Nuclear Modification of Clavulanic Acid. Preparation of Optically Active 1-Oxaceph-3-ems

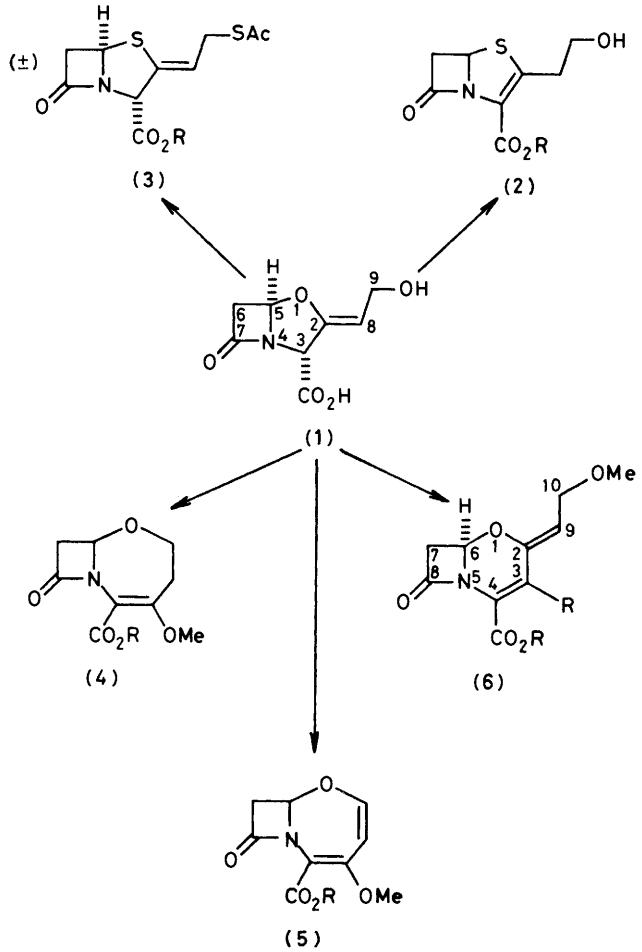
Gerald Brooks, Brian C. Gasson, T. Trefor Howarth, Eric Hunt,* and Kong Luk
Beecham Pharmaceuticals Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ

Lithium (*Z*)-(6*R*)-3-benzyloxycarbonyl-2-(2-methoxyethylidene)-1-oxaceph-3-em-4-carboxylate and lithium (*Z*)-(6*R*)-2-(2-methoxyethylidene)-1-oxaceph-3-em-4-carboxylate have been prepared from clavulanic acid by way of an intramolecular Wittig reaction. Also from clavulanic acid, methyl (*Z*)-(6*R*)-3-methoxy-2-(2-methoxyethylidene)-1-oxaceph-3-em-4-carboxylate has been synthesised by way of an intramolecular carbene-insertion reaction.

A number of nuclear modifications of the natural β-lactamase inhibitor clavulanic acid (**1**) have been described during recent years. These have allowed the conversion of the natural product (**1**) into the penem system (**2**),[1] the 2-alkylidenepenam system (**3**),[2] and the two 4,7-fused β-lactam systems (**4**) and (**5**)[3] (all as racemates). We now describe an extension to this methodology whereby the acid (**1**) may be converted into the optically active 1-oxaceph-3-em system (**6**).

Numerous methods are available for the preparation of optically active 1-oxacephalosporins (**7**) from penicillins,[4] and the racemic 7-unsubstituted systems (**8**) and (**9**) have been synthesised from 4-acetoxyazetidin-2-one.[5] For the synthesis of optically active 1-oxaceph-3-ems from clavulanic acid (**1**), we required a process whereby the oxazolidine ring of the acid (**1**) could be expanded to the dihydro-oxazine ring of the oxacephem system, without disturbing the chirality at C-5 (which becomes C-6 in the oxacephem). One approach to this would involve opening the oxazolidine ring, incorporating any necessary extra carbon atoms and functionality, and then forming the oxacephem by closure of the dihydro-oxazine ring. For derivatives of clavulanic acid, a useful method whereby the five-membered ring can be opened without disturbing the chirality at C-5 consists of oxidation with selenium dioxide and t-butyl hydroperoxide,[6] a reaction which gives rise to a 3-hydroxylated derivative in tautomeric equilibrium with the ring-opened ketone [*e.g.* (**10**)].[7] The availability of compounds such as (**10**) immediately suggested a convenient route to oxacephems by way of an intramolecular Wittig reaction, a method that has been much used for the synthesis of both cephems[8] and oxacephems.[4,5]

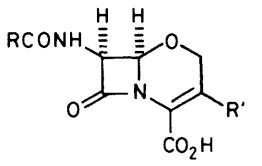
Benzyl 9-*O*-methylclavulanate† (**11a**) was oxidised using a mixture of selenium dioxide and t-butyl hydroperoxide to give the 3-hydroxylated derivative (**12a**) in 87% yield. The n.m.r. spectrum of this product in chloroform showed that it exists as a 2:1 mixture of ring-opened (**13a**) and ring-closed (**12a**) forms. Compound (**12a**/**13a**) was brought into reaction with 4-nitrobenzyl glyoxylate to give a mixture of epimeric alcohols (**14a**), and these were converted into the mixed chlorides (**15a**) using thionyl chloride and 2,6-lutidine. Treatment of the epimeric α-chloro-esters (**15a**) with triphenylphosphine and 2,6-lutidine in dioxane at 55 °C resulted in the formation of the oxacephem (**17a**), which was isolated by chromatography [32% overall yield from (**12a**)]. By analogy with previous syntheses of this type,[4,5] we propose that this reaction proceeds by initial formation of a stabilised phosphorane (**16a**) which then participates in an intramolecular Wittig reaction with the reactive α-keto-ester moiety. By starting with 4-nitrobenzyl 9-*O*-methylclavulanate (**11b**) and using the same sequence of reactions, the crystalline 3,4-bis-(4-nitrobenzyloxycarbonyl)-oxacephem (**17b**) was prepared in an overall yield of 12.5%. In assigning structures (**17a** and **b**) to the oxacephem products we assumed that the geometry of the exocyclic double bond in the starting clavulanates (**11a** and **b**) would be retained in the oxacephems.‡ For conversion of ester (**17a**) into the oxacephem-



