# Syntheses based on 1,2-Secopenicillins. Part I. Oxidation

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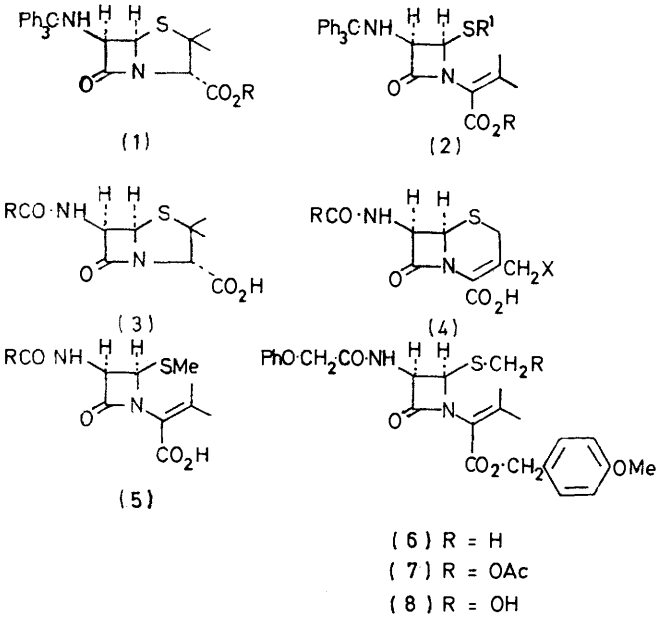
Attempts to introduce oxygenated substituents into the allylic methyl groups of derivatives of (3*R*,4*R*)-3-amino-1-(1-carboxy-2-methylprop-1-enyl)-4-mercaptoazetidin-2-one failed. Instead lead tetra-acetate and certain other oxidants attacked the sulphur atom and the adjacent carbon atoms, whereas osmium tetraoxide or potassium permanganate removed the complete substituent from the β-lactam nitrogen atom.

THE action of certain alkylating agents together with strong anhydrous bases converts 6β-(triphenylmethylamino)penicillanates (1) into non-fused azetidinones (2) [1,2] with retention of the *cis*-stereochemistry about the β-lactam ring which is characteristic of both penicillins (3) and cephalosporins (4). The present paper [3] is the first of a series which will describe attempts to utilise such azetidinones as starting materials for new semisynthetic β-lactam antibiotics.

Since typical 1,2-secopenicillins (5) did not themselves display antibacterial activity [1,2] it was desirable to reconstruct some form of bicyclic system. Our first approach to the construction of the ceph-3-em system of the cephalosporins (4) involved initial attempts to introduce oxygenated substituents into one or both of the allylic methyl groups of the secopenicillanate (6).

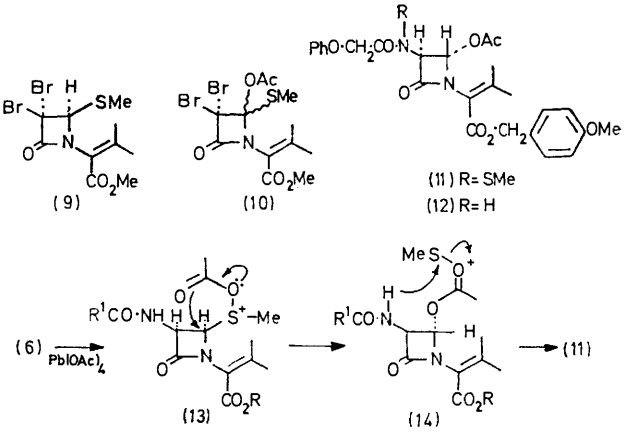
Lead tetra-acetate in refluxing benzene attacked compound (6) readily, but none of the four products isolated by silica gel chromatography proved to have undergone allylic substitution. One was simply the



(1) (2) (3) (4) (5)

(6) R = H
(7) R = OAc
(8) R = OH

*S*-oxide of the starting material (both stereoisomers in the ratio 9 : 1) and another the acetoxymethylthioazetidinone (7). The latter is analogous to the 2-acetoxy-3-methylcephem obtained, rather than the



(9) (10) (11) R = SMe (12) R = H (13) (14)

