Synthesis of Some 1-Oxa-1-dethiacephalosporins

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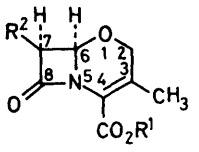
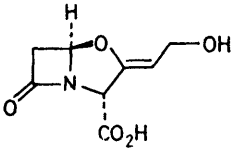
The penicillin-derived (3*R*,4*R*)-4-methylsulphonyl-3-triphenylmethylaminoazetidin-2-one (14) has been converted into various (6*R*,7*S*)-1-oxa-1-dethiacephalosporins, the dihydro-oxazine ring being closed by an intramolecular Wittig reaction. The isomerisation and cyclopropanation of the double bond in (6*R*,7*S*)-t-butyl 3-methyl-7-triphenylmethylamino-1-oxa-1-dethiaceph-3-em-4-carboxylate (21; $R^1 = CMe_3$) have been investigated.

We have recently reported [1] the synthesis of the bicyclic system (1) and its 2-ethylidene analogue. Our initial interest was prompted by the hope that the compounds might have similar properties to clavulanic acid (2), a potent inhibitor of β-lactamases.[2] Although this proved not to be the case, it was clear that the established procedures could be extended to the synthesis of 1-oxa-1-dethiacephalosporins (3). It was surmised that these compounds might display comparable antibacterial activity to their 1-thia-analogues.



(1) $R^1 = R^2 = H$
(3) $R^1 = H$, $R^2 = R^3CONH$
(13) $R^1 = CMe_3$, $R^2 = H$



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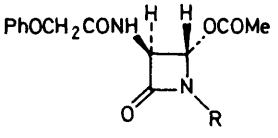
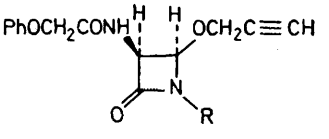
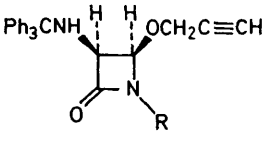


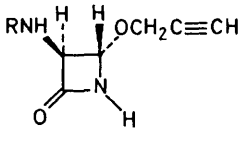
(4) R = H
(5) R = $C(:CMe_2)CO_2Me$



(6) R = H
(9) R = $CHOH.CO_2CMe_3$
(10) R = $CHCl.CO_2CMe_3$
(11) R = $C(:PPh_3)CO_2CMe_3$



(15) R = H
(17) R = $CHOH.CO_2CMe_3$
(18) R = $CHCl.CO_2CMe_3$
(19) R = $C(:PPh_3)CO_2CMe_3$



(7) R = $PhOCH_2CO$
(16) R = Ph_3C

When our work began such derivatives (3) were unknown, but subsequently they have been synthesised [3] and shown to possess good bioactivity.[4] Whereas the approach adopted by Christensen afforded racemic products, our route has the advantage of providing derivatives with the requisite (6*R*,7*S*) stereochemistry. The synthesis of similar optically active compounds has been very recently exemplified,[5] utilising some of the methodology previously described by us for cephalosporin synthesis.[6]

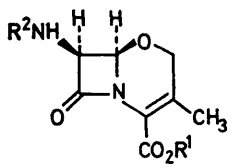
Following our earlier investigations, (3*S*,4*S*)-4-acetoxy-3-phenoxyacetamidoazetidin-2-one (4) was selected as a suitable starting material. Mercury(II) acetate oxidation [7] of methyl phenoxymethylpenicillinate gave the acetoxy-derivative (5), from which the *N*-substituent was oxidatively cleaved [8] to provide (4) in 70% overall yield. Warming the azetidinone (4) with prop-2-yn-1-ol in benzene containing zinc acetate afforded a 1 : 1 mixture of the *cis*- and *trans*-4-(prop-2-ynyloxy)-3-(phenoxyacetamido)azetidin-2-ones (6) and (7). These were readily separated by chromatography and the *cis*-isomer was converted into (6*R*,7S)-t-butyl 3-methyl-7-phenoxyacetamido-1-oxa-1-dethiaceph-3-em-4-carboxylate (8; $R^1 = CMe_3$) using the established reaction sequence.[1]

The azetidinone (6) was condensed with an excess of t-butyl glyoxylate to give the α-hydroxy-ester (9), which with thionyl chloride afforded the α-chloro-ester (10), both products being mixtures of isomers. Treatment with triphenylphosphine and 2,6-lutidine then gave the acetylenic phosphorane (11), which was hydrated using mercury(II) chloride in piperidine to provide (12). The desired intramolecular Wittig reaction occurred when the ketone (12) was refluxed in dry dioxan under nitrogen for 16 h, and the oxacephem (8; $R^1 = CMe_3$) was isolated in excellent yield. Removal of the t-butyl group by brief exposure to trifluoroacetic acid gave the corresponding 1-oxa-1-dethiacephalosporinate (8; $R^1 = H$). This can be contrasted with the behaviour of the unsubstituted derivative (13), when a similar reaction disrupted the β-lactam.[1]

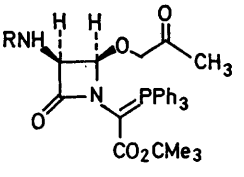
At about this time one of our colleagues [9] had found that the methylsulphonyl group of (14) could be readily displaced by thiols in the presence of base. Under these conditions alcohols were not so effective. However, use of the sulphone (14) was attractive to us for two reasons. First, the material was readily available in two steps [8] from benzyl 6β-(triphenylmethylamino)penicillanate, and secondly, the amino-protecting group can be removed from the final bicyclic system under mild conditions, allowing a range of acylated derivatives to be prepared.

Thus it was pleasing to discover that (14) reacted smoothly with prop-2-yn-1-ol in refluxing benzene containing zinc acetate, to give a mixture of the two

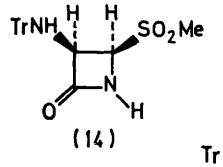
isomeric propargyloxyazetidinones (15) and (16). Using a precisely similar reaction sequence to that previously used to prepare the acylamino-derivative (8; $R^1 = CMe_3$), the *cis*-isomer was converted into the oxacephem (21; $R^1 = CMe_3$). Detritylation with toluene-*p*-sulphonic acid gave the primary amine (22; $R^1 = CMe_3$) which was acylated and finally de-esterified to provide the free acids (24; $R^1 = H$) and (25; $R^1 = H$). The final products displayed antibacterial activity (see Table) which did not necessarily parallel that found in their 1-thia-analogues. Thus one of the most active 3-methylcephems is the D-phenylglycyl derivative, cephalexin, but in the oxygen series the corresponding compound (24; $R^1 = H$) was the least active product. A possible explanation for this has been recently suggested.[5]



(8) R^2 = $PhOCH_2CO$
(21) R^2 = Ph_3C
(22) R^2 = H
(23) R^2 = D—PhCH($NHCO_2CMe_3$)CO
(24) R^2 = D—PhCH(NH_3^+) $CF_3CO_2^-$
(25) R^2 = D—PhCH(OH)CO

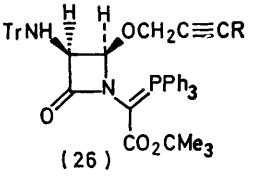


(12) R = $PhOCH_2CO$
(20) R = Ph_3C



(14)

Tr = Ph_3C

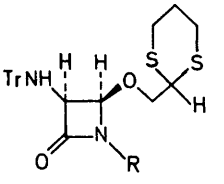


(26)

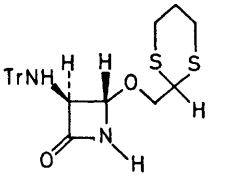
Unfortunately the above route could not be extended to the use of 3-substituted prop-2-ynyl alcohols, because the corresponding propynyl ethers (26) could not be hydrated. Since the direct use of α-hydroxy-ketones in the initial sulphone displacement reaction was unsuccessful, we sought an alternative method of protecting the carbonyl functionality, which would provide greater synthetic versatility.

