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SYNTHESIS OF 3-FUNCTIONALISED CEPHALOSPORINS BY PHOTOINITIATED BROMINATION

TRANSFORMATIONS OF 2,2,2-TRICHLOROETHYL 1S, 6R, 7R)-3-BROMOMETHYL-7-FORMAMIDOCEPH-3-EM-4-CARBOXYLATE, 1-OXIDE

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Abstract—The 3-bromomethyl derivative **2c**, obtained by photoinitiated bromination of the corresponding 3-Me compound **1c**, has been converted into the antibiotics cephalothin **18** and cephaloridine **20**. Reaction of **2c** with lithium dimethyl- and diphenyl-cuprate led to the intermediates **22** and **24** respectively. Further transformation of **24** provided the 3-benzyl derivative **27**, an isostere of cephaloridine.

In the preceding paper[1] we described the photoinitiated bromination of penicillin-derived 3-methylceph-3-em 1S-oxide esters **1** to give the corresponding 3-bromomethyl derivatives **2**. The utility of the latter compounds in the synthesis of 3-substituted cephalosporins was demonstrated by the conversion of **2b** and **2c** into the 3-methylthiomethyl amine **3**. We now describe further examples of the elaboration of **2c** into therapeutically useful cephalosporins.

Deformylation of the 3-bromomethyl compound **2c** with concentrated hydrochloric acid in tetrahydrofuran (THF) at +6° for 30 hr gave the unstable chloromethyl amine **4** (40–70%). Alternatively, on addition of phosphorus oxychloride (*ca* 2 molar equivs) to a suspension of **2c** in dry methanol a solution was briefly obtained and then the stable 3-chloromethyl and 3-bromomethyl hydrochloride salts **6** and **7** cocrystallised in good yield (> 80%). Deformylation of **2c** with phosphorus tribromide gave the 3-bromomethyl hydrobromide salt **8** in near-quantitative yield.

Coupling of the 3-chloromethyl amine **4** with thien-2-ylacetic acid by means of N, N'-dicyclohexylcarbodiimide provided the thien-2-ylacetamido derivative **9** (λ_{max} (EtOH) 276 nm; *NB.* **9** and related compounds also have an absorption maximum at *ca* 234 nm attributed to the thien-2-yl moiety).

Direct acylation a mixture of the hydrochloride salts **6** and **7** with thien-2-ylacetyl chloride in methylene chloride in the presence of N,N-dimethylacetamide (DMA) gave products, i.e. **9** and **10**, in which the proportion of the 3-chloromethyl component was greatly enhanced during the acylation process. When the reaction was performed with ethylene oxide instead of DMA halogen exchange was greatly reduced. Acylation of the hydrobromide salt **8** under the latter conditions gave essentially pure 3-bromomethyl ester **10** (λ_{max} (EtOH) 283 nm). In addition to differences in their UV maxima, the two esters **9** and **10** could be distinguished by their PMR spectra in diemthylsulphoxide-d_6. The AB quartet attributed to the protons attached to C-3' had branches centered at δ4.56 and 4.72 for the chloromethyl ester **9** and at slightly higher field, δ4.51 and 4.66 for the bromomethyl ester **10**.

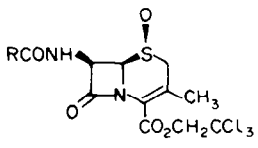
Reaction of the 3-bromomethyl ester **10** with potassium acetate in N,N-dimethylformamide (DMF) containing a small amount of acetic acid gave the 3-acetoxymethyl ester **12** in 68% yield. Since the 3-chloromethyl compound **9** was unreactive under these conditions, mixtures of **9** and **10** were converted into the more reactive iodomethyl ester **11** (λ_{max} (EtOH) 294 nm) by stirring with sodium iodide in acetone whereafter the 3-acetoxymethyl ester **12** was obtained by the above procedure.

Reduction of the sulphoxide **12** with potassium iodide/acetyl chloride in acetic acid[2] gave the known sulphide **15**[3,4] in 65% yield. Removal of the ester function was achieved by a modification of the method of Woodward *et al.*[3], *viz* by stirring a solution of **15** in anhydrous formic acid with Zn dust containing a small amount of $ZnCl_2$. Purification by ion-exchange chromatography gave cephalothin **18** which was isolated as the sodium salt **19** in 26% yield. Earlier workers have described routes to cephalothin **18**, a widely used antibiotic,[5] from cephalosporin C[6] and by total synthesis.[3] The penicillin-based procedure of the Lilly group[7] may in principle also be used for the synthesis of cephalothin **18**, as may other related procedures developed in their and other laboratories.[8]

The conversion of cephalothin **18** to cephaloridine **20**, another important antibiotic,[9] by displacement of the acetoxy group by pyridine[10] has been discussed in detail by Taylor.[11] We have found a direct route to cephaloridine **20** from the readily available 3-bromomethyl intermediate **2c**.

Thus on stirring a solution in pyridine of the 3-chloromethyl derivative **9** a solid was slowly deposited. This was collected to give the hygroscopic chloride salt **13** in 67% yield. The salt was suspended in methylene chloride and sufficient DMF was added to give a solution. Upon adding phosphorus trichloride[12] and stirring, the sulphide **16** was precipitated from solution in 73% yield. Reductive deesterification of **16** was accomplished as previously described for **15** and after purification by ion-exchange chromatography, cephaloridine **20** was isolated from an aqueous solution as its crystalline hydronitrate salt **21**[13] in 47% yield. This material proved identical to a sample of hydronitrate salt prepared from authentic cephaloridine **20**.

Whilst the replacement of the acetoxy group of cephalosporanic acids by a variety of nucleophiles is well documented[14], there are relatively few examples in which carbon nucleophiles have been employed.[15] Reactions of lithium dialkyl- or diaryl-cuprates with alkyl halides have been shown to give high yields of



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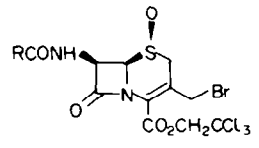
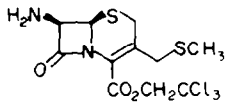


2

a R = $PhCH_2$- b: R = $PhOCH_2$- c R = H



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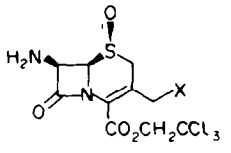
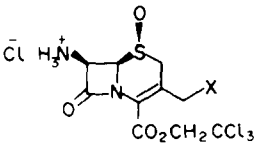
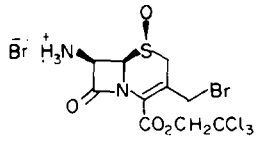


4 X = Cl
5 X = Br



6 X = Cl
7 X = Br



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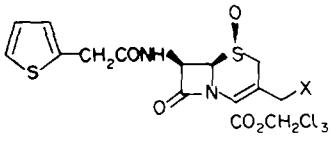
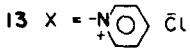
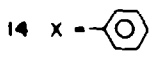
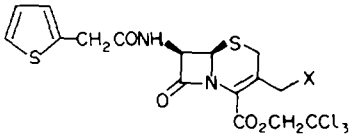
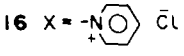
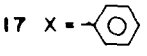


9 X = Cl
10 X = Br
11 X = I
12 X = $OCOCH_3$
13 X = 
14 X = 



15 X = $OCOCH_3$
16 X = 
17 X = 

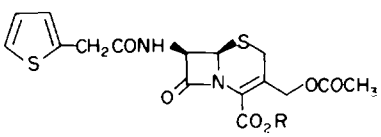
carbon–carbon coupled products.[16] It was of interest to examine the reaction of the 3-bromomethyl ester **2c** with such reagents.