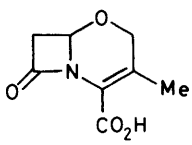
R and R′ = various (see text and refs. 1—3 for details)

† The allylic hydroxy group of clavulanic acid must be protected so that it does not interfere in the later stages of the synthesis; since a removable protecting group was not necessary in this synthesis, the methyl ether (**11**) was chosen as the starting material.

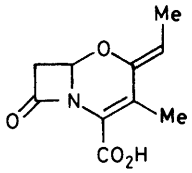
‡ The alternative structures, with the exocyclic double bond in the *E*-configuration, are sterically more congested and hence thermodynamically less stable. Isomerisation of the double bond, even if it could occur, would therefore seem to be unlikely.



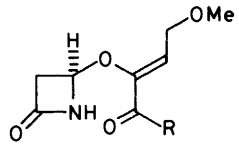
(7)



(8)



(9)



(10)

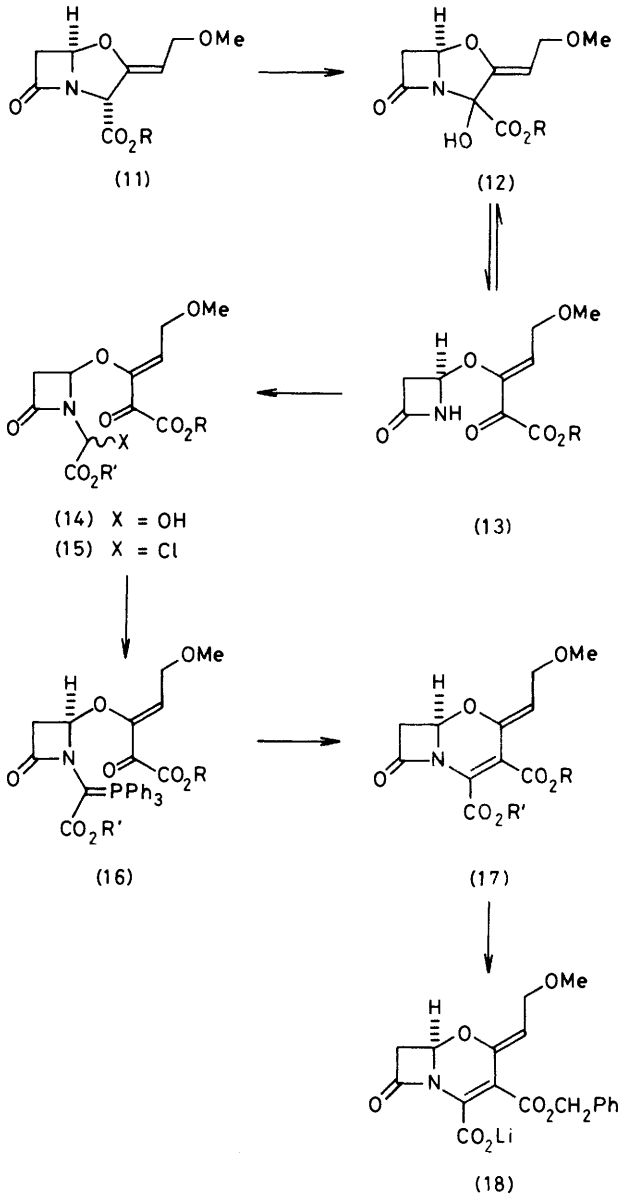
R and R′ = various (see ref. 4 for details)

4-carboxylic acid, the 4-nitrobenzyl group was removed by reduction using iron powder and ammonium chloride; the resulting gummy acid was neutralised with lithium hydroxide to give the lithium oxacephem-4-carboxylate (**18**) in 52% yield.

The above general route has also been used to prepare the 3-unsubstituted oxacephem (**23**) starting from the known[7b] 3-hydroxyclavam (**19**).* Compound (**19**) reacted with benzyl glyoxylate to give a mixture of epimeric alcohols (**21**) (83%). Then, using the same process as before, the mixed alcohols (**21**) were converted into the epimeric chlorides (**22**) and hence into the oxacephem (**23**) (62% overall yield). Compound (**23**) appeared to be surprisingly unstable. Controlled hydrolysis (pH 11.3—11.7) using lithium hydroxide gave the lithium oxacephem-4-carboxylate (**24**) in 75% yield. The geometry of the exocyclic double bond in compound (**24**) was established by n.m.r. experiments. By using nuclear Overhauser difference spectroscopy (250 MHz; D_2O solution), a nuclear Overhauser effect was observed between the protons at C-3 (δ 6.51) and C-9 (δ 5.32), thus demonstrating that the exocyclic double bond has the *Z*-configuration.