The 1,3-dithian group has attractions as a protecting group for the aldehyde function because of its relative ease of removal [10] and its potential for the introduction of further substituents by alkylation at the 2-position.[11] Reaction of the sulphone (14) with 2-hydroxymethyl-1,3-dithian [12] in the presence of zinc acetate gave the expected azetidinones (27) and (28). Successive treatment of (27) with t-butyl glyoxylate, thionyl chloride, and triphenylphosphine then gave the phosphorane (31) by way of intermediates (29) and (30). Despite the plethora of methods available for the removal of the 1,3-dithian protecting group, the use of methyl iodide in refluxing aqueous acetone containing barium carbonate [13] was the only procedure that proved satisfactory in our case. When the phosphorane (31) was reacted under these conditions, the oxacephem (32; $R^1 = CMe_3$) was isolated in 40—50% yield. Thus the initially formed aldehyde spontaneously cyclised in the same way as the analogous thia-derivative.[14] A by-product which still contained the phosphorane moiety was also obtained (5—15%). The material gave a poorly resolved n.m.r. spectrum, but was characterised as (33) by reaction with t-butyl glyoxylate to yield a product which was clearly the olefin (34). The usual detritylation, acylation, and deprotection sequence then allowed the preparation of the free acids (36; $R^1 = H$) and (37; $R^1 = H$). Neither compound showed any improvement in biological activity over the corresponding 3-methyl derivatives (see Table). Although it was possible to prepare substituted dithianylphosphoranes (38), *e.g.* with $R = p\text{-}CH_2C_6H_4CO_2CH_2C_6H_4OCH_3\text{-}p$, no satisfactory method of deprotection could be found. Thus the range of C-3 substituents was severely limited and once again an alternative approach was investigated.

To assess the methodology, the methallyloxyazetidinones (39) and (40) were prepared from the sulphone (14) in the usual way. Condensation of (39) with t-butyl glyoxylate gave the α-hydroxy-ester (41). At this stage it was convenient to generate the carbonyl group and this was accomplished by low-temperature ozonolysis to provide the ketone (42). The latter was



(27) R = H
(29) R = CHOH.CO_2CMe_3
(30) R = CHCl.CO_2CMe_3
(31) R = C(:PPh_3)CO_2CMe_3



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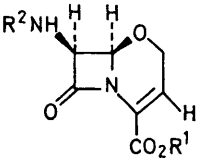
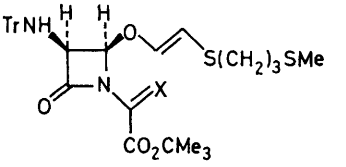
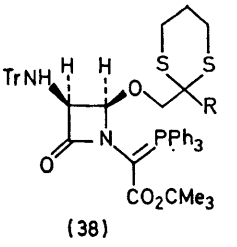


(32) R^2 = Ph_3C
(35) R^2 = H
(36) R^2 = D—PhCH(OH)CO
(37) R^2 = $PhOCH_2CO$

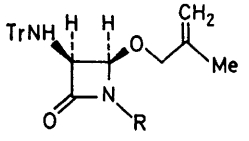


(33) X = PPh_3
(34) X = $CHCO_2CMe_3$ (*trans*)

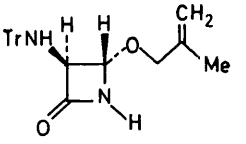


(38)

converted, *via* the chloro-ester (43) into the phosphorane (20) and thence to the oxacephem (21; $R^1 = CMe_3$). No significant intramolecular cyclisation was observed during the treatment of (43) with triphenylphosphine (55 °C in dry dioxan). This route has more general application than the two others described, provided the requisite substituted allylic alcohols can be synthesised. The synthesis of the 3-benzyl nucleus (44) has been previously mentioned [15] and further details are available in a patent.[16]



(39) R = H
(41) R = CHOH·CO_2CMe_3



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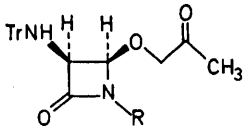
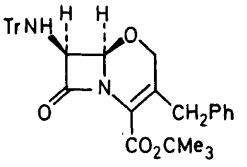


(42) R = CHOH·CO_2CMe_3
(43) R = CHCl·CO_2CMe_3



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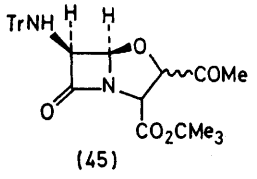

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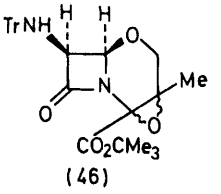


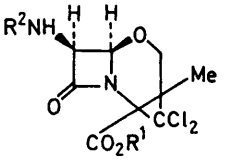
(46)

It seemed to us that the α-chloro-ester (43) might be a possible precursor to the oxapenam ring system (45), by base-induced intramolecular cyclisation. Accordingly the ester (43) was treated with potassium t-butoxide in t-butyl alcohol–tetrahydrofuran to give two products. These proved to be the oxacepham epoxide isomers (46), formed in a ratio of 5 : 1. A similar reaction in the sulphur series has been shown to give a mixture of penam and epoxycepham.[17] Clearly the replacement of sulphur by oxygen sufficiently deactivates the α-methylene so that the only process observed is an intramolecular Darzens reaction.

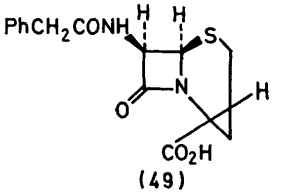
We now decided to explore some of the chemistry of the fused dihydro-oxazine system. Allylic bromination of deacetoxycephalosporin with *N*-bromosuccinimide (NBS) is an important entry into a number of C-3 substituted derivatives. The reaction has no utility in the Δ^3 (sulphide) series, but works well in the Δ^2 series.[18] Consequently we were not surprised to discover that azobisisobutyronitrile-initiated bromination of (8; $R^1 = CMe_3$) using NBS in hot carbon tetrachloride gave no isolable product except starting material.

In an attempt to isomerise the double bond into the Δ^2 position, the oxacephem (21; $R^1 = CMe_3$) was treated with lithium di-isopropylamide in tetrahydrofuran at −76 °C. Essentially unchanged starting material was recovered, along with a very minor, crystalline product (7%). The i.r. and n.m.r. spectra indicated that the dichlorocyclopropyl compound (47; $R^1 = CMe_3$) was a possible structure, and field-desorption mass spectrometry confirmed this assignment. Analysis of the starting material showed the presence of chlorine (3.5%) presumably in the form of chloroform (*ca.* 0.17 mol), since the materials had been isolated from this solvent. Addition of base generated dichlorocarbene, which added across the Δ^3 double bond. No such addition has been reported in the 1-thia-series. When the process was repeated with the required quantity of chloroform, the dichlorocyclopropyl compound (47; $R^1 = CMe_3$) was obtained as a single isomer in 62% yield. The trityl group was removed and replaced by phenoxyacetyl to give (48; $R^1 = CMe_3$). Cleavage of the ester then afforded the acid (48; $R^1 = H$) which was biologically inactive. Long has reported that the cyclopropacepham (49) also lacks antibacterial activity.[19]

Treatment of (21; $R^1 = CMe_3$) with potassium t-butoxide gave the desired isomeric material (50; $R^1 = CMe_3$) (65%). The latter contained *ca.* 10% of the Δ^3 isomer (n.m.r.), which could not be removed by crystallisation or chromatography. However, chromatographic separation was successfully achieved after removal of the trityl group. Acylation of the amino-compound (51; $R^1 = CMe_3$) with phenoxyacetyl chloride then gave the pure Δ^2 derivative (52; $R^1 = CMe_3$). Removal of the t-butyl group provided the acid (52; $R^1 = H$) which was devoid of antibacterial activity. Finally, treatment of the ester (52; $R^1 = CMe_3$) with NBS as previously described for the conjugated isomer (8; $R^1 = CMe_3$) caused rapid loss of β-lactam and no C-3 functionalisation was achieved.



