Total Synthesis of Analogues of the β-Lactam Antibiotics. Part 6.[1] (6*R**)-4-(t-Butoxycarbonyl)-2-methoxycarbonyl-3-oxacepham 1,1-Dioxides†

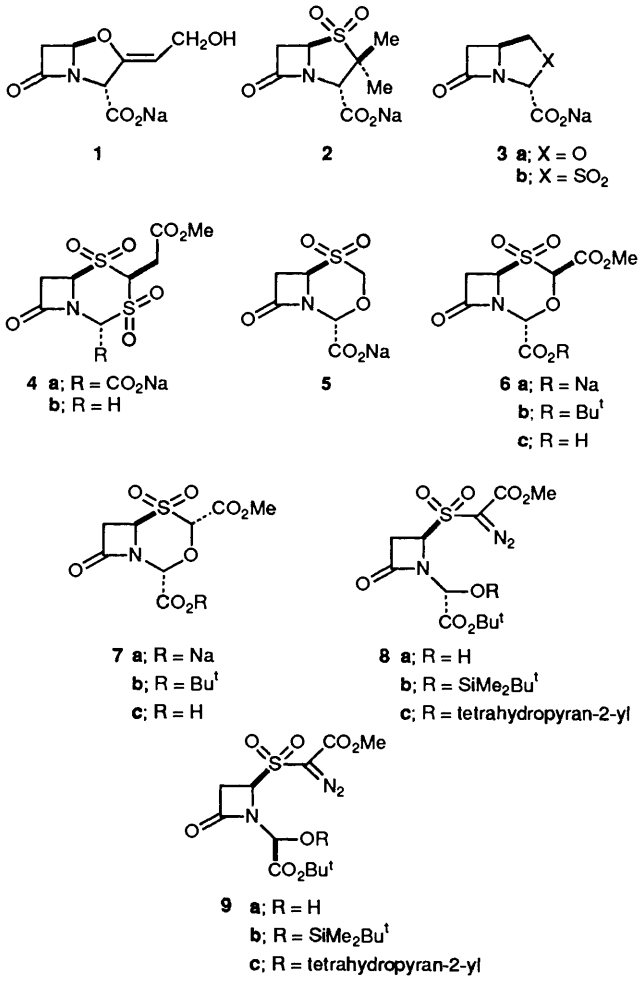
Peter H. Crackett,[a] Paul Sayer,[a] Richard J. Stoodley *,[a] and Colin W. Greengrass[b]
[a] *Department of Chemistry, UMIST, P.O. BOX 88, Manchester M60 1QD, UK*
[b] *Pfizer Central Research, Sandwich, Kent CT13 19NJ, UK*

The (2*S**,4*R**)/(2*R**,4*R**)- and (2*R**,4*S**)/(2*S**,4*S**)-diastereoisomers of the title compound, *i.e.* compounds **6b/7b** and **22/23**, have been prepared by a strategy involving final closure of the 2,3-bond in which a novel carbenoid-insertion reaction is implicated. Thus, in the presence of rhodium(II) acetate, t-butyl (α*R**)-α-{(4*R**)-4-[diazo(methoxycarbonyl)methylsulphonyl]-2-oxoacetidin-1-yl}-α-(tetrahydropyran-2-yloxy)acetate **8c** (both as a 3:1 and as a 1:2 mixture of epimers) afforded a 3:1 mixture of the oxacepham dioxides **6b/7b**. Under similar conditions, the (α*S**)-diastereoisomer of compound **8c**, *i.e.* **9c** (as a 2:1 mixture of epimers), gave rise to a 2:1 mixture of the oxacepham dioxides **22/23**. The diazo compounds **8c** and **9c** were prepared from methyl α-[(2*R**)-4-oxoazetidin-2-ylthio]acetate **12a** by sequential reactions with t-butyl α,α-dihydroxyacetate (to give **17a/18a**), acidic dihydropyran (to furnish **17e/18e**), potassium permanganate (to yield **15d/16d**), and *p*-carboxybenzenesulphonyl azide.

Deprotection of the t-butyl ester moiety of compounds **6b/7b** was achieved by using trifluoroacetic acid but the derived sodium salts **6a/7a** failed to synergise the action of ampicillin against β-lactamase-producing bacteria.

The potent β-lactamase-inhibitory properties of sodium clavulanate **1**[2] and sulbactam sodium salt **2**[3] have prompted us to prepare related bicyclic β-lactams for biological evaluation. The isoclavam carboxylate **3a**,[4] our initial target, turned out to be somewhat unstable in aqueous sodium and, in our hands, showed no activity; subsequently, however, the material was claimed to be a β-lactamase inhibitor.[5] Our second target, the isopenam dioxide **3b**,[6] was stable in aqueous solution but it failed to inhibit the β-lactamase from *Pseudomonas aeruginosa*. Recently, we prepared the thiacephem dioxide **4a**,[1,7] which incorporates structural characteristics common to both compounds **2** and **3b**; however, it underwent a spontaneous (and unexpected) decarboxylation in water to give compound **4b**, precluding its biological assessment.

With 3-oxocepham‡ dioxides, *e.g.* compound **5**, which possess structural features common to both compounds **2** and **3a**, such a decarboxylation is unlikely. In this paper, we describe the first examples§ of 3-oxocepham dioxides. The synthetic route that was evolved, in which the bicyclic system was constructed by final closure of the 2,3-bond, is notable in that a novel carbenoid cyclisation is implicated.



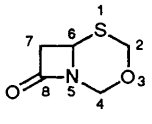
Results and Discussion

It is well established that carbenoids derived from diazo compounds undergo insertion reactions into O–H bonds.[9] In consequence, we selected the oxacepham dioxides **6a/7a** as our targets, hoping that the projected precursors, compounds **6b/7b**, would be accessible from the diazo sulphone **8a**.

Initially, we planned to assemble compounds **8a/9a** from the azetidinone **10** and t-butyl dihydroxyacetate[10] by using Woodward methodology.[11] However, the plan was thwarted by

† Part of this work was presented at the 10th International Congress of Heterocyclic Chemistry, held in Waterloo, Ontario, Canada, in 1985 (R. J. Stoodley, in *Lectures in Heterocyclic Chemistry*, ed. R. N. Castle and V. Snieckus, Hetero Corporation, USA, 1985, vol. 8, p. 183).

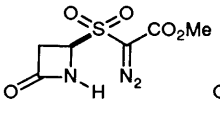
‡ This trivial name is used to describe the following ring system which is numbered as shown.



§ Subsequent to our work, 3-oxacephams have been prepared by ketene/imine cycloadditions (ref. 8).

our inability to derive the precursor **10**. Non-β-lactam products arose when the azetidinone **11a** was subjected to typical diazo-transfer conditions (*p*-$MeC_6H_4SO_2N_3$–piperidine–CH_2Cl_2).[12] The sulphone **11a** was prepared (87% yield after chromatography) by oxidation of the sulphide **12a**[13] with potassium permanganate in aq. acetic acid; in turn, the sulphide **12a** was obtained (61% yield after chromatography) by treatment of the acetoxyazetidinone **13** with methyl mercaptoacetate and sodium carbonate in aq. acetone.

Speculating that the non-β-lactam products arose from the azetinone **14**, formed as an intermediate from the azetidinone **11a** by a base-induced β-elimination, we undertook the synthesis of compound **11b**. Treatment of the azetidinone **12a** with t-butyldimethylsilyl chloride (TBDMSCl) and imidazole in *N*,*N*-dimethylformamide (DMF)[14] gave compound **12b** (86% yield after chromatography), which underwent oxidation ($KMnO_4$–aq. HOAc) to afford the sulphone **11b** (82% yield after recrystallisation). Again, however, non-β-lactam products emerged when compound **11b** was subjected to diazo-transfer conditions.



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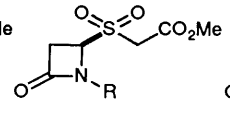
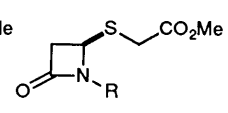
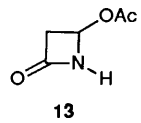


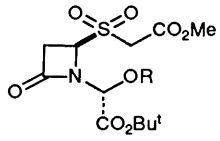
11 a; R = H
b; R = $SiMe_2Bu^t$



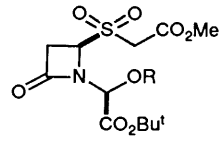
12 a; R = H
b; R = $SiMe_2Bu^t$



13

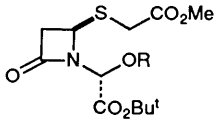


15 a; R = H
b; R = $SiMe_2Bu^t$
c; R = Ac
d; R = tetrahydropyran-2-yl

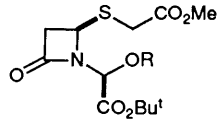


16 a; R = H
b; R = $SiMe_2Bu^t$
c; R = Ac
d; R = tetrahydropyran-2-yl

14



17 a; R = H
b; R = $SiMe_2Bu^t$
c; R = Ac
d; R = C(OMe)Me_2
e; R = tetrahydropyran-2-yl



18 a; R = H
b; R = $SiMe_2Bu^t$
c; R = Ac
d; R = C(OMe)Me_2
e; R = tetrahydropyran-2-yl

Next, we attempted to access the targets **8a**/**9a** by way of precursors of types **15**/**16** and **17**/**18**. Since it was unlikely that the amido alcohol moiety would survive the diazo-transfer conditions, a hydroxy-protecting group was deemed necessary. Obviously, as well as being compatible with the diazo-transfer reaction, the protecting group had to be removable without damage to the diazo and amido alcohol functions. The t-butyldimethylsilyl group[14] was selected for an initial study.