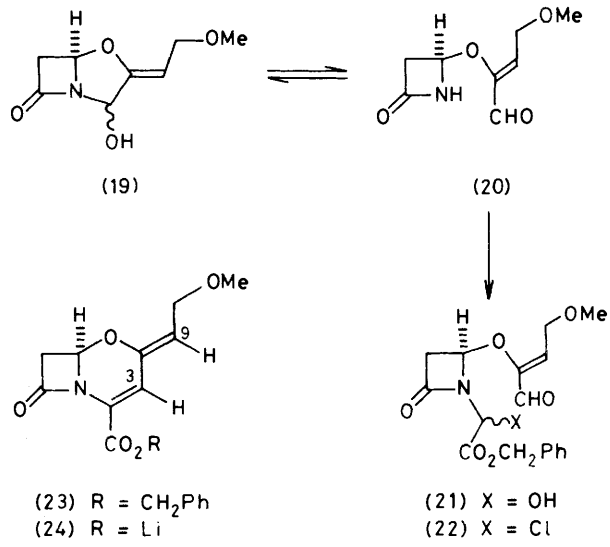
We have also developed an alternative route from clavulanic acid to oxacephems, in which an intramolecular carbene-insertion reaction is used to form the dihydro-oxazine ring. This alternative synthesis also uses the selenium dioxide oxidation reaction to open the clavulanic acid oxazolidine ring, but, unlike the Wittig route, the extra carbon required for forming the oxacephem system is inserted before the ring-opening reaction by means of an Arndt-Eistert synthesis.[9]

Thus, 9-*O*-methylclavulanic acid (**25**) was converted into a mixed anhydride with pivaloyl chloride and this was allowed to react with diazomethane to give the diazo ketone (**26**) (22%). Rearrangement of the diazo ketone was brought about with silver oxide in methanol to give the homologous methyl ester (**27**) (63%).† A small amount of an unstable by-product was also isolated from this reaction; from its spectral properties this was tentatively identified as the conjugated diene (**32**). The oxazolidine ring in compound (**27**) was then opened by oxidation with selenium dioxide and t-butyl hydroperoxide to give the keto ester (**28**) (70%); the ring-closed tautomer of compound (**28**) was not observed by n.m.r. in chloroform



(11) (12) (13) (14) X = OH (15) X = Cl (16) (17) (18)

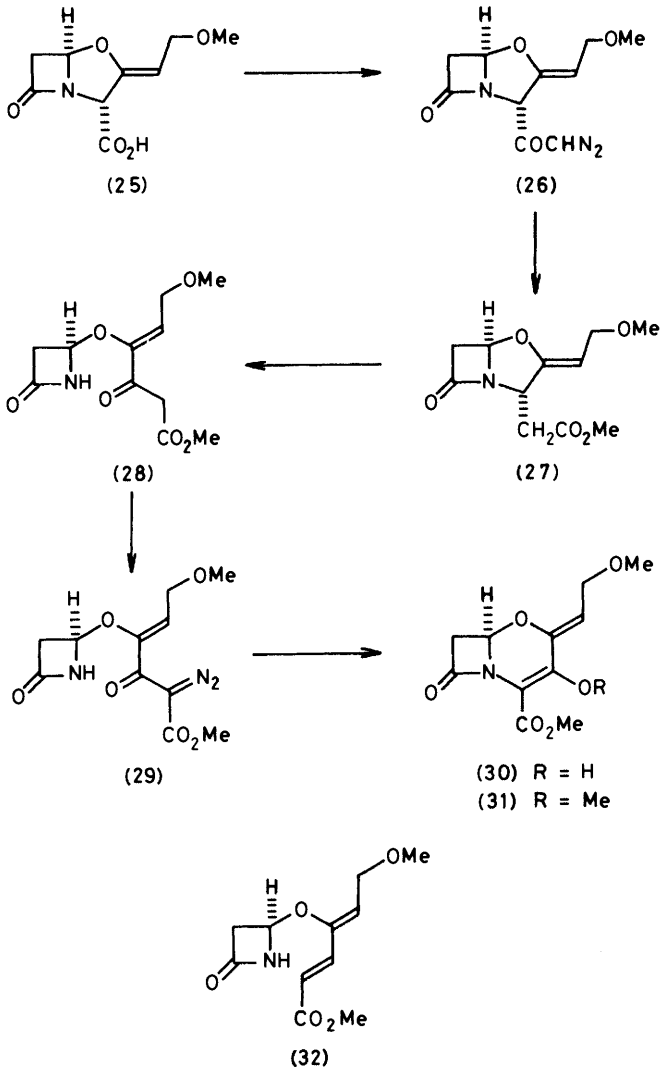
Scheme. a; R = benzyl, R′ = 4-nitrobenzyl b; R = R′ = 4-nitrobenzyl



(19) (20) (23) R = CH_2Ph (24) R = Li (21) X = OH (22) X = Cl

*Compound (**19**) is in tautomeric equilibrium with the aldehyde (**20**); in chloroform solution the ring-opened form (**20**) is favoured over the ring-closed form (**19**) by 6:1.[7b]

† The stereochemistry assigned to compound (**27**) is that expected for a product of the Wolff rearrangement.[10]



solution. The keto ester was converted into the diazo compound (**29**) (69%) using toluene-4-sulphonyl azide and triethylamine, and this was cyclised to the oxacephem (**30**) in the presence of rhodium(II) acetate in refluxing benzene. The 3-hydroxyoxacephem (**30**) appeared to be rather unstable, and so the crude product from the rhodium(II) acetate-catalysed reaction was treated with diazomethane to give the 3-methoxy derivative (**31**). The crystalline oxacephem (**31**) was isolated by chromatography [17% overall from (**29**)].

Experimental

M.p.s were determined using a Kofler hot-stage apparatus. Except where stated otherwise, i.r. spectra and specific rotations were recorded for solutions in chloroform, u.v. spectra were recorded for solutions in ethanol, and ^{1}H n.m.r. spectra were recorded at 90 MHz for solutions in $CDCl_3$ with $SiMe_4$ as internal standard. Mass spectra were determined using a V.G. Micromass 70-70F instrument. Merck silica gel 60 was used for t.l.c. and for column chromatography with ethyl acetate–light petroleum (b.p. 60—80 °C) mixtures as eluant. Solutions were dried using magnesium sulphate and solvents were removed by evaporation under reduced pressure using a rotary evaporator with bath temperature below 30 °C. Ether is diethyl ether.

