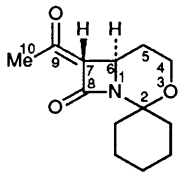
Olivanic Acid Analogues. Part 8.[1] Halogenation and Sulphenylation Reactions leading Selectively to *cis*-Carbapenem Precursors; Stereospecific Synthesis of (±)-6-Epithienamycin

John H. Bateson,* Alison M. Robins and Robert Southgate
SmithKline Beecham Pharmaceuticals, Research Division, Brockham Park, Betchworth, Surrey, RH3 7AJ, UK

Introduction of halogen or sulphenyl substituents at C-7 of ketone **1**, followed by stereospecific reduction steps, provides a selective route either to the (*6RS,7RS,9RS*) isomer **11** or to the (*6RS,7RS,9SR*) isomer **14** of 7-(1-hydroxyethyl)-8-oxo-3-oxa-1-azabicylo[4.2.0]octane-2-spirocyclohexane. The synthetic utility of chloride **6** is illustrated by its transformation to (±)-6-epithienamycin **25**, and to the C-6 epimers of a (±)-6-chloroolivanic acid analogue **39**.

cis-Carbapenem derivatives constitute a significant proportion of the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid† antibacterial substances isolated from natural sources. Southgate and Elson reviewed[2] the known *cis*-olivanic acids, including the potent broad-spectrum antibiotics MM 4550 and MM 13902, together with the carpetimycins and pluracidomycins. Although there have been many published syntheses of *trans*-substituted carbapenems, relatively few stereospecific routes to their thermodynamically less stable *cis*-counterparts have been reported. Such investigations have included PS-5 and olivanic acid systems[3–9] together with syntheses of the *cis*-carpetimycins.[10–12] We now describe in full[13] our versatile procedure for the synthesis of *cis*-β-lactams in the olivanic acid natural product series.[14] The sequence permits the side-chain hydroxy group to be introduced stereospecifically in either stereochemical configuration from a common precursor.



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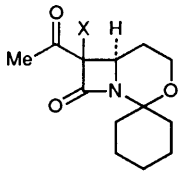
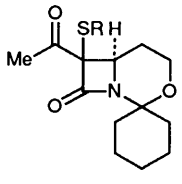


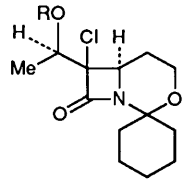
2 X = Cl
3 X = Br



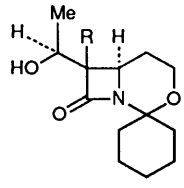
4 R = *p*-Tolyl
5 R = Me

Halogenation of the readily accessible *trans*-ketone **1**[15] with chloramine-T in acetonitrile gave a single chloroketone **2**, m.p. 108–110 °C (68%). With *N*-bromosuccinimide (NBS) in refluxing benzene in the presence of azobisisobutyronitrile (AIBN), the corresponding bromoketone **3**, m.p. 103–105 °C (85%) was rapidly obtained. Reaction of **1** with *p*-tolylsulphenyl toluene-*p*-sulphonate in the presence of triethylamine gave a single arylsulphenyl ketone **4**, m.p. 120–121 °C (76%); use of methanesulphenyl methanesulphonate provided **5**, m.p. 83 °C (83%). Although we believe the ketones **2**–**5** to be substituted at the least hindered, α-face of the 3-oxa-1-azabicyclo[4.2.0]octane ring system, we have not obtained proof of the C-7 stereochemistry.

Reduction of chloroketone **2** with sodium borohydride in



6 R = H
7 R = CO_2PNB



8 R = S–Me
9 R = SMe
10 R = Br

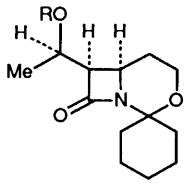
ethanol–tetrahydrofuran (THF) afforded a mixture of alcohol epimers (5:2 ratio). However, with either potassium or lithium tri(*s*-butyl)borohydrides ('Selectride'®) a single alcohol **6** (91%) was obtained. Subsequent dehalogenation with tributyltin hydride (AIBN initiation) gave **11** (49%). Hydrogen atom delivery to the α-face of the intermediate C-7 carbon radical provided a *cis*-carbapenem [δ(CD_3COCD_3) 3.10 ($^3J_{6,7}$ = 5.4 Hz and $^3J_{7,9}$ = 8.2 Hz, 7α-H)]. In contrast, reduction of sulphenyl ketones **4** and **5** with sodium borohydride gave alcohols **8** and **9** in excellent yield; 'K-Selectride' effected reversion to ketone **1**. Desulphurisation of **8** or **9** with tributyltin hydride then gave alcohol **14** (93%, 36 h and 97%, 60 h, respectively). This differed from **11** only in the sterochemistry of its hydroxy group [δ(CD_3COCD_3) 3.10 ($^3J_{6,7}$ = 5.3 Hz and $^3J_{7,9}$ = 10.6 Hz, 7α-H)].‡ The alcohols **11** and **14** are attractive synthetic precursors of the *cis*-carbapenem antibiotics. The ^{1}H NMR coupling constants (*vide supra*) supported the assigned structures.[16,17]

Bromoketone **3** behaved in an anomalous manner; reaction with sodium borohydride gave a bromoalcohol **10**. Subsequent tributyltin hydride reduction provided *inter alia* alcohol **14** only in moderate yield as the major product. Reaction with Selectride® reagents again caused reductive reversion to ketone **1** (59%).

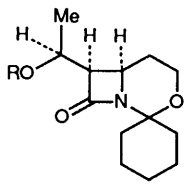
Confirmation of our structural assignments was obtained by conversion of **11** and **14** to the respective methanesulphonates **12** and **15**. Elimination of methanesulphonic acid under E2 conditions ($NaHCO_3$, MeOH, heat) provided, in turn,

† This paper employes systematic numbering based on the azabicyclo-[3.2.0]hept-2-ene system throughout. Trivial nomenclature in respect of the terms 'carbapenem' and 'carbapenam' does not apply.

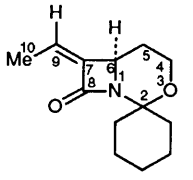
‡ The stereochemistry of the reduction of chloroketone **2** clearly depends on the bulk of the reagent. A plausible explanation for total reversal of the stereochemical outcome for reduction of sulphides **4** and **5** invokes a functional group directing effect arising from the strong boron–sulphur interaction.



11 R = H
12 R = $MeSO_2$
13 R = CO_2PNB



14 R = H
15 R = $MeSO_2$



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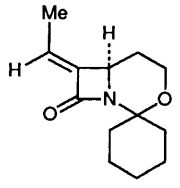
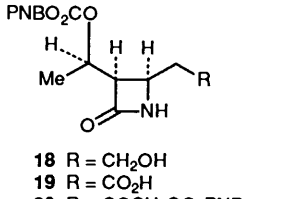


17

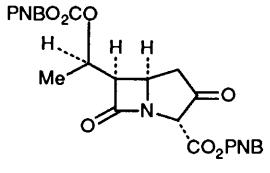
PNB = *p*-$NO_2C_6H_4CH_2$

ethylidene compounds **16** and **17**. These were obtained in ratios (9:1, 96%) and (1:19, 98%), respectively. Correlation of ^1H NMR data, including deshielding effects and allylic coupling constants, with that observed in previous work in these laboratories[16] and elsewhere[17] permits the hydroxyethyl-relative stereochemistries of **11** (6*RS*,7*RS*,9*RS*) and **14** (6*RS*,7*RS*,9*SR*) to be deduced as indicated. [Selected NMR data: **16** $\delta_H(CDCl_3)$ 2.02 (3 H, dd, *J*/Hz 6.5 and 1, 10-H_3) and 5.68 (1 H, qd, *J*/Hz 6.5 and *ca.* 1, 9-H); homoallylic and allylic couplings respectively on 10-H_3 and 9-H resonances (*Z*-series). **17** $\delta_H(CDCl_3)$ 1.71 (3 H, d, *J*/Hz 6.5, 10-H_3) and 6.11 (1 H, dq, *J*/Hz 6.5 and 1, 9-H); 1 Hz allylic coupling only on olefinic signals (*E*-series).]