(47) R^2 = Ph_3C
(48) R^2 = $PhOCH_2CO$



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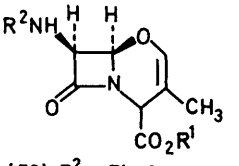

(50) R^2 = Ph_3C
(51) R^2 = H
(52) R^2 = $PhOCH_2CO$

EXPERIMENTAL

I.r. spectra were recorded for solutions in chloroform unless otherwise stated. U.v. spectra were determined for solutions in ethanol with a Unicam SP 1800 spectrometer.

Antibacterial activity *

Bacterium	Oxacephems (R^1 = H) (8)	(24)	(25)	(36)	(37)	Cephalexin
β-Haemolytic *Streptococcus*	0.05	250	0.1	0.02	0.25	0.25
Staphylococcus aureus Oxford	0.25	>250	2.5	0.5	0.25	1.25
Staphylococcus Russell †	0.50	>250	50	25	0.25	5.0
Escherichia coli	250	>250	5.0	12.5	>100	12.5
Klebsiella aerogenes	25	>250	5.0	12.5	>100	5.0

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

^{1}H N.m.r. spectra were recorded on either a Varian EM-360 or Perkin-Elmer R 12a 60 MHz instrument for solutions in $CDCl_3$ with tetramethylsilane as internal standard, unless stated otherwise. 90-MHz Spectra were obtained on a Perkin-Elmer R 32 instrument. Mass spectra were determined with an A.E.I. MS 9 machine. M.p.s were determined with a Kofler hot-stage apparatus. A Perkin-Elmer 141 polarimeter was used to determine specific rotations. Merck Kieselgel 60 (particle size <0.063 mm) was used for column chromatography, with ethyl acetate–light petroleum as eluant. Light petroleum refers to the fraction of b.p. 60—80 °C. Anhydrous magnesium sulphate was used for drying solutions.

(3S,4S)-4-*Acetoxy*-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-3-(*phenoxyacetamido*)*azetidin*-2-*one* (5).—Methyl phenoxymethylpenicillinate (20.3 g) was heated to 95 °C with mercury(II) acetate (36.3 g) in glacial acetic acid (250 ml). The cooled mixture was filtered to remove mercury(I) acetate, and the filtrate evaporated. The residue was taken up in ethyl acetate and the solution washed with aqueous sodium hydrogencarbonate. The mixture was filtered through Kieselguhr to remove precipitated solid, and the organic layer separated, washed with brine, dried, and evaporated. Chromatography afforded the crystalline *product* (5) (14.9 g), m.p. 161° (ethyl acetate–light petroleum), $\nu_{max.}$ 3 320, 1 780, 1 760, 1 690, and 1 630 cm^{-1}; δ 2.02 (3 H, s), 2.1 (3 H, s), 2.24 (3 H, s), 3.79 (3 H, s), 4.56 (2 H, s), 5.11 (1 H, dd, *J* 1.5 and 8 Hz), 6.27 (1 H, d, *J* 1.5 Hz), 6.83—7.45 (5 H, m), 7.6 (1 H, d, *J* 8 Hz) (Found: C, 58.4; H, 5.7; N, 6.9. $C_{19}H_{22}N_2O_7$ requires C, 58.5; H, 5.6; N, 7.2%).

(3S,4S)-4-*Acetoxy*-3-(*phenoxyacetamido*)*azetidin*-2-*one* (4).—The lactam (5) (15.6 g) was oxidised in the same way [8] as the corresponding benzyl ester to give the azetidinone (4) (5.56 g), m.p. 144° (lit.,[8] 144—145°).

(3S,4R)-(6) and (3S,4S)-3-*Phenoxyacetamido*-4-(*prop*-2-*ynyloxy*)*azetidin*-2-*one* (7).—The *trans*-acetate (4) (2.78 g), prop-2-yn-1-ol (1.68 g), and powdered zinc acetate dihydrate (1.1 g) were stirred at 80 °C in toluene for 3.5 h. The mixture was filtered and the filtrate evaporated. Chromatography of the residue gave the trans-*isomer* (7) (430 mg), m.p. 149° (ethyl acetate–light petroleum), $[\alpha]_D^{22}$ +22.0° (*c* 0.53 in $CHCl_3$); $\nu_{max.}$ (Nujol) 3 310, 3 250, 3 180, 2 100, 1 780, 1 765, and 1 680 cm^{-1}; δ[$CDCl_3$ + $(CD_3)_2SO$] 2.6 (1 H, t, *J* 2 Hz), 4.35 (2 H, d, *J* 2 Hz), 4.58, (2 H, s), 4.77 (1 H, dd, *J* 1.5 and 8 Hz), 5.28 (1 H, d, *J* 1.5 Hz), 6.9—7.6 (5 H, m), 7.93 (1 H, d, *J* 8 Hz), and 8.13 (1 H, s, exchanges) (Found: C, 61.1; H, 5.2; N, 9.8. $C_{14}H_{14}N_2O_4$ requires C, 61.3; H, 5.1; N, 10.2%).

Further elution gave the cis-*isomer* (6) (414 mg), m.p. 96° (ethyl acetate–light petroleum), $[\alpha]_D^{22}$ +9.5° (*c* 1.01 in $CHCl_3$); $\nu_{max.}$ 3 340, 3 230, 1 780, and 1 690 cm^{-1}; δ 2.55 (1 H, t, *J* 2 Hz), 4.27 (2 H, d, *J* 2 Hz), 4.6 (2 H, s), 5.4 (1 H, d, *J* 4 Hz), 5.57 (1 H, dd, *J* 4 and 8 Hz), and 6.9—7.7 (7 H, m) (Found: C, 61.1; H, 5.6; N, 10.1. $C_{14}H_{14}N_2O_4$ requires C, 61.3; H, 5.1; N, 10.2%).

(3S,4R)-1-[*Hydroxy*(*t-butoxycarbonyl*)*methyl*]-3-(*phenoxyacetamido*)-4-(*prop*-2-*ynyloxy*)*azetidin*-2-*one* (9).—t-Butyl glyoxylate monohydrate (1.48 g) was refluxed in benzene (6 ml) for 0.5 h with provision for the removal of water. The azetidinone (6) (274 mg) was added in benzene (4 ml) and the mixture refluxed for 1 h. The cooled benzene solution was washed with water (×5), dried, and evaporated. Chromatography gave an amorphous solid (9) (244 mg), $\nu_{max.}$ 3 340, 3 225, 1 780, 1 730, and 1 690 cm^{-1}; δ 1.58 and 1.63 (together 9 H, s), 2.63 (1 H, t, *J* 2 Hz), 4.22 and 4.35 (together 2 H, 2 × dd, *J* 2 Hz), 4.3 br (1 H, s, exchanges), 4.63 (2 H, s), 5.3—5.8 (3 H, m), and 7.0—7.7 (6 H, m).