Oxidation of Benzyl 9-O-*Methylclavulanate* (**11a**) *with Selenium Dioxide*.—t-Butyl hydroperoxide (1.9 ml; containing 30% t-butyl alcohol) was dissolved in dry dichloromethane (100 ml) and selenium dioxide (850 mg) was added. Benzyl 9-*O*-methylclavulanate[11] (**11a**) (2.3 g) was added to the stirred suspension, and the mixture was then refluxed for 0.5 h. The mixture was cooled and washed with saturated aqueous sodium hydrogen carbonate. The solution was dried, the solvent was removed, and the residue was chromatographed to give benzyl 3-hydroxy-9-*O*-methylclavulanate (**12a**) as a pale yellow gum (2.1 g), $[\alpha]_D^{21}$ + 53.8° (*c* 1.1); $\nu_{max.}$ 3 420, 3 250, 1 790, 1 740, 1 690, and 1 640 cm^{-1}; the n.m.r. spectrum showed that this compound existed as a 2:1 mixture of ring-opened (major) tautomer (**13a**) and ring-closed (minor) tautomer (**12a**), δ 2.85—3.30 (5 H, complex m, including s at δ 3.18 and 3.30), 4.00 (2 H, minor tautomer, d, *J* 7 Hz), 4.20 (2 H, major tautomer, d, *J* 6 Hz), 4.80 (1 H, minor tautomer, t, *J* 7 Hz), 5.00—5.45 (*ca.* 3 H, complex m, including s at δ 5.30), 5.53 (1 H, minor tautomer, dd, *J* 2 and 1 Hz), 6.44 (1 H, major tautomer, t, *J* 6 Hz), 6.87 br (1 H, major tautomer, s), 7.30 (5 H, minor tautomer, s), and 7.36 (5 H, major tautomer, s); *m/z* (ammonia chemical ionisation) 337 ([*M* + NH_4]$^+$, 15%), 269 (70), 268 (100), 254 (10), 238 (22), 236 (19), 108 (45), 87 (23), and 70 (23).

4-*Nitrobenzyl* (Z)-(6R)-3-*Benzyloxycarbonyl*-2-(2-*methoxyethylidene*)-1-*oxaceph*-3-*em*-4-*carboxylate* (**17a**).—Benzyl 3-hydroxy-9-*O*-methylclavulanate (**12a**) (1.0 g) and 4-nitrobenzyl glyoxylate monohydrate (780 mg) were dissolved in dry benzene (20 ml) and the mixture was refluxed with azeotropic removal of water for 1 h. The solution was cooled to room temperature, triethylamine (30 mg) was added, and the mixture was set aside for 1.5 h. The solvent was removed to yield a yellow gum (1.75 g); $\nu_{max.}$ 3 260, 1 780, 1 745, 1 690, 1 640, 1 610, 1 525, and 1 350 cm^{-1}.

The yellow gum (1.75 g) and 2,6-lutidine (500 mg) were dissolved in dry tetrahydrofuran (20 ml) and the solution was stirred at 0 °C while thionyl chloride (560 mg) in dry tetrahydrofuran (5 ml) was added dropwise over 5 min. The mixture was stirred for a further 15 min at 0 °C and then benzene (10 ml) was added and the mixture was filtered. The solvent was removed from the filtrate, more dry benzene (20 ml) was added, and again the solvent was removed. The residue was dissolved in dry dioxane (30 ml) and 2,6-lutidine (330 mg) and triphenylphosphine (1.6 g) were added to the solution, which was stirred at 55 °C (bath temperature) for 6 h, and then at room temperature for a further 17 h. The mixture was diluted with ethyl acetate (100 ml) and washed with dilute hydrochloric acid, water, dilute aqueous sodium hydrogen carbonate, and saturated brine. The solution was dried, the solvent was removed, and the resulting gum was chromatographed to give the *oxacephem* (**17a**) as a pale yellow gum (490 mg), $[\alpha]_D^{20}$ −12.8° (*c* 1.0); $\lambda_{max.}$ 265 (ε 14 200) and 313 (15 600) nm; $\nu_{max.}$ 1 803, 1 740, 1 735, 1 610, 1 595, 1 530, and 1 355 cm^{-1}; δ (250 MHz) 3.13 (1 H, dd, *J* 16 and 1.2 Hz), 3.31 (3 H, s), 3.51 (1 H, dd, *J* 16 and 3.5 Hz), 4.1 (1 H, dd, *J* 14 and 6 Hz), 4.24 (1 H, dd, *J* 14 and 7 Hz), 5.19 (1 H, dd, *J* 3.5 and 1.2 Hz), 5.20 (1 H, d, *J* 12 Hz), 5.23 (1 H, d, *J* 13.5 Hz), 5.25 (1 H, d, *J* 12 Hz), 5.30 (1 H, d, *J* 13.5 Hz), 5.37 (1 H, dd, *J* 7 and 6 Hz), 7.35 (5 H, s), 7.56 (2 H, d, *J* 8.5 Hz), and 8.19 (2 H, d, *J* 8.5 Hz); *m/z* 494 (*M*$^+$, 1%), 403 (6), 361 (32), 316 (8), 272 (4), 208 (6), 166 (5), 136 (47), 91 (100), and 85 (8) (Found: *M*$^+$, 494.135. $C_{25}H_{22}N_2O_9$ requires *M*, 494.137).