No carbapenem antibiotic containing the relative stereochemistry present in **11** has yet been isolated from natural sources. We have demonstrated the utility of our procedures by the provision of a synthesis of such a molecule, 6-epithienamycin **25**. *p*-Nitrobenzyloxycarbonyl protection of **11** gave carbonate ester **13**. Acid hydrolysis of the tetrahydrooxazine ring liberated the alcohol **18** and then Jones' oxidation provided carboxylic acid **19**. Conversion to the acylimidazolide, followed by reaction with the magnesium salt of *p*-nitrobenzyl hydrogenmalonate $[Mg(O_2CCH_2CO_2PNB)_2]$[18] gave β-keto ester **20**. Diazo-transfer with toluene-*p*-sulphonyl azide and triethylamine in acetonitrile afforded diazo ester **21**. Intramolecular carbene insertion in refluxing benzene in the presence of a catalytic quantity of rhodium acetate provided the 3,7-dioxo-1-aza-bicyclo[3.2.0]heptane **22** in quantitative yield. The remaining steps were closely similar to those also reported[4] by Vasella for the final stages of his synthesis from glucose: enol-activation using diphenylphosphinothioyl chloride gave **23**; displacement with *N*-*p*-nitrobenzyloxycarbonylaminoethanethiol then afforded triester **24** [λ_{max}(EtOH)/nm 314, 264]. Hydrogenolysis in the presence of sodium phosphate buffer at pH 7 liberated (±)-6-epithienamycin **25** (51%) [$\lambda_{max}(H_2O)$ 288 nm]. This unnatural isomer did not exhibit the broad spectrum antibacterial potency of thienamycin. We have also prepared a 6-chloro substituted carbapenem **39** from chloro alcohol **6**. Using an analogous sequence *via* carbonate **7**, carboxylic acid **27** and transformation to diazo ester **29**, we obtained the chlorinated bicyclic ketone **30**. However, in this series we were unable to achieve C-3 substitution of the derived activated enols, using acylated aminoethanethiols.



18 R = CH_2OH
19 R = CO_2H
20 R = $COCH_2CO_2PNB$
21 R = $COC(N_2)CO_2PNB$



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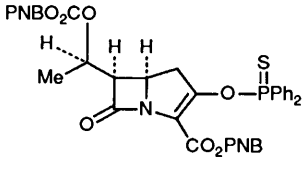

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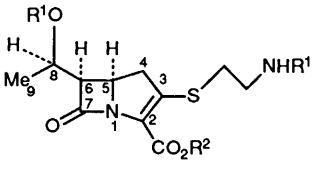
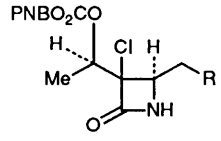
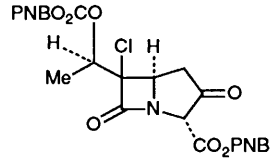


24 R^1 = CO_2PNB, R^2 = PNB
25 R^1 = H, R^2 = Na

Consequently, we chose to examine our alternative thiolester–phosphorane intramolecular Wittig cyclisation strategy;[19] reaction of alcohol **26** with *p*-nitrobenzyl glyoxylate gave **31**. Selective silylation of the primary hydroxy group provided the protected t-butyldimethylsilyl ether **32** as a mixture of α-hydroxy ester epimers (1:1). Conversion to phosphorane **33** was achieved using the established method (i, $SOCl_2$, 2,6-lutidine; ii, Ph_3P, 2,6-lutidine).[20] To our surprise, we obtained a mixture of



26 R = CH_2OH
27 R = CO_2H
28 R = $COCH_2CO_2PNB$
29 R = $COC(N_2)CO_2PNB$



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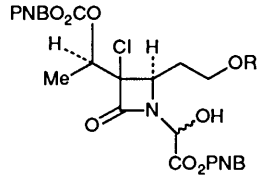
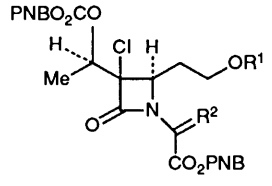


31 R = H
32 R = $SiMe_2Bu^t$

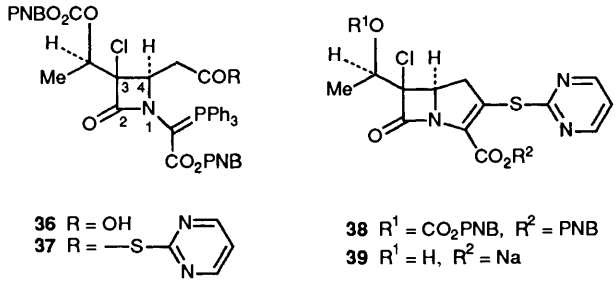


33 R^1 = $SiMe_2Bu^t$, R^2 = PPh_3
34 R^1 = H, R^2 = PPh_3
35 R^1 = H, R^2 = CH_2

silylether–phosphoranes, indicating that an isomerisation had taken place. We conclude this to be a triphenylphosphine–chloride ion-mediated epimerisation at C-3 involving the α-chloro, β-alkoxycarbonyloxy system of **33**. After hydrolysis of the silyl ether group (5 mol dm^{-3} HCl, THF, r.t.), the two separable alcohol–phosphoranes **34** were obtained as foams (each 39%). In each case the mass spectrum (FAB, thioglycerol) exhibited the expected molecular ion (MH^+, 826). Although we are unable to assign stereochemistries to the individual chloroazetidinones, we have progressed both isomers [**34a**, least polar and **34b** most polar (*c.f.* Experimental Section)] through our synthetic sequence. Further characterisation of the individual phosphoranes was obtained by reaction of each with an excess of formaldehyde (dioxane–water) to give the vinylidene derivatives **35a** and **35b** (NMR spectra).

Jones' oxidation of each alcohol–phosphorane provided acids **36a** and **36b**. Activation *via* the diethylphosphoric anhydride [$(Et_2O)_2P(O)Cl$, Et_3N, THF], followed by reaction

with the lithium salt of pyrimidine-2-thiol, yielded the pyrimidinethiol esters **37a** and **37b** (66–68%). Thermal cyclisation



36 R = OH
37 R = —S— (N)

38 $R^1 = CO_2PNB$, R^2 = PNB
39 R^1 = H, R^2 = Na

(2 h) produced the respective protected carbapenems **38a** (26%) and **38b** (52%). Finally, hydrogenolysis of the *p*-nitrobenzyl ester functions gave the (±) sodium salts **39a** [$\lambda_{max}(H_2O)$/nm 297 and 243] and **39b** [$\lambda_{max}(H_2O)$/nm 296 and 241]. These are chlorinated analogues related to a synthetic 5,6-*trans*-3-pyrimidinylthio olivanic acid derivative, prepared previously in these laboratories.[21]

Experimental

The experimental techniques employed in this work were as described in Part 2 of the series.[22] Unless stated otherwise, IR spectra were recorded for solutions in methylene dichloride using a Perkin-Elmer 197 instrument. UV spectra were recorded using a Pye-Unicam SP7-500 spectrometer. NMR spectra were obtained at 90 MHz on a Perkin-Elmer R32, and at 250 MHz on a Bruker WM250 instrument for solutions in $CDCl_3$ using tetramethylsilane as internal standard (unless otherwise stated). Coupling constant values *J* are given in Hz. Mass spectra were determined with AEI MS9 or VG 7070F spectrometers. HPLC was conducted using a Beckmann system employing a C-18 μBondpak reverse-phase column (Waters), with pH 4.7 0.005 mol dm^{-3} ammonium dihydrogen orthophosphate buffer containing acetonitrile as eluent, and employing UV detection at λ = 240 nm. 'K-Selectride'® refers to potassium tri(s-butyl) borohydride.

All compounds are racemic; NMR assignments refer to that enantiomer which is depicted.

7-*Acetyl*-7-*chloro*-8-*oxo*-3-*oxa*-1-*azabicyclo*[4.2.0]*octane*-2-*spirocyclohexane* **2**.—(6*RS*,7*SR*) 7-Acetyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane-2-spirocyclohexane **1**[15] (2.37 g, 10 mmol) and chloramine-T (*N*-chlorotoluene-*p*-sulphonamide, sodium salt·$3H_2O$) (3.10 g, 11 mmol) were stirred in acetonitrile (50 cm^3) at room temperature for 30 min. The acetonitrile was removed *in vacuo* and the white residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried and evaporated to give a semi-solid (4.13 g). This was chromatographed on silica gel (Art. 9385), eluting with ethyl acetate–hexane (1:2) to give the chloro ketone **2** (2.56 g). It crystallised ($CHCl_3$–Et_2O–hexane) as felted needles (1.86 g, 68%), m.p. 108–110 °C (Found: C, 57.8; H, 6.65; N, 5.2; Cl, 12.75%; M^+, 271.0975. $C_{13}H_{18}ClNO_3$ requires C, 57.5; H, 6.7; N, 5.15; Cl, 13.05%; M, 271.0975); $\nu_{max}(CHCl_3)/cm^{-1}$ 1775 and 1710; δ_H(90 MHz) 1.3–1.6 (6 H, m), 1.6–2.0 (6 H, m), 2.37 (3 H, s), 3.7–3.9 (2 H, m, CH_2O) and 3.89 (1 H, dd, *J* 11 and 5, 6-H).

