C-Nucleosides. Part 2.[1] Preparation of 2-[(1*R*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentyl]thiazole-4-carboxamide ('Carbocyclic' Tiazofurin) and its Antipode

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Benzyl 6β-aminopenicillanate 1β-oxide **9c** underwent *N*-acylation with (1*R**,2*S**,3*R**,4*R**)-2,3-dibenzoyloxy-4-(benzoyloxymethyl)cyclopentanecarbonyl chloride **11b**—assembled in nine steps from trinorbornadiene—to give a mixture of the penicillins **10d** and **13c**, which were readily separated by chromatography. The less polar material, identified as the diastereoisomer **10d** by its conversion into (1*R*,5*R*,6*R*,7*S*)-6,7-isopropylidenedioxy-3-oxabicyclo[3.2.1]octan-2-one **24**, was transformed into the title compound **1b** by a four-step sequence. In a similar manner, the penicillin **13c** was converted into carbatiazofurin enantiomer *ent*-**1b**. Both carbatiazofurin **1b** and its enantiomer displayed cytotoxicity against a breast carcinoma cell line.

C-Nucleosides—compounds in which a sugar is linked at position 1 to a heterocycle by way of a C–C bond—are of considerable interest because of the antibacterial, antitumour and antiviral properties of certain representatives. In the biologically active members, the sugar is D-ribofuranose and it is β-linked to a 5- or 6-membered heterocycle. Examples include tiazofurin **1a**,[2] pyrazofurin **2a**,[3] showdomycin **3a**,[3] formycin **4**,[3] formycin B **5**[3] and oxazinomycin **6a**.[3]

Relatively little attention has been directed at analogues of *C*-nucleosides in which the furanose ring oxygen is replaced by a methylene group—carbocyclic *C*-nucleosides. Three such analogues of the bioactive *C*-nucleosides have been described: (±)-carbapyrazofurin **2b**,[4] (±)-carbashowdomycin **3b**[4,5] and (±)-carbaoxazinomycin **6b**.[6] However, there have been no reports that such compounds are biologically active.

To date, all syntheses of carbocyclic *C*-nucleosides have involved the assembly of the heterocycle on a carbafuranose derivative bearing a functionalised *C*-appendage at position 1.[4–9] In the case of the analogues of the bioactive *C*-nucleosides, the carbafuranose derivatives **7** and **8** have played a central role. For example, the (±)-carbafuranose **7a** was used by Just and Kim in the synthesis of (±)-carbapyrazofurin **2b** and (±)-carbashowdomycin **3b**,[4] the (±)-relative **7b** in the elaboration of (±)-carbashowdomycin **3b**,[5] the relative **7c** in the assembly of a potential precursor of carbashowdomycin **3b**,[9] and the (±)-carbafuranose **8** in the construction of (±)-carbaoxazinomycin **6b**.[6]

Our interest in *C*-nucleosides and their relatives stemmed from the recognition that useful heterocyclic moieties might be derived from 6β-aminopenicillanic acid **9a** by exploiting known rearrangements of its *N*-acyl derivatives (penicillins). Thus, using this tactic, we recently reported[1] a synthesis of tiazofurin **1a**—a synthetic *C*-nucleoside with significant antitumour properties and broad-spectrum antiviral properties.[2] In the process, the penicillin **10a**—assembled from the acid chloride **11a** and the penicillanate **9b**—was converted into the thiazole **12a** by the action of sodium hydroxide in dimethyl sulfoxide DMSO. Tiazofurin **1a** was then derived from the thiazole **12a** by an ozonolysis–methanolysis sequence.

In view of the interesting bioactivity of tiazofurin **1a** (indeed, the compound has been subjected to clinical evaluation[10]), we wished to prepare carbatiazofurin **1b** and to evaluate it biologically. Our plan was to extend the aforecited methodology by preparing the penicillin **10b** and effecting its transformation into the thiazole **12b** and thence the target **1b**. We now report on the outcome of this work.

Results and Discussion

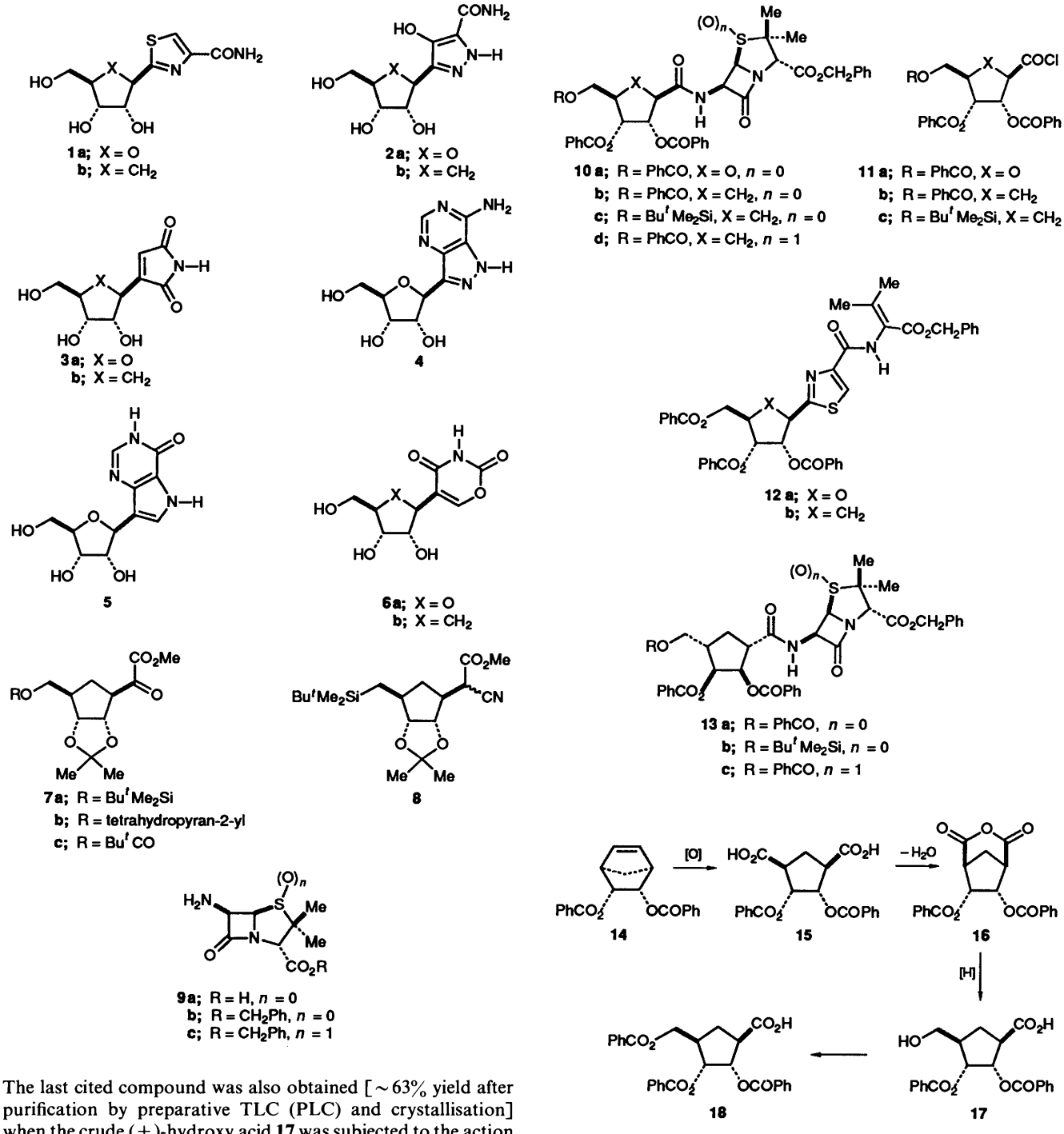
In principle, the penicillin **10b** should be accessible from the penicillanate **9b** and either the acid chloride **11b** or its racemate. Of course, the use of the racemic acylating agent would lead to the co-production of the penicillin **13a** and it would be necessary to separate the desired diastereoisomer **10b** from the mixture. However, since it would be of interest to convert the penicillin **13a** into carbatiazofurin enantiomer *ent*-**1b** and to examine the biological profile of the last cited compound, we opted to undertake the synthesis of the (±)-acid **18**.

The planned route to the (±)-acid **18** is outlined in Scheme 1. Thus, it was envisaged that oxidation of the known bicyclic alkene **14**[11] would provide the diacid **15**, which would be convertible into the anhydride **16**. Reduction of the last cited material would give the (±)-hydroxy acid **17** which would serve as a precursor of the target.

The bicyclic alkene **14** was prepared in low overall yield (~18%) from trinorbornadiene by the two-step procedure of Shealy and Clayton.[11] Dihydroxylation of trinorbornadiene ($KMnO_4$–NaOH–Na_2SO_3, aq. acetone, −65 °C) provided, after chromatography, the diol **19a** in 29% yield (lit.,[11] 28%). Benzoylation, effected in chloroform with benzoyl chloride in the presence of pyridine and 4-(dimethylamino)pyridine (DMAP), gave the dibenzoate **14** in 62% yield after chromatography and crystallisation. Oxidative cleavage of the bicyclic alkene **14** with potassium permanganate at ~7 °C in a two-phase system involving ethyl acetate, 2,2,4-trimethylpentane and water under an atmosphere of carbon dioxide (conditions prescribed[11] for effecting the conversion of the bicyclic alkene **19b** into the diacid **20a**) provided the diacid **15** in 80% yield after crystallisation. It was necessary to perform the crystallisation step immediately after the preparation because of the instability of the crude diacid **15** in the non-crystalline state.

Attempts to convert the diacid **15** into the anhydride **16** using acetic anhydride were unsatisfactory. However, the use of ethyl ethynyl ether[11] in chloroform provided the required material in 90% yield as a moisture-sensitive solid. In accord with the presence of the anhydride moiety, compound **16** displayed strong IR absorptions at 1821 and 1769 cm^{-1}.

Treatment of the anhydride **16** with sodium borohydride in *N*,*N*-dimethylformamide (DMF) furnished the (±)-hydroxy acid **17** as a slightly impure foam in ~89% yield. Without purification, the (±)-hydroxy acid **17** was subjected to the action of benzoyl chloride in pyridine; work-up, however, gave only a neutral product in modest yield (~37% after chromatography) which was identified as the (±)-lactone **21**.