Lithium (Z)-(6R)-3-*Benzyloxycarbonyl*-2-(2-*methoxyethylidene*)-1-*oxaceph*-3-*em*-4-*carboxylate* (**18**).—The di-ester (**17a**) (390 mg) in tetrahydrofuran (10 ml) was treated with M-ammonium chloride (10 ml) and iron powder (1.3 g). The mixture was stirred for 20 min and then more iron powder (1.3 g) and M-ammonium chloride (1 ml) were added. Stirring was continued for 15 min, ethyl acetate (150 ml) was added, and H_2S was bubbled through the solution for 5 min. The mixture was

filtered and the solid was washed with water. The aqueous layer of the filtrate was saturated with sodium chloride and the mixture was again filtered. M-HCl (5 ml) was added to the filtrate, the filtrate was shaken, and the layers were separated. The organic layer was extracted with phosphate buffer (0.067M; pH 7; 3 × 50 ml). The combined extracts were overlayered with ethyl acetate (50 ml), M-HCl (9 ml) was added, the mixture was shaken, and the layers were separated. The aqueous layer was extracted twice more with ethyl acetate (50 ml portions), and the combined organic layers were dried. The solvent was removed to yield a pale yellow gum (190 mg). The gum was dissolved in a mixture of tetrahydrofuran (10 ml) and water (10 ml) and the pH was brought to 7.0 by adding 0.1M-lithium hydroxide. The tetrahydrofuran was removed, and the residue was diluted with water (20 ml) and washed with ether (2 × 10 ml). The solution was filtered and the water was removed from the filtrate to give a colourless gum. The gum was dissolved in acetone (2 ml) and ether (25 ml) was added slowly to the solution. The resulting precipitate was collected, washed with ether, and dried *in vacuo* to give the *lithium oxacephem-4-carboxylate* (**18**) as a white powder (150 mg), $[\alpha]_D^{22}$ + 26.9° (*c* 0.8, water); $\lambda_{max.}$(water) 303 nm (ε 17 900); $\nu_{max.}$(KBr) 1 770, 1 720, 1 625, 1 585, and 1 420 cm^{-1}; δ(D_2O) 3.06 (1 H, dd, *J* 16 and 1.5 Hz), 3.19 (3 H, s), 3.47 (1 H, dd, *J* 16 and 3.5 Hz), 4.05 (2 H, d, *J* 7 Hz), 5.08 (1 H, t, *J* 7 Hz), 5.20 (1 H, dd, *J* 3.5 and 1.5 Hz), 5.24 (2 H, s), and 7.40 (5 H, s) (Found: C, 55.05; H, 4.5; N, 3.6. $C_{18}H_{16}LiNO_7 \cdot 1.5H_2O$ requires C, 55.1; H, 4.85; N, 3.55%).

4-*Nitrobenzyl* 9-O-*Methylclavulanate* (**11b**).—4-Nitrobenzyl clavulanate[12] (3.0 g) in dichloromethane (20 ml) was treated with silver oxide (2.0 g), anhydrous calcium sulphate powder (4.0 g), and methyl iodide (2.0 ml), and the mixture was stirred in the dark for 60 h. The mixture was filtered, the solvent was removed from the filtrate, and the resulting gum was chromatographed to give the *methyl ether* (**11b**) as colourless needles (1.8 g), m.p. 85—86 °C (ethyl acetate–light petroleum); $[\alpha]_D^{20}$ + 49.4° (*c* 2.75); $\nu_{max.}$ 1 805, 1 755, 1 695, 1 605, 1 525, and 1 350 cm^{-1} (Found: C, 55.2; H, 7.9; N, 4.65. $C_{16}H_{16}N_2O_7$ requires C, 55.15; H, 8.05; N, 4.65%).

Oxidation of 4-*Nitrobenzyl* 9-O-*Methylclavulanate* (**11b**) *with Selenium Dioxide*.—Using a process exactly analogous to that described for the oxidation of benzyl 9-*O*-methylclavulanate, the methyl ether (**11b**) (1.7 g) was oxidised with a mixture of selenium dioxide (550 mg) and t-butyl hydroperoxide (1.25 ml; containing 30% t-butyl alcohol). 4-*Nitrobenzyl* 3-*hydroxy*-9-O-*methylclavulanate* (**12b**)* was obtained as a pale yellow gum (1.15 g), $[\alpha]_D^{20}$ + 54.3° (*c* 1.0); $\lambda_{max.}$ 267 nm (ε 12 300); $\nu_{max.}$ 3 420, 3 250, 1 790, 1 745, 1 690, 1 640, 1 615, 1 530, and 1 355 cm^{-1}; the n.m.r. spectrum showed that this compound existed as a 2:1 mixture of ring-opened (major) tautomer (**13b**) and ring-closed (minor) tautomer (**12b**), δ 2.85—3.40 (5 H, complex m including s at δ 3.26 and 3.33), 4.03 (2 H, minor tautomer, d, *J* 7 Hz), 4.22 (2 H, major tautomer, d, *J* 5.5 Hz), 4.85 (1 H, minor tautomer, t, *J* 7 Hz), 5.10—5.60 (*ca.* 3 H, complex m, including s at δ 5.39), 6.48 (1 H, major tautomer, t, *J* 5.5 Hz), 6.78br (1 H, major tautomer, s), 7.55 (2 H, d, *J* 8.5 Hz), 8.22 (2 H, minor tautomer, d, *J* 8.5 Hz), and 8.24 (2 H, major tautomer, d, *J* 8.5 Hz); *m/z* 364 (M^+, 0.5%), 333 (0.3), 304 (1), 153 (14), 136 (32), 124 (5), 107 (12), 106 (15), 90 (15), 89 (22), 87 (63), 85 (22), 78 (23), 77 (30), 70 (45), 55 (95), and 45 (100) (Found: M^+, 364.089. $C_{16}H_{16}N_2O_8$ requires *M*, 364.087).