Treatment of a solution of lithium dimethylcuprate (5 molar equivs) generated from methyl lithium and cuprous bromide in ether at −70°, with a THF solution of **2c** realised a 51% yield of the 3-ethyl ester **22** (λ_{max} (EtOH) 269 nm) after an aqueous ammonium chloride work-up. The structure of **22** was confirmed by a less direct synthesis from **2c** described below.[17]

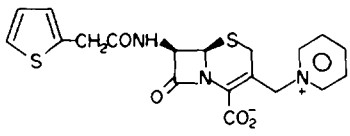
The 3-bromomethyl sulphoxide **2c** in methylene chloride was reacted with triphenylphosphine at room temperature: the solution of the intermediate phosphonium salt **23** was cooled to −18° and treated with phosphorus tribromide[4] in order to reduce the sulphoxide function. Further treatment of the reaction solution with aqueous formaldehyde in the presence of sodium hydrogen carbonate at room temperature gave after work-up the 3-vinyl derivative **25** (λ_{max} (EtOH) 297 nm) in an overall yield of 23%. The timing of the reduction step in the sequence is crucial because a condensation occurs between ceph-3-em-sulphoxides and formaldehyde to give 2-methylene derivatives.[18] Hydrogenation of the 3-vinyl sulphide **25** over 10%-palladium on charcoal furnished the 3-Et compound **26** which was oxidised directly with peracetic acid to give the sulphoxide **22** (77% yield), identical with the material obtained more directly from the lithium dimethylcuprate reaction. The 3-ethyl derivatives **22** and **26** and the 3-vinyl derivative **25** may be converted by established procedures into the 7β-acylamido derivatives possessing the valuable features described by Shingler and Weir.[17,19]

Workers at the Beecham Research Laboratories have described a novel synthesis of cephalosporins *via* secopenicillin intermediates.[20,21] Amongst the compounds prepared was the 3-benzyl analogue **27**, an isostere of cephaloridine **20**. We independently developed a route to 3-benzyl cephalosporins by way of the 3-bromoethyl sulphoxide **2c**.

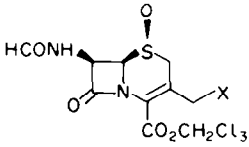
Reaction of **2c** with lithium diphenylcuprate gave variable yields (32 and 70%) of the 3-benzyl sulphoxide **24** dependent on the precise experimental conditions. Deformylation of **24** with phosphorus oxychloride in methanol afforded the amine hydrochloride salt **28** (87%



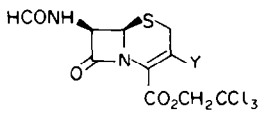
18 R = H
19 R = Na



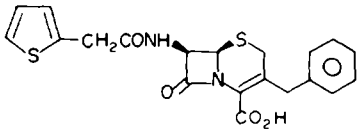
20 betaine
21 HNO_3 salt



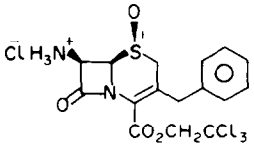
22 X = CH_3
23 X = $\overset{+}{P}Ph_3$ $\bar{B}r$
24 X = 



25 Y = $-CH=CH_2$
26 Y = $-CH_2CH_3$



27



28

yield) which could be transformed into a variety of biologically active 7β-acylamide derivatives. For example, acylation with thien-2-ylacetyl chloride in DMF in the presence of calcium carbonate gave the sulphoxide **14** (57% yield). Reduction of the sulphoxide function with KI/acetyl chloride in DMF furnished an 80% yield of the corresponding sulphide **17**, which was deesterified with Zn in 5%-aqueous formic acid to give the 3-benzyl derivative **27**[21] as a crystalline solid in 33% yield. The antibacterial activity of **27** was in agreement with that outlined by the Beecham workers.[21]

The transformations described in this and the preceding paper[1] demonstrate the feasibility of obtaining from penicillins a wide range of 3-functionalised cephalosporins by way of the photoinitiated bromination of 3-methyl ceph-3-em 1S-oxide esters.

EXPERIMENTAL

General experimental procedures are as outlined in the preceding paper.[1]

N-Deformylation of 2,2,2-trichloroethyl (1S, 6R, 7R)-*3-bromomethyl-7-formamidoceph-3-em-4-carboxylate 1-oxide* **2c**

With conc HCl *in THF.* A suspension of **2c** (1.00 g, 2.13 mmol) in THF (8 ml) at 6° was treated with a soln of conc HCl (2 ml) in THF (2 ml), also at 6°. The mixture was stored at 6° for 30 hr, poured into ice-water (100 ml) and washed with EtOAc (3 × 50 ml). The washings were back-extracted with 2N HCl (3 × 50 ml) and the combined aq phases were layered with EtOAc (150 ml) and adjusted to pH 7 with $NaHCO_3$. The aq phase was re-extracted with EtOAc (3 × 80 ml), and the combined EtOAc extract was washed with sat brine (80 ml), dried and evaporated to a yellow foam (534 mg, 63.2%). Part (525 mg) of the foam was stirred with ether (25 ml) to give *2,2,2-trichloroethyl* 1S, 6R, 7R)-*7-amino-3-chloromethylceph-3-em 4-carboxylate 1-oxide* **4** as a yellow powder (384 mg, 46.2%), m.p. > 250°, $[\alpha]_D$ + 35°, λ_{max} (MeOH) 277 nm (ϵ 6900), ν_{max} ($CHBr_3$) 3370 and 3300 (NH_2), 1785 (azetidin-2-one), 1734 (CO_2R) and 1040 cm^{-1} (S → O), δ 3.76, 4.03 (AB-q, J18; C_2-H_2), 4.57, 4.71 (AB-q, J11; CH_2Cl), 4.92, 5.01 (AB-q, J5; C_7-H and C_6-H), 5.02, 5.19 (AB-q, J12; CH_2CCl_3) [Found: C, 30.8; H, 2.7; N, 6.8; S, 8.2; total halogen content 3.75 g atom/mol. $C_{10}H_{10}Cl_4N_2O_4S$ (396.1) requires C, 30.3; H, 2.5; N, 7.1; S, 8.1%, total halogen content 4 g atom/mol].

