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SYNTHESIS OF FUNCTIONALISED CEPHALOSPORINS

DIPHENYLMETHYL(1S,6R,7S)-3-BROMOMETHYL-7-FORMAMIDO-7-METHOXYCEPH-3-EM-4-CARBOXYLATE-1-OXIDE: A USEFUL INTERMEDIATE IN THE PREPARATION OF 7α-METHOXYCEPHALOSPORINS

K. BIGGADIKE, D. C. HUMBER,* B. LAUNDON, A. G. LONG and M. V. J. RAMSAY
Chemical Research Department, Glaxo Group Research Ltd., Greenford, Middlesex, England

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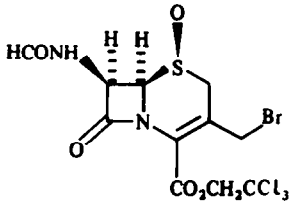
Abstract—The N-formamido cephalosporins **4a** and **4b** undergo direct methoxylation at the 7α-position to give the 7α-methoxy derivatives **5a** and **5b**. These were converted to other 7β-acylamido compounds by the sequence: oxidation, deformylation, acylation and reduction. The 3-bromomethyl derivatives **2b**, **6b** and **8b** proved amenable to nucleophilic substitution with 5-mercapto-1-methyltetrazole.

In an earlier paper[1] we described the preparation of the 3-bromomethyl ceph-3-em sulphoxide **1** and demonstrated its utility in the synthesis of cephalosporins substituted at the 3- and 7-positions.[1,2] We now describe the preparation of the 3-bromomethyl sulphoxide intermediate **2b** bearing a 7α-methoxy group. Since their isolation from *Streptomyces* cultures[3,4] 7α-methoxycephalosporins have aroused considerable scientific and commercial interest.[5,6]

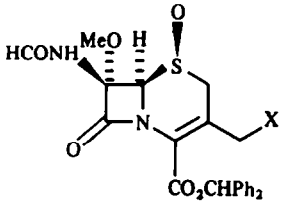
We first sought to establish that a 7α-methoxy group could be introduced[7] into a 7β-formamido compound and that the N-formyl group could be subsequently removed and replaced by other acyl groups. We chose to do this in the stable 3-methylceph-3-em series thereby avoiding any possible complicating reactions at a 3-bromomethyl group.

Basification of the salt **3**[8] followed by formylation with ethyl formate containing a little formic acid gave the N-formyl derivative **4a** in 87% yield. Direct methoxylation of **4a** by the procedure of the Lilly group[7] provided the 7α-methoxy analogue **5a** in near quantitative yield. The sulphide **5a** was oxidised with peracetic acid to give a *ca* 2:1 mixture of the 1S- and 1R-sulphoxides **2a** and **6a** respectively (49% yield). This unexpected result contrasts with a similar oxidation of the 7α-H analogue **4a** which furnished the 1S-oxide **7a** stereospecifically in 90% yield. Evidently the 7α-methoxy group counteracts the very strong "reagent approach control" normally exerted by the formamido NH proton[1] (a further example is given below).

Cooper *et al.*[9] assigned stereochemistry to pairs of 7α-H 7β-acylamidocephalosporin 1S- and 1R-oxide isomers by PMR spectroscopy. They compared the chemical shifts of the 7β-amide proton resonances in different solvents. Because of the reduced ability of the 7β-amide proton to hydrogen bond this method did not prove applicable in the 7α-methoxy series. We have made our assignments on the basis of UV spectroscopy (Table 1): in the 7α-H series the 1S-oxides have higher extinction coefficients at the respective maxima than their IR-isomers, with the parent sulphides having intermediate values. We have assumed that this



1



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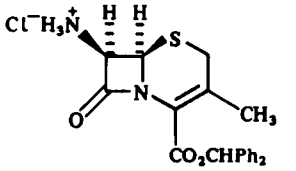

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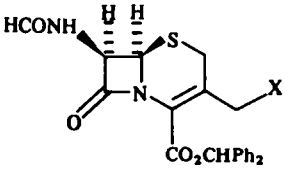

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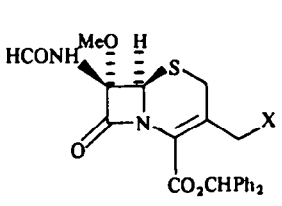
X = (see overleaf)



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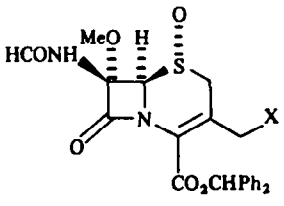

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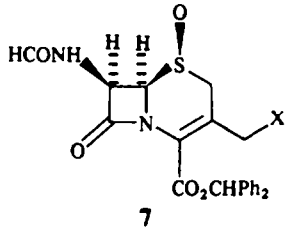

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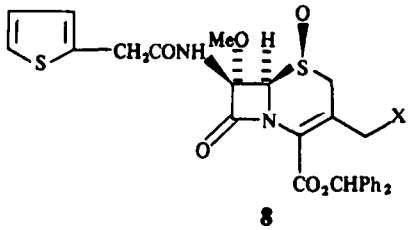

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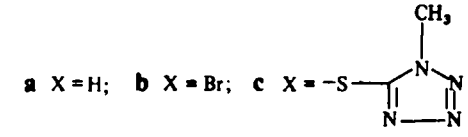
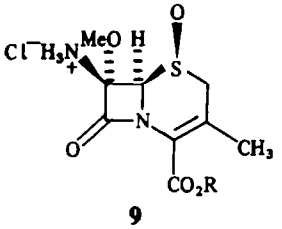


a X = H; b X = Br; c X = –S–

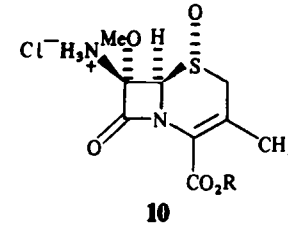
difference holds in the 7α-OMe series. (This interpretation neglects minor interferences from chromophores in the 7β-acylamido group.)

Deformylation of the 1S-oxide **2a** with phosphorus oxychloride in methanol[1] gave the crystalline hydrochloride salt **9** in 77% yield. Similar treatment of **6a** gave the salt **10** in 74% yield. Attempts to obtain PMR spectra of either salt (pyridine-d_5 or dimethylsulphoxide-d_6) or to convert them to their respective free bases were unsuccessful because of decomposition.[10] The salt **9** suspended in dichloromethane containing propylene oxide was acylated with an equivalent of phenylacetyl chloride. When solution was obtained the reaction mixture was worked-up and the crude sulphoxide then reduced with potassium iodide/acetyl chloride in N,N-dimethylformamide (DMF)[11] to give the known[12,13] phenylacetamido derivative **11** (39% yield).

