-lactam antibiotic, and the full structure of antibiotic PS-5 has recently been reported by Ishikura and his co-workers [4] to be structure (1). Antibiotic PS-6 is closely related structurally to PS-5, with an isopropyl group instead of an ethyl group at C-6.

Both antibiotics display a broad spectrum of antibacterial activity against Gram-positive bacteria, including β-lactamase-producing organisms.[5] Efficient



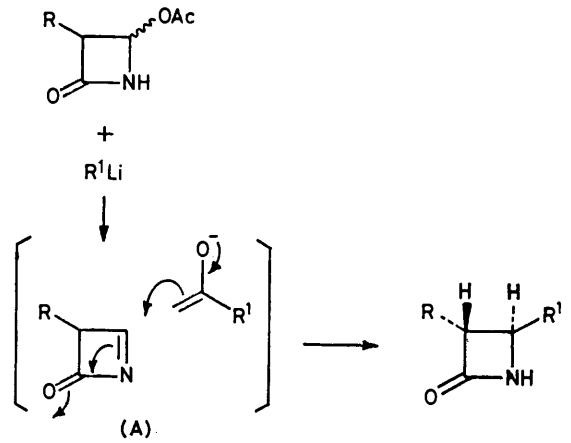
(1) $R^1 = R^3 = H$, $R^2 = Ac$
(2) $R^1 = Me$, $R^2 = Ac$, $R^3 = H$
(3) $R^1 = H$, $R^2 = Ac$, $R^3 = CH_2Ph$
(4) $R^1 = H$, $R^2 = Ac$, $R^3 = CH_2C_6H_4NO_2$-*p*
(5) $R^1 = Me$, $R^2 = CO_2CH_2C_6H_4NO_2$-*p*, $R^3 = Bu^t$

preparation of these new β-lactams has recently received considerable attention. We report a facile stereoselective synthesis of the benzyl ester (3) and *p*-nitrobenzyl ester (4) of antibiotic PS-5 and the bis-protected PS-6 derivative (5).

RESULTS AND DISCUSSION

The key reaction in this synthesis is a new carbon–carbon bond formation at the C-4-position of azetidin-2-ones, as described before.[6] On consideration of the accepted reaction mechanism, *i.e.* Michael addition of enolate to the intermediate (A), it was expected that this reaction with 3-substituted azetidin-2-ones would lead to the derivatives with a *trans*-relationship between the C-3 and C-4 substituents.

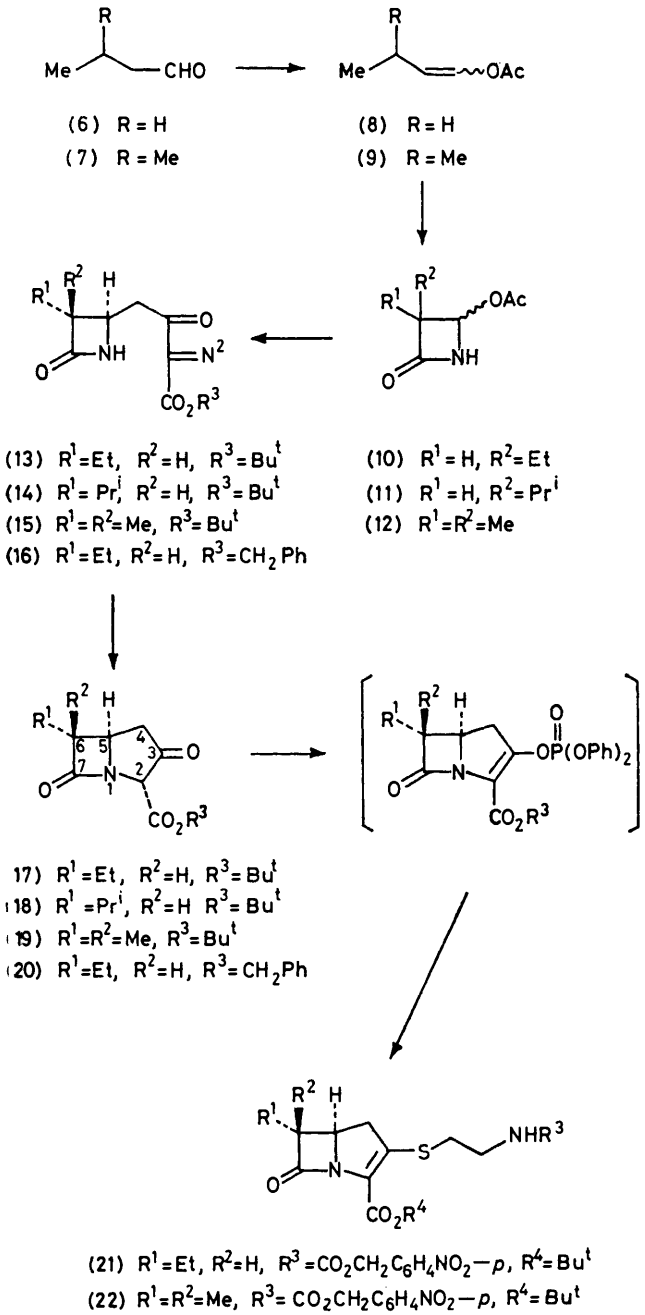
Thus, 3-substituted 4-acetoxyazetidin-2-ones were prepared as follows. According to House's procedure,[7] n-butyraldehyde (6) was treated with acetic anhydride in the presence of sodium acetate to give the enol acetate (8) ($E : Z = 3 : 2$) in 38% yield. Similar treatment on isovaleraldehyde (7) afforded the corresponding enol acetate (9) ($E : Z = 3 : 2$) in 40.3% yield. These enol acetates were converted to the azetidinones (10) and (11) by treatment with chlorosulphonyl isocyanate (CSI)