With phosphorus oxychloride in MeOH. A suspension of **2c** (2.34 g, 5 mmol) in dry MeOH (20 ml) was stirred and treated dropwise with $POCl_3$ (1 ml, 10.9 mmol) over *ca* 4 min. The temp rose to and remained at 50 ± 5° during the course of the addition. By the end of the addition **2c** had gone into soln and after *ca* 1 min a fluffy white solid began to crystallise and within 5 min the mixture had set solid. After dilution with ether (25 ml) and brief refrigeration, the solid was collected, washed well with ether and dried to give a mixture of the hydrochlorides **6** and **7** of 2,2,2-trichloroethyl (1S, 6R, 7R)-7-amino-3-chloromethyl and bromomethylceph-3-em-4-carboxylate 1-oxide (1.99 g, >83.5%), m.p. >200°, $[\alpha]_D$ + 7.5°, λ_{max} (MeOH) 280 nm ($E^{1\%}_{1cm}$ 180).

With phosphorus tribromide in MeOH. A suspension of **2c** (4.69 g, 10 mmol) in a mixture of dry MeOH (40 ml) and ether (40 ml) was stirred and cooled in an ice-bath, and PBr_3 (472 ml, 40 mmol) was added over 20 min so that the mixture was kept below 10°. The solid had all dissolved after a further 20 min; after another 10 min a solid began to crystallise. The suspension was stirred for 20 min, diluted with ether and refrigerated for 30 min. The solid was collected, washed with ether (150 ml) and dried to give *2,2,2-trichloroethyl* (1*S*,6*R*,7*R*)-*7-amino-3-bromomethylceph-3-em-4-carboxylate 1-oxide hydrobromide* **8** (5.11 g, 98.0%), m.p. > 200°, $[\alpha]_D$ − 20°, λ_{max} (MeOH) 283 nm (ϵ 8250), ν_{max} broad 2600 (NH_3^+), 1790 (azetidin-2-one), 1730 (CO_2R) and 993 cm^{-1} (S → O), δ 3.6 (broad signal; NH_3), 4.14 (s; C_2-H_2), 4.60 (s; CH_2Br), 5.10, 5.24 (AB-q, J12; CH_2CCl_3), 5.22 (d, J5; C_6-H), 5.44 (d, J5; C_7-H) [Found: C, 22.9; H, 2.2; N, 5.2; S, 5.8; total halogen content 4.6 g atom/mol. $C_{10}H_{11}Br_2Cl_3N_2O_4S$ (521.5) requires C, 23.0; H, 2.1; N, 5.4; S, 6.15%; total halogen content 5 g atom/mol].

Acylation of **4** *with thien-2-ylacetic acid*/N,N'-*dicyclohexylcarbodiimide*

A soln of **4** (221 mg, 0.56 mmol) in dry CH_2Cl_2 (3 ml) was treated with a soln of dicyclohexylcarbodiimide (118 mg, 0.57 mmol) in CH_2Cl_2 (2 ml), followed by a soln of thien-2-ylacetic acid (76 mg, 0.53 mmol) in CH_2Cl_2 (1 ml), the sols being rinsed in

with CH_2Cl_2 (3 ml). The mixture was stirred for 1 hr at 20°, refrigerated for 15 hr and filtered from precipitated dicyclohexylurea (87.5 mg). The filtrate was evaporated and the residue was dissolved in EtOAc–ether (4:1; 25 ml). The soln was washed successively with 3% $NaHCO_3$aq, 2N HCl, 3% $NaHCO_3$aq and saturated brine, dried and evaporated. The residue was crystallised from EtOH-water (9:1; 10 ml) to give *2,2,2-trichloroethyl* (1S, 6R, 7R)-*3-chloromethyl-7-(thien-2-ylacetamido) ceph-3-em-4-carboxylate* 1-*oxide* **9** (134 mg, 46.3%), m.p. 167–9°, λ_{max} 234, 276 nm (ϵ 10040, 7750), ν_{max} 3300 (NH), 1780 (azetidin-2-one), 1738 (CO_2R), 1654 and 1528 (CONH) and 1032 cm^{-1} (S→O), δ 3.74, 4.02 (AB-q, J18; C_2-H_2), 3.75, 3.95 (AB-q, J16; CH_2CONH), 4.56, 4.72 (AB-q, J11; CH_2Cl), 5.02 (d, J5; C_6-H), 5.05, 5.21 (AB-q, J12; CH_2CCl_3), 5.90 (dd, J5, 8: C_7-H), 6.94, 7.35 (two m; C_4H_3S), 8.42 (d, J8; NH).

Acylation of **7** *with thien-2-ylacetyl chloride*/N,N-*dimethylacetamide*

A soln of thien-2-ylacetyl chloride (177 mg, 1.1 mmol) in CH_2Cl_2 (5 ml) was added to a stirred suspension of **7** (477 mg, 1 mmol; estimated to contain <10% of **6**, λ_{max} (MeOH) 282.5 nm, in CH_2Cl_2 (10 ml) at 0–5°. Dimethylacetamide (5 ml) was added and the resulting solution was stirred at 0-5° for 45 min then poured into water (40 ml). The organic phase was washed with 3% $NaHCO_3$aq (20 ml) and water (40 ml), dried and evaporated to a gel. This was treated with ether (10 ml) and re-evaporated to a solid which was collected using ether to give **9** (472 mg, 90.8%) as white prisms, m.p. 164–166°, $[\alpha]_D$ + 41°, λ_{max} 234, 277 nm (ϵ 10250, 8250), containing *ca* 10% of **10** as estimated by UV. Part (301 mg) was purified by prep tlc on silica gel, eluting with CH_2Cl_2–acetone (4:1), to give a gelatinous solid (212.5 mg) which was crystallised from EtOH–water (3:1; 20 ml) to give **9** as needles (102.5 mg), m.p. 180–181°, $[\alpha]_D$ + 45° [Found: C, 37.05; H, 2.85; Cl, 25.9; N, 5.2; S, 11.8. $C_{16}H_{14}Cl_4N_2O_5S_2$ (520.3) requires: C, 36.9; H, 2.7; Cl, 27.3; N, 5.4; S, 12.3%], having spectra similar to those reported above.