7-*Acetyl*-7-*bromo*-8-*oxo*-3-*oxa*-1-*azabicylo*[4.2.0]*octane*-2-*spirocyclohexane* **3**.—Ketone **1** (12.50 g) and *N*-bromosuccinimide (9.40 g) in benzene (300 cm^3) were heated at reflux in the presence of AIBN (0.050 g) for 5 min. The reaction mixture was chromatographed on silica gel (Art. 9385), eluting rapidly with ethyl acetate–hexane (1:3). Crystallisation (chloroform–hexane) gave the *bromo ketone* **3** as felted needles (14.2 g, 85%), m.p. 103–105 °C (Found: C, 49.5; H, 5.7; N, 4.3; Br, 25.4. $C_{13}H_{18}BrNO_3$ requires C, 49.4; H, 5.7; N, 4.4; Br, 25.3%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1770 and 1715; δ_H(90 MHz) 1.3–2.3 (12 H, m), 2.40 (3 H, s), 3.75–3.87 (2 H, m, CH_2O) and 4.00 (1 H, dd, *J* 11 and 5, 6-H).

7-*Acetyl*-8-*oxo*-7-(*toluene*-p-*sulphenyl*)-3-*oxa*-1-*azabicyclo*-[4.2.0]*octane*-2-*spirocyclohexane* **4**.—Ketone **1** (8.50 g, 36 mmol) in methylene dichloride (200 cm^3) and *p*-tolylsulphenyl toluene-*p*-sulphonate (10.00 g, 36 mmol) were stirred with triethylamine (4.35 g, 5.6 cm^3; 43 mmol, 1.2 mol equiv.) at room temperature for 16 h. The solvent was evaporated and the residue chromatographed on silica gel (Art. 9385), eluting with ethyl acetate–hexane (1:9). The *aryl thioketone* **4** crystallised (EtOAC–hexane) as needles (9.8 g, 76%), m.p. 120–121 °C (Found: C, 66.7; H, 7.2; N, 3.6; S, 8.7%; M^+, 359.1582. $C_{20}H_{25}NO_3S$ requires C, 66.8; H, 7.0; N, 3.9; S, 8.9%; M, 359.1553); $\nu_{max}(CHCl_3)/cm^{-1}$ 1755, 1705, 1595 and 1360; δ_H(90 MHz) 0.9–2.3 (12 H, m), 2.33 (3 H, s, ArCH_3), 2.36 (3 H, s, CH_3CO), 3.66–3.87 (3 H, m, 6-H and CH_2O) and 7.13 (2 H, *J* 7) and 7.44 (2 H, *J* 7) (both AA′BB′).

7-*Acetyl*-7-*methylthio*-8-*oxo*-3-*oxa*-1-*azabicylo*[4.2.0]*octane*-2-*spirocyclohexane* **5**.—Ketone **1** (15.0 g) and methanesulphenyl methanesulphonate (9.0 g) in methylene chloride (60 cm^3) containing triethylamine (20 cm^3) was stirred at 50 °C for 3 h. The reaction mixture was concentrated *in vacuo* and chromatographed on silica gel (Art. 9385), eluting with ethyl acetate–hexane (1:5). The *methyl thioketone* **5** crystallised from ether–hexane as needles (14.86 g, 83%), m.p. 83 °C (Found: C, 59.2; H, 7.2; N, 4.9; S, 11.7. $C_{14}H_{21}NO_3S$ requires C, 59.3; H, 7.5; N, 4.9; S, 11.3%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1760 and 1700; δ_H(90 MHz) 1.35–1.95 (12 H, m), 2.11 (3 H, s, CH_3O), 2.28 (3 H, s, CH_3S), 3.70 (1 H, dd, *J* 10 and 5, 6-H) and 3.75–3.9 (2 H, m, CH_2O).

(6RS,9RS)-7-*Chloro*-7-(1-*hydroxyethyl*)-8-*oxo*-3-*oxa*-1-*aza*-*bicyclo*[4.2.0]*octane*-2-*spirocyclohexane* **6**.—Chloroketone **2** (0.250 g) in dry THF (15 cm^3) was cooled to −70 °C, 'L-Selectride'® (1.1 cm^3 of a 1 mol dm^{-3} solution in THF; 1.2 mol equiv.) was added, and the mixture was stirred for 1 h. Saturated aqueous ammonium chloride (10 cm^3) was added, and the mixture was diluted at room temperature with ethyl acetate. The organic layer was dried, evaporated, and the residue chromatographed on silica gel (Art. 9385). Elution with ethyl acetate–hexane (1:1) provided the chloro alcohol **6** as a gum (0.228 g, 91%); ν_{max}/cm^{-1} 3550 and 1755; δ_H(250 MHz) 1.45 [3 H, d, *J* 6.5, $CH_3CH(OH)$], 1.4–1.95 (10 H, m,), 2.07 (1 H, m), 2.32 (1 H, m), 3.75–4.0 (3 H, complex m, CH_2O and 6-H) and 4.16 [1 H, m, $CH(OH)$].

Reaction of **2** with 'K-Selectride' provided **6** in comparable yield, though less cleanly. Reaction of **2** with sodium borohydride in ethanol–THF gave **6** and its (6*RS*,9*SR*)-isomer (5:2 ratio; 91%).

Reduction of Bromo ketone **3** with 'K-Selectride'®.—Bromo ketone **3** (0.125 g, 0.4 mmol) in THF (3 cm^3) was cooled to −50 °C. 'K-Selectride' (0.45 cm^3 of a 1 mol dm^{-3} solution in THF) was added and the mixture stirred for 20 min. The reaction was quenched with saturated aqueous ammonium chloride, diluted with ethyl acetate, and the organic layer separated, dried and evaporated. Chromatography of the residue on silica gel (Art. 9385), eluting with ethyl acetate–hexane (2:5) gave, *inter alia*, ketone **1** (0.55 g, 59%) (IR, NMR).

(6RS,9SR)-7-(1-*Hydroxyethyl*)-8-*oxo*-7-(*toluene*-p-*sulphen*-*yl*)-3-*oxa*-1-*azabicyclo*[4.2.0]*octane*-2-*spirocyclohexane* **8**.—A solution of ketone **4** (7.00 g, 19.5 mmol) in ethanol (200 cm^3)–THF (30 cm^3) was reduced with an excess of sodium

borohydride (0.741 g, 19.5 mmol; 4 mol equiv.), added portionwise, at 0 °C for 30 min. Saturated aqueous ammonium chloride was added, the solvents evaporated and the aqueous residue extracted with ethyl acetate. The extracts were dried, evaporated and crystallised (EtOAc–Et_2O–hexane) to give the *alcohol* **8** as needles (6.70 g, 95%), m.p. 114 °C (Found: C, 66.45; H, 7.4; N, 3.85; S, 8.95%; M^+, 361.1702. $C_{20}H_{27}NO_3S$ requires C; 66.45; H, 7.5; N, 3.9; S, 8.9%; M, 361.1709); ν_{max}/cm^{-1} 3400br, 1735 and 1595; δ_H(90 MHz) 0.9–2.0 (10 H, m), 1.49 [3 H, d, *J* 6.5, $CH_3CH(OH)$], *ca.* 2.1 (1 H, br s, OH, D_2O exch.), 2.0–2.3 (2 H, m), 2.30 (3 H, s, $ArCH_3$), 3.50 (1 H, dd, *J* 13 and 6, 6α-H), 3.6–3.85 (2 H, m, CH_2O), 4.37 [1 H, m, $W_{\frac{1}{2}}$ 16 Hz, $CH(OH)$] and 7.12 (2 H, *J* 8) and 7.50 (2 H, *J* 8) (both AA′BB′).

A similar experiment using aryl thioketone **4** (0.179 g, 0.5 mmol) and 'K-Selectride' (0.5 mmol) provided ketone **1** (0.108 g, 0.46 mmol; 92%) (IR, NMR).