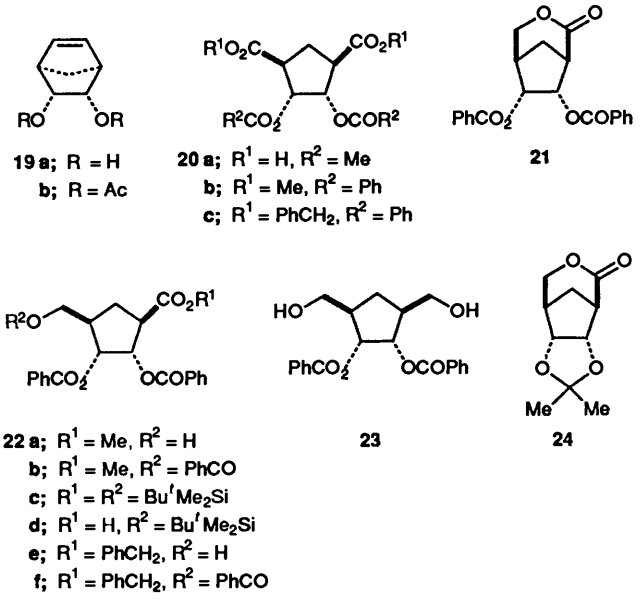


Scheme 1

The last cited compound was also obtained [~63% yield after purification by preparative TLC (PLC) and crystallisation] when the crude (±)-hydroxy acid **17** was subjected to the action of ethyl ethynyl ether in chloroform.

It was envisaged that the (±)-hydroxy acid **17** would be convertible into the target (±)-acid **18** by way of the (±)-intermediates **22a** and **22b**. Treatment of the product obtained by sodium borohydride reduction of the anhydride **16** with methanolic hydrogen chloride gave three materials, which were separated by chromatography. The first eluted material, isolated in 5% yield, was identified as the diester **20b**; the same product was obtained (85% yield) by treatment of the anhydride **16** with methanolic hydrogen chloride. The second fraction, obtained in 58% yield, was the desired (±)-hydroxy ester **22a**. The third eluted material, obtained in 2% yield, was the diol **23**; the last cited product also arose (21% yield) when the anhydride **16** was subjected to the action of sodium borohydride in tetrahydrofuran (THF). In the presence of benzoyl chloride and pyridine, the (±)-alcohol **22a** was transformed into the (±)-benzoate **22b** (84% yield after chromatography). Attempts to convert the (±)-ester **22b** into the (±)-acid **18** by the use of ethanethiol–aluminium bromide[12] or lithium iodide–pyridine[13] were unproductive (an impure material, which lacked a methyl ester absorption in its ^{1}H NMR spectrum, was isolated from the latter reaction in low yield but it could not be purified).

The report that it is possible to convert a *tert*-butyldimethylsilyl ester function into an acid chloride moiety in the presence of a *tert*-butyldimethylsilyl ether group[14] prompted us to prepare the (±)-disilyl compound **22c**. The synthesis was best achieved by treatment of the crude (±)-hydroxy acid **17** with *tert*-butyldimethylsilyl triflate and triethylamine in dichloromethane at −20 °C; following chromatography, the (±)-product **22c** was obtained in ~85% yield. Disappointingly, under the



literature conditions [$(COCl)_2$, DMF (cat.), CH_2Cl_2], there was no evidence for the production of the desired (±)-acid chloride **11c** (loss of both silyl groups occurred). It was possible selectively to deprotect the silyl ester function of the (±)-disilyl compound **22c** by the use of either potassium carbonate in methanol–THF–water or tetrabutylammonium fluoride (TBAF) in THF; the former procedure gave the better yield (84%) of the (±)-acid **22d**. However, attempts to transform the last cited compound into the (±)-acid chloride **11c** were again thwarted by desilylation. Efforts were also made to derive the penicillins **10c** and **13b** by subjecting the (±)-acid **22d** and the aminopenicillanate **9b**[1] to a variety of coupling conditions; again, these were unproductive.

The possibility of preparing the (±)-acid **18** by way of the (±)-intermediates **22e** and **22f** was next examined. Treatment of the product obtained by reduction of the anhydride **16** with sodium borohydride in DMF with acidic benzyl alcohol provided two materials, which were separated by chromatography. The first eluted material, isolated in 4% yield, was the dibenzyl ester **20c**. The second fraction, obtained in 68% yield, was the desired (±)-hydroxy ester **22e**. It underwent benzoylation to give (90% yield after chromatography) the (±)-benzoate **22f**, which then underwent hydrogenolysis (H_2, Pd–C, EtOAc) to furnish the (±)-acid **18** in 89% yield.

It was gratifying to find that the (±)-acid **18** could be transformed into the (±)-acid chloride **11b**, which reacted with the aminopenicillanate **9b**[1] (DMAP, CH_2Cl_2) to give a 1:1 mixture of the penicillins **10b** and **13a**. Unfortunately, the mixture, which was isolated in 63% yield after chromatography, could not be fractionated!

In the hope that they would be amenable to separation, the penicillin sulfoxides **10d** and **13c** were selected for preparation. Treatment of the aminopenicillanate **9b** (as its *p*-$MeC_6H_4SO_3H$ salt) with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane–DMF provided, after chromatography and crystallisation, the sulfoxide **9c** in 92% yield. The sulfoxide **9c** reacted with the (±)-acid chloride **11b** to give, after chromatographic fractionation, the penicillin **10d** in 42% yield and the penicillin **13c** in 40% yield (the basis of the stereochemical assignment will be discussed later). It is worth noting that the penicillins **10d** and **13c** showed a marked difference in their chromatographic mobilities (the former being more mobile).

Under reductive conditions (PBr_3, DMF, −7 °C),[15] the sulfoxide **10d** was transformed into the sulfide **10b** (76% yield after chromatography) and the sulfoxide **13c** into the sulfide **13a** (80% yield after chromatography).

Having accomplished the synthesis of the penicillins **10b** and **13a**, attention was turned to effecting their conversion into carbatiazofurin **1b** and its enantiomer. Using the optimum conditions devised for effecting the **10a** → **12a** transformation (NaOH in aq. DMSO; reflux in xylene),[1] the penicillin **10b** was transformed into the thiazole **12b** which was isolated, after chromatography, as a slightly impure foam in ~50% yield; PLC provided compound **12b**, $[\alpha]_D$ −116 (CH_2Cl_2), in a pure state. Similarly, the penicillin **13a** was transformed into the pure thiazole enantiomer *ent*-**12b**, $[\alpha]_D$ +102 (CH_2Cl_2). The 300 MHz ^1H NMR spectra of compounds **12b** and *ent*-**12b** were indistinguishable, in accord with their enantiomeric relationship.

Sequential treatment of compound **12b** with ozone in dichloromethane at −78 °C and methanolic ammonia provided, after chromatography, carbatiazofurin **1b**, $[\alpha]_D$ −52 (MeOH), in 49% yield. Similarly, carbatiazofurin enantiomer *ent*-**1b**, $[\alpha]_D$ +51 (MeOH), was prepared (53% after chromatography). Again, the spectroscopic properties of compound **1b** and its enantiomer were indistinguishable.

Tiazofurin **1a** is reported to show a small negative optical rotation {$[\alpha]_D$ −9 (EtOH)}.[1,2] Very tentatively therefore, the laevorotatory carbatiazofurin was considered to possess the stereostructure **1b**.

In the hope of shedding some light on the stereochemical issue, the CD spectra of the carbatiazofurins and tiazofurin **1a** were determined. However, a comparison of the spectra of the former compounds, shown in Fig. 1, and tiazofurin **1a**, illustrated in Fig. 2, failed to resolve the problem.

The possibility of establishing the stereostructures of compounds **10d** and **13c** by chemical means was next considered. It was envisaged that, when subjected to a hydrolysis–isopropylidenation sequence, the former penicillin would afford the bicyclic lactone **24** and the latter penicillin the bicyclic lactone enantiomer *ent*-**24**. The bicyclic lactone **24** (originally obtained in racemic form by Just *et al.*[7]) has been prepared by the groups of Ohno,[16] who reports $[\alpha]_D$ +44.4 ($CHCl_3$), and Koizumi,[17] who claims $[\alpha]_D$ + 46.7 ($CHCl_3$).

In a preliminary study, the (±)-ester **22b** was heated with hydrochloric acid and the product was stirred with acidic acetone. Following chromatography and crystallisation, the (±)-bicyclic lactone **24** was isolated in 14% yield. When subjected to a corresponding reaction and purification sequence, the penicillin **10d** afforded the bicyclic lactone **24**, $[\alpha]_D$ +22 ($CHCl_3$), in 7% yield. Similarly, the penicillin **13c** gave the bicyclic lactone enantiomer *ent*-**24**, $[\alpha]_D$ −21 ($CHCl_3$), in 29% yield. Although the optical rotations were notably lower than the literature values,* there can be little doubt concerning the stereochemical assignment of the penicillins **10d** and **13c** and their subsequent transformation products.

Compounds **1a**, **1b** and *ent*-**1b** were tested against a breast carcinoma cell line. Tiazofurin **1a** was cytotoxic at a concentration of 0.1 mmol dm^{-3} whereas carbatiazofurin **1b** and carbatiazofurin enantiomer *ent*-**1b** were toxic at a concentration of 1 mmol dm^{-3}.

Experimental

Dry solvents, referred to in the ensuing experiments, were prepared in the following manner: chloroform and dichloromethane were distilled from calcium hydride; THF was distilled from

* The m.p.s of the samples (m.p. 132–134 °C for **24** and m.p. 130–131 °C for *ent*-**24**) were also lower than the literature values for compound **24** (m.p. 140–141.5[16] and 140–143 °C;[17] there was insufficient material in the samples to allow us to effect its recrystallisation).