(A)

in methylene chloride at 0 °C for 2 h, followed by reductive hydrolysis of the N–S bond, in 48 and 21.3% yields, respectively. Since the configuration at C-4 should be controlled in the Michael addition reaction of nucleophile to the intermediate (A), a stereoisomeric *cis,trans* mixture of the β-lactams (10) and (11) was used in the next reaction without separation. The β-lactam (10) was treated with t-butyl α-diazoacetoacetate [8] in the presence of lithium hexamethyldisilazide at 78 °C for 2 h, to afford the C-4-substituted product (13) in 12% yield. Its i.r. spectrum showed the expected amide, diazo, and ester absorptions at 3 430, 2 170, 1 760, 1 720, and 1 648 cm^{-1}. In our synthetic scheme, the diazo-group plays two important roles; in protection of the active methylene during substitution, and in reaction as a carbene precursor in the subsequent insertion reaction. The diazo-compound (13) was then thermally cyclised in the presence of rhodium acetate [9] to the bicyclic keto-ester (17) in quantitative yield, whose n.m.r. spectrum exhibited a characteristic C-5-proton at δ 3.87 as a double triplet (*J* 2 and 7 Hz), and the C-2-proton as a singlet at δ 4.52, and its i.r. spectrum showed carbonyl absorptions at 1 770 and 1 735 cm^{-1}. The *trans*-configuration of the C-5 and C-6 substituents in the bicyclic keto-ester (17) was easily deduced from the n.m.r. coupling constant, and the proposed reaction mechanism is therefore presumed to be

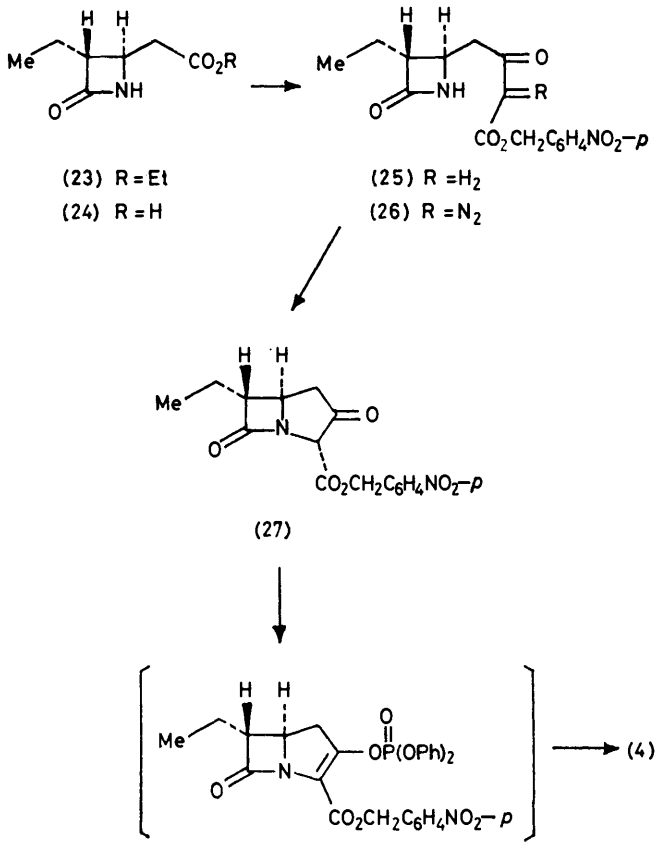
correct. In a similar manner, the bicyclic keto-esters (18) and (19) were synthesised in three steps, in 13 and 3% over-all yields, from (11) and (12),[10] respectively. The spectral data of (18) (see Experimental section), again indicated the *trans*-configuration at C-5 and C-6. Introduction of the *N*-*p*-nitrobenzyloxycarbonylcysteamine moiety to (17) was achieved by adoption of