We next turned our attention to preparation of the desired intermediate **2b**. Photobromination of **7a** with



9



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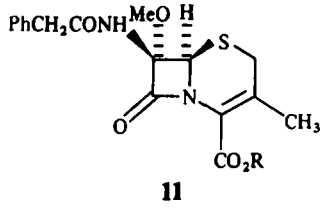

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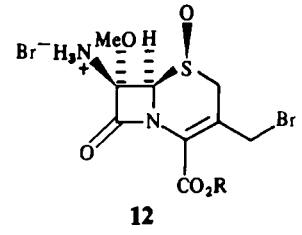

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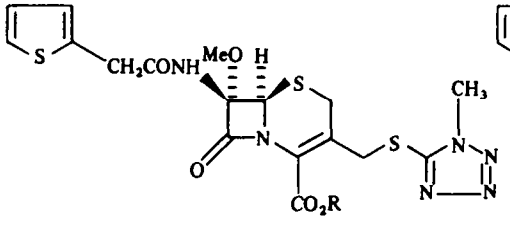

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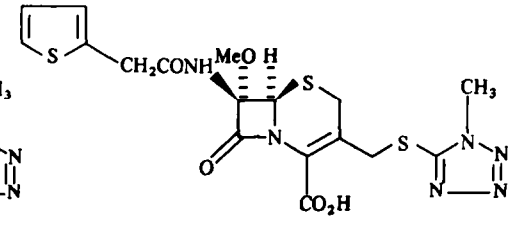
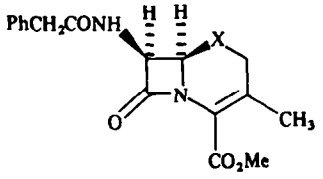
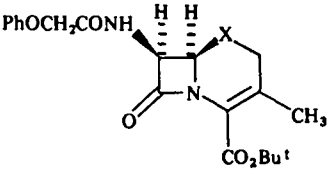
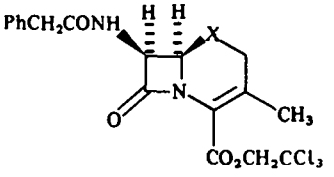
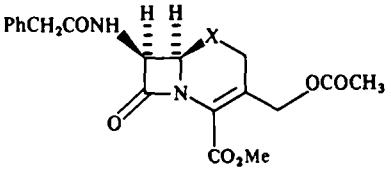
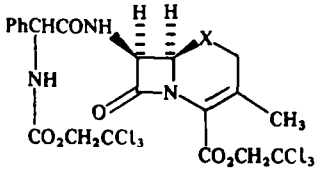
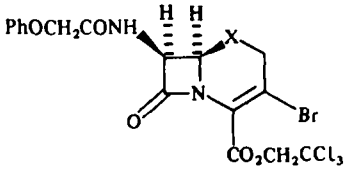
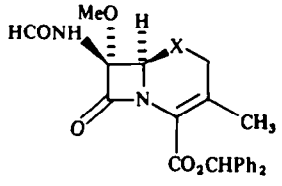
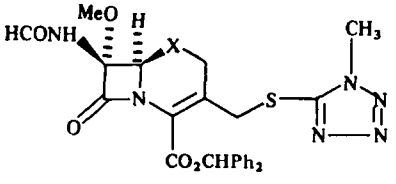


14

R = $CHPh_2$

Table 1. UV Absorption spectra (in EtOH) of some ceph-3-em esters and their 1S- and 1R-oxides: λ_{max} values with corrected extinction coefficients in parentheses

X =			
	i 259 nm (ε 6,550)	i 265 nm (ε 8,150)	i 265 nm (ε 5,150)
	i 268.5 nm (ε 7,850) 274.5 nm (ε 7,000)	i 263 nm (ε 9,150) 267.5 nm (ε 9,250)	i 263 nm (ε 6,500) 268 nm (ε 6,700)
	ii 259 nm (ε 6,360)	iii 269 nm (ε7,450)	iii 269 nm (ε4,850)
	iv 260 nm (ε 7,800)	v 267 nm (ε 8,800)	vi 268 nm (ε 6,310)
	i, ii 262 nm (ε 6,000)	ii 269 nm (ε 7,500)	vi 265 nm (ε 3,850)
	iii 269 nm (ε 8,700) 275.5 nm (ε 9,050)	iii 276 nm (ε 9,850)	iii 268 nm (ε 6,750) 275 nm (ε 7,150)
	vi 259 nm (ε 5,525)	vi 269.5 nm (ε 7,770)	vi 259 nm (ε 4,475)
	vi 269.5 nm (ε 7,230)	vi 281.5 nm (ε 9,770)	vi 275 nm (ε 5,970)

i UK Patent 1,326, 531; ii Ref. 22; iii Ref. 1; iv Ref. 20; v Ref. 21; vi Experimental Section.

1,3-dibromo-5,5-dimethylhydantoin in 1,2-dichloroethane at −10°[1] gave the 3-bromomethyl derivative **7b** in 60% yield. Reduction of the oxide **7b** with phosphorus tribromide[14] at −20° gave the corresponding sulphide **4b** (77% yield). This reduction step proved necessary because of the different structural requirements of the bromination and methoxylation reactions. Thus it has not proved possible to halogenate 3-methylceph-3-em esters under a variety of conditions[1,15] and neither has it been possible to introduce a 7α-methoxy group directly into a ceph-3-em sulphoxide unless the C_2-position is protected.[16] We have observed however, that the bromine atom of 3-bromomethyl sulphoxide esters is more amenable to nucleophilic displacement than in the analogous sulphides and that problems of double bond isomerisation[17] are avoided.

Methoxylation of the sulphide **4b** was accomplished as previously described for **4a** to give the 7α-methoxy derivative **5b**. The crude product was oxidised directly with *m*-chloroperbenzoic acid to give a mixture of sulphoxides from which the more polar 1S-oxide **2b** (λ_{max}^{EtOH} 285 nm, ε 9,700) crystallised in 33% yield. The less polar 1R-oxide **6b** (λ_{max}^{EtOH} 280 nm, ε 4,900) was isolated from the liquors by chromatography (17% yield).

