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PHOTOINITIATED BROMINATION OF 3-METHYLCEPH-3-EM 1S-OXIDE ESTERS

A CONVENIENT SYNTHESIS OF 3-SUBSTITUTED CEPHALOSPORINS FROM PENICILLINS

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Abstract—Photoinitiated bromination of 3-methyl-ceph-3-em 1S-oxide esters **2**, readily obtained from penicillins, gave the corresponding 3-bromomethyl derivatives **5**. The 3-bromomethyl 1S-oxides **5b** and **5c** were converted into the salts **12** and **13** of the 3-methylthiomethyl amine **11**, which could be transformed into compounds with useful antibacterial activity.

3-Methylcephems **1** are readily available by rearrangement of the corresponding penicillin sulphoxide esters.[1-3] We report the conversion of these compounds into 3-bromomethyl-ceph-3-em 1S-oxide derivatives **2**, which have proved useful for the preparation of a wide range of 3-substituted cephalosporins.[4-7]

Direct halogenation of the ceph-3-em esters **1a** and **1b** under a variety of conditions, was unsuccessful[8] and we wished to avoid the need for prior isomerisation of the endocyclic double bond to facilitate the required functionalisation.[9]

Instead we studied the bromination of the corresponding sulphoxides. Oxidation of the esters **1a**, **1b** with peracetic acid gave the respective 1S-oxide derivatives **2a**[10], **2b**[11] in 60–70% yield, accompanied by a minor amount (< 5%) of the 1R-oxide isomer **3a**, **3b**.[11] Oxidation of **1a** with *m*-chloroperbenzoic acid gave the sulphone **4a** in 8% yield as a minor product. The formation of minor amounts of 1R-oxides in the above reactions can be attributed to the existence of a weaker "reagent approach control" effect than that pertaining in comparable penicillins.[12] The sulphone **4a** arises by further oxidation of initially formed 1R-oxide **3a** since we have observed that ceph-3-em 1R-oxides are readily oxidised to sulphones under mild conditions, whereas more forcing conditions (e.g. elevated temp) are necessary to effect further oxidation of ceph-3-em 1S-oxides.[13]

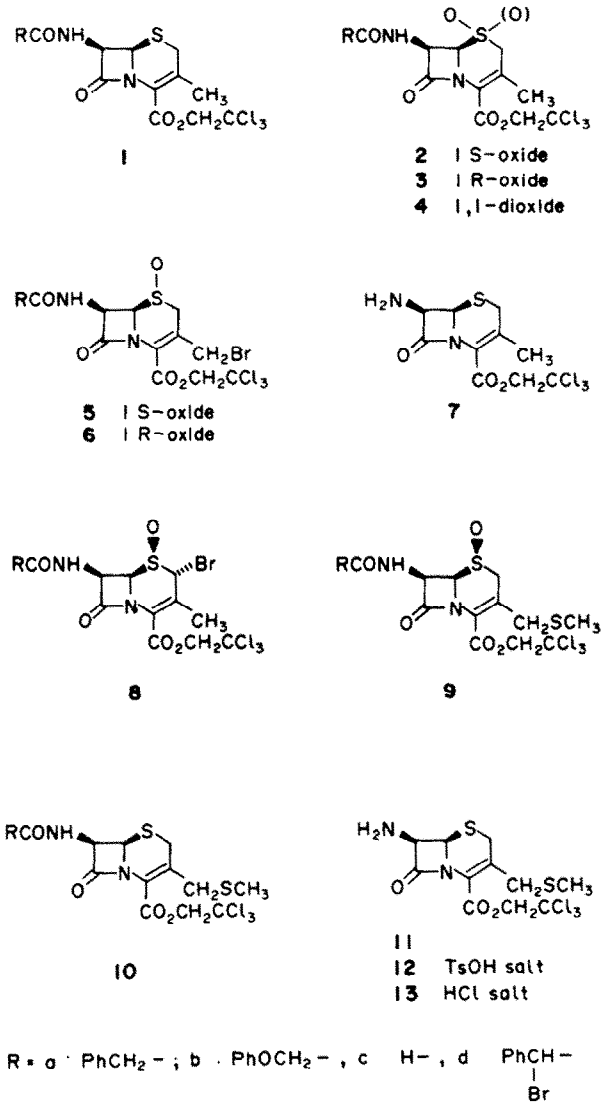
Photoinitiated brominations of the 1S-oxide ester **2a** with N-bromosuccinimide (NBS) in refluxing chloroform gave the 3-bromomethyl derivative **5a** in yields of *ca* 30%. Also isolated were small amounts (1–2% of each) of the products **2d** and **5d** (as *ca* 1:1 mixtures of diastereomers) resulting from attack at the benzylic position of the phenylacetamido side-chain.[14] A sample of **2d** (also a *ca* 1:1 mixture of diastereomers) was prepared by acylation of the amine ester **7** with RS-2-bromophenylacetic acid/N,N'-dicyclohexylcarbodiimide followed by oxidation with peracetic acid. Photoiniated bromination of **2d** with NBS and UV light gave the 3-bromomethyl derivative **5d** contaminated with *ca* 10% of starting material.

In contrast, photoinitiated bromination of **2a** with NBS in refluxing benzene gave a cleaner reaction and a higher yield of the required product **5a** than for the corresponding reactions using chloroform as solvent.[15] In addition the dibromo compound **5d** was formed (*ca* 5%), together with a less-polar new product which proved to be the 2-bromo derivative **8a** (*ca* 25% yield). This material was assigned the 2α-(i.e. 2R-)-configuration by PMR spectroscopy: thus coupling (1.5 Hz) between the axial C_6- and $C_{2\alpha}$-protons[12,16] which occurs in the spectrum of the starting 2-unsubstituted compound **2a** is not found in the spectrum of the 2-bromo compound **8a**. Debromination of **8a** by treatment with Zn in tetrahydrofuran containing acetic acid gave **2a** in 28% yield. It is likely that **8a** arised by an ionic mechanism.[17] In accord with this hypothesis treatment of **2a** with sodium bistrimethylsilylamide followed by bromine gave the 2α-bromo compound **8a** in 37% yield.

Photobromination of **2a** with NBS in 1,2-dichloroethane at −20° gave **5a** (55%) and **5d** (11%); only a trace amount of the 2α-bromo derivative **8a** was detected by TLC. Reaction of the 7β-phenoxyacetamido derivative **2b** under similar conditions gave the 3-bromomethyl analogue **5b** in 61% yield.

Archer and DeMarco have shown[18] that penicillin 1S-oxide esters undergo partial stereomutation upon photolysis. We were unable to detect any such isomerisation during photobromination of the 1S-oxides **2**. A reference sample of the 3-bromomethyl 1R-oxide **6b** was prepared by reduction of the 1S-oxide **5b** with phosphorus tribromide[11] (50% yield) followed by re-oxidation with NBS[19] in aqueous acetic acid containing potassium acetate (28% yield).