The azetidinone **12a** was converted into the amido alcohols **17a**/**18a** (80% yield after chromatography), as a 1:1 mixture of diastereoisomers, by reaction with t-butyl dihydroxyacetate and triethylamine in tetrahydrofuran (THF). When treated with TBDMSCl and imidazole in DMF, the amido alcohols **17a**/**18a** were transformed into the *O*-silyl derivatives **17b**/**18b** (62% yield after chromatography), as a 3:1 mixture of diastereoisomers. On the basis of subsequent evidence to be discussed later, the major diastereoisomer was assigned the stereostructure **17b**.

Under the usual oxidative conditions, the 3:1 mixture of sulphides **17b**/**18b** was converted into a 3:1 mixture of the sulphones **15b**/**16b** (89% yield after chromatography). In the presence of toluene-*p*-sulphonyl azide and piperidine in dichloromethane, the aforecited mixture afforded a 3:1 mixture of the diazo derivatives **8b**/**9b** (53% yield after chromatography); the major diazo compound **8b** was isolated in 20% yield from the mixture by fractional crystallisation. The use of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in place of piperidine in the diazo-transfer reaction led to an improvement in the yield of compounds **8b**/**9b** (86% yield after chromatography); after crystallisation, the major diastereoisomer **8b** was obtained in 34% yield.

Of the several conditions examined to induce the transformation **8b** ⟶ **8a**, only those described by Newton *et al.*[15] showed any hint of success. Thus, subjection of the *O*-silyl derivative **8b** to the action of 40% aq. hydrofluoric acid in acetonitrile led, after chromatography, to the isolation of the amido alcohol **8a** as a single diastereoisomer in 11% yield.

In spite of the abysmal yield in the deprotection step, we were able to examine the proposed cyclisation reaction. Gratifyingly, when treated in benzene with a catalytic quantity of rhodium(II) acetate,[16] the diazo compound **8a** was converted into a less polar product, which was isolated as a solid in 58% yield after chromatography and crystallisation. Analytical and spectroscopic evidence left little doubt that the product was a 2:1 mixture of the oxacepham dioxides **6b**/**7b** (the evidence for the stereochemical assignment will be discussed later). In particular, the material showed a strong IR absorption at 1795 cm^{-1} for the β-lactam carbonyl group.

In the hope of improving the yield of compounds **8a**/**9a**, the acetyl group was examined next as the alcohol-protecting group. When treated with acetic anhydride and pyridine, the amido alcohols **17a**/**18a** afforded the *O*-acetyl derivatives **17c**/**18c** (74% yield after chromatography) which underwent oxidation with potassium permanganate to give the sulphones **15c**/**16c** (69% yield after chromatography); compounds **17c**/**18c** and **15c**/**16c** were each isolated as 1:1 mixtures of diastereoisomers. Disappointingly, when subjected to the action of toluene-*p*-sulphonyl azide and piperidine in dichloromethane, compounds **15c**/**16c** afforded non-β-lactam products.

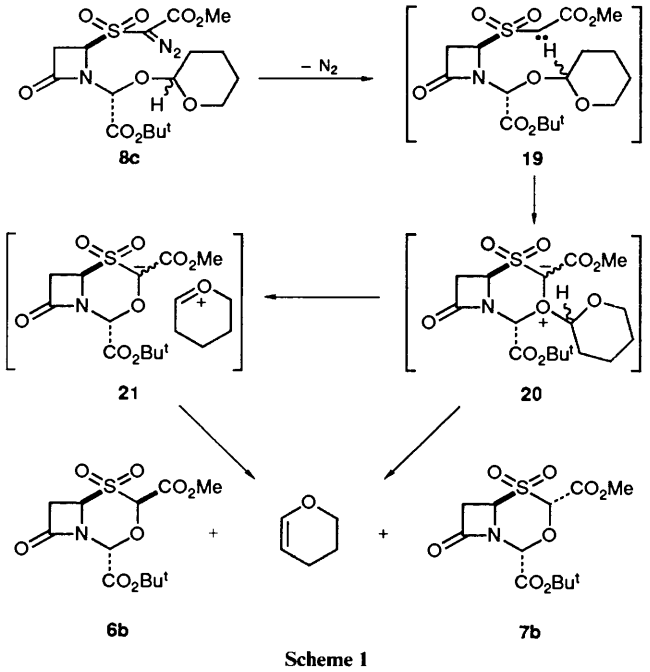
Two other acid-sensitive hydroxy-protecting groups were also examined. The first of these, the 2-methoxypropan-2-yl group,[17] turned out to be too acid labile. Thus, treatment of the amido alcohols **17a**/**18a** in 2-methoxypropene with a trace of phosphoryl trichloride gave the adducts **17d**/**18d** (81% yield after chromatography), as a 1:1 mixture of diastereoisomers. Under the oxidative conditions, however, the sulphides **17d**/**18d** were transformed into the sulphone **15a** or **16a** (42% yield after chromatography) which, surprisingly, appeared to be a single diastereoisomer by 300 MHz ^1H NMR spectroscopy. Attempts to reprotect the hydroxy function of compound **15a** or **16a** [CH_2=C(OMe)Me–$POCl_3$] led to non-β-lactam products. As expected, non-β-lactam materials also resulted when compound **15a** or **16a** was subjected to the diazo-transfer conditions.

The tetrahydropyran-2-yl (THP) group[18] was the last alcohol-protecting group to be investigated. Treatment of the amido alcohols **17a**/**18a** in dihydropyran with a trace of toluene-*p*-sulphonic acid (PTSA) gave a 1:1 mixture of the adducts **17e**/**18e** (each as a 1:1 mixture of epimers) (93% yield after chromatography). Oxidation of the sulphides **17e**/**18e** with potassium permanganate led, after chromatography, to the isolation of three fractions. The first (24% yield) and second fractions (29% yield) were considered to possess the stereostructure **15d** on the basis of subsequent findings (see later); by NMR spectroscopy, the first fraction comprised a 3:1 mixture of epimers *A* and *B* whereas the second fraction comprised a 1:2 mixture of the same epimers. The third fraction

was resubjected to chromatography to give compound **16d** (19% yield) as a 2:1 mixture of epimers *A* and *B*.

Although the sulphone **15d** underwent the diazo-transfer reaction when treated with toluene-*p*-sulphonyl azide and piperidine in dichloromethane, difficulty was experienced in freeing the product **8c** of tolyl-containing materials. The problem was overcome by the use of *p*-carboxybenzene-sulphonyl azide.[19] Thus, the last cited material reacted with the sulphone **15d** (as a 3:1 mixture of epimers *A* and *B*) in acetonitrile in the presence of triethylamine to give, after work-up (which involved washing of a solution of the product in CH_2Cl_2 with aq. $NaHCO_3$) and chromatography, the diazo compound **8c** (as a 3:1 mixture of epimers *A* and *B*) in 70% yield. Fractional crystallisation of the mixture led to the isolation of epimer *A* of the diazo compound **8c** in an analytically pure state. In the similar manner, the sulphone **15d** (as a 1:2 mixture of epimers *A* and *B*) afforded the diazo compound **8c** (as a 1:2 mixture of epimers *A* and *B*) in 67% yield and the sulphone **16d** (as a 2:1 mixture of epimers *A* and *B*) gave rise to the diazo compound **9c** (as a 2:1 mixture of epimers *A* and *B*) in 84% yield. Fractional crystallisation of the last cited mixture gave epimer *A* of compound **9c** in an analytically pure state. Numerous attempts were made to remove the THP group from compound **8c** but these proved to be fruitless.

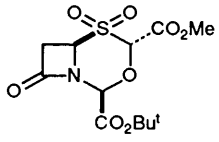
The mechanistic speculation outlined in Scheme 1 prompted us to examine the reaction of compound **8c** with rhodium(II) acetate. Thus, it was reasoned that the carbene intermediate **19** (or its carbenoid equivalent) might afford the ylide **20** which, either directly or by way of the ion-pair **21**, might give rise to the oxacepham dioxides **6b** and **7b** and dihydropyran.



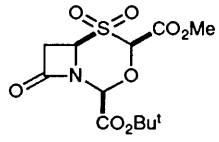
Scheme 1

Gratifyingly, when treated with rhodium(II) acetate in dichloromethane, the diazo compound **8c** (both as 3:1 and 1:2 mixtures of epimers *A* and *B*) was transformed into a 3:1 mixture of the oxacephams **6b**/**7b** in 44–63% yield. The isomeric mixture, which could not be separated by chromatography or fractional crystallisation, was obtained in an analytically pure state and its spectroscopic properties matched those of the product obtained from the reaction of the diazo compound **8a** with rhodium(II) acetate.

Under corresponding conditions, the diazo compound **9c** (as a 2:1 mixture of epimers *A* and *B*) afforded a crystalline product (55% yield after chromatography) as an inseparable 2:1 mixture of isomers. Analytical and spectroscopic considerations left little doubt that the product was a 2:1 mixture of the oxacepham dioxides **22**/**23** (the evidence for the stereochemistry of these compounds will be discussed shortly). In particular, the IR spectrum featured a strong absorption at 1785 cm^{-1} for the β-lactam carbonyl group.