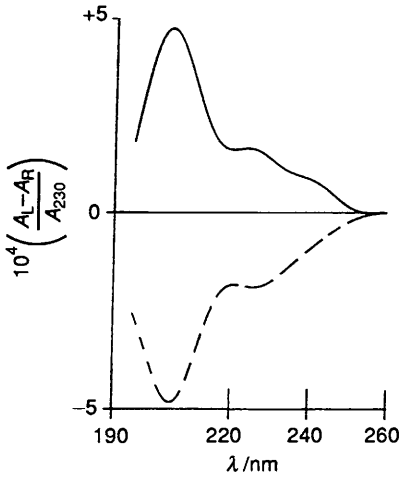


Fig. 1 Fourier-transform-filtered CD spectra (EtOH) of (−)-carbatiazofurin **1b** (bottom) and its enantiomer (top), normalised with respect to the prominent shoulder at 230 nm in the UV spectra

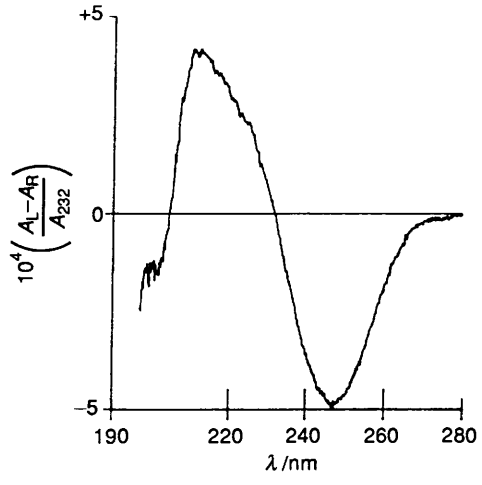


Fig. 2 CD spectrum (EtOH) of (−)-tiazofurin **1a**, normalised with respect to the prominent shoulder at 232 nm in the UV spectrum

sodium–benzophenone; DMF was stored over 4 Å molecular sieves; pyridine was distilled from barium oxide and stored over sodium hydroxide pellets. Light petroleum refers to that fraction boiling in the range 30–60 °C.

PLC was carried out using Whatman silica gel 60A PK6F plates. Optical rotations, given in 10^{-1} deg cm^2 g^{-1}, were measured at ~20 °C using either a Thorn Automation Type 243 or an Optical Activity 1000 polarimeter. A JASCO J600 spectropolarimeter was employed to measure CD spectra. IR Spectra were recorded in solution (with solvent subtraction) using a Nicolet 5SXC FT IR spectrometer. For other chromatographic and instrumental details, see Part 1.[1] UV Extinction coefficients (ε) are presented in cm^2 mmol^{-1}; coupling constants (J) and separations are shown in Hz.

Preparation of (2-exo,3-exo)-*Bicyclo*[2.2.1]*hept*-5-*ene*-2,3-*diol* **19a**.[11]—Finely powdered potassium permanganate (15.8 g, 0.1 mol) was added over a period of 10 min to a vigorously stirred, cooled (Me_2CO–solid CO_2) solution of trinorbornadiene (25 cm^3, 21.4 g, 0.232 mol) in acetone (220 cm^3), while the temperature of the mixture was maintained at −67 °C (±3 °C) for 1 h. An ice-cold solution of sodium hydroxide (4.0 g, 0.1 mol) and sodium sulfite (13.0 g, 0.103 mol) in water (70 cm^3) was added in portions over a period of 5 min, the temperature of the mixture being maintained at −65 °C (±5 °C). After 10 min, the mixture was allowed to warm to room temperature. The solid material was allowed to settle and the supernatant liquid was decanted. The solid was washed with 90% aq. acetone (3 × 100 cm^3) and the combined decants were concentrated. The residue was extracted with chloroform (4 × 50 cm^3) and the extracts were concentrated. Subjection of the residue to silica gel column chromatography [light petroleum–EtOAc (2:1) as eluent] gave the title diol **19a** (8.41 g, 29%), m.p. 119–120 °C (lit.,[11] 118 °C); $\nu_{max}(CHBr_3)$/cm^{-1} 3602 and 3482 (OH); λ_{max}(EtOH)/nm 204 (ε 2900); δ(250 MHz; $CDCl_3$) 1.64 and 1.89 [each 1 H, dt (J 9, 1 and 1) and d (J 9), 7-H_2], 2.71 (2 H, t, J 1, 1-and 4-H), 3.02 (2 H, br s, 2 × OH), 3.71 (2 H, s, 2- and 3-H) and 6.04 (2 H, s, 5- and 6-H) (Found: C, 66.8; H, 7.9. Calc. for $C_7H_{10}O_2$: C, 66.65; H, 8.00%).

Preparation of (5-exo,6-exo)-5,6-*Dibenzoyloxybicyclo*[2.2.1]*hept*-2-*ene* **14**.[11]—(*a*) A solution of benzoyl chloride (6.51 cm^3, 7.88 g, 56.1 mmol) in dry chloroform (15 cm^3) was added under nitrogen to a stirred solution of the diol **19a** (3.22 g, 25.5 mmol) in dry chloroform (50 cm^3) containing pyridine (4.54 cm^3, 4.44 g, 56.1 mmol) and DMAP (0.62 g, 5.1 mmol). After 18 h, the solution was diluted with chloroform (60 cm^3) and washed successively with 10% hydrochloric acid (2 × 30 cm^3), saturated aq. sodium hydrogen carbonate (2 × 30 cm^3) and water (2 × 30 cm^3). Evaporation of the dried ($MgSO_4$) organic phase gave a pale-yellow oil, which was subjected to silica gel chromatography [light petroleum–EtOAc (2:1) as eluent]. Crystallisation of the purified product from chloroform–light petroleum gave the title dibenzoate **14** (5.29 g, 62%), m.p. 126–128 °C (lit.,[11] 118–118.5 °C); $\nu_{max}(CHBr_3)$/cm^{-1} 1718 (ester C=O); λ_{max}(EtOH)/nm 228 (ε 24 300), 273 (1800) and 282 (1400); δ(250 MHz; $CDCl_3$) 1.89 and 2.30 [each 1 H, br d (separation 9) and d (J 9), 7-H_2], 3.07 (2 H, br s, 1- and 4-H), 5.10 (2 H, s, 5- and 6-H), 6.28 (2 H, s, 2- and 3-H) and 7.21–7.31, 7.42–7.51 and 7.84–7.92 (4, 2 and 4 H, each m, 2 × Ph); m/z (FAB) 335 (MH^+, 10%), 213 (42) and 105 ($C_7H_5O^+$, 100) (Found: C, 75.5; H, 5.5. Calc. for $C_{21}H_{18}O_4$: C, 75.45; H, 5.45%).

(*b*) Trinorbornadiene (125 cm^3, 107 g, 1.16 mol) was converted, as before, into the diol **19a** which, without purification, was treated with benzoyl chloride. Crystallisation of the product afforded the dibenzoate **14** (33.8 g, 9%).

Preparation of t-4,t-5-*Dibenzoyloxycyclopentane*-r-1,c-3-*dicarboxylic Acid* **15**.—A solution of the alkene **14** (26.4 g, 78.9 mmol) in 2,2,4-trimethylpentane (70 cm^3) and ethyl acetate (400 cm^3) was layered on top of water (880 cm^3). The stirred mixture was cooled in ice and treated during 2 h with a solution of potassium permanganate (48.3 g, 30.6 mmol) in water (766 cm^3). During the addition, a steady stream of carbon dioxide was passed through the mixture which was maintained at 5–10 °C using an ice-bath. As soon as the addition was complete, sulfur dioxide was passed through the mixture (maintained below 15 °C) until a colourless solution resulted. The mixture was concentrated (to ~300 cm^3), cooled in ice, acidified with conc. hydrochloric acid (28 cm^3) and extracted with diethyl ether (7 × 300 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to leave a residue, which was crystallised from ethyl acetate–light petroleum to give the *title diacid* **15** (25.3 g, 80%), m.p. 179–180 °C; ν_{max}(Nujol)/cm^{-1} 1726 (ester C=O) and 1718 (acid C=O); λ_{max}(EtOH)/nm 228 (ε 24 500), 273 (1900) and 282 (1500); δ(250 MHz; CD_3SOCD_3–D_2O) 1.99–2.17 and 2.60–2.76 (each 1 H, m, 2-H_2), 3.25–3.40 (2 H, m, 1- and 3-H), 5.66 (2 H, br d, separation 4, 4- and 5-H) and 7.41–7.52, 7.60–7.70 and 7.82–7.92 (4, 2 and 4 H, each m, 2 × Ph); m/z (FAB) 399 (MH^+, 9%) and 105 ($C_7H_5O^+$, 100) (Found: C, 63.3; H, 4.7. $C_{21}H_{18}O_8$ requires C, 63.30; H, 4.55%).

Preparation of t-4,t-5-*Dibenzoyloxycyclopentane*-r-1,c-3-*dicarboxylic Acid Anhydride* **16**.—50% Ethyl ethynyl ether in hexanes (6.96 cm^3, 5.00 g, 36 mmol) was added to a stirred suspension of the diacid **15** (7.20 g, 18.0 mmol) in dry chloroform (70 cm^3) under nitrogen. Evaporation after 18 h gave a brown solid, which was suspended in cold (Me_2CO–solid CO_2), dry THF. The mixture was filtered under nitrogen and the solid was washed with cold, dry THF. The dried product (6.21 g, 90%), which because of its sensitivity to moisture was stored *in vacuo* (over P_2O_5), was identified as the *title anhydride* **16**, m.p. 78–79 °C; $\nu_{max}(CD_3SOCD_3)/cm^{-1}$ 1821 and 1769 (anhydride C=O) and 1729 (ester C=O); $\lambda_{max}(CH_2Cl_2)/nm$ 275 (ε 2300) and 284 (1800); δ(250 MHz; $CDCl_3$) 2.45 and 2.69 [each 1 H, d (*J* 14) and dt (*J* 14, 4 and 4), 2-H_2], 3.61 (2 H, d, *J* 4, 1- and 3-H), 5.82 (2 H, s, 4- and 5-H) and 7.24–7.36, 7.48–7.58 and 7.80–7.89 (4, 2 and 4 H, each m, 2 × Ph); *m/z* (FAB) 381 (MH^+, 3%), 259 ($C_{14}H_{11}O_5^+$, 11) and 105 ($C_7H_5O^+$, 100) (Found: C, 66.3; H, 4.3. $C_{21}H_{16}O_7$ requires C, 66.30; H, 4.25%).