4-*Nitrobenzyl* (Z)-(6R)-3-(4-*Nitrobenzyloxycarbonyl*)-2-(2-*methoxyethylidene*)-1-*oxaceph*-3-*em*-4-*carboxylate* (**17b**).—The 4-nitrobenzyl ester (**12b**) (1.15 g) was converted into the oxacephem (**17b**) using the process described for the preparation of the oxacephem (**17a**) from the benzyl ester (**12a**). The *oxacephem* (**17b**) was obtained as colourless needles (330 mg), m.p. 117—118 °C (ethyl acetate–light petroleum); $[\alpha]_D^{20}$ −33.2° (*c* 0.75); $\lambda_{max.}$ 265 (ε 20 200) and 314 nm (16 700); $\nu_{max.}$ 1 802, 1 738, 1 610, 1 590, 1 525, and 1 355 cm^{-1}; δ (250 MHz) 3.16 (1 H, dd, *J* 16 and 1.5 Hz), 3.33 (3 H, s), 3.54 (1 H, dd, *J* 16 and 4 Hz), 4.11 (1 H, dd, *J* 14 and 6 Hz), 4.25 (1 H, dd, *J* 14 and 7 Hz), 5.22 (1 H, dd, *J* 4 and 1.5 Hz), 5.26 (1 H, d, *J* 13.5 Hz), 5.27 (1 H, d, *J* 13.5 Hz), 5.30 (1 H, dd, *J* 7 and 6 Hz), 5.38 (1 H, d, *J* 13.5 Hz), 5.40 (1 H, d, *J* 13.5 Hz), 7.55 (2 H, d, *J* 8.5 Hz), 7.58 (2 H, d, *J* 8.5 Hz), 8.21 (2 H, d, *J* 8.5 Hz), and 8.22 (2 H, d, *J* 8.5 Hz); *m/z* 539 (M^+, 0.5%), 511 (0.5), 480 (2), 403 (5), 375 (6), 361 (48), 250 (4), 208 (17), 166 (40), 136 (100), 106 (31), 78 (70), and 77 (13) (Found: C, 55.85; H, 7.75; N, 3.9%; M^+, 539.120. $C_{25}H_{21}N_3O_{11}$ requires C, 55.65; H, 7.8; N, 3.9%; *M*, 539.122).

(4R)-1-[(RS)-1-*Benzyloxycarbonyl*-1-*hydroxymethyl*]-4-[(Z)-1-*formyl*-3-*methoxyprop*-1-*enyloxy*]*azetidin*-2-*one* (**21**).—A solution of the 3-hydroxyclavam (**19**)[7b] (0.48 g) and benzyl glyoxylate (1.5 g) in benzene (40 ml) was refluxed with azeotropic removal of water for 2 h. The solution was cooled and filtered, and the solvent was removed from the filtrate. The residue was chromatographed to give the mixed epimeric hydroxy esters (**21**) as a colourless gum (0.75 g), $[\alpha]_D^{31}$ −42.3° (*c* 1.0); $\lambda_{max.}$ 243 nm (ε 7 900); $\nu_{max.}$ 3 520, 1 780, 1 750, and 1 690 cm^{-1}; δ 2.96 and 2.99 (1 H, both dd, *J* 16 and 2 Hz), 3.1—3.5 (4 H, m, including s at δ 3.31), 4.0—4.6 (3 H, m, becoming 2 H, m on D_2O exchange), 5.21 (2 H, s), 5.43 (1 H, s), 5.57 and 5.77 (1 H, both dd, *J* 3.5 and 2 Hz), 6.07 and 6.10 (1 H, both t, *J* 6 Hz), 7.32 (5 H, s), and 9.15 (1 H, s); *m/z* (ammonia chemical ionization) 367 ($[M + NH_4]^+$, 5%), 350 ($[M + H]^+$, 2), 269 (3), 251 (3), 223 (8), 203 (100), 182 (90), 171 (18), 154 (25), 134 (40), 108 (75), 105 (30), 91 (35), 87 (70), 84 (50), 70 (65), and 44 (45).

Benzyl (Z)-(6R)-2-(2-*Methoxyethylidene*)-1-*oxaceph*-3-*em*-4-*carboxylate* (**23**).—The mixed hydroxy esters (**21**) (390 mg) in dry tetrahydrofuran (12 ml) at −20 °C were treated with 2,6-lutidine (145 mg) and then with a solution of thionyl chloride (160 mg) in dry tetrahydrofuran (1 ml). The cooling bath was removed and the mixture was stirred while it warmed to room temperature. The mixture was filtered and the solvent was removed from the filtrate. The resulting oil was dissolved in benzene (10 ml), and again the solvent was removed. The residue was dissolved in dry dioxane (10 ml) and was treated with 2,6-lutidine (360 mg) and triphenylphosphine (600 mg). The solution was stirred at 60 °C (bath temperature) for 21 h. The mixture was cooled, diluted with ethyl acetate (50 ml), and washed with 0.5M-HCl and water. The solution was dried, the solvent was removed, and the residue was chromatographed to give the *oxacephem* (**23**) as a colourless gum (220 mg), $[\alpha]_D^{31}$ −35.9° (*c* 1.0); $\lambda_{max.}$ 304 nm (ε 17 900); $\nu_{max.}$ 1 795, 1 725, 1 635, and 1 600 cm^{-1}; δ 3.01 (1 H, d, *J* 16 Hz), 3.2—3.6 (4 H, m, including s at δ 3.30), 3.9—4.4 (2 H, m), 5.0—5.4 (4 H, m), 6.58 (1 H, s), and 7.2—7.5 (5 H, m); *m/z* 315 (M^+, 2%), 273 (20), 258 (4), 242 (10), 154 (5), and 91 (100) (Found: M^+, 315.111. $C_{17}H_{17}NO_5$ requires *M*, 315.111).