Replacement of the Br atom of 3-bromomethyl ceph-3-em 1S-oxides proceeds readily, as illustrated by the reaction of **5b** with methanethiol in N,N-dimethylformamide (DMF) containing triethylamine (1 molar equiv) to give the 3-methylthiomethyl derivative **9b** in 62% yield. Performing the displacement reaction on the 3-bromomethyl sulphoxide ensures that the double-bond in the cephem remains in the desired 3,4-position. Conversion of **9b** into **11**, an intermediate to biologically useful compounds,[4] was accomplished by the following sequence of reactions. Reduction of the sulphoxide **9b** with KI/AcCl[20] in DMF gave the corresponding sulphide **10b** in 95% yield. Removal of the phenoxyacetamido side-chain of **10b** by the imidoyl-halide procedure[21] gave the amino ester **11** isolated as its crystalline toluene-4-sulphonate salt **12** in 72% yield.



Scheme 1.

Simpler derivatives of the amino ester **7** can also be functionalised in a similar manner. Thus reaction of **7** with ethyl formate at reflux followed by oxidation with peracetic acid gave the N-formamido 1S-oxide **2c** in 78% yield. No minor products attributable to the corresponding 1R-oxide or 1,1-dioxide were observed, which suggests that the directing influence of the formamido side-chain is stronger than that of those described above and that the strength of the H-bond between the 1S-oxide and the amide proton more closely resembles the penicillin situation.[14]

Photoinitiated bromination of **2c** in 1,2-dichloroethane at −20° using NBS or 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and a trace of water,[23] gave the 3-bromomethyl derivative **5c** in *ca* 60% yield. Reaction of **5c** with methanethiol gave an 85% yield of the 3-methylthiomethyl derivative **9c**. Reduction of **9c** with KI/AcCl in glacial acetic acid afforded the corresponding sulphide **10c** in 61% yield. Removal of the N-formyl group was conveniently effected[24] by adding phosphorus oxychloride to a suspension of **10c** in methanol, whereupon the amine hydrochloride salt **13** crystallised in 88% yield. By utilising DMF as solvent for both the displacement and reduction steps and by performing the deformylation reaction on the crude sulphide **10c**, the hydrochloride salt **13** was obtained in 81% overall yield from the 3-bromomethyl derivative **5c**. Furthermore, by using 1,2-dichloroethane as solvent and formic acid/acetic anhydride rather than ethyl formate for the N-formylation step, the 3-bromomethyl derivative **5c** could be obtained in an overall yield of *ca* 50% from the 7β-amine **7** without isolation of intermediates.

Our route to 3-bromomethyl ceph-3-ems complements other procedures used to convert penicillins into 3-functionalised cephalosporins. Ishimaru and Imamoto[25] utilised the NBS bromination of a secopenicillin intermediate whilst Kukolja,[26] Koppel[27] and colleagues trapped with bromine the allylic anion generated from a 3-*exo*-methylene-cepham.

EXPERIMENTAL

Unless stated otherwise 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% concentration. UV spectra were obtained 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 HA100 (100 MHz). Coupling constants are quoted in Hz. Solns were dried over $MgSO_4$. Silica gel for column chromatography refers to Merck (7734) (type 60). Kieselgel G was Merck TLC grade (7731) (type 60). Peracetic acid was a 30–40% soln in AcOH. The Hanovia 125 W Hg arc was placed in a Pyrex tube with its own cooling jacket, restricting the light to ≥ 300 nm.

2,2,2-Trichloroethyl (1*S*, 6*R*, 7*R*) - 3 - *methyl* - 7 - *phenylacetamido* - *ceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide* **2a**

By oxidation of **1a**[2] *with peracetic acid.* A soln of **1a** (8.36 g, 18 mmol) in CH_2Cl_2 (100 ml) was cooled to 5° and stirred with peracetic acid soln (20 ml, 26 mmole) for 10 min. H_2O_2 soln (4 ml, 3.6 mmol) was added and stirring was continued for 30 min. The soln was washed twice each with water and 3% $NaHCO_3$aq, and water, and dried. Evaporation to a gel and crystallisation from MeOH gave **2a** (2.8 g, 32.4%) as white crystals, m.p. 199–199.5°, $[\alpha]_D$ + 97° ($CHCl_3$). Concentration of the liquors gave a second crop (0.82 g, 9.5%), m.p. 195–197°, $[\alpha]_D$ + 105° ($CHCl_3$). The filtrate was evaporated and the residue was chromatographed on Kieselgel G (150 g, CH_2Cl_2–acetone) to give impure **1a** (0.56 g, 7%), followed by **2a** (2.29 g, 27.5%), m.p. 190–198°, $[\alpha]_D$ + 105.5° ($CHCl_3$), part of which was crystallised from MeOH to give white needles, m.p. 200.5–202° (dec), $[\alpha]_D$ + 108° ($CHCl_3$), λ_{max} 269 nm (ε 7450), ν_{max} ($CHBr_3$) 3400 (NH), 1800 (azetidin-2-one), 1740 (CO_2R), 1680 and 1510 (CONH) and 1043 cm^{-1} (S→O), δ ($CDCl_3$) 2.18 (s; Me), 3.18, 3.61 (AB-q, J18; C_7–H_2), 3.60 (s; CH_2Ph), 4.48 (d, J4.5; C_6–H), 4.77, 5.00 (AB-q, J12; CH_2CCl_3), 5.99 (dd, J4.5, 10; C_7–H), 6.84 (d, J10; NH), 7.29 (s; Ph) [Found: C, 45.3; H, 3.5; Cl, 22.0; N, 5.6; S, 6.5. $C_{18}H_{17}Cl_3N_2O_5S$ (479.8) requires: C, 45.1; H, 3.6; Cl, 22.2; N, 5.8; S, 6.7%]. Further elution gave the 1R-oxide **3a** (0.21 g, 2.4%), m.p. 168–178°, $[\alpha]_D$ − 199° ($CHCl_3$), which was crystallised from acetone to give white needles, m.p. 181–189° (dec), $[\alpha]_D$ − 237° ($CHCl_3$), λ_{max} 269 nm (ε 4,850), ν_{max} ($CHBr_3$) 1780 (azetidin-2-one), 1726 (CO_2R), 1670 and 1510 (CONH) and 1038 cm^{-1} (S→O), δ ($CDCl_3$) 2.33 (s; Me), 3.42, 4.09 (AB-q, J16.5; C_2–H_2), 3.59 (s; CH_2Ph), 4.47 (d, J4.5; C_6–H), 4.86 (s; CH_2CCl_3), 5.16 (dd, J4.5, 7.5; C_7–H), 6.97 (d, J7.5; NH), 7.28 (s; Ph) [Found: C, 45.2; H, 3.6; Cl, 21.9; N, 5.6; S, 6.6%].