(6RS,9SR)-7-(1-*Hydroxyethyl*)-7-*methylthio*-3-*oxa*-1-*azabicyclo*[4.2.0]*octane*-2-*spirocyclohexane* **9**.—A solution of ketone **5** (0.283 g, 1 mmol) in ethanol (15 cm^3)–THF (2 cm^3) was cooled to 0 °C. An excess of sodium borohydride (0.020 g, 0.53 mmol) was added and the mixture was stirred for 1 h. Recovery and chromatography as for **4**, and crystallisation (EtOAC–hexane) gave *alcohol* **9** (0.242 g, 86%), m.p. 95–97 °C (Found: C, 58.9; H, 8.2; N, 5.0; S, 10.9%; M^+, 285.1400. $C_{14}H_{23}NO_3S$ requires C, 58.9; H, 8.1; N, 4.9; S, 11.2%; M, 285.1399); ν_{max}/cm^{-1} 3600 and 1745; δ_H (250 MHz) 1.44 [3 H, d, *J* 6.5, $CH_3CH(OH)$], 1.4–1.95 (10 H, m), 2.02 (1 H, br s, OH), 2.24 (3 H, s, CH_3S), 2.12–2.38 (2 H, m), 3.71 (1 H, dd, *J* 11 and 5), 3.82–3.93 (2 H, m, CH_2O) and 4.38 [1 H, m, $CH(OH)$].

(6RS,7RS,9RS)-7-(1-*Hydroxyethyl*)-8-*oxo*-3-*oxa*-1-*azabicyclo*[4.2.0]*octane*-2-*spirocyclohexane* **11**.—Chloro alcohol **6** (0.176 g) and tributyltin hydride (0.75 g, 4 mol equivs.) in acetone (10 cm^3) was heated at reflux in the presence of AIBN (0.010 g) for 6 h. Evaporation, and chromatography of the residue on silica gel (Art. 9385), eluting with ethyl acetate–hexane (1:1–2:1) gave cis-β-*lactam* **11** as an oil (0.076 g, 49%) (Found: M, 239.1530. $C_{13}H_{21}NO_3$ requires M, 239.1521); ν_{max}/cm^{-1} 3600 and 1740; δ_H(250 MHz; $CDCl_3$) 1.21 [3 H, d, *J* 6.5, $CH_3CH(OH)$], 1.25–2.0 (11 H, m), 2.30 (1 H, m), 2.93 (3 H, s, OH, D_2O exch.), 3.11 (1 H, dd, *J* 9 and 5, 7α-H), 3.73 (1 H, dt, *J* 12 and 5, 6α-H), 3.86 (2 H, dd, *J* 9 and 2, CH_2O) and 4.23 [1 H, br m, simplifying to dq, *J* 9 and 6.5 on D_2O exch., $CH(OH)$]; δ_H(250 MHz; CD_3COCD_3) 1.18 [3 H, d, *J* 6.5, $CH_3CH(OH)$], 1.25–2.0 (*ca.* 11 H, m), 2.25 (1 H), 3.10 (1 H, dd, *J* 8.2 and 5.4, 7α-H), 3.73–3.95 (3 H, complex m, CH_2O and 6α-H) and 4.15 [1 H, dq, *J* 8 and 6.5, $CH(OH)$].

(6RS,7RS,9SR)-7-(1-*Hydroxyethyl*)-8-*oxo*-3-*oxa*-1-*azabicyclo*[4.2.0]*octane*-2-*spirocyclohexane* **14**.—(i) *From aryl thioalcohol* **8**. A solution of alcohol **8** (6.00 g, 16.6 mmol) in acetone (75 cm^3, AnalaR) was heated with an excess of tributyltin hydride (20 cm^3) in the presence of AIBN (0.5 g) at reflux in an argon atmosphere for 36 h. Evaporation gave an oil which, in toluene, was chromatographed on silica gel (15 × 4 cm, 1:1 mixture Art. 9385 and Art. 7729 grades). Elution with ethyl acetate–hexane (1:1) removed the excess reagent; continued elution (1:1–2:1) gave the cis-β-*lactam* **14** as an oil (3.70 g, 15.5 mmol; 93%) (Found: M^+, 239.1537. $C_{13}H_{21}NO_3$ requires M, 239.1521); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420br and 1735; δ_H(250 MHz; $CDCl_3$) 1.41 [3 H, d, *J* 6.5, $CH_3CH(OH)$], 1.45–1.90 (10 H, m), 2.05 (1 H, m), 2.30 (1 H, m), 2.45 (1 H, br s, OH), 3.16 (1 H, dd, *J* 10.2 and 5.1, 7α-H), 3.76 (1 H, dt, *J* 11 and 5, 6α-H), 3.88 (2 H, m, CH_2O) and 4.23 [1 H, m, $W_{\frac{1}{2}}$ *ca.* 17 Hz, $CH(OH)$]; δ_H(250 MHz; CD_3COCD_3) 1.29 [3 H, d, *J* 7, $CH_3CH(OH)$], 1.30–2.00 (11 H, m), 2.22 (1 H, m), 3.10 (1 H, dd, *J* 10.6 and 5.3, 7α-H), 3.73–3.83 (2 H, m, 6α-H and 4-H), 3.93 (1 H, td, *J* 11 and 3, 4-H) and 4.08 [1 H, 7 lines, $CH(OH)$].

(ii) *From methyl thioalcohol* **9**. Similarly, alcohol **9** (0.72 g) in AnalaR acetone (7 cm^3) was heated with tributyltin hydride (2.5 cm^3) and AIBN (0.05 g) for 64 h. Chromatography gave cis-β-*lactam* **14** (5.9 g, 97%), identical (^1H NMR) with the sample obtained in method (i).

(iii) *From bromo ketone* **3**. Reduction of bromo ketone **3** (0.316 g, 1 mmol) with sodium borohydride (0.015 g) as described for **4** gave *inter alia* a crude bromo alcohol as a foam (0.258 g), containing (NMR spectrum) ketone **1** (*ca.* 30%). This mixture was then reduced immediately with tributyltin hydride as in (i) (2.5 h). Chromatography gave ketone **1** (0.57 g), followed by the cis-β-*lactam* **14** (0.139 g, 58% overall from **3**).

(6RS,7RS,9RS)-7-[(1-*Methanesulphonoxy*)*ethyl*]-8-*oxo*-3-*oxa*-1-*azabicyclo*[4.2.0]*octane*-2-*spirocyclohexane* **12**.—Alcohol **11** (0.030 g) in methylene dichloride (1 cm^3) was stirred with methanesulphonyl chloride (0.018 g) and triethylamine (0.2 cm^3) at 0 °C for 1 h. The solution was diluted with ethyl acetate, washed well with brine, dried and evaporated. The residue, in toluene, was chromatographed on silica gel (Art. 9385). Elution with ethyl acetate–hexane (1:1) gave the *mesylate* **11** as a gum (0.034 g, 85%) (Found: M^+, 317.1303. $C_{14}H_{23}NO_5S$ requires M^+, 317.1297); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740, 1350 and 1165; δ_H(250 MHz) 1.29 [3 H, d, *J* 6.5, $CH_3CH(OH)$], 1.2–2.1 (11 H, m), 2.21 (1 H, m), 3.01 (3 H, s, SO_2CH_3), 3.31 (1 H, dd, *J* 9 and 5, 7α-H), 3.75–3.92 (3 H, m, CH_2O and 6α-H) and 5.26 [1 H, dq, *J* 9 and 6.5, $CH(OH)$].

(6RS,7RS,9SR)-7-[(1-*Methanesulphonyloxy*)*ethyl*]-8-*oxo*-3-*oxa*-1-*azabicyclo*[4.2.0]-*octane*-2-*spirocyclohexane* **15**.—Mesylate **15** was prepared similarly from alcohol **14** (0.015 g) and methanesulphonyl chloride (0.009 g). It crystallised from methanol as needles (0.019 g, 95%), m.p. 133 °C (Found: M^+, 317.1293. $C_{14}H_{23}NO_5S$ requires M, 317.1297); ν_{max}/cm^{-1} 1740, 1350 and 1170; δ_H(250 MHz) 1.37–1.41 (2 H, m), 1.63 [3 H, d, *J* 6, $CH_3CH(OH)$], 1.65–1.92 (8 H, m), 2.00 (1 H, m), 2.19 (1 H, m), 3.04 (3 H, s, SO_2CH_3), 3.42 (1 H, dd, *J* 10 and 5, 7α-H), 3.79 (1 H, dt, *J* 12 and 5, 6α-H), 3.89 (2 H, m, CH_2O) and 5.18 [1 H, dq, *J* 10 and 6, $CH(OH)$].