Nucleophilic displacement of the bromine atom of sulphoxides **2b** and **6b** proceeds readily. For example, reaction with 5-mercapto-1-methyltetrazole in DMF in the presence of sodium bicarbonate gave the 3-substituted derivatives **2c** and **6c** (88% and 63% respectively). Reduction of each oxide with KI/AcCl in DMF gave the same sulphide **5c**. Deformylation of **2b** with phosphorus tribromide in methanol[1] gave the hydrobromide salt **12** in 90% yield. As was the case with the hydrochloride salts **9** and **10**, the salt **12** was too unstable in Me_2SO-d_6 to allow characterisation by PMR spectroscopy. Attempts to acylate **12** with (thien-2-yl)acetyl chloride in dichloromethane/propylene oxide were unsuccessful. Other workers have also noted the poor nucleophilicity of cephalosporin 7β-amines with a geminal 7α-methoxy group.[5] However, by addition of *ca* 2 equivalents of powdered magnesium sulphate or preferably magnesium oxide to the reaction medium, the acylated derivative **8b** could be obtained in modest yield (22 to 27%).

Displacement of the bromine atom of **8b** with 5-mercapto-1-methyltetrazole by the procedure outlined above gave the sulphoxide **8c** (64% yield). This was followed by reduction of the sulphoxide function with KI/AcCl in DMF to give the ester **13** (61% yield). Removal of the ester function from **13** with trifluoracetic acid in anisole gave the biologically active acid **14** (73% yield).[18]

Despite the lack of selectivity in the oxidation step and the low yields obtained in the acylation reactions, the above sequence demonstrates the utility of the intermediate **2b**. It has proved particularly useful for the preparation of compounds such as the acid **14** which have not been readily attainable by the direct methoxylation route. Lunn and Mason[19] have also reported difficulties with the direct methoxylation technique in cases where there are other sites in the molecule capable of forming anions.

EXPERIMENTAL

Unless otherwise stated the following procedures were adopted. M.ps were obtained on a Kofler Microblock and are uncorrected. Optical rotations were measured at 20–30° in DMSO soln at 0.8–1.2% concentrations. UV spectra were recorded in EtOH soln. IR spectra were recorded on either a Perkin–Elmer model 21 or 521 and were obtained as Nujol mulls. PMR spectra were obtained on 5–10% solns in DMSO-d_6 on a Varian A60 (60 MHz) or a Varian HA 100 (100 MHz). Coupling constants are quoted in Hz. Solns were dried over $MgSO_4$.

Diphenylmethyl(6R,7R) - 7 - *formamido* - 3 - *methylceph* - 3 - *em* - 4 - *carboxylate* **4a**. A mixture of the hydrochloride salt **3**[8] (103 g, 248 mmol), $NaHCO_3$ (55 g, 655 mmol), water (1.25 l) and CH_2Cl_2 (1.25 l) was stirred for 30 min. The aq phase was extracted with CH_2Cl_2 (2 × 250 ml). The organic portions were dried and evaporated and the residue dissolved in HCO_2Et (1 l) containing HCO_2H (5 ml). The soln was heated at reflux for 18 hr and evaporated. The residual solid was treated with EtOAc (350 ml) then ether (350 ml) to give **4a** as a white crystalline solid (88.5 g, 87%), m.p. 136–140°, $[\alpha]_D$ +38°, λ_{max} 258 nm (ε 6820), ν_{max} 3330 (NH), 1772 (azetidin-2-one), 1708 (CO_2R), 1656 and 1524 cm^{-1} (CONH), δ 2.07 (s; Me), 3.44, 3.68 (AB-q, J = 18; C_2-H_2), 5.17 (d, J = 5; C_6-H), 5.81 (dd, J = 5, 9; C_7-H), 6.93 (s; $Ph_2C\underline{H}$), 7.2–7.7 (m; Ph_2), 8.21 (s; CHO), 9.07 (d, J = 9; NH). [Found: C, 64.6; H, 4.9; N, 6.7; S, 7.7. $C_{22}H_{20}N_2O_4S$ (408.5) requires: C, 64.7; H, 4.9; N, 6.9; S, 7.9%.]

Diphenylmethyl (6R,7S) - 7 - *formamido* - 7 - *methoxy* - 3 - *methylceph* - 3 - *em* - 4 - *carboxylate* **5a**. A soln of **4a** (8.17 g, 20 mmol) in THF (160 ml) was added to a stirred mixture of LiOMe (2.66 g, 70 mmol), THF (500 ml) and MeOH (80 ml) at −70° under dry N_2. After 2 min t-butyl hypochlorite (4.8 ml, 40 mmol) was added and after a further 20 min the mixture was poured into iced water (2 l) containing NH_4Cl and $Na_2S_2O_5$ then extracted with EtOAc (3 × 0.5 l). The combined extracts were washed with NaCl aq (0.5 l), dried and evaporated to give **5a** as a yellow foam (8.8 g, *ca* 100%), $[\alpha]_D$ +50°, λ_{max} 265 nm (ε 5090). A portion of similar material from an identical experiment was purified by prep TLC on silica gel, eluting with benzene–EtOAc (3 : 1) to give **5a** as a white foam (290 mg), $[\alpha]_D$ +58° ($CHCl_3$), λ_{max} 259 nm (ε 5525), ν_{max} ($CHBr_3$) 3380, 3340 (NH), 1772 (azetidin-2-one), 1718 (CO_2R) and 1700 cm^{-1} (CHO), δ 2.11 (s; Me), 3.44 (s; C_2-H_2), 3.51 (s; OMe), 5.20 and 5.26 (s, rotamers; C_6-H), 6.93 (s; $C\underline{H}Ph_2$), 7.2–7.7 (m; Ph_2), 8.28 (s; CHO), 9.30 and 9.46 (s, rotamers; NH). [Found: C, 63.15; H, 5.0; N, 6.2; S, 7.0. $C_{23}H_{22}N_2O_5S$ (438.5) requires: C, 63.0; H, 5.1; N, 6.4; S, 7.3%.]