(3S,4R)-1-[*t-Butoxycarbonyl*(*triphenylphosphoranylidene*)*methyl*]-3-(*phenoxyacetamido*)-4-(*prop*-2-*ynyloxy*)*azetidin*-2-*one* (11).—A solution of the hydroxy-ester (9) (1.713 g) in dry tetrahydrofuran (40 ml) was cooled to −15 °C and treated with dry 2,6-lutidine (0.74 ml), followed during 1—2 min by thionyl chloride (0.45 ml) in tetrahydrofuran (5 ml). After 20 min a precipitate was removed and the filtrate evaporated to leave the α-chloro-ester (10) as an amorphous solid (1.8 g), $\nu_{max.}$ 3 315, 3 220, 1 755, 1 670, and 1 625 cm^{-1}. The total crude product was dissolved in dry dioxan (50 ml) containing lutidine (0.98 ml) and triphenylphosphine (2.22 g). The mixture was heated under nitrogen at 50 °C for 21 h, cooled, and filtered. The filtrate was evaporated and the residue taken up in ethyl acetate and washed successively with very dilute hydrochloric acid, brine, aqueous sodium hydrogencarbonate, and brine again. The organic layer was separated, dried, and evaporated and the residue purified by chromatography to give the phosphorane (11) as an amorphous solid (1.78 g), $\nu_{max.}$ 3 315, 3 220, 1 755, 1 670, and 1 625 cm^{-1}.

(3S,4R)-1-[*t-Butoxycarbonyl*(*triphenylphosphoranylidene*)*methyl*]-3-(*phenoxyacetamido*)-4-(2-*oxopropyloxy*)*azetidin*-2-*one* (12).—The acetylenic phosphorane (11) (1.77 g) was dissolved in piperidine (15 ml) and mercury(II) chloride (1.48 g) added. After stirring at room temperature for 10 min the mixture was poured into ethyl acetate and the solution washed with dilute hydrochloric acid. The organic layer was separated, washed with aqueous sodium hydrogencarbonate and brine, dried, and evaporated. Chromatography of the product gave the keto-phosphorane (12) as an amorphous solid (1.4 g), $\nu_{max.}$ 3 300, 1 755, 1 710, 1 670, and 1 620 cm^{-1}.

(6R,7S)-*t-Butyl* 7-*Phenoxyacetamido*-3-*methyl*-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylate* (8; R^1 = CMe_3).—A solution of the ketone (12) (1.44 g) in dry dioxan (50 ml) was refluxed under nitrogen for 16 h, cooled, and evaporated. Chromatography of the residue gave the *oxacephem* (8; R^1 = CMe_3) as an amorphous solid (664 mg), $[\alpha]_D^{21}$ −39.5° (*c* 1.38 in $CHCl_3$); $\lambda_{max.}$ 264 nm (ε 9 050); $\nu_{max.}$ 3 320, 1 785, 1 707,

1 685, and 1 640 cm^{-1}; δ 1.58 (3 H, s), 2.05 (2 H, s), 4.37 (2 H, s), 4.63 (2 H, s), 5.17 (1 H, d, *J* 4 Hz), 5.67 (1 H, dd, *J* 4 and 9 Hz), and 6.9—7.6 (6 H, m) (Found: M^+, 388.168 1. $C_{20}H_{24}N_2O_6$ requires *M*, 388.163 4).

(6R,7S)-7-*Phenoxyacetamido*-3-*methyl*-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylic Acid* (8; R^1 = H).—The t-butyl ester (8; R^1 = CMe$_3$) (297 mg) was dissolved in anhydrous trifluoroacetic acid (5 ml). After 10 min the solution was evaporated, the residue treated with toluene and the mixture re-evaporated (×3). The residue was dissolved in ethyl acetate and extracted (×2) with saturated sodium hydrogencarbonate solution. The combined extracts and aqueous washings were covered with ethyl acetate, cooled to 0 °C, and treated with 20% hydrochloric acid (to pH 2.8), and the layers were separated. The solvent layer was washed with brine, dried, and evaporated to leave the amorphous free acid (8; R^1 = H) (168 mg), $[\alpha]_D^{21}$ −39.9° (*c* 1.04 in $CHCl_3$); $\lambda_{max.}$ 263 nm (ε 6 577); $\nu_{max.}$ (KBr) 3 400br, 1 782, 1 710, 1 680, and 1 640 cm^{-1}; δ 2.1 (3 H, s), 4.43 (2 H, s), 4.67 (2 H, s), 5.23 (1 H, d, *J* 4 Hz), 5.8 (1 H, dd, *J* 4 and 9 Hz), 6.8—7.7 (6 H, m), and 8.53br (1 H, s, exchanges).

(3S,4R)-(15) *and* (3S,4S)-4-(*Prop*-2-*ynyloxy*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (16).—The sulphone [8] (14) (4.06 g) was refluxed in dry benzene (50 ml) containing prop-2-yn-1-ol (1.69 g) and powdered zinc acetate dihydrate (1.05 g). After 4 h the cooled solution was decanted off and the residual solid triturated with ethyl acetate. These extracts were combined with the benzene fraction and evaporated. Chromatography gave the cis-*isomer* (15) as an amorphous solid (478 mg), $[\alpha]_D^{21}$ +5.56° (*c* 1.71 in $CHCl_3$); $\nu_{max.}$ 3 330, 3 245, 2 970, and 1 772 cm^{-1}; δ 2.40 (1 H, t, *J* 3 Hz), 3.01 (1 H, d, *J* 10 Hz, exchanges), 3.6 and 3.96 (2 H, ABq, *J* 15 Hz, each signal shows further coupling *J* 3 Hz), 4.06—4.45 (2 H, m), 6.80 (1 H, s, exchanges), and 7.2—7.9 (15 H, m) (Found: M^+, 382.167 5. $C_{25}H_{22}N_2O_2$ requires *M*, 382.168 1).

Further elution provided the trans-*isomer* (16) (473 mg), m.p. 123—124° (chloroform–light petroleum), $[\alpha]_D^{22}$ −87.6° (*c* 1.21 in $CHCl_3$); $\nu_{max.}$ 3 330, 3 245, 2 970, and 1 772 cm^{-1}; δ 2.40 (1 H, t, *J* 2 Hz), 2.73br (1 H, s, exchanges), 3.54 and 3.80 (2 H, ABq, *J* 15 Hz, each signal shows further coupling *J* 2 Hz), 4.00—4.30 (2 H, m), and 6.9—7.7 (16 H, m, 1 H, exchanges) (crystallisation from chloroform–light petroleum gave crystals containing chloroform of crystallisation) (Found: C, 63.0; H, 4.5; N, 5.7; Cl, 21.2. $C_{25}H_{22}N_2O_2$·$CHCl_3$ requires C, 62.2; H, 4.6; N, 5.6; Cl, 21.1%).

(3S,4R)-1-[*Hydroxy*(*t-butoxycarbonyl*)*methyl*]-4-(*prop*-2-*ynyloxy*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (17).—The azetidinone (15) (515 mg) was treated with t-butyl glyoxylate monohydrate (1.89 g) as described for (9) to give the α-hydroxy-ester (17) as an amorphous solid (511 mg), $\nu_{max.}$ 3 400, 3 218, 1 770, and 1 728 cm^{-1}. The n.m.r. spectrum showed singlets (after D_2O exchange) at δ 5.25 and 5.28 for the C*H*–OH protons of the two isomers.

(3S,4R)-1-[*t-Butoxycarbonyl*(*triphenylphosphoranylidene*)*methyl*]-4-(*prop*-2-*ynyloxy*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (19).—The α-hydroxy-ester (17) (512 mg) was converted into the phosphorane (19) (407 mg) as described for (11), $\nu_{max.}$ 3 230, 1 750, and 1 632 cm^{-1}.

(3S,4R)-1-[*t-Butoxycarbonyl*(*triphenylphosphoranylidene*)*methyl*]-4-(2-*oxopropyloxy*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (20).—Reaction of the phosphorane (19) (400 mg) with mercury(II) chloride (287 mg) in piperidine (6 ml) at room temperature for 1.25 h as described for (12) gave the methyl ketone (20) as an amorphous solid, $\nu_{max.}$ 1 756, 1 712, and 1 630 cm^{-1}.