7-[(Z)-*Ethylidene*]-8-*oxo*-3-*oxa*-1-*azabicyclo*[4.2.0]*octane*-2-*spirocyclohexane* **16**.—Mesylate isomer **12** (0.025 g) and sodium hydrogen carbonate (0.007 g) in absolute methanol (2 cm^3) were heated at reflux in an argon atmosphere for 30 min. The methanol was evaporated and the residue, in ethyl acetate, was chromatographed on silica gel (Art. 9385; 4 × 1 cm) eluting with ethyl acetate–hexane (1:1). The *Z-olefin* **16**, was obtained as a gum (0.017 g, 96%) (Found: M^+, 221.1411. $C_{13}H_{19}NO_2$ requires M, 221.1416); ν_{max}/cm^{-1} 1745; δ_H(250 MHz) 1.25–1.95 (11 H, m), 2.02 (3 H, dd, *J* 6.5 and 1, 10-H_3), 2.32 (1 H, m), 3.77–3.85 (2 H, m, CH_2O), 4.25 (1 H br dd, *J* 11 and 5, 6α-H) and 5.68 (1 H, qd, *J* 6.5 and *ca.* 1, 9-H). Minor signals at δ 1.71 (10-H_3) and 6.11 (9-H) showed the presence of the *E*-isomer **17** (10%).

7-[(E)-*Ethylidene*]-8-*oxo*-3-*oxa*-1-*azabicyclo*[4.2.0]*octane*-2-*spirocyclohexane* **17**.—Mesylate **15** (0.013 g) in absolute methanol (1 cm^3) was heated at reflux in the presence of sodium hydrogen carbonate (0.0035 g) in an argon atmosphere for 30 min. Purification as for isomer **16** gave the E-*olefin* **17** as a gum (0.009 g, 98%) (Found: M^+, 221.1415. $C_{13}H_{19}NO_2$ requires M, 221.1416); ν_{max}/cm^{-1} 1740; δ_H(250 MHz) 1.2–1.6 (6 H, m), 1.71 (3 H, d, *J* 6.5, 10-H_3), 1.75–2.0 (5 H, m), 2.36 (1 H, m), 3.77–3.94 (2 H, m, CH_2O), 4.11 (1 H, dd, *J* 11 and 5, 6α-H) and 6.11 (1 H, dq, *J* 6.5 and 1, 9-H). Minor signals at δ 2.02 (10-H_3) and 5.68 (9-H) indicated the presence of $\gtrsim$ 5% of the *Z*-isomer **16**.

(3RS,4RS)-4-(2-*Hydroxyethyl*)-3-[(1RS)-1-p-*nitrobenzyloxycarbonyloxyethyl*]*azetidin*-2-*one* **18**.—A solution of alcohol **11**

(1.41 g, 5.9 mmol) in THF (10 cm^3) was added rapidly to lithium diisopropylamide (7.0 mmol) in THF (10 cm^3) at −70 °C in an atmosphere of argon. After stirring for 10 min, *p*-nitrobenzyl chloroformate (1.53 g, 7.0 mmol, 1.2 mol equivs.) in THF (6 cm^3) was added, and stirring maintained whilst warming the solution to room temperature (1 h). Saturated aqueous ammonium chloride (25 cm^3) was added and the THF phase separated. Evaporation of an aliquot provided the *p*-nitrobenzyloxycarbonyloxy-protected derivative **13**; ν_{max}/cm^{-1} 1780, 1740, 1610, 1525 and 1345.

The solution of crude **13** in THF was stirred with 5 mol dm^{-3} sulphuric acid at 50 °C for 24 h. The mixture was neutralised with aqueous sodium hydrogen carbonate and the aqueous phase extracted with ethyl acetate. The combined organic phases were dried, evaporated and the residue was chromatographed on silica gel (Art. 9385). Elution with ethyl acetate–hexane (7:3) gave *alcohol* **18** which crystallised from EtOAc–hexane (1.16 g, 58% overall from alcohol **11**), m.p. 153–154 °C (Found: C, 52.9; H, 5.35; N, 8.1. $C_{15}H_{18}N_2O_7$ requires C, 53.2; H, 5.4; N, 8.3%); ν_{max}(KBr)/cm^{-1} 3260, 1750, 1740, 1610, 1525 and 1350; δ_H(250 MHz; CD_3COCD_3) 1.44 (3 H, d, *J* 6.5), 1.7–1.9 (2 H, m), 3.40 (1 H, ddd, *J* 6, 4.5 and 1, 3-H), 3.66 (3 H, br m, CH_2OH plus OH), 3.87 (1 H, ddd, *J* 9.5, 6 and 4, 4-H), 5.13 [1 H, dq, *J* 6.5 and 4.5, $CH_3CH(OR)$], 5.31 (1 H, *J* 14) and 5.39 (1 H, d, *J* 14) (both ABq, CH_2Ar), 7.22 (1 H, br s, NH), and 7.71 (2 H, *J* 9) and 8.27 (2 H, *J* 9) (both AA′BB′); *m/z* (NH_3 gas, CI) 339 (MH^+).

{(3RS,4RS)-3-[(1RS)-1-p-*Nitrobenzyloxycarbonyloxyethyl*]-2-*oxoazetidin*-4-*yl*}*acetic acid* **19**.—The alcohol **18** (0.50 g, 1.48 mmol) in acetone (50 cm^3) was stirred with Jones' reagent (0.62 cm^3, 3.3 mol equiv.) at 0 °C for 30 min. Isopropanol (5 cm^3) was added, and the solvents removed *in vacuo*. The residue was adsorbed onto silica gel (5 g) and applied to the top of a column of silica gel (Art. 9385). Elution with ethyl acetate gave the *acid* **19** as a foam (Found: C, 51.4; H, 4.8; N, 7.7. $C_{15}H_{16}N_2O_8$ requires C, 51.1; H, 4.5; N, 7.95%); ν_{max}/cm^{-1} 3500–2500, 3400, 1750, 1610, 1525 and 1340; δ_H(90 MHz; CD_3COCD_3), 1.42 [3 H, d, *J* 7, $CH_3CH(OR)$], 2.65 (2 H, d, *J* 8, CH_2CO_2H), 3.44 (1 H, m, 3-H), 3.60 (*ca.* 2 H, NH and CO_2H), 4.05 (1 H, m, 4-H), 5.07 [1 H, m, $CH_3CH(OR)$], 5.31 (2 H, s, CH_2Ar) and 7.67 (2 H, *J* 8) and 8.24 (2 H, *J* 8) (both AA′BB′).

Using a similar sequence, we prepared the (1′RS,3SR,4SR)-*carboxylic acid* isomer from tetrahydrooxazine alcohol **14**, as a foam (Found: C, 51.3; H, 4.7; N, 7.6%); ν_{max}(CHCl)/cm^{-1} 3500–2500br, 1750sh, 1740, 1605, 1525 and 1350; δ_H(250 MHz; CD_3COCD_3) 1.43 [3 H, d, *J* 6.5, $CH_3CH(OR)$], 2.63 (2 H, d, *J* 7, CH_2CO_2H), 3.48 (1 H, br ddd, *J* 10, 5.5 and 0.5, 3-H), 4.12 (1 H, br td, *J* 7 and 5.5, 4-H), 5.09 [1 H, dq, *J* 10 and 6.5, $CH_3CH(OR)$], 5.33 (2 H, s, CH_2Ar), 7.40 (1 H, br s, NH), 7.70 (2 H, d, *J* 8) and 8.27 (*J* 8) (both AA′BB′) and 9.06 (1 H, br s, CO_2H).

(4RS)-3-*Chloro*-4-(2-*hydroxyethyl*)-3-[1(RS)-1-p-*nitrobenzyloxycarbonyloxyethyl*]*azetidin*-2-*one* **26**.—The *chloroalcohol* **26** was obtained from the tetrahydrooxazine **6** using an analogous protection–hydrolysis sequence. It crystallised (EtOAc–hexane), m.p. 124–125 °C (Found: C, 48.6; H, 4.7; N, 7.4; Cl, 9.2. $C_{15}H_{17}ClN_2O_7$ requires C, 48.3; H, 4.6; N, 7.5; Cl, 9.5%); ν_{max}/cm^{-1} 3600, 3400, 1785, 1750, 1610, 1525 and 1345; δ_H(250 MHz) 1.50 [3 H, d, *J* 7, $CH_3CH(OR)$], 1.95 (3 H, CH_2CH_2OH and OH), 3.75 (1 H, m) and 3.89 (1 H, m) (both CH_2OH), 3.98 (1 H, dd, *J* 11 and 3.5, 4-H), 5.25 (1 H, *J* 14) and 5.32 (1 H, *J* 14) (both ABq, CH_2Ar), 5.38 [1 H, q, *J* 7, $CH_3CH(OR)$], 6.75 (1 H, br s, NH), and 7.59 (2 H, *J* 8) and 8.22 (2 H, *J* 8) (both AA′BB′).

