Synthesis of (5*R*)-(*Z*)-6-(1-Methyl-1,2,3-triazol-4-ylmethylene)penem-3-carboxylic Acid, a Potent Broad Spectrum β-Lactamase Inhibitor, from 6-Aminopenicillanic Acid[1]

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(5*R*)-(*Z*)-6-(1-Methyl-1,2,3-triazol-4-ylmethylene)penem-3-carboxylic acid **34** (BRL 42715) has been prepared from 6-aminopenicillanic acid **4** (6-APA) by a short, stereoselective and efficient route *via* the novel intermediate, *p*-methoxybenzyl (5*R*,6*S*)-6-bromopenem-3-carboxylate **17**.

Elaboration of 6-APA **4** to the azetidinone disulfide **10** by established methodology, followed by reductive formylation provided the crystalline C-4 formylthio-azetidinone derivative **29**. Cyclization of the oxalimide **28**, obtained by ozonolysis of the formylthio derivative **29**, to the crystalline 6α-bromopenem ester **17** was effected by way of the phosphite-mediated carbonyl–carbonyl coupling reaction.

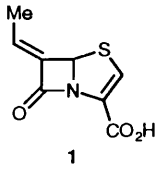
Sequential treatment of bromopenem **17** with lithium diphenylamide, 1-methyl-1,2,3-triazole-4-carbaldehyde, and acetic anhydride gave a diastereoisomeric mixture of acylated bromohydrins **32**; reductive elimination of this mixture afforded a separable mixture of (*Z*)- and (*E*)-triazolylmethylene penem esters, **33** and **35** respectively. Lewis acid-mediated deprotection of ester **33** provided (5*R*)-(*Z*)-6-(1-methyl-1,2,3-triazol-4-ylmethylene)penem-3-carboxylic acid **34** (BRL 42715) as a crystalline sodium salt monohydrate.

The 6-heterocyclylmethylene penems, represented by BRL 42715, are potent inhibitors of bacterial β-lactamases and their combination with an appropriate penicillin or cephalosporin results in good synergistic activity against a broad range of β-lactamase-producing bacteria.

The penems were first reported by R. B. Woodward and co-workers in 1976 and were regarded as structural hybrids of penicillins and cephalosporins.[2] Initial studies therefore concentrated on the synthesis of penems that incorporated an acylamino substituent at the C-6 position. Although such compounds were found to have limited chemical stability, their intrinsic antibacterial activity prompted further investigation. The discovery of the olivanic acids and thienamycin[3] led to the introduction of the 1-hydroxyethyl substituent at the C-6 position of the penem nucleus.[4] Those compounds possessing the thienamycin-like (5*R*,6*S*,8*R*)-stereochemistry were found to display potent, broad-spectrum antibacterial activity and it is this series that has received most attention.[5]

A report from these laboratories[6] meanwhile described the dehydration of such C-6 1-hydroxyethyl penems to provide a novel class of 6-ethylidenepenems **1**. Whilst they possessed only poor antibacterial activity, the 6-ethylidene penems **1** inhibited a wide range of bacterial β-lactamases. From further studies involving the preparation of a series of 6-heterocyclylmethylenepenems[7] emerged a potent inhibitor of both penicillinases and cephalosporinases, (5*R*)-(*Z*)-6-(1-methyl-1,2,3-triazol-4-ylmethylene)penem-3-carboxylic acid **34** (BRL 42715).[8] The spectrum and degree of activity observed with BRL 42715 represent a significant improvement over other known β-lactamase inhibitors and the combination of this agent with an appropriate penicillin or cephalosporin results in good synergistic activity against a broad range of β-lactamase-producing bacteria.[8,9]

Previous routes to the alkylidene and heterocyclylmethylene penems gave racemic compounds.[10] The present paper describes a convenient and chiral synthesis of the title compound



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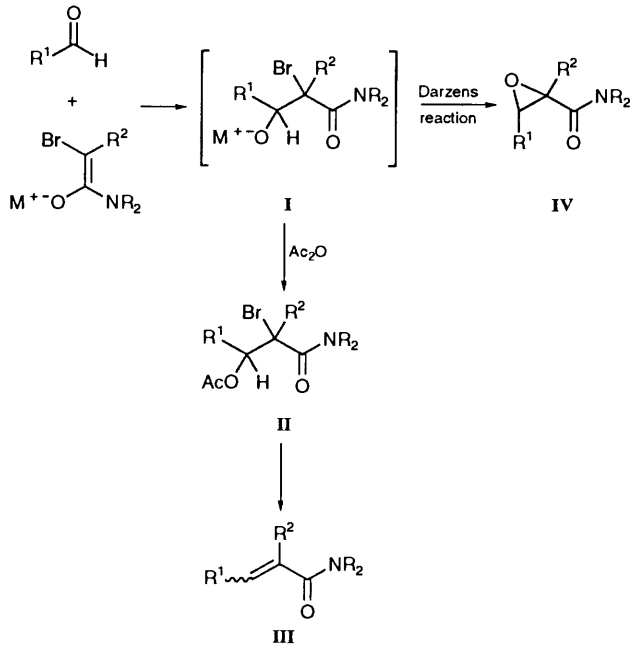
34 from 6-aminopenicillanic acid (6-APA) **4**, *via* a novel and versatile intermediate, *p*-methoxybenzyl (5*R*,6*S*)-6-bromopenem-3-carboxylate **17**. Our synthetic strategy was influenced by the desire to (i) elaborate the inexpensive and readily available chiral synthon, 6-APA **4**, to the triazolylmethylene penem **34** with the utilization of as much of the original penam framework as possible; (ii) retain the (5*R*)-stereochemical integrity of 6-APA **4**; (iii) introduce the C-6 substituent as late as possible in the synthetic sequence, thereby maximizing the versatility of the route; (iv) prepare the penem **34** in large quantities in the pilot plant.

We envisaged that the 6α-bromopenem ester **17** would be an appropriate synthetic intermediate in that it should exploit the ability of the bromine atom to enhance the acidity of the adjacent C-6 proton† and, in doing so, permit the introduction of a variety of C-6 substituents at a late stage in the synthetic sequence.

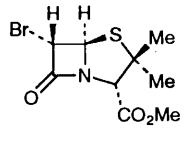
† Earlier attempts to utilize a penem unsubstituted at C-2 and C-6 as a late-stage synthetic intermediate were unfruitful;[11] aldol reactions at the C-6 position were low yielding because of the comparable acidity of the C-2 proton.



Scheme 1

Aldol-type condensation reactions of α-halogeno esters[12] and α-halogeno *N,N*-disubstituted amides[13] with aldehydes and ketones to prepare α,β-epoxy esters and amides are well known. We reasoned that if the initial intermediate **I** in this Darzens reaction (Scheme 1) could be trapped with acetic anhydride, then reductive elimination of the resulting β-bromo acetate **II** by the method of House[14] would provide the desired olefin **III**,* rather than the epoxide **IV**.

In order to test our hypothesis, the base-catalysed condensation of the 6α-bromopenam ester **2**[16] with an aromatic aldehyde was investigated. Thus, reaction of compound **2** with lithium bis(trimethylsilyl)amide (LiHMDS) in tetrahydrofuran (THF) at −78 °C, followed by 3,5-dimethoxybenzaldehyde provided the bromohydrin **3** in moderate yield. This result encouraged us to embark upon the synthesis of the 6α-bromopenem ester **17**; the *p*-methoxybenzyl ester was chosen as the carboxylic acid-protecting group for its compatibility with the ozonolytic and strongly basic conditions that were anticipated for the synthesis of the 6α-bromopenem-3-carboxylate ring system.



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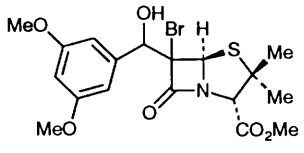
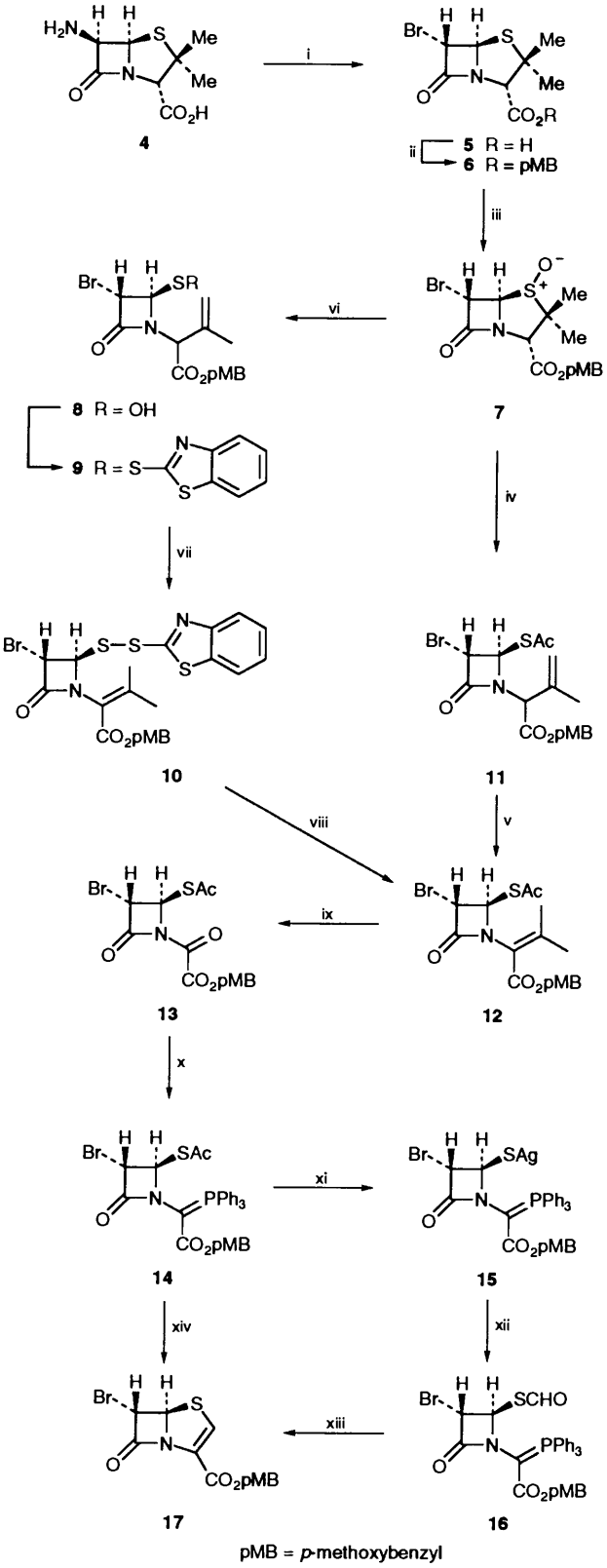