22



23

The aforecited findings are of interest in a number of respects. First, they reveal that a THP ether can act as an equivalent of a hydroxy group with respect to diazo-insertion reactions. Obviously, groups which can fulfil a protecting role and which are also activated for subsequent reaction without the need for a separate deprotection step are of considerable synthetic merit. Secondly, the finding that the stereochemistry at the amido alcohol/ether centre of the reactants is retained at position 4 of the products, *i.e.* **8c** ⟶ **6b**/**7b** and **9c** ⟶ **22**/**23**, emphasises that the cyclisation reaction is subject to kinetic control with respect to this stereocentre. Thirdly, the stereochemistry at the acetal centre of the reactant has no bearing on the stereochemistry at position 2 of the products, at least with respect to the transformation **8c** ⟶ **6b**/**7b**. Moreover, the observation that the diazo compounds **8a** and **8c** gave the oxyacephams **6b** and **7b** in a similar ratio may imply that the C(2) stereochemistry of the products is subject to thermodynamic control.

The assignment of the stereostructures **6b** and **7b** to the major 3:1 pair of oxacepham dioxides and of the stereostructures **22** and **23** to the minor 2:1 pair of oxacepham dioxides was based upon NMR spectroscopy. Thus, the routine 300 MHz ^1H NMR spectra showed singlets at δ 5.37, 5.43, 5.68 and 6.12 (0.25, 0.25, 0.75 and 0.75 H) for the major pair and at δ 5.03, 5.41, 5.55 and 6.14 (0.33, 0.66, 0.33 and 0.66 H) for the minor pair. Obviously, these signals had to be attributed to the 2- and 4-hydrogen atoms of the oxacepham dioxides **6b**, **7b**, **22** and **23**. Whilst the 2-hydrogen atoms are likely to appear at lower field than their 4-counterparts, it was important to provide a firmer basis for their assignment.

The 2-hydrogen atoms are expected to be more acidic than the 4-hydrogen atoms and, consequently, they are likely to undergo deuterium exchange more readily. In the presence of deuterium oxide and triethylamine, the signals at δ 5.37 and 6.12 disappeared from the NMR spectrum of the major pair whereas those at δ 5.55 and 6.14 disappeared from the NMR spectrum of the minor pair. Evidently, in the minor diastereoisomer of the major pair of oxacepham dioxides, the 2-hydrogen atom appears at slightly higher field (δ 5.37) than the 4-hydrogen atom (δ 5.43); in the other isomers, the 2-hydrogen atoms resonate at lower field than their 4-counterparts.

The major and minor pairs of oxacepham dioxides were subjected to nuclear Overhauser difference (NOED) spectroscopic studies. For the predominant diastereoisomer of the major pair, irradiation of the 2-hydrogen atom caused an 11% enhancement of the 4-hydrogen atom and a 14% enhancement of the 6-hydrogen atom; irradiation of the 4-hydrogen atom resulted in a 5% enhancement of the 2-hydrogen atom; and irradiation of the 6-hydrogen atom caused 20 and 5% enhancements of the 2- and 4-hydrogens atoms. For the minor diastereoisomer, irradiation of the 2-hydrogen atom brought about a 20% enhancement of the 4-hydrogen atom; irradiation of the 4-hydrogen atom caused a 29% enhancement of the 2-hydrogen; and irradiation of the 6-hydrogen atom caused no

enhancements. These results strongly suggest that the minor diastereoisomer possesses the stereostructure **7b** and that the major diastereoisomer possesses the stereostructure **6b** or **23**.

For the major diastereoisomer of the minor pair of oxacepham dioxides, irradiation of the 2-hydrogen atom effected an 8% enhancement of the 4-hydrogen atom; irradiation of the 4-hydrogen atom enhanced the 2-hydrogen atom by 8% and the 6-hydrogen atom by 6%; and irradiation of the 6-hydrogen atom resulted in a 5% enhancement of the 2-hydrogen atom and a 13% enhancement of the 4-hydrogen atom. For the minor diastereoisomer, irradiation of the 2-hydrogen atom caused a 20% enhancement of the 4-hydrogen atom; irradiation of the 4-hydrogen atom brought about a 28% enhancement of the 2-hydrogen atom; and irradiation of the 6-hydrogen atom effected a 10% enhancement of the 2-hydrogen atom. These results suggest that the major diastereoisomer possesses the stereostructure **22** and that the minor diastereoisomer possesses the stereostructure **23**. Accordingly, the major diastereoisomer of the major pair of oxacepham dioxides is assigned the stereostructure **6b**.

A closer examination of the normal 300 MHz ^{1}H NMR spectra of the oxacepham dioxides revealed long-range coupling (J 1 Hz) between the 4- and 7α-hydrogen atoms only in the case of the major diastereoisomer of the minor pair. However, when the spectra were plotted using resolution-enhancement techniques, the situation because much more complex and several long-range effects became apparent. Thus, for the predominant diastereoisomer of the major pair, *i.e.* compound **6b**, long-range coupling ($J \leqslant 0.5$ Hz) was in evidence between the 2- and 4-hydrogen atoms, the 2- and 6-hydrogen atoms, and the 4- and 6-hydrogen atoms. For the minor diastereoisomer, *i.e.* compound **7b**, similar long-range coupling was noted between the 2- and 6-hydrogen atoms and the 4- and 7β-hydrogen atoms. For the predominant diastereoisomer of the minor pair, *i.e.* compound **22**, long-range coupling ($J \leqslant 0.5$ Hz) was observed between the 2- and 6-hydrogen atoms, the 4- and 6-hydrogen atoms, and the 4- and 7β-hydrogen atoms in addition to long-range coupling (J 1.3 Hz) between the 4- and 7α-hydrogen atoms. For the minor diastereoisomer, *i.e.* compound **23**, long-range coupling (J 0.8 Hz) was observed between the 4- and 7α-hydrogen atoms.

Earlier, it was noted in the case of cephams that long-range coupling ($J \sim 1$ Hz) occurs between the 4- and 7α-hydrogen atoms only when the former are α-orientated.[20] The observation that the compounds assigned the stereostructures **22** and **23** showed a similar effect reinforces our stereochemical assignments.

The finding that the major pair of oxacepham dioxides comprised a 3:1 mixture of the 2-epimers **6b** and **7b** established that their precursors shared the same geometry adjacent to the t-butoxycarbonyl group. In consequence, the mixture of diazo precursors, *i.e.* **8c**, and the mixture of sulphone precursors, *i.e.* **15d**, were epimeric at the acetal centre. Similarly, the stereostructures **8a** and **8b** were assigned to the related precursors. The assignment of the stereostructures **22** and **23** to the 3:1 mixture of the minor pair of oxacepham dioxides revealed that the mixture of diazo precursors, *i.e.* **9c**, and the mixture of sulphone precursors, *i.e.* **16d**, were epimeric at the acetal centre.

When subjected to the action of trifluoroacetic acid (TFA), the 3:1 mixture of the oxacepham esters **6b**/**7b** was converted into a 3:1 mixture of the oxacepham acids **6c**/**7c**, which treated with sodium hydrogen carbonate in aq. acetone or sodium 2-ethylhexanoate in ethanol–butan-1-ol–diethyl ether to give a 3:1 mixture of the oxacepham salts **6a**/**7a**. Although stable in deuterium oxide over a period of 24 h, the salts **6a**/**7a** did undergo deuterium exchange of the 2-hydrogen atoms. The mixture failed to synergise the effect of ampicillin against β-lactamase-producing bacteria, suggesting that the oxacephams **6a**/**7a** lacked β-lactamase-inhibitory properties.

Experimental

Dry solvents, referred to in the ensuing experiments, were prepared as follows: THF was dried over calcium hydride and, immediately prior to use, was distilled; pyridine was dried over potassium hydroxide, distilled, and stored over 4 Å molecular sieves; DMF and acetonitrile were stored over 4 Å molecular sieves; dichloromethane was distilled from anhydrous calcium chloride. Light petroleum refers to that fraction boiling in the range 40–60 °C. 300 MHz ^{1}H NMR spectra were recorded on a Bruker AC300. For ^{1}H NMR spectra, J-values are given in Hz. For chromatographic and other instrumental details, see Parts 1[4] and 2.[6]

Preparation of Methyl α-[(2R*)-4-*Oxoazetidin*-2-*ylthio*]-*acetate* **12a**.[5]—A solution of sodium carbonate (8.00 g, 75.5 mmol) in water (80 cm^3) was added in drops during 0.25 h to a stirred solution of the acetoxyazetidinone **13** (8.01 g, 62.0 mmol) and methyl mercaptoacetate (6.70 cm^3, 74.9 mmol) in a mixture of acetone (50 cm^3) and water (80 cm^3). When the reaction was complete (TLC; *ca.* 2.5 h), the mixture was concentrated (to remove Me_2CO) and extracted with ethyl acetate. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave the title compound **12a** (6.67 g, 61%) as a chromatographically homogeneous syrup; ν_{max}(film)/cm^{-1} 3320 (NH), 1765 (β-lactam C=O) and 1740 (ester C=O); λ_{max}(EtOH)/nm 210 (ε 1900); δ(60 MHz; $CDCl_3$) 2.95 (1 H, ddd, J 16, 3 and 1, COC*H*HCH), 3.35 (1 H, dd, J 16 and 5, COCH*H*CH), 3.45 (2 H, s, SCH_2CO), 3.80 (3 H, s, MeO), 4.95 (1 H, dd, J 5 and 3, CH_2CHS) and 7.40 (1 H, br s, NHCO) [addition of D_2O caused the ddd at δ 2.95 to collapse to a dd (J 16 and 3) and the s at δ 7.40 to disappear]; m/z (EI) 148, 102 ($M^+ - C_3H_5O_2$) and 70 ($C_3H_4NO^+$, base peak).