By oxidation of **1a**[2] *with m-chloroperbenzoic acid.* A soln of **1a** (18.56 g, 40 mmol) in CH_2Cl_2 (200 ml) was stirred at 0–10°, and a soln of *m*-chloroperbenzoic acid (8.91 g, 4.94 mmol oxidant/g, 44 mmol) in CH_2Cl_2 (150 ml) was added over 5 min. The mixture was stirred for 15 min, washed with 3% $NaHCO_3$ aq (4 × 100 ml), combined with a CH_2Cl_2 backwash (100 ml) of the aq phases and dried. Evaporation and chromatography of the residual solid on silica gel (500 g; CH_2Cl_2–acetone) gave a white solid (1.625 g, 8.2%), m.p. 237–242°, $[\alpha]_D$ + 19°, which was crystallised from acetone to give **4a**, m.p. 241–244°, $[\alpha]_D$ + 18°, λ_{max} 266 nm (ε 9150), ν_{max} 1790 (azetidin-2-one), 1730 (CO_2R) and 1670 and 1530 cm^{-1} (CONH), δ 2.13 (s; Me), 4.37 (broad s; C_7–H_2), 3.67 (s; CH_2Ph), 5.17 (s; CH_2CCl_3), 5.40 (d, J5; C_6–H), 6.00 (dd, J5, 8.5; C_7–H), 7.35 (s; Ph), 8.78 (d, J8.5; NH) [Found: C, 43.6; H, 3.4; Cl, 21.6; N, 5.1; S, 6.4. $C_{18}H_{17}Cl_3N_2O_6S$ (495.8) requires: C, 43.6; H, 3.5; Cl, 21.5; N, 5.7; S, 6.5%]. Further elution gave **2a** (16.32 g, 85%), m.p. 193–200°, $[\alpha]_D$ + 104° ($CHCl_3$).

2,2,2-Trichloroethyl (1*S*, 6*R*, 7*R*) - 3 - *methyl* - 7 - *phenoxyacetamido* - *ceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide* **2b**[11]

A soln of **1b**[2] (4.80 g, 10 mmol) in CH_2Cl_2 (50 ml) was treated with peracetic acid soln (1.9 ml, 10 mmol) at 20–30° with stirring for 3 min. The soln was washed with water (2 × 20 ml) and 3% $NaHCO_3$aq (20 ml), dried and evaporated to a white solid (5.075 g) containing up to 5% of the 1R-oxide **3b** by TLC which was crystallised from a mixture of MeOH (50 ml) and acetone (15 ml) to give **2b** as white needles (3.10 g, 62.6%), m.p. 172–177°, $[\alpha]_D$ + 65° ($CHCl_3$). Recrystallisation from MeOH–acetone gave needles, m.p. 173–178°, $[\alpha]_D$ + 67° ($CHCl_3$) [Found: C, 43.7; H, 3.6; Cl, 21.4; N, 5.2; S, 6.6. Calc for $C_{18}H_{17}Cl_3N_2O_6S$ (495.8) C, 43.6; H, 3.5; Cl, 21.5; N, 5.7; S, 6.5%], having spectra similar to those reported.[11,12]

Photo-initiated bromination of **2a** *to give* 2,2,2-*trichloroethyl* (1*S*, 6*R*, 7*R*) - 3 - *bromomethyl* - 7 - *phenylacetamidoceph* - 3 - *em* - 4 - *carboxylate* 1-*oxide* **5a**

In refluxing chloroform. A soln of **2a** (4.80 g, 10 mmol) in dry, EtOH-free $CHCl_3$ (240 ml) was heated to reflux and illuminated by 8 × 40 W fluorescent strip-lights. NBS (1.78 gm 10 mmol) was added and the mixture was heated under reflux for 3 hr, further portions of NBS (each 445 mg, 2.5 mmol) being added after 1, 1.5, 1.75 and 2 hr. The soln was evaporated and the residue was dissolved in CH_2Cl_2–acetone (9:1; 25 ml) and chromatographed on Kieselgel G (240 g). Elution with CH_2Cl_2–acetone (9:1) gave a pale yellow crystalline solid (389 mg) which was recrystallised from acetone–ether to give a *ca* 1:1 diastereomeric mixture of 2,2,2-*trichloroethyl* (1*S*, 2′*R*, 6*R*, 7*R*)- *and* (1*S*, 2′*S*, 6*R*, 7*R*) - 3 - *bromomethyl* - 7 - (2′ - *bromophenylacetamido*)*ceph* - 3 - *em* - 4 - *carboxylate* 1-*oxide* **5d** as white needles (150 mg, 2.4%), m.p. 193–194° (dec), $[\alpha]_D$ + 21°, λ_{max} 284 nm (ε 9820), ν_{max} ($CHBr_3$) 3350 (NH), 1798 (azetidin-2-one), 1735 (CO_2R), 1672 and 1510 (CONH) and 1044 cm^{-1} (S→O), δ 3.75, 4.03 and 3.87, 4.11 (two Ab-q totalling 2H, J19; C_7–H_2), 4.51, 4.66 and 4.55, 4.71 (two Ab-q totalling 2H, J12; CH_2Br), 5.07, 5.28 (AB-q, J12; CH_2CCl_3), 5.10 (d, J4.5; C_6–H), 5.92 (dd, J4.5, 8; C_7–H), 5.99, 6.08 (two s totalling 1H; PhC**H**Br), 7.36, 7.58 (two m; Ph), 8.90 (d, J8; NH) [Found: C, 34.3; H, 2.3; N, 4.4; S, 5.3; total halogen content, 4.88 g atom/mol. $C_{18}H_{15}Br_2Cl_3N_2O_5S$ (637.6) requires: C, 33.9; H, 2.4; N, 4.4; S, 5.0%; total halogen content 5 g atom/mol]. Further elution gave a second pale yellow crystalline solid (100 mg) which was recrystallised from acetone–ether to give a *ca* 1:1 diastereomeric mixture of **2d** as white needles (41 mg, 0.7%), m.p. 201–204° (dec), $[\alpha]_D$ + 119°, λ_{max} 267.5 nm (ε 8670) [Found: C, 38.8; H, 3.0; N, 4.7; S, 5.9%; total halogen content 3.95 g atom/mol], having spectra similar to those of authentic **2d** (*vide infra*). Further elution gave **5a** as an off-white solid (1.76 g, 31.5%), m.p. 158–161° (dec), $[\alpha]_D$ + 32°, part of which was crystallised from acetone–ether (2:1) to give white crystals, m.p. 163–166°, $[\alpha]_D$ + 32°, λ_{max} 284 nm (ε 9500), ν_{max} 3290 (NH), 1776 (azetidin-2-one), 1730 (CO_2R), 1654 and 1520 (CONH) and 1030 cm^{-1} (S→O), δ 3.53, 3.74 (AB-q, J14; $PhCH_2$), 3.77, 4.05 (AB-q, J18; C_7–H_2); 4.51, 4.67 (AB-q, J10; CH_2Br), 5.02 (d, J5; C_6–H), 5.07, 5.25 (AB-q, J12; CH_2CCl_3), 5.89 (dd, J5, 8; C_7–H), 7.28 (s; Ph), 8.41 (d, J8; NH) [Found: C, 38.6; H, 2.7; N, 4.8; S, 5.8; total halogen content 3.95 g atom/mol. $C_{18}H_{16}BrCl_3N_2O_5S$ (558.7) requires: C, 38.7; H, 2.9; N, 5.0; S, 5.7%; total halogen content 4 g atom/mol].

