Synthesis of 6-(Substituted Methylene) Carbapenem Derivatives from 6-Aminopenicillanic Acid[1]

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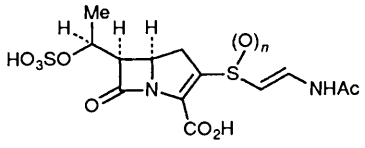
The key intermediate in the preparation of novel 6-(substituted methylene) carbapenem derivatives is *p*-methoxybenzyl (5*R*,6*R*)-6-bromo-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate **26**, which was prepared in several steps from 6-aminopenicillanic acid **14** *via* (3*R*,4*R*)-4-allyl-3-bromoazetidin-2-one **21**. Sequential treatment of the aforementioned ester **26** with either lithium diisopropylamide or lithium diphenylamide, 1-methyl-1*H*-1,2,3-triazole-4-carbaldehyde and acetic anhydride provided a diastereoisomeric mixture of acylated bromohydrins **28**; reductive elimination then afforded the isomeric (*E*)- and (*Z*)-6-triazolylmethylene carbapenem esters **29** and **31**, respectively. Lewis acid-mediated deprotection of the 6-bromo and 6-[(*E*)-triazolylmethylene] esters **26** and **29** gave the sodium salts of (5*R*,6*R*)-6-bromo-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid **27** and (5*R*)-6-[(*E*)-(1-methyl-1*H*-1,2,3-triazol-4-yl)methylene]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid **30**, respectively.

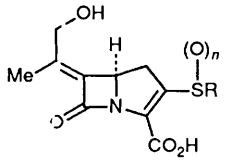
In addition, condensation of the anion, generated by deprotonation of the 6-bromo ester, with acetaldehyde, followed by acylation and reductive elimination furnished the isomeric (*E*)- and (*Z*)-ethylidene carbapenem esters.

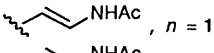
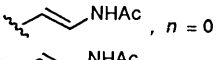
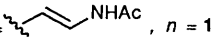
Whilst the (*E*)-6-triazolylmethylene carbapenem displayed low levels of antibacterial activity, it possessed no β-lactamase-inhibitory activity whatsoever. The 6-bromocarbapenem was devoid of both antibacterial and β-lactamase-inhibitory activity.

Since the isolation of the olivanic acids[2,3] and thienamycin[4] from soil microorganisms, a great deal of interest has been shown by a number of groups in the total synthesis and chemical modification of such compounds.[5] Whilst most attention has focused upon the antibacterially active 6-(1-hydroxyethyl)carbapenem derivatives, certain members of the carbapenem family of antibiotics, notably the sulphated olivanic acids MM 4550 **1** and MM 13902 **2**[2] and the asparenomycins **3**–**5**,[6] display potent β-lactamase-inhibitory activity.

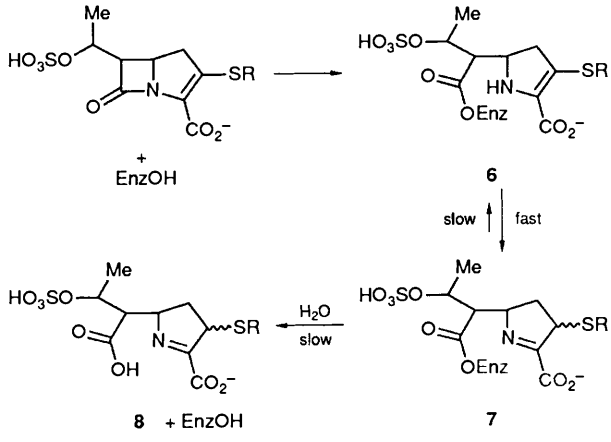


1 MM 4550, *n* = 1
2 MM 13902, *n* = 0



3 Asparenomycin A; R =  , *n* = 1
4 Asparenomycin B; R =  , *n* = 0
5 Asparenomycin C; R =  , *n* = 1

Inhibition of β-lactamases by carbapenems involves acylation of the active-site serine residue. Knowles and co-workers[7] have demonstrated that the progressive inhibition of the TEM β-lactamase by the olivanic acids is due to rearrangement of the Δ^2-pyrroline intermediate **6** to the tautomeric and thermodynamically more stable Δ^1-pyrroline **7** (Scheme 1). The resultant acyl-enzyme complex is believed to be stable to subsequent hydrolytic breakdown, thereby disrupting the catalytic activity of the enzyme.