Acylation of **8** *with thien-2-ylacetyl chloride*/*ethylene oxide*

A soln of ethylene oxide (40 ml) in dry CH_2Cl_2 (30 ml), followed by thien-2-ylacetyl chloride (1.2 ml, 1.05 equiv.) was added to a stirred suspension of **8** (4.94 g, 9.5 mmol) in dry CH_2Cl_2 (40 ml). The solid went into solution after *ca* 2 min. After a further 2 min the soln was washed with 2.4% Na_2CO_3aq (50 ml), combined with a CH_2Cl_2 backwash (25 ml) of the aq phase, washed with water (50 ml) and satd NaBr aq (50 ml), dried and evaporated. The residue was triturated with petrol, b.p. 40–60°, to give *2,2,2-trichloroethyl* (1S, 6R, 7R)-*bromomethyl-7-(thien-2-ylacetamido)ceph-3-em-4-carboxylate* 1-*oxide* **10** (4.94 g, 92%), m.p. *ca* 120° (dec.), $[\alpha]_D$ + 23°, λ_{max} 232, 283 nm (ϵ 11350, 9100), δ 3.78, 4.03 (AB-q, J18; C_2-H_2), 3.85 (broad s; $C_4H_3SCH_2$), 4.51, 4.66 (Ab-q, J11; CH_2Br), 5.02 (d, J5; C_6-H), 5.05, 5.23 (AB-q, J12; CH_2CCl_3), 5.90 (dd, J5, 9; C_7-H), 6.94, 7.36 (two m; C_4H_3S), 8.44 (d, J9; NH).

2,2,2-Trichlorethyl (1S, 6R, 7R) - 3 - *iodomethyl* - 7 - (*thien* - 2 - *ylacetamido*)*ceph-3-em-4-carboxylate* 1-*oxide* **11**

A soln of a *ca* 1:2 mixture of **10** and **9** (2.82 g, *ca.* 5 mmol) in acetone (70 ml) was protected from the light, NaI (2.25 g, 15 mmol) was added, and the mixture was stirred for 1.5 hr, poured into water (100 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The combined extract was evaporated and the residue was triturated with EtOAc (*ca* 15 ml) to give **11** as a pale yellow solid [2.02 g, 66%), m.p. 185° (dec.), $[\alpha]_D$ − 7.6°, λ_{max} 227.5, 294 nm (ϵ 12650, 9300), ν_{max} 3370, 3360 (NH), 1777, 1765 (azetidin-2-one), 1724, 1714 (CO_2R), 1678 and 1505 (CONH) and 1005 cm^{-1} (S→O), δ 3.77, 3.95 (AB-q, J16; CH_2CONH), 3.95 (s; C_2-H_2), 4.43, 4.58 (AB-q, J9; C_3-CH_2I), 5.01 (d, J5; C_6-H), 5.05, 5.24 (AB-q, J12; CH_2CCl_3), 5.85 (dd, J5, 8.5; C_7-H), 6.95, 7.37 (two m; C_4H_3S), 8.39 (d, J8.5; NH) [Found: C, 31.1; H, 2.3; N, 4.4; S, 10.8; total halogen 3.94 g atom/mol. $C_{16}H_{14}Cl_3IN_2O_5S_2$ (611.7) requires C, 31.4; H, 2.3; N, 4.6; S, 10.5%; total halogen 4 g atom/mol].

2,2,2-Trichloroethyl (1S, 6R, 7R)-*3-acetoxymethyl-7-(thien-2-ylaeetamido)ceph-3-em-4-carboxylate* 1-*oxide* **12**

AcOH (4.72 ml) and KOAc (2.32 g, 23.6 mmol) were added to a soln of **10** (2.66 g, 4.72 mmol) in DMF (100 ml). The mixture was stirred at 22° for 3 hr and diluted with EtOAc and water (each 200 ml). The aq phase was extracted with EtOAc (3 × 100 ml) and the combined EtOAc extract was washed with water (2 × 50 ml), stirred with charcoal and $MgSO_4$ for 1 hr, filtered through Celite and evaporated. The oily residue was triturated with petrol to give **12** (1.71 g, 68%), m.p. 130–132°, $[\alpha]_D$ + 85.5°, λ_{max} 236, 269 nm (ϵ 11300, 7600), ν_{max} 3330 (NH), 1792 (azetidin-2-one), 1730 and 1720 (CO_2R), 1658 and 1530 (CONH) and 1055 cm^{-1} (S→O), δ 2.03 (s; $OCOCH_3$), 3.64, 4.03 (AB-q, J18; C_2-H_2), 3.77, 3.95 (AB-q, J16; CH_2CONH), 4.69, 5.13 (AB-q, J14; C_3-CH_2OCOCH_3), 4.97 (d, J5; C_6-H), 5.00, 5.19 (AB-q, J12; CH_2CCl_3), 5.90 (dd, J5, 9; C_7-H), 6.95, 7.36 (two m, C_4H_3S), 8.40 (d, J9; NH) [Found: C, 39.6; H, 3.2; Cl, 19.5; N, 4.9; S, 11.9. $C_{18}H_{17}Cl_3N_2O_7S_2$ (543.85) requires C, 39.75; H, 3.15; Cl, 19.6; N, 5.15; S, 11.8%].

In a similar experiment using a *ca* 1:2 mixture of **10** and **9** (1.41 g, *ca* 2.5 mmol), the produce was a mixture of **12** and unchanged **9** (0.56 g), λ_{max} 235, 273 nm ($E_1^{\%}$ cm 180, 143), tlc R_f (CH_2Cl_2–acetone; 4:1) 0.60, 0.69. In a further experiment using **11** (1.53 g, 2.5 mmol) **12** was obtained as a buff solid (0.66 g, 50%), m.p. 129–30°, $[\alpha]_D$ + 86°, λ_{max} 237, 272 nm (ϵ 10950, 7900).

2,2,2-Trichloroethyl (6R, 7R)-*3-acetoxymethyl-7-(thien-2-ylacetamido)ceph-3-em-4-carboxylate* **15**[3,4]

KI (3.0 g) and AcCl (0.5 ml) were added to a soln of **12** (534 mg, 1 mmol) in AcOH (25 ml). Iz was liberated immediately. The mixture was stirred for 10 min at 20° and a soln of $Na_2S_2O_5$ (0.4 g) in water (10 ml) was added. The solvent was removed *in vacuo* and the residue was distributed between EtOAc and water (each 25 ml). The aq phase was extracted with EtOAc (12 ml) and the combined organic phase was washed with 3% $NaHCO_3$aq (2 × 25 ml) and NaClaq (25 ml), dried and evaporated to a yellow gum. Crystallisation from aq IMS gave **15** as white crystals (336 mg, 65%), m.p. 116–117° (lit.[3] 120–3°, [4]120–122°), $[\alpha]_D$ + 56°, λ_{max} 237, 264 nm (ϵ 10900, 6750), ν_{max} 3330 (NH), 1765 (azetidin-2-one), 1720 (CO_2R) and 1680 and 1535 cm^{-1} (CONH), δ 2.04 (s; $OCOCH_3$), 3.54, 3.76 (AB-q, J18; C_2-H_2), 3.77 (s; CH_2CONH), 4.76, 4.99 (AB-q, J13; C_3-CH_2OCOCH_3), 4.95, 5.17 (AB-q, J12; CH_2CCl_3), 5.20 (d, J5; C_6-H), 5.77 (dd, J5, 8; C_7-H), 6.95, 7.36 (two m; C_4H_3S), 9.14 (d, J8; NH). Recrystallisation from IMS raised the m.p. to 117-9°, λ_{max} 238, 265 nm (ϵ 11700, 7050) [Found: C, 40.6; H, 3.3; Cl, 19.6; N, 5.3; S, 12.15. Calc. for $C_{18}H_{17}Cl_3N_2O_6S_2$ (527.85): C, 41.0; H, 3.25; Cl, 20.15; N, 5.3; S, 12.15%].