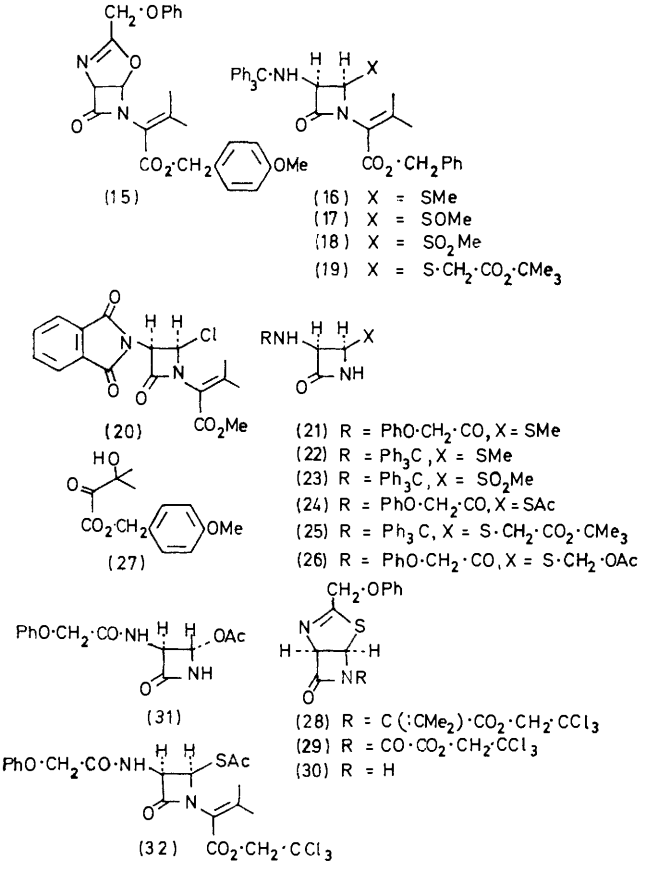
3-(acetoxymethyl)cephem, by the action of lead tetra-acetate on a deacetoxycephalosporin ester.[4] It displayed an unexpected property in that mild acidic hydrolysis gave the hydroxymethyl sulphide (8) as a moderately stable compound, no further breakdown to a mercaptoazetidinone being observed.

Formation of the acetoxymethyl compound (7) and the sulphoxide had precedents in a model oxidation of the dibromoazetidinone (9).[5] The third product from the dibromo-compound was the acetoxy-derivative (10), but whereas the azetidinone (6) was also attacked by lead tetra-acetate at position 4, the end-products were different owing to participation of the 3-acylamino-substituent. The major product (40%) of the action of lead tetra-acetate on compound (6) was an amorphous solid formulated as the *N*-methylthio-derivative (11), the result of a remarkable migration of the methylthio-group probably involving the intermediates (13) and (14). The *N*-methylthio-group was readily removed by reduction with triphenylphosphine to give the sulphur-free azetidinone (12) which, in common with (11), had the *trans*-configuration as indicated by a characteristic coupling constant of 1.5 Hz for the β-lactam protons.[6] The methyl ester corresponding to (12) was recently obtained by the action of mercury(II) acetate on penicillin V methyl ester.[7]

[1] J. P. Clayton, J. H. C. Nayler, R. Southgate, and P. Tolliday, *Chem. Comm.*, 1971, 590.
[2] E. G. Brain, I. McMillan, J. H. C. Nayler, R. Southgate, and P. Tolliday, *J.C.S. Perkin I*, 1975, 562.
[3] Preliminary report, E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1972, 229.
[4] R. D. G. Cooper, P. V. DeMarco, C. P. Murphy, and L. A. Spangle, *J. Chem. Soc.* (*C*), 1970, 340.
[5] J. P. Clayton, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1974, 22.
[6] K. D. Barrow and J. M. Spotswood, *Tetrahedron Letters*, 1965, 3325.
[7] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1973, 32.

The fourth product from the action of lead tetra-acetate on compound (6) was the oxazoline (15), resulting from displacement of the sulphur substituent by intramolecular participation of the amide oxygen atom. The same oxazoline (15) was obtained by treating the *p*-methoxybenzyl ester of penicillin V with t-butyl hypochlorite and triethylamine as described for penicillin G methyl ester.[8]

The azetidinone (6) was next oxidised with *m*-chloroperbenzoic acid to a 1 : 1 mixture of stereoisomeric sulphoxides, which was then heated with acetic anhydride to see how the products of Pummerer rearrangement compared with those obtained from the lead tetra-acetate reaction. Two of the products proved to be the same [(11) and (15)] but the acetoxymethyl sulphide (7) surprisingly was not observed, and a third




product proved to be the *trans*-acetoxyazetidinone (12). It is possible that compound (12) arose from (15) by reaction with acetic acid, a cleavage known to occur [9] in similar fused oxazolines.

We next attempted allylic bromination of the azetidinone (6) with *N*-bromosuccinimide, but the only product isolated was the oxazoline (15). The tritylamino-compound (16) likewise failed to undergo allylic substitution with *N*-bromosuccinimide although, in the presence of water, the sulphoxide was formed as a single crystalline isomer. These results are in marked contrast to the ready bromination o the sulphur-free analogue (20) in one or both allylic methyl groups.[10]

Having failed to functionalise the allylic methyl groups in (6), we next investigated possible oxidative additions to the double bond. In a model experiment with the dibromoazetidinone (9), treatment with osmium tetraoxide resulted in cleavage of the nitrogen substituent, the products being (4*R*)-3,3-dibromo-4-methylthioazetidin-2-one and an α-keto-ester.[5] Similarly the 3-phenoxyacetamidoazetidinone (6) afforded the simple azetidinone (21) and the α-keto-ester (27), together with some sulphone corresponding to the starting material. The tritylamino-azetidinone (22) was likewise obtained from its *N*-substituted analogue (16), but the corresponding sulphoxide (17) gave only the sulphone (18).