3

Our first approach to the 6α-bromopenem **17** proceeded *via* the 4-(acetylthio)azetidinone **12** (Scheme 2). 6-APA **4** was converted into 6(*S*)-bromopenicillanic acid **5** by the method of John *et al.*[16] Esterification of the dicyclohexylamine salt of acid **5** with *p*-methoxybenzyl bromide, followed by oxidation of the resulting ester **6** with *m*-chloroperbenzoic acid (MCPBA) afforded the sulfoxide **7** in 45–60% yield from 6-APA **4**. Sulfoxide **7** was then heated to reflux in toluene with 2-mercaptobenzothiazole. In this procedure, originally estab-

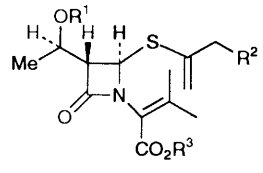
* A similar reaction, which involves the formation of olefins from α-alkyl-β-bromoalkyl ethers by treatment with zinc, was first reported by L. C. Swallen and C. E. Boord,[15] and is known as the Boord reaction.



Scheme 2 *Reagents and conditions:* i, HBr, $NaNO_2$, aq. MeOH, 5 °C, 1 h; ii, (a) $HN(c\text{-}C_6H_{11})_2$, diethyl ether–light petroleum (2:1), 5 °C, 16 h; (b) *p*-$MeOC_6H_4CH_2Br$, DMF, 25 °C, 18 h; iii, MCPBA, CH_2Cl_2, 5 °C, 1.5 h; iv, Ac_2O, $P(OPr^i)_3$, benzene, reflux, 8 h; v, EtOAc, Et_3N (0.1 mol equiv.), 25 °C, 20 min; vi, 2-mercaptobenzothiazole, toluene, reflux, 2 h; vii, Et_3N (0.1 mol equiv.), toluene, 5 °C, 2 h; viii (a) Ac_2O, AcOH, PPh_3, −20 °C, 65 min; (b) pyridine, −20 to 25 °C, 3 h; ix (a) O_3, EtOAc, −76 °C; (b) 45% aq. $NaHSO_3$; x, PPh_3 (4 mol equiv.), $P(OEt)_3$ (1 mol equiv.), toluene, 25 °C, 18 h; xi, $AgNO_3$, Et_3N, CH_2Cl_2–MeOH, 5 °C, 40 min; xii, AcOCHO, DMAP (1 mol equiv.), Et_3N·HCl (10 mol equiv.), CH_2Cl_2, 5–25 °C, 10 min; xiii, EtOAc–CH_2Cl_2, 25 °C, 30 min; xiv, (a) $AgNO_3$, DMAP, MeCN, 25 °C, 30 min; (b) AcOCHO, DMAP, NaI (10 mol equiv.), MeCN, 5–25 °C, 30 min

lished by Kamiya *et al.*[17] for penicillin sulfoxide esters, the sulfenic acid **8** formed from sulfoxide **7** at elevated temperatures was intercepted by the mercaptan, giving the disulfide **9**. The latter was transformed by base-catalysed double-bond isomerization into the conjugated ester disulfide **10** (quantitative yield from **7**). Reductive acylation of disulfide **10** by the method of Woodward[18] then provided the acetylthio derivative **12** (90% yield). Alternatively, the acetylthio derivative **12** could be prepared from the sulfoxide **7**, *via* the β,γ-unsaturated ester **11**, by heating a solution of sulfoxide **7**, acetic anhydride and triisopropyl phosphite to reflux in benzene for 8 h.[19] Double-bond isomerization then provided compound **12** in 50% yield. Ozonolysis of isopropylidene derivative **12** furnished the oxalimide **13**, which was converted into the triphenylphosphorane **14** by treatment with triphenylphosphine (4 mol equiv.) and triethyl phosphite (1 mol equiv.)[20] (53%). Removal of the acetyl group in **14** by treatment with silver nitrate and triethylamine in methanol provided the silver thiolate **15** (93%), which was formylated using acetic formic anhydride, 4-(dimethylamino)pyridine (DMAP) and triethylamine hydrochloride in dichloromethane. The formylthio derivative **16** thus obtained cyclized at room temperature to yield the desired 6α-bromopenem ester **17** (44%). A significant improvement to this reaction sequence was the elaboration of the acetylthio phosphorane **14** to the 6α-bromopenem **17** in good yield without isolation of the silver thiolate **15**. Thus, treatment of compound **14** with silver nitrate and DMAP in acetonitrile, followed by acetic formic anhydride, sodium iodide and DMAP provided the pure crystalline *p*-methoxybenzyl (5*R*,6*S*)-6-bromopenem-3-carboxylate **17** in 65% yield after rapid silica gel column chromatography.

The above procedure utilizes the well established intramolecular Wittig reaction, first reported by R. B. Woodward,[2] for the construction of the penem ring system. More recently, Farmitalia Carlo Erba scientists[21] have reported a novel method for the synthesis of C-2 substituted penem derivatives **20**, which involves a reductive carbonyl–carbonyl coupling reaction for the ring closure. Thus, addition of a trialkyl phosphite (2 mol equiv.) to a solution of the oxalimide derivative **19** in refluxing toluene or xylene (1–10 h) afforded the bicyclic penem derivatives **20** in good yields (40–70%). The key oxalimides **19** for this cyclization procedure were generated by ozonolysis of both double bonds in the azetidinone precursor **18**.



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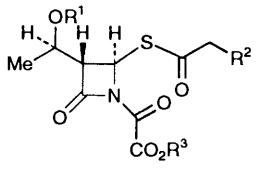

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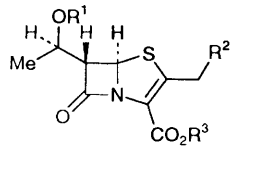

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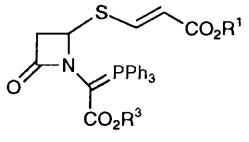
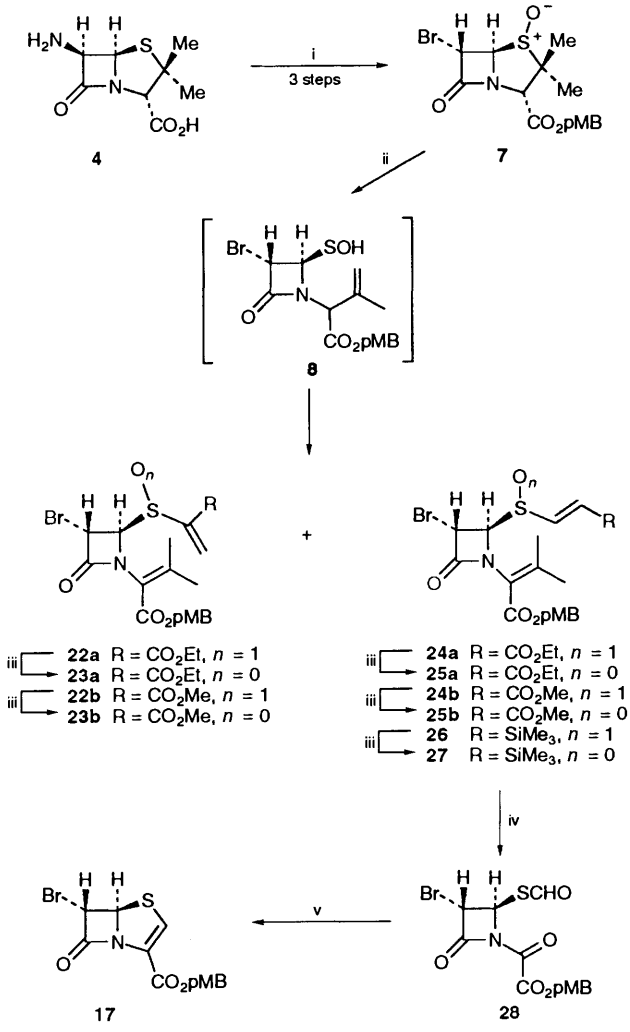


21

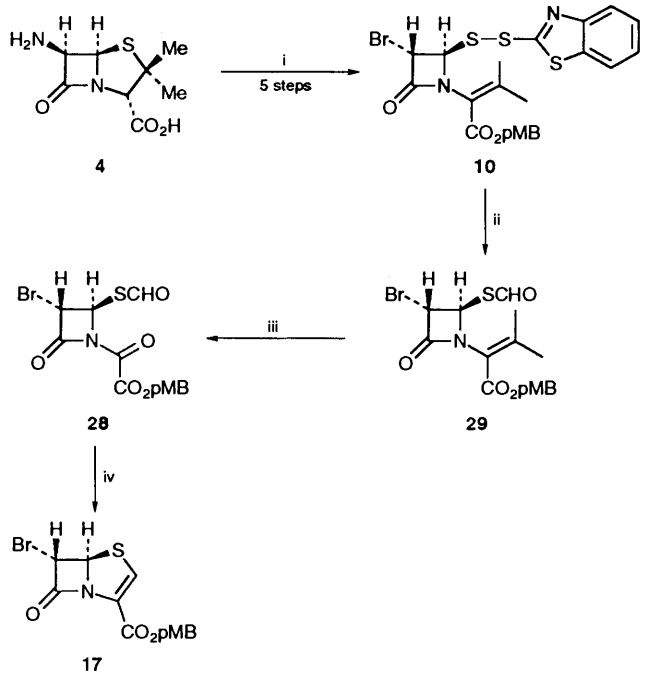
It occurred to us that the phosphite-mediated cyclization of the formylthio oxalimide derivative **28** should provide a more direct synthesis of the 6α-bromopenem **17**. Woodward had already demonstrated the use of the thioacrylate derivative **21** as a stable synthetic intermediate from which the thioformyl substituent could later be generated for the intramolecular