Preparation of Methyl α-[(2R*)-4-*Oxoazetidin*-2-*ylsulphonyl*]*acetate* **11a** (*with E. Roberts*).—A solution of potassium permanganate (0.500 g, 3.16 mmol) in water (10 cm^3) was added dropwise to a stirred, ice-cooled solution of the sulphide **12a** (0.200 g, 1.14 mmol) in 60% aq. acetic acid (10 cm^3). After 45 min, the mixture was decolourised by the addition of 30% aq. hydrogen peroxide and then partitioned between ethyl acetate and water. The organic phase was washed successively with water, saturated aq. sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated. Purification of the residue by silica-gel column chromatography (EtOAc as eluent) gave the *title compound* **11a** (0.206 g, 87%) as a crystalline solid. After recrystallisation from methanol, the sample showed m.p. 89–90 °C; ν_{max}(KBr)/cm^{-1} 3440 and 3280 (NH), 1775 (β-lactam C=O) and 1705 (ester C=O); λ_{max}(EtOH)/nm 205 (ε 820); δ(60 MHz; $CDCl_3$) 3.40 (2 H, br d, separation 3 Hz, $COCH_2CH$), 3.80 (3 H, s, MeO), 4.15 (2 H, br s, SO_2CH_2CO), 5.05 (1 H, br t, separation 3 Hz, $COCH_2CH$) and 7.30 (1 H, br s, CONH) (addition of D_2O caused the signal at δ 7.30 to disappear and the signals at δ 3.40 and 5.05 to sharpen); m/z (EI) 149 and 43 ($CHNO^+$, base peak) (Found: C, 34.8; H, 4.2; N, 6.7. $C_6H_9NO_5S$ requires C, 34.8; H, 4.40; N, 6.75%).

Preparation of Methyl α-[(2R*)-1-(*t-Butyldimethylsilyl*)-4-*oxoazetidin*-2-*ylthio*]*acetate* **12b**.—TBDMSCl (0.387 g, 2.57 mmol) and imidazole (0.233 g, 3.42 mmol) were added to a stirred solution of the azetidinone **12a** (0.300 g, 1.71 mmol) in dry DMF (10 cm^3). After 2 h, the mixture was diluted with ethyl acetate and washed with water (× 3). Evaporation of the dried

($MgSO_4$) organic phase and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave the *title compound* **12b** (0.426 g, 86%) as a chromatographically homogeneous syrup; ν_{max}(film)/cm^{-1} 1760 (β-lactam C=O) and 1745 (ester C=O); λ_{max}(EtOH)/nm 211 (ε 2000); δ(60 MHz; $CDCl_3$) 0.30 (6 H, s, Me_2Si), 0.96 (9 H, s, Me_3C), 3.07 (1 H, dd, *J* 16 and 2, COC*H*HCH), 3.28 (2 H, s, SCH_2CO), 3.53 (1 H, dd, *J* 16 and 4, COCH*H*CH), 3.70 (3 H, s, MeO) and 4.74 (1 H, dd, *J* 4 and 2, $COCH_2CH$); *m/z* (EI) 232 ($M^+ - C_4H_9$, base peak) (Found: $M^+ - C_4H_9$, 232.0474. $C_8H_{14}NO_3SSi$ requires *m/z* 232.0464).

Preparation of Methyl α-[(2R*)-1-(*t-Butyldimethylsilyl*)-4-*oxoazetidin*-2-*ylsulphonyl*]*acetate* **11b**.—A solution of potassium permanganate (0.512 g, 3.24 mmol) in water (5 cm^3) was added dropwise to a stirred, ice-cooled solution of the sulphide **12b** (0.426 g, 1.47 mmol) in glacial acetic acid (5 cm^3). After 1 h, the mixture was decolourised by the addition of 30% aq. hydrogen peroxide and then partitioned between ethyl acetate and water. The organic phase was washed successively with saturated aq. sodium hydrogen carbonate and brine, dried ($MgSO_4$), and concentrated. Recrystallisation of the residue from ethanol–light petroleum gave the *title compound* **11b** (0.390 g, 82%), m.p. 74–75 °C; ν_{max}(KBr)/cm^{-1} 1770 (β-lactam C=O) and 1755 (ester C=O); λ_{max}(EtOH)/nm 208 (ε 1700); δ(60 MHz; $CDCl_3$) 0.31 (6 H, s, Me_2Si), 0.98 (9 H, s, Me_3C), 3.35 (1 H, d, separation 3 Hz, COC*H*HCH), 3.42 (1 H, d, separation 5 Hz, COCH*H*CH), 3.80 (3 H, s, MeO), 3.99 (2 H, s, SO_2CHCO) and 4.99 (1 H, dd, *J* 5 and 3, $COCH_2CH$); *m/z* (EI) 195 (base peak) (Found: C, 44.7; H, 7.1; N, 4.3. $C_{12}H_{23}NO_5SSi$ requires C, 44.85; H, 7.20; N, 4.35%).

Preparation of t-Butyl (αR*)/(αS*)-α-*Hydroxy*-α-[(2R*)-2-*methoxycarbonylmethylthio*-4-*oxoazetidin*-1-*yl*]*acetate* **17a**/**18a**.—t-Butyl dihydroxyacetate (17.5 g, 10.2 mmol) and triethylamine (0.875 cm^3, 6.27 mmol) were added to a solution of the azetidinone **12a** (10.0 g, 57.1 mmol) in dry THF (100 cm^3). When the reaction was complete (TLC), the mixture was diluted with ethyl acetate and the solution washed with brine. Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave a 1:1 mixture of the *title compounds* **17a**/**18a** (13.9 g, 80%); ν_{max}(film)/cm^{-1} 3450 (OH), 1775 (β-lactam, C=O) and 1740 (ester C=O); λ_{max}(EtOH)/nm 209 (ε 1100); δ(60 MHz; $CDCl_3$) 1.55 (9 H, s, Me_3C), 3.03 (1 H, dd, *J* 16 and 3, COC*H*HCH), 3.30–3.73 (3 H, m, COCH*H*CH and SCH_2CO), 3.78 (3 H, s, MeO), 4.35–4.55 (1 H, m, OH) and 4.90–5.36 (2 H, m, $COCH_2CH$ and NC*H*OH) [addition of D_2O caused the m at δ 4.35–4.55 to disappear and the m at δ 4.90–5.36 to appear as a dd (1 H, *J* 5 and 3) at δ 5.11 and as two s (each 0.5 H) at δ 5.26 and 5.36]; *m/z* (EI) 232 ($M^+ - C_4H_9O$), 204 ($M^+ - C_5H_9O_2$) and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_4H_9O$, 232.0641. $C_8H_{10}NO_5S$ requires *m/z* 232.0644).

Preparation of t-Butyl (αR*)/(αS*)-α-(*t-Butyldimethylsiloxy*)-α-[(2R*)-2-*methoxycarbonylmethylthio*-4-*oxoazetidin*-1-*yl*]*acetate* **17b**/**18b**.—TBDMSCl (4.26 g, 28.3 mmol) and imidazole (2.37 g, 34.8 mmol) were added to a stirred, ice-cooled solution of the 1:1 mixture of the hydroxyacetates **17a**/**18a** (5.23 g, 17.1 mmol) in dry DMF (45 cm^3). When the reaction was complete (TLC; *ca.* 3 h), the mixture was diluted with ethyl acetate and the solution was washed with brine (×3). Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave a 3:1 mixture of the *title compounds* **17b**/**18b** (4.45 g, 62%) as a syrup; ν_{max}(film)/cm^{-1} 1775 (β-lactam C=O) and 1740 (ester C=O); λ_{max}(EtOH)/nm 211 (ε 1100); δ(60 MHz; $CDCl_3$) 0.20 (6 H, s, Me_2Si), 0.92 (9 H, s, Me_3CSi) 1.50 (9 H, s, Me_3CO), 2.82 (0.75 H, dd, *J* 16 and 3, 0.75 × COC*H*HCH), 3.05–3.70 (3.25 H, m, 0.25 × COC*H*HCH, COCH*H* and SCH_2CO), 3.71 (3 H, s, MeO), 5.07 and 5.27 (0.25 and 0.75 H, each dd, *J* 5 and 3, $COCH_2CH$) and 5.44 and 5.49 (0.25 and 0.75 H, each s, NCHO); *m/z* (EI) 419 (M^+), 361, 318 ($M^+ - C_5H_9O_2$), 306 ($M^+ - C_6H_{13}Si$) and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 318.1213. $C_{13}H_{24}NO_4SSi$ requires *m/z* 318.1195).

Preparation of t-Butyl (αR*)/(αS*)-α-(*t-Butyldimethylsiloxy*)-α-[(2R*)-2-*methoxycarbonylmethylsulphonyl*-4-*oxoazetidin*-1-*yl*]*acetate* **15b**/**16b**.—A solution of potassium permanganate (3.51 g, 22.2 mmol) in water (30 cm^3) was added dropwise to a stirred, ice-cooled solution of the sulphides **17b**/**18b** (4.40 g, 10.5 mmol) in glacial acetic acid (15 cm^3). After 1 h, the mixture was decolourised by the addition of 30% aq. hydrogen peroxide and then extracted with ethyl acetate (×3). The combined organic extracts were washed successively with saturated aq. sodium hydrogen carbonate, water, and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave a 3:1 mixture of the *title compounds* **15b**/**16b** (4.20 g, 89%) as a syrup; ν_{max}(film)/cm^{-1} 1790 (β-lactam C=O) and 1745 (ester C=O); λ_{max}(EtOH)/nm 208 (ε 900); δ(60 MHz; $CDCl_3$) 0.15 and 0.20 (1.5 and 4.5 H, each s, Me_2Si), 0.92 (9 H, s, Me_3C), 1.40 (9 H, s, Me_3CO), 3.25–3.50 (2 H, m, $COCH_2CH$), 3.80 (3 H, s, MeO), 4.03, 4.05, 4.87 and 4.89 (0.25, 0.75, 0.25 and 0.75 H, each d, *J* 18, SO_2CH_2CO) and 5.31–5.61 (2 H, m, CH_2CHSO_2 and NCHO); *m/z* (EI) 394 ($M^+ - C_4H_9$), 350 ($M^+ - C_5H_9O_2$), 338 ($M^+ - C_6H_{13}Si$) and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 350.1122. $C_{13}H_{24}NO_6SSi$ requires *m/z* 350.1093).