In refluxing benzene. A soln of **2a** (5.00 g, 10.4 mmol) in benzene (500 ml) was stirred and heated to reflux and illuminated by 8 × 40 W fluorescent strip-lights. NBS (3 g, 16.85 mmol) was added and the mixture was heated under reflux for 30 min and evaporated. The residual yellow gum was dissolved in CH_2Cl_2–acetone (10:1; 10 ml) and chromatographed on Kieselgel G (150 g). Elution with CH_2Cl_2–acetone (10:1) gave a yellow semi-solid which was triturated with acetone–ether to give **5d** (0.38 g, 5.7%), m.p. 190–192° (dec), $[\alpha]_D$ + 15.3°. Evaporation of the mother liquors gave 2,2,2-*trichloroethyl* (1*R*, 2*R*, 6*R*, 7*R*) - 2 - *bromo* - 3 - *methyl* - 7 - *phenylacetamidoceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide* **8a** as a yellow foam (1.33 g, 23.2%), $[\alpha]_D$ − 121° ($CHCl_3$), λ_{max} 289 nm (ε 6600), ν_{max} ($CHBr_3$) 3400 (NH), 1808 (azetidin-2-one), 1744 (CO_2R), 1686 and 1506 (CONH) and 1050 cm^{-1} (S→O). δ ($CDCl_3$) 2.26 (s; Me), 3.59 (s; $PhCH_2$), 4.80, 4.93 (AB-q, J12; CH_2CCl_3), 5.07 (s; C_7–H), 5.11 (d, J5; C_6–H), 6.08 (dd, J5, 10; C_7–H), 6.64 (d, J10; NH), 7.28 (s; Ph). [Found: total halogen content 4.05 g atom/mol). Further elution gave **5a** as a cream solid (2.40 g, 41%), m.p. 150–155°, $[\alpha]_D$ + 31°.

In 1,2-dichloroethane at −20°. A soln of **2a** (5.0 g, 10.4 mmol) in 1,2-dichloroethane (400 ml) was stirred at −20° under dry N_2 with NBS (2.78 g, 15.6 mmol), and illuminated for 3.5 hr with a Hanovia 125 W medium pressure Hg arc, the temp being kept at −20° throughout. The soln was washed with water (2 × 200 ml), combined with a dichloroethane backwash (50 ml) of the aq phases and evaporated. The residual orange solid was chromatographed on Kieselgel G (250 g). Elution with CH_2Cl_2–acetone (9:1) gave **5d** (0.75 g, 11.3%), m.p. 191–192° (dec), $[\alpha]_D$ + 5.1°, followed by **5a** obtained as two batches: (i) (0.90 g, 15.5%), m.p. 150–155° (dec), $[\alpha]_D$ + 31.5°; (ii) (2.31 g, 39.8%), m.p. 156–168° (dec), $[\alpha]_D$ + 37°.

2,2,2-Trichloroethyl (1*S*, 2'*RS*, 6*R*, 7*R*) - 7 - (2' - *bromophenyl* - *acetamido*) - 3 - *methylceph* - 3 - *em* - 4 - *carboxylate* 1-*oxide* **2d**

A soln of RS-2-bromophenylacetic acid (2.6 g, 12.1 mmol) in dry CH_2Cl_2 (10 ml) was added slowly to a soln of **7**[2] (3.5 g, 10.1 mmol) and dicyclohexylcarbodiimide (2.5 g, 10.1 mmol) in dry CH_2Cl_2 (40 ml). The mixture was stirred at *ca* 25° for 2 hr and then at 5° overnight, filtered and evaporated. The residual brown oil was dissolved in EtOAc (50 ml) and washed with 3% $NaHCO_3$aq (2 × 50 ml) and brine (50 ml), and evaporated to an oil which on dilution with ether (10 ml) and pptn with petrol, b.p. 60–80°, gave 2,2,2-*trichloroethyl* (2'*RS*, 6*R*, 7*R*) - 7 - (2' - *bromophenylacetamido*) - 3 - *methylceph* - 3 - *em* - 4 - *carboxylate* **1d** as a cream solid (4.80 g, 88.5%), m.p. 98–115°, $[\alpha]_D$ + 62° ($CHCl_3$), ν_{max} 3275 (NH), 1766 (azetidin-2-one), 1730 (CO_2R), 1660 and 1535 cm^{-1} (CONH), δ ($CDCl_3$) 2.20 (s; Me), 3.20, 3.52 and 3.23, 3.52 (two superimposed Ab-q totalling 2H, J19; C_7–H_2), 4.77, 4.95 (AB-q, J12; CH_2CCl_3), 5.01 (d, J4.5; C_6–H), 5.42, 5.45 (two s totalling 1H; PhC**H**Br), 5.68, 5.72 (two superimposed dd totalling 1H, J4.5, 8.5; C_7–H), 7.2–7.6 (m; Ph) [Found: C, 40.6; H, 3.1; N, 5.3; S, 5.8; total halogen content 3.94 g atom/mol. $C_{18}H_{16}BrCl_3N_2O_4S$ (542.7) requires: C, 39.8; H, 3.0; N, 5.2; S, 5.9; total halogen content 4 g atom/mol].

A soln of **1d** (1.542 g, 2.85 mmol) in CH_2Cl_2 (40 ml) was treated with peracetic acid (0.54 ml, 2.85 mmol) at 25°. The mixture was stirred for 5 min, $NaHCO_3$ (0.5 g) was added and stirring was continued for 5 min. The mixture was filtered and the filtrate was evaporated to give **2d** as a white solid containing traces of the 1R-oxide **3d** by TLC. Crystallisation from acetone gave **2d**, m.p. 199–204°, $[\alpha]_D$ + 110°, λ_{max} 266 nm (ϵ 9100), ν_{max} 1754 (azetidin-2-one), 1724 (CO_2R), 1698, 1675 and 1512 (CONH) and 1020 (S→O), δ 2.17 (s; Me), 3.84 (m; C_7–H_2), 5.04 (d, J5; C_6–H), 5.11 (s; CH_2CCl_3), 5.80 (dd, J5, 8; C_7–H), 6.04 and 6.10 (two s totalling 1H; PhC**H**Br), 7.3–7.8 (m; Ph), 8.80 (d, J8; NH) [Found: C, 39.0; H, 3.0; N, 4.7; S, 5.7; total halogen content 3.94 g atom/mol. $C_{18}H_{16}BrCl_3N_2O_5S$ (558.7) requires: C, 38.7; H, 2.9; N, 5.0; S, 5.7%; total halogen content 4 g atom/mol].

Photo-initiated bromination of **2d**. A soln of **2d** (3.0 g, 5.36 mmol) and NBS (1.43 g, 8.04 mmol) in 1,2-dichloroethane (150 ml) was irradiated at 0° for 1.25 hr with a Hanovia 125 W medium pressure Hg arc. The soln was washed with water (3 × 75 ml), combined with a dichloroethane backwash (75 ml) of the aq phases, dried and evaporated to a sticky solid. Trituration with MeOH gave **5d** as a pale yellow solid (2.19 g), m.p. 187–189°, $[\alpha]_D$ + 19°, containing *ca* 10% of **2d** by TLC and PMR spectroscopy.