Scheme 3 *Reagents and conditions:* i, See (i), (ii) and (iii) in Scheme 2; ii, (a) HC≡CR, toluene, reflux, 3 h; (b) Et_3N (0.1 mol equiv.), CH_2Cl_2, 25 °C; iii, PBr_3, DMF, −10 °C, 20 min; iv, (a) O_3, EtOAc, −76 °C; (b) aq. Na_2SO_3–$Na_2S_2O_5$ (pH 7.0); v, $P(OMe)_3$ (5 mol equiv.), toluene, 50 °C, 1 h

Wittig ring-closure reaction.[22] We therefore sought the preparation of the C-4 β-(alkoxycarbonyl)ethenylthio derivative **25**. Barton *et al.*[23] have described the syntheses of the C-3 acylamino analogues from penicillin sulfoxides by conjugate addition of the thermally generated sulfenic acids to propiolic acid esters. Similar addition of sulfenic acid **8** to various alkyl esters of propiolic acid provided the desired vinyl sulfoxides **24a,b** accompanied by varying amounts of the undesired regioisomers **22a,b** after double-bond isomerization (Scheme 3). Addition of sulfenic acid **8** to trimethylsilylacetylene meanwhile was more specific, resulting in the formation of a single regioisomer, the 4-[(E)-2-(trimethylsilyl)ethenylthio] derivative **27** in 73% yield after double-bond isomerization and reduction of the sulfoxide **26**. We were now in a position to generate the formylthio oxalimide derivative **28**, in order to investigate the phosphite-mediated carbonyl–carbonyl coupling reaction for the preparation of C-2 unsubstituted penem derivatives. Indeed, ozonolysis of compound **27** at low temperature gave the desired oxalimide **28** after careful reduction* of the ozonide. Gratifyingly, treatment of compound **28** with trimethyl phosphite in toluene at 50 °C for 1 h

* In order to avoid degradation of product, the saturated sodium sulfite solution that was used during the reductive work-up procedure was adjusted to pH 7.0 by the addition of sodium metabisulfite ($Na_2S_2O_5$).



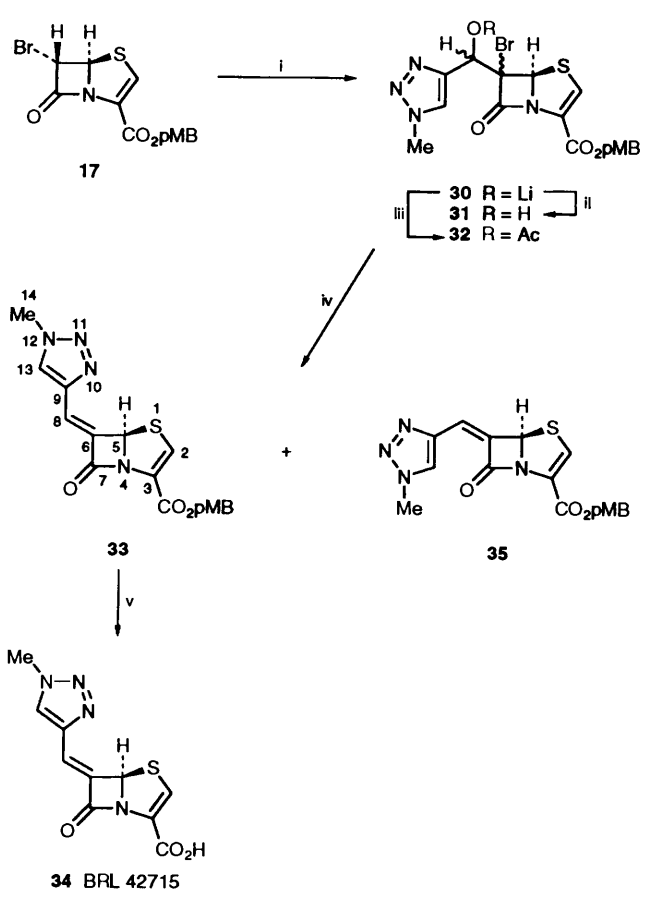
Scheme 4 *Reagents and conditions:* i, See (i), (ii), (iii), (vi) and (vii) in Scheme 2; ii, pyridine (1 mol equiv.), AcOCHO (10 mol equiv.), PPh_3 (1 mol equiv.), MeCN, −20 °C, 1 h, then 0 °C, 1 h; iii, (a) O_3, EtOAc, −78 °C; (b) $P(OMe)_3$ (5 mol equiv.), EtOAc, 20 °C for 16 h and then reflux for 45 min

provided the 6α-bromopenem **17**, albeit in low yield (20%), after silica gel column chromatography.

Instead of 'masking' the C-4 formylthio substituent during the synthetic sequence, we next sought to introduce the formylthio substituent directly and as late in the sequence as possible. In what proved to be the shortest, most efficient and preferred route to the 6α-bromopenem ester **17** from 6-APA **4**, the disulfide **10** was converted in high yield (77%) into the crystalline formylthio derivative **29** by reductive formylation (pyridine, acetic formic anhydride, triphenylphosphine) (Scheme 4).* Ozonolysis, followed by trimethyl phosphite-mediated cyclization of oxalimide **28** then gave the bromopenem ester **17** in 48% yield.

With the bromopenem ester **17** in hand, we were now in a position to investigate its condensation with the triazole aldehyde and the subsequent introduction of the exocyclic double bond. To our satisfaction, sequential treatment of **17** with LiHMDS, 1-methyl-1,2,3-triazole-4-carbaldehyde[24] and acetic acid in THF at −76 °C provided a 5:2:1:1 diastereoisomeric mixture of bromohydrins **31** in 68% yield (Scheme 5). The major isomer could be isolated as a single component after silica gel column chromatography, whilst the minor isomers were obtained as a mixture. Acylation of the major isomer of compound **31** using acetic anhydride, triethylamine and DMAP in THF gave a single isomer of the β-bromo acetate **32**, which upon reductive elimination (zinc and acetic acid in THF) provided a separable 5:1 mixture of the (*Z*)-and (*E*)-triazolylmethylenepenem esters, **33** and **35**, respectively (69% yield). Similar treatment of the 2:1:1 mixture of minor bromohydrin isomers **31** gave a 5:2 mixture of elimination products **33** and **35**, respectively, in 65% yield.

The configurations of the geometrical isomers were assigned by ^1H NMR spectroscopy on the basis of the anisotropic deshielding effect of the β-lactam carbonyl on the 8-H vinyl



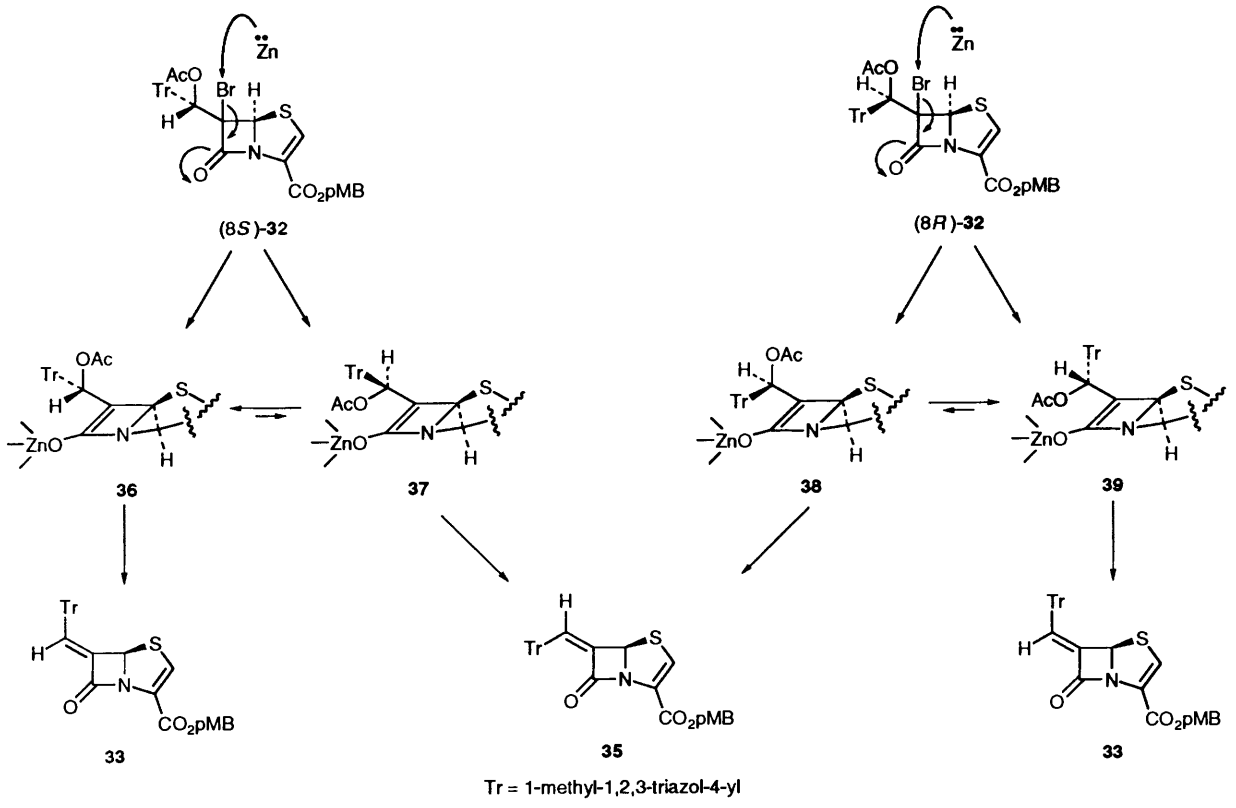
Scheme 5 *Reagents and conditions:* i, Ph_2NLi, THF, −76 °C immediately followed by 1-methyl-1,2,3-triazole-4-carbaldehyde, −76 °C, 1 min; ii, AcOH, −76 °C, 20 min; iii, Ac_2O, −76 to 20 °C; iv, Zn, AcOH, THF, 25 °C, 30 min or Zn, TMEDA dihydrochloride, NH_4Cl (4 mol equiv.), DMF, 20 °C, 1 h; v (a) $AlCl_3$ (2.5 mol equiv.), anisole–CH_2Cl_2, −40 °C, 10 min; (b) aq. Na_2HPO_4, −40 to 20 °C during 10 min; (c) pH 7.0 to 2.0 (2.5 mol dm^{-3} H_2SO_4), 5 °C