{(4RS)-3-*Chloro*-3-[(1RS)-1-p-*nitrobenzyloxycarbonyloxyethyl*]-2-*oxoazetidin*-4-*yl*}*acetic acid* **27**.—Jones' oxidation of chloro alcohol **26** (0.771 g) (*vide supra*) followed by chromatography and crystallisation (EtOAc–hexane) gave the title *chloro carboxylic acid* **27** (0.688 g, 86%), m.p. 182 °C (Found: C, 47.0; H, 4.1; N, 7.2; Cl, 9.2. $C_{15}H_{15}ClN_2O_8$ requires C, 46.6; H, 3.9; N, 7.2; Cl, 9.2%); ν_{max}(KBr)/cm^{-1} 3600–2800, 3310, 1770, 1740, 1610, 1525 and 1350; δ_H(250 MHz; CD_3COCD_3) 1.50 [3 H, d, *J* 6.5, $CH_3CH(OR)$], 2.80 (1 H, dd, *J* 16 and 8) and 3.01 (1 H, dd, *J* 16 and 5, CH_2CO_2H), 3.28 (2 H, br s, D_2O exch., CO_2H, NH), 4.20 (1 H, dd, *J* 8 and 5, 4-H), 5.39 [3 H, m, CH_2Ar (ABq) and $CH_3CH(OR)$ (quin.)], and 7.72 (2 H, *J* 8) and 8.29 (2 H, *J* 8) (both AA′BB′).

p-*Nitrobenzyl* (3RS,4RS)-4-{3-[(1RS)-1-p-*Nitrobenzyloxycarbonyloxyethyl*]-2-*oxoazetidin*-4-*yl*}-3-*oxobutanoate* **20**.—Acid **19** (0.446 g, 1.23 mmol) in dry THF was stirred with 1,1′-carbonyldiimidazole (0.247 g, 1.52 mmol; 1.2 mol equiv.) in an argon atmosphere for 7 h. Freshly prepared magnesium *p*-nitrobenzyl hydrogen malonate[18] (0.380 g, 0.76 mmol; 0.6 mol equiv.) was added to the solution of acyl imidazolide and stirring continued for 18 h. The mixture was filtered, evaporated, and the residue chromatographed on silica gel (Art. 7729), eluting with ethyl acetate–hexane (1:1–7:3), to give the β-keto ester **20** as a foam; ν_{max}/cm^{-1} 3410, 1770, 1750, 1720sh, 1610, 1525 and 1350; δ_H(250 MHz) 1.47 [3 H, d, *J* 6.5, $CH_3CH(OR)$], 2.92 (2 H, m, 4-H_2), 3.46 (1 H, m, 3′-H), 3.50 (2 H, s, 2′-H_2), 4.12 (1 H, m, 4′-H), 5.01 [1 H, m, $CH_3CH(OR)$], 5.25 (2 H, s, CH_2Ar), 5.27 (2 H, s, CH_2Ar), 6.10 (1 H, br s, NH), 7.51 and 7.57 (each 2 H, *J* 8) and 8.23 (4 H, *J* 8) (2 × AA′BB′); *m/z* [M^+ DAP (diamylphenol); FAB] 530 (MH^+).

p-*Nitrobenzyl* (4RS)-4-{3-*Chloro*-3-[(1RS)-1-p-*Nitrobenzyloxycarbonyloxyethyl*]-2-*oxoazetidin*-4-*yl*}-3-*oxobutanoate* **28**.—The chloro-β-keto ester **28** (0.390 g, 33%) was obtained similarly from carboxylic acid **27** (0.800 g), as a foam; ν_{max}/cm^{-1} 3400, 1790, 1750, 1720, 1610, 1525 and 1350; δ_H(90 MHz) 1.46 [3 H, d, *J* 6.5, $CH_3CH(OR)$], 3.03 (2 H, d, *J* 5, 4-H_2), 3.55 (2 H, m, 2-H_2), 4.16 (1 H, m, 4′-H), 5.25 [5 H, m, $CH_3CH(OR)$ and 2 × CH_2Ar], 6.40 (1 H, br, NH) and 7.49 and 7.52 (each 2 H, *J* 9) and 8.20 (4 H, *J* 9) (2 × AA′BB′); *m/z* (M^+ DAP/$CHCl_3$; FAB) 564 (MH^+).

p-*Nitrobenzyl* (3RS,4RS)-2-*Diazo*-4-{3-[(1RS)-1-p-*nitrobenzyloxycarbonyloxyethyl*]-2-*oxoazetidin*-4-*yl*}-3-*oxobutanoate* **21**.—A solution of β-keto ester **20** (0.085 g) in dry acetonitrile (2 cm^3) at 0 °C in an argon atmosphere was treated successively with toluene-*p*-sulphonyl azide (0.035 g, 1.1 mol equiv.), and triethylamine (90 mm^3, 4 mol equiv.) in acetonitrile (1 cm^3). The stirred solution was allowed to warm to room temperature (1.5 h). Evaporation, and chromatography of the residue on silica gel (Art. 7729), eluting with ethyl acetate–hexane (7:3–1:0) gave the diazo ester **21** as a white foam (0.89 g, 100%); ν_{max}/cm^{-1} 3410, 2145, 1770, 1750, 1720, 1655, 1610, 1525 and 1350; δ_H(250 MHz) 1.52 [3 H, d, *J* 6.5, $CH_3CH(OR)$], 3.16 (1 H, dd, *J* 18 and 9) and 3.29 (1 H, dd, *J* 18 and 4) (both 4-H_2), 3.48 (1 H, ddd, *J* 5.5, 4.5 and 1.5, 3′-H), 4.18 (1 H, ddd, *J* 9, 5.5 and 4, 4′-H), 5.10 [1 H, dq, *J* 6.5 and 4.5, $CH_3CH(OR)$], 5.27 (2 H, s, CH_2Ar), 5.28 (1 H, *J* 14) and 5.35 (1 H, *J* 14) (both ABq, CH_2Ar), 6.07 (1 H, br s, NH), and 7.52, 7.57, 8.23 and 8.27 (each 2 H, *J* 8) (2 × AA′BBA); *m/z* (M^+ DAP; FAB) 556 (MH^+).

p-*Nitrobenzyl* (3RS,4RS)-4-{3-*Chloro*-3-[(1RS)-1-p-*nitrobenzyloxycarbonyloxyethyl*]-2-*diazo*-2-*oxoazetidin*-4-*yl*}-3-*oxobutanoate* **29**.—The chlorodiazo ester **29** (0.295 g, 78%) was obtained similarly from chloro-β-keto ester **28** (0.360 g) as a foam; ν_{max}/cm^{-1} 3410, 2150, 1790, 1755, 1720, 1705sh, 1655, 1610, 1525 and 1350; *m/z* (M^+ DAP; FAB) 590 (MH^+).

(5RS,6RS,8RS)-p-*Nitrobenzyl* 3,7-*Dioxo*-6-(1-p-*nitrobenzyloxycarbonyloxyethyl*)-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxyl*-

ate **22**.—Diazo ester **21** (0.087 g) and rhodium acetate (0.005 g) in dry benzene was deoxygenated by bubbling a stream of argon gas through the solution for 10 min. The mixture was then heated at reflux in an argon atmosphere for 1 h. It was cooled, filtered through a short column of Celite to give the ketone **22** as a gum (0.083 g, 100%); ν_{max}/cm^{-1} 1775, 1750, 1610, 1525 and 1350; δ_H(*inter alia*) 4.76 (1 H, s, 2β-H); *m/z* (M^+, DAP; FAB) 528 (MH^+).

(5RS,8RS)-p-*Nitrobenzyl* 6-*Chloro*-3,7-*dioxo*-6-(1-p-*nitrobenzyloxycarbonyloxyethyl*)-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* **30**.—Chlorodiazo ester **29** (0.043 g) similarly gave the gummy chloro ketone **30** (0.037 g); ν_{max}/cm^{-1} 1795, 1750, 1610, 1525 and 1350; δ_H (*inter alia*) 4.81 (1 H, s, 2β-H); *m/z* (M^+, DAP; FAB) 562 (MH^+).

(5RS,6RS,8RS)-p-*Nitrobenzyl* 3-*Diphenylthiophosphinoyl*-6-(1-p-*nitrobenzyloxycarbonyloxyethyl*)-7-*oxo*-1-*azabicyclo*-[3.2.0]*hept*-2-*ene*-2-*carboxylate* **23**.—Ketone **22** (0.083 g) was dissolved in dry acetonitrile (4 cm^3) and cooled to 0 °C in an argon atmosphere. Diisopropylethylamine (28 mm^3), and diphenylphosphinothioyl chloride (0.040 g) in acetonitrile (1 cm^3) were added and the mixture stirred for 30 min. The mixture was diluted with ethyl acetate, washed with brine, dried, and evaporated. Flash chromatography of the residue on silica gel (Art. 9385), eluting with ethyl acetate, provided the enol–thiophosphinate **23** (0.075 g, 64%); ν_{max}/cm^{-1} 1785, 1750, 1720, 1625, 1610, 1525 and 1345.