A more convenient procedure for the removal of αβ-unsaturated *N*-substituents from a variety of azetidinones was then found in treatment with potassium permanganate at ice-bath temperature. When the azetidinone (16) was so oxidised with aqueous potassium permanaganate in acetone containing a little acetic acid, removal of the *N*-substituent was accompanied by oxidation at sulphur, the product being the sulphone (23).

Oxidation at sulphur did not occur however if acidic reaction conditions were avoided. To this end it was often convenient to carry out the oxidation in aqueous pyridine, sometimes with acetone or dimethylformamide as co-solvent, and this technique permitted selective removal of the *N*-substituent from the typical 4-alkylthioazetidinones (19), (16), and (7). The same technique was extended to the 4-acetoxyazetidinone (12) and the fused thiazoline–azetidinone (28),[11] which gave compounds (31) and (30), respectively. Finally, oxidation of the 4-(acetylthio)azetidinone (32) [12] to (24) with permanganate was carried out in phosphate buffer in order to avoid hydrolysis of the thioester group by the potassium hydroxide generated.

Independently of our work, two other groups have developed methods for converting 1,2-secopenicillins into *N*-unsubstituted azetidinones. In one method,[13] which resembles ours in being oxidative, treatment of compound (28) with ozone at −78 °C gave the oxamic ester (29), which on subsequent treatment with methanol and a trace of sodium methoxide afforded (30). In the non-oxidative procedure [14] 1,3-dipolar addition of diazomethane to the double bond of esters corresponding to secopenicillin (5) was followed by conversion of the

[8] J. C. Sheehan, in 'Molecular Modifications in Drug Design,' Amer. Chem. Soc. Advances in Chemistry Series, No. 45, Washington, 1964, p. 15.
[9] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1974, 181.
[10] S. Wolfe, W. S. Lee, J. B. Ducep, and G. Kannengiesser, *Canad. J. Chem.*, 1972, **50**, 2898.
[11] R. D. G. Cooper and F. L. José, *J. Amer. Chem. Soc.*, 1970, **92**, 2575.
[12] L. D. Hatfield, J. Fisher, F. L. José, and R. D. G. Cooper, *Tetrahedron Letters*, 1970, 4897.
[13] R. D. G. Cooper and F. L. José, *J. Amer. Chem. Soc.*, 1972, **94**, 1021.
[14] D. H. R. Barton, D. G. T. Greig, P. G. Sammes, and M. V. Taylor, *Chem. Comm.*, 1971, 845.

adduct into a simple azetidinone by reductive elimination of a pyrazoline. Permanganate oxidation complements these procedures in giving the desired simple azetidinone in a single operation, and has proved to be a key step in a novel conversion of penicillins into certain new types of cephalosporin.[15]

## EXPERIMENTAL

I.r. spectra were recorded for solutions in chloroform unless stated otherwise. $^1$H N.m.r. spectra were recorded on a Varian A-60 instrument for solutions in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise. Mass spectra were determined with an A.E.I. MS 9 machine. Merck silica gel GF 254 was used for t.l.c. and Merck silica gel H for column chromatography, with ethyl acetate–light petroleum as eluant. Light petroleum refers to the fraction of b.p. 60—80°. M.p.s were determined with a Kofler hot-stage apparatus.

*Reaction of* (3R,4R)-1-(1-p-*Methoxybenzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylthio*-3-(*phenoxyacetamido*)*azetidin*-2-*one* (6) *with Lead Tetra-acetate*.—The lactam (6) [2] (243 mg) and lead tetra-acetate (350 mg; dried *in vacuo*) were mixed, and dry benzene (20 ml) was added. The mixture was refluxed for 15 min and then the benzene was removed under reduced pressure and the residue extracted with ethyl acetate (3 × 25 ml). The extract was washed with saturated aqueous sodium hydrogen carbonate and then brine, dried ($Na_2SO_4$), and evaporated to yield an oil (250 mg). Chromatography on silica gave (3S,4S)-4-*acetoxy*-1-(1-p-*methoxybenzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-[(N-*methylthio*)*phenoxyacetamido*]*azetidin*-2-*one* (11) (110 mg) as an amorphous solid, $\nu_{max.}$ 1 780, 1 765sh, 1 710br, and 1 630 cm$^{-1}$; δ 1.98 (3 H, s), 2.02 (3 H, s), 2.27 (3 H, s), 2.45 (3 H, s), 3.78 (3 H, s), 5.07 (2 H, s), 5.16 (2 H, s), 5.7 (1 H, d, *J* 1.5 Hz), 6.28 (1 H, d, *J* 1.5 Hz), 6.75—7.47 (9 H, m) (Found: C, 60.1; H, 5.7; N, 5.0; S, 5.6. $C_{27}H_{30}N_2O_8S$ requires C, 59.7; H, 5.6; N, 5.1; S, 5.9%).