Preparation of (1R*,2S*,3R*,4R*)-2,3-*Dibenzoyloxy*-4-(*hydroxymethyl*)*cyclopentane*-1-*carboxylic Acid* **17**.—Finely powdered sodium borohydride (1.25 g, 33.0 mmol) was dissolved in dry DMF (100 cm^3) and to the ice-cooled solution was added a solution of the anhydride **16** (5.00 g, 13.1 mmol) in dry DMF (100 cm^3) under nitrogen. After 1 h, the mixture was concentrated and the residue was partitioned between 10% hydrochloric acid (100 cm^3) and ethyl acetate (100 cm^3). The organic phase was extracted with aqueous sodium hydrogen carbonate (3 × 100 cm^3). The combined aqueous extracts were acidified with 10% hydrochloric acid and extracted with ethyl acetate (4 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated to leave mainly the title compound **17** (4.51 g, ~89%) as a foam; $\nu_{max}(CD_3SOCD_3)/cm^{-1}$ 3400br (OH) and 1722 (ester C=O); δ(250 MHz; $CDCl_3$–D_2O) *inter alia* 1.88–2.04 and 2.33–2.51 (each 1 H, m, 5-H_2), 2.52–2.67 (1 H, m, 4-H), 3.24–3.38 (1 H, m, 1-H), 3.78 (2 H, d, separation 4, CH_2OH), 5.49 (1 H, t, *J* 6, 3-H), 5.75 (1 H, t, *J* 6, 2-H) and 7.30–7.45, 7.48–7.60 and 7.88–8.05 (4, 2 and 4 H, each m, 2 × Ph); *m/z* (CI; CH_4) 384 (MH^+, 41%), 123 (100) and 105 ($C_7H_5O^+$, 94).

Preparation of (1R*,5R*,6R*,7S*)-6,7-*Dibenzoyloxy*-3-*oxabicyclo*[3.2.1]*octan*-2-*one* **21**.—(*a*) Benzoyl chloride (0.035 cm^3, 0.042 g, 0.30 mmol) was added to a stirred, ice-cooled solution of the crude hydroxy acid **17** (0.020 g, ~0.052 mmol) in dry pyridine (1 cm^3). After 20 h, the mixture was concentrated and the residue partitioned between ethyl acetate and 10% hydrochloric acid. The organic phase was washed successively with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$) and concentrated. Subjection of the resultant red oil to silica gel column chromatography [hexanes–EtOAc (1:1) as eluent] and crystallisation of the purified product from chloroform–hexanes gave the title compound **21** (0.007 g, ~37%). The 300 MHz ^1H NMR spectrum of the material matched that of the sample obtained in the following experiment.

(*b*) 50% Ethyl ethynyl ether in hexanes (0.018 cm^3, 0.013 g, 0.18 mmol) was added to a stirred, ice-cooled solution of the crude hydroxy acid **17** (0.070 g, ~0.182 mmol) in dry chloroform (1 cm^3) under argon. After 18 h, the mixture was concentrated and the residue was subjected to PLC [hexanes–EtOAc (1:1) as eluent]. Crystallisation of the purified product from chloroform–hexanes gave the *title lactone* **21** (0.042 g, ~63%) as a pale-yellow solid, m.p. 118–119 °C; $\nu_{max}(KBr)/cm^{-1}$ 1730 (δ-lactone C=O) and 1710 (ester C=O); $\lambda_{max}(EtOH)/nm$ 230 (ε 22 600); δ(300 MHz; $CDCl_3$) 2.14 and 2.55–2.65 [each 1 H, br d (*J* 12) and m, 8-H_2], 2.72–2.77 (1 H, m, 5-H), 3.33 (1 H, dd, *J* 4 and 2.5, 1-H), 4.46 and 4.51 [each 1 H, dd (*J* 11.5 and 3.5) and dt (*J* 11.5, 1.5 and 1.5), 4-H_2], 5.61 (1 H, dd, *J* 6 and 0.5, 6-H), 5.72 (1 H, dd, *J* 6 and 0.5, 7-H) and 7.18–7.25, 7.33–7.40, 7.43–7.50, 7.53–7.59, 7.74–7.80 and 7.91–7.97 (2, 2, 1, 1, 2 and 2 H, each m, 2 × Ph); *m/z* (FAB) 367 (MH^+, 5%) and 105 ($C_7H_5O^+$, 100) (Found: C, 69.0; H, 5.3. $C_{21}H_{18}O_6$ requires C, 68.85; H, 4.95%).

Reaction of the Anhydride **16** *with Sodium Borohydride in DMF followed by Methanolic Hydrogen Chloride*.—A solution of sodium borohydride (0.420 g, 11.1 mmol) in dry DMF (60 cm^3) was added to a stirred, ice-cooled solution of the anhydride **16** (3.00 g, 7.89 mmol) in dry DMF (60 cm^3). After 2.5 h, the solvent was evaporated off and the residue was dissolved in methanol (20 cm^3). The ice-cooled solution was stirred for 30 min with a saturated solution of hydrogen chloride in methanol (30 cm^3). Evaporation of the solvent left an oil, which was dissolved in ethyl acetate (60 cm^3). The solution was washed successively with 10% hydrochloric acid (2 × 40 cm^3), saturated aq. sodium hydrogen carbonate (2 × 40 cm^3) and water (30 cm^3). Evaporation of the dried ($MgSO_4$) organic phase and subjection of the resultant oil to silica gel column chromatography [light petroleum–EtOAc (3:1) as eluent] gave three fractions.

The first eluted material (0.167 g, 5%) was identified as the dimethyl ester **20b** on the basis of its 250 MHz ^1H NMR spectrum.

The second eluted material (1.83 g, 58%) was identified as methyl (1*R**,2*S**,3*R**,4*R**)-2,3-dibenzoyloxy-4-(hydroxymethyl)cyclopentane-1-carboxylate **22a** on the basis of its NMR spectrum; δ(250 MHz; $CDCl_3$) 1.79–1.96 and 2.32–2.48 (each 1 H, m, 5-H_2), 2.49–2.65 (2 H, m, 4-H and OH), 3.23–3.37 (1 H, m, 1-H), 3.75 (5 H, br s, MeO_2C and CH_2OH), 5.50 (1 H, t, *J* 6, 3-H), 5.73 (1 H, t, *J* 6, 2-H) and 7.30–7.47, 7.48–7.60 and 7.89–8.07 (4, 2 and 4 H, each m, 2 × Ph).

The third eluted material (0.058 g, 2%) was mainly the diol **23** on the basis of 250 MHz ^1H NMR spectroscopy.

Preparation of Dimethyl t-4,t-5-*Dibenzoyloxycyclopentane*-r-1,c-3-*dicarboxylate* **20b**.—A saturated solution of hydrogen chloride in methanol (4 cm^3) was added to a stirred, ice-cooled solution of the anhydride **16** (0.100 g, 0.263 mmol) in dry chloroform (1 cm^3). After 1.5 h, the mixture was concentrated and the residue was partitioned between ethyl acetate and aq. sodium hydrogen carbonate. The organic phase was dried ($MgSO_4$) and concentrated to leave the *title dimethyl ester* **20b** (0.094 g, 85%) as a crystalline solid, m.p. 90–91 °C; $\nu_{max}(CHBr_3)/cm^{-1}$ 1731 (ester C=O); $\lambda_{max}(EtOH)/nm$ 229 (ε 25 000), 274 (1900) and 282 (1500); δ(250 MHz; $CDCl_3$) 2.24–2.39 and 2.54–2.69 (each 1 H, m, 2-H_2), 3.22–3.37 (2 H, m, 1- and 3-H), 3.76 (6 H, s, 2 × MeO_2C), 5.79–5.87 (2 H, m, 4- and 5-H) and 7.31–7.42, 7.49–7.58 and 7.89–7.97 (4, 2 and 4 H, each m, 2 × Ph); *m/z* (FAB) 427 (MH^+, 6%) and 105 ($C_7H_5O^+$, 100) (Found: C, 64.6; H, 5.3. $C_{23}H_{22}O_8$ requires C, 64.8; H, 5.20%).

Reaction of the Anhydride **16** *with Sodium Borohydride in THF*.—A solution of sodium borohydride (0.008 g, 0.21 mmol) in dry THF (1 cm^3) was added to a stirred solution of the anhydride **16** (0.050 g, 0.13 mmol) in dry THF (1 cm^3) under nitrogen. After 1.5 h, 10% hydrochloric acid (1 cm^3) was added to the mixture which, after another 0.5 h, was diluted with ethyl acetate and water. Evaporation of the dried ($MgSO_4$) organic phase gave *t*-4,*t*-5-dibenzoyloxy*r*-1,*c*-3-di(hydroxymethyl)cyclopentane **23** (0.011 g, 21%) as a syrup, $\nu_{max}(CHBr_3)/cm^{-1}$ 3495 (OH) and 1711 (ester C=O); δ(250 MHz; $CDCl_3$) 1.42–1.60 and 2.04–2.21 (each 1 H, m, 2-H_2), 2.21–2.47 (2 H, br s, 2 × OH), 2.47–2.64 (2 H, m, 1- and 3-H), 3.65–3.84 (4 H, m, 2 × CH_2OH), 5.34–5.44 (2 H, m, 4- and 5-H) and 7.28–7.45, 7.49–7.60 and 7.93–8.05 (4, 2 and 4 H, each m, 2 × Ph); *m/z* (CI; NH_3) 388 (MNH_4^+, 30%), 371 (MH^+, 100), 353 ($MH^+ - H_2O$, 60) and 249 ($C_{14}H_{18}O_4^+$, 100).