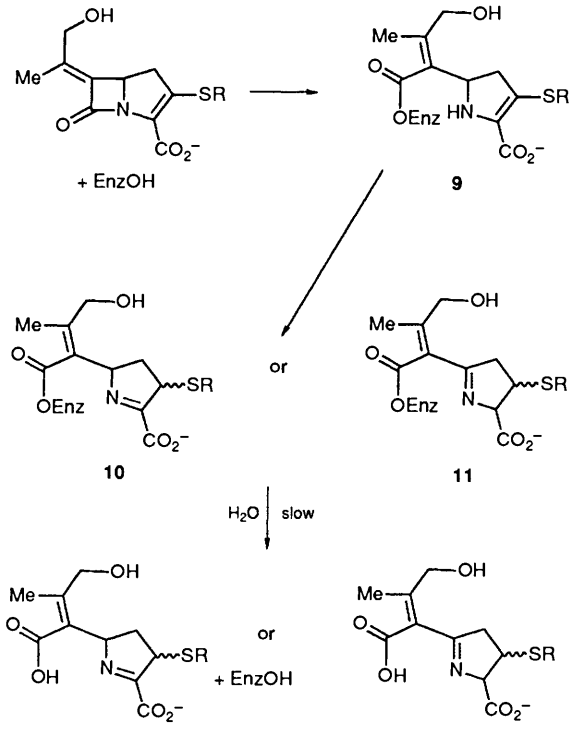


Scheme 1

Similarly, the asparenomycins, which possess the hydroxyisopropylidene group at C-6, inhibit the β-lactamase enzyme by formation of a particularly stable acyl–enzyme complex. The initially formed acrylic ester **9** may then rearrange to either the Δ^1-pyrroline **10** or the Δ^5-pyrroline **11** (Scheme 2).[8]

Recent reports from these laboratories[9–13] have described the preparation of a series of 6-(substituted methylene) penem derivatives which display excellent β-lactamase-inhibitory activity. Structure–activity relationships revealed that the 6-heterocyclylmethylene penems were more active than the 6-alkylidene penems. In particular, the triazolylmethylene penem BRL 42715 **12** is a potent inhibitor of a wide range of penicillinases and cephalosporinases. This prompted us to incorporate the C-6 triazolylmethylene moiety into the carbapenem nucleus, with a view to improving upon the β-lactamase inhibitory activity of the alkylidene carbapenem derivatives, asparenomycins A, B and C.

We now report the convenient and chiral synthesis of (5*R*)-

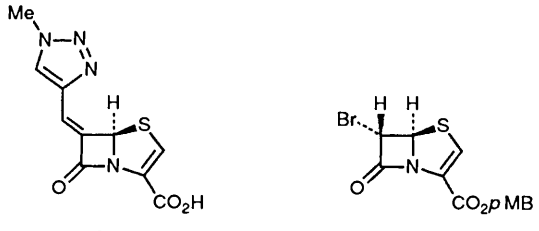


Scheme 2

6-[(*E*)-(1-methyl-1*H*-1,2,3-triazol-4-yl)methylene]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid **30** from 6-aminopenicillanic acid **14** *via* a novel and versatile intermediate, the 6α-bromocarbapenem ester **26**.