proton and the 13-H triazole proton. The vinyl proton of the (*Z*)-isomer **33** appeared at δ 7.03, downfield from that of the (*E*)-isomer **35**, which appeared at δ 6.90 (solvent $CDCl_3$). The converse was true of the triazole proton, which appeared at δ 7.70 in isomer **33** and δ 8.74 in isomer **35**. Nuclear Overhauser enhancement spectroscopy (NOESY) provided additional confirmation of assignments. Irradiation at 13-H in isomer **33** gave rise to positive enhancements at both 5-H and 8-H, due to the rapid rotation of the C(8)–C(9) bond in solution.

Concern over chemical stability of the bromohydrins **31** prompted us to investigate the conversion of the 6α-bromopenem ester **17** directly into the triazolylmethylenepenem ester without isolation of either the bromohydrin **31** or the acylated derivative **32**. Indeed, addition of excess of acetic anhydride to the lithium alkoxide **30** at −76 °C, followed by treatment with zinc and acetic acid (−78 °C to room temperature) gave a 5:2 mixture of the (*Z*)- and (*E*)-triazolylmethylenepenem esters, **33** and **35** respectively, in 67% yield.

This reaction sequence was, however, not without problems. Yields were reduced considerably if the reagents were not added in quick succession, or if the temperature during formation of the bromopenem anion or the alkoxide **30** was allowed to rise substantially above −70 °C. These factors imposed severe limitations on the potential for scale-up. At this stage, only strong, proton-specific bases such as LiHMDS (pK_a 29.5)[25] had been employed for the deprotonation of the bromopenem **17**. Since formation of the desired carbanion was evidently very rapid with such bases, it seemed possible that a weaker, proton-

* Sodium iodide (10 mol equiv.) was initially used in the reductive formylation;[1] it was subsequently found to be unnecessary.



Scheme 6

specific base might be used in this reaction with advantage. Indeed, rapid sequential treatment of bromopenem **17** with lithium diphenylamide (pK_a 22.4),[26] 1-methyl-1,2,3-triazole-4-carbaldehyde and acetic anhydride at −76 °C, followed by reductive elimination using zinc and acetic acid, provided the isomeric mixture of triazolylmethylenepenems, **33** and **35** (ratio 5:2), in favourable yield (67%). More interesting, however, was the observation that this base could be added at −20 °C without any dramatic reduction in yield (59%). Furthermore, this base offered the opportunity for a more leisurely addition of reagents, as well as the more convenient protocol of addition of bromopenem **17** to a preformed solution of base in THF, without any reduction in yield. This we attributed to the very low basicity of diphenylamine (pK_a 0.85)[27], which is produced after deprotonation of the bromopenem.

Having developed a more practical and manageable process, we considered ways of improving the stereoselectivity of the condensation-reductive elimination reaction sequence and thus influencing the (*Z*)- (*E*)-ratio in favour of the desired (*Z*)-olefin **33**. Variation of the base and solvent, as well as the use of chelating agents, in the aldol condensation had little influence on the diastereoisomeric ratio of bromohydrins, or on the final ratio of (*Z*)- and (*E*)-olefins. We therefore concentrated our efforts on improving the stereoselectivity of the reductive elimination process. Reduction of the acylated bromohydrins **32** with a variety of metals, as well as zinc, in various solvents and in the presence of various buffers was investigated. Of these, the use of zinc and ammonium chloride in dimethylformamide (DMF) looked the most encouraging, producing a 5:1 mixture of (*Z*)- and (*E*)-olefins. It was then found that the addition of *N,N,N',N'*-tetramethylethylenediamine dihydrochloride (TMEDA·2HCl) improved the selectivity even further, an 8:1 ratio of (*Z*)- to (*E*)-olefins, **33** and **35** respectively, being obtained in 72% overall yield from bromopenem **17**. Unfortunately this elimination procedure did not proceed in THF. The preferred method for the elaboration of the bromopenem **17** to the triazolylmethylenepenem **33** therefore involved addition of the bromopenem **17** to a solution of lithium diphenylamide in THF at −76 °C, followed by the sequential addition of a solution of 1-methyl-1,2,3-triazole-4-carbaldehyde in THF, and acetic anhydride; the crude 4:1:1:1 diastereoisomeric mixture of acylated bromohydrins **32** was then isolated, redissolved in DMF, and subjected to reductive elimination using zinc, ammonium chloride and TMEDA·2HCl to provide the (*Z*)-triazolylmethylenepenem **33** (64%) and the (*E*)-triazolylmethylenepenem **35** (8%). Reduction of the major isomer of the acylated bromohydrin using these conditions produced the (*Z*)- and (*E*)-olefins in the ratio 93:7.

The mechanism and stereochemistry of elimination reactions involving halogenohydrin derivatives and zinc have been studied in detail by House [14] and Cristol.[28] They found that the elimination reactions of β-bromoalkyl acetates by zinc were completely lacking in stereospecificity and concluded that the reaction must proceed in a stepwise manner involving a carbanionic intermediate (E1cB) rather than a concerted *trans* elimination (E2), which is observed with simple vicinal dihalides. Factors that are believed to influence the course of the reaction in favour of a stepwise elimination mechanism are: (i) delocalization of the partial negative charge that has been imposed upon the carbon atom β to the acetoxy group by nucleophilic attack of the metal on the halogen atom;* (ii) steric hindrance in the transition state that would lead to a *cis* olefin. Both factors are pertinent to the reductive elimination of compound **32** and we therefore believe that the stereoselectivity observed in the zinc–ammonium chloride–TMEDA·2HCl–DMF-mediated elimination of acylated bromohydrins **32** may

* Electron-withdrawing substituents, such as carbonyl groups, that are in conjugation with the carbanion would facilitate such delocalization.

best be explained by a stepwise reaction mechanism involving the intermediacy of a zinc-enolate transition state.* In the first stage of this elimination reaction, nucleophilic attack by the metal on the bromine atom of the two (8*S*)-isomers of compound **32** may proceed to form two possible zinc-enolate intermediates, **36** and **37**, whereby the acetoxy group is orthogonal to the C(6)–C(7) enolate double bond (Scheme 6). Tightly bound ligands at the metal atom in zinc-enolate intermediate **37**, in which the orthogonal acetoxy group occupies the α-face, would experience non-bonded interactions with the triazole ring. The less sterically congested transition state with the acetoxy group at the β-face (**36**) would therefore be favoured. Similarly, the favoured transition state in the case of the (8*R*)-isomers of compound **32** would be that enolate whereby the acetoxy group occupies the α-face (**39**); in this transition state, steric interactions between the metal ligands and the C-8 substituent are also minimized. The favoured zinc-enolate intermediates **36** and **39** would then afford the desired (*Z*)-olefin **33**. In the absence of chelating agent, the zinc-enolate intermediates are less sterically congested and stereoselectivity is reduced.

Finally, Lewis acid-mediated deprotection[29] of the *p*-methoxybenzyl ester **33** afforded the monohydrated sodium salt of (5*R*)-(*Z*)-6-(1-methyl-1,2,3-triazol-4-ylmethylene)penem-3-carboxylic acid **34** in 75% yield, obtained as a yellow solid after crystallization from aq. acetone.

This completes the synthesis of (5*R*)-(*Z*)-6-(1-methyl-1,2,3-triazol-4-ylmethylene)penem-3-carboxylic acid **34** (BRL 42715) from the cheap, readily available chiral starting material 6-aminopenicillanic acid **4** by a short, stereoselective route, which is amenable to large-scale operation. The versatility of the synthetic intermediate, *p*-methoxybenzyl (5*R*,6*S*)-6-bromopenem-3-carboxylate **17**, for the preparation of a range of potent, broad-spectrum β-lactamase inhibitors will be demonstrated in future communications.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. UV spectra were recorded on a Pye Unicam SP7-500 UV–VIS spectrophotometer. IR spectra were recorded on a Perkin–Elmer 197 or 983 machine. ^{1}H NMR spectra were recorded at 90 MHz on a Perkin–Elmer R32 and at 250 MHz on a Bruker WM250 instrument with tetramethylsilane as internal standard for spectra in $CDCl_3$ and [$^2H_7$]DMF, and acetonitrile as external standard for spectra in D_2O. *J* Values are given in Hz. Mass spectra were recorded on either a VG-ZAB double-focussing spectrometer, a VG TRIO-2 quadrupole spectrometer, or a Finnigan MAT TSQ70 spectrometer. Fast-atom bombardment (FAB) mass spectra were recorded using either 1-thioglycerol or 3-nitrobenzyl alcohol/sodium acetate (3-NOBA/NA) as matrix. Optical rotations ($[\alpha]_D/10^{-1}$ deg cm^2 g^{-1}) were measured on an Optical Activity Ltd. AA-1000 polarimeter. The purity of all compounds was tested by TLC on Merck pre-coated silica gel 60 F_{254} plates. Preparative chromatography was carried out on columns of Merck silica gel 60, using the slightly increased pressure provided by a Medcalf Hyflo pump. THF was dried over sodium hydride and distilled immediately before use.