SCHEME 1

Merck's method [11] as follows. Treatment of (17) with diphenyl chlorophosphate in the presence of *NN*-dimethylaminopyridine and ethyldi-isopropylamine in dry acetonitrile gave the isolable phosphate, which without isolation was reacted with *N*-*p*-nitrobenzyloxycarbonylcysteamine at 0 °C to furnish the antibiotic PS-5 derivative (21) in *ca.* 70% yield from (17). In a similar manner, the bicyclic keto-esters (18) and (19) were converted to the bis-protected PS-6 derivative (5) and 6,6-dimethyl compound (22) in 74 and 58% yields from (18) and (19), respectively.

The benzyl ester of antibiotic PS-5 was synthesised by an analogous route in order to confirm the structures, including the stereochemistry, of our synthetic carbapenems. The β-lactam (10) was treated with benzyl α-diazoacetoacetate in the presence of lithium hexamethyldisilazide to afford the diazo-compound (16), which was then cyclised to the bicyclic keto-ester (20)



SCHEME 2

by heating at 80 °C in the presence of rhodium acetate. *N*-Acetoxycysteamine [12] was successfully introduced to (20), *via* the phosphate intermediate, as described above, to give antibiotic PS-5 benzyl ester (3), whose spectroscopic data were indistinguishable from those provided by Dr. T. Ishikura of the Sanraku Ocean Co., Ltd.

Finally the deblockable PS-5 *p*-nitrobenzyl ester was synthesised by an alternative route. The β-lactam (10) was treated with ethyl acetate in the presence of lithium hexamethyldisilazide to afford the ester (23), which was then hydrolysed with 0.25N sodium hydroxide to give the acid (24). The imidazolide of the acid (24) was treated with the magnesium salt of mono-*p*-nitrobenzyl malonate [11] to furnish the β-keto-ester (25). The diazo-

exchange reaction of the keto-ester with tosyl azide gave the diazo-compound (26), which was converted to the bicyclic keto-ester (27) as described above. Introduction of *N*-acetylcysteamine to (27) afforded PS-5 *p*-nitrobenzyl ester (4), whose spectral data were superimposable on those provided by Dr. T. Ishikura.

Thus, a short and stereoselective synthesis of PS-5 and PS-6 antibiotics has been achieved by using a new carbon–carbon bond formation reaction at the C-4-position of 4-acetoxyazetidin-2-ones.

EXPERIMENTAL

I.r. spectra were obtained with a Hitachi 260-10 spectrometer, n.m.r. spectra with JEOL-PMX-60 and JEOL-PS-100 spectrometers ($SiMe_4$ as internal reference), and mass spectra with Hitachi M-52G and JEOL-JMS-01SG-2 spectrometers.

But-1-enyl Acetate (8).—A mixture of n-butyraldehyde (100 g), acetic anhydride (330 g), and sodium acetate (14 g) was heated at 80 °C for 12 h. After cooling the resulting mixture was diluted with n-pentane (100 ml), washed with water, saturated aqueous sodium hydrogencarbonate, and water, and dried (Na_2SO_4). Evaporation of the solvent gave a colourless oil, which was purified by distillation to afford the enol acetate (8) (*E* : *Z ca.* 3 : 2) (56 g, 38%), b.p. 45—55 °C at 20 mmHg, $\nu_{max.}$ ($CHCl_3$) 1 750 cm^{-1} (C=O).

3-Methylbut-1-enyl Acetate (9).—A mixture of isovaleraldehyde (100 g), acetic anhydride (330 g), and sodium acetate (15 g) was heated at 90 °C for 12 h, and worked up as above to afford the enol acetate (9) (*E* : *Z ca.* 3 : 2) (60 g, 40.3%), b.p. 38—65 °C at 20 mmHg, $\nu_{max.}$ ($CHCl_3$) 1 750 cm^{-1} (C=O).