Preparation of Methyl (1R*,2S*,3R*,4R*)-2,3-*Dibenzoyloxy*-4-(*benzoyloxymethyl*)*cyclopentane*-1-*carboxylate* **22b**.—Benzoyl chloride (0.35 cm^3, 0.427 g, 3.04 mmol) was added to a stirred, ice-cooled solution of the alcohol **22a** (0.607 g, 1.46 mmol) in dry chloroform (6 cm^3) containing dry pyridine (0.86 cm^3, 0.844 g, 10.67 mmol). The mixture was allowed to warm to room temperature and, after 5 h, was concentrated. The residue was partitioned between chloroform and 10% hydrochloric acid and the organic phase was washed with saturated aq. sodium hydrogen carbonate followed by water. Evaporation of the dried ($MgSO_4$) organic layer and subjection of the oily residue to silica gel column chromatography [light petroleum–EtOAc (5:1) as eluent] gave the *title compound* **22b** (0.616 g, 84%) as an oil, $\nu_{max}(CHBr_3)/cm^{-1}$ 1724 (ester C=O); λ_{max}(EtOH)/nm 229 (ε 35 400), 274 (2700) and 282 (2200); δ(300 MHz; $CDCl_3$) 1.94 and 2.53 (each 1 H, dt, *J* 13, 9 and 9, 5-H_2), 2.84–3.01 (1 H, m, 4-H), 3.27–3.39 (1 H, m, 1-H), 3.74 (3 H, s, MeO_2C), 4.51 (2 H, d, separation 6, CH_2OCO), 5.63 (1 H, t, *J* 6, 3-H), 5.84 (1 H, t, *J* 6, 2-H) and 7.28–7.43, 7.46–7.57, 7.88–7.97 and 7.99–8.07 (6, 3, 4 and 2 H, each m, 3 × Ph); *m/z* (FAB) 503 (MH^+, 5%), 381 (10) and 105 ($C_7H_5O^+$, 100) (Found: C, 69.2; H, 5.4. $C_{29}H_{26}O_8$ requires C, 69.3; H, 5.20%).

Preparation of tert-*Butyldimethylsilyl* (1R*,2S*,3R*,4R*)-2,3-*Dibenzoyloxy*-4-(tert-*butyldimethylsiloxymethyl*)*cyclopentane*-1-*carboxylate* **22c**.—*tert*-Butyldimethylsilyl triflate (0.147 cm^3, 0.169 g, 0.64 mmol) and triethylamine (0.134 cm^3, 0.097 g, 0.96 mmol) were added to a stirred, cooled (CCl_4–solid CO_2-bath) solution of the crude hydroxy acid **17** (0.062 g, ~0.16 mmol) in dry dichloromethane (1 cm^3) under argon. After 1.5 h, the mixture was allowed to warm to room temperature and was concentrated. Subjection of the residue to silica gel column chromatography [hexanes–EtOAc (1:1) as eluent] gave the *title compound* **22c** (0.084 g, ~85%) as an oil, ν_{max}(film)/cm^{-1} 1725 (ester C=O); λ_{max}(EtOH)/nm 203 (ε 25 300), 229 (36 200), 274 (2800) and 281 (2300); δ(300 MHz; $CDCl_3$) 0.08, 0.10 and 0.27 (3, 3 and 6 H, each s, 2 × Me_2Si), 0.90 and 0.92 (each 9 H, s, 2 × Me_3C), 1.89 and 2.36 [each 1 H, ddd (*J* 13, 10.5 and 8.5) and dt (*J* 13, 9 and 9), 5-H_2], 2.46–2.58 (1 H, m, 4-H), 3.30 (1 H, dt, *J* 10, 8.5 and 8.5, 1-H), 3.71 and 3.84 [each 1 H, dd (*J* 10 and 4) and dd (*J* 10 and 5), CH_2O], 5.48 (1 H, t, *J* 5, 3-H), 5.67 (1 H, dd, *J* 8 and 5, 2-H) and 7.29–7.41, 7.46–7.56 and 7.89–7.98 (4, 2 and 4 H, each m, 2 × Ph); *m/z* (FAB) 613 (MH^+, 20%), 555 ($C_{29}H_{39}O_7Si_2^+$, 36), 481 ($C_{27}H_{33}O_6Si^+$, 34) and 179 (100) (Found: C, 64.8; H, 7.8; Si, 8.9. $C_{33}H_{48}O_7Si_2$ requires C, 64.7; H, 7.9; Si, 9.15%).

Preparation of (1R*,2S*,3R*,4R*)-2,3-*Dibenzoyloxy*-4-(tert-*butyldimethylsiloxymethyl*)*cyclopentane*-1-*carboxylic Acid* **22d**.—(*a*) A solution of potassium carbonate (0.100 g, 0.72 mmol) in water (1 cm^3) was added to a stirred solution of the silyl ester **22c** (0.201 g, 0.33 mmol) in methanol (3 cm^3)–THF (1 cm^3). After 1 h, the mixture was concentrated to ~25% of its volume and diluted with brine (6 cm^3). The solution was washed with ethyl acetate (2 ×). Acidification of the aqueous phase with 10% hydrochloric acid was followed by extraction with ethyl acetate (2 ×). Evaporation of the dried ($MgSO_4$) organic layer gave the title acid **22d** (0.137 g, 84%) as an oil, ν_{max}(film)/cm^{-1} 3400br (OH) and 1725 (ester C=O); λ_{max}(EtOH)/nm 202 (ε 16 100), 229 (22 300) and 273 (1600); δ(300 MHz; $CDCl_3$) 0.07 and 0.09 (each 3 H, s, Me_2Si), 0.92 (9 H, s, Me_3C), 1.99 and 2.40 [each 1 H, ddd (*J* 13, 10 and 8.5) and dt (*J* 13, 8.5 and 8.5), 5-H_2], 2.51–2.61 (1 H, m, 4-H), 3.35 (1 H, apparent q, separation 8, 1-H), 3.73 and 3.96 [each 1 H, dd (*J* 10 and 4) and dd (*J* 10 and 5), CH_2O], 5.48 (1 H, t, *J* 5, 3-H), 5.70 (1 H, dd, *J* 7.5 and 5, 2-H) and 7.29–7.42, 7.46–7.57 and 7.90–7.99 (4, 2 and 4 H, each m, 2 × Ph); *m/z* (FAB) 499 (MH^+, 100), 481 ($C_{27}H_{33}O_6Si^+$, 55) and 179 (65).

(*b*) A solution of TBAF in THF (1 mol dm^{-3}; 0.15 cm^3, 0.15 mmol) was added to a stirred solution of the silyl ester **22c** (0.095 g, 0.15 mmol) in dry THF (1 cm^3) under argon. After 0.75 h, the mixture was concentrated and the residue was dissolved in ethyl acetate (2 cm^3). The solution was washed successively with 10% hydrochloric acid (2 cm^3) and brine (2 cm^3), dried ($MgSO_4$) and concentrated to leave the acid **22d** (0.059 g, 77%), identified by its 300 MHz ^1H NMR spectrum.

Reaction of the Anhydride **16** *with Sodium Borohydride in DMF followed by Hydrogen Chloride in Benzyl Alcohol*.—A solution of sodium borohydride (0.25 g, 6.61 mmol) in dry DMF (20 cm^3) was added to a stirred, ice-cooled solution of the anhydride **16** (1.00 g, 2.63 mmol) in dry DMF (20 cm^3). After 5 h, the mixture was concentrated and the residue was partitioned between ethyl acetate (20 cm^3) and saturated aq. sodium hydrogen carbonate (20 cm^3). Following acidification with 10% hydrochloric acid, the aqueous layer was extracted with ethyl acetate (3 × 20 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated. The residue was dissolved in chloroform (1 cm^3) and treated with a saturated solution of hydrogen chloride in benzyl alcohol (2 cm^3) for 1 h. Evaporation of the solvent (with addition of water to produce an azeotrope) gave an oil, which was subjected to silica gel column chromatography [hexanes–EtOAc (5:3) as eluent] to afford two fractions.

The first eluted material was crystallised from chloroform–hexanes to give *dibenzyl* t-4,t-5-*dibenzoyloxycyclopentane*-r-1,c-3-*dicarboxylate* **20c** (0.060 g, 4%), m.p. 77–78 °C; ν_{max}(KBr)/cm^{-1} 1740 and 1720 (ester C=O); λ_{max}(EtOH)/nm 204 (ε 25 200) and 230 (24 600); δ(300 MHz; $CDCl_3$) 2.34 and 2.63 (each 1 H, dt, *J* 13.5, 9 and 9, 2-H_2), 3.27–3.38 (2 H, m, 1- and 3-H), 5.18 (4 H, AB q, *J* 13, separation of inner lines 2, 2 × CH_2Ph), 5.84–5.91 (2 H, m, 4- and 5-H) and 7.25–7.40, 7.49–7.57 and 7.87–7.94 (14, 2 and 4 H, each m, 4 × Ph); *m/z* (FAB) 579 (MH^+, 12%), 105 ($C_7H_5O^+$, 90) and 91 ($C_7H_7^+$, 100) (Found: C, 72.4; H, 5.1. $C_{35}H_{30}O_8$ requires C, 72.65; H, 5.25%).

The second eluted material, isolated as a syrup (0.850 g, 68%), was *benzyl* (1R*,2S*,3R*,4R*)-2,3-*dibenzoyloxy*-4-(*hydroxymethyl*)*cyclopentane*-1-*carboxylate* **22e**, ν_{max}(film)/cm^{-1} 3500br (OH) and 1725 (ester C=O); λ_{max}(EtOH)/nm 201 (ε 44 200) and 229 (30 600); δ(300 MHz; $CDCl_3$) 1.87 and 2.41 (each 1 H, dt, *J* 13, 9.5 and 9.5, 5-H_2), 2.48–2.70 (2 H, m, 4-H and OH), 3.30–3.41 (1 H, m, 1-H), 3.76 (2 H, br d, separation 4.5, CH_2OH), 5.18 (2 H, s, CH_2Ph), 5.51 (1 H, t, *J* 5, 3-H), 5.74 (1 H, dd, *J* 7 and 5.5, 2-H) and 7.25–7.43, 7.49–7.59 and 7.89–8.01 (9, 2 and 4 H, each m, 3 × Ph) (in a COSY 90° experiment, the following connectivities were established: δ 5.74 to 5.51 to 2.48–2.70 to 2.41 to 1.87; δ 5.74 to 3.30–3.41 to 2.41; δ 3.76 to 2.48–2.70 to 1.87; δ 3.30–3.41 to 1.87); *m/z* (FAB) 475 (MH^+, 100%) and 149 (63) (Found: C, 71.1; H, 5.6. $C_{28}H_{26}O_7$ requires C, 70.85; H, 5.50%).