Debromination of **8a**. A soln of **8a** (280 mg, 0.5 mmol) in dry THF (20 ml) was stirred at 25° for 5 min with Zn dust (600 mg, 10 mmol; activated by washing with 2N HCl, water, THF) and AcOH (0.1 ml), filtered and evaporated. The residual foam was dissolved in CH_2Cl_2–acetone (4:1; 2 ml) and purified by prep TLC on Kieselgel G to give **2a** as a glass (68 mg; 28%), identified by TLC and PMR spectroscopy.

Base-catalysed bromination of **2a**. Sodium bistrimethylsilylamide (223 mg, 1.23 mmol) was added to a stirred soln of **2a** (579 mg, 1.21 mmol) in CH_2Cl_2 (30 ml) at 20°. The resulting very dark brown colour was almost discharged by the addition of 1.21 M Br_2 soln (1 ml, 1.21 mmol) in CH_2Cl_2. The soln was washed with water, evaporated and chromatographed on Kieselgel G. Elution with CH_2Cl_2–acetone (4:1) gave **8a** as a pale brown foam (248 mg, 37%), $[\alpha]_D$ – 121.5° ($CHCl_3$), λ_{max} 287 nm (ϵ 6700), having PMR spectra identical with material obtained above by photo-initiated bromination in benzene.

Photo-initiated bromination of **2b** *to give* 2,2,2-*trichloroethyl* (1*S*, 6*R*, 7*R*) - 3 - *bromomethyl* - 7 - *phenoxyacetamidoceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide* **5b**

A soln of **2b** (3.26 g, 6.57 mmol) in 1,2-dichloroethane (150 ml) was stirred at – 10° under dry N_2 with NBS (1.76 g, 9.9 mmol) and illuminated for 85 min with a Hanovia 125 W medium pressure Hg arc, the temp being kept at 0 to – 10°. The soln was washed with water (3 × 75 ml), combined with a dichloroethane backwash (75 ml) of the aq phases and evaporated to a yellow gum. Trituration with MeOH gave **5b** as an off-white solid (2.12 g, 56.0%), m.p. 148.5–150°, $[\alpha]_D$ – 30°; chromatography of the liquors gave more **5b** (0.20 g, 5.3%), m.p. 152–155.5°, $[\alpha]_D$ – 36°. Crystallisation from MeOH gave white needles, m.p. 157–161°, $[\alpha]_D$ – 36°, λ_{max} 276 nm (ϵ 9850), inflexions at 271, 282 nm (ϵ 8650, 9500), ν_{max} 3420 (NH), 1789 (azetidin-2-one), 1745 (CO_2R), 1702 and 1521 (CONH) and 1024 cm^{-1} (S→O), δ 3.83, 4.13 (AB-q, J18; C_7–H_2), 4.58 (s; $PhOCH_2$), 4.68 (s; CH_2Br), 5.08, 5.24 (AB-q, J12; CH_2CCl_3), 5.13 (d, J5; C_6–H), 6.07 (dd, J5, 9; C_7–H), 6.80 to 7.40 (m; PhO), 8.15 (d, J9; NH) [Found: C, 37.4; H, 2.8; N, 4.8; S, 5.6; total halogen content 3.92 g atom/mol. $C_{18}H_{16}BrCl_3N_2O_6S$ (574.7) requires C, 37.6; H, 2.8; N, 4.9; S, 5.6% total halogen content 4 g atom/mol].

2,2,2-Trichloroethyl (1*R*, 6*R*, 7*R*) - 3 - *bromomethyl* - 7 - *phenoxy* - *acetamidoceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide* **6b**

PBr_3 (1.42 ml, 14.8 mmol) was added to a soln of **5b** (5.73 g, 9.96 mmol) in CH_2Cl_2 (100 ml) at – 50°. The mixture was stirred at – 50° for 1 hr and allowed to warm to 0° over 30 min. Excess 3% $NaHCO_3$aq was added to the mixture which was stirred for 5 min. The organic phase was washed with water (50 ml), dried and evaporated to a foam. Chromatography on Kieselgel G (200 g; benzene–EtOAc, 3:1) gave 2,2,2 - *trichloroethyl* (6*R*, 7*R*) - 3 - *bromomethyl* - 7 - *phenoxyacetamidoceph* - 3 - *em* - 4 - *carboxylate* as a pale yellow foam (2.77 g, 49.7%), $[\alpha]_D$ – 2.7°, λ_{max} 269, 275.5 nm (ϵ 8700, 9050), ν_{max} ($CHBr_3$) 3410 (NH), 1780 (azetidin-2-one), 1734 (CO_2R) and 1690 and 1512 cm^{-1} (CONH), δ 3.61, 3.84 (AB-q, J18, C_7–H_2), 4.44, 4.59 (AB-q, J11; CH_2Br), 4.61 (s; $PhOCH_2$), 5.00, 5.21 (AB-q, J12; CH_2CCl_3), 5.25 (d, J5; C_6–H), 5.79 (dd, J5, 8; C_7–H), 6.80–7.40 (m; PhO), 9.16 (d, J8; NH).

NBS (155 mg, 0.87 mmol) was added to a mixture of the above 3-bromomethyl sulphide (473 mg, 0.85 mmol) and AcOK (162 mg, 1.65 mmol) in AcOH (15 ml) and water (5 ml) at *ca* 0°. The mixture was stirred for 45 min and added to CH_2Cl_2 (100 ml) and water (50 ml). The organic phase was washed with 3% $NaHCO_3$aq (2 × 50 ml), dried and evaporated. The residual yellow oil was chromatographed on Kieselgel G (15 g; CH_2Cl_2–acetone, 4:1) to give **6b** as white needles (141 mg, 28%), m.p. 172–173.5° (dec), $[\alpha]_D$ – 166°, λ_{max} 268, 275 nm (ϵ 6750, 7150), inflexions at 263, 282 nm (ϵ 5,850, 6400), ν_{max} 3270 and 3230 (NH), 1754 (azetidin-2-one), 1722 (CO_2R), 1710 and 1526 (CONH) and 1028 cm^{-1} (S→O), δ 3.83, 4.31 (Ab-q, J16; C_7–H_2), 4.54 (s; CH_2Br), 4.64 (s; $PhOCH_2$), 4.98 (d, J5; C_6–H), 5.07 5.24 (AB-q, J12; CH_2CCl_3), 5.77 (dd, J5, 8; C_7–H), 6.90–7.50 (m; PhO), 9.36 (d, J8; NH) [Found: C, 37.2; H, 2.9; N, 4.6; S, 5.5%; total halogen content 3.95 g atom/mol].