Further elution produced (1S,5R)-3-*phenoxymethyl*-6-(1-p-*methoxybenzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (15) (12 mg), $\nu_{max.}$ 1 785, 1 720, 1 658, and 1 630 cm$^{-1}$; δ 1.8 (3 H, s), 2.2 (3 H, s), 3.79 (3 H, s), 4.63 (2 H, s), 5.01 and 5.23 (2 H, ABq, *J* 12 Hz), 5.24 (1 H, d, *J* 3.5 Hz), 5.99 (1 H, d, *J* 3.5 Hz), 6.76—7.42 (9 H, m) (Found: C, 65.8; H, 5.6; N, 6.4%; $M^+$, 436. $C_{24}H_{24}N_2O_6$ requires C, 66.0; H, 5.5; N, 6.4%; *M*, 436).

The third product eluted was (3R,4R)-4-*acetoxymethylthio*-1-(1-p-*methoxybenzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (7) (95 mg), isolated as an oil, $\nu_{max.}$ 3 390, 1 770, 1 750, 1 720, 1 695, and 1 630 cm$^{-1}$; δ[$(CD_3)_2SO$] 1.9, 2.0, and 2.2 (each 3 H, s), 3.75 (3 H, s), 4.57 (2 H, s), 4.88 and 5.12 (2 H, ABq, *J* 12 Hz), 5.08 (1 H, dd, *J* 5 and 8 Hz), 5.13 (2 H, s), 5.38 (1 H, d, *J* 5 Hz), 6.8—7.5 (9 H, m), and 8.9 (1 H, d, *J* 8 Hz, slowly exch. $D_2O$) (Found: $M^+$, 542.172 1. $C_{27}H_{30}N_2O_8S$ requires *M*, 542.177 2).

The final product eluted was a mixture of the two stereoisomeric sulphoxides, (3R,4R)-1-(1-p-*methoxybenzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylsulphinyl*-3-*phenoxyacetamidoazetidin*-2-*one* (40 mg), which could just be separated into two spots by several elutions of the t.l.c. plate, the ratio of less polar to the more polar being *ca.* 9 : 1 (n.m.r.); $\nu_{max.}$ 3 300, 1 785, 1 720, 1 690, 1 630, and 1 062 cm$^{-1}$; δ (major isomer) 2.15, 2.29, and 2.33 (each 3 H, s), 3.8 (3 H, s), 4.57 (2 H, s), 4.58 (1 H, d, *J* 5 Hz), 5.03 and 5.27 (2 H, ABq, *J* 12 Hz), 6.01 (1 H, dd, *J* 5 and 10 Hz), 6.77—7.5 (9 H, m), 8.72 (1 H, ill-defined d, *J* 10 Hz) (Found: C, 59.9; H, 5.6; N, 5.5; S, 6.6. $C_{25}H_{28}N_2O_7S$ requires C, 60.0; H, 5.6; N, 5.6; S, 6.4%).

(3R,4R)-4-*Hydroxymethylthio*-1-(1-p-*methoxybenzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (8).—The acetate (7) (0.285 g) in methanol (19 ml) and 2N-hydrochloric acid (0.9 ml) was left overnight at room temperature, then diluted with ethyl acetate, washed with water (× 3), dried, and evaporated. Crystallisation of the residue from ethyl acetate–light petroleum gave the *hydroxymethyl sulphide* (8) (0.172 g) as white plates, m.p. 95—100°, $\nu_{max.}$ 3 550br, 3 400, 1 770, 1 720, and 1 690 cm$^{-1}$; δ 1.97 (3 H, s), 3.00br (1 H, s, exch. $D_2O$), 3.77 (3 H, s), 4.55 (4 H, s, $2CH_2$), 5.02 and 5.26 (2 H, ABq, *J* 12 Hz), 5.30—5.45 (2 H, m, β-lactam protons), and 6.8—7.7 (10 H, ArH and NH); δ[$(CD_3)_2CO$] 2.03 (3 H, s), 2.18 (3 H, s) 4.42 (1 H s, exch. $D_2O$), 3.78 (3 H, s), 4.58 (2 H, s), 4.66 (2 H, s), 5.16 (2 H, s), 5.33 (1 H dd, *J* 8.5 and 4.5 Hz), 5.52 (1 H, d, *J* 4.5 Hz), 6.8—7.5 (9 H, m, ArH), and 8.25 (1 H, d, *J* 8.5 Hz) (Found: C, 60.0; H, 5.7; N 5.4. $C_{25}H_{28}N_2O_7S$ requires C 60.0; H, 5.6; N, 5.6%).

(3S,4S)-4-*Acetoxy*-1-(1-p-*methoxybenzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (12).—The lactam (11) (1.05 g) was dissolved in chloroform and cooled in an ice-bath to *ca.* 5 °C. Triphenylphosphine (510 mg) was added in portions over 5 min, and then the solution was evaporated. Chromatography of the product on silica afforded the *product* (12) (971 mg) as an amorphous solid, $\nu_{max.}$ 3 390, 1 780, 1 760 1 720, 1 700, and 1 630 cm$^{-1}$; δ 1.98 (6 H, s), 2.2 (3 H, s), 3.67 (3 H, s), 4.46 (2 H, s), 5.05 (1 H, dd, *J* 1.5 and 10 Hz), 5.13 (2 H, s), 6.18 (1 H, d, *J* 1.5 Hz), 6.7—7.7 (10 H, m), δ[$(CD_3)_2SO$] 1.97 (6 H, s), 2.12 (3 H, s), 3.73 (3 H, s), 4.57 (2 H, s), 4.8 (1 H, dd, *J* 1.5 and 8 Hz), 5.11 (2 H, s), 6.24 (1 H, d, *J* 1.5 Hz), 6.8—7.5 (9 H, m), and 8.93 (1 H, ill-defined d, *J* 8 Hz, exch. $D_2O$) (Found: C, 62.7; H 5.8; N, 5.4. $C_{26}H_{28}N_2O_8$ requires C, 62.9; H, 5.7; N 5.6%).