4-Acetoxy-3-ethylazetidin-2-one (10).—To a stirred solution of the enol acetate (8) (10 g) in dry methylene chloride (10 ml) was added chlorosulphonyl isocyanate (7 ml) dropwise at 0 °C. After stirring for a further 2 h at 0 °C, the mixture was poured into an aqueous solution (300 ml) of sodium hydrogencarbonate (20 g) and sodium sulphide (10 g) at 0 °C with stirring. Stirring was again continued at 0 °C for 0.5 h and the mixture was extracted with methylene chloride. Evaporation of the solvent gave a yellow oil, which was chromatographed on silica gel using methylene chloride as eluant to afford the β-*lactam* (10) (*trans* : *cis ca.* 1 : 1) (5.4 g, 48%) as a yellow oil (Found: C, 53.25; H, 7.15; N, 8.70. $C_7H_{11}NO_3$ requires C, 53.50; H, 7.05; N, 8.90%); $\nu_{max.}$ ($CHCl_3$) 3 400 (NH) and 1 780, 1 740 cm^{-1} (C=O); δ ($CDCl_3$) 1.06 (6 H, t, *J* 7 Hz, CH_2Me), 1.73 (4 H, q, *J* 7 Hz, CH_2Me), 2.10 (6 H, s, OAc), 3.13 (2 H, br t, *J* 7 Hz, C-3-H), 5.53 (1 H, br s, C-4-H), 5.85 (1 H, d, *J* 4 Hz, C-4-H), and 6.93 (2 H, br s, NH).

4-Acetoxy-3-isopropylazetidin-2-one (11).—The enol acetate (9) (10 g) was treated with chlorosulphonyl isocyanate (7 ml) and worked up as above to afford the β-*lactam* (11) (*trans* : *cis ca.* 1 : 1) (2.6 g, 21.3%) as a yellow oil (Found: C, 55.95; H, 7.70; N, 8.05. $C_8H_{13}NO_3$ requires C, 56.10; H, 7.65; N, 8.20%); $\nu_{max.}$ ($CHCl_3$) 3 405 (NH) and 1 770, 1 735 cm^{-1} (C=O); δ ($CDCl_3$) 2.07 (6 H, s, OAc), 2.80—3.12 (2 H, m, C-3-H), 5.57 (1 H, br s, C-4-H), 5.85 (1 H, d, *J* 4 Hz, C-4-H), and 7.03 (2 H, br s, NH).

4-(3-Diazo-2-oxo-3-t-butoxycarbonylpropyl)-3-ethylazetidin-2-one (13).—To a stirred solution of lithium hexamethyldisilazide [prepared from n-butyl-lithium (0.64 g) and hexamethyldisilazane (1.61 g)] in tetrahydrofuran (10 ml) was added t-butyl α-diazoacetoacetate (1.84 g) at −78 °C, in a current of nitrogen. After stirring for a further 1.5 h at −78 °C, a solution of the β-lactam (10) (1.57 g) in tetrahydrofuran (5 ml) was added and the resulting mixture was again stirred at −78 °C for 2 h. The mixture was treated with water and extracted with methylene chloride. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent at 35 °C gave a reddish gum, which was chromatographed on silica gel using methylene chloride–acetone (95 : 5 v/v) as eluant to afford the diazo-compound (13) (337 mg, 12%) as a colourless gum; $\nu_{max.}$ ($CHCl_3$) 3 430 (NH), 2 170 (diazo), and 1 760, 1 720, 1 648 cm^{-1} (C=O); δ ($CDCl_3$) 1.03 (3 H, t, *J* 7 Hz, CH_2Me), 1.56 (9 H, s, Bu^t), 3.66 (1 H, m, C-4-H), and 6.10 (1 H, br s, NH).

4-(3-Diazo-2-oxo-3-t-butoxycarbonylpropyl)-3-isopropylazetidin-2-one (14).—The β-lactam (11) (1.71 g) was treated with the lithium salt of t-butyl α-diazoacetoacetate (1.84 g) and worked up as above to yield the diazo-compound (14) (417 mg, 14.1%) as a colourless gum; $\nu_{max.}$ ($CHCl_3$) 3 400 (NH), 2 140 (diazo), and 1 755, 1 710, 1 640 cm^{-1} (C=O); δ ($CDCl_3$) 0.98 (3 H, d, *J* 7 Hz, $CHMe$) 1.07 (3 H, d, *J* 7 Hz, $CHMe$), 1.53 (9 H, s, Bu^t), 3.50—3.85 (1 H, m, C-4-H), and 6.10 (1 H, br s, NH).