Sodium (6R, 7R)-*3-acetoxymethyl-7-(thien-2-ylacetamido) ceph-3-em-4-carboxylate*[22] **19**

A soln of **15** (2.71 g, 5.2 mmol) in anhyd formic acid (50 ml) was added to a suspension of Zn dust (2.7 g) and $ZnCl_2$ (60 mg) in anhyd formic acid (50 ml) cooled in an ice-bath. The cooling bath was withdrawn and the mixture was stirred at *ca* 25° for 5 hr, refrigerated overnight and filtered through a pad of Celite. The filter-bed was washed with formic acid, and the filtrate and wash were passed through a column of Deacidite FF ion-exchange resin (Cl^- cycle; 25 ml), elution with 98-100% formic acid. The eluate (180 ml) was evaporated *in vacuo* and the residue was distributed between EtOAc (100 ml) and 3% $NaHCO_3$ aq (400 ml), some solid remaining undissolved. The EtOAc phase was extracted with 3% $NaHCO_3$aq (50 ml), and the combined aq phase was layered with EtOAc (50 ml) and acidified to pH 1 with 2N HCl. The aq phase was re-extracted with EtOAc (50 ml) and the combined EtOAc extract was washed with NaClaq (25 ml), dried and evaporated. The residual foam was dissolved in acetone (10 ml) and a 10% solution of sodium 2-ethylhexanoate in acetone was added dropwise until pptn was complete. The suspension was refrigerated overnight and the solid was collected, washed with acetone and dried to give **19** as a hydrate (0.60 g, 26%), $[\alpha]_D$ + 106°, λ_{max} (pH 6 phosphate) 237 nm (ϵ 13800), inflexion at 260 nm (ϵ 7750), ν_{max} 3500 cm^{-1} (H_2O) otherwise having IR and PMR spectra similar to material[22] obtained by acylation of (6R, 7R)-3-acetoxymethyl-7-aminoceph-3-em-4-carboxylic acid derived from cephalosporin C [Found: C, 44.2; H, 3.7; N, 6.5; Na, 4.8; S, 15.2. Calc. for $C_{16}H_{15}N_2NaO_6S_2.H_2O$ (436.45) C, 44.0; H, 3.9; N, 6.4; Na, 5.3; S, 14.7%].

2,2,2-*Trichloroethyl* (1*S*,6*R*,7*R*)-N-[7-(*thien*-2-*ylacetamido*)-*ceph*-3-*em*-3-*ylmethyl*] *pyridinium chloride* 4-*carboxylate* 1-*oxide* **13**

A soln of **9** (942 mg, 1.81 mmol) in dry pyridine (7 ml) was stirred at *ca* 20° for 1.5 hr while a solid was steadily deposited. An equal volume of ether was added and the solid was collected and washed well with ether to give **13** as a pale brown powder (752 mg, 67.3%), m.p. 156–160°, λ_{max} 237, 263 nm (ϵ 10200, 9150), inflexion at 275 nm (ϵ 6700), ν_{max} 3700 to 3100 (NH and H_2O), 1795 (azetidin-2-one), 1734 (CO_2R), 1660 and 1510 (CONH) and 1040 cm^{-1} (S→O), δ 3.84 (s; CH_2CONH), 3.70, 4.08 (AB-q, J18; C_2-H_2), 5.01, 5.20 (AB-q, J12; CH_2CCl_3), 5.11 (d, J5; C_6-H), 5.75 (broad s; C_3-CH_2N^+), 5.99 (dd, J5, 9; C_7-H), 6.93, 7.34 (two m; C_4H_3S), 8.20, 8.65, 9.00 (three m; $C_5H_5N^+$), 8.50 (d; J9; NH). Analytical data was obtained on the product from a similar experiment [Found: C, 40.1; H, 3.3; N, 6.5; S, 10.5; total halogen content 3.9 g atom/mol. $C_{21}H_{19}Cl_4N_3O_5S_2.H_2O$ (617.4) requires: C, 40.85; H, 3.4; N, 6.8; S, 10.4%; total halogen content 4.0 g atom/mol].

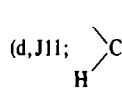
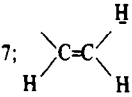
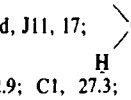
2,2,2-*Trichloroethyl* (6*R*,7*R*)-N-[7-(*thien*-2-*ylacetamido*)-*ceph*-3-*em*-3-*ylmethyl*] *pyridinium chloride* 4-*carboxylate* **16**

Dry DMF (1 ml) was added to a suspension of **13** (1.05 g, 1.75 mmol) in dry CH_2Cl_2 (18 ml) and the resulting solution was treated with PCl_3 (0.57 ml, 6.5 mmol). The solution was stirred at *ca* 21° for 1.5 hr while a solid precipitated. The mixture was refrigerated for 30 min and the solid was collected and washed well with dry CH_2Cl_2 to give **16** as a hygroscopic white powder (741 mg, 72.6%), m.p. 154–155°, $[\alpha]_D$ −8°, λ_{max} 238, 260 nm (ϵ 11300, 10450), ν_{max} 3180 (NH), 1780 (azetidin-2-one), 1738 (CO_2R) and 1690 and 1550 cm^{-1} (CONH), δ 3.59 (broad s; C_2-H_2), 3.77 (s; CH_2CONH), 5.01, 5.21 (AB-q, J12; CH_2CCl_3), 5.25 (d, J5; C_6-H), 5.72 (broad s; C_3-CH_2N^+), 5.84 (dd, J5, 9; C_7-H), 6.92, 7.35 (two m; C_4H_3S), 8.25, 8.68, 9.03 (three m; $C_5H_5N^+$), 9.18 (d, J9; NH). Satisfactory analytical data could not be obtained, possibly owing to the hygroscopic nature of the compound.