2,2,2-Trichloroethyl (1*S*, 6*R*, 7*R*) - 3 - *methylthiomethyl* - 7 - *phenoxyacetamidoceph* - 3 - *em* - 4 - *carboxylate* 1-*oxide* **9b**

Methanethiol (0.60 ml, 11.15 mmol) in DMF (5 ml) at – 20° was added to a stirred soln of **5b** (5.48 g, 9.5 mmol) in DMF (50 ml) also at – 20°. NEt_3 (1.42 ml, 10.2 mmol) was added, causing a brown colour which slowly lightened to pale yellow as the soln was allowed to warm to 25° over 1 hr. CH_2Cl_2 (100 ml) was added and the soln was washed with water (6 × 50 ml), dried and evaporated to a brown solid. Trituration with ether–MeOH (30 ml; 6:1) gave **9b** as an off-white solid (3.18 g, 61.8%), m.p. 175–183°, $[\alpha]_D$ 0°. Crystallisation from MeOH gave white crystals, m.p. 178–182°, $[\alpha]_D$ + 0.2°, λ_{max} 269, 275 nm (ϵ 9250, 9350), inflexion at 264 nm (ϵ 8250), ν_{max} 3387 (NH), 1770 (azetidin-2-one), 1738 (CO_2R), 1698 and 1522 (CONH) and 1024 cm^{-1} (S→O), δ 2.01 (s; SCH_3), 3.58, 3.76 (AB-q, J13; CH_2SCH_3), 3.81, 4.18 (AB-q, J18; C_7–H_2), 4.70 (s; $PhOCH_2$), 5.03, 5.23 (AB-q, J12; CH_2CCl_3), 5.13 (d, J4.5; C_6–H), 6.06 (dd, J4.5, 9; C_7–H), 6.90–7.50 (m; PhO), 8.17 (d, J9; NH) [Found: C, 42.1; H, 3.5; Cl, 19.6; N, 5.2; S, 11.8. $C_{19}H_{19}Cl_3N_2O_6S_2$ (541.9) requires: C, 42.1; H, 3.5; Cl, 19.7; N, 5.2; S, 11.8%].

2,2,2-Trichloroethyl (6*R*, 7*R*) - 3 - *methylthiomethyl* - 7 - *phenoxyacetamidoceph* - 3 - *em* - 4 - *carboxylate* **10b**

KI (2 g, 12 mmol) and acetyl chloride (1 ml, 14 mmol) were added to a stirred soln of **9b** (1.08 g, 2 mmol) in DMF (10 ml) at 26°. The mixture was stirred for 10 min, the brown I_2 colour was discharged by the addition of a soln of $Na_2S_2O_5$ in aq DMF, and CH_2Cl_2 (100 ml) and water (50 ml) were added. The aq phase was extracted with CH_2Cl_2 (10 ml) and the combined organic phases were washed with water (3 × 50 ml), dried and evaporated. The

residual oil was dissolved in ether (25 ml), washed with water (3 × 10 ml), dried and evaporated to give **10b** as a pale yellow foam (1.00 g, 95%), $[\alpha]_D$ + 37.5°, λ_{max} 269,275 nm (ϵ 8300, 8050), inflexion at 264 nm (ϵ 7600), ν_{max} ($CHBr_3$) 3450 (NH), 1788 (azetidin-2-one), 1740 (CO_2R), 1698 and 1525 cm^{-1} (CONH), δ 2.03 (s; SCH_3), 3.57, 3.78 (AB-q, J13; CH_2SCH_3), 3.71 (s; C_7–H_2), 4.63 (s; $PhOCH_2$), 4.98, 5.18 (AB-q, J13; CH_2CCl_3), 5.27 (d, J4.5; C_6–H), 5.71 (dd, J4.5, 8; C_7–H), 6.80–7.50 (m; PhO), 9.13 (d, J8; NH) [Found: C, 43.6; H, 3.7; Cl, 19.9; N, 5.1; S, 12.2. $C_{19}H_{19}Cl_3N_2O_5S_2$ (525.8) requires: C, 43.4; H, 3.6; Cl, 20.2; N, 5.3; S, 12.2%].

2,2,2-Trichloroethyl (6*R*, 7*R*) - 7 - *amino* - 3 - *methylthiomethyl-ceph* - 3 - *em* - 4 - *carboxylate hydrogen toluene* - 4 - *sulphonate* **12**

A soln of **10b** (3.72 g, 7.075 mmol) in CH_2Cl_2 (20 ml) was added to a suspension of PCl_5 (2.36 g, 11.3 mmol) in pyridine (0.92 ml, 11.5 mmol) at −20°. The resulting soln was stirred at −20° for 2 hr, at 0° for 1 hr and 18° for 2 hr, and added to MeOH (50 ml). Water (100 ml) and EtOAc (50 ml) was added and the pH was raised to 7.1 with $NaHCO_3$. The organic phase was washed with water, dried and evaporated, and the residue was dissolved in MeOH–ether (10 ml, 2:1). To this soln was added a soln of toluene-4-sulphonic acid monohydrate (2.0 g, 10.5 mmol) in MeOH (15 ml) and ether (5 ml). The soln was seeded and chilled at −15° for 2 hr to give **12** as off-white crystals (1.83 g, 47%), m.p. 184–187° (dec), $[\alpha]_D$ + 3.4°, λ_{max} (MeOH) 268 nm (ϵ 6750). Evaporation of the liquors and crystallisation of the residue from MeOH–ether gave a second crop of **12** as off-white crystals (0.95 g, 25%), m.p. 186–188° (dec), $[\alpha]_D$ + 7.1°, λ_{max} (MeOH) 268 nm (ϵ 6500), δ 2.06 (s; SCH_3), 2.32 (s; $CH_3C_6H_4$), 3.76 (s; C_2–H_2), 3.67, 3.86 (AB-q, J13; CH_2SCH_3), 5.02, 5.16 (AB-q, J13; CH_2CCl_3), 5.18, 5.34 (AB-q, J5; C--H and C_6H), 7.13, 7.52 (two d, J8; $CH_3C_6H_4SO_3^-$).

2,2,2-Trichloroethyl (1*S*, 6*R*, 7*R*) - *formamido* - 3 - *methyl-ceph* - 3 - *em* - 4 - *carboxylate* 1-*oxide* **2c**