(3R,4R)-1-(1-p-*Methoxybenzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylsulphinyl*-3-*phenoxyacetamidoazetidin*-2-*one*.—The lactam (6) (227 mg) was dissolved in dry chloroform (20 ml) and cooled to *ca.* 5 °C in an ice-bath. *m*-Chloroperbenzoic acid (85 mg) was added in portions over 2—3 min and the solution stirred for a further 20 min. The mixture was extracted with aqueous sodium hydrogen carbonate and brine, then dried ($Na_2SO_4$). Evaporation of the solvent layer left an oil (240 mg), which was chromatographed on silica. The product (220 mg), a viscous gum which could not be induced to crystallise, was a *ca.* 1 : 1 mixture of the two stereoisomeric sulphoxides (by n.m.r.); $\nu_{max.}$ 3 300, 1 785, 1 720, 1 690, 1 630, and 1 062 cm$^{-1}$; δ (more polar isomer—deduced from the n.m.r. of the mixture) 2.26 and 2.33 (6 H and 3 H, two s), 3.8 (3 H, s), 4.59 (2 H, s), 4.9 (1 H, d, *J* 5 Hz), 5.08 and 5.37 (2 H, ABq, *J* 12 Hz), 5.87 (1 H, dd, *J* 5 and 10 Hz), 6.77—7.5 (9 H, m), and 7.88 (1 H, ill-defined d, *J* 10 Hz).

*Reaction of* (3R,4R)-1-(1-p-*methoxybenzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylsulphinylazetidin*-2-*one with Acetic Anhydride*.—The sulphoxide mixture (118 mg) was dissolved in dry redistilled acetic anhydride (8 ml), refluxed for 2 h, then evaporated, and the oily residue was

[15] J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1973, 58.

chromatographed on silica to provide three products, (11) (35 mg), (15) (10 mg), and (12) (30 mg).

*Reaction of* 1-(1-p-*Methoxybenzyloxycarbonyl-2-methylprop-1-enyl*)-4-*methylthio*-3-*phenoxyacetamidoazetidin*-2-*one* (6) *with* N-*Bromosuccinimide*.—The lactam (6) (244 mg) was dissolved in dry carbon tetrachloride (30 ml) and *N*-bromosuccinimide (90 mg) and azobisisobutyronitrile (14 mg) were added. The mixture was refluxed for 16 h under nitrogen in the dark, filtered, and evaporated to dryness. Chromatography on silica afforded starting material (6) (11 mg) and the oxazoline (15) (15 mg).

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylsulphinyl*-3-*triphenylmethylaminoazetidin*-2-*one* (17).—(3*R*,4*R*)-1-(1-Benzyloxycarbonyl-2-methylprop-1-enyl)-4-methylthio-3-triphenylmethylaminoazetidin-2-one (16) (200 mg, 0.356 mmol) was dissolved in 1,2-dimethoxyethane, cooled to −30 °C, and stirred while a mixture of *N*-bromosuccinimide (72 mg, 0.40 mmol) and water (2.6 ml) in 1 2-dimethoxyethane (5.0 ml) was added dropwise. The mixture was then left at 4 °C for 16 h, poured into water (50 ml), and extracted with ether. The extract was dried ($MgSO_4$) and evaporated and the residue chromatographed to give an oil (100 mg, 49%) which crystallised on trituration with ether. Recrystallisation from ether gave the *methylsulphinyl derivative* (17) as a single stereoisomer, m.p. 200—203°, $\nu_{max.}$ (Nujol) 3 390, 1 775, and 1 720 $cm^{-1}$; δ 2.02 (3 H, s), 2.18 (3 H, s), 2.39 (3 H, s), 3.78br (1 H, d, *J* 10 Hz, exch. $D_2O$), 4.37 (1 H, d, *J* 5 Hz), 4.70 (1 H, dd, *J* 10 and 5 Hz; d, *J* 5 Hz on $D_2O$ exch.), 4.93 and 5.18 (2 H, ABq, *J* 13 Hz), and 7.1—7.5 (20 H, m) (Found: C, 72.7; H, 5.9; N, 4.6; S, 5.3. $C_{35}H_{34}N_2O_4S$ requires C, 72.6; H, 5.9; N, 4.8; S, 5.5%).