(6*R*,7*R*)-*N*-[7-(*Thien*-2-*ylacetamido*)*ceph*-3-*em*-3-*ylmethyl*]-*pyridinium*-4-*carboxylate hydronitrate* **21**

$ZnCl_2$ (20 mg), Zn dust (2.0 g) and a soln of **16** (2.0 g, 3.43 mmol) in anhyd formic acid (40 ml) were added successively to stirred anhyd formic acid (40 ml) cooled to 0–5°. The cooling bath was withdrawn and the mixture was stirred at 22° for 2 hr and filtered through a pad of Celite. The filter-bed was washed with formic acid (5 ml), and the combined filtrate and wash were evaporated *in vacuo*. The residual oil was dissolved in formic acid–water (4:1; 10 ml) and this solution was passed through a column of Deacidite FF ion-exchange resins (Cl^- cycle, 20 ml above OAc^-, 20 ml). Elution with formic acid-water (4:1) gave a fraction (50 ml) with optical activity which was evaporated *in vacuo*. The residue was dissolved in a mixture of water (40 ml) and acetic acid (3 ml) and the soln was washed with ether (2 × 40 ml). The aq phase was combined with a water backwash (40 ml) of the ether washings, filtered, degassed and freeze-dried to give impure **20** as a pale brown granular solid (1.145 g), λ_{max} (H_2O) 238 nm ($E^{1\%}_{1cm}$ 274), inflexion at 255 nm ($E^{1\%}_{1cm}$ 241). Part (500 mg) of this solid was dissolved in water (2.5 ml) and conc HNO_3 was added dropwise until crystallisation took place. The mixture was refrigerated and filtered to give **21** as off-white prisms (360 mg, 46.7%), m.p. 135–6°, $[\alpha]_D$ −6° (acetone-water; 1:1) (lit.[13] −16°), λ_{max} (H_2O) 238 nm ($E^{1\%}_{1cm}$ 287), inflexion at 255 nm ($E^{1\%}_{1cm}$ 250) (lit.[13] λ_{max} 240 nm ($E^{1\%}_{1cm}$ 318, ϵ 15350), inflexion at 255 nm ($E^{1\%}_{1cm}$ 289, ϵ 13950), having IR and PMR spectra similar to material[13] prepared from cephaloridine derived from cephalosporin C. Analytical data were obtained on a sample from a preliminary experiment, m.p. 142–143°, $[\alpha]_D$ −14° (acetone-water; 1:1), λ_{max} (H_2O) 238 nm (ϵ 15550), inflexion at 255 nm (ϵ 14050) [Found: C, 44.8; H, 3.8; N, 10.7; S, 12.7. Calc for $C_{19}H_{18}N_4O_7S_2.2H_2O$ (514.55) C, 44.35; H, 4.3; N, 10.9; S, 12.5%].

2,2,2-*Trichloroethyl* (1*S*, 6*R*, 7*R*)-3-*ethyl*-7-*formamidoceph*-3-*em*-4-*carboxylate* 1-*oxide* **22**

Via reduction of **25**. A soln of **2c** (10 g, 21.3 mmol) and triphenylphosphine (7.0 g, 26.7 mmol) in CH_2Cl_2 (400 ml) was stirred at 20–25° for 18 hr in the dark. The resulting solution of **23** was cooled to −18° and stirred while a soln of PBr_3 (3.03 ml, 31.2 mmol) in CH_2Cl_2 (50 ml) was added over 30 min. The soln was stirred for a further hr and 40% formaldehyde soln (80 ml) and satd $NaHCO_3$aq (320 ml) were added. The mixture was stirred at 20–25° for 1 hr and the aq phase was extracted with CH_2Cl_2 (50 ml). The combined organic phase was washed with water (120 ml), dried and evaporated, and the residual dark-red oil was chromatographed on Kieselgel G (300 g) in CH_2Cl_2-acetone (1:1) and then on silica gel (350 g) in CH_2Cl_2- acetone (9:1). The appropriate fractions were combined and evaporated, and the residue was triturated with MeOH to give 2,2,2-*trichloroethyl* (6*R*, 7*R*)-7-*formamido* 3-*vinylceph*-3-*em*-4-*carboxylate* **25** as white crystals (1.875 g, 22.8%), m.p. 121–2°, $[\alpha]_D$ −64° ($CHCl_3$), λ_{max} 297 nm (ϵ 13700). A portion (250 mg) was recrystallised from MeOH (5 ml) to give white needles (123 mg), m.p. 125-7°, $[\alpha]_D$, $[\alpha]_D$ −72° ($CHCl_3$), λ_{max} 298.5 nm (ϵ 13750), ν_{max} ($CHBr_3$) 3410 (NH), 1792 (azetidin-2-one), 1740 (CO_2R), 1700 and 1500 (CONH) and 920 cm^{-1} (=CH_2), δ ($CDCl_3$) 3.53, 3.79 (AB-q, J18; C_2-H_2), 4.80, 5.07 (AB-q, J12; CH_2CCl_3), 5.10 (d, J5; C_6-H), 5.45 (d, J11;  , 5.59 d, J17;  , 5.94 (dd, J5, 9; C_7-H), 6.66 (d, J9; NH), 7.17 dd, J11, 17;  , 8.29 (s, CHO) [Found: C, 37.6; H, 2.9; Cl, 27.3; N, 7.4; S, 8.4. $C_{12}H_{11}Cl_3N_2O_4S$ (385.7) requires C, 37.4; H, 2.9; Cl, 27.6; N, 7.3; S, 8.3%].

A soln of **25** (1.5 g, 3.89 mmol) in EtOAc (50 ml) was added to a suspension of 10% Pd on C (3 g) in EtOAc (100 ml) which had previously been flushed with N_2 and saturated with H_2. The mixture was stirred at 20–25° for 4 hr while a slow stream of H_2 was passed through it, and then filtered through Kieselguhr. The filter bed was washed with EtOAc, and the filtrate and wash were concentrated and passed through a short column of Kieselgel G. The eluate was evaporated to give 2,2,2-*trichloroethyl* (6R, 7R)-3-*ethyl*-7-*formamidoceph*-3-*em*-4-*carboxylate* **26** as a white foam (1.314 g, 87%), $[\alpha]_D$ +73.5°($CHCl_3$, λ_{max} 266 nm (ϵ 5850), ν_{max} ($CHBr_3$) 3440 (NH), 1784 (azetidin-2-one), 1736 (CO_2R) and 1695 and 1502 cm^{-1} (CONH), δ($CDCl_3$) 1.18 (t, J; CH_2 CH_3), 2.2 to 2.9 (m, C_3-CH_2CH_3), 3.34, 3.56 (AB-q, J18; C_2-H_2), 4.83, 5.00 (AB-q, J12; CH_2CCl_3), 5.06 (d, J5; C_6-H), 5.88 (dd, J5, 9; C_7-H), 6.56 (d, J9; NH), 8.32 (s; CHO) [Found: C, 37.5; H, 3.4; Cl, 26.2, N, 7.2; S, 7.9. $C_{12}H_{13}Cl_3N_2O_4S.\frac{1}{6}C_3H_8O_2$ (400.4) requires: C, 37.5; H, 3.6; Cl, 26.6; N, 7.0; S, 8.0%).