(5RS,8RS)-p-*Nitrobenzyl* 6-*Chloro*-3-*diphenylthiophosphinoyl*-6-(1-p-*nitrobenzyloxycarbonyloxyethyl*)-7-*oxo*-1- *azabicyclo*-[3.2.0]*hept*-2-*ene*-2-*carboxylate*.—Chloroketone **30** (0.037 g) was converted similarly to the enol-thiophosphinate; ν_{max}/cm^{-1} 1795, 1750, 1720, 1625–1610br, 1525 and 1350. We were unable to achieve displacement reactions (*vide infra*) using protected aminoethanethiols, with this substrate.

(5RS,6RS,8RS)-p-*Nitrobenzyl* 3-[2-(p-*Nitrobenzyloxycarbonylamino*)*ethylthio*]-6-(1-p-*nitrobenzyloxycarbonyloxyethyl*)-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **24**.—Enol thiophosphinate **23** (0.070 g) in dry acetonitrile (2 cm^3) was cooled to 0 °C in an argon atmosphere. Diisopropylethylamine (0.022 g, 30 mm^3; 1.8 mol equiv.) was added, followed by 2-(*p*-nitrobenzyloxycarbonylamino)ethanethiol (0.028 g; 1.1 mol equiv.). The reaction mixture was stirred at room temperature for 4.5 h, then diluted with ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate and dried. Evaporation and flash chromatography of the residue on silica gel (Art. 9385), eluting with ethyl acetate–hexane (7:3–1:0) gave the triply-protected carbapenem **24** as an oil (0.016 g, 22%); λ_{max}(EtOH)/nm 314 and 264; ν_{max}/cm^{-1} 3450, 1790, 1750sh, 1730, 1610, 1525 and 1350; δ_H(250 MHz) 1.44 (3 H, d, *J* 6.5, 9-H_3), 2.97 (2 H, m, SCH_2), 3.18 (2 H, dd, *J* 9.5 and 3, 4-H_2), 3.39 (2 H, br q, *J* 7, CH_2NH), 3.79 (1 H, dd, *J* 7.5 and 6, 6α-H), 4.33 (1 H, br dd, *J* 9.5 and 6, 5α-H), 5.19 and 5.26 (each 2 H, s, CH_2Ar), 5.26 (1 H, *J* 14) and 5.48 (1 H, *J* 14) (both ABq, CH_2Ar); irradiation at the frequency of the 9-H_3 and 6-H protons, located the 8-H resonance at *ca.* 5.2, 7.50, 7.56 and 7.64 (each 2 H, *J* 8) and 8.23 (6 H, *J* 8) (3 × AA′BB′); *m/z* (M^+ DAP; FAB) 766 (MH^+).

(5RS,6RS,8RS) *Sodium* 3-(2-*Aminoethyl*)*thio*-6-(1-*hydroxyethyl*)-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **25**.—The triester **24** (0.010 g) was added to dioxan (6 cm^3)–water (4 cm^3) and 0.05 mol dm^{-3} pH 7 sodium phosphate buffer (1 cm^3) containing 10% Pd–C catalyst (0.010 g; prehydrogenated in the solvents for 10 min). The mixture was shaken vigorously in an atmosphere of hydrogen for 2.5 h, and then filtered through Celite. Evaporation of the dioxan gave a colourless aqueous solution, which was washed with ethyl acetate (×2). The resulting aqueous solution contained (±)-6-epithienamycin **25** (0.0013 g, 51%); $\lambda_{max}(H_2O)$/nm 288.2 (*c.f.* thienamycin, 298.7 nm), homogeneous by HPLC.

p-*Nitrobenzyl* {(4RS)-3-*Chloro*-4-(2-*hydroxyethyl*)-3-[(1RS)-1-p-*nitrobenzyloxycarbonyloxyethyl*]-2-*oxoazetidin*-1-*yl*}*hydroxyacetate* **31**.—Alcohol **26** (4.36 g) and *p*-nitrobenzyl glyoxylate (2.92 g; 1.1 mol equiv.) in dry benzene (250 cm^3) were heated at reflux in a Dean–Stark apparatus for 21 h. The solvent was removed *in vacuo*, and the residue partitioned between ethyl acetate and brine. The organic layer was dried, concentrated and chromatographed, eluting to EtOAc–hexane (1:1–4:1), to give α-hydroxyester **31** (4.65 g, 68%); ν_{max}/cm^{-1} 3600, 3520, 1785, 1755, 1610, 1525 and 1350; δ_H(90 MHz) 1.55 [3 H, d, *J* 6.5, $CH_3CH(OR)$], 2.05 (2 H, m, CH_2OH), 3.7–4.3 (5 H, m, CH_2OH, 4-H, and 2 × OH), 4.8–5.1 (1 H, m, CHOH), 5.34 (4 H, m, 2 × CH_2Ar), 5.6 [1 H, m, $CH_3CH(OR)$] and 7.53 (4 H, *J* 8) and 8.19 (4 H, *J* 8) (both AA′BB′).

p-*Nitrobenzyl* {(4RS)-4-(2-*t*-*Butyldimethylsilyloxyethyl*)-3-*chloro*-3-[(1RS)-1-p-*nitrobenzyloxycarbonyloxyethyl*]-2-*oxo*-1-*azetidin*-1-*yl*}*hydroxyacetate* **32**.—Diol **31** (2.33 g) in dimethylformamide (25 cm^3) was cooled to 0 °C. t-Butylchlorodimethylsilane (0.60 g, 1 mol equiv.) and triethylamine (0.55 cm^3) were added and stirring maintained for 1.5 h. Recovery in ethyl acetate and chromatography on silica gel (Art. 7729), eluting with EtOAc–hexane (1:1) gave a mixture of the two α-hydroxy ester epimers of silyl ether **32** (1.34 g, 48%) [Found: $(M - Bu)^+$, 638.1228. $C_{26}H_{29}ClN_3O_{12}Si$ requires *m/z* 638.1209]; ν_{max}/cm^{-1} 2855, 1780, 1750, 1610, 1525 and 1350.

p-*Nitrobenzyl* {(4RS)-4-*t*-*Butyldimethylsilyloxyethyl*-3-*chloro*-3-[(1RS)-1-*p*-*nitrobenzyloxycarbonyloxyethyl*]-2-*oxo*-*azetidin*-1-*yl*}*triphenylphosphoranylideneacetate* **33**.—Hydroxy ester **32** (1.3 g) was treated successively with thionyl chloride (0.27 cm^3) and 2,6-lutidine (0.43 cm^3) in THF and with triphenylphosphine (0.98 g)–2,6-lutidine (0.43 cm^3) in dioxan according to our established procedure.[20] This gave, after chromatography, a mixture of two inseparable silyl ether-phosphoranes **33** (1.055 g, 60%); ν_{max}/cm^{-1} 2855, 1760, 1740sh, 1625br, 1610, 1525 and 1350.

p-*Nitrobenzyl* [3-*Chloro*-4-(2-*hydroxyethyl*)-3-(1-p-*nitrobenzyloxycarbonyloxyethyl*)-2-*oxoazetidin*-1-*yl*]*triphenylphosphoranylideneacetate* **34**.—Silyl ether-phosphoranes **33** (1.055 g) were stirred in THF (20 cm^3) containing 5 mol dm^{-3} hydrochloric acid (2 cm^3) for 3 h. The mixture was neutralised with aqueous sodium hydrogen carbonate and diluted with ethyl acetate. The organic layer was separated, washed with brine, dried and evaporated. Chromatography on silica gel (Art. 7729) eluting with EtOAC–hexane (7:3) gave the least polar isomer of the title alcohol-phosphorane **34a** (0.355 g). Elution with ethyl acetate provided a second isomer **34b** (0.356 g) (total yield 77%). Each isomer was a white foam; ν_{max}/cm^{-1} 3600, 1765, 1630, 1610, 1525 and 1350; *m/z* (M^+, thioglycerol; FAB) 826 (MH^+); TLC analysis, elution with ethyl acetate: **34a** R_f 0.54, **34b** R_f 0.44.

p-*Nitrobenzyl* 2-[3-*Chloro*-4-(2-*hydroxyethyl*)-3-(1-p-*nitrobenzyloxycarbonyloxyethyl*)-2-*oxoazetidin*-1-*yl*]*acrylate* **35**.—Each alcohol-phosphorane **34** (0.035 g) in dioxane (1 cm^3) was stirred with an excess of aqueous formaldehyde (0.5 cm^3) overnight. Evaporation gave a residue which was chromatographed on silica gel (Art. 9385). Elution with ethyl acetate–hexane (7:3) gave the corresponding acrylate. Isomer **35a**, ν_{max}/cm^{-1} 3600, 1775, 1750, 1730, 1610, 1525 and 1350; δ_H(250