(6R,7S)-*t-Butyl* 7-*Triphenylmethylamino*-3-*methyl*-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylate* (21; R^1 = CMe$_3$).—A solution of the oxo-phosphorane (20) (258 mg) in dry dioxan (10 ml) was refluxed under nitrogen for 16 h, cooled, and evaporated. Chromatography of the residue provided the *oxacephem* (21; R^1 = CMe$_3$) as an amorphous solid, $[\alpha]_D^{22.5}$ −8.5° (*c* 1.6 in $CHCl_3$); $\lambda_{max.}$ 268 nm (ε 6 400); $\nu_{max.}$ 1 780, 1 710, and 1 640 cm^{-1}; δ 1.52 (9 H, s), 1.91 (3 H, s), 3.13 (1 H, d, *J* 11 Hz exchanges), 3.86 (1 H, d, *J* 4 Hz), 4.06 (2 H, s), 4.30 (1 H, dd, *J* 4 and 11 Hz, collapses to d, *J* 4 Hz on exchange), and 7.10—7.80 (15 H, m) (Found: C, 74.9; H, 6.7; N, 5.4. $C_{31}H_{32}N_2O_4$ requires C, 75.0; H, 6.5; N, 5.7%).

(6R,7S)-*t-Butyl* 7-(D-α-*Phenylglycyl*)*amino*-3-*methyl*-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylate* (23; R^1 = CMe$_3$).—The oxacephem (21; R^1 = CMe$_3$) (260 mg) was dissolved in dry methylene chloride (16 ml) and cooled to −20 °C and toluene-*p*-sulphonic acid hydrate (108 mg) in the minimum volume of methanol was added dropwise. The solution was kept at 0 °C for 16 h, when the solvent was removed and the residue diluted with ethyl acetate and aqueous sodium hydrogencarbonate. The organic layer was separated, washed with brine, dried, and evaporated to give the crude amino-compound (22; R^1 = CMe$_3$) as a solid. The latter, dissolved in dry tetrahydrofuran (8 ml), was added dropwise over 5 min at −20 °C to the mixed anhydride prepared by dropwise addition of a solution of *N*-(t-butoxycarbonyl)-D-α-phenylglycine (142 mg), triethylamine (58 mg), and dibenzylamine (1 drop) in dry tetrahydrofuran (5 ml) to methyl chloroformate (54 mg) in dry tetrahydrofuran (18 ml) at −20 °C. The mixture was stirred at −20 °C for a further 2 h and then for 1 h at 0 °C. The mixture was then filtered, and the triethylamine hydrochloride washed copiously with ethyl acetate. The filtrate and washings were evaporated and the residue taken up in ethyl acetate and washed with 5% aqueous sodium hydrogencarbonate and brine. The organic layer was separated, dried and evaporated to a gum, which after chromatography gave the required *ester* (23; R^1 = CMe$_3$) (187 mg), $[\alpha]_D^{21.5}$ −53.6° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$ 3 415, 1 792, 1 711, 1 708, 1 695, and 1 650sh cm^{-1}; $\lambda_{max.}$ 265 nm (ε 7 400); δ 1.45 (9 H, s), 1.57 (9 H, s), 2.01 (3 H, s), 4.21 (2 H, s), 5.03 (1 H, d, *J* 4 Hz), 5.3 (1 H, d, *J* 7 Hz), 5.65 (1 H, dd, *J* 4 and 10 Hz), 5.80 (1 H, d, *J* 7 Hz), 6.93 (1 H, d, *J* 10 Hz), and 7.48 (5 H, s) (Found: C, 61.5; H, 7.0; N, 8.6. $C_{25}H_{33}N_3O_7$ requires C, 61.6; H, 6.8; N, 8.6%).

(6R,7S)-7-(D-α-*Phenylglycylamino*)-3-*methyl*-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylic Acid, Trifluoroacetic Acid Salt* (24; R^1 = H).—The oxacephem ester (23; R^1 = CMe$_3$) (52 mg) was dissolved in neat trifluoroacetic acid (1 ml). After 7 min the solvent was evaporated, and the residue re-evaporated from toluene (×3). Trituration of the product with ether gave the *trifluoroacetic acid salt* (24; R^1 = H) as an off-white solid (36 mg), $[\alpha]_D^{21}$ −6.41° (*c* 0.6 in MeOH); $\lambda_{max.}$ 260 nm (ε 7 060); $\nu_{max.}$ (KBr) 3 440br, 3 000br, 1 770, 1 680br, and 1 630sh cm^{-1} (Found: C, 48.1; H, 4.8; N, 9.2. $C_{18}H_{18}F_3N_3O_7$ requires C, 48.5; H, 4.0; N, 9.4%).

(6R,7S)-*t-Butyl* 7-(D-*mandelylamino*)-3-*methyl*-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylate* (25; R^1 = CMe$_3$).—The oxacephem (21; R^1 = CMe$_3$) (200 mg) was detritylated as previously described and the crude amino-compound (22;

$R^1 = CMe_3$) was dissolved in dry methylene chloride (6 ml) at −20 °C. D-Mandelyl *O*-carboxyanhydride (79 mg) was added and the mixture stirred at −20 °C for 1 h. The mixture was washed with dilute aqueous sodium hydrogencarbonate and brine, and the organic layer dried and evaporated. Chromatography gave the *acylamino-oxacephem* (25; $R^1 = CMe_3$) as an amorphous solid (106 mg), $\nu_{max.}$ 3 320, 1 787, 1 710, 1 683, and 1 650sh cm^{-1}; δ 1.55 (9 H, s), 2.00 (3 H, s), 4.30br (3 H, s, collapses to sharp s, 2 H, on exchange), 5.07 (1 H, d, *J* 4 Hz), 5.17 (1 H, s), 5.53 (1 H, dd, *J* 4 and 10 Hz, becomes d, *J* 4 Hz on exchange), 7.47 (5 H, s), 7.53 (1 H, d, *J* 10 Hz, exchanges) (Found: M^+, 388.161 0. $C_{20}H_{24}N_2O_6$ requires *M*, 388.163 4).

(6R,7S)-7-(D-*Mandelylamino*)-3-*methyl*-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylic Acid* (25; $R^1 = H$).—The ester (25; $R^1 = CMe_3$) (64 mg) was deprotected as described for (24; $R^1 = H$) to give the free acid (25; $R^1 = H$) as a buff solid (46 mg), $[\alpha]_D^{22}$ −39.9° (*c* 0.8 in MeOH); $\lambda_{max.}$ 260 nm (ε 4 160); $\nu_{max.}$ (KBr) 3 400br, 1 771, and 1 660br cm^{-1}.

(3S,4R)-(27) *and* (3S,4S)-4-[(1,3-*Dithian*-2-*yl*)*methoxy*]-3-(*triphenylmethylamino*)*azetidin*-2-*one* (28).—Powdered zinc acetate dihydrate (710 mg) and 2-hydroxyethyl-1,3-dithian (2.4 g) were stirred under reflux in benzene (20 ml) for 0.5 h with provision for the removal of water. After 30 min the sulphone (14) (4.06 g) was added to the cooled mixture and the refluxing continued for a further 2.25 h. The solution was filtered and the filtrate evaporated to afford a brown oily residue. Chromatography gave the cis-*isomer* (27) (1.046 g) m.p. 190° (ethyl acetate–light petroleum), $[\alpha]_D^{22}$ +29° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$ (Nujol) 3 360, 1 782, and 1 775 cm^{-1}; δ 2.0 (2 H, m), 2.83 (4 H, t, *J* 5 Hz), 3.07 (1 H, d, *J* 10 Hz, exchanges), 3.35 (2 H, m), 4.13 (3 H, m), 6.77br (1 H, s, exchanges), and 7.1—7.8 (15 H, m) (Found: C, 68.2; H, 5.8; N, 5.9; S, 12.9. $C_{27}H_{28}N_2O_2S_2$ requires C, 68.1; H, 5.9; N, 5.9; S, 13.4%).