A soln of **26** (1.083 g, 2.81 mmol) in CH_2Cl_2 (25 ml) was cooled to 0–5° and treated with peracetic acid (0.98 equiv.) and then stirred for 30 min. The soln was washed with water (100 ml) and 3% $NaHCO_3$aq (10 ml), dried and evaporated. The residual oil was triturated with MeOH-ether to give **22** as white crystals (1.008 g, 89%), m.p. 160–165° (dec), λ_{max} 269 nm (ϵ 7650), part (250 mg) of which was subjected to preparative TLC on silica gel eluting with acetone-CH_2Cl_2 (1:1) to give a gelatinous solid (212 mg). This solid was crystallised from hot MeOH (5 ml) to give white fluffy needles (146 mg), m.p. 170–171°, $[\alpha]_D$ +76°, λ_{max} 271 nm (ϵ 7850), ν_{max} 3400 (NH), 1780 (azetidin-2-one), 1720 (CO_2R), *ca.* 1720 and 1502 (CONH) and 1010 cm^{-1} (S–O), δ ($CDCl_3$) 1.19 (t, J7; CH_2CH_3), 2.2 to 3.0 (m; C_3-CH_2CH_3), 3.29, 3.81 (AB-q, J18; C_2-H_2), 4.62 (d, J5; C_6-H), 4.88, 5.06 (AB-q, J12, CH_2CCl_3), 6.14 (dd, J5, 10; C_7-H), 7.00 (d, J10, NH), 8.30 (s; CHO) [Found: C, 35.6; H, 3.2; Cl, 26.1; N, 6.9; S, 7.6. $C_{12}H_{13}Cl_3N_2O_5S$ (403.7) requires: C, 35.7; H, 3.25; Cl, 26.35; N, 6.9; S, 7.9%).

By reaction with lithium dimethylcuprate. A soln of 1.15 M MeLi in ether (21.7 ml, 25 mmol) was added to a suspension of cuprous bromide (1.82 g, 12.7 mmol) in ether (10 ml) at −10–0° under dry N_2. The soln was then cooled to −70° and a soln of **2c** (2.303 g, 4.9 mmol) in THF (60 ml) was added with stirring at −60 to −70°. More THF (20 ml) was added at −60 to −70° and the mixture was then stirred at −70 to −75° for 1.5 hr. Saturated NH_4Claq (20 ml) was added at −55 to −70° and the mixture was partitioned between CH_2Cl_2 (200 ml) and water (100 ml). The aq phase was washed with CH_2Cl_2 (100 ml) and the combined

organic phase was dried, filtered through Kieselguhr and evaporated to a pale-yellow gel which was triturated with MeOH (*ca* 5 ml) to give **22** as a white crystalline solid (1.011 g, 51%), m.p. 172–174°, λ_{max} 269 nm (ϵ 7750), part (250 mg) of which was subjected to preparative TLC on silica gel eluting with acetone-CH_2Cl_2 (1:1) to give a gelatinous solid (194 mg). This solid was crystallised from hot MeOH (5 ml) to give white needles (176 mg), m.p. 175–176°, $[\alpha]_D$ +86.5°. λ_{max} 270.5 nm (ϵ 7800) [Found: C, 35.1; H, 3.2; Cl, 25.8; N, 6.7; S, 7.7%], having IR and PMR spectra similar to those reported above.

2,2,2-*Trichloroethyl* (1S, 6R, 7R)-3-*benzyl*-7-*formamidoceph*-3-*em*-4-*carboxylate* 1-*oxide* **24**

A soln of 1.725 M PhLi in ether–benzene (58 ml, 100 mmol) was added slowly to a stirred suspension of cuprous bromide (7.17 g, 50 mmol) in dry THF (150 ml) at −15° under dry N_2. The resulting mixture was recooled from 0 to −75° and stirred while a soln of **2c** (11.7 g, 25 mmol) in dry THF (450 ml) was added at −70 to −75° over 1.5 hr. The mixture was stirred at −75° for a further 1.5 hr and saturated NH_4Claq (100 ml) was added at −60 to −75°. The mixture was partitioned between CH_2Cl_2 (300 ml) and water (300 ml) and filtered. The aq phase was extracted with CH_2Cl_2 (2 × 150 ml), and the combined organic phase was washed with water (2 × 200 ml), combined with a CH_2Cl_2 backwash (150 ml) of the aq washes, dried and evaporated to low volume. The resulting suspension was diluted with EtOH and ether and cooled to give **24** (7.4 g, 63.5%), λ_{max} 272 nm (ϵ 9800). Evaporation of the filtrate gave a second crop of **24** (0.75 g, 6.4%), λ_{max} 272 nm (ϵ 9650). In a similar experiment using cuprous iodide, **2c** (4.68 g, 10 mmol) gave **24** (1.509 g, 32.4%), m.p. 188–191° (dec). Chromatography of the liquors gave more **24** (0.501 g, 10.8%), m.p. 188–194° (dec.), $[\alpha]_D$ + 27°, λ_{max} 272.5 nm (ϵ 9750), inflexions at 262, 267.5 nm (ϵ 8400, 9400), ν_{max} 3290 (NH), 1780 (azetidin-2-one), 1743 (CO_2R), 1648 and 1535 (CONH) and 1020 cm^{-1} (S→O), δ 3.57, 3.82 (AB-q, J18; C_2-H_2), 3.89 (s; C_3-$CH_2C_6H_5$), 5.05, 5.26 (AB-q, J12; CH_2CCl_3), 5.06 (d, J5; C_6-H), 6.01 (dd, J5, 10; C_7-H), 7.31 (s; C_6H_5), 8.21 (s; CHO), 8.41 (d, J10; NH) [Found: C, 43.8; H, 3.2; Cl, 22.5; N, 6.0; S, 7.1 $C_{17}H_{15}Cl_3N_2O_5S$ (465.8) requires: C, 43.8; H, 3.25; Cl, 22.8; N, 6.0; S, 6.9%].

2,2,2-*Trichloroethyl* (1S, 6R, 7R)-7-*amino*-3-*benzylceph*-3-*em*-4-*carboxylate* 1-*oxide hydrochloride* **28**

$POCl_3$ (0.86 ml, 9.34 mmol) was added to a suspension of **24** (2.177 g, 4.67 mmol) in MeOH (15 ml) cooled to 5°, causing the solid to dissolve. The product began to crystallise after 1 min. The mixture was stirred at 5° for 1.25 hr, diluted with ether (15 ml) and chilled at −14° for 1 hr to give **28** as white crystals (1.937 g, 87.5%), m.p. 189–194° (dec), $[\alpha]_D$ −17°, λ_{max} 273.5 nm (ϵ 9450), inflexions at 262, 268 nm (ϵ 880, 7650), ν_{max} ($CHBr_3$) 3150–2500 (bonded NH_3^+), 1782 (azetidin-2-one), 1740 (CO_2R) and 1012 cm^{-1} (S→O), δ 3.76, 3.98 (AB-q, J16; C_3-$CH_2C_6H_5$), 3.82 (s; C_2-H_2), 5.04, 5.24 (AB-q, J12; CH_2CCl_3), 5.18, 5.34 (AB-q, J4; C_7-H and C_6-H), 7.29 (s; C_6H_5) [Found: C, 40.6; H, 3.4; Cl, 29.5; N, 5.6; S, 6.6. $C_{16}H_{16}Cl_4N_2O_4S$ (474.2) requires C, 40.5; H, 3.4; Cl, 29.9; N, 5.9; S, 6.8%].