Attempts to store the oxacephem (**23**) as the neat gum resulted in noticeable deterioration, even after 19 h. The compound could be kept satisfactorily, however, as a dilute (*ca.* 2%) solution in ethyl acetate at 4 °C.

Lithium (Z)-(6R)-2-(2-*Methoxyethylidene*)-1-*oxaceph*-3-*em*-4-*carboxylate* (**24**).—The oxacephem benzyl ester (**23**) (180 mg) in tetrahydrofuran (3 ml) and water (3 ml) was stirred while 0.1M-lithium hydroxide was added dropwise so as to maintain the pH of the solution between 11.3 and 11.7. After 2 h, the

* Stereochemistry at C-3 unknown; compound (**12b**) is in tautomeric equilibrium with the ring-opened ketone (**13b**).

hydrolysis appeared to be complete (t.l.c.), and the pH was adjusted to 7.5 using 0.1M-HCl. The solution was washed once with ethyl acetate. The solvent was removed and the residue was chromatographed on cellulose (Whatman CC31), using 4:1:1 butan-1-ol–ethanol–water. Fractions containing the oxacephem were combined and the solvent was removed. The residue was dissolved in water (3 ml), filtered, and freeze-dried to give the *lithium oxacephem-4-carboxylate* (**24**) as a pale yellow powder (99 mg), $[\alpha]_D^{22}$ + 31.7° (*c* 1.0, water); $\lambda_{max.}$(water) 295 nm (ε 16 100); $\nu_{max.}$(KBr) 1 765, 1 625, and 1 590 cm^{-1}; δ (D_2O; 250 MHz) 3.11 (1 H, d, *J* 16 Hz), 3.37 (3 H, s), 3.54 (1 H, dd, *J* 16 and 3.5 Hz), 4.1—4.4 (2 H, m), 5.2—5.4 (2 H, m), and 6.51 (1 H, s) (Found: C, 49.7; H, 4.95; N, 5.85. $C_{10}H_{10}LiNO_5 \cdot 0.5H_2O$ requires C, 50.0; H, 4.6; N, 5.85%); evidence for the molecular weight was obtained from the positive-ion fast atom bombardment mass spectrum,* which for a suspension of the salt (**24**) in glycerol showed *inter alia* *m/z* 330 ([*M* + Li + glycerol]$^+$, 35%), 324 ([*M* + H + glycerol]$^+$, 25), 238 ([*M* + Li]$^+$, 75), and 232 ([M + H]$^+$, 100).

(Z)-(3R,5R)-3-*Diazoacetyl*-2-(2-*methoxyethylidene*)*clavam* (**26**). —9-*O*-Methylclavulanic acid (**25**) (from 8.76 g of lithium 9-*O*-methylclavulanate[11]) in dry tetrahydrofuran (100 ml) was treated, at 0 °C, with dry pyridine (3 ml) and pivaloyl chloride (4.5 ml). The mixture was stirred at 0 °C for 1.5 h and was then filtered. The filtrate was added to an ethereal solution of diazomethane (from 10.75 g of *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide[13]) and the mixture was set aside for 45 min. Sufficient acetic acid was added to destroy the remaining diazomethane and the solution was decanted from insoluble material. The solvent was removed and the residue was dissolved in ethyl acetate (100 ml) and washed with water, dilute citric acid, water, dilute aqueous sodium hydrogen carbonate, water, and saturated brine. The solution was dried, the solvent was removed, and the residue was chromatographed to give the diazo ketone (**26**) as a pale yellow oil (1.8 g), $\nu_{max.}$ 2 120, 1 805, 1 695, and 1 645 cm^{-1}; δ 3.05 (1 H, d, *J* 17 Hz), 3.29 (3 H, s), 3.48 (1 H, dd, *J* 3 and 17 Hz), 4.01 (2 H, d, *J* 7 Hz), 4.88 (1 H, s), 4.91 (1 H, dt, *J* 1.5 and 7 Hz), 5.58 (1 H, d, *J* 3 Hz), and 5.64 (1 H, s).

(Z)-(3S,5R)-3-*Methoxycarbonylmethyl*-2-(2-*methoxyethylidene*)*clavam* (**27**).—The diazo ketone (**26**) (2.17 g) in methanol (50 ml) was treated with silver oxide (500 mg) and the mixture was stirred at 30—40 °C (bath temperature) for 1.5 h. The mixture was cooled and filtered and the solvent was removed from the filtrate. The resulting oil was chromatographed to give the *clavam* (**27**) and the diene (**32**). The clavam (**27**) was obtained as a colourless oil (1.38 g), $[\alpha]_D^{20}$ + 108.5° (*c* 1.0); $\nu_{max.}$ 1 805, 1 745, 1 700, and 1 315 cm^{-1}; δ 2.63 (2 H, d, *J* 6 Hz), 2.95 (1 H, d, *J* 17 Hz), 3.27 (3 H, s), 3.36 (1 H, dd, *J* 17 and 3 Hz), 3.68 (3 H, s), 3.99 (2 H, d, *J* 7 Hz), 4.53 (1 H, dt, *J* 1 and 7 Hz), 4.83 (1 H, dt, *J* 1 and 6 Hz), and 5.58 (1 H, d, *J* 3 Hz); *m/z* 241 (*M*$^+$, 0.3%), 210 (22), 172 (20), 168 (74), 167 (15), 154 (17), 140 (18), 128 (35), 127 (51), 126 (46), 108 (100), 85 (52), 55 (60), and 54 (77) (Found: *M*$^+$, 241.095. $C_{11}H_{15}NO_5$ requires *M*, 241.094). The diene (**32**) was obtained as a colourless oil (65 mg), $\lambda_{max.}$ 263 nm (ε 19 000); $\nu_{max.}$ 3 420, 1 785, 1 720, 1 650, and 1 630 cm^{-1}.