Preparation of p-*Methoxybenzyl* (5R,6S)-6-*Bromopenem*-3-*carboxylate* **17** via p-*Methoxybenzyl* 2-[(3S,4R)-4-*Acetylthio*-3-*bromo*-2-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* **12** (*Scheme* 2).—

Dicyclohexylammonium salt of 6α-*bromopenicillanic acid* **5**. A solution of 6-aminopenicillanic acid **4** (144 g, 0.67 mol) in methanol (1333 cm^3)–water (500 cm^3) was stirred at 0 °C and treated slowly with hydrobromic acid (48%; 500 cm^3), the temperature being maintained below 5 °C. After the addition was complete, sodium nitrite (68.7 g, 1.0 mol) was added portionwise during *ca.* 15 min, and the resulting solution was stirred without cooling for a further 1 h. The mixture was then poured into a mixture of water (1333 cm^3) and chloroform (1333 cm^3) and the organic layer was separated. The aqueous layer was re-extracted with chloroform (2 × 833 cm^3). The combined organic layers were washed successively with water (833 cm^3) and brine (833 cm^3), dried ($MgSO_4$), and evaporated to give a green oil. The oil was redissolved in diethyl ether (1000 cm^3), diluted with light petroleum (b.p. 40–60 °C; 500 cm^3) and cooled in an ice-bath. To the stirred solution was added, in one portion, a solution of dicyclohexylamine (166 cm^3, 0.83 mol) in diethyl ether (160 cm^3). After being stirred overnight at 4 °C, the solid mixture was filtered, and the residue was washed with diethyl ether–light petroleum (1 : 1) and dried *in vacuo* to give the *salt of the title acid* **5** (218.4 g, 70%) as a solid, $\delta_H(CDCl_3)$ 0.8–2.3 (26 H, br m), 2.6–3.3 (2 H, br m), 4.33 (1 H, s), 4.75 (1 H, d, *J* 2), 5.35 (1 H, d, *J* 2) and 8.2–9.3 (br, exch. D_2O) (Found: C, 51.95; H, 7.4; N, 5.95; Br, 17.05; S, 6.9. $C_{20}H_{33}BrN_2O_3S$ requires C, 52.05; H, 7.2; N, 6.05; Br, 17.3; S, 6.95%).

p-*Methoxybenzyl* 6-*bromopenicillanate* **6**. A solution of phosphorus tribromide (11.7 cm^3, 0.123 mol) in dry diethyl ether (25 cm^3) was added, dropwise during 15 min, to a stirred mixture of 4-methoxybenzyl alcohol (51.6 g, 0.37 mol) and pyridine (25 drops) in dry diethyl ether (500 cm^3) at 10 °C. After being stirred without cooling for 15 min, the mixture was washed successively with brine (100 cm^3), saturated aq. $NaHCO_3$ (100 cm^3) and brine (100 cm^3). The dried ($MgSO_4$) organic layer was evaporated to low volume, diluted with DMF (250 cm^3) and added dropwise to a stirred solution of the dicyclohexylamine salt of acid **5** (172.7 g, 0.37 mol) in DMF (1000 cm^3) at 10 °C. After being stirred at room temperature for 18 h, the mixture was poured into a mixture of water (2000 cm^3) and ethyl acetate (2000 cm^3). The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (2 × 1000 cm^3). The combined organic layers were washed successively with 5% aq. citric acid (1000 cm^3), saturated aq. $NaHCO_3$ (1000 cm^3) and brine (1000 cm^3). The dried ($MgSO_4$) organic layer was evaporated to give the *title ester* **6** (133 g, 89%) as an oil, which crystallized on storage, m.p. 73–74 °C; $\delta_H(CDCl_3)$ 1.31 (3 H, s), 1.52 (3 H, s), 3.74 (3 H, s), 4.47 (1 H, s), 4.70 (1 H, d, *J* 2), 5.08 (2 H, s), 5.35 (1 H, d, *J* 2), 6.80 (2 H, d, *J* 8) and 7.25 (2 H, d, *J* 8) (Found: C, 48.0; H, 4.45; N, 3.5; Br, 19.75; S, 7.9. $C_{16}H_{18}BrNO_4S$ requires C, 48.0; H, 4.55; N, 3.5; Br, 19.95; S, 8.0%).

p-*Methoxybenzyl* 6-*bromopenicillanate* 1-*oxide* **7**. A solution of MCPBA (78.5 g, 0.455 mol) in dichloromethane (700 cm^3) was added, over a period of 30 min, to a stirred solution of the ester **6** (165.5 g, 0.413 mol) in dichloromethane (1600 cm^3) at 5 °C. After 1 h at 5 °C the mixture was filtered and the filtrate was washed successively with saturated aq. $NaHCO_3$ (2 × 500 cm^3), water (500 cm^3) and brine (500 cm^3). The dried ($MgSO_4$) organic layer was evaporated and the residual oil was triturated with ethyl acetate to give the *title sulfoxide* **7** (122.8 g, 71%) as a crystalline solid, m.p. 137–139 °C; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 1802, 1755, 1615 and 1520; $\delta_H(CDCl_3)$ 1.45 (3 H, s), 2.00 (3 H, s), 4.18 (3 H, s), 4.90 (1 H, s), 5.40 (2 H, s), 5.52 (1 H, s), 5.56 (1 H, s), 7.25 (2 H, d, *J* 8) and 7.68 (2 H, d, *J* 8) (Found: C, 46.3; H, 4.35; N, 3.45; S, 7.7. $C_{16}H_{18}BrNO_5S$ requires C, 46.15; H, 4.35; N, 3.35; S, 7.7%).

p-*Methoxybenzyl* 2-[(3S,4R)-4-(*benzothiazol*-2-*yldithio*)-3-*bromo*-2-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* **10**. A mixture of the sulfoxide **7** (124.8 g, 0.3 mol) and 2-mercaptobenzothi-

* A completely concerted *trans* elimination of the 4 : 1 : 1 : 1 diastereoisomeric mixture of acylated bromohydrins **32** would yield, at best, a 5 : 2 mixture of olefins.

azole (50.1 g, 0.3 mol) was heated in refluxing toluene (2400 cm^3) with provision for the azeotropic removal of water (Dean–Stark apparatus) for 1 h. The mixture was cooled to 5 °C and treated with triethylamine (3.0 g, 0.03 mol). After being stirred at 5 °C for 2 h, the mixture was washed successively with 5% aq. citric acid (2 × 600 cm^3), water (600 cm^3) and brine (600 cm^3). The dried ($MgSO_4$) organic layer was evaporated and the residue was chromatographed over silica gel, eluting with ethyl acetate–hexane mixtures to give the *title disulfide* **10** (169.5 g, 100%) as an oil, $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1785 and 1720; $\delta_H(CDCl_3)$ 1.92 (3 H, s), 2.14 (3 H, s), 3.77 (3 H, s), 5.02 (1 H, d, *J* 2), 5.19 (2 H, m), 5.39 (1 H, d, *J* 2) 6.79–8.10 (8 H, m) (Found: C, 48.85; H, 3.55; N, 4.85; Br, 14.14; S, 16.8%; M^+, 563.9852. $C_{23}H_{21}BrN_2O_4S_3$ requires C, 48.85; H, 3.75; N, 4.95; Br, 14.13; S, 17.0%; M, 563.9846).

p-*Methoxybenzyl* 2-[(3S,4R)-4-*acetylthio*-3-*bromo*-2-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* **12**. Triphenylphosphine (3.9 g, 14.89 mmol) was added, portionwise during 20 min, to a stirred solution of the disulfide **10** (7.8 g, 13.79 mmol) in a mixture of acetic anhydride (66 cm^3) and glacial acetic acid (22 cm^3) under nitrogen at −20 °C. After being stirred at −20 °C for a further 45 min the mixture was treated with pyridine (44 cm^3) and allowed to attain room temperature. After being stirred at room temperature for 3 h the mixture was evaporated to an oil, which was redissolved in ethyl acetate (50 cm^3) and washed successively with 5% aq. citric acid and brine. The dried ($MgSO_4$) organic layer was evaporated and the residue was chromatographed over silica gel, eluting with ethyl acetate–hexane mixtures to give the *title azetidinone* **12** (5.5 g, 90%) $\nu_{max}(CHCl_3)/cm^{-1}$ 1785 and 1720; $\delta_H(CDCl_3)$ 1.95 (3 H, s), 2.24 (3 H, s), 2.31 (3 H, s), 3.80 (3 H, s), 4.80 (1 H, d, *J* 2), 5.21 (2 H, s), 5.71 (1 H, d, *J* 2), 6.92 (2 H, d, *J* 9) and 7.42 (2 H, d, *J* 9) (Found: C, 48.65; H, 4.45; N, 3.05; S, 7.3; Br, 18.05. $C_{18}H_{20}BrNO_5S$ requires C, 48.9; H, 4.55; N, 3.15; S, 7.25; Br, 18.05%).