Diphenylmethyl (1R,6R,7S) *and* (1S,6R,7S) - 7 - *formamido* - 7 - *methoxy* - 3 - *methylceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide* **2a** *and* **6a**. Peracetic acid soln (8 ml, 20 mmol) was added to a stirred soln of **5a** (8.8 g, *ca* 20 mmol) in CH_2Cl_2 (200 ml) at 5°. The soln was stirred for 30 min then washed with water (containing some $Na_2S_2O_5$), 3% $NaHCO_3$ aq and water (100 ml each), dried and evaporated to a foam (7.99 g). A portion of this (7.63 g) crystallised from acetone–cyclohexane (1 : 1; 100 ml) to give the 1S-oxide **2a** (1.67 g, 19%), m.p. 178–179°, $[\alpha]_D$ +186°, λ_{max} 270 nm (ε 7770), ν_{max} 3300 (NH), 1778 (azetidin-2-one), 1714 (CO_2R), 1700 (CONH) and 1054 cm^{-1} (S → O), δ 2.00 (s; Me), 3.44 (s; OMe), 3.70 (s; C_2-H_2), 5.02 and 5.12 (s, rotamers; C_6-H), 6.98 (s; $C\underline{H}Ph_2$), 7.2–7.7 (m; Ph_2), 8.24 and 8.34 (s, rotamers; CHO), 9.84 (s; NH). [Found: C, 60.8; H, 5.1; N, 5.9; S, 6.8. $C_{23}H_{22}N_2O_6S$ (454.5) requires: C, 60.8; H, 4.9; N, 6.2; S, 7.1%.] Liquor material was chromatographed on Kieselgel G (300 g). Elution with CH_2Cl_2–acetone (7 : 3) gave the 1R-oxide **6a** as a pale yellow foam (1.44 g, 17%) which crystallised from acetone–ether (1 : 1) as white prisms (0.89 g), m.p. 185–187°, $[\alpha]_D$ −216°, λ_{max} 259 nm (ε 4475), ν_{max} 3210 and 3150 (NH), 1774 (azetidin-2-one), 1724 (CO_2R), 1694 and 1660 (CONH) and 1020 cm^{-1} (S → O), δ 2.17 (s; Me), 3.55 (s; OMe), 3.70 and 4.00 (AB-q, J = 17; C_2-H_2), 4.79 and 5.10 (s, rotamers; C_6-H), 6.95 (s; $C\underline{H}Ph_2$), 7.2–7.7 (m; Ph_2), 8.49 and 8.26 (s, rotamers; CHO), 9.72 (s; NH). [Found: C, 60.9; H, 4.8; N, 6.0; S, 7.2%.] Further elution with acetone–CH_2Cl_2 (7 : 3) gave additional 1S-oxide **2a** (1.08 g, 12.5%).

Diphenylmethyl (1S,6R,7S) - 7 - *amino* - 7 - *methoxy* - 3 - *methylceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide hydrochloride* **9**. $POCl_3$ (0.65 ml, 7.08 mmol) was added dropwise over 2 min to

a stirred suspension of **2a** in MeOH (15 ml) at *ca* 5°. After 5 min all the solid had dissolved and after 20 min a new white solid crystallised. This was collected, washed with ether and dried to give **9** (1.02 g, 77%), m.p. 105–108°, λ_{max} (MeOH) 265 nm (ε 6970), ν_{max} *ca* 2600 (NH_3^+), 1788 (azetidin-2-one), 1726 (CO_2R) and 1040 cm^{-1} (S → O). [Found: C, 55.8; H, 4.9; Cl, 7.3; N, 5.3; S, 6.9. $C_{22}H_{23}ClN_2O_5S \cdot 0.5\,H_2O$ (471.95) requires C, 56.0; H, 5.1; Cl, 7.5; N, 5.9; S, 6.8%.]

Similar treatment of **6a** with $POCl_3$ in MeOH gave *diphenylmethyl* (1R,6R,7S) - 7 - *amino* - 7 - *methoxy* - 3 - *methylceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide hydrochloride* **10** (50.5%), m.p. 113–116°, λ_{max} (MeOH) 258.5 nm (ε 5140), ν_{max} 2720, 2610 and 2520 (NH_3^+), 1796 (azetidin-2-one), 1720 (CO_2R) and 1036 cm^{-1} (S → O). [Found: C, 56.3; H, 5.1; Cl, 7.4; N, 6.0; S, 6.9. $C_{22}H_{23}ClN_2O_5S \cdot 0.5\,H_2O$ (471.95) requires: C, 56.0; H, 5.1; Cl, 7.5; N, 5.9; S, 6.8%.]

Diphenylmethyl (6R,7S) - 7 - *methoxy* - 3 - *methyl* - 7 - *phenylacetamidoceph* - 3 - *em* - 4 - *carboxylate* **11**. The hydrochloride **9** (915 mg, 1.98 mmol) was added to a stirred mixture of phenylacetyl chloride (0.26 ml, 1.97 mmol) and propylene oxide (15 ml) in CH_2Cl_2 (40 ml). After *ca* 15 min all the solid had dissolved and the soln was stored at +5° for 30 min then diluted with EtOAc (250 ml) and washed with water, 3% $NaHCO_3$ aq and water (80 ml each), dried and evaporated to a yellow foam (1.10 g). This was dissolved in DMF (20 ml) and the stirred soln cooled to 0° and treated with KI (1.315 g, 7.92 mmol) followed by AcCl (0.28 ml, 3.92 mmol). I_2 was liberated almost immediately. After 1 hr the mixture was diluted with water (100 ml) containing a little $Na_2S_2O_5$ and extracted with EtOAc (3 × 50 ml). The combined extracts were washed with 0.5 N HCl, 3% $NaHCO_3$ aq and NaCl aq (80 ml) then dried and evaporated to a yellow foam (999 mg). This was subjected to prep TLC on silica gel eluting with PhMe–EtOAc (4:1) to give **11** as a pale yellow foam solvated with EtOAc (0.25 mol) (408 mg, 39%), $[\alpha]_D$ +75° ($CHCl_3$), λ_{max} 259 nm (ε 5840) [lit.[12] give IR and PMR values only; lit.[13] give no spectral data or physical constants], ν_{max} ($CHBr_3$) 3426 (NH), 1770 (azetidin-2-one), 1720 (CO_2R), 1690 and 1496 cm^{-1} (CONH), δ 2.05 (s; Me), 3.40 (s; C_2-H_2), 3.46 (s; OMe), 3.62 (s; CH_2CO), 5.15 (s; C_6-H), 6.92 (s; C<u>H</u>Ph_2), 7.2–7.7 (m; Ph_2 and P<u>h</u>CH_2) 9.46 (s; NH), with signals at δ 1.22, 2.02 and 4.09 indicating the presence of EtOAc (0.25 mol). [Found: C, 67.2; H, 5.4; N, 4.9; S, 5.8. $C_{30}H_{28}N_2O_5S \cdot 0.25\,CH_3CO_2C_2H_5$ (550.6) requires: C, 67.6; H, 5.5; N, 5.1; S, 5.8%.]