Results and Discussion

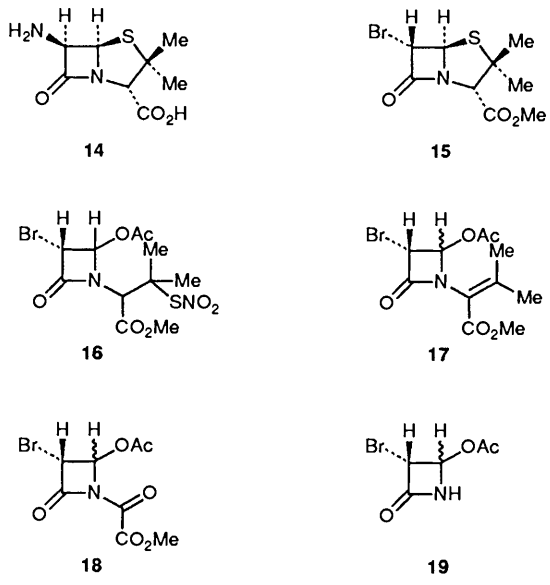
The great potential of 6-aminopenicillanic acid **14** for the synthesis of optically active, non-classical β-lactams has been recognised on numberous occasions. Indeed, the synthesis of BRL 42715 **12** utilised this cheap, chiral starting material and proceeded *via* the novel 6α-bromopenem **13**.[14,15] We have employed a similar strategy for the synthesis of the triazolylmethylene carbapenem **30**, which proceeds *via* the analogous 6α-bromocarbapenem **26**.



12 **13**

p MB = *p*-Methoxybenzyl

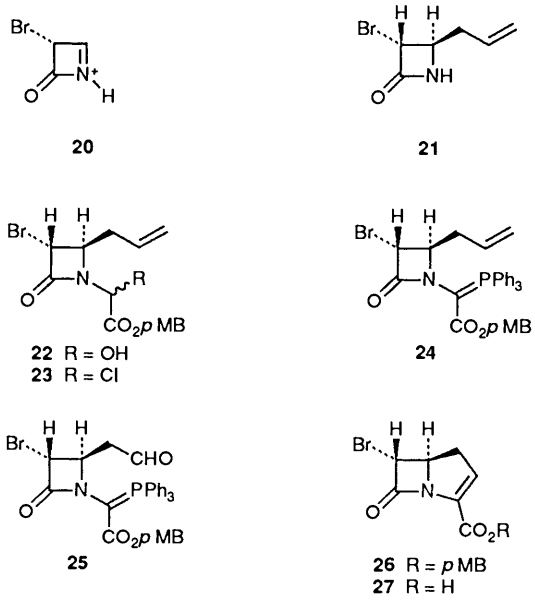
The 6α-bromopenicillanate ester **15** was prepared from 6-aminopenicillanic acid **14** by the method of John *et al.*[16] Elaboration to the diastereoisomeric mixture of (3*R*,4*RS*)-4-acetoxy-3-bromoazetidin-2-ones **17** was achieved by utilisation of the method first described by Schering chemists for the preparation of 4-acyloxy-3-(1-hydroxyalkyl)azetidin-2-ones from 6-(1-hydroxyalkyl)penicillanate esters.[17] Thiazolidine ring cleavage is effected by treatment with acetyl nitrate in 1,2-dichloroethane and is believed to proceed *via* the thionitrate intermediate **16**. Base-catalysed β-elimination subsequently provided the diastereoisomeric mixture of isopropylidene



14 **15** **16** **17** **18** **19**

derivatives **17** in 39% yield. Ozonolysis of the isopropylidene compounds **17** furnished the oxalimide **18**, which was cleaved by base-catalysed methanolysis to yield the diastereoisomeric mixture of (3*R*,4*RS*)-4-acetoxy-3-bromoazetidin-2-ones **19** in 86% yield.

The introduction of the C-4 alkyl substituent was achieved in a stereospecific manner by the method of Kraus and Neuenschwander.[18] Reaction of either diastereoisomer of the acetoxyazetidinone **19**, or the diastereoisomeric mixture, with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether (1.2 mol equiv.) (CH_2Cl_2; room temp.; 2 h) provided the (3*R*,4*R*)-4-allyl-3-bromoazetidin-2-one **21**[19] in good yield (71%). The use of titanium tetrachloride–allyltrimethylsilane or boron trifluoride–tetraallyl tin[20] to effect the amidoalkylation reaction resulted in substantially lower yields. The *trans*-stereochemistry of the product was apparent from the 3-H–4-H vicinal coupling constant of 1.7 Hz and presumably resulted from addition to the least sterically hindered β-face of the intermediate acyliminium ion **20**.