4-(3-Diazo-2-oxo-3-t-butoxycarbonylpropyl)-3,3-dimethylazetidin-2-one (15).—The β-lactam (12) (1.57 g) was treated with the lithium salt of t-butyl α-diazoacetoacetate (1.84 g) and worked up as above to afford the diazo-compound (15) (90 mg, 3.2%) as a colourless gum; $\nu_{max.}$ ($CHCl_3$) 3 405 (NH), 2 135 (diazo), and 1 760, 1 705, 1 640 cm^{-1} (C=O); δ ($CDCl_3$) 1.18 (3 H, s, C-3-Me), 1.37 (3 H, s, C-3-Me), 1.53 (9 H, s, Bu^t), 3.50—3.87 (1 H, m, C-4-H), and 6.07 (1 H, br s, NH).

t-Butyl trans-6α-*Ethyl-3,7-dioxo-1-azabicyclo*[3.2.0]*heptane-2-carboxylate* (17).—A solution of the diazo-compound (13) (100 mg) in dry benzene (10 ml) in the presence of a catalytic amount of rhodium acetate was warmed at 80 °C in a current of nitrogen for 0.5 h. After filtration and washing of the solid with benzene, the combined filtrates were evaporated to give the bicyclic keto-ester (17) (85.5 mg, 95%) as a colourless gum, $\nu_{max.}$ ($CHCl_3$) 1 770 and 1 735 cm^{-1} (C=O); δ ($CDCl_3$) 1.09 (3 H, t, *J* 7 Hz, CH_2Me), 1.42 (9 H, s, Bu^t), 3.87 (1 H, dt, *J* 2 and 7 Hz, C-5-H), 4.52 (1 H, s, C-2-H); *m/e* 197 ($M^+ - 56$), 152, and 96.

t-Butyl trans-6α-*Isopropyl-3,7-dioxo-1-azabicyclo*[3.2.0]*heptane-2-carboxylate* (18).—Thermal cyclisation of the diazo-compound (14) (100 mg) in benzene (10 ml) in the presence of a catalytic amount of rhodium acetate was carried out as above to furnish the bicyclic keto-ester (18) (83.3 mg, 92%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 760 and 1 735 cm^{-1} (C=O); δ ($CDCl_3$) 1.06 (3 H, d, *J* 7 Hz, $CHMe$), 1.12 (3 H, d, *J* 7 Hz, $CHMe$), 1.42 (9 H, s, Bu^t), 3.86 (1 H, dt, *J* 2 and 7 Hz, C-5-H), and 4.51 (1 H, s, C-2-H); *m/e* 211, 167, 166, and 111.

t-Butyl 6,6-*Dimethyl-3,7-dioxo-1-azabicyclo*[3.2.0]*heptane-2-carboxylate* (19).—The diazo-compound (15) (100 mg) was treated with a catalytic amount of rhodium acetate as above to give the bicyclic keto-ester (19) (85.5 mg, 95%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 760 and 1 735 cm^{-1} (C=O); δ ($CDCl_3$) 1.20 (3 H, s, C-6-Me) 1.48 (9 H, s, Bu^t), 1.57 (3 H, s, C-6-Me), and 4.45 (1 H, s, C-2-H).

Bis-protected PS-6 (5).—To a stirred solution of the keto-ester (18) (60 mg) in acetonitrile (3 ml) was added ethyldi-isopropylamine (35 mg) and diphenyl chlorophosphate (72 mg) at 0 °C in a current of nitrogen. After the stirring had been continued for 1 h at 0 °C, ethyldi-isopropylamine

(35 mg) and *N*-*p*-nitrobenzyloxycarbonylcysteamine (63 mg) was added to the above solution and stirred at 0 °C for 1.5 h. Evaporation of the solvent gave a yellowish oil which was subjected to silica gel column chromatography. Elution with benzene–acetone (95 : 5 v/v) afforded the bis-protected PS-6 (5) (84.0 mg, 74%), m.p. 118 °C; $\nu_{max.}$ $(CHCl)_3$ 3 410 (NH), 1 770 and 1 720 (C=O), and 1 345 cm^{-1} (NO_2); δ ($CDCl_3$) 0.98 (3 H, d, *J* 6.5 Hz, CH*Me*Me), 1.06 (3 H, d, *J* 6.5 Hz, CHMe*Me*), 1.53 (9 H, s, Bu^t), 3.91 (1 H, dt, *J* 3 and 9 Hz, C-5-H), 5.17 (2 H, s, CH_2Ar), 7.45 (2 H, d, *J* 9 Hz, aromatic protons), and 8.16 (2 H, d, *J* 9 Hz, aromatic proton); *m/e* 505 (M^+) (Found: M^+, 505.1865. $C_{24}H_{31}N_3O_7S$ requires *M*, 505.1882).