Diphenyl (1S,6R,7R) - 7 - *formamido* - 3 - *methylceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide* **7a**. Peracetic acid soln (5.9 ml, 14.7 mmol) was added to a stirred soln of **4a** (6.0 g, 14.7 mmol) in 1,2-dichloroethane (200 ml). After 30 min the reaction soln was washed with water (100 ml) and 3% $NaHCO_3$ aq (50 ml), dried and diluted to 400 ml with 1,2-dichloroethane. 50 ml of this soln was evaporated to give **7a** as a white crystalline solid (732 mg, 94%). Recrystallisation of a small portion of this material from acetonitrile provided an analytical sample, m.p. 190.5–191°, $[\alpha]_D$ +63°, λ_{max} 266 nm (ε 8360), ν_{max} 3380 and 3330 (NH), 1790 (azetidin-2-one), 1714 (CO_2R), 1680, 1660 and 1520 (CONH) and 1034 cm^{-1} (S → O), δ 2.07 (s; Me), 3.67 and 3.90 (ABq, J = 20; C_2-H_2), 4.99 (d, J = 5; C_6-H), 5.99 (dd, J = 5, 9; C_7-H), 6.96 (s; C<u>H</u>Ph_2), 7.2–7.7 (m; Ph_2), 8.19 (s; CHO), 8.38 (d, J = 9; NH). [Found: C, 62.0; H, 4.7; N, 6.7; S, 7.6. $C_{22}H_{20}N_2O_5S$ (424.5) requires C, 62.25; H, 4.75; N, 6.6; S, 7.55%.]

Diphenylmethyl (1S,6R,7R) - 3 - *bromomethyl* - 7 - *formamidoceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide* **7b**. The remainder of the soln of **7a** (*ca* 12.1 mmol) in 1,2-dichloromethane (350 ml) described above was cooled to −10° and stirred with a soln of NaOAc (4.84 g, 59 mmol) in water (25 ml) (adjusted to pH 7 with HOAc) and DBDMH (2.7 g, 9.65 mmol). The mixture was illuminated for 40 min with a Hanovia 125 W medium pressure Hg arc then washed with $Na_2S_2O_5$ aq (200 ml) and water (100 ml), dried and evaporated to give a residue which was treated with EtOAc–ether to give **7b** in 2 crops (total 3.8 g, 60%), m.p. 162–167°. Recrystallisation from acetone–ether gave white prisms, m.p. 169.5–170°, $[\alpha]_D$ −14°, λ_{max} (MeOH) 278 nm (ε 8770), ν_{max} 3280 (NH), 1772 (azetidin-2-one), 1710 (CO_2R), 1654 and 1510 (CONH) and 1020 cm^{-1} (S → O), δ 3.80 and 4.05 (AB-q, J = 18; C_2-H_2), 4.43 and 4.62 (AB-q, J = 11; CH_2Br), 5.06 (d, J = 5; C_6-H), 6.09 (dd, J = 5, 9; C_7-H), 7.02 (s; C<u>H</u>Ph_2), 7.2–7.7 (m; Ph_2), 8.21 (s; CHO), 8.48 (d, J = 9; NH). [Found: C, 52.4; H, 3.8; Br, 15.9; N, 5.2; S, 6.4. $C_{22}H_{19}BrN_2O_5S$ (521.4) requires C, 52.5; H, 3.8; Br, 15.9; N, 5.6; S, 6.4%.]

Diphenylmethyl (6R,7R) - 3 - *bromomethyl* - 7 - *formamidoceph* - 3 - *em* - 4 - *carboxylate* **4b**. A soln of PBr_3 (4.75 ml, 50 mmol) in CH_2Cl_2 (100 ml) was added over 15 min to a stirred suspension of **7b** (10.0 g, 20 mmol) in CH_2Cl_2 (400 ml) at −20°. The mixture was stirred for 45 min then $NaHCO_3$ (10.5 g, 125 mmol) was added followed by water (300 ml) at such a rate that the temp did not rise above 0°. The layers were separated and the aqueous portion extracted with further CH_2Cl_2 (100 ml). The combined extracts were dried, treated with charcoal, filtered and evaporated to low volume. Addition of excess petroleum ether precipitated **4b** as a white amorphous solid (7.48 g, 77%), $[\alpha]_D$ −20° ($CHCl_3$), λ_{max} 269 nm (ε 7470), ν_{max} ($CHBr_3$) 3380 (NH), 1790 (azetidin-2-one), 1724 (CO_2R), 1700 and 1502 (CONH) and 1020 cm^{-1} (S → O), δ ($CDCl_3$) 3.38 and 3.75 (AB-q, J = 18, C_2-H_2), 4.30 (s, CH_2Br), 5.01 (d, J = 5; C_6-H), 5.90 (dd, J = 5, 9; C_7-H), 6.57 (d, 9; NH), 7.00 (s; C<u>H</u>Ph_2), 7.37 (s; Ph_2), 8.22 (s; CHO) together with a singlet at δ 5.30 corresponding to CH_2Cl_2 (0.25 mol). This material was used directly in the next stage without further purification.

Diphenyl (1R,6R,7S) *and* (1S,6R,7S) - 3 - *bromomethyl* - 7 - *formamido* - 7 - *methoxyceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxides* **6b** *and* **2b**. A soln of **4b** (14.32 g, 29.4 mmol) in dry THF (80 ml) at −70° was added over 2 min to a stirred soln of LiOMe (1.78 g, 47 mmol) in MeOH (90 ml) and THF (500 ml) at −70° under dry N_2. t-Butylhypochlorite (4.66 ml, 39.1 mmol) was added and after 4 min the soln was added to a stirred mixture of EtOAc (750 ml) and NH_4Cl aq (containing some $Na_2S_2O_5$) (750 ml). The layers were separated and the organic phase washed with NaCl aq and dried to give a crude soln of *diphenylmethyl* (6R,7S) - 3 - *bromomethyl* - 7 - *formamido* - 7 - *methoxyceph* - 3 - *em* - 4 - *carboxylate* **5b**. This was cooled to −20° and treated with 90% *m*-chloroperbenzoic acid (5.83 g, 30 mmol). The mixture was stirred for 5 min then allowed to warm to room temp over 1 hr, washed with $NaHCO_3$ aq and NaCl aq (300 ml of each), then dried and evaporated to a foam which crystallised from CH_2Cl_2–ether to afford the 1S-oxide **2b** as white prisms (5.18 g, 33%), m.p. 148–150°, $[\alpha]_D$ +178° (*c* 0.11; $CHCl_3$), λ_{max} 285 nm (ε 9700), ν_{max} ($CHBr_3$) 3430 (NH), 1790 (azetidin-2-one), 1724 (CO_2R), 1694 and 1486 (CONH) and 1050 cm^{-1} (S → O), δ ($CDCl_3$) 3.47 (s; OMe), 3.36 and 3.68 (AB-q, J = 18; C_2-H_2), 4.10 and 4.50 (AB-q, J = 11; CH_2Br), 4.68 (s; C_6-H), 6.99 (s; C<u>H</u>Ph_2), 7.2–7.6 (m; Ph_2), 7.74 (s; NH), 8.34 (s; CHO). [Found: C, 51.6; H, 4.0; Br, 14.6; N, 5.1; S, 6.1. $C_{23}H_{21}BrN_2O_6S$ (533.4) requires: C, 51.8; H, 4.0; Br, 15.0; N, 5.3; S, 6.0%.] The liquors were purified by prep TLC on silica gel, eluting with CH_2Cl_2–Me_2CO (2:1) to give the 1R-oxide **6b** as an amorphous solid (2.67 g, 17%), m.p. 87–94°, $[\alpha]_D$ −198° (*c* 0.14; $CHCl_3$), λ_{max} 280 nm (ε 4900), ν_{max} ($CHBr_3$) 3420 (NH), 1790 (azetidin-2-one), 1720 (CO_2R), 1692 and 1490 (CONH) and 1042 cm^{-1} (S → O), δ ($CDCl_3$) 3.51 (s; OMe), 3.63 and 4.09 (AB-q, J = 18; C_2-H_2), 4.38 and 4.55 (AB-q, J = 10; CH_2Br), 4.56 (s; C_6-H), 6.99 (s; C<u>H</u>Ph_2), 7.2–7.7 (m; Ph_2 and NH), 8.20 and 8.30 (s, rotamers; CHO). [Found: C, 50.9; H, 4.1; Br, 14.0; N, 4.85; S, 5.95. $C_{23}H_{21}BrN_2O_6S \cdot 0.5\,H_2O$ (542.4) requires C, 50.9; H, 4.1; Br, 14.7; N, 5.1; S, 5.9%.]