Methyl (Z)-(6R)-3-*Methoxy*-2-(2-*methoxyethylidene*)-1-*oxaceph*-3-*em*-4-*carboxylate* (**31**).—t-Butyl hydroperoxide (1.3 ml; containing 30% t-butyl alcohol) in dry dichloromethane (15 ml) was treated with selenium dioxide (320 mg) and the mixture was stirred for 0.5 h. The clavam (**27**) (1.38 g) in dichloromethane (20 ml) was added and the mixture was stirred and refluxed for 2.5 h. The solvent was removed and the resulting residue was chromatographed to give the azetidinone (**28**) as a pale yellow gum (1.04 g), $[\alpha]_D^{20}$ + 5.5° (*c* 1.0); $\nu_{max.}$ 3 420, 1 780, 1 750, and 1 695 cm^{-1}; δ 2.95 (1 H, d, *J* 17 Hz), 3.22 (1 H, ddd, *J* 17, 5, and 3 Hz), 3.35 (3 H, s), 3.68 (2 H, s), 3.73 (3 H, s), 4.19 (2 H, d, *J* 7 Hz), 5.39 (1 H, dd, *J* 1 and 3 Hz), 6.26 (1 H, t, *J* 7 Hz), and 6.92 br (1 H, s).

The azetidinone (**28**) (1.04 g) in acetonitrile (15 ml) was treated with toluene-*p*-sulphonyl azide (1.0 g) and the solution was cooled to 0 °C. Triethylamine (410 mg) in acetonitrile (15 ml) was added slowly, with stirring, and the mixture was stirred at 0 °C for 50 min. The solvent was removed and the residue was chromatographed to give the α-diazo β-keto ester (**29**) as a yellow gum (787 mg), $\nu_{max.}$ 2 140, 1 790, 1 735, and 1 635 cm^{-1}; δ 2.98 (1 H, dd, *J* 17 and 1 Hz), 3.20 (1 H, ddd, *J* 17, 5, and 3 Hz), 3.33 (3 H, s), 3.82 (3 H, s), 4.14 (2 H, d, *J* 7 Hz), 5.34 (1 H, dd, *J* 5 and 1 Hz), 5.92 (1 H, t, *J* 7 Hz), and 6.88 br (1 H, s).

The α-diazo β-keto ester (787 mg) in benzene (50 ml) was treated with rhodium(II) acetate (5 mg) and the mixture was refluxed for 1 h. The mixture was cooled and filtered, and the solvent was removed. The residue was dissolved in ethyl acetate (50 ml) and treated with small portions of ethereal diazomethane until the reaction appeared to be complete (t.l.c.). The solvent was removed and the residue was chromatographed to give the *oxacephem* (**31**) as colourless crystals (125 mg), m.p. 107—109 °C (ethyl acetate–light petroleum); $[\alpha]_D^{20}$ −23.6° (*c* 1.0); $\lambda_{max.}$ 308 nm (ε 14 300); $\nu_{max.}$ 1 800, 1 730, and 1 600 cm^{-1}; δ 2.98 (1 H, dd, *J* 17 and 1 Hz), 3.34 (3 H, s), 3.39 (1 H, dd, *J* 17 and 3 Hz), 3.81 (3 H, s), 3.87 (3 H, s), 4.15 (2 H, dd, *J* 7 and 3 Hz), 5.20 (1 H, dd, *J* 3 and 1 Hz), and 5.71 (1 H, t, *J* 7 Hz) (Found: C, 53.2; H, 5.6; N, 5.15. $C_{16}H_{16}N_2O_7$ requires C, 53.5; H, 5.6; N, 5.2%).

Acknowledgements

We thank Mr. J. W. Tyler for performing the n.m.r. experiments.

References

1 P. C. Cherry, C. E. Newall, and N. S. Watson, *J. Chem. Soc., Chem. Commun.*, 1979, 663.
2 P. C. Cherry, D. N. Evans, C. E. Newall, N. S. Watson, P. Murray-Rust, and J. Murray-Rust, *Tetrahedron Lett.*, 1980, 561.
3 G. Brooks and E. Hunt, *J. Chem. Soc., Perkin Trans. 1*, 1983, 115.
4 W. Nagata, M. Narisada, and T. Yoshida in 'Chemistry and Biology of β-Lactam Antibiotics,' ed. R. B. Morin and M. Gorman, Academic Press, New York, 1982, vol. 2, pp. 1—98.
5 C. L. Branch, J. H. C. Nayler, and M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1450.
6 M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, 1977, **99**, 5526.
7 (*a*) E. Hunt and I. I. Zomaya, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1509; (*b*) G. Brooks and E. Hunt, *ibid.*, 1983, 2513.
8 R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, 1972, **55**, 408; R. Scartazzini and H. Bickel, *ibid.* p. 423; J. H. C. Nayler, N. F. Osborne, M. J. Pearson, and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1615.
9 W. E. Bachmann and W. S. Stuve, *Org. React.*, 1942, **1**, 38.
10 K. B. Wiberg and T. W. Hutton, *J. Am. Chem. Soc.*, 1956, **78**, 1640.
11 T. T. Howarth and R. J. Ponsford, B. P., 1,565,209/1980.
12 T. T. Howarth, A. G. Brown, and T. J. King, *J. Chem. Soc., Chem. Commun.*, 1976, 266.
13 Th. J. de Boer and H. J. Backer, *Org. Synth.*, Coll. Vol. 4, 1963, p. 250.

* Obtained using a VG-ZAB mass spectrometer with high-energy xenon atoms as the fast atoms.

Received 16th *December* 1983; *Paper* 3/2213