*Treatment of* (3R,4R)-1-(1-p-*Methoxybenzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylthio*-3-*phenoxyacetamidoazetidin*-2-*one* (6) *with Osmium Tetraoxide*.—The lactam (6) (188 mg) was dissolved in dry benzene (4 ml) and pyridine (0.4 ml), and osmium tetraoxide (100 mg) in dry benzene (1 ml) was added. The mixture was left in the dark at room temperature for 15 h. Ethyl acetate (15 ml) was added and hydrogen sulphide bubbled through the mixture for 20 min. The black precipitate was filtered off and washed with ethyl acetate (2 × 10 ml), and the filtrate and washings were evaporated to dryness at room temperature to yield a dark oil (189 mg). Silica gel chromatography afforded three products besides starting material (6) (53 mg). The first, (3R,4R)-4-*methylthio*-3-*phenoxyacetamidoazetidin*-2-*one* (21) (25 mg), was obtained as white needles, m.p. 170—172° (from ethyl acetate–petroleum), $\nu_{max.}$ (Nujol) 3 280, 1 765, 1 740, and 1 680 $cm^{-1}$; δ[$(CD_3)_2SO$] 1.97 (3 H, s), 3.22br (1 H, s, $D_2O$ exch.), 4.6 (2 H, s), 4.9 (1 H, d, *J* 5 Hz), 5.28 (1 H, dd, *J* 5 and 10 Hz), 6.7—7.5 (5 H, m), 8.77 (1 H, d, *J* 10 Hz, exch. $D_2O$) (Found: $M^+$, 266.073 6. $C_{12}H_{14}N_2O_3S$ requires *M*, 266.072 5).

The α-oxo-ester (27) (26 mg) was isolated as a liquid, $\nu_{max.}$ 3 500, 1 740, and 1 730 $cm^{-1}$; δ 1.47 (6 H, s), 3.06br (1 H, s, $D_2O$ exch.), 3.81 (3 H, s), 5.26 (2 H, s), and 6.91 and 7.36 (2 H, ABq, *J* 9 Hz) (Found: C, 61.3; H, 6.6. $C_{13}H_{16}O_5$ requires C, 61.9; H, 6.4%).

The third product was (3R,4R)-1-(1-p-*methcxybenzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylsulphonyl*-3-*phenoxyacetamidoazetidin*-2-*one* (18 mg), obtained as an amorphous solid, $\nu_{max.}$ 3 365, 1 790, 1 720, 1 700, 1 630, 1 322, and 1 143 $cm^{-1}$; δ 2.13 (3 H, s), 2.25 (3 H, s), 2.38 (3 H, s), 3.8 (3 H, s), 4.55 (2 H, s), 5.02 and 5.28 (2 H, ABq, *J* 12 Hz), 5.07 (1 H, d, *J* 5 Hz), 5.9 (1 H, dd, *J* 5 and 10 Hz), and 7.8 (1 H, ill-defined d, *J* 10 Hz) (Found: C, 58.3; H, 5.6; N, 5.3; S, 6.4. $C_{27}H_{30}N_2O_{10}S$ requires C, 58.1; H, 5.4; N, 5.4; S, 6.2%).

*Oxidation of* (3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylthio*-3-*triphenylmethylaminoazetidin*-2-*one* (16) *with Osmium Tetraoxide*.—Compound (16) (206 mg, 0.364 mmol) was added to a solution of osmium tetraoxide (100 mg, 0.394 mmol) in dry tetrahydrofuran (10 ml) containing pyridine (0.4 ml). The mixture was stirred in the dark for 65 h, then ethyl acetate (15 ml) was added and hydrogen sulphide was passed through the solution for 45 min. After filtration through kieselguhr the solvents were removed to leave a dark oil (140 mg). This was chromatographed to give (3R,4R)-4-*methylthio*-3-*triphenylmethylaminoazetidin*-2-*one* (22) (72 mg, 57%) as a solid foam, $\nu_{max.}$ 3 390, 3 270, and 1 770 $cm^{-1}$; δ 1.82 (3 H, s), 2.99br (1 H, d, *J* 8 Hz, exch. $D_2O$), 4.19 (1 H, d, *J* 5 Hz), 4.3—4.6 (1 H, complex), 6.2br (1 H, s, exch. $D_2O$), and 7.1—7.7 (15 H, m) (Found: $M^+$, 374.147 8. $C_{23}H_{22}N_2OS$ requires *M*, 374.145 3).

*Oxidation of* (3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylsulphinyl*-3-*triphenylmethylaminoazetidin*-2-*one* (17) *with Osmium Tetraoxide*.—Osmium tetraoxide (100 mg) was dissolved in tetrahydrofuran (8 ml) and pyridine (0.2 ml) was added. The lactam (17) (228 mg) was added and the mixture was stirred in the dark for 3½ days. Ethyl acetate (20 ml) was then added and $H_2S$ was passed through the mixture for 1 h. The mixture was filtered through kieselguhr and the solvents were removed to leave an oil (250 mg) which crystallised. Recrystallisation from ether gave (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylsulphonyl*-3-*triphenylmethylaminoazetidin*-2-*one* (18), m.p. 170—172°; $\nu_{max.}$ 1 785, 1 720, 1 625, 1 310, and 1 135 $cm^{-1}$; δ 2.08 (3 H, s), 2.19 (3 H, s), 2.48 (3 H, s), 3.45br (1 H, d, *J* 9 Hz, exch. $D_2O$), 4.55—4.84 (2 H, m), 4.94 and 5.20 (2 H, ABq, *J* 12 Hz), 7.1—7.5 (20 H, m) (Found: C, 70.5; H, 5.8; N, 4.5; S, 5.5. $C_{35}H_{34}N_2O_5S$ requires C, 70.7; H, 5.7; N, 4.7; S, 5.4%).