(*b*) The aforecited reaction was repeated using the anhydride **16** (5.00 g, 13.2 mmol). Work-up as before gave the benzyl ester **22e** (2.76 g, 44%).

Preparation of Benzyl (1R*,2S*,3R*,4R*)-2,3-*Dibenzoyl*-4-(*benzoyloxymethyl*)*cyclopentane*-1-*carboxylate* **22f**.—A mixture of the alcohol **22e** (2.76 g, 5.82 mmol), dry chloroform (66 cm^3), dry pyridine (4.70 cm^3, 4.60 g, 58.2 mmol), benzoyl chloride (3.36 cm^3, 4.07 g, 28.9 mmol) and DMAP (1.07 g, 8.76 mmol) was stirred under argon for 24 h. The solution was then concentrated and the residue, dissolved in ethyl acetate (200 cm^3), was washed successively with 10% hydrochloric acid (2 × 65 cm^3), saturated aq. sodium hydrogen carbonate (2 × 65 cm^3) and water (2 × 65 cm^3). The dried ($MgSO_4$) organic phase was concentrated and the resultant oil was subjected to silica gel column chromatography [hexanes–EtOAc (4:1) as eluent] to give the *title compound* **22f** (3.02 g, 90%) as a syrup,

ν_{max}(film)/cm^{-1} 1730 (ester C=O); λ_{max}(EtOH)/nm 201 (ε 59 500), 230 (42 900), 269 (3000), 274 (3300) and 281 (2700); δ(300 MHz; $CDCl_3$) 1.95 and 2.53 (each 1 H, dt, *J* 13, 9 and 9, 5-H_2), 2.84–2.97 (1 H, m, 4-H) 3.38 (1 H, dt, *J* 9, 9 and 7, 1-H), 4.48 and 4.52 (each 1 H, dd, *J* 12 and 6, CH_2OCO), 5.64 (1 H, t, *J* 5.5, 3-H), 5.85 (1 H, dd, *J* 6.5 and 5.5, 2-H) and 7.25–7.42, 7.48–7.57 and 7.89–8.06 (14, 4 and 2 H, each m, 4 × Ph); *m/z* (FAB) 579 (MH^+, 5%), 457 ($C_{28}H_{25}O_6^+$, 7) and 105 ($C_7H_5O^+$, 100) (Found: C, 72.4; H, 5.2. $C_{35}H_{30}O_8$ requires C, 72.65; H, 5.25%).

Preparation of (1R*,2S*,3R*,4R*)-2,3-*Dibenzoyloxy*-4-(*benzoyloxymethyl*)*cyclopentane*-1-*carboxylic Acid* **18**.—A stirred mixture of the benzyl ester **22f** (2.32 g, 4.01 mmol), 10% palladium–charcoal (1.2 g, 0.52 mass equiv.) and ethyl acetate (35 cm^3) was left under hydrogen for 14 h. The mixture was then filtered through Celite and the filtrate was concentrated to give the *title compound* **18** (1.75 g, 89%) as a foam, ν_{max}(KBr)/cm^{-1} 3000br (OH) and 1725 (ester C=O); λ_{max}(EtOH)/nm 202 (ε 30 300), 229 (35 200), 274 (2700) and 281 (2200); δ(300 MHz; $CDCl_3$) 1.99 and 2.56 (each 1 H, dt, *J* 13.5, 9 and 9, 5-H_2), 2.87–3.02 (1 H, m, 4-H), 3.36 (1 H, dt, *J* 9, 9 and 6, 1-H), 4.52 (2 H, d, separation 5.5, CH_2OCO), 5.60 (1 H, t, *J* 7, 3-H), 5.84 (1 H, t, *J* 5.5, 2-H) and 7.30–7.41, 7.47–7.57 and 7.89–8.06 (6, 3 and 6 H, each m, 3 × Ph); *m/z* (FAB) 489 (MH^+, 82%), 367 (78) and 307 (100) (Found: C, 68.5; H, 4.6. $C_{28}H_{24}O_8$ requires C, 68.85; H, 4.95%).

Preparation of Benzyl 6β-[(1′R,2′S,3′R,4′R)-2′,3′-*Dibenzoyloxy*-4′-(*benzoyloxymethyl*)*cyclopentane*-1′-*carboxamido*]*penicillanate* **10b** *and Benzyl* 6β-[(1′S,2′R,3′S,4′S′)-2′,3′-*Dibenzoyloxy*-4′-(*benzoyloxymethyl*)*cyclopentane*-1′-*carboxamido*]*penicillanate* **13a**.—Oxalyl dichloride (0.004 cm^3, 0.006 g, 0.047 mmol) followed by a drop of DMF were added to a stirred, cooled (ice–NaCl bath) solution of the (±)-acid **22f** (0.019 g, 0.039 mmol) in dry dichloromethane (0.75 cm^3). After 0.5 h, a further quantity of oxalyl dichloride (0.004 cm^3, 0.006 g, 0.047 mmol) was added and the mixture was allowed to warm to room temperature. Evaporation left an oil, which was dissolved in dry dichloromethane (0.75 cm^3). A solution of the amine **9b** (0.021 g, 0.068 mmol) in dry dichloromethane (0.75 cm^3) followed by DMAP (0.005 g, 0.041 mmol) were added and the mixture was stirred under argon for 1 h. The residue, obtained on evaporation of the solvent, was dissolved in chloroform (1 cm^3) and the solution was washed successively with 10% hydrochloric acid (2 × 1 cm^3) and water (1 cm^3). Evaporation of the dried ($MgSO_4$) organic phase and subjection of the residue to silica gel column chromatography [hexanes–EtOAc (1:1) as eluent] gave a foam (0.019 g, 63%), which was mainly a 1:1 mixture of the title compounds **10b** and **13a**; δ(300 MHz; $CDCl_3$) *inter alia* 1.38, 1.41, 1.57 and 1.64 (each 3 H, s, 2 × 2-Me_2), 2.17–2.35 (4 H, m, 2 × 5′-H_2), 2.94–3.08 (2 H, m, 2 × 4′-H), 3.14–3.25 (2 H, m, 2 × 1′-H), 4.49 and 4.52 (each 1 H, s, 2 × 3-H), 4.54 (4 H, d, separation 6, 2 × CH_2OCOPh), 5.20 (4 H, s, 2 × CH_2Ph), 5.34 and 5.40 (each 1 H, dd, *J* 9 and 5.5, 2 × 3′-H), 5.58 and 5.61 (each 1 H, d, *J* 4.5, 2 × 5-H), 5.72 (2 H, dd, *J* 9 and 4.5, 2 × 6-H) and 7.30–7.43, 7.45–7.62 and 7.90–8.04 (~22, 8 and 12, each m, 8 × Ph and 2 × CONH).

Preparation of Benzyl 6β-*Aminopenicillanate* 1β-*Oxide* **9c**.—MCPBA (~80%; 14.1 g, ~65 mmol) was added to a stirred, ice-cooled solution of the toluene-*p*-sulfonic acid (PTSA) salt of the penicillanate **9b** (30.0 g, 62.6 mmol) in a mixture of dichloromethane (180 cm^3) and DMF (120 cm^3). After 2 h, the mixture was filtered and the filtrate was partitioned between saturated aq. sodium hydrogen carbonate (250 cm^3) and chloroform (100 cm^3). The aqueous layer was extracted with chloroform (2 × 100 cm^3) and the combined organic extracts were washed with water (80 cm^3), dried ($MgSO_4$) and concentrated. Subjection of the residue to silica gel column chromatography [EtOAc–PrOH–water (4:1:2; upper phase) as eluent; column packed using EtOAc] and crystallisation of the purified product from chloroform–hexanes gave the *title compound* **9c** (18.6 g, 92%), m.p. 146–148 °C (decomp.); $[\alpha]_D$ + 280 (0.5% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3420 and 3330 (NH), 1770 (β-lactam C=O) and 1750 (ester C=O); λ_{max}(EtOH)/nm 205 (ε 12 000), 257 (850), 263 (880) and 268 (850); δ(300 MHz; $CDCl_3$) 1.07 and 1.65 (each 3 H, s, 2-Me_2), 2.2 (2 H, br s, NH_2), 4.64 (1 H, s, 3-H), 4.69 (1 H, d, *J* 5, 5-H), 4.92 (1 H, d, *J* 5, 6-H), 5.16 and 5.29 (each 1 H, d, *J* 12, CH_2Ph) and 7.38 (5 H, s, Ph); *m/z* (FAB) 323 (MH^+, 19%), 205 (37) and 91 ($C_7H_7^+$, 100) (Found: C, 55.9; H, 5.5; N, 8.7; S, 10.2. $C_{15}H_{18}N_2O_4S$ requires C, 55.9; H, 5.65; N, 8.70; S, 9.95%).

Reaction of the (±)-*Acid* **18** *with Oxalyl Dichloride followed by the Aminopenicillanate* **9c**.—Oxalyl dichloride (0.106 cm^3, 0.154 g, 1.21 mmol) followed by two drops of DMF were added to a stirred, cooled (ice–NaCl bath) solution of the (±)-acid **18** (0.459 g, 0.94 mmol) in dry dichloromethane (3 cm^3) under argon. The mixture was allowed to warm to room temperature over a period of 1.25 h and concentrated (with addition of PhMe and re-evaporation). The resultant oil was dissolved in dry, ethanol-free chloroform (5 cm^3) and the solution was treated with the amine **9c** (0.315 g, 0.98 mmol) and DMAP (0.121 g, 0.99 mmol). After 1.5 h, the mixture was concentrated and the residue was dissolved in ethyl acetate (30 cm^3). The solution was washed successively with 10% hydrochloric acid (2 × 10 cm^3) and water (2 × 10 cm^3), dried ($MgSO_4$) and concentrated. Subjection of the resultant oil to silica gel column chromatography [hexanes–EtOAc (2:1) as eluent] gave two fractions.