Bis-protected PS-5 (21).—To a stirred solution of the keto-ester (17) (66 mg) in acetonitrile (4 ml) in the presence of a catalytic amount of *NN*-dimethylaminopyridine was added ethyldi-isopropylamine (41 mg) and diphenyl chlorophosphate (85 mg) at 0 °C in a current of nitrogen. The mixture was further treated with ethyldi-isopropylamine (41 mg) and *N*-*p*-nitrobenzyloxycarbonylcysteamine (81 mg) as above to yield the bis-protected PS-5 (21) (85.8 mg, 67%), m.p. 124 °C; $\nu_{max.}$ ($CHCl_3$) 3 425 (NH), 1 770 and 1 720 (C=O), and 1 345 cm^{-1} (NO_2); δ ($CDCl_3$) 1.03 (3 H, t, *J* 7 Hz, CH_2Me), 1.53 (9 H, s, Bu^t), 1.77 (2 H, br q, *J* 7 Hz, CH_2Me), 3.91 (1 H, dt, *J* 3 and 9 Hz, C-5-H), 5.16 (2 H, s, CH_2Ar), 5.39 (1 H, br s, N*H*), 7.46 (2 H, d, *J* 8 Hz, aromatic protons), and 8.18 (2 H, d, *J* 8 Hz, aromatic proton); *m/e* 491 (M^+) (Found: M^+, 491.1772. $C_{23}H_{29}N_3O_5S$ requires *M*, 491.1726).

t-Butyl 6,6-*Dimethyl*-7-*oxo*-3-[2-(p-*nitrobenzyloxycarbonyl-amino*)*ethylthio*]*bicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (22).—The bicyclic keto-ester (19) (60 mg) was converted to the carbapenem (22) (70 mg, 60%), a colourless oil, as above; $\nu_{max.}$ ($CHCl_3$) 3 420 (NH), 1 770 and 1 720 (C=O), and 1 345 cm^{-1} (NO_2); δ ($CDCl_3$) 1.22 (3 H, s, C-6-Me), 1.45 (3 H, s, C-6-Me), 1.52 (9 H, s, Bu^t), 3.93 (1 H, dt, *J* 3 and 8 Hz, C-5-H), 5.12 (2 H, s, CH_2Ar), 5.29 (1 H, br s, NH), 7.36 (2 H, d, *J* 8 Hz, aromatic protons), and 8.90 (2 H, d, *J* 8 Hz, aromatic protons).

4-(3-*Benzyloxycarbonyl*-3-*diazo*-2-*oxopropyl*)-3-*ethylazeti-din*-2-*one* (16).—4-Acetoxy-3-ethylazetidin-3-one (10) (1.57 g) was treated with benzyl α-diazoacetoacetate (2.18 g) in the presence of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (1.61 g) and n-butyl-lithium (0.64 g)] as in the case of (11) to give the diazo-compound (16) (345 mg, 11%) as a colourless oil; $\nu_{max.}$ ($CDCl_3$) 3 410 (NH), 2 120 (diazo), and 1 750, 1 710, 1 640 cm^{-1} (C=O); δ ($CDCl_3$) 1.00 (3 H, t, *J* 8 Hz, CH_2Me), 1.70 (2 H, br q, *J* 8 Hz, CH_2Me), 2.78 (1 H, dt, *J* 2 and 8 Hz, C-3-H), 2.98 (1 H, dd, *J* 8 and 18 Hz, C-1′-H), 3.34 (1 H, dd, *J* 4.5 and 18 Hz, C-1′-H), 3.64 (1 H, ddd, *J* 2, 4.5 and 8 Hz, C-4-H), 5.24 (1 H, d, *J* 8 Hz, CH*H*Ph), 5.36 (1 H, d, *J* 8 Hz, C*H*HPh), 6.02 (1 H, br s, NH), and 7.22 (5 H, s, Ph).

Benzyl trans-6α-*Ethyl*-3,7-*dioxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (20).—A solution of the diazo-compound (16) (200 mg) in dry benzene (10 ml) in the presence of a catalytic amount of rhodium acetate was warmed at 80 °C for 0.5 h in a current of nitrogen. After filtration the filtrate was evaporated to give the bicyclic keto-ester (20) (169.5 mg, 93%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 765 (C=O); δ ($CDCl_3$) 1.10 (3 H, t, *J* 7 Hz, CH_2Me), 1.93 (2 H, dq, *J* 6 and 7 Hz, CH_2Me), 2.43 (1 H, dd, *J* 8 and 17 Hz, C-4-H), 2.93 (1 H, dd, *J* 8 and 17 Hz, C-4-H), 3.13 (1 H, dt, *J* 2 and 6 Hz, C-6-H), 3.94 (1 H, dt, *J* 2 and 8 Hz, C-5-H), 4.73 (1 H, s, C-2-H), 5.20 (1 H, d, *J* 8 Hz, C*H*HPh), 5.25 (1 H, d, *J* 8 Hz, CH*H*Ph), and 7.40 (5 H, s, Ph); *m/e* 287 (M^+) (Found: M^+, 287.1156. $C_{16}H_{17}NO_4$ requires *M*, 287.1130).