A mixture of the toluene-2-sulphonate[2] of 7 (155.5 g, 0.3 mol), Na_2CO_3 (36 g, 0.34 mol), water (600 ml) and EtOAc (600 ml) was stirred for 1.5 hr and the aq phase was extracted with EtOAc (230 ml). The combined organic phase was washed with water (600 ml), dried and evaporated to a brown oil which was dissolved in ethyl formate heated under reflux for 1 hr and evaporated *in vacuo*. The brown oil was redissolved in EtOAc (600 ml), washed with 2N HCl, water, 3% $NaHCO_3$aq and water (each 600 ml), dried and evaporated. The residual pale yellow foam was dissolved in CH_2Cl_2 (1 l.), and the soln was cooled in ice and stirred whilst peracetic acid (0.285 mol) was added over 35 min. Stirring was continued for 30 min, CH_2Cl_2 (1 l.), was added, and the soln was washed with water (800 ml), 3% $NaHCO_3$aq 1.5 l., 800 ml), dried and concentrated to *ca* 400 ml. MeOH (450 ml) was added and the stirred soln was cooled slowly to 0° to give **2c** as a fine off-white solid. Concentration of the liquors gave two further crops of **2c** (total 91.2 g, 78%), m.p. 168–171° (dec), $[\alpha]_D$ + 104.5°. Crystallisation from EtOH gave **2c** as a hemi-ethanol solvate, m.p. 176–181°, $[\alpha]_D$ + 107°, λ_{max} 269 nm (ϵ 7700), ν_{max} ($CHBr_3$) *ca* 3600 (EtOH), 3440 (NH), 1800 (azetidin-2-one), 1741 (CO_2R), 1698 and 1509 (CONH) and 1041 cm^{-1} (S→O), δ ($CDCl_3$) 2.26 (s; Me), 3.29, 3.72 (AB-q, J18; C_2–H_2), 4.58 (d, J4; C_6–H), 4.84, 5.01 (AB-q, J11; CH_2CCl_3), 6.07 (dd, J4, 10; C_7–H), 7.09 (d, J10; NH), 8.26 (s; CHO) with typical signals at δ 1.24 and 3.66 confirmed the presence of EtOH (0.5 mol) [Found: C, 35.0; H, 3.4; Cl, 25.5; N, 6.7; S, 7.7 $C_{11}H_{11}Cl_3N_2O_5S.0.5C_2H_5OH$ (412.7) requires: C, 34.9; H, 3.4; Cl, 25.8; N, 6.8; S, 7.8%].

Photo-initiated bromination of **2c** *to give* 2,2,2 - *trichloroethyl* (1*S*, 6*R*, 7*R*) - 3 - *bromomethyl* - 7 - *formamidoceph* - 3 - *em* - 4 - *carboxylate* 1 - *oxide* **5c**

With N-*bromosuccinimide*. A soln of **2c** (9.75 g, 25 mmol) in dry 1,2-dichloroethane (400 ml) was stirred at −20° under dry N_2 with NBS (6.67 g, 37.5 mmol) and illuminated for 6 hr with a Hanovia 125 W medium pressure Hg arc, the temp being kept at −20° throughout. The soln was washed with pH7 phosphate buffer (2 × 200 ml), combined with a dichloroethane backwash (200 ml) of the aq phases, dried and evaporated to low volume to give **9c** as an off-white solid (6.63 g, 56.6%), m.p. 162–165°, $[\alpha]_D$ − 5°, λ_{max} 282.5 nm (ϵ 9300). Crystallisation from $CHCl_3$/petrol, b.p. 40–60° (5:2) gave white needles, m.p. 173–174°, $[\alpha]_D$ + 4.3°, λ_{max} 283 nm (ϵ 10000), ν_{max} 3300 (NH), 1780 (azetidin-2-one), 1730 and 1714 (CO_2R), 1652 and 1516 (CONH) and 1024 cm^{-1} (S→O), δ 3.80, 4.07 (AB-q, J18; C_2–H), 4.53, 4.67 (AB-q, J10; CH_2Br), 5.08, 5.23 (AB-q, J12; CH_2CCl_3), 5.06 (d, J5; C_6–H), 6.01 (dd, J5, 9; C_7–H), 8.16 (s; CHO), 8.40 (d, J9; NH) [Found: C, 28.1; H, 2.1; N, 6.0; S, 6.9; total halogen content 4.00 g atom/mol. $C_{11}H_{10}BrCl_3N_2O_5S$ (468.6) requires: C, 28.2; H, 2.15; N, 6.0; S, 6.8%; total halogen content 4.00 g atom/mol].

With 1,3-*dibromo*-5,5-*dimethylhydantoin*. A soln of **2c** (5.0 g, 12.8 mmol) in 1,2-dichloroethane (250 ml) containing 0.2% w/v of water was stirred at −20° with DBDMH (2.74 g, 9.6 mmol) and illuminated for 1.25 hr with a Hanovia 125 W medium pressure Hg arc, the temp being kept at −20° throughout. The soln was washed with water (2 × 125 ml), combined with a dichloroethane backwash (125 ml) of the aq phases, dried and evaporated to low volume to give **5c** as a white solid (3.80 g, 63.3%), m.p. 167–169°, $[\alpha]_D$ − 0.2°, λ_{max} 283 nm (ϵ 9350).

Without isolation of **2c**. A mixture of the toluene-4-sulphonate[2] of 7 (207 g, 0.4 mol), $NaHCO_3$ (42 g, 0.5 mol), water (500 ml) and 1,2-dichloroethane (500 ml) was stirred for 30 min. The aq phase was extracted with 1,2-dichloroethane (2 × 70 ml). The organic phases were washed with NaClaq, combined with a dichloroethane backwash of the aq phase, dried and diluted to 1 l. with 1,2-dichloroethane. The soln was cooled to 15–20° and sitrred for 1 hr with part (405 ml) of a soln prepared by mixing formic acid (40 ml) and Ac_2O (40 ml) at 5° and diluting the mixture to 425 ml with 1,2-dichloroethane. The soln was cooled to 8° and treated with peracetic acid (0.414 mol) at 8–15° until TLC (CH_2Cl_2 acetone, 1:1) showed the reaction to be complete. The soln was washed with NaClaq (3 × 200 ml) and 3% $NaHCO_3$aq–NaClaq (1:1, 3 × 200 ml), combined with 1,2-dichloroethane backwashes (2 × 100 ml) of the aq phases and diluted to 2 l. with 1,2-dichloroethane. UV analysis of an aliquot of this soln indicated the yield of **2c** was 94%.

Part (513 ml) of this soln was diluted to 2 l. with 1,2-dichloroethane and stirred at −1° with DBDMH (22.0 g, 77 mmol), $NaHCO_3$ (10.75 g, 128 mmol) and water (20 ml). The mixture was illuminated for 1.5 hr with a Hanovia 125 W medium pressure Hg arc, the temp being kept at *ca* −1° throughout. The soln was washed with water (3 × 1 l.), combined with a dichloroethane backwash (1 l.) of the aq phases, dried and evaporated to low volume to give **5c** as a white solid (23.46 g, 48.8%), m.p. 165–167°, $[\alpha]_D$ − 1.4°, λ_{max} 283 nm (ϵ 9550).