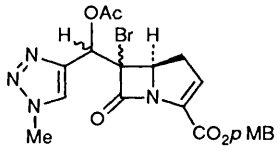


20 **21** **22** R = OH **23** R = Cl **24** **25** **26** R = *p*MB **27** R = H

The bicyclic carbapenem ring system was then constructed by means of the well established intramolecular Wittig

cyclisation reaction, first reported by Woodward.[21] Condensation of the azetidinone **21** with *p*-methoxybenzyl glyoxylate afforded a diastereoisomeric mixture of hemi-aminals **22**. Conversion into the chlorides **23** by reaction with thionyl chloride and 2,6-lutidine (2,6-dimethylpyridine), followed by treatment with excess of triphenylphosphine and 2,6-lutidine, provided the azetidinone phosphorane **24** in 61% yield. Selective oxidation of the allylic double bond of the phosphorane **24** could be achieved by ozonolysis in the presence of excess of trifluoroacetic acid (TFA), the phosphorane moiety being protected against ozonolytic cleavage by reversible protonation.[22] Thus, ozonolysis of phosphorane **24** in ethyl acetate–TFA (3:1) at −78 °C, followed by neutralisation with sodium hydrogen carbonate, produced the aldehyde **25**, which spontaneously cyclised to the 6α-bromocarbapenem derivative **26** (64% yield). This, to our knowledge, is the first report of a 6-halogenocarbapenem derivative. Deprotection of the *p*-methoxybenzyl ester **26** was effected by reaction with aluminium trichloride and anisole[23] in dichloromethane to provide the sodium salt of the 6α-bromo-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid **27** in 69% yield.

The base-catalysed C-6 alkylation of the 6α-bromopenem ester **13** makes use of the ability of the bromine atom to increase the acidity of the adjacent proton and then to stabilise the resulting anion.[14,15] This was also the case for the 6α-bromocarbapenem **26** and the base-catalysed alkylation of the 6α-bromocarbapenem reported herein represents the first successful C-6 alkylation reaction on the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate ring system. All previous syntheses have relied upon the introduction of the desired substituent at the *pro*-C-6 position prior to construction of the bicyclic ring system, *i.e.* on the monocyclic azetidinone precursor, thereby minimising the number of chemical manipulations on the chemically labile carbapenem derivative.



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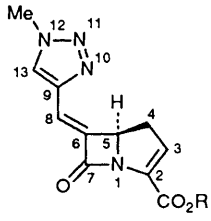
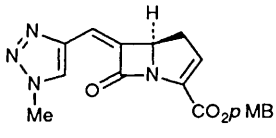


29 R = *p*MB
30 R = H



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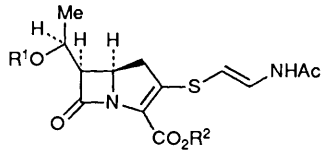
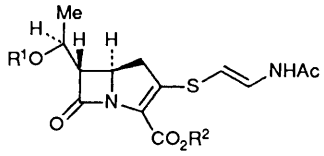
Accordingly, reaction of the 6α-bromocarbapenem *p*-methoxybenzyl ester **26** with either lithium diphenylamide[14] or lithium diisopropylamide (LDA) at −78 °C in tetrahydrofuran (THF) provided the C-6 anion, which was treated sequentially with 1-methyl-1*H*-1,2,3-triazole-4-carbaldehyde[24] and acetic anhydride to afford a 5:2:1 diastereoisomeric mixture of acylated bromohydrins **28** in 56% yield. Reductive elimination of the diastereoisomeric mixture **28**, using activated zinc and acetic acid in THF, provided the (*E*) and (*Z*) isomers of the triazolylmethylene carbapenem ester, compounds **29** and **31**, in 45 and 13% yield, respectively. The configurations of the geometrical isomers were assigned by ^{1}H NMR spectroscopy on the basis of the anisotropic deshielding effect of the β-lactam carbonyl on the 8-H vinyl proton and the 13-H triazole proton. The 8-H vinyl proton of the (*E*)-isomer **29** appears at δ 7.05, downfield from that of the (*Z*)-isomer **31** (δ 6.88), due to the deshielding effect on this proton. In the (*Z*)-isomer **31** it is the triazole proton that is deshielded by the β-lactam carbonyl and appears at δ 8.76, downfield from that of the (*E*)-isomer, which appears at δ 7.64.