PS-5 Benzyl Ester (3).—To a stirred solution of the keto-ester (20) (84 mg) in acetonitrile (3 ml) was added ethyldi-isopropylamine (43 mg) and diphenyl chlorophosphate (89 mg) at 0 °C in a current of nitrogen. After the stirring had been continued for 0.5 h at 0 °C, ethyldi-isopropylamine (43 mg) and *N*-acetylcysteamine (40 mg) were added to the above solution, which was further stirred for 1.5 h at 0 °C. The mixture was diluted with dry benzene (30 ml), washed with 0.1M phosphate buffer solution, and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was chromatographed on Bio-Beads SX-3 (20 g) using benzene as eluant to afford the PS-5 benzyl ester (3) (43 mg, 38%), whose spectral data were indistinguishable from the spectra of authentic material provided by Dr. Ishikura.

4-*Ethoxycarbonylmethyl*-3-*ethylazetidin*-2-*one* (23).—To a stirred solution of lithium hexamethyldisilazide [prepared from n-butyl-lithium (0.64 g) and hexamethyldisilazane (1.61 g)] in tetrahydrofuran (10 ml) was added ethyl acetate (0.88 g) at −78 °C in a current of nitrogen. After the stirring had been continued for 1.5 h at −40 °C, a solution of the β-lactam (10) (1.57 g) in tetrahydrofuran (10 ml) was added and the resulting mixture was again stirred at −40 °C for 1 h. The mixture was treated with water and extracted with methylene chloride. Evaporation of the solvent gave a yellow oil, which was chromatographed on silica gel using methylene chloride–acetone (95 : 5 v/v) as eluant to afford the ester (23) (296 mg, 16%) as a pale yellow oil; $\nu_{max.}$ ($CHCl_3$) 3 400 (NH), and 1 755, 1 720 cm^{-1} (C=O); δ ($CDCl_3$) 1.02 (3 H, t, *J* 7 Hz, CH_2Me), 1.26 (3 H, t, *J* 7 Hz, CH_2Me), 1.68 (2 H, q, *J* 7 Hz, CH_2Me), 3.61 (1 H, dt, *J* 3 and 7 Hz, C-3-H), 4.20 (2 H, q, *J* 7 Hz, CH_2Me), and 6.79 (1 H, br s, NH); *m/e* 186 ($M^+ + 1$) (Found: $M^+ + 1$, 186.1108. $C_9H_{16}NO_3$ requires *M*, 186.1129).

4-*Carboxymethyl*-3-*ethylazetidin*-2-*one* (24).—To a stirred solution of the ester (23) (413 mg) in ethanol (20 ml) was added 0.25N sodium hydroxide (11.1 ml) dropwise at room temperature. After stirring for 1 h, the mixture was diluted with water (20 ml) and washed with ether. The aqueous layer was acidified with 10% hydrochloric acid and extracted with chloroform. The chloroform layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave the *acid* (24) (272 mg, 78%) as colourless needles, m.p. 105—108 °C (methylene chloride–benzene) (Found: C, 53.40; H, 6.90; N, 9.05. $C_7H_{11}NO_3$ requires C, 53.50; H, 7.05; N, 8.90%); $\nu_{max.}$ ($CHCl_3$) 1 750 and 1 725 cm^{-1} (C=O); δ ($CDCl_3$) (3 H, t, *J* 7 Hz, CH_2Me), 1.68 (2 H, q, *J* 7 Hz, CH_2Me), 3.46—3.83 (1 H, m, C-4-H), 6.70 (1 H, s, NH), and 10.63 (1 H, br s, OH).