MHz) 1.54 (3 H, d, *J* 6), 1.71 (1 H, br s, OH), 2.07 (2 H, m, CH_2CH_2OH), 3.87 (3 H, m, 4-H and CH_2OH), 5.26 [1 H, q, *J* 6, $CH_3CH(OR)$], 5.26 (2 H, s) and 5.34 (2 H, s) (2 × CH_2Ar), 6.15 and 6.19 (each d, *J ca.* 2, $=CH_2$), 7.53 and 7.56 (each 2 H, *J* 9) and 8.24 (4 H, d, *J* 9) (2 × AA′BB′). Isomer **35b**; ν_{max}/cm^{-1} 3480, 1775, 1750, 1730, 1610, 1525 and 1350; δ_H(250 MHz) 1.56 [3 H, d, *J* 6.5, $CH_3CH(OH)$], 2.02 (2 H, m, CH_2CH_2OH), 2.21 (1 H, br s, OH), 3.55–3.80 (3 H, m, 4-H and CH_2OH), 5.27 (2 H, s, CH_2Ar), 5.30 (2 H, *J* 14) and 5.35 (2 H, *J* 14) (ABq, CH_2Ar), 5.42 [1 H, q, *J* 6.5, $CH_3CH(OR)$], 6.05 (1 H, d, *J* 2) and 6.25 (1 H, d, *J* 2, $=CH_2$), 7.56 (4 H, d, *J* 9) and 8.23 and 8.26 (each 2 H, *J* 9) (2 × AA′BB′).

p-*Nitrobenzyl* [4-*Carboxymethyl*-3-*chloro*-3-(1-p-*nitrobenzyloxycarbonyloxyethyl*)-2-*oxoazetidin*-1-*yl*]-*triphenylphosphoranylideneacetate* **36**.—Alcohol-phosphorane isomer **34a** (0.320 g) in acetone (20 cm^3) was oxidised with Jones' reagent (0.16 cm^3, 3.3 equiv.) at 0 °C for 3 h. Isopropanol (3 cm^3) was added, and the solvents were evaporated and the residue adsorbed on silica gel (Art. 9385). Chromatography as for **19** gave acid-phosphorane **36a** as a foam (0.165 g, 51%); ν_{max}/cm^{-1} 1765, 1750, 1715, 1625br, 1610, 1525 and 1350; *m/z* (M^+, thioglycerol; FAB) 840 (MH^+).

Isomer **36b** was prepared similarly (0.220 g, 66%) from **34b** (0.326 g), also as a foam; ν_{max}/cm^{-1} 1770, 1750, 1715sh, 1625br, 1610, 1525 and 1350; *m/z* (M^+, thioglycerol; FAB) 840 (MH^+).

p-Nitrobenzyl [3-*Chloro*-3-(1-p-*nitrobenzyloxycarbonyloxyethyl*)-2-*oxo*-4-(2-*pyrimidin*-2-*ylthiocarbonylmethyl*)*azetidin*-1-*yl*]*triphenylphosphoranylideneacetate* **37**.—Acid-phosphorane **36a** (0.148 g) in dry THF (10 cm^3) was stirred with triethylamine (30 mm^3, 1.2 mol equiv.) and diethyl chlorophosphate (32 mm^3, 1.2 mol equiv.) in an argon atmosphere for 2 h. Freshly prepared lithium 2-pyrimidinyl thiolate (0.025 g, 1.2 equiv.) was added, and the mixture stirred for 3 h. Evaporation gave a red residue which was chromatographed on silica gel (Art. 7729), eluting with ethyl acetate–hexane (7:3). Thiolester-phosphorane **37a** was obtained as a yellow foam (0.112 g, 68%); ν_{max}/cm^{-1} 1765, 1750sh, 1715sh, 1620br, 1550, 1525, 1380 and 1350.

Isomer **37b** (0.140 g, 66%) was also obtained from **36b** (0.191 g). It was a yellow foam; ν_{max}/cm^{-1} 1765, 1750sh, 1720sh, 1625br, 1610, 1550, 1525, 1380 and 1350.

p-*Nitrobenzyl* 6-*Chloro*-(1-p-*nitrobenzyloxycarbonyloxyethyl*)-7-*oxo*-3-(*pyrimidin*-2-*ylthio*)-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate*.—(i) *Isomer* **38a**. Thiolester **37a** (0.092 g) in dry toluene (90 cm^3) ('degassed' with argon) was heated at reflux in and argon atmosphere for 2 h. The solvent was evaporated, and the residue chromatographed on silica gel (Art. 9385), eluting with ethyl acetate–hexane (7:3–1:0) to give the carbapenem diester **38a** as a gum (0.017 g, 26%); λ_{max}(EtOH)/nm 320 and 261; ν_{max}/cm^{-1} 1800, 1750, 1735sh, 1610, 1550, 1525, 1380 and 1350; δ_H(90 MHz) 1.54 (3 H, d, *J* 6.5, 9-H_3), 3.62 (1 H, dd, *J* 19 and 8) and 3.95 (1 H, dd, *J* 19 and 12) (both 4-H_2), 4.30 (1 H, dd, *J* 12 and 8, 5α-H), 4.9 (1 H, m, 8-H), 5.2–5.5 (4 H, m, 2 × CH_2Ar), 7.13 (1 H, t, *J* 5), 7.23 and 7.47 (each 2 H, *J* 9) and 8.12 (4 H, *J* 9) (2 × AA′BB′) and 8.44 (2 H, d, *J* 5); *m/z* (M^+, thioglycerol; FAB) 656 (MH^+).

(ii) *Isomer* **38b**. This was obtained (0.051 g, 52%) similarly from thiolester **37b** (0.140 g); λ_{max}(EtOH)/nm 321 and 266; ν_{max}/cm^{-1} 1800, 1755, 1735sh, 1610, 1550, 1525, 1380 and 1350; δ(250 MHz) 1.53 (3 H, d, *J* 6.5, 9-H_3), 3.29 (1 H, dd, *J* 19 and 9) and 3.86 (1 H, dd, *J* 19 and 11.5) (both 4-H_2), 4.57 (1 H, dd, *J* 11.5 and 9, 5α-H), 5.25 (2 H, s, CH_2Ar), 5.33 (1 H, *J* 14) and 5.50 (1 H, *J* 14) (both ABq, CH_2Ar), 5.39 (1 H, q, *J* 6.5, 8-H), 7.13 (1 H, t, *J* 5), 7.25, 7.66, 8.20 and 8.22 (each 2 H, *J* 9, 2 × AA′BB′) and 8.59 (2 H, d, *J* 5); *m/z* (M^+, thioglycerol; FAB) 656 (MH^+).

Sodium 6-*Chloro*-1(1-*hydroxyethyl*)-7-*oxo*-3-(*pyrimidin*-2-*ylthio*)-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **39**.—(i) *Isomer* **39a**. Prepared from diester **38a** (0.017 g) as an aqueous solution containing **39a** (0.0035 g, 35%) using our established hydrogenolysis conditions;[20,21] $\lambda_{max}(H_2O)$/nm 297 and 243. Lyophilisation of an aliquot gave a solid; ν_{max}(KBr)/cm^{-1} 1760, 1610, 1560 and 1380; δ_H(250 MHz; D_2O) 1.36 (3 H, d, *J* 6.5, 9-H_3), 3.53–3.72 (2 H, m, 4-H_2), 3.93 (1 H, q, *J* 6.5, 8-H), 4.26 (1 H, dd, *J* 11 and 9, 5α-H), 7.33 (1 H, t, *J* 5) and 8.52 (2 H, d, *J* 5, pyrimidine-H_3).

(ii) *Isomer* **39b**. From diester **38b** (0.045 g) as an aqueous solution containing **39b** (0.0093 g, 37%); $\lambda_{max}(H_2O)$/nm 296 and 241. Lyophilisation gave a solid; ν_{max}(KBr)/cm^{-1} 1762, 1605, 1560 and 1380; δ_H(250 MHz; D_2O) 1.34 (3 H, d, *J* 6.5, 9-H_3), 3.11 (1 H, dd, *J* 18 and 9.5) and 3.41 (1 H, dd, *J* 18 and 10.5) (both 4-H_2), 4.36 (1 H, q, *J* 6.5, 8-H), 4.52 (1 H, t, *J* 10, 5α-H), 7.35 (1 H, t, *J* 5) and 8.64 (2 H, d, *J* 5, pyrimidine-H_3).

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