Preparation of t-Butyl (αR*)/(αS*)-α-(*t-Butyldimethylsiloxy*)-α-{(2R*)-2-[*diazo*(*methoxycarbonyl*)*methylsulphonyl*]-4-*oxoazetidin*-1-*yl*}*acetate* **8b**/**9b**.—(*a*) Toluene-*p*-sulphonyl azide (3.24 g, 16.4 mmol) and piperidine (1.6 cm^3, 16.2 mmol) were added to a stirred solution of the 3:1 mixture of sulphones **15b**/**16b** (4.00 g, 8.86 mmol) in dry dichloromethane (10 cm^3). After 20 h, the mixture was diluted with ethyl acetate and washed with brine. Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave a 3:1 mixture of the title compounds **8b**/**9b** (2.22 g, 53%) as a syrup.

Crystallisation of the mixture from diethyl ether–light petroleum gave the (αR*)-*diastereoisomer* of the *title compound* **8b** (0.827 g, 20%), m.p. 88–89 °C; ν_{max}(KBr)/cm^{-1} 2150 (C=N^+=N^-), 1800 (β-lactam C=O), 1750 (ester C=O) and 1710 (diazo ester C=O); λ_{max}(EtOH)/nm 220 (ε 5600) and 223 (5400); δ(60 MHz; $CDCl_3$) 0.15 and 0.20 (each 3 H, s, Me_2Si), 0.90 (9 H, s, Me_3C), 1.47 (9 H, s, Me_3CO), 3.30–3.50 (2 H, m, $COCH_2CH$), 3.82 (3 H, s, MeO) and 5.37–5.60 (2 H, m, $COCH_2CH$ and NCHO); *m/z* (EI) 376 ($M^+ - C_5H_9O_2$), 364 ($M^+ - C_6H_{13}Si$) and 57 ($C_4H_9^+$, base peak) (Found: C, 45.3; H, 6.4; N, 8.7. $C_{18}H_{31}N_3O_8SSi$ requires C, 45.3; H, 6.5; N, 8.8%).

The filtrate from the aforecited crystallisation was concentrated to leave a syrup (1.35 g) which was mainly a 1:1 mixture of the (α*R**)- and (α*S**)-diastereoisomers of the title compound; δ(60 MHz, $CDCl_3$) *inter alia* 0.14, 0.18, 0.19 and 0.24 (each 1.5 H, s, Me_2Si), 0.90 (9 H, s, Me_3CSi), 1.47 (9 H, s, Me_3CO), 3.23–3.53 (2 H, m, $COCH_2CH$), 3.81 (3 H, s, MeO), 5.27 (0.5 H, dd, *J* 6 and 3, 0.5 × $COCH_2CH$) and 5.35–5.60 (1.5 H, m, 0.5 × $COCH_2CH$ and NCHO).

(*b*) A 3:1 mixture of the sulphones **15b**/**16b** (0.506 g, 1.12 mmol) was subjected to the aforecited conditions but DBN (0.444 cm^3, 8.45 mmol) was substituted for piperidine. Work-up

and purification of the product as before gave the title compound (0.460 g, 86%). Crystallisation of the mixture from diethyl ether–light petroleum afforded the (αR*)-diastereoisomer **8b** (0.183 g, 34%), m.p. 88–89 °C, identified by its ^{1}H NMR spectrum.

Preparation of t-Butyl (αR*)-α-{(2R*)-2-[*Diazo(methoxycarbonyl)methylsulphonyl*]-4-*oxoazetidin*-1-*yl*}-α-*hydroxyacetate* **8a**.—A solution of the silyl ether **8b** (0.500 g, 1.05 mmol) in a 1:4 mixture of 40% hydrofluoric acid and acetonitrile (25 cm^3) was left until the starting material had disappeared (TLC; *ca.* 48 h). The mixture was then diluted with ethyl acetate and washed successively with aq. sodium hydrogen carbonate and brine. Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave the title compound **8a** (0.040 g, 11%); ν_{max}(film)/cm^{-1} 3450 (OH), 2160 (C=N$^+$=N$^-$), 1785 (β-lactam C=O), 1735 (ester C=O) and 1715 (diazo ester C=O); λ_{max}(EtOH)/nm 214 (ε 14 500) and 245 (12 000); δ(60 MHz; $CDCl_3$) 1.51 (9 H, s, Me_3C), 3.40–3.56 (2 H, m, $COCH_2CH$), 3.87 (3 H, s, MeO), 4.10 (1 H, br s, OH), 5.20 (1 H, dd, *J* 5 and 3, $COCH_2CH$) and 5.40 (1 H, br s, NCHO) (addition of D_2O caused the s at δ 4.10 to disappear and that at δ 5.40 to sharpen); *m/z* (EI) 262 ($M^+ - C_5H_9O_2$) and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 262.0137. $C_7H_8N_3O_6S$ requires *m/z* 262.0134).

Preparation of t-Butyl (αR*)/(αS*)-α-*Acetoxy*-α-[(2R*)-2-*methoxycarbonylmethylthio*-4-*oxoazetidin*-1-*yl*]*acetate* **17c**/**18c**.—Acetic anhydride (0.349 cm^3, 3.92 mmol) was added to a stirred solution of a 1:1 mixture of the hydroxyacetates **17a**/**18a** (0.505 g, 1.65 mmol) in dry pyridine (5 cm^3). After 22 h, water (5 cm^3) was added to the mixture, which was then stirred for 15 min and partitioned between ethyl acetate and dil. hydrochloric acid. The organic phase was washed successively with saturated aq. sodium hydrogen carbonate, water, and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave a 1:1 mixture of the *title compounds* **17c**/**18c** (0.424 g, 74%) as a syrup; ν_{max}(film)/cm^{-1} 1785 (β-lactam C=O) and 1745br (ester C=O); λ_{max}(EtOH)/nm 218 (ε 600); δ(300 MHz; $CDCl_3$) 1.50 and 1.51 (each 4.5 H, s, Me_3C), 2.27 (3 H, s, MeCO), 3.09 and 3.15 (each 0.5 H, dd, *J* 16 and 3, $COCHHCH$), 3.28, 3.40, 3.49 and 3.57 (each 0.5 H, d, *J* 16, SCH_2CO), 3.40–3.50 (1 H, m, $COCHHCH$), 3.75 and 3.76 (each 1.5 H, s, MeO), 5.05 and 5.09 (each 0.5 H, dd, *J* 5 and 3, $COCH_2CH$) and 6.13 and 6.15 (each 0.5 H, s, NCHO); *m/z* (EI) 286, 274 ($M^+ - C_4H_9O$), 246 ($M^+ - C_5H_9O_2$) and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 246.0445. $C_9H_{12}NO_5S$ requires *m/z* 246.0436).

Preparation of t-Butyl (αR*)/(αS*)-α-*Acetoxy*-α-[(2R*)-2-*methoxycarbonylmethylsulphonyl*-4-*oxoazetidin*-1-*yl*]*acetates* **15c**/**16c**.—A solution of potassium permanganate (0.100 g, 0.633 mmol) in water (10 cm^3) was added dropwise to a stirred, ice-cooled solution of a 1:1 mixture of the sulphides **17c**/**18c** (0.100 g, 0.288 mmol) in glacial acetic acid (5 cm^3). After 14 h, the mixture was decolourised by the addition of 30% aq. hydrogen peroxide and then extracted with ethyl acetate (× 3). The combined organic layers were washed successively with saturated aq. sodium hydrogen carbonate, water, and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave a 1:1 mixture of the *title compounds* **15c**/**16c** (0.076 g, 69%) as a syrup; ν_{max}(film)/cm^{-1} 1800 (β-lactam C=O) and 1745 (ester C=O); λ_{max}(EtOH)/nm 218 (ε 500) and 275 (70); δ(300 MHz; $CDCl_3$) 1.50 and 1.52 (each 4.5 H, s, Me_3C), 2.17 and 2.20 (each 1.5 H, s, MeCO), 3.37–3.80 (2 H, m, $COCH_2CH$), 3.84 and 3.85 (each 1.5 H, s, MeO), 4.05, 4.12, 4.52 and 4.55 (each 0.5 H, d, *J* 15, SO_2CH_2CO), 5.38 and 5.45 (each 0.5 H, dd, *J* 6 and 3, CH_2CHSO_2) and 6.17 and 6.44 (each 0.5 H, s, NCHO); *m/z* (EI) 306 ($M^+ - C_3H_5O_2$), 278 ($M^+ - C_5H_9O_2$) and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 278.0357. $C_9H_{12}NO_7S$ requires *m/z* 278.0334).