Diphenylmethyl (1S,6R,7S) - 7 - *amino* - 3 - *bromomethyl* - 7 - *methoxyceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide hydrobromide* **12**. Compound **2b** (1.60 g, 3 mmol) was added portionwise to a freshly prepared soln of PBr_3 (0.74 ml, 7.8 mmol) in MeOH (22 ml) stirred at 0°. The mixture was stirred for 2 min then ether (75 ml) and after a further 1 hr petroleum ether (32 ml) were added. The precipitated solid was collected to give **12** (1.59 g, 90%), m.p. 95° (dec) ν_{max} *ca* 2600 (NH_3^+), 1784 (azetidin-2-one), 1724 (CO_2R) and 1000 cm^{-1} (S → O). [Found: C, 42.8; H, 3.9; Br, 25.95; N, 4.3; S, 5.4. $C_{22}H_{22}N_2Br_2O_5S \cdot 1.5\,H_2O$ (613.3) requires: C, 43.1; H, 4.2; Br, 26.1; N, 4.6; S, 5.2%.]

Diphenylmethyl (1S,6R,7S) - 7 - *formamido* - 7 - *methoxy* - 3 - (1 - *methyltetrazol* - 5 - *ylthiomethyl*)*ceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide* **2c**. A mixture of **2b** (500 mg, 0.93 mmol),

5-mercapto-1-methyltetrazole (120 mg, 1.43 mmol) and $NaHCO_3$ (83 mg, 1 mmol) in DMF (2 ml) was stirred for 1 hr then diluted with EtOAc (200 ml) and successively washed with $NaHCO_3$ aq (100 ml), water (2 × 200 ml) and NaCl aq (100 ml). The soln was dried and evaporated and the residue chromatographed on silica gel (20 g) using CH_2Cl_2–acetone to give a foam (546 mg) which was triturated with ether to give **2c** (466 mg 88%), m.p. 111–115°, $[\alpha]_D$ +74° (*c* 0.18; $CHCl_3$), λ_{max} 281.5 nm (ε 9770), ν_{max} ($CHBr_3$) 3370 (NH), 1780 (azetidin-2-one), 1710 (CO_2R), 1690 and 1480 (CONH) and 1050 cm^{-1} (S → O), δ ($CDCl_3$) 3.50 (s; OMe), 3.80 (s; NMe), 3.50 and 3.93 (AB-q, J = 18; C_2-H_2), 4.14 and 4.46 (AB-q, J = 14; CH_2S), 4.72 (s; C_6-H), 7.00 (s; C<u>H</u>Ph_2), 7.2–7.7 (m; Ph_2), 7.88 (s; NH), 8.36 (s; CHO). [Found: C, 52.2; H, 4.3; N, 14.2; S, 11.1. $C_{25}H_{24}N_6O_6S_2 \cdot 0.5\,H_2O$ (577.7) requires: C, 52.0; H, 4.3; N, 14.55; S, 11.1%.]

Similar treatment of **6b** afforded *diphenylmethyl* (1R,6R,7S)-7-*formamido*-7-*methoxy*-3-(1-*methyltetrazol*-5-*ylthiomethyl*)*ceph*-3-*em*-4-*carboxylate* 1-*oxide* **6c** (63%), m.p. 95–105°, $[\alpha]_D$ −135° (*c* 0.10), λ_{max} 275 nm (ε 5970), ν_{max} ($CHBr_3$) 3450 (NH), 1794 (azetidin-2-one), 1720 (CO_2R), 1696 and 1486 (CONH), and 1044 cm^{-1} (S → O), δ 3.53 (s; OMe), 3.90 (s; NMe), 3.85 and 4.20 (AB-q, J = 18 Hz; C_2-H_2), 4.64 (s; C_6-H); 4.18 and 4.72 (AB-q, J = 14; CH_2S), 6.94 (s; C<u>H</u>Ph_2), 7.2–7.7 (m; Ph_2), 8.26 (s; CHO), 9.80 (s; NH). [Found: C, 51.9; H, 4.2; N, 14.5; S, 11.1%.]