2,2,2-Trichloroethyl (1*S*, 6*R*, 7*R*) - 7 - *formamido* - 3 - *methyl-thiomethylceph* - 3 - *em* - 4 - *carboxylate* 1-*oxide* **9c**

Methanethiol (2.2 ml, 41 mmol) in DMF (50 ml) cooled to *ca* −20° was added to a soln of **5c** (14.06 g, 30 mmol) in DMF (200 ml) also at −20°. NEt_3 (4.2 ml, 30 mmol) was added and the soln was allowed to warm to 17° over 1 hr and then flushed with N_2 overnight to remove excess thiol. One half of the soln was added to water (600 ml) and extracted with CH_2Cl_2 (200, 2 × 100 ml). The combined extracts were washed with 2N HCl and water (each 200 ml), dried and evaporated to a pale yellow waxy solid. Crystallisation from MeOH (20 ml) gave **9c** as white needles (5.25 g, 80.4%), m.p. 178–179°, $[\alpha]_D$ + 36°, λ_{max} 274 nm (ϵ 8250). Evaporation of the liquors and crystallisation of the residue from methanol (10 ml) gave a second crop of **9c** (0.32 g, 4.9%), m.p. 175–176°, $[\alpha]_D$ + 40.5°, λ_{max} 275 nm (ϵ 8450), ν_{max} 3370 (NH), 1760 (azetidin-2-one), 1732 (CO_2R), 1696 and 1498 (CONH) and 1010 cm^{-1} (S→O), δ 2.01 (s; SCH_3), 3.68 (s; CH_2SCH_3), 3.80, 4.18 (AB-q, J18; C_2–H_2), 5.06, 5.26 (AB-q, J12; CH_2CCl_3), 5.11 (d, J4.5; C_6–H), 6.01 (dd, J4.5, 9; C_7–H), 8.21 (s; CHO), 8.47 (d, J9; NH). Analytical data were obtained on material from a preliminary expt. Crystallisation from MeOH gave white needles, m.p. 176–177°, $[\alpha]_D$ + 41°, λ_{max} 275 nm (ϵ 8600) [Found: C, 33.3; H, 3.0; Cl, 24.1; N, 6.6; S, 14.4. $C_{12}H_{13}Cl_3N_2O_5S_2$ (435.7) requires: C, 33.1; H, 3.0; Cl, 24.4; N, 6.4; S, 14.7%].

2,2,2-Trichloroethyl (6R, 7R) - 7 - formamido - 3 - methylthiomethylceph - 3 - em - 4 - carboxylate **10c**

KI (15.0 g, 90 mmol), followed by acetyl chloride (2.5 ml, 35 mmol) were added to a soln of **9c** (2.18 g, 5 mmol) in AcOH (100 ml). Iodine was liberated at once. The mixture was stirred at *ca* 20° for 10 min, cooled in ice and treated with 0.5 M $Na_2S_2O_3$aq to destroy the iodine. The pale yellow soln was concentrated *in vacuo* to remove the bulk of the AcOH, and added to CH_2Cl_2 (250 ml) and water (250 ml). The aq phase was extracted with CH_2Cl_2 (2 × 100 ml), and the combined organic phases were washed with 3% $NaHCO_3$aq (2 × 100 ml) and water (100 ml), dried and evaporated. The residual white foam was treated with acetone (50 ml) and insoluble S removed by filtration. Evaporation of the filtrate and crystallisation of the residue from MeOH–water (10:1, 16.5 ml) gave **10c** as white needles (1.16 g, 55.2%), m.p. 100–102°, $[\alpha]_D$ + 30°, λ_{max} 270.5 nm (ϵ 7650), ν_{max} 3300 (NH), 1770 (azetidin-2-one), 1718 (CO_2R), 1662 and 1508 cm^{-1} (CONH), δ 2.04 (s; SCH_3), 3.58, 3.78 (AB-q, J15; CH_2SCH_3), 3.72 (s; C_7–H_2), 4.99, 5.20 (AB-q, J12; CH_2CCl_3), 5.30 (d, J5; C_6–H), 5.81 (dd, J5, 9; C_7–H), 8.19 (s; CHO), 9.12 (d, J9; NH) [Found: C, 34.3; H, 3.1; Cl, 25.0; N, 6.6; S, 15.6. $C_{12}H_{13}Cl_3N_2O_4S_2$ (419.7) requires: C, 34.3; H, 3.2; Cl, 25.3; N, 6.7; S, 15.3%]. A second crop of **10c** (117 mg, 5.6%), m.p. 97–98°. $[\alpha]_D$ + 30°, λ_{max} 270.5 nm (ϵ 7650), was obtained by evaporation of the liquors and crystallisation of the residue from MeOH–water (10:1, 5.5 ml).

2,2,2-Trichloroethyl (6R, 7R) - 7 - amino - 3 - methylthiomethylceph - 3 - em - 4 - carboxylate hydrochloride **13**

From **10c**. $POCl_3$ (0.5 ml, 5.47 mmol) was added dropwise over 3 min to a stirred suspension of **10c** (1.05 g, 2.5 mmol) in dry MeOH (10 ml). The solid dissolved during the addition, the temp rising to *ca* 45°. After 1 min crystallisation ensued and the mixture rapidly set solid. Dilution with ether (10 ml) and stirring gave **13** as a feathery white solid (0.94 g, 88%), m.p. 169–172° (dec), $[\alpha]_D$ + 5.3°, λ_{max} (MeOH) 272.5 nm (ϵ 6640), ν_{max} *ca* 2630 (NH_3^+), 1785 (azetidin-2-one) and 1732 cm^{-1} (CO_2R), δ 2.03 (s; SCH_3), 3.60, 3.83 (AB-q, J17; C_7–H_2), 3.77 (s; CH_2SCH_3), 4.99, 5.12 (AB-q, J12; CH_2CCl_3), 5.10 (d, J5; C_6–H), 5.30 (d, J5; C_7–H) [Found: C, 31.2; H, 3.3; Cl, 33.0; N, 6.6; S, 15.0. $C_{11}H_{14}Cl_4N_2O_3S_2$ (428.2) requires: C, 30.85; H, 3.3; Cl, 33.1; N, 6.55; S, 15.0%].

From **5c** *without isolation of intermediates.* A soln of **5c** (23.43 g, 50 mmol) in DMF (300 ml) was cooled to −5° and condensed methanethiol (3.0 ml, *ca* 56 mmol) was rinsed in with DMF (50 ml) precooled to −20°. NEt_3 (7.0 ml, 50 mmol) was added and the soln was allowed to warm to 15° over 30 min, then degassed at 15 mm for 30 min. More DMF (50 ml) was added to give a clear soln which was cooled to −5°. KI (16.6 g, 100 mmol) was added, followed by acetyl chloride (7.2 ml, 100 mmol) over a period of 2 min. I_2 was liberated after 2 min. The soln was stirred for 1 hr without cooling, refrigerated overnight at −17° and warmed to *ca* 25° over 1 hr, and a soln of $Na_2S_2O_5$ (16.6 g, *ca* 75 mmol) in water (80 ml) was added. The pale orange soln was poured into water (1.5 l.) and extracted with CH_2Cl_2 (1000, 500, 250 ml). The combined extracts were washed with water, 2N HCl, water and 3% $NaHCO_3$aq (100 ml of each), dried and evaporated. The residual amber gum was dissolved in dry MeOH (160 ml) and $POCl_3$ (4.6 ml, 50 mmol) was added over 4 min to the ice-cooled soln. The mixture was stirred for 45 min, crystallisation commencing after 30 min, diluted with ether (75 ml) and cooled for 1 hr to give **13** (13.49 g, 63.2%), m.p. 170–172° (dec), $[\alpha]_D$ 7°, λ_{max} (MeOH) 272.5 nm (ϵ 6630). Progressive concentration of the liquors provided three further crops of similar material (1.87, 1.82, 0.19 g; total 18.1%).

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