2,2,2-*Trichloroethyl* (1S, 6R, 7R)-3-*benzyl*-7-(*thien*-2-*ylacetamido*-*ceph*-3-*em*-4-*carboxylate* 1-*oxide* **14**

$CaCO_3$ (1.16 g) and thien-2-ylacetyl chloride (851 mg, 533 mmol) were added to a stirred soln of **28** (2.5 g, 5.27 mmol) in DMF (15 ml) cooled to 5°. The mixture was stirred at 5° for 1.25 hr, filtered and partitioned between CH_2Cl_2 (500 ml) and water (200 ml). The organic phase was washed with water, 2N HCl, 3% $NaHCO_3$aq and water (each 200 ml), dried and evaporated to a dark oil which was dissolved in EtOAc (250 ml). This solution was washed with water (3 × 100 ml), dried, decolorised with charcoal, filtered and evaporated to low volume when crystallisation ensued. This suspension was diluted with ether to give **14** (1.705 g, 57.5%), m.p. 188–92° (dec), $[\alpha]_D$ +44°, λ_{max} 232.5, 272.5 nm (ϵ 12900, 9800), inflexions at 261, 267 nm (ϵ 8350, 9450), ν_{max} ($CHBr_3$) 3380 (NH), 1798 (azetidin-2-one), 1740 (CO_2R), 1680 and 1510 (CONH) and 1040 cm^{-1} (S→O), δ 3.53, 3.75 (AB-q, J18; C_2-H_2), 3.87 (s; $C_4H_3SCH_2$ and C_3-$CH_2C_6H_5$), 5.01 (d, J5; C_6-H), 5.04, 5.24 [AB-q, J12; CH_2CCl_3), 5.88 (dd, J5, 9; C_7-H), 6.98, 7.38 (two m; C_4H_3S), 7.30 (s; C_6H_5), 8.37 (d, J9; NH) [Found: C, 46.8; H, 3.3; Cl, 18.7; N, 5.0; S, 11.3. $C_{22}H_{19}Cl_3N_2O_5S_2$ (561.9) requires: C, 47.0; H, 3.4; Cl, 18.9; N, 5.0; S, 11.4%].

2,2,2-*Trichloroethyl* (6R, 7R)-3-*benzyl*-7-(*thien*-2-*ylacetamido*-*ceph*-3-*em*-4-*carboxylate* **17**

KI (4.0 g, 24 mmol) and acetyl chloride (0.43 ml, 6 mmol) were added to a stirred soln of **14** (1.684 g, 3.0 mmol) in dry DMF (6 ml) cooled to 5°. The mixture was stirred at 5° for 1 hr and 5% $Na_2S_2O_5$aq-DMF (1:1) was added to discharge the I_2. The mixture was partitioned between EtOAc (100 ml) and water (50 ml), and the organic phase was washed with water and 1% $Na_2S_2O_5$aq (each 50 ml), combined with an EtOAc backwash (50 ml) of the combined aq phase, dried and evaporated to a yellow oil which was dissolved in EtOAc (100 ml). This solution was washed with water (2 × 50 ml), dried and evaporated to a foam (1.528 g) which was chromatographed on Kieselgel G (19 g). CH_2Cl_2-acetone (19:1) eluted a pale yellow foam which was triturated with ether to give **17** as pale yellow crystals (1.30 g, 80%), m.p. 142–144°, $[\alpha]_D$ −25°, λ_{max} 234.5, 259, 265.5, 271 nm (ϵ 13000, 7850, 8150, 8000), ν_{max} ($CHBr_3$) 3360 (NH), 1776 (azetidin-2-one), 1734 (CO_2R) and 1675 and 1504 cm^{-1} (CONH), δ ($CDCl_3$) 3.14, 3.41 (AB-q, J18; C_2-H_2), 3.62, 4.10 (AB-q, J14; C_3-$CH_2C_6H_5$), 3.82 (s; $C_4H_3SCH_2$), 4.80, 5.04 (AB-q, J12; CH_2CCl_3), 5.02 (d, J4; C_6-H), 5.84 (dd, J9, 4; C_7-H), 6.41 (d, J9; NH), 6.98, 7.3 (two m; C_4H_3S), 7.28 (s; C_6H_5) [Found: C, 48.3; H, 3.6; Cl, 19.4; N, 4.6; S, 11.6. $C_{22}H_{19}Cl_3N_2O_4S_2$ (545.9) requires: C, 48.4; H, 3.5; Cl, 19.5; N, 5.1; S, 11.75%].

(6R, 7R)-3-*Benzyl*-7-(*thien*-2-*ylacetamido*)-*ceph*-3-*em*-4-*carboxylic acid* **27**[21]

Zn dust (3.0 g) was added to a soln of **17** (4.99 mg; 0.915 mmol) in 5% aq formic acid (19 ml) cooled in an ice-bath. The mixture was stirred at *ca* 5° for 5 min, diluted with EtOAc and filtered through Kieselguhr. The filtrate was added to EtOAc (25 ml) and water (75 ml) and the pH of the mixture was adjusted to 8 with 2N NaOH. The organic phase was extracted with 3% $NaHCO_3$aq (3 × 50 ml) and the aq phases were combined, covered with EtOAc (50 ml), and acidified to 2.5 with 2N HCl. The aq phase was reextracted with EtOAc (3 × 50 ml) and the combined EtOAc extract was dried and evaporated to an off-white foam. Trituration with ether containing a few drops of MeOH gave **27** as white crystals (127 mg, 32.6%), m.p. 151–156°, $[\alpha]_D$ −1° [lit.[21] −63° (*c* 1; $CHCl_3$)], λ_{max} (pH 6 phosphate buffer) 236 nm (ϵ 15100), inflexions at 262, 267 nm (ϵ 10350, 9700) [lit.[21] λ_{max} (EtOH) 237, 265.5 nm (ϵ 11600, 6900)], ν_{max} ($CHBr_3$) 3390 (NH), 3550–2400 (bonded OH), 1780 (azetidin-2-one), 1738 (CO_2H) and 1682 and 1507 cm^{-1} (CONH), δ 3.18, 3.56 (AB-q, J18; C_2-H_2), 3.57, 4.01 (AB-q, J15; C_3-$CH_2C_6H_5$), 3.77 (s; $C_4H_3SCH_2$), 5.15 (d, J5; C_6-H), 5.68 (dd, J5, 8; C_7-H), 6.97, 7.3 (two m; C_4H_3S), 7.33 (s; C_6H_5), 9.13 (d, J8; NH) [Found: C, 57.9; H, 4.6; N, 6.6; S, 15.2. $C_{20}H_{18}N_2O_4S_2$ (414.5) requires C, 57.95; H, 4.4; N, 6.8; S, 15.5%].

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