Diphenylmethyl (6R,7S)-7-*formamidoceph*-7-*methoxy*-3-(1-*methyltetrazol*-5-*ylthiomethyl*)*ceph*-3-*em*-4-*carboxylate* **5c**. KI (120 mg, 0.73 mmol) then acetyl chloride (30 mg, 0.38 mmol) were added to stirred soln of **2c** in DMF (1 ml) at 0°. The mixture was stirred for 1½ hr then diluted with CH_2Cl_2 and washed with $Na_2S_2O_5$ aq, dried and evaporated to a gum. This was precipitated from acetone/petroleum ether to give **5c** as an off-white solid (55 mg, 57%), m.p. 86–88°, $[\alpha]_D$ −34° (*c* 0.08; $CHCl_3$), λ_{max} 269.5 nm (ε 7230), ν_{max} ($CHBr_3$) 3450 and 3400 (NH rotamers), 1780 (azetidin-2-one), and 1710 cm^{-1} (CO_2R and CONH), δ ($CDCl_3$) 3.55 and 3.61 (s, rotamers; OMe), *ca* 3.57 (partly obscured; C_2-H_2), 3,86 (s; NMe), 4.30 and 4.52, 4.30 and 4.66 (AB-q, J = 14, rotamers; CH_2S), 4.99 and 5.09 (s, rotamers; C_6-H), 6.97 (s; C<u>H</u>Ph_2), 7.2–7.7 (m; Ph_2) 8.38, 8.54 and 8.66 (s, rotamers; NH and CHO). [Found: C, 54.1; H, 4.4; N, 14.8; S, 11.6. $C_{25}H_{24}N_6O_5S_2$ (552.6) requires: C, 54.3; H, 4.4; N, 15.2; S, 11.6%.]

A similar reduction of the 1R-oxide **6c** gave **5c** (73%), m.p. 84–86°, identical with the material described above.

Diphenylmethyl (1S,6R,7S)-3-*bromomethyl*-7-*methoxy*-7-(*thien*-2-*yl*)*acetamidoceph*-3-*em*-4-*carboxylate* 1-*oxide* **8b**. (Thien-2-yl)acetyl chloride (80 mg, 0.5 mmol) and propylene oxide (0.5 ml) were added to a stirred suspension of **12** (270 mg, 0.44 mmol) and MgO (40 mg, 1.0 mmol) in CH_2Cl_2 (10 ml) at 0°. The mixture was stirred for 5½ hr; filtered and evaporated. The residue was purified by prep TLC on silica gel, eluting with CH_2Cl_2–acetone (3:2) to give **8b** as an off-white solid, m.p. 104–106° (dec), $[\alpha]_D$ +101.5° (*c* 0.15; $CHCl_3$) λ_{max} 283 nm (ε 9250) ν_{max} ($CHBr_3$) 3360 (NH), 1780 (azetidin-2-one), 1718 (CO_2R) and 1678 and 1490 cm^{-1} (CONH), δ ($CDCl_3$) 3.38 (s; OMe), 3.33 and 3.57 (AB-q, J = 18; C_2-H_2), 3.84 (s; CH_2CO), 4.04 and 4.46 (AB-q, J = 10; CH_2Br), 4.70 (s; C_6-H), 6.9–7.6 (m, Ph_2CH, NH and C_4H_3S). [Found: C, 53.1; H, 3.9; Br, 12.5; N, 4.5; S, 9.5. $C_{28}H_{25}BrN_2O_6S_2$ (629.55) requires: C, 53.4; H, 4.0; Br, 12.6; N, 4.45; S, 10.0%.]

Diphenylmethyl (1S,6R,7S)-7-*methoxy*-3-(1-*methyltetrazol*-5-*ylthiomethyl*)-7-(*thien*-2-*yl*)*acetamidoceph*-3-*em*-4-*carboxylate* 1-*oxide* **8c**. A soln of **8b** (103 mg, 0.16 mmol) in DMF (0.5 ml) was treated with 5-mercapto-1-methyltetrazole (32 mg, 0.28 mmol) and $NaHCO_3$ (30 mg, 0.36 mmol). The mixture was stirred for 1 hr then diluted with EtOAc and successively washed with sat $NaHCO_3$ aq, 2 N HCl and NaCl aq then dried and evaporated to give a gum. This was purified by prep TLC on silica gel, eluting with CH_2Cl_2–acetone (4:1) to give **8c** as a white solid (70 mg, 64%), m.p. 103–112°, $[\alpha]_D$ +4° (*c* 0.15; $CHCl_3$), λ_{max} 282 nm (ε 9690), ν_{max} ($CHBr_3$) 3380 (NH), 1782 (azetidin-2-one), 1714 (CO_2R), 1680 and 1492 (CONH) and 1052 cm^{-1} (S → O), δ ($CDCl_3$) 3.42 (s; OMe), 3.49 and 3.84 (AB-q partly obscured, J = 18; C_2-H_2), 3.75 (s; NMe), 3.85 (s; CH_2CO), 4.10 and 4.38 (AB-q, J = 14; C_3-CH_2), 4.76 (s; C_6-H), 6.95–7.6 (m; Ph_2CH and C_4H_3S), 7.64 (s; NH). [Found: C, 53.5; H, 4.15; N, 12.3; S, 14.3. $C_{30}H_{28}N_6O_5S_3 \cdot 0.5\,H_2O$ (673.8) requires: C, 53.5; H, 4.3; N, 12.5; S, 14.3%.]

Diphenylmethyl (6R,7S)-7-*methoxy*-3-(1-*methyltetrazol*-5-*ylthiomethyl*)-7-(*thien*-2-*yl*)*acetamidoceph*-3-*em*-4-*carboxylate* **13**. KI (75 mg, 0.45 mmol) then acetyl chloride (0.02 ml, 0.23 mmol) were added to a stirred soln of **8c** (75 mg, 0.11 mmol) in DMF (0.5 ml) at 0°. The mixture was stirred for 1½ hr then diluted with EtOAc and successively washed with water containing NH_4Cl and $Na_2S_2O_5$, sat $NaHCO_3$ aq, 2 N HCl and NaCl aq, dried and evaporated to a gum. This was purified by prep TLC on silica gel, eluting with CH_2Cl_2–acetone (9:1) to give **13** as a white solid (44 mg, 61%), m.p. 82–84°, $[\alpha]_D$ −35° (*c* 0.12, $CHCl_3$), λ_{max} 275 nm (ε 7310), ν_{max} ($CHBr_3$) 3360 (NH), 1762 (azetidin-2-one), 1710 (CO_2R), 1690 and 1488 cm^{-1} (CONH), δ ($CDCl_3$) 3.50 (s; OMe), 3.57 (s; C_2-H_2), 3.83 (s; NMe), 3.88 (s; CH_2CO), 4.24 and 4.50 (AB-q, J = 13; C_3-CH_2), 5.04 (s; C_6-H), 6.70 (s; NH), 6.8–7.6 (m; Ph_2CH and C_4H_3S). [Found: C, 55.2; H, 4.3; N, 12.7; S, 14.8. $C_{30}H_{28}N_6O_5S_3$ (648.8) requires: C, 55.5; H, 4.3; N, 12.95; S, 15.0%.]