The first eluted material (0.313 g, 42%), isolated as a foam which crystallised on addition of diethyl ether–hexanes, was *benzyl* 6β-[(1′R,2′S,3′R,4′R)-2′,3′-*dibenzoyloxy*-4′-(*benzoyloxymethyl*)*cyclopentane*-1′-*carboxamido*]*penicillanate* 1β-*oxide* **10d**, m.p. 79–80 °C; $[\alpha]_D$ +116 (0.3% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3380br (NH), 1800 (β-lactam C=O), 1750sh and 1725 (ester C=O) and 1680 (amide C=O); λ_{max}(EtOH)/nm 203 (ε 40 900), 229 (40 000), 269 (3000), 274 (3200) and 281 (2600); δ(300 MHz; $CDCl_3$) 1.03 and 1.60 (each 3 H, s, 2-Me_2), 2.11 and 2.37 (each 1 H, dt, *J* 14, 9.5 and 9.5, 5′-H_2), 2.86–3.00 (1 H, m, 4′-H), 3.10 (1 H, dt, *J* 9, 9 and 6, 1′H), 4.52 (2 H, apparent dd, separation 6 and 1.5, CH_2OCO), 4.66 (1 H, s, 3-H), 5.05 (1 H, d *J* 4.5, 5-H), 5.17 and 5.29 (each 1 H, d, *J* 12, CH_2Ph), 5.55 (1 H, t, *J* 6, 3′-H), 5.62 (1 H, t, *J* 6, 2′-H), 6.09 (1 H, dd, *J* 10 and 4.5, 6-H) and 7.29–7.42, 7.47–7.56, 7.91–7.96 and 8.03–8.08 (11, 4, 4 and 2 H, each m, 4 × Ph and CONH) [addition of D_2O caused the signal of δ 6.09 to appear as a d (*J* 4.5)]; *m/z* (FAB) 793 (MH^+, 100%) (Found: C, 64.9; H, 5.2; N, 3.6; S, 4.4. $C_{43}H_{40}N_2O_{11}S$ requires C, 65.15; H, 5.10; N, 3.55; S, 4.05%).

The second eluted material (0.299 g, 40%), isolated as a foam, was *benzyl* 6β-[(1′S,2′R,3′S,4′S)-2′,3′-*dibenzoyloxy*-4′-(*benzoyloxymethyl*)*cyclopentane*-1′-*carboxamido*]*penicillanate* 1β-*oxide* **13c**; $[\alpha]_D$ +92 (0.3% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3350br (NH), 1795 (β-lactam C=O), 1750sh and 1725 (ester C=O) and 1680 (amide C=O); λ_{max}(EtOH)/nm 202 (ε 44 600), 229 (39 000), 274 (2900) and 281 (2400); δ(300 MHz; $CDCl_3$) 1.06 and 1.67 (each 3 H, s, 2-Me_2), 2.00 and 2.40 (each 1 H, dt, *J* 13.5, 9 and 9, 5′-H_2), 2.82–2.96 (1 H, m, 4′-H), 3.16–3.27 (1 H, m, 1′-H), 4.52 (2 H, d, separation 5.5, CH_2OCO), 4.69 (1 H, s, 3-H), 4.99 (1 H, d, *J* 4.5, 5-H), 5.17 and 5.29 (each 1 H, d, *J* 12, CH_2Ph), 5.61–5.70 (2 H, m, 2′- and 3′-H), 6.06 (1 H, dd, *J* 10 and 4.5, 6-H) and 7.39–7.57, 7.90–7.97 and 8.04–8.07 (15, 4 and 2 H, each m, 4 × Ph and CONH) [addition of D_2O caused the signal at δ 6.06 to appear as a d (*J* 4.5)]; *m/z* (FAB) 793 (MH^+, 5%) and 149 (100) (Found: C, 64.8; H, 5.4; N, 3.5; S, 4.4%).

An attempt to scale up the reaction (5 ×) led to considerably reduced yields of compounds **10d** and **13c**.

Reduction of the Penicillin Sulfoxides **10d** *and* **13c**.—(*a*) Phosphorus(III) bromide (0.10 cm^3, 0.282 g, 1.04 mmol) was added to a stirred, cooled (−7 °C; ice–NaCl bath) solution of the sulfoxide **10d** (0.380 g, 0.48 mmol) in dry DMF (4 cm^3). After 0.5 h, ice-cold, saturated aq. sodium hydrogen carbonate (7 cm^3) was added and the mixture was extracted with ethyl acetate (5 × 20 cm^3). The combined organic extracts were washed with water (5 × 20 cm^3), dried ($MgSO_4$) and concentrated. Subjection of the resultant oil to silica gel column chromatography [hexanes–EtOAc (3:1) as eluent] gave *benzyl* 6β-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-*dibenzoyloxy*-4′-(*benzoyloxymethyl*)*cyclopentane*-1′-*carboxamido*]*penicillanate* **10b** (0.283 g, 76%) as a foam; $[\alpha]_D$ +126 (0.3% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3340 (NH), 1785 (β-lactam C=O), 1720 (ester C=O) and 1685 (amide C=O); λ_{max}(EtOH)/nm 204 (ε 35 400), 229 (38 800), 269 (3000), 274 (3200) and 281 (2700); δ(300 MHz; $CDCl_3$) 1.39 and 1.57 (each 3 H, s, 2-Me_2), 2.28 (2 H, br t, separation 9.5, 5′-H_2), 2.94–3.10 (1 H, m, 4′-H), 3.20 (1 H, dt, *J* 9, 9 and 4, 1′-H), 4.49 (1 H, s, 3-H), 4.54 (2 H, d, separation 6, CH_2OCO), 5.20 (2 H, s, CH_2Ph), 5.35 (1 H, dd, *J* 9 and 5, 3′-H), 5.58 (1 H, dd, *J* 5 and 4, 2′-H), 5.61 (1 H, d, *J* 4, 5-H), 5.73 (1 H, dd, *J* 9 and 4, 6-H), 7.30–7.41, 7.48–7.58 and 7.92–8.05 (11, 3 and 6 H, each m, 4 × Ph) and 7.62 (1 H, br d, *J* 9, CONH); *m*/*z* (FAB) 528 ($C_{30}H_{26}NO_8^+$, 5%), 250 ($C_{13}H_{16}NO_2S^+$, 37) and 105 ($C_7H_5O^+$, 100) (Found: C, 66.2; H, 5.2; N, 3.7; S, 4.5. $C_{43}H_{40}N_2O_{10}S$ requires C, 66.5; H, 5.20; N, 3.60; S, 4.15%).

(*b*) The sulfoxide **13c** (0.414 g, 0.522 mmol) was subjected to the action of phosphorus(III) bromide as described in the foregoing experiment. Work-up and purification as before gave *benzyl* 6β-[(1′*S*,2′*R*,3′*S*,4′*S*)-2′,3′-*dibenzoyloxy*-4′-(*benzoyloxymethyl*)*cyclopentane*-1′-*carboxamido*]*penicillanate* **13a** (0.325 g, 80%) as a foam; $[\alpha]_D$ + 75 (0.2% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3340 (NH), 1785 (β-lactam C=O), 1720 (ester C=O) and 1685 (amide C=O); λ_{max}(EtOH)/nm 202 (ε 52 400), 229 (39 400), 274 (3000) and 281 (2500); δ(300 MHz; $CDCl_3$) 1.41 and 1.64 (each 3 H, s, 2-Me_2), 2.15–2.37 (2 H, m, 5′-H_2), 2.93–3.07 (1 H, m, 4′-H), 3.18 (1 H, dt, *J* 8, 8 and 4, 1-H), 4.52 (1 H, s, 3-H), 4.54 (2 H, d, separation 6, CH_2OCO), 5.20 (2 H, s, CH_2Ph), 5.39 (1 H, dd, *J* 9 and 5, 3′-H), 5.58 (1 H, d, *J* 4, 5-H), 5.61 (1 H, dd, *J* 5 and 4, 2′-H), 5.72 (1 H, dd, *J* 9 and 4, 6-H) and 7.32–7.42, 7.48–7.62 and 7.94–8.05 (11, 4 and 6 H, each m, 4 × Ph and CONH) [addition of D_2O caused the signal of δ 5.72 to appear as a d (*J* 4) and the integral of the signal at δ 7.48–7.62 to reduce to 3 H]; *m*/*z* (FAB) 777 (MH^+, 8%), 528 ($C_{30}H_{26}NO_8^+$, 12) and 250 ($C_{13}H_{16}NO_2S^+$, 100) (Found: C, 66.2; H, 5.4; N, 3.7; S, 4.4%).

Rearrangement of the Penicillanates **10b** *and* **13a**.—(*a*) Sodium hydroxide (1 mol dm^{-3}; 0.26 cm^3, 0.26 mmol) was added to a stirred solution of the penicillanate **10b** (0.200 g, 0.26 mmol) in DMSO (4 cm^3). After 0.75 h, the mixture was acidified with hydrochloric acid (~5 mol dm^{-3}), diluted with water (8 cm^3) and extracted with ethyl acetate (5 × 8 cm^3). The combined organic extracts were washed with brine (5 × 8 cm^3), dried ($MgSO_4$) and concentrated. The residue was dissolved in dry xylenes (4 cm^3) and the solution was heated under reflux for 35 min. Evaporation, and subjection of the oil to silica gel column chromatography [hexanes–EtOAc (4:1) as eluent], gave *benzyl* 2-{2-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-*dibenzoyl*-4′-(*benzoyloxymethyl*)*cyclopentyl*]*thiazole*-4-*carboxamido*}-3-*methylbut*-2-*enoate* **12b** (0.098 g, ~50%) as a slightly impure foam. A portion was purified further by PLC [hexanes–EtOAc (1:1) as eluent] to give the pure product; $[\alpha]_D$ −116 (0.2% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3380 (NH), 1720 (ester C=O) and 1675 (amide C=O); λ_{max}(EtOH)/nm 202 (ε 52 800) and 230 (46 700); δ(300 MHz; $CDCl_3$) 1.85 and 2.20 (each 3 H, s, CMe_2), 2.12 and 2.73 [each 1 H, dt (*J* 14, 9.5 and 9.5) and dt (*J* 14, 9 and 9), 5′-H_2], 2.96–3.09 (1 H, m, 4′-H), 4.05 (1 H, dt, *J* 9, 9 and 7, 1′-H), 4.57 (2 H, d, separation 5.5, CH_2OCO), 5.19 (2 H, s, CH_2Ph), 5.77 (1 H, t, *J* 5.5, 3′-H), 5.84 (1 H, dd, *J* 7 and 5.5, 2′-H), 7.22–7.41, 7.47–7.58 and 7.92–8.04 (11, 3 and 6 H, each m, 4 × Ph), 8.06 (1 H, s, thiazole-H) and 8.47 (1 H, br s, CONH); *m*/*z* (FAB) 759 (MH^+, 19%) and 105 ($C_7H_5O^+$, 100) (Found: C, 68.3; H, 5.1; N, 3.8; S, 4.6. $C_{43}H_{38}N_2O_9S$ requires C, 68.05; H, 5.05; N, 3.70; S, 4.20%).

(*b*) The penicillanate **13a** (0.410 g, 0.53 g) was subjected to the action of sodium hydroxide as described in the aforecited experiment. Work-up and purification as before gave *benzyl* 2-{2-[(1′*S*,2′*R*,3′*S*,4′*S*)-2′,3′-*dibenzoyl*-4′-(*benzoyloxymethyl*)*cyclopentyl*]*thiazole*-4-*carboxamido*}-3-*methylbut*-2-*enoate* *ent*-**12b** (0.270 g, ~67%) as a slightly impure foam. A portion was purified further by PLC [hexanes–EtOAc (1:1) as eluent] to give the pure thiazole *ent*-**12b**; $[\alpha]_D$ +102 (0.2% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3380 (NH), 1720 (ester C=O) and 1675 (amide C=O); λ_{max}(EtOH)/nm 203 (ε 56 200) and 230 (54 500); δ(300 MHz; $CDCl_3$) as for compound **12b**; *m*/*z* (FAB) 759 (MH^+, 13%) and 105 ($C_7H_5O^+$, 100) (Found: C, 67.8; H, 5.1; N, 3.5; S, 4.6%).

Reaction of Compounds **12b** *and* ent-**12b** *with Ozone followed by Methanolic Ammonia*.—(*a*) Ozone was passed into a stirred, cooled (Me_2CO–solid CO_2 bath) solution of compound **12b** (0.219 g, 0.288 mmol) in dry dichloromethane (12 cm^3) until a blue colour developed. After 0.5 h, the mixture was aerated and allowed to warm to room temperature. Evaporation left a residue, which was stirred with methanolic ammonia (20 cm^3) (prepared by saturating MeOH with gaseous NH_3) for 48 h. The mixture was filtered through Celite and the filtrate was concentrated. Subjection of the product to silica gel column chromatography [EtOAc–PrOH–water (4:1:2; upper phase) as eluent; column packed using EtOAc] gave 2-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-*dihydroxy*-4′-(*hydroxymethyl*)*cyclopentyl*]*thiazole*-4-*carboxamide* **1b** (0.036 g, 49%) as a syrup; $[\alpha]_D$ −52 (0.2% in MeOH); ν_{max}(film)/cm^{-1} 3350br (NH and OH) and 1665 (amide C=O); λ_{max}(EtOH)/nm 205 (ε 17 100) and 232 (7300); δ(300 MHz; D_2O) 1.64 and 2.45 [each 1 H, ddd (*J* 13, 11 and 8.5) and dt (*J* 13, 8.5 and 8.5), 5′-H_2], 2.19–2.32 (1 H, m, 4′-H), 3.53–3.72 (3 H, m, CH_2OH and 1′-H), 4.01 (1 H, dd, *J* 5 and 3.5, 3′-H), 4.16 (1 H, dd, *J* 9 and 5.5, 2′-H) and 8.18 (1 H, s, thiazole-H); *m*/*z* (FAB) 259 (MH^+, 100%) (Found: C, 46.2; H, 5.2; N, 10.5; S, 12.8. $C_{10}H_{14}N_2O_4S$ requires C, 46.50; H, 5.45; N, 10.85; S, 12.40%).

(*b*) Compound *ent*-**12b** (0.360 g, 0.47 mmol) was subjected to the action of ozone and methanolic ammonia as described in the aforecited experiment. Work-up and purification of the product as before gave 2-[(1′*S*,2′*R*,3′*S*,4′*S*)-2′,3′-*dihydroxy*-4′-(*hydroxymethyl*)*cyclopentyl*]*thiazole*-4-*carboxamide* ent-**1b** (0.065 g, 53%) as a syrup; $[\alpha]_D$ +51 (0.3% in MeOH); ν_{max}(film)/cm^{-1} 3350br (NH and OH) and 1665 (amide C=O); λ_{max}(EtOH)/nm 205 (ε 14 200) and 234 (5700); δ(300 MHz; CD_3SOCD_3) 1.67 and 2.30 [each 1 H, ddd (*J* 13, 10.5 and 8) and dt (*J* 13, 8.5 and 8.5), 5′-H_2], 2.06–2.18 (1 H, m, 4′-H), 3.35–3.56 (3 H, m, 1′-H and CH_2OH), 3.85 (1 H, apparent q, separation 4.5, 3′-H), 3.90–4.00 (1 H, m, 2′-H), 4.63 (1 H, d, *J* 4.5, 3′-OH), 4.73 (1 H, t, *J* 5.5, CH_2OH), 4.99 (1 H, *J* 6.5, 2′-OH), 7.64 and 7.71 (each 1 H, br s, $CONH_2$) and 8.20 (1 H, s, thiazole-H); δ(300 MHz; D_2O) as for compound **1b** (in a COSY 90° experiment, the following connectivities were established: δ 4.16 to 4.01 to 2.19–2.32 to 1.64 to 2.45 to 2.19–2.32 to 3.53–3.72; δ 4.16 to 3.53–3.72 to 2.45; δ 3.53–3.72 to 1.64); δ_C (100 MHz; D_2O) 31.56 (C-5′), 47.06 and 48.02 (C-1′ and -4′), 64.35 (CH_2O), 74.76 and 79.02 (C-2′ and -3′), 126.4 (C-5), 148.7 (C-4), 166.8 (C-2) and 175.1 (CO) (a DEPT 135° experiment caused the signals at δ_C 31.56 and 64.35 to invert and those at δ_C 148.7, 166.8 and 175.1 to disappear); *m*/*z* (FAB) 259 (MH^+, 100%) (Found: C, 46.5; H, 5.2; N, 10.5; S, 12.8%).

Preparation of (1R*,5R*,6R*,7S*)-6,7-*Isopropylidenedioxy*-3-*oxabicyclo*[3.2.1]*octan*-2-*one* **24**.—A solution of the (±)-ester **22b** (0.411 g, 0.82 mmol) in a mixture of ethanol (4.5 cm^3) and 10% hydrochloric acid (9.5 cm^3) was heated under reflux for 16 h. The solution was concentrated and the residue partitioned between chloroform (4 cm^3) and water (10 cm^3). The aqueous phase was washed with chloroform (10 × 4 cm^3). Concentration of the aqueous phase left a residue, which was stirred with dry acetone (2 cm^3) containing a crystal of PTSA. After 5 days, the mixture was filtered and the filtrate was concentrated. Subjection of the residue to silica gel column chromatography [hexanes–EtOAc (2:1) as eluent; column packed using hexanes–EtOAc–Et_3N (66:33:1)] gave the title (±)-lactone **24** (0.022 g, 14%), m.p. 130–132 °C (lit;[7] 128–129 °C); ν_{max} (KBr)/cm^{-1} 1745 (δ-lactone C=O); λ_{max}(EtOH)/nm 226 (ε 240); δ(300 MHz; $CDCl_3$) 1.33 and 1.48 (each 3 H, s, CMe_2), 1.88 and 2.22–2.31 [each 1 H, br d (separation 12) and m, 8-H_2], 2.43–2.49 (1 H, m, 5-H), 3.00 (1 H, dd, *J* 4 and 1, 1-H), 4.19 and 4.33 [each 1 H, ddd (*J* 11, 2 and 1) and dd (*J* 11 and 4), 4-H_2], 4.58 (1 H, dd, *J* 5.5 and 1, 6-H) and 4.62 (1 H, dd, *J* 5.5 and 1, 7-H); *m/z* (FAB) 199 (MH^+, 100%) and 133 (88) (Found: C, 60.7; H, 6.8. Calc. for $C_{10}H_{14}O_4$: C, 60.6; H, 7.10%).

Reaction of the Sulfoxides **10d** *and* **13c** *with Hydrochloric Acid followed by Acidic Acetone*.—(*a*) A solution of the penicillin sulfoxide **10d** (0.176 g, 0.22 mmol) in ethanol (3.5 cm^3) and 10% hydrochloric acid (3.5 cm^3) was heated under reflux for 16 h. Evaporation left a residue, which was partitioned between chloroform (4 cm^3) and water (8 cm^3). The aqueous phase was washed with chloroform (10 × 4 cm^3). Concentration of the aqueous phase left a residue, which was stirred with dry acetone (4 cm^3) containing a crystal of PTSA. After 5 days, the mixture was processed and purified as described in the preceding experiment to give (1*R*,5*R*,6*R*,7*S*)-6,7-isopropylidenedioxy-3-oxabicyclo[3.2.1]octan-2-one **24** (0.003 g, 7%) as needles, m.p. 132–134 °C (lit.,[16] 140–141.5; lit.,[17] 140–143 °C); $[\alpha]_D$ +22 (0.3% in $CHCl_3$) {lit.,[16] $[\alpha]_D^{25}$ +44.4 (1% in $CHCl_3$); lit.,[17] $[\alpha]_D^{25}$ +46.7 (0.48% in $CHCl_3$)}. The 300 MHz ^1H NMR and FAB mass spectra matched those of the racemic material.

(*b*) The penicillin sulfoxide **13c** (0.182 g, 0.23 mmol) was subjected to the aforecited hydrolytic and acetalisation conditions. Work-up and purification as before gave (1*S*,5*S*,6*S*,7*R*)-6,7-isopropylidenedioxy-3-oxabicyclo[3.2.1]octan-2-one *ent*-**24** (0.013 g, 29%) as needles, m.p. 130–131 °C; $[\alpha]_D$ −21 (0.6% in $CHCl_3$). The 300 MHz ^1H NMR and FAB mass spectra matched those of the racemic material.

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