Preparation of t-Butyl (αR*)/(αS*)-α-[(2R*)-2-*Methoxycarbonylmethylthio*-4-*oxoazetidin*-1-*yl*]-α-(2-*methoxypropan*-2-*yloxy*)*acetate* **17d**/**18d**.—A trace of the phosphoryl trichloride was added to a stirred solution of a 1:1 mixture of the hydroxyacetates **17a**/**18a** (0.318 g, 1.04 mmol) in 2-methoxypropene (1 cm^3). When the reaction was complete (TLC; *ca.* 90 min), the mixture was concentrated and the residue was dissolved in ethyl acetate. After having been washed successively with water and brine, the solution was dried ($MgSO_4$), and evaporated. Purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave a 1:1 mixture of the *title compounds* **17d**/**18d** (0.320 g, 81%) as a syrup; ν_{max}(film)/cm^{-1} 1775 (β-lactam C=O) and 1740 (ester C=O); δ(300 MHz; $CDCl_3$) 1.37, 1.40, 1.41 and 1.47 (each 1.5 H, s, Me_2C), 1.49 and 1.50 (each 4.5 H, s, Me_3C), 2.84 and 3.00 (each 0.5 H, dd, *J* 15 and 3, $COCHHCH$), 3.22 and 3.28 (each 1.5 H, s, MeO), 3.32–3.49 (2 H, m, $COCHHCH$ and $SCHHCO$), 3.58 and 3.79 (each 0.5 H, d, *J* 16, $SCHHCO$), 3.75 (3 H, s, MeO), 5.10 and 5.30 (each 0.5 H, dd, *J* 6 and 3, CH_2CHS) and 5.56 and 5.61 (each 0.5 H, s, NCHO); *m/z* (EI) 276 ($M^+ - C_5H_9O_2$) and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 276.0925. $C_{11}H_{18}NO_5S$ requires *m/z* 276.0906).

Preparation of t-Butyl (αR*)- *or* (αS*)-α-*Hydroxy*-α[(2R*)-2-*methoxycarbonylmethylsulphonyl*-4-*oxoazetidin*-1-*yl*]*acetate* **15a** *or* **16a**.—A solution of potassium permanganate (0.250 g, 1.58 mmol) in water (10 cm^3) was added dropwise to a stirred, ice-cooled solution of a 1:1 mixture of compounds **17d**/**18d** (0.280 g, 0.742 mmol) in glacial acetic acid (5 cm^3). After 1 h, the mixture was decolourised by the addition of 30% aq. hydrogen peroxide and was then extracted with ethyl acetate (× 3). The combined organic layers were washed successively with saturated aq. sodium hydrogen carbonate, water, and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) gave the title compound **15a** or **16a** (0.107 g, 43%) as a chromatographically homogeneous syrup which appeared to be a single diastereoisomer; ν_{max}(film)/cm^{-1} 3440br (OH), 1785 (β-lactam C=O) and 1740 (ester C=O); δ(300 MHz; $CDCl_3$) 1.54 (9 H, s, Me_3C), 3.41 (1 H, dd, *J* 16 and 6, $COCHHCH$), 3.53 (1 H, dd, *J* 16 and 3, $COCHHCH$), 3.83 (3 H, s, MeO), 4.01 (1 H, br d, *J* 6, $CHOH$), 4.11 and 4.61 (each 1 H, d, *J* 15, SO_2CH_2CO), 5.34 (1 H, dd, *J* 6 and 3, CH_2CHSO_2) and 5.50 (1 H, br d, *J* 4, $NCHOH$) (addition of D_2O caused the br d at δ 4.01 to disappear and the dd at δ 5.34 to collapse to a s); *m/z* (EI) 236 ($M^+ - C_5H_9O_2$), 200 ($M^+ - C_3H_5O_4S$) and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 236.0243. $C_7H_{10}NO_6S$ requires *m/z* 236.0229).

Preparation of t-Butyl (αR*)/(αS*)-α-[(2R*)-2-*Methoxycarbonylmethylthio*-4-*oxoazetidin*-1-*yl*]-α-(*tetrahydropyran*-2-*yloxy*)*acetate* **17e**/**18e**.—A small amount of PTSA monohydrate was added to a stirred solution of a 1:1 mixture the hydroxyacetates **17a**/**18a** (7.00 g, 22.8 mmol) in dihydropyran (50 cm^3). When the reaction was complete (TLC; *ca.* 3 h), the mixture was diluted with ethyl acetate and washed successively with water and brine. Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel chromatography [light petroleum–EtOAc (9:1) as eluent] gave a syrup (8.26 g, 93%) which comprised a 1:1 mixture of the *title compounds* **17e**/**18e**, each as a 1:1 mixture of epimers;

ν_{max}(film)/cm^{-1} 1775 (β-lactam C=O) and 1740 (ester C=O); λ_{max}(EtOH)/nm 221 (ε 1100); δ(60 MHz; $CDCl_3$) 1.50 (9 H, s, Me_3C), 1.50–1.85 (6 H, m, $CH_2CH_2CH_2$), 2.90–3.90 (6 H, m, $COCH_2CH$, SCH_2CO and OCH_2CH_2), 3.75 (3 H, s, MeO), 4.75–5.30 (2 H, m, $COCH_2CH$ and OCHO) and 5.30, 5.35, 5.45 and 5.60 (each 0.25 H, s, NCHO); *m/z* (EI) 390 (MH^+), 288 ($M^+ - C_5H_9O_2$) and 85 ($C_4H_9O^+$, 100) (Found: MH^+, 390.1589. $C_{17}H_{28}NO_7S$ requires *m/z* 390.1586).

Preparation of t-Butyl (αR*)- *and* (αS*)-α-[(2R*)-2-*Methoxycarbonylmethylsulphonyl-2-oxoazetidin-1-yl*]-α-(*tetrahydropyran-2-yloxy*)*acetate* **15d** *and* **16d**.—A solution of potassium permanganate (6.70 g, 42.4 mmol) in water (90 cm^3) was added dropwise to a stirred, ice-cooled solution of a 1:1 mixture of the sulphides **17e**/**18e** (8.00 g, 20.5 mmol) in glacial acetic acid (30 cm^3). After 90 min, the mixture was decolourised with 30% aq. hydrogen peroxide and was then extracted with ethyl acetate (× 3). The combined organic extracts were washed successively with saturated aq. sodium hydrogen carbonate, water, and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by silica-gel column chromatography [light petroleum–EtOAc (7:3) as eluent] led to the isolation of three syrupy fractions.

The first-eluted fraction (2.04 g, 24%) was identified as the (αR*)-*diastereoisomer* of the *title compound* **15d** as a 3:1 mixture of epimers *A* and *B*; ν_{max}(film)/cm^{-1} 1790 (β-lactam C=O) and 1745 (ester C=O); λ_{max}(EtOH)/nm 209 (ε 700); δ(300 MHz; $CDCl_3$) 1.51 and 1.52 (2.25 and 6.75 H, each s, Me_3C), 1.50–1.83 (6 H, m, $CH_2CH_2CH_2$), 3.40 (1 H, dd, *J* 16 and 5, $COCHHCH$), 3.50 (1 H, dd, *J* 16 and 3, $COCHHCH$), 3.57–3.68 and 3.83–3.92 (each 1 H, m, OCH_2CH_2), 3.82 and 3.83 (0.75 and 2.25 H, each s, MeO), 4.08, 4.10, 4.77 and 4.82 (0.75, 0.25, 0.75 and 0.25 H, each d, *J* 16, SO_2CH_2CO), 4.93–4.96 and 5.01–5.04 (0.75 and 0.25 H, each m, OCHO), 5.53 and 5.58 (0.75 and 0.25 H, each dd, *J* 5 and 3, $COCH_2CH$) and 5.68 and 5.75 (0.25 and 0.75 H, each s, NCHO); *m/z* (EI) 320 ($M^+ - C_5H_9O_2$) and 85 ($C_4H_9O^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 320.0821. $C_{12}H_{18}NO_7S$ requires *m/z* 320.0804).

The second eluted fraction (2.54 g, 23%) was identified (220 MHz ^{1}H NMR spectroscopy) as the (αR*)-diastereoisomer of the title compound **15d**, as a 1:2 mixture of epimers *A* and *B*.

The third eluted fraction was resubjected to silica-gel column chromatography (Et_2O as eluent) to give a syrup (1.66 g, ~19%) which was predominantly the (αS*)-*diastereoisomer* of the *title compound* **16d** as a 2:1 mixture of epimers *A* and *B*; ν_{max}(film)/cm^{-1} 1790 (β-lactam C=O) and 1745 (ester C=O); λ_{max}(EtOH)/nm 209 (ε 900); δ(300 MHz; $CDCl_3$) *inter alia* 1.50 and 1.51 (3 and 6 H, each s, Me_3C), 1.50–1.82 (6 H, m, $CH_2CH_2CH_2$), 3.28 and 3.33 (0.33 and 0.66 H, each dd, *J* 16 and 6, $COCHHCH$), 3.44–3.58 (2 H, m, $COCHHCH$ and $OCHHCH_2$), 3.78–3.90 (1 H, m, $OCHHCH_2$), 3.83 (3 H, s, MeO), 4.03, 4.04, 4.73 and 4.78 (0.66, 0.33, 0.33 and 0.66 H, each d, *J* 15, SO_2CH_2CO), 4.70–4.75 and 4.90–4.94 (0.33 and 0.66 H, each m, OCHO), 5.36 and 5.53 (0.66 and 0.33 H, each dd, *J* 6 and 3, $COCH_2CH$) and 5.44 and 5.50 (0.66 and 0.33 H, each s, NCHO); *m/z* (EI) 320 ($M^+ - C_5H_9O_2$) and 87 ($C_4H_9O^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 320.0814. $C_{12}H_{18}NO_7S$ requires *m/z* 320.0804).