*Oxidation with Potassium Permanganate*.—*Method A*. (3*R*,4*R*)-1-(1-Benzyloxycarbonyl-2-methylprop-1-enyl)-4-methylthio-3-triphenylmethylaminoazetidin-2-one (16) (400 mg) was dissolved in acetone (20 ml) and the mixture was cooled in an ice-bath. Glacial acetic acid (0.5 ml) was then added, followed by a solution of potassium permanganate (350 mg) in water (15 ml), added over 2 h. The mixture was stirred for a further 2 h, then ethyl acetate and dilute brine were added and the manganese dioxide was filtered off. The ethyl acetate layer was dried and evaporated; chromatography of the residue gave (3R,4R)-4-*methylsulphonyl*-3-*triphenylmethylaminoazetidin*-2-*one* (23) (150 mg), $\nu_{max.}$ 3 650, 1 790, 1 310, and 1 135 $cm^{-1}$; δ 2.62 (3 H, s), 3.53 (1 H, d, *J* 10 Hz, exch. $D_2O$), 4.32 (1 H, d, *J* 5 Hz), 4.75 (1 H, dd, *J* 5 and 10 Hz; d, *J* 5 Hz on $D_2O$ exch.), 6.75br (1 H, s, exch. $D_2O$), and 7.0—7.6 (15 H, m). Crystallisation from acetone–water gave crystals, m.p. 112—115° containing acetone of crystallisation (Found: C, 67.2; H, 5.9; N, 6.2; S, 7.2. $C_{23}H_{22}N_2O_3S,C_3H_6O$ requires C, 67.2; H, 6.0; N, 6.0; S, 6.9%).

*Method B*. (3*R*,4*R*)-1-(1-Benzyloxycarbonyl-2-methylprop-1-enyl)-4-(t-butoxycarbonylmethylthio)-3-triphenylmethylaminoazetidin-2-one [2] (19) (3 g) was dissolved in pyridine (30 ml) and water (2 ml), then cooled in an ice-bath. Powdered potassium permanganate (1.07 g) was added in portions over a few minutes and the mixture

stirred in the cold for 1 h. After dilution with ethyl acetate and brine the mixture was treated with sulphur dioxide until clear, then the layers were separated. The solvent phase was washed successively with aqueous sodium hydrogen carbonate, water, 2N-hydrochloric acid, and water again, then dried and evaporated. The residual gum (2.6 g) was chromatographed on silica gel (80 g) to give starting material (0.45 g) and (3R,4R)-4-(*t-butoxycarbonylmethylthio*)-3-*triphenylmethylaminoazetidin*-2-*one* (25) (0.68 g, 32%) as an amorphous solid, $\nu_{max.}$ 3 350, 1 765, and 1 720 $cm^{-1}$; δ 1.44 (9 H, s), 2.78 and 3.08 (2 H, ABq, *J* 15 Hz), *ca.* 3.0br (1 H, s, exch. $D_2O$), 4.40—4.70 (2 H, m, collapsing to s on $D_2O$ exch., β-lactam protons), 6.40br (1 H, s, exch. $D_2O$), and 7.10—7.65 (15 H, m, ArH) (Found: $M^+$, 474.199 8. $C_{28}H_{30}N_2O_3S$ requires *M*, 474.197 7).

Similar oxidation of (3*R*,4*R*)-1-(1-benzyloxycarbonyl-2-methylprop-1-enyl)-4-methylthio-3-triphenylmethylaminoazetidin-2-one (16) (220 mg) afforded benzyl 3-hydroxy-3-methyl-2-oxobutyrate (40 mg) and (3*R*,4*R*)-4-methylthio-3-triphenylmethylaminoazetidin-2-one (22) (90 mg, 60%), identical with material obtained by using osmium tetraoxide.