Preparation of p-*methoxybenzyl* 2-[(3S,4R)-4-*acetylthio*-3-*bromo*-2-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* **12** *directly from* p-*methoxybenzyl* 6-*bromopenicillanate* 1-*oxide* **7**. A mixture of the sulfoxide **7** (0.416 g, 1 mmol), acetic anhydride (0.47 cm^3, 4.99 mmol) and triisopropyl phosphite (0.27 cm^3, 1.1 mmol) was heated in refluxing benzene under dry argon for 8 h. The mixture was evaporated and the residue was reevaporated from xylene (2 × 5 cm^3). The crude product was dissolved in ethyl acetate (5 cm^3) and was treated with triethylamine (0.010 g). After 20 min at room temperature the mixture was diluted with ethyl acetate (5 cm^3) and washed successively with 5% aq. citric acid (1 cm^3), brine (1 cm^3), saturated aq. $NaHCO_3$ (1 cm^3) and brine (3 × 1 cm^3). The dried ($MgSO_4$) organic layer was evaporated and the residue was chromatographed over silica gel, eluting with ethyl acetate–hexane mixtures to give the title azetidinone **12** (0.221 g, 50%), identical with that previously described.

p-*Methoxybenzyl* 2-[(3S,4R)-4-*acetylthio*-3-*bromo*-2-*oxoazetidin*-1-*yl*]-2-*triphenylphosphoranylideneacetate* **14**. Ozonized oxygen was bubbled through a solution of the azetidinone **12** (0.250 g, 0.566 mmol) in ethyl acetate (5 cm^3) at −76 °C until a permanent blue solution was obtained (TLC indicated that no starting material remained). The excess of ozone was removed by the passage of argon. The mixture was diluted with ethyl acetate (5 cm^3) and washed successively with 45% aq. sodium hydrogen sulfite (1 cm^3), brine (1 cm^3), saturated aq. $NaHCO_3$ (1 cm^3) and brine (3 × 1 cm^3). The dried ($MgSO_4$) organic layer was evaporated to give *p*-methoxybenzyl 2-[(3*S*,4*R*)-4-acetylthio-3-bromo-2-oxoazetidin-1-yl]-2-oxoacetate **13** (0.229 g, 97%) as a gum, $\nu_{max}(CHCl_3)/cm^{-1}$ 1830, 1755 and 1725; $\delta_H(CDCl_3)$ 2.38 (3 H, s), 3.82 (3 H, s), 5.06 (1 H, d, *J* 2.5), 5.32 (2 H, s), 5.71 (1 H, d, *J* 2.5), 6.93 (2 H, d, *J* 9) and 7.41 (2 H, d, *J* 9).

A solution containing the oxalimide **13** (0.210 g, 0.505 mmol), triphenylphosphine (0.530 g, 2.02 mmol) and triethyl phosphite (0.084 g, 0.50 mmol) in dry toluene (5 cm^3) was stirred at room temperature for 18 h. The mixture was then diluted with toluene (5 cm^3) and washed with brine (3 × 1 cm^3). The dried ($MgSO_4$) organic layer was evaporated and the residue was chromatographed over silica gel, eluting with ethyl acetate–hexane mixtures to yield the title phosphorane **14** (0.176 g, 53%) as a foam, $\nu_{max}(CHCl_3)/cm^{-1}$ 1775, 1695 and 1615; *m/z* (FAB, thioglycerol) 662, 664 (1 : 1, MH^+).

Silver (3S,4R)-3-*Bromo*-1-[1-(p-*methoxybenzyloxycarbonyl*)-1-*triphenylphosphoranylidenemethyl*]-2-*oxoazetidine*-4-*thiolate* **15**. A solution of triethylamine (0.067 g, 0.48 mmol) in methanol (1 cm^3) was added, dropwise over a period of 1 min, to a stirred mixture of the phosphorane **14** (0.340 g, 0.51 mmol), dry dichloromethane (4 cm^3) and silver nitrate (4.46 cm^3 of a 0.15 mol dm^{-3} solution in methanol) at ice-bath temperature. The mixture was stirred at ice-bath temperature for 40 min, evaporated to half volume and filtered. The residue was washed successively with a little cold methanol and dry diethyl ether and was dried *in vacuo* to give the title silver salt **15** (0.346 g, 93%) as a buff coloured solid, ν_{max}(Nujol)/cm^{-1} 1765 and 1615.

p-*Methoxybenzyl* (5R,6S)-6-*bromopenem*-3-*carboxylate* **17**. A stirred, ice-bath cooled solution of the silver salt **15** (0.182 g, 0.25 mmol) in dry dichloromethane (3 cm^3) was treated with acetic formic anhydride (0.20 cm^3) and DMAP (0.031 g, 0.25 mmol). The ice-bath was removed and the vigorously stirred mixture was treated with triethylamine hydrochloride (0.350 g, 2.5 mmol). After 10 min the mixture was diluted with ethyl acetate (10 cm^3) and filtered through Kieselguhr, the residue being washed with ethyl acetate (10 cm^3). The combined filtrates were washed successively with 5% aq. citric acid (3 cm^3), brine (3 cm^3), saturated aq. $NaHCO_3$ (3 cm^3) and brine (3 × 3 cm^3). The dried ($MgSO_4$) organic layer was kept at room temperature for 30 min and was then evaporated. The residue was chromatographed over silica gel, eluting with dichloromethane to give the *title bromopenem ester* **17** (0.041 g, 44%) as a solid, m.p. 102–104 °C (needles from ethyl acetate–hexane); $[\alpha]_D^{20}$ +83 (*c* 1.0, $CHCl_3$); λ_{max}(EtOH)/nm 321 (ε 7065 dm^3 mol^{-1} cm^{-1}), 280 (6697), 274 (6663) and 226 (16 060); $\nu_{max}(CHCl_3)/cm^{-1}$ 1805 and 1715; $\delta_H(CDCl_3)$ 3.81 (3 H, s), 5.15 (1 H, dd, *J* 1.5 and 1), 5.17 and 5.23 (2 H, ABq, *J* 12), 5.76 (1 H, d, *J* 1.5), 6.90 (2 H, dd, *J* 6.7 and 2), 7.25 (1 H, d, *J* 1) and 7.35 (2 H, dd, *J* 6.7 and 2) (Found: C, 45.4; H, 3.2; N, 3.7; Br, 21.4; S, 8.5%; M^+, 368.9673. $C_{14}H_{12}BrNO_4S$ requires C, 45.4; H, 3.3; N, 3.8; Br, 21.6; S, 8.7%; M, 368.9671).

Preparation of p-*Methoxybenzyl* (5R,6S)-6-*bromopenem*-3-*carboxylate* **17** *directly from* p-*methoxybenzyl* 2-[(3S,4R)-4-*acetylthio*-3-*bromo*-2-*oxoazetidin*-1-*yl*]-2-*triphenylphosporanylideneacetate* **14** *without isolation of the silver salt* **15**. To a stirred solution of the phosphorane **14** (69.8 g, 0.105 mol) in acetonitrile (1600 cm^3) were added DMAP (16.7 g, 0.137 mol) and a solution of silver nitrate (23.2 g, 0.137 mol) in acetonitrile (75 cm^3). After being stirred at room temperature for 30 min, the solution was cooled to 5 °C and treated in rapid succession with DMAP (12.9 g, 0.105 mol), acetic formic anhydride (84 cm^3) and sodium iodide (158 g, 1.05 mol). The cooling bath was removed and the mixture was stirred at ambient temperature for 30 min. The reaction mixture was partitioned between ethyl acetate and water and filtered through Celite. The organic solution was separated, washed successively with 5% aq. citric acid (500 cm^3), saturated aq. $NaHCO_3$ (2 × 500 cm^3) and brine (500 cm^3) and was dried over $MgSO_4$. The solution, after filtration, was evaporated and the residue was chromatographed rapidly over silica gel. Elution with 25% ethyl acetate–hexane provided the pure bromopenem ester **17** (25.1 g, 65%) as a crystalline solid from ethyl acetate–hexane. This material was identical with that previously described.

Preparation of p-*Methoxybenzyl* (5R,6S)-6-*Bromopenem*-3-*carboxylate* **17** via p-*Methoxybenzyl* 2-{(3S,4R)-3-*Bromo*-2-*oxo*-4-[(E)-2-*trimethylsilylvinylthio*]*azetidin*-1-*yl*}-3-*methylbut*-2-*enoate* **27** (*Scheme* 3).—

p-*Methoxybenzyl* 2-{(3S,4R)-3-*Bromo*-2-*oxo*-4-[(E)-2-*trimethylsilylvinylthio*]*azetidin*-1-*yl*}-3-*methylbut*-2-*enoate* **27**. A mixture of the sulfoxide **7** (4.2 g, 10.1 mmol) and trimethylsilylacetylene (2.8 cm^3) was heated to reflux in toluene (30 cm^3) for 3 h. The solution was then evaporated and the residue was dissolved in dichloromethane (30 cm^3). The solution was treated with triethylamine (20 drops) to yield, after evaporation, the crude sulfoxide **26**, $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1790, 1725 and 1615; *m*/*z* (NH_3 DCI) 514, 516 (1:1, MH^+) and 531, 533 (1:1, MNH_4^+).