Preparation of t-Butyl (αR*)-α-{(2R*)-2-[*Diazo*(*methoxycarbonyl*)*methylsulphonyl*]-4-*oxoazetidin-1-yl*}-α-(*tetrahydropyran-2-yloxy*)*acetate* **8c**.—(*a*) Triethylamine (2.6 cm^3, 18.6 mmol) was added to a stirred mixture of *p*-carboxybenzenesulphonyl azide (1.00 g, 4.4 mmol) and compound **15d** (as a 3:1 mixture of epimers *A* and *B*) (1.50 g, 3.56 mmol) in dry acetonitrile (50 cm^3) whereupon a clear solution resulted. A precipitate formed after 30 min, which was filtered off after a further 90 min. The filtrate was diluted with ethyl acetate and washed successively with aq. sodium hydrogen carbonate, water, and brine. Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel column chromatography [light petroleum–EtOAc (7:3) as eluent] gave a solid (1.11 g, 70%) which was the title compound as a 3:1 mixture of epimers *A* and B δ(300 MHz; $CDCl_3$) 1.48 and 1.49 (2.25 and 6.75 H, each s, Me_3C), 1.52–1.80 (6 H, m, $CH_2CH_2CH_2$), 3.40–3.52 (2 H, m, $COCH_2CH$), 3.54–3.66 and 3.82–3.93 (each 1 H, m, OCH_2CH_2), 3.88 and 3.90 (0.75 and 2.25 H, each s, MeO), 4.92–4.96 (1 H, m, OCHO), 5.50 (0.25 H, dd, *J* 5 and 3, 0.25 × $COCH_2CH$), 5.64–5.67 (1 H, m, 0.75 × $COCH_2CH$ and 0.25 × NCHO) and 5.76 (0.75 H, s, 0.75 × NCHO).

A portion of the above material was crystallised from diethyl ether–light petroleum to give *epimer* A of the *title compound* **8c**, m.p. 109–111 °C; ν_{max}(KBr)/cm^{-1} 2140 (C=N$^+$=N$^-$), 1790 (β-lactam C=O), 1745 (ester C=O) and 1725 (diazo ester C=O); λ_{max}(EtOH)/nm 225 (ε 5000); δ(300 MHz; $CDCl_3$) 1.49 (9 H, s, Me_3C), 1.50–1.78 (6 H, m, $CH_2CH_2CH_2$), 3.45–3.48 (2 H, 4 lines, separation 2, 3 and 1 Hz, $COCH_2CH$), 3.59–3.69 and 3.85–3.95 (each 1 H, m, OCH_2CH_2), 3.90 (3 H, s, MeO), 4.92–4.94 (1 H, m, OCHO), 5.65 (1 H, dd, *J* 5 and 3, $COCH_2CH$) and 5.76 (1 H, s, NCHO); *m/z* (EI) 346 ($M^+ - C_5H_9O_2$) and 85 (base peak) (Found: $M^+ - C_5H_9O_2$, 346.0725. $C_{12}H_{16}N_3O_7S$ requires *m/z* 346.0709) (Found: C, 45.5; H, 5.8; N, 9.2. $C_{17}H_{25}N_3O_9S$ requires C, 45.65; H, 5.65; N, 9.40%).

(*b*) Compound **15d** (as a 1:2 mixture of epimers *A* and *B*) (2.00 g, 4.75 mmol) was treated with triethylamine and *p*-carboxybenzenesulphonyl azide in acetonitrile as described in the aforecited experiment. Work-up and purification of the product as before gave a material which was resubjected to silica-gel column chromatography (Et_2O as eluent). The resultant product (1.42 g, 67%) was the title compound **8c** as a 1:2 mixture of epimers *A* and *B* (300 MHz ^{1}H NMR spectroscopy).

Preparation of t-Butyl (αS*)-α-{(2R*)-2-[*Diazo*(*methoxycarbonyl*)*methylsulphonyl*]-4-*oxoazetidin-1-yl*}-α-(*tetrahydropyran-2-yloxy*)*acetate* **9c**.—Compound **16d** (as a 2:1 mixture of epimers *A* and *B*) (1.50 g, 3.56 mmol) was treated with triethylamine and *p*-carboxybenzenesulphonyl azide in acetonitrile as described in the previous experiment. Work-up and purification of the product as before gave a solid (1.34 g, 84%) which was predominantly the title compound **9c** as a 2:1 mixture of epimers *A* and *B*; δ(300 MHz; $CDCl_3$) *inter alia* 1.48 and 1.50 (3 and 6 H, each s, Me_3C), 1.50–1.90 (6 H, m, $CH_2CH_2CH_2$), 3.32 and 3.37 (0.33 and 0.66 H, each dd, *J* 16 and 6, $COCHHCH$), 3.43–3.53 and 3.80–3.91 (each 1 H, m, OCH_2CH), 3.54 and 3.59 (0.66 and 0.33 H, each dd, *J* 16 and 3, $COCHHCH$), 3.868 and 3.872 (2 and 1 H, each s, MeO), 4.67–4.72 and 4.82–4.86 (0.33 and 0.66 H, each m, OCHO), 5.25 and 5.44 (0.66 and 0.33 H, each dd, *J* 6 and 3, $COCH_2CH$) and 5.42 and 5.45 (0.66 and 0.33 H, each s, NCHO).

A portion of the above material was recrystallised from diethyl ether–light petroleum to give *epimer* A of the *title compound* **9c**, m.p. 109–111 °C; ν_{max}(KBr)/cm^{-1} 2140 (C=N$^+$=N$^-$), 1790 (β-lactam C=O), 1740 (ester C=O) and 1720 (diazo ester C=O); λ_{max}(EtOH)/nm 230 (ε 7300); δ(220 MHz; $CDCl_3$) 1.49 (9 H, s, Me_3C), 1.50–1.90 (6 H, m, $CH_2CH_2CH_2$), 3.35 (1 H, dd, *J* 16 and 6, $COCHHCH$), 3.45–3.60 (2 H, m, $COCHHCH$ and $OCHHCH$), 3.87 (4 H, s with br base, MeO and $OCHHCH$), 4.80–4.85 (1 H, m, OCHO), 5.24 (1 H, dd, *J* 6 and 3, $COCH_2CH$) and 5.42 (1 H, s, NCHO); *m/z* (EI) 346 ($M^+ - C_5H_9O_2$) and 85 (base peak) (Found: $M^+ - C_5H_9O_2$, 346.0725. $C_{12}H_{16}N_3O_7S$ requires *m/z* 346.0709) (Found: C, 45.7; H, 5.9; N, 9.3. $C_{17}H_{25}N_3O_9S$ requires C, 45.65; H, 5.65; N, 9.40%).

Preparation of (2S*,4R*,6R*)/(2R*,4R*,6R*)-4-(*t-Butoxycarbonyl*)-2-*methoxycarbonyl*-2-*oxacepham* 1,1-*Dioxides* **6b**/**7b**.—(*a*) A catalytic quantity of rhodium(II) acetate was added to a stirred solution of the diazo compound **8a** (0.024 g, 0.07 mmol) in dry benzene (5 cm^3). When the reaction was complete (TLC; *ca.* 18 h), the mixture was concentrated and the residue was subjected to silica-gel column chromatography (light petroleum–EtOAc; gradient elution) to give a 3:1 mixture of the *title compounds* **6b**/**7b** (0.014 g, 58%). After crystallisation from ethanol–light petroleum, the sample displayed m.p. 124–126 °C; ν_{max}(KBr)/cm^{-1} 1795 (β-lactam C=O) and 1740 (ester C=O); δ(300 MHz; $CDCl_3$) 1.53 (9 H, s, Me_3C), 3.57 and 3.60 (0.75 and 0.25 H, each dd, *J* 16 and 5, 7-Hα), 3.72 and 3.80 (0.25 and 0.75 H, each dd, *J* 16 and 2, 7-Hβ), 3.95 and 3.96 (0.75 and 2.25 H, each s, MeO), 5.16 and 5.20 (0.25 and 0.75 H, each dd, *J* 5 and 2, 6-H), 5.43 and 5.65 (0.25 and 0.75 H, each s, 4-H) and 5.36 and 6.09 (0.25 and 0.75 H, each s, 2-H); *m/z* (EI) 234 ($M^+ - C_5H_9O_2$) and 57 ($C_4H_9^+$, base peak) (Found: C, 42.6; H, 5.1; N, 4.3. $C_{12}H_{17}NO_8S$ requires C, 43.0; H, 5.10; N, 4.20%).