Further elution gave the trans-*isomer* (28) as an amorphous solid (771 mg), $[\alpha]_D^{22}$ −96.4° (*c* 1.82 in $CHCl_3$); $\nu_{max.}$ 3 420 and 1 770 cm^{-1}; δ 2.07 (2 H, m), 2.83 (5 H, m, 1 H exchanges), 3.27 (2 H, m), 3.97 (1 H, t, *J* 5.5 Hz), 4.13 (1 H, d, *J* 10 Hz, collapses to s on exchange), 4.27 (1 H, s), 6.73br (1 H, s, exchanges), and 7.2—7.7 (15 H, m) (Found: C, 67.9; H, 6.1; N, 5.9; S, 13.4%).

(3S,4R)-4-[(1,3-*Dithian*-2-*yl*)*methoxy*]-1-[*hydroxy*-(*t-butoxycarbonyl*)*methyl*]-3-(*triphenylmethylamino*)*azetidin*-2-*one* (29).—Treatment of the azetidinone (27) (7.034 g) with t-butyl glyoxylate monohydrate (17.44 g) as described for (9) provided the hydroxy-compound (29) (6.75 g) as an amorphous solid, $\nu_{max.}$ 3 400, 1 770, and 1 728 cm^{-1}.

(3S,4R)-1-*t-Butoxycarbonyl*(*triphenylphosphoranylidene*)-*methyl*]-4-[(1,3-*dithian*-2-*yl*)*methoxy*]-3-(*triphenylmethylamino*)*azetidin*-2-*one* (31).—Treatment of the α-hydroxy-ester (29) (6.46 g) with thionyl chloride and then triphenylphosphine as described for (11) gave the phosphorane (31) as an amorphous solid (8.18 g), $\nu_{max.}$ 1 760 and 1 630br cm^{-1}.

(6R,7S)-*t-Butyl* 7-*Triphenylmethylamino*-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylate* (32; $R^1 = CMe_3$).—The phosphorane (31) (1.02 g) was dissolved in 96% acetone–water (35 ml) and barium carbonate (6 g) and methyl iodide (3 ml) added. The mixture was stirred under reflux for 6 h, cooled, and filtered through Kieselguhr. The filtrate was evaporated and the residue dissolved in ethyl acetate. The solution was washed with water, dried and evaporated. Chromatography afforded the *oxacephem* (32; $R^1 = CMe_3$) as an amorphous solid (288 mg), $[\alpha]_D^{22}$ −2.9° (*c* 2.56 in $CHCl_3$); $\lambda_{max.}$ 265 nm (ε 4 760); $\nu_{max.}$ 3 310, 1 795, 1 720, and 1 643 cm^{-1}; δ 1.5 (9 H, s), 3.13 (1 H, d, *J* 10 Hz, exchanges), 3.83 (1 H, d, *J* 4 Hz), 4.0—4.67 (3 H, m), 6.25 (1 H, t, *J* 3 Hz), and 7.0—7.8 (15 H, m) (Found: C, 75.0; H, 6.2; N, 5.8. $C_{30}H_{30}N_2O_4$ requires C, 74.7; H, 6.3; N, 5.8%).

Further elution of the column gave the phosphorane (33) as an amorphous solid (57 mg), $\nu_{max.}$ 3 300, 1 765, and 1 634 cm^{-1}. The latter was dissolved in benzene (3 ml) containing t-butyl glyoxylate (60 mg), and the solution was refluxed under nitrogen with provision for the removal of water. After 2 h the solvent was evaporated and the residue chromatographed to give (2R,3S)-*di-t-butyl* [(E)-2-(5-*methylthiopent*-1-*enyloxy*)-3-*triphenylmethylamino*-4-*oxoazetidin*-1-*yl*]*fumarate* (34) as an amorphous solid (30 mg), $\nu_{max.}$ 3 290, 1 785, 1 710br, and 1 628 cm^{-1}; δ 1.5 (9 H, s), 1.63 (9 H, s), 1.80 (2 H, m), 2.03 (3 H, s), 2.3—2.9 (4 H, m), 3.25 (1 H, d, *J* 10 Hz, exchanges), 4.93 (1 H, d, *J* 5.5 Hz), 5.17 (1 H, d, *J* 4 Hz), 5.82 (1 H, d, *J* 5.5 Hz), 6.42 (1 H, s), and 7.15—7.85 (15 H, m) (Found: C, 67.7; H, 5.5; N, 3.9; S, 8.7. $C_{40}H_{38}N_2O_6S_2$ requires C, 68.0; H, 5.4; N, 4.0; S, 9.1%).

(6R,7S)-*t-Butyl* 7-(D-*Mandelylamino*)-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylate* (36; $R^1 = CMe_3$).—The oxacephem (32; $R^1 = CMe_3$) (121 mg) was detritylated and the crude amino-compound (35; $R^1 = CMe_3$) acylated as described for (25; $R^1 = CMe_3$) to give the *acylamino-derivative* (36; $R^1 = CMe_3$) (75 mg), $[\alpha]_D^{20}$ −53.7° (*c* 1.03 in $CHCl_3$); $\nu_{max.}$ 3 330, 1 792, 1 715, 1 680, and 1 635 cm^{-1}; δ 1.55 (9 H, s), 4.17br (1 H, s, exchanges), 4.48 (2 H, d, *J* 3 Hz), 5.02 (1 H, d, *J* 4 Hz), 5.13 (1 H, s), 5.58 (1 H, dd, *J* 4 and 10 Hz), 6.42 (1 H, t, *J* 3 Hz), 7.45 (5 H, s), 7.53 (1 H, d, *J* 10 Hz) (Found: C, 60.8; H, 5.8; N, 7.6. $C_{19}H_{22}N_2O_6$ requires C, 61.0; H, 5.9; N, 7.5%).

(6R,7S)-7-(D-*Mandelylamino*)-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylate* (36; $R^1 = H$).—The ester (36; $R^1 = CMe_3$) (77 mg) was dissolved in trifluoroacetic acid (2 ml). After 5 min the reaction was worked-up as described for (24; $R^1 = H$) to provide the free acid (36; $R^1 = H$) as a pale yellow solid (55 mg), $\nu_{max.}$ (KBr) 3 400br, 1 770, and 1 660 cm^{-1}.

(6R,7S)-*t-Butyl* 7-(*Phenoxyacetamido*)-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylate* (37; $R^1 = CMe_3$).—The free base (35; $R^1 = CMe_3$) prepared from the oxacephem (32; $R^1 = CMe_3$) (242 mg) as described for (22; $R^1 = CMe_3$) was dissolved in dry methylene chloride (5 ml) and the solution cooled to −20 °C. Triethylamine (101 mg) was added followed by the dropwise addition of phenoxyacetyl chloride (94 mg) in dry methylene chloride (3 ml). After 5 min the solution was washed successively with aqueous sodium hydrogencarbonate, dilute hydrochloric acid, and brine, dried, and evaporated. Chromatography gave the *acylated derivative* (37; $R^1 = CMe_3$) as an amorphous solid (132 mg), $[\alpha]_D^{20}$ −15° (*c* 1.05 in $CHCl_3$); $\nu_{max.}$ 3 350, 1 790, 1 710, 1 690, and 1 635 cm^{-1}; δ 1.57 (9 H, s), 4.59 (2 H, d, *J* 3 Hz), 4.63 (2 H, s), 5.13 (1 H, d, *J* 5 Hz), 5.8 (1 H, dd, *J* 5 and 8 Hz), 6.45 (1 H, t, *J* 3 Hz), and 6.9—7.7 (6 H, m) (Found: M^+, 374.147 8. $C_{19}H_{22}N_2O_6$ requires *M*, 374.147 8).