*Method C.* (3*R*,4*R*)-4-Acetoxymethylthio-1-(1-*p*-methoxybenzyloxycarbonyl-2-methylprop-1-enyl)-3-phenoxyacetamidoazetidin-2-one (7) (272 mg) was dissolved in acetone (7 ml) containing pyridine (0.25 ml) and cooled to 5 °C. Potassium permanganate (79 mg) in water (5 ml) was added dropwise over 1 h and the mixture was stirred at 5 °C until no longer pink (30 min), then filtered through kieselguhr, with thorough washing with ethyl acetate and water. The organic layer of the filtrate was separated, dried ($Na_2SO_4$), and evaporated. Chromatography gave starting material (135 mg) and (3R,4R)-4-*acetoxymethylthio*-3-*phenoxyacetamidoazetidin*-2-*one* (26) (29 mg), which crystallised from ethyl acetate as needles, m.p. 178—179°; $\nu_{max.}$ (Nujol) 3 250, 1 770, 1 755, and 1 650 $cm^{-1}$; δ[$(CD_3)_2SO$] 2.03 (3 H, s), 3.22br (1 H, s, $D_2O$ exch.), 4.55 (2 H, s), 5.13 (2 H, s), 5.17 (2 H, m), 6.78—7.55 (5 H, m), and 8.8br (1 H, $D_2O$ exch.) (Found: C, 51.3; H, 5.0; N, 8.4; S, 9.6. $C_{14}H_{16}N_2O_5S$ requires C, 51.9; H, 5.0; N, 8.6; S, 9.9%), *m/e* 324 ($M^+$, $C_{14}H_{16}N_2O_5S$), 281 (PhO·$CH_2$·CO·NH·CH=CH·S·$CH_2$·OAc)$^+$, and 134 ($^+NH_2$=CH·S·$CH_2$·OAc).

Similar oxidation of (1*R*,5*R*)-6-[2-methyl-1-(2,2,2-trichloroethoxycarbonyl)prop-1-enyl]-3-phenoxymethyl-4-thia-2,6-diazabicyclo[3.2.0]hept-2-en-7-one [11] (28) (200 mg) gave (1*R*,5*R*)-3-phenoxymethyl-4-thia-2,6-diazabicyclo[3.2.0]hept-2-en-7-one (30) (50 mg), m.p. 156—158° (from acetone–light petroleum) (lit.,[13] 157—158°); $\nu_{max.}$ 3 375 and 1 780 $cm^{-1}$; δ[$CDCl_3$–$(CD_3)_2SO$] 4.97 (2 H, s), 5.5 (1 H, d, *J* 4 Hz), 5.9—6.1 (1 H, m), 6.8—7.5 (5 H, m), 8—8.3br (1 H, s, exch.) (Found: C, 56.4; H, 4.3; N, 11.7; S, 13.8. Calc. for $C_{11}H_{10}N_2O_2S$: C, 56.4; H, 4.3; N, 12.0; S, 13.7%).

*Method D.* (3*S*,4*S*)-4-Acetoxy-1-(1-*p*-methoxybenzyloxycarbonyl-2-methylprop-1-enyl)-3-phenoxyacetamidoazetidin-2-one (12) (500 mg) was dissolved in a mixture of dimethylformamide (5 ml), pyridine (5 ml), and water (1 ml) and the solution cooled to −5 °C. Powdered potassium permanganate (263 mg) was added and the mixture stirred at 0 °C for 1 h. (CAUTION! Solid potassium permanganate should not be added to neat dimethylformamide, in which it dissolves easily, since a violent exothermic reaction ensues.) Ethyl acetate was added and sulphur dioxide was passed through the cooled mixture until all the manganese dioxide had been removed. The mixture was washed with dilute hydrochloric acid, until the aqueous layer was acidic, then with dilute aqueous sodium hydrogen carbonate and brine. The organic layer was separated, dried, and evaporated. The product was recrystallised from ethyl acetate–petroleum to afford (3S,4S)-4-*acetoxy*-3-*phenoxyacetamidoazetidin*-2-*one* (31) (171 mg), m.p. 144—145°; $\nu_{max.}$ 3 370, 1 793, 1 745, and 1 690 $cm^{-1}$; δ 2.12 (3 H, s), 4.53 (2 H, s), 5.0 (1 H, dd, *J* 2 and 9 Hz, collapsing to d, *J* 2 Hz on $D_2O$ exch.), 5.95 (1 H, d, *J* 2 Hz), 6.8—7.6 (6 H, m), 7.73 (1 H, d, *J* 9 Hz, exch. with $D_2O$) (Found: C, 56.0; H, 5.3; N, 10.3. $C_{13}H_{14}N_2O_5$ requires C, 56.1; H, 5.0; N, 10.1%).*

*Method E.* (3*R*,4*R*)-4-Acetylthio-1-[2-methyl-1-(2,2,2-trichloroethoxycarbonyl)prop-1-enyl]-3-phenoxyacetamidoazetidin-2-one (32) [12] (349 mg) in acetone (20 ml), cooled in ice, was treated with potassium permanganate (208 mg) in water (6 ml) and pH 7 phosphate buffer (4 ml) in portions over 25 min. The product was extracted with ethyl acetate then washed with brine, dried ($Na_2SO_4$), and evaporated. The residue was separated by column chromatography to give (3R,4R)-4-*acetylthio*-3-*phenoxyacetamidoazetidin*-2-*one* (24) (259 mg, 59%), m.p. 138—141° (from benzene–light petroleum), $\nu_{max.}$ 3 340, 1 780, and 1 690 $cm^{-1}$; δ 2.31 (3 H, s), 4.57 (2 H, s), 5.45—5.9 (2 H, m), 6.67br (1 H, s, exch.), and 6.8—7.6 (6 H, m) (Found: C, 52.8; H, 4.7; N, 9.4; S, 10.9. $C_{13}H_{14}N_2O_4S$ requires C, 53.0; H, 4.8; N, 9.5; S, 10.9%).

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