(*b*) A catalytic quantity of rhodium(II) acetate was added to a stirred solution of the diazo compound **8c** (as a 3:1 mixture of epimers *A* and *B*) (1.00 g, 2.23 mmol) in dry dichloromethane (40 cm^3). The resultant green solution was left overnight and then diluted with ethyl acetate and washed successively with water and brine. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel column chromatography [light petroleum–EtOAc (7:3) as eluent] gave a residue (0.335 g, 45%) which comprised a 3:1 mixture of the title compounds **6b**/**7b**. After crystallisation from dichloromethane–diethyl ether, the sample displayed m.p. 130–132 °C; ν_{max}(KBr)/cm^{-1} 1800 (β-lactam C=O) and 1735 (ester C=O); λ_{max}(EtOH)/nm 212 (ε 1200); δ(300 MHz; $CDCl_3$; resolution enhanced) 1.55 (9 H, s, Me_3C), 3.59 and 3.61 (0.75 and 0.25 H, each dd, *J* 16 and 4.8, 7-Hα), 3.74 and 3.83 [0.25 and 0.75 H, ddd (*J* 16, 1.5 and 0.5) and dd (*J* 16 and 1.8), 7-Hβ], 3.96 and 3.97 (0.75 and 2.25 H, each s, MeO), 5.18 and 5.23 [0.25 and 0.75 H, dd (*J* 4.5 and 1.8) and ddd (*J* 4.7, 1.7 and 0.5), 6-H], 5.43 and 5.68 [0.25 and 0.75 H, br s and t (*J* 0.5), 4-H] and 5.37 and 6.12 (0.25 and 0.75 H, each br s, 2-H) [irradiation of the s at δ 6.12 caused the t at δ 5.68 to collapse to a d (*J* 0.5) and the ddd at δ 5.23 to sharpen; irradiation of the t at δ 5.68 caused the s at δ 6.12 to sharpen and the ddd at δ 5.23 to collapse to a dd (*J* 4.7 and 1.7); irradiation of the ddd at δ 5.23 caused the s at δ 6.12 to appear as a d (separation 0.3 Hz), the t at δ 5.68 to appear as a d (*J* 0.5), and the dd at δ 3.83 and 3.59 to appear as d (*J* 16); irradiation of the s at δ 5.43 caused the ddd at δ 3.74 to collapse to a d (*J* 16 and 1.5); irradiation of the s at δ 5.37 caused the dd at δ 5.18 to sharpen; irradiation of the dd at δ 5.18 caused the ddd at δ 3.74 to collapse to a dd (*J* 16 and 0.5) and the dd at δ 3.83 to collapse to a d (*J* 16) (in an NOED experiment, irradiation of the signal at δ 6.12 caused an 11% enhancement of the signal at δ 5.68 and a 14% enhancement of the signal at δ 5.23; irradiation of the signal at δ 5.68 caused a 5% enhancement of that at δ 6.12; irradiation of the signal at δ 5.23 enhanced the signal at δ 6.12 by 20% and that at δ 5.68 by 5%; irradiation of the signal at δ 5.43 resulted in a 29% enhancement of the signal at δ 5.37; irradiation of the signal at δ 5.37 caused a 20% enhancement of that at δ 5.43; irradiation of the signal at δ 5.18 resulted in no enhancements)]; *m/z* (EI) 234 ($M^+ - C_5H_9O_2$) and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 234.0085. $C_7H_8NO_6S$ requires *m/z* 234.0072) (Found: C, 43.2; H, 5.1; N, 4.2. $C_{12}H_{17}NO_8S$ requires C, 43.0; H, 5.10; N, 4.20%).

(*c*) The diazo compound **8c** (as a 1:2 mixture of epimers *A* and *B*) (1.00 g, 2.23 mmol) was treated with rhodium(II) acetate in dichloromethane as described in the aforecited experiment. Work-up and purification as before gave a residue (0.456 g, 63%) which comprised a 3:1 mixture of the title compounds **6b**/**7b** by 300 MHz ^{1}H NMR spectroscopy.

Preparation of (2R*,4S*,6R*)/(2S*,4S*,6R*)-4-(*t-Butoxycarbonyl*)-2-*methoxycarbonyl*-2-*oxacepham* 1,1-*Dioxides* **22**/**23**.—The diazo compound **9c** (as a 2:1 mixture of epimers *A* and *B*) (1.00 g, 2.23 mmol) was treated with rhodium(II) acetate in dichloromethane as described in the previous experiment [part (*a*)]. Work-up and purification of the product as before gave a residue (0.410 g, 55%) which comprised a 2:1 mixture of the *title compounds* **22**/**23**. After crystallisation from dichloromethane–diethyl ether, the sample showed m.p. 130–132 °C; ν_{max}(KBr)/cm^{-1} 1785 (β-lactam C=O) and 1760 and 1745 (ester C=O); δ(300 MHz; $CDCl_3$; resolution enhanced) 1.55 (9 H, s, Me_3C), 3.54 and 3.57 [0.33 and 0.66 H, ddd (*J* 16, 5 and 0.7) and ddd (*J* 16, 5 and 1.3), 7-Hα], 3.75 and 3.78 [0.66 and 0.33 H, ddd (*J* 16, 1.7 and 0.4) and dd (*J* 16 and 1.7, 7-Hβ], 3.95 and 3.96 (1 and 2 H, each s, MeO), 5.03 and 5.41–5.42 [0.33 and 0.66 H, d (*J* 0.8) and m, 4-H], 5.06 and 5.08 [0.66 and 0.33 H, ddt (*J* 5, 1.7, 0.5 and 0.5), and dd (*J* 5 and 1.7), 6-H] and 5.55 and 6.14 (0.33 and 0.66 H, s and br s, 2-H) [irradiation of the s at δ 6.14 caused a slight modification to the m at δ 5.41–5.42 and the collapse of the ddt at δ 5.06 to a ddd (*J* 5, 1.7 and 0.5); irradiation of the m at δ 5.41–5.42 caused the ddt at δ 5.06 to collapse to a ddd (*J* 5, 1.7 and 0.4), the ddd at δ 3.75 to collapse to a dd (*J* 16 and 1.7), and the ddd at δ 3.57 to collapse to a dd (*J* 16 and 5); irradiation of the s at δ 5.55 caused no effect (in an NOED spectroscopic study, irradiation of the signal at δ 6.14 caused an 8% enhancement of that at δ 5.42; irradiation of the signal at δ 5.42 enhanced that at δ 6.14 by 9% and that at δ 5.06 by 6%; irradiation of the signal at δ 5.06 caused a 5% enhancement of that at δ 6.14 and a 13% enhancement of that at δ 5.42; irradiation of the signal at δ 5.55 resulted in a 25% enhancement of that at δ 5.03; irradiation of the signal at δ 5.08 caused a 28% enhancement of that at δ 5.55; irradiation of the signal at δ 5.03 enhanced that at δ 5.55 by 28%)]; *m/z* (EI) 234 ($M^+ - C_5H_9O_2$) (Found: $M^+ - C_5H_9O_2$, 234.0071. $C_7H_8NO_6S$ requires *m/z* 234.0072) (Found: C, 42.9; H, 4.9; N, 4.0. $C_{12}H_{17}NO_8S$ requires C, 43.0; H, 5.10; N, 4.20%).

Deuterium Exchange of the Oxacephams **6b**/**7b** *and* **22**/**23**.—(*a*) Triethylamine (0.021 cm^3, 0.15 mmol) and a drop of deuterium oxide were added to a 3:1 mixture of the oxacephams **6b**/**7b** (0.050 g, 0.149 mmol) in deuteriochloroform (0.5 cm^3); the signals at δ 5.37 and 6.12 disappeared according to 300 MHz ^{1}H NMR spectroscopy.

(*b*) The aforecited experiment was repeated using a 2:1 mixture of the oxacephams **22**/**23**; the signals at δ 5.55 and 6.14 disappeared according to 300 MHz ^{1}H NMR spectroscopy.

Preparation of the Sodium Salts of (2S*,4R*,6R*)/(2R*,4R*,6R*)-4-*Carboxy*-2-*methoxycarbonyl*-3-*oxacepham* 1,1-*Dioxides* **6a**/**7a**.—TFA (0.5 cm^3) was added to a solution of a 3:1 mixture of the oxacephams **6b**/**7b** (0.190 g, 0.567 mmol) in deuteriochloroform (0.1 cm^3). The reaction was monitored by ^{1}H NMR spectroscopy and, when complete (*ca.* 90 min), the solution was concentrated to leave a syrup which was mainly a 3:1 mixture of (2S*,4R*,6R*)/(2R*,4R*6R*)-4-carboxy-2-methoxycarbonyl-3-oxacepham 1,1-dioxides **6c**/**7c**; δ(300 MHz; CD_3COCD_3) *inter alia* 3.55 and 3.62 [0.25 and 0.75 H, br d (separation 16 Hz) and dd (*J* 16 and 1.5), 7-Hβ], 3.71–3.86 (1 H, m, 7-Hα), 3.88 and 3.89 (0.75 and 2.25 H, each s, MeO), 5.26 and 5.47 (0.25 and 0.75 H, each dd, *J* 4.5 and 1, 6-H), 5.80 and 5.97 (0.25 and 0.75 H, each s, 4-H) and 6.03 and 6.22 (0.25 and 0.75 H, each s, 2-H).

Sodium hydrogen carbonate (0.007 g, 0.086 mmol) in water (0.5 cm^3) was added to a stirred solution of a portion (0.032 g) of the foregoing product in acetone (0.5 cm^3). After 15 min, the mixture was partitioned between water and ethyl acetate. The aq. layer was freeze-dried to leave mainly a 3:1 mixture of the

title salts **6a**/**7a** (0.015 g); δ(300 MHz; D_2O) (immediately after dissolution) *inter alia* 3.56–3.82 (2 H, m, 7-H_2), 3.94 and 3.95 (2.25 and 0.75 H, each s, MeO), 5.35 and 5.47 [0.25 and 0.75 H, dd (*J* 4 and 1.5) and dd (*J* 4 and 2), 6-H], 5.54 and 5.79 (0.25 and 0.75 H, each s, 4-H) and 6.08 and 6.24 (each 0.2 H, s, 0.2 × 2-H) (after 12 h, the signals at δ 6.08 and 6.24 had disappeared; no further change was apparent after 24 h).

A solution of sodium 2-ethylhexanoate in a mixture of butan-1-ol and diethyl ether was added in drops to a solution of a portion (0.090 g) of the crude acids **6c**/**7c** in ethanol (1 cm^3) until no further precipitate was produced. The mixture was centrifuged and the supernatant was discarded. Diethyl ether was added to the solid and the mixture was stirred and recentrifuged (repeated × 3). The dried (*in vacuo*; P_2O_5) pale-yellow solid (0.037 g) was mainly a 3:1 mixture of the salts **6a**/**7a** by 300 MHz ^{1}H NMR spectroscopy.

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