(6R,7S)-7-(*Phenoxyacetamido*)-1-*oxa*-1-*dethiaceph*-3-*em*-4-*carboxylate* (37; $R^1 = H$).—Deprotection of (37; $R^1 = CMe_3$) (61 mg) as described for (8; $R^1 = H$) gave the acid (37; $R^1 = H$) as a solid (45 mg), $[\alpha]_D^{21}$ +5.2° (*c* 0.45 in MeOH); $\lambda_{max.}$ 258 nm (ε 4 730); $\nu_{max.}$ 3 340, 2 980br, 1 790, 1 720sh, 1 690, and 1 640sh cm^{-1}.

(3S,4R)-(39) *and* (3S,4S)-4-(2-*Methylprop*-2-*enyloxy*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (40).—The sulphone (14) (4.6 g) was heated in dry toluene (50 ml) at 80 °C with 2-methylprop-2-en-1-ol (2.16 g) and zinc acetate dihydrate (1.1 g) for 7 h. The cooled solution was decanted, and the residual solid triturated with ethyl acetate. These extracts were combined with the toluene fraction, evaporated, and chromatographed to give the cis-*isomer* (39) (874 mg), m.p. 167° (chloroform–ether), $[\alpha]_D^{22}$ −14.4° (*c* 1.41 in $CHCl_3$); $\nu_{max.}$ 3 330, 1 765, and 1 650 cm^{-1}; δ 1.65 (3 H, s), 3.0br (1 H, s, exchanges), 3.4 (2 H, s), 4.13 (1 H, d, *J* 4 Hz), 4.27 (1 H, d, *J* 4 Hz), 4.88 (2 H, s), 6.47br (1 H, s, exchanges), and 7.03—7.67 (15 H, m) (Found: C, 78.3; H, 6.6; N, 7.0. $C_{26}H_{26}N_2O_2$ requires C, 78.4; H, 6.5; N, 7.0%).

Further elution gave the trans-*isomer* (40) as an amorphous solid (668 mg), $\nu_{max.}$ 3 330, 1 765, and 1 650 cm^{-1}; δ 1.63 (3 H, s), 2.82 (1 H, s, exchanges), 3.48br (2 H, s), 4.13 (1 H, s), 4.27 (1 H, s), 4.88 (2 H, s), 5.7br (1 H, s, exchanges), and 7.03—7.67 (15 H, m) (Found: C, 78.3; H, 6.5; N, 7.0. $C_{26}H_{26}N_2O_2$ requires C, 78.4; H, 6.5; N, 7.0%).

(3S,4R)-1-[*Hydroxy*-(*t-butoxycarbonyl*)*methyl*]-4-(2-*methylprop*-2-*enyloxy*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (41).—Reaction of the azetidinone (39) (796 mg) with t-butyl glyoxylate (1.58 g) as described for (9) gave the hydroxy-ester (41) as an amorphous solid (972 mg), $\nu_{max.}$ 3 400, 3 300, 1 765, 1 730, and 1 650 cm^{-1}.

(3S,4R)-1-[*Hydroxy*-(*t-butyloxycarbonyl*)*methyl*]-4-(2-*oxopropyloxy*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (42).—The hydroxyazetidinone (41) (573 mg) was dissolved in dry ethyl acetate (10 ml) and the solution cooled to −76 °C. Ozonised oxygen was passed through the solution until t.l.c. showed no starting material. The flow was replaced by nitrogen for 30 min and then triphenylphosphine (312 mg) added in the minimum volume of ethyl acetate. The mixture was allowed to warm to room temperature and after 1 h the solvent was evaporated. Chromatography afforded the ketone (42) which was isolated as an amorphous solid (470 mg), $\nu_{max.}$ 3 400, 3 300, 1 770, 1 730, and 1 710sh cm^{-1}.

Successive treatment of the product (42) with thionyl chloride and triphenylphosphine as described for (11) gave the phosphorane (20), which, on heating in dioxan, provided the oxacephem (21; $R^1 = CMe_3$) identical to that prepared using the acetylenic route.

(6R,7S)-*t-Butyl* 3,4-*Epoxy*-7-*triphenylmethylamino*-3-*methyl*-1-*oxa*-1-*dethiacepham*-4-*carboxylate* (46).—The α-hydroxy-ester (42) (400 mg) was dissolved in dry tetrahydrofuran (12 ml) at −20 °C and lutidine (114 mg) added, followed by the dropwise addition of thionyl chloride (135 mg) in tetrahydrofuran (1 ml) over 1—2 min. The precipitate was removed and the filtrate evaporated to leave the α-chloro-ester (43) as an amorphous solid (420 mg). The total product was dissolved in dry tetrahydrofuran (10 ml) and t-butyl alcohol (2 ml) at −20 °C, and potassium t-butoxide (108 mg) added. After 40 min the mixture was poured into ethyl acetate–water and the organic layer separated, washed successively with dilute hydrochloric acid and brine, dried, and evaporated. Chromatography gave the *minor epoxide isomer* (46) (39 mg), $\nu_{max.}$ 3 300, 1 790, and 1 750 cm^{-1}; δ(90 MHz) 1.31 (3 H, s), 1.53 (9 H, s), 2.98 (1 H, d, *J* 10 Hz, exchanges), 3.61 and 3.97 (2 H, ABq, *J* 13 Hz), 3.63 (1 H, d, *J* 4 Hz), 4.03 (1 H, dd, *J* 4 and 10 Hz, collapses to d, *J* 4 Hz on exchange), and 7.1—7.6 (15 H, m) (Found: M^+, 512. $C_{31}H_{32}N_2O_5$ requires *M*, 512).

Further elution of the column provided the *major epoxide isomer* (46) (193 mg), m.p. 176—177° (ethyl acetate–light petroleum), $\nu_{max.}$ 3 300, 1 795, and 1 740 cm^{-1}; δ 1.30 (3 H, s), 1.47 (9 H, s), 2.95 (1 H, d, *J* 10 Hz, exchanges), 3.37 and 3.90 (2 H, ABq, *J* 14 Hz), 3.60 (1 H, d, *J* 4 Hz), 4.20 (1 H, dd, *J* 4 and 10 Hz, collapses to d, *J* 4 Hz on exchange), and 7.1—7.7 (15 H, m) (Found: C, 72.7; H, 6.3; N, 5.3; $C_{31}H_{32}N_2O_5$ requires C, 72.7; H, 6.3; N, 5.5%).

(6R,7S)-*t-Butyl* 3,4-*Dichloromethylene*-7-*triphenylmethylamino*-3-*methyl*-1-*oxa*-1-*dethiacepham*-4-*carboxylate* (47; $R^1 = CMe_3$).—The oxacephem (21; $R^1 = CMe_3$) (496 mg) was dissolved in dry tetrahydrofuran (6 ml) containing freshly distilled chloroform (240 mg) and the solution cooled to −76 °C. Lithium di-isopropylamide [prepared by adding n-butyl-lithium (0.41 ml of a 2.4M solution in hexane) to freshly distilled di-isopropylamine (131 mg) in dry tetrahydrofuran (2 ml) at 0 °C] was added, and after 30 min at −76 °C and 2.5 h at 0 °C the mixture was poured into ethyl acetate–brine. The organic layer was separated, washed with dilute hydrochloric acid and brine, dried, and evaporated. Chromatography and trituration of the purified material with ether gave the dichlorocyclopropyl derivative (47; $R^1 = CMe_3$) as a solid (223 mg) containing *ca.* 10% of starting material (n.m.r.), $\nu_{max.}$ 3 300, 1 790, and 1 730 cm^{-1}; δ(90 MHz) 1.33 (3 H, s), 1.44 (9 H, s), 2.8 (1 H, d, *J* 8 Hz, exchanges), 3.33 and 3.91 (2 H, ABq, *J* 12 Hz), 3.46 (1 H, d, *J* 4 Hz), 4.17 (1 H, dd, *J* 4 and 8 Hz, collapses to d, *J* 4 Hz on exchange), and 7.1—7.6 (15 H, m) (Found: M^+, 578. $C_{32}H_{32}Cl_2N_2O_4$ requires *M*, 578).