The above sulfoxide **26** was dissolved in DMF (30 cm^3), and the solution was cooled to −10 °C and treated with phosphorus tribromide (0.95 cm^3, 10.0 mmol). After 20 min at −10 °C the mixture was treated with ethyl acetate, toluene and saturated aq. $NaHCO_3$. The organic layer was separated, and washed with water. The dried ($MgSO_4$) organic solution was evaporated and the residue was chromatographed over silica gel, eluting with ethyl acetate–dichloromethane mixtures, to yield the title azetidinone **27** (3.65 g, 73%) as a gum, $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1780 and 1722; $\delta_H(CDCl_3)$ (Me_3Si obscured by TMS signal) 1.9 and 2.2 (6 H, each s), 3.7 (3 H, s), 4.6 (1 H, d, *J* 2), 5.0 (2 H, ABq), 5.1 (1 H, d, *J* 2), 5.8 and 6.3 (2 H, ABq, *J* 18), 6.8 and 7.2 (4 H, ABq, *J* 8.7); *m*/*z* 497.0712 (M^+) ($C_{21}H_{28}BrNO_4SSi$ requires M, 497.0692).

p-*Methoxybenzyl* (5R,6S)-6-*bromopenem*-3-*carboxylate* **17**. Ozonized oxygen was passed into a solution of the azetidinone **27** (0.500 g, 1.0 mmol) in ethyl acetate (100 cm^3) at −76 °C until a strong blue colour persisted. Excess of ozone was then blown off with nitrogen, toluene was added, and the resulting solution was washed with aq. sodium sulfite–sodium 'metabisulfite' ($Na_2S_2O_5$) (saturated aq. sodium sulfite adjusted to pH 7.0 by the addition of sodium 'metabisulfite'). The organic layer was then washed with water, dried ($MgSO_4$), and evaporated to yield *p*-methoxybenzyl 2-[(3*S*,4*R*)-3-bromo-4-formylthio-2-oxoazetidin-1-yl]-2-oxoacetate **28** as an oil, ν_{max}(film)/cm^{-1} 1830, 1750, 1720 and 1690sh; $\delta_H(CDCl_3)$ 3.8 (3 H, s,), 5.3 (2 H, s), 5.0 and 5.8 (2 H, each d, *J* 3), 6.8 and 7.4 (4 H, ABq) and 10.1 (1 H, s).

The oxalimide **28** was then dissolved in dry toluene (50 cm^3) and the solution was heated at 50 °C for 1 h with trimethyl phosphite (0.60 cm^3, 5 mmol) under argon. After cooling, the solution was evaporated to small volume and applied to a column of silica gel. Elution with ethyl acetate–hexane mixtures afforded the title bromopenem ester **17** (0.074 g, 20%) which was identical with that previously described.

Preparation of p-*Methoxybenzyl* (5R,6S)-6-*Bromopenem*-3-*carboxylate* **17** *via* p-*Methoxybenzyl* 2-[(3S,4R)-3-*Bromo*-4-*formylthio*-2-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* **29** (*Scheme* 4).—

p-*Methoxybenzyl* 2-[(3S,4R)-3-*bromo*-4-*formylthio*-2-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* **29**. A stirred solution of the disulfide **10** (169.5 g, 0.3 mol) in acetonitrile (840 cm^3) was cooled to −15 °C under argon and treated sequentially with pyridine (23.7 g, 0.3 mol), acetic formic anhydride (246 g, 3 mol) and triphenylphosphine (78.6 g, 0.3 mol) (portionwise during 15 min). The reaction solution was stirred for a further 45 min at −15 °C and was then allowed to attain 0 °C over a period of 1 h. The resulting suspension was filtered and the residual solid was washed with cold acetonitrile (300 cm^3). The combined filtrates were partitioned between cold toluene (2500 cm^3) and water (2500 cm^3). The organic phase was washed successively with chilled water (2500 cm^3), saturated aq. $NaHCO_3$ (2000 cm^3) and brine (2000 cm^3). The organic solution was dried ($MgSO_4$), treated with decolourizing charcoal (5 g), filtered, and evaporated to yield a yellow, partly crystalline oil. This semi-solid was digested in cold ethanol (450 cm^3) and stored at −20 °C for 1 h. The precipitate was collected by filtration, washed with cold ethanol, and dried *in vacuo* over phosphorus pentoxide to yield the *title compound* **29** as a pale yellow crystalline solid (99.2 g, 77%), m.p. 89–90 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1788, 1721 and 1690; $\delta_H(CDCl_3)$ 1.93 (3 H, s), 2.25 (3 H, s), 3.78 (3 H, s), 4.78 (1 H, d, *J* 2), 5.18 (2 H, s), 5.75 (1 H, d, *J* 2), 6.85 and 7.30 (4 H, ABq) and 9.95 (1 H, s) (Found: C, 47.7; H, 4.2; N, 3.25; S, 7.4; Br, 18.65. $C_{17}H_{18}BrNO_5S$ requires C, 47.65; H, 4.25; N, 3.25; S, 7.5; Br, 18.65%).

p-*Methoxybenzyl* (5R,6S)-6-*bromopenem*-3-*carboxylate* **17**. The (formylthio)azetidinone **29** (42.8 g, 0.1 mol) was dissolved in ethyl acetate (1000 cm^3) and the solution was cooled to −76 °C. Ozonized oxygen was passed through the vigorously stirred solution until a blue colour persisted. The solution was then purged with argon for 30 min, and treated with trimethyl phosphite (61.8 g, 0.5 mol) at −76 °C. The mixture was allowed to warm slowly to ambient temperature and was stirred at this temperature for 16 h. The solution was then heated to reflux for 45 min. After cooling, the solution was evaporated to small volume at reduced pressure and applied to a column of silica gel. Elution with ethyl acetate–hexane mixtures provided the title compound **17** as a crystalline solid (17.76 g, 48%) from diethyl ether. This material was identical with that already described.

Elaboration of p-*Methoxybenzyl* (5R,6S)-6-*Bromopenem*-3-*carboxylate* **17** *to* (5R)-(Z)-6-(1-*Methyl*-1,2,3-*triazol*-4-*ylmethylene*)*penem*-3-*carboxylic Acid* **34** (*Scheme* 5).—

p-*Methoxybenzyl* (5R)-6-*bromo*-6-[*hydroxy*-(1-*methyl*-1,2,3-*triazol*-4-*yl*)*methyl*]*penem*-3-*carboxylate* **31**. A solution of LiHMDS (0.75 cm^3 of a 0.93 mol dm^{-3} solution in hexane; 0.70 mmol) was diluted with dry THF (1 cm^3) and added, in one portion, to a vigorously stirred solution of the bromopenem **17** (0.250 g, 0.68 mmol) in dry THF (10 cm^3) at −76 °C under dry argon. After 15–20 s the vigorously stirred mixture was treated, in one portion, with a solution of 1-methyl-1,2,3-triazole-4-carbaldehyde[24] (0.090 g, 0.81 mmol) in dry THF (2 cm^3). After a further 15–20 s, the mixture was treated with a solution of glacial acetic acid (0.2 cm^3) and water (0.2 cm^3) in THF (1 cm^3). The mixture was diluted with ethyl acetate (20 cm^3) and washed successively with brine (2 cm^3), saturated aq. $NaHCO_3$ (2 cm^3) and brine (3 × 2 cm^3). The dried ($MgSO_4$) organic layer was evaporated and the residue was chromatographed over silica gel, eluting with ethyl acetate–hexane mixtures to give two fractions. The less polar fraction contained a single isomer of the title bromohydrin **31** (0.131 g, 40%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3600–3100, 1795 and 1710; $\delta_H(CDCl_3)$ 3.2–3.7 (1 H, br), 3.80 (3 H, s), 4.10 (3 H, s), 5.16 and 5.24 (2 H, ABq, *J* 12), 5.72 (1 H, br s), 6.14 (1 H, s), 6.89 (2 H, d, *J* 8.7), 7.34 (s) and 7.35 (d, *J* 8.7) (together 3 H) and 7.69 (1 H, d, *J* 0.4); *m*/*z* (EI) 481.0187 (MH^+) ($C_{18}H_{17}BrN_4O_5S{\cdot}H^+$ requires *m*/*z* 481.0181); *m*/*z* (NH_3 DCI) 481, 483 (1:1, MH^+); *m*/*z* (FAB, 3-NOBA/NA) 503, 505 (1:1, MNa^+).

The more polar fraction contained a 2:1:1 mixture of three isomers of the title bromohydrin **31** (0.090 g, 28%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3600–3100, 1800 and 1710; $\delta_H(CDCl_3)$ 3.81 (3 H, s), 4.08, 4.11 and 4.13 (3 H, each s), 5.16–5.27 (2 H, m), 5.38 ($\frac{1}{4}$ H, s), 5.48 ($\frac{1}{4}$ H, s), 5.53 ($\frac{1}{2}$ H, s), 6.11 ($\frac{1}{2}$ H, s), 6.35 ($\frac{1}{4}$ H, s), 6.39 ($\frac{1}{4}$ H, s), 6.87–6.93 (2 H, m), 7.25–7.37 (3 H, m), 7.70 ($\frac{1}{4}$ H, s), 7.79 ($\frac{1}{2}$ H, s) and 7.80 ($\frac{1}{4}$ H, s); *m*/*z* (EI) 481.0192 (MH^+) ($C_{18}H_{17}BrN_4O_5S{\cdot}H^+$ requires *m*/*z*, 481.0181); *m*/*z* (NH_3 DCI) 481, 483 (1:1, MH^+).