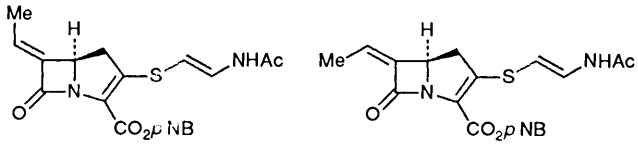
Aluminium trichloride-mediated deprotection of the ester **29** in anisole–dichloromethane afforded the sodium salt of (5*R*)-6-[(*E*)-(1-methyl-1*H*-1,2,3-triazol-4-yl)methylene]-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylic acid **30** in 68% yield, thereby completing the chiral synthesis of a novel carbapenem derivative from 6-aminopenicillanic acid, *via* a novel and versatile intermediate, the 6α-bromocarbapenem **26**.



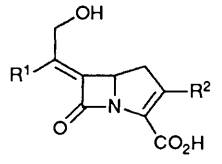
32 $R^1 = R^2 = H$, MM 22382
33 $R^1 = S(O)_2Me$, $R^2 = p$NB



34 $R^1 = R^2 = H$, MM 22383
35 $R^1 = S(O)_2Me$, $R^2 = p$NB

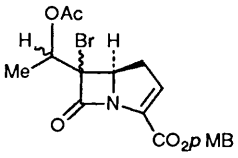


36 *p*NB = *p*-Nitrobenzyl **37**



38 R^1 = Me, R^2 = H, SR, CH_2R
39 R^1 = H, R^2 = H, SR, CH_2R

Indeed, the versatility of the 6α-bromocarbapenem **26** was demonstrated by its reaction with aliphatic aldehydes. The syntheses of C-6 ethylidene carbapenem derivatives in optically active form were first reported by Beecham scientists.[25] Stereospecific base-catalysed elimination of the mesyl ester **33** derived from MM 22382 **32** provided the (*E*)-isomer **36** of the ethylidene carbapenem, whilst base-catalysed elimination of the mesyl ester **35** derived from MM 22383 **34** gave the (*Z*)-isomer **37**. Subsequently, the syntheses of racemic alkylidene carbapenem analogues **38** of the asparenomycins have been reported by Shionogi scientists,[26] commencing from 4-allylazetidin-2-one. Alkylidene carbapenem derivatives could also be prepared from the 6α-bromocarbapenem **26**, sequential treatment of which with LDA, acetaldehyde, and acetic anhydride, at −78 °C in THF, provided a diastereoisomeric mixture of acylated bromohydrins **40**. Reductive elimination then gave a separable mixture of (*E*)-and (*Z*)-ethylidene carbapenem esters. In this instance the major product was the (*Z*)-isomer **42**, which was isolated in 14% overall yield. The (*E*)-isomer **41** was obtained in 9% yield. Again the structural assignments of the reaction



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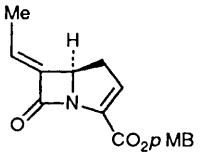

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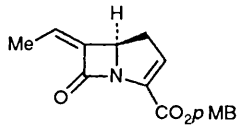

42

products were based upon a comparison of the ^{1}H NMR chemical shifts of the 8-H vinylic proton and the vinylic methyl protons.

Disappointingly, neither the bromocarbapenem **27** nor the triazolylmethylene carbapenem **30** possessed any β-lactamase-inhibitory activity. Whilst bromocarbapenem **27** was also devoid of antibacterial activity, the heterocyclylmethylene carbapenem **30** displayed low levels of activity against *Escherichia coli* (64–128 μg cm^{