The mother-liquors from the ether trituration were essentially starting material (21; $R^1 = CMe_3$) (192 mg).

(6R,7S)-*t-Butyl* 3,4-*Dichloromethylene*-7-*phenoxyacetamido*-3-*methyl*-1-*oxa*-1-*dethiacepham*-4-*carboxylate* (48; $R^1 = CMe_3$).—Detritylation and acylation of (47; $R^1 = CMe_3$) (215 mg) with phenoxyacetyl chloride as described for (37; $R^1 = CMe_3$) gave the pure *oxacepham* (48; $R^1 = CMe_3$) as a solid (80 mg). Chromatography efficiently separated the required product (48; $R^1 = CMe_3$) from the Δ^3 derivative (8; $R^1 = CMe_3$); $\nu_{max.}$ 3 355, 1 800, 1 730, and 1 690 cm^{-1}; δ 1.43 (3 H, s), 1.47 (9 H, s), 3.66 and 4.05 (2 H, ABq, *J* 12 Hz), 4.33 (2 H, s), 4.61 (1 H, s, *J* 4 Hz), 5.58 (1 H, dd, *J* 4 and 10 Hz collapses to d, *J* 4 Hz on exchange), and 6.8—7.5 (6 H, m, reduced to 5 H on exchange) (Found: M^+, 470.101 41. $C_{21}H_{24}Cl_2N_2O_6$ requires *M*, 470.101 13).

(6R,7S)-3,4-*Dichloromethylene*-7-*phenoxyacetamido*-3-*methyl*-1-*oxa*-1-*dethiacepham*-4-*carboxylic Acid* (48; R^1 = H).—Removal of the t-butyl group from (48; $R^1 = CMe_3$) (80 mg) as described for (8; R^1 = H) gave the free *acid* (48; R^1 = H) as a solid (20 mg); $\nu_{max.}$ (KBr) 3 410, 1 780, 1 730, and 1 695 cm^{-1}; $\lambda_{max.}$ 270 (ε 1 420) and 276 nm (1 130); δ 1.50 (3 H, s), 3.81 and 4.18 (2 H, ABq, *J* 13 Hz), 4.5 (2 H, s), 4.80 (1 H, d, *J* 4 Hz), 5.57 (1 H, dd, *J* 4 and 10 Hz), and 5.85br (1 H, s, exchanges) (Found: M^+, 414.038 36. $C_{17}H_{16}Cl_2N_2O_6$ requires *M*, 414.038 53).

(6R,7S)-*t-Butyl* 7-*Triphenylmethylamino*-3-*methyl*-1-*oxa*-1-*dethiaceph*-2-*em*-4-*carboxylate* (50; $R^1 = CMe_3$).—The lactam (21; $R^1 = CMe_3$) (496 mg) was dissolved in dry tetrahydrofuran (6 ml) and the solution cooled to −76 °C under argon. Potassium t-butoxide (1.5 ml of 0.718M solution in t-butyl alcohol) was added, and after 20 min the temperature was allowed to reach −20 °C. After a further 30 min the mixture was poured into ethyl acetate–brine, the organic layer separated, washed with brine, dried, and evaporated. Chromatography gave an amorphous solid

(330 mg) which consisted of starting material (21; $R^1 = CMe_3$) (10%) and the Δ^2 derivative (50; $R^1 = CMe_3$) $\nu_{max.}$ 1 775, 1 730, and 1 655 cm^{-1}; δ(90 MHz), 1.36 (9 H, s), 1.54 (3 H, s), 2.95br (1 H, s, exchanges), 4.10—4.35 (3 H, m), 6.10 (1 H, m), and 7.1—7.6 (15 H, m).

(6R,7S)-*t-Butyl* 7-*Phenoxyacetamido*-3-*methyl*-1-*oxa*-1-*dethiaceph*-2-*em*-4-*carboxylate* (52; $R^1 = CMe_3$).—The oxacephem (50; $R^1 = CMe_3$) (229 mg) was dissolved in methylene chloride (3 ml) at −20 °C and toluene-*p*-sulphonic acid (96 mg) was added in the minimum volume of methanol. After 3 h at −5 °C the solvent was evaporated and the residue dissolved in ethyl acetate–sodium hydrogencarbonate. The organic layer was separated, washed with brine, dried, and evaporated. Chromatography then afforded the pure primary amine (51; $R^1 = CMe_3$) as a solid (77 mg), $\nu_{max.}$ 3 330, 1 780, 1 735, and 1 655 cm^{-1}; δ(90 MHz) 1.2—1.4 (2 H, m, exchanges), 1.5 (9 H, s), 1.67 (3 H, d, *J* 2 Hz), 4.40 (2 H, m), 5.27 (1 H, d, *J* 4 Hz), and 6.35 (1 H, m).

The amino-compound (51; $R^1 = CMe_3$) (77 mg) was dissolved in dry methylene chloride (3 ml) at −20 °C and triethylamine (46 mg) added, followed by the dropwise addition of phenoxyacetyl chloride (57 mg) in methylene chloride (1 ml). The mixture was washed with aqueous sodium hydrogencarbonate followed by brine, dried, and evaporated. Chromatography gave the *acylated derivative* (52; $R^1 = CMe_3$) as an amorphous solid (105 mg), $\nu_{max.}$ 3 340, 1 790, 1 735, 1 690, and 1 655 cm^{-1}; $\lambda_{max.}$ 270 (ε 1 500) and 276 nm (1 300); δ(90 MHz) 1.47 (9 H, s), 1.63 (3 H, d, *J* 2 Hz), 4.42 (1 H, s), 4.52 (2 H, s), 5.37 (1 H, d, *J* 3.5 Hz), 5.62 (1 H, dd, *J* 3.5 and 10 Hz), 6.31 (1 H, m), and 6.9—7.5 (6 H, m) (Found: M^+, 388.163 60. $C_{20}H_{24}N_2O_6$ requires *M*, 388.163 42).

(6R,7S)-7-*Phenoxyacetamido*-3-*methyl*-1-*oxa*-1-*dethiaceph*-2-*em*-4-*carboxylic Acid* (52; $R^1 = H$).—The ester (52; $R^1 = CMe_3$) (100 mg) was deprotected with anhydrous trifluoroacetic acid as described for (8; $R^1 = H$) to give the *acid* (52; $R^1 = H$) as a solid (30 mg), m.p. 132—135° (ethyl acetate–light petroleum), $\nu_{max.}$ 3 340, 1 785, 1 730, 1 685, and 1 655 cm^{-1}; $\lambda_{max.}$ 270 (ε 1 540) and 276 nm (1 300); δ(90 MHz) 1.70 (3 H, d, *J* 2 Hz), 4.48 (1 H, s), 4.54 (2 H, s), 5.50 (1 H, d, *J* 3.5 Hz), 5.58 (1 H, dd, *J* 3.5 and 10 Hz), 6.3 (1 H, m), 6.7—7.4 (6 H, m), and 9.20 (1 H, s, exchanges) (Found: M^+, 332.100 33. $C_{16}H_{16}N_2O_6$ requires *M*, 332.100 82).

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