(6R,7S)-7-*Methoxy*-3-(1-*methyltetrazol*-5-*ylthiomethyl*)-7-(*thien*-2-*yl*)-*acetamidoceph*-3-*em*-4-*carboxylic acid* **14**. The ester **13** (324 mg, 0.5 mmol) was dissolved in a mixture of CF_3CO_2H (1.2 ml) and anisole (0.4 ml) and after 4 min the solvents were removed *in vacuo* and the residue partitioned between EtOAc (25 ml) and 3% $NaHCO_3$ aq (30 ml). The aqueous portion was extracted with further EtOAc (20 ml) then covered with EtOAc (50 ml) and acidified to pH 2 with conc HCl. The organic layer was washed with H_2O and NaCl aq (25 ml each) then dried and evaporated to dryness. The residue was dissolved in acetone (25 ml), treated with charcoal and filtered through kieselguhr. The filtrate was evaporated to a foam which was dissolved in EtOAc. The solution was treated with petroleum ether to give **14** as a white amorphous powder (275 mg, 73%), λ_{max} (0.1 M pH 6 phosphate buffer) 236 and 265 nm (ε 15,060, 9350), ν_{max} 3500 (H_2O), 3290 (NH), 1772 (azetidin-2-one), 1700 (CO_2H) and 1680 and 1520 cm^{-1} (CONH), δ 4.40 (s; OMe), 4.46 and 4.76 (AB-q, J = 18; C_2-H_2), 4.84 (s; CH_2CO), 4.95 (s; NMe), 4.22 and 4.41 (AB-q, J = 14; C_3-CH_2), 5.11 (s; C_6-H), 7.00 and 7.40 (two m; C_4H_3S), 9.49 (s; NH). [Found: C, 41.0; H, 3.85; N, 16.3; S, 18.9. $C_{17}H_{18}N_6O_5S_3 \cdot H_2O$ (500.6) requires: C, 40.8; H, 4.0; N, 16.8; S, 19.2%.]

Methyl (1R,6R,7R)-3-*acetoxymethyl*-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate*, 1-*oxide* (Table 1). A soln of iodobenzene dichloride (1.62 g, 5.0 mmol) in pyridine (10 ml) was added over 10 min to a stirred soln of methyl (6R,7R)-3-acetoxymethyl-7-phenylacetamidoceph-3-em-4-carboxylate[20] (0.98 g, 2.42 mmol) in pyridine–water (4:1, 25 ml) at −10° in the absence of light. The mixture was stirred for 1 hr at −10° then diluted with CH_2Cl_2 (50 ml) and successively washed with 2 N HCl, water, 3% $NaHCO_3$ aq and NaCl aq (2 × 125 ml each), dried and evaporated to brown solid (589 mg), A portion (338 mg) was subjected to prep TLC on silica gel, eluting with CH_2Cl_2–acetone (4:1). The less polar component proved to be methyl (1S,6R,7R)-3-acetoxymethyl-7-phenylacetamidoceph-3-em-4-carboxylate, 1-oxide (78 mg, 13.3%), as a white solid m.p. 223°, λ_{max} 268 nm (ε 8410) [lit.[21] m.p. 222–225°, λ_{max} 267 nm (ε 8800)]. The more polar component proved to be the title 1R-oxide (180 mg, 30.8%), m.p. 166–168° which crystallised from ethanol–petroleum ether (9:1) to give off-white prisms (107 mg), m.p. 173–174.5°, $[\alpha]_D$ −150°, λ_{max} 268 nm (ε 6310), ν_{max} 3290 (NH), 1777 (azetidin-2-one), 1730 ($COCH_3$), 1720 (CO_2CH_3), 1647 and 1515 (CONH) and 1052 cm^{-1} (S → O), δ 2.05 (s; $OCOCH_3$), 3.56 (s; CH_2CO), 3.60 and 4.22 (AB-q, J = 18; C_2-H_2), 3.78 (s; CO_2CH_3), 4.62 and 5.00 (AB-q, J = 14; C<u>H</u>$_2$$OCOCH_3$), 4.82 (d, J = 5; C_6-H), 5.62 (dd, J = 5, 8, C_7-H), 7.21 (s; Ph), 9.16 (d, J = 8; NH). [Found: C, 54.1; H, 5.0; N, 6.6; S, 7.5. $C_{19}H_{20}N_2O_7S$ (420.4) requires: C, 54.3; H, 4.8; N, 6.7; S, 7.6%.]

2,2,2-*Trichloroethyl* (1R,6R,7R,2′R)-3-*methyl*-7-(2′-*phenyl*-

2' - [2,2,2 - *trichloroethoxycarbonylamino*]*acetamido*)*ceph* - 3 - *em* - 4 - *carboxylate*, 1 - *oxide* (Table 1). t-Butyl hypochlorite (2.2 ml, 19 mmol) was added to a stirred soln of 2,2,2-trichloroethyl (6R,7R,2'R) - 3 - methyl - 7 - (2' - phenyl - 2' - [2,2,2 - trichloroethoxycarbonylamino]acetamido)ceph - 3 - em - 4- carboxylate[22] (7.5 g, 11.2 mmol) in pyridine (200 ml) containing water (5.2 ml) at −40°. The mixture was stirred at −40° for 2 min then 2 N SO_2 aq (75 ml) was added and the mixture poured into 20% H_3PO_4 aq (1 l). The mixture was extracted with EtOAc (3 × 300 ml) and the combined extracts washed with sat $NaHCO_3$ aq (2 × 400 ml) and water (2 × 400 ml) then dried and evaporated to a brown foam which crystallised from hot acetone (20 ml) to give the title 1R-oxide as a white crystalline solid (3.7 g, 48.6%), m.p. 212–214°, $[\alpha]_D$ −132°, λ_{max} 265 nm (ε 3850), ν_{max} 3390 and 3240 (NH), 1760 (azetidin-2-one), 1745 (ester), 1732 ($NHCO_2R$), 1680 and 1510 (CONH) and 1040 cm^{-1} (S → O), δ 2.18 (s; Me), 3.66 and 4.10 (AB-q, J = 17; C_2-H_2), 4.72 (d, J = 5; C_6-H), 4.83 and 5.06 (s; $CO_2CH_2CCl_3$), 5.38 (d, J = 8; PhC<u>H</u>), 5.60 (dd, J = 5, 8; C_7-H), 7.2–7.6 (m; Ph), 8.47 (d, J = 8; $NHCO_2R$), 9.37 (d, J = 8; CONH). [Found: C, 36.8; H, 2.8; Cl, 30.5; N, 5.8; S, 4.8. $C_{21}H_{19}Cl_6N_3O_7S \cdot 0.5\,H_2O$ (679.2) requires: C, 37.1; H, 3.0; Cl, 31.3; N, 6.2; S, 4.7%.]

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