3-*Ethyl*-4-(2-*oxo*-3-p-*nitrobenzyloxycarbonylpropyl*)*azeti-din*-2-*one* (25).—Carbonyldi-imidazole (178 mg) was added to a solution of the acid (24) (157 mg) in tetrahydrofuran (5 ml). After stirring at ambient temperature for 6 h, the magnesium salt of mono-*p*-nitrobenzyl malonate [11] was added. The mixture was stirred for 2 h at ambient temperature and the solvent removed *in vacuo*. The residue was chromatographed on silica gel using benzene–acetone (97 : 3 v/v) as eluant to afford the keto-ester (25) (220 mg, 66%) as a colourless gum; $\nu_{max.}$ ($CHCl_3$) 3 410 (NH), and 1 760, 1 720 cm^{-1} (C=O); δ ($CDCl_3$) 1.00 (3 H, t, *J* 7 Hz, CH_2Me), 1.70 (2 H, q, *J* 7 Hz, CH_2Me), 2.65 (1 H, dt, *J* 2 and 7 Hz, C-3-H), 3.63 (2 H, s, COH_2CO), 5.30 (2 H, s, CH_2Ar), 6.46 (1 H, br s, NH), 7.53 (2 H, d, *J* 8 Hz, aromatic protons), and 8.26 (2 H, d, *J* 8 Hz, aromatic protons); *m/e*

335 ($M^+ + 1$) and 334 (M^+) (Found: M^+, 334.1189. $C_{16}H_{18}N_2O_6$ requires M, 334.1166).

4-(3-*Diazo*-2-*oxo*-3-p-*nitrobenzyloxycarbonylpropyl*)-3-*ethylazetidin*-2-*one* (26).—To a stirred solution of the keto-ester (25) (100 mg) in acetonitrile (4 ml) was added triethylamine (35 mg) and tosyl azide (66 mg) at 0 °C. After stirring for 2 h, the solvent was evaporated to give the residue, which was subjected to silica gel column chromatography. Elution with benzene–acetone (95 : 5 v/v) afforded the diazo-compound (26) (105 mg, 97%) as a colourless gum; $\nu_{max.}$ ($CHCl_3$) 3 420 (NH), 2 140 (diazo), and 1 760, 1 720, 1 650 cm^{-1} (C=O); δ ($CDCl_3$) 1.00 (3 H, t, *J* 7 Hz, CH_2Me), 1.73 (2 H, q, *J* 7 Hz, CH_2Me), 2.83 (1 H, dt, *J* 2 and 7 Hz, C-3-H), 3.66 (1 H, m, C-4-H), 5.36 (2 H, s, CH_2Ar), 6.23 (1 H, s, NH), 7.53 (2 H, d, *J* 8 Hz, aromatic protons), and 8.26 (2 H, d, *J* 8 Hz, aromatic protons).

p-*Nitrobenzyl* trans-6α-*Ethyl*-3,7-*dioxo*-1-*azabicyclo*[3.2.0]-*heptane*-2-*carboxylate* (27).—A solution of the diazo-compound (26) (100 mg) in dry benzene (10 ml) in the presence of a catalytic amount of rhodium acetate was warmed at 80 °C in a current of nitrogen for 0.5 h. After filtration and washing of the solid with benzene, the combined filtrates were evaporated to give the bicyclic keto-ester (27) (91 mg, 99%) as a colourless gum; $\nu_{max.}$ ($CHCl_3$) 1 765 and 1 750 cm^{-1} (C=O); δ ($CDCl_3$) 1.10 (3 H, t, *J* 7 Hz, CH_2Me), 1.90 (2 H, q, *J* 7 Hz, CH_2Me), 3.16 (1 H, dt, *J* 3 and 7 Hz, C-6-H), 3.90 (1 H, dt, *J* 3 and 8 Hz, C-5-H), 4.76 (1 H, s, C-2-H), 5.29 (2 H, s, CH_2Ar), 7.49 (2 H, d, *J* 8 Hz, aromatic protons), and 8.19 (2 H, d, *J* 8 Hz, aromatic protons); *m/e* 332 (M^+) (Found: M^+, 332.1026. $C_{16}H_{16}N_2O_6$ requires M, 332.1009).

PS-5 p-*Nitrobenzyl Ester* (4).—To a stirred solution of the keto-ester (27) (60 mg) in acetonitrile (3 ml) was added ethyldi-isopropylamine (26 mg) and diphenyl chlorophosphate (53.5 mg) at 0 °C in a current of nitrogen. After stirring for 0.5 h at 0 °C, ethyldi-isopropylamine (26 mg) and *N*-acetylcysteamine (24 mg) were added to the above solution, which was further stirred for 2 h at 0 °C. The mixture was diluted with dry benzene (30 ml), washed with 0.1M phosphate buffer solution, and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was chromatographed on silica gel using benzene–acetone (95 : 5 v/v) as eluant to furnish the PS-5 *p*-nitrobenzyl ester (4) (55.6 mg, 71%), whose spectral data were indistinguishable from those provided by Dr. T. Ishikura.

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