Preparation of p-*methoxybenzyl* (5R)-(Z)-6-(1-*methyl*-1,2,3-*triazol*-4-*ylmethylene*)*penem*-3-*carboxylate* **33** *and* p-*methoxybenzyl* (5R)-(E)-6-(1-*methyl*-1,2,3-*triazol*-4-*ylmethylene*)*penem*-

3-carboxylate **35** *using zinc and acetic acid in THF for the reductive elimination of the acylated bromohydrins* **32**. A solution of diphenylamine (0.233 g, 1.38 mmol) in THF (25 cm^3) at −20 °C under argon was treated with n-butyllithium (0.925 cm^3; 1.5 mol dm^{-3} solution in hexane; 1.40 mmol). The resulting solution was stirred at ambient temperature for 10 min before being cooled to −76 °C under argon. A solution of the bromopenem ester **17** (0.500 g, 1.35 mmol) in dry THF (5 cm^3) was added to the above rapidly stirred solution of lithium diphenylamide in THF. After 15–20 s, the vigorously stirred mixture was treated with a solution of 1-methyl-1,2,3-triazole-4-carbaldehyde (0.180 g, 1.62 mmol) in dry THF (5 cm^3). After a further 15–20 s, the resulting solution, containing a mixture of the lithium salts of the bromohydrins **31**, was treated with a solution of acetic anhydride (0.40 cm^3, 4.30 mmol) in dry THF (4 cm^3). The cooling bath was removed and the mixture was stirred for 10 min. The resulting solution containing a mixture of the acetates **32** was treated with glacial acetic acid (0.40 cm^3) and activated zinc dust (0.500 g). After being stirred at ambient temperature for 15 min, the mixture was filtered through Kieselguhr and the residue was washed with ethyl acetate (2 × 10 cm^3). The combined filtrates were diluted with ethyl acetate and washed successively with brine, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed over silica gel and elution with ethyl acetate–hexane gave two fractions. The less polar fraction provided the (E)-*isomer* **35** of the title penem as a yellow solid (0.099 g, 19%), m.p. 181–183 °C (clusters of needles from ethyl acetate–hexane); $[\alpha]_D^{20}$ −244 (*c* 1.0, $CHCl_3$); λ_{max}(EtOH)/nm 296 (ε 19 400 dm^3 mol^{-1} cm^{-1}) and 224 (18 500); ν_{max}($CHCl_3$)/cm^{-1} 1775, 1715 and 1685sh; δ_H($CDCl_3$) 3.81 (3 H, s), 4.14 (3 H, s), 5.19 and 5.24 (2 H, ABq, *J* 12.6), 6.42 (1 H, d, *J* 0.7), 6.90 (3 H, s and d, *J* 8.7), 7.33 (s) and 7.36 (d, *J* 8.7) (together 3 H) and 8.74 (1 H, s) (Found: C, 56.5; H, 4.0; N, 14.6; S, 8.2. $C_{18}H_{16}N_4O_4S$ requires C, 56.2; H, 4.2; N, 14.6; S, 8.3%).

The more polar fraction provided the (Z)-*isomer* **33** of the title penem as a yellow solid (0.247 g, 48%), m.p. 183–184 °C (clusters of small needles from ethyl acetate–hexane); $[\alpha]_D^{20}$ +399 (*c* 1.0, $CHCl_3$); λ_{max}(EtOH)/nm 285 (ε 25 300 dm^3 mol^{-1} cm^{-1}) and 226 (18 040); ν_{max}($CHCl_3$)/cm^{-1} 1780 and 1710; δ_H($CDCl_3$) 3.81 (3 H, s), 4.14 (3 H, s), 5.17 and 5.25 (2 H, ABq, *J* 12), 6.62 (1 H, d, *J* 1.1), 6.89 (2 H, d, *J* 8.7), 7.03 (1 H, d, *J* 1.1), 7.27 (1 H, s), 7.36 (2 H, d, *J* 8.7) and 7.70 (1 H, s) (Found: C, 56.5; H, 4.2; N, 14.6; S, 8.1%).

Preparation of p-*methoxybenzyl* (5R)-(Z)-6-(1-*methyl*-1,2,3-*triazol*-4-*ylmethylene*)*penem*-3-*carboxylate* **33** *and* p-*methoxybenzyl* (5R)-(E)-6-(1-*methyl*-1,2,3-*triazol*-4-*ylmethylene*)*penem*-3-*carboxylate* **35** *using zinc, ammonium chloride and* N,N,N′,N′-*tetramethylethylenediamine dihydrochloride in DMF for the reductive elimination of the acylated bromohydrins* **32**. n-Butyllithium (0.93 cm^3; 1.5 mol dm^{-3} solution in hexane; 1.40 mmol) was added to a stirred solution of diphenylamine (0.230 g, 1.36 mmol) in dry THF (25 cm^3) at −10 °C under argon. The resulting solution was stirred at ambient temperature for 10 min before being cooled to −76 °C. A solution of the bromopenem **17** (0.500 g, 1.35 mmol) in dry THF (5 cm^3), a solution of 1-methyl-1,2,3-triazole-4-carbaldehyde (0.180 g, 1.62 mmol) in dry THF (5 cm^3) and a solution of acetic anhydride (0.40 cm^3, 4.30 mmol) in dry THF (4 cm^3) were then added in rapid succession to the vigorously stirred solution of lithium diphenylamide in THF. The cooling bath was removed and, after the mixture had been stirred for a further 10 min, ethyl acetate and aq. $NaHCO_3$ were added. The separated organic layer was washed twice with brine, dried ($MgSO_4$), and evaporated to yield a diastereoisomeric mixture of acetates **32** as an oil.

This oil was dissolved in dry DMF (20 cm^3) and the solution was stirred at 20 °C for 1 h with ammonium chloride (0.220 g, 4.00 mmol), TMEDA dihydrochloride (0.190 g, 1 mmol) and activated zinc powder (0.260 g, 4.00 mmol). Ethyl acetate and 5% aq. citric acid were then added. The organic solution was washed successively with brine, aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed over silica gel, eluting with a gradient of 50–90% ethyl acetate–hexane. The first eluted component was diphenylamine. This was followed by the (*E*)-isomer **35** of the title penem (0.042 g, 8%). The third eluted component was the (*Z*)-isomer **33** of the title penem (0.330 g, 64%). Both the (*E*)- and the (*Z*)-penem esters prepared by this method were identical with samples prepared by the previous method.

The diastereoisomeric mixture of acylated bromohydrins **32** could be isolated in pure form, as a foam, by silica gel column chromatography, eluting with ethyl acetate–hexane mixtures, ν_{max}(CH_2Cl_2)/cm^{-1} 1805, 1755 and 1715; δ_H($CDCl_3$) 2.04 (s), 2.09 (s), 2.18 (s), 2.25 (s) (together 3 H; proportions 1 : 1 : 1 : 4 respectively); 3.81 (3 H, s); 4.09 (s), 4.11 (s), 4.12 (s) (together 3 H); 5.1–5.27 (2 H, m); 6.12 (s), 6.30 (s), 6.34 (s), 6.39 (s), 6.42 (s), 6.58 (s), 6.80 (s), 6.90 (2 H, d, *J* 8.6), 6.94 (s) (together 4 H); and 7.22 (s), 7.24 (s), 7.28 (s), 7.31 (s), 7.32–7.38 (d + s), 7.52 (s), 7.70 (s), 7.76 (s) (together 4 H) (Found: C, 46.05; H, 3.65; N, 10.3; S, 6.15. $C_{20}H_{19}BrN_4O_6S$ requires C, 45.95; H, 3.65; N, 10.7; S, 6.15%).

Sodium salt of (5R)-(Z)-6-(1-*methyl*-1,2,3-*triazol*-4-*ylmethylene*)*penem*-3-*carboxylic acid* **34**.

A solution of the ester **33** (1.75 g, 4.56 mmol) in dry dichloromethane (25 cm^3) was added dropwise, over a period of 5 min, to a stirred solution of aluminium trichloride (1.52 g, 11.4 mmol) in anisole (19 cm^3)–dry dichloromethane (4 cm^3) at −40 °C under argon. After the mixture had been stirred at −40 °C for an additional 10 min, aq. disodium hydrogen phosphate (163.5 cm^3 of a 0.5 mol dm^{-3} solution) was added. The cooling bath was removed and the resulting suspension was stirred vigorously at ambient temperature for 15 min. The suspension was then filtered through Celite, washing well with water. The aqueous layer was separated and washed with diethyl ether. The stirred aqueous solution was adjusted to pH 2.0 by the addition of 2.5 mol dm^{-3} sulfuric acid. The resulting suspension was cooled at 5 °C for 15 min and the precipitate was collected by filtration over glass fibre filter paper, to provide the carboxylic acid **34** as a yellow solid.

A sample of this solid was dried using the minimum volume of acetone, followed by diethyl ether to provide *yellow needles*; ν_{max}(Nujol)/cm^{-1} 3182br, 1775, 1720, 1700 and 1614; δ_H[$(CD_3)_2$-SO] 4.10 (3 H, s), 6.64 (1 H, d, *J* 0.7), 7.32 (1 H, d, *J* 0.7), 7.57 (1 H, s), 8.39 (1 H, s) and 12.87 (1 H, br s) (Found: C, 45.55; H, 2.95; N, 21.15; S, 12.1. $C_{10}H_8N_4O_3S$ requires C, 45.45; H, 3.05; N, 21.2; S, 12.1%).

The above carboxylic acid **34**, after being washed with water, was resuspended in water (25 cm^3). The vigorously stirred suspension was adjusted to pH 7.0 by the careful addition of 0.1 mol dm^{-3} aq. sodium hydroxide (27.7 cm^3). The resulting solution was filtered through glass fibre filter paper and the filtrate was evaporated at reduced pressure to ~4 cm^3. The *sodium salt of the title acid* **34** crystallized from this solution and the yellow crystalline solid (0.578 g, 42%) was collected by filtration and washed successively with acetone (2 × 2 cm^3) and diethyl ether (2 × 2 cm^3); $[\alpha]_D^{20}$ +514 (*c* 1.0, H_2O); λ_{max}(H_2O)/nm 365 (ε/dm^3 mol^{-1} cm^{-1} 1880) and 282 (23 720) ν_{max}(KBr)/cm^{-1} 3605, 1749, 1688, 1663, 1589, 1558, 1397 and 1274; δ_H(D_2O) 4.11 (3 H, s), 6.57 (1 H, s), 7.02 (1 H, s), 7.17 (1 H, s) and 8.14 (1 H, s) (Found: C, 39.6; H, 2.85; N, 18.35; S, 10.5. $C_{10}H_7N_4NaO_3S$·H_2O requires C, 39.45; H, 2.95; N, 18.4; S, 10.55%). The mother liquors were concentrated to ~2 cm^3 and an additional quantity of crystalline sodium salt monohydrate (0.145 g, 10%), $[\alpha]_D^{20}$ +504 (*c* 1.0, H_2O) was obtained, thus providing a total yield of 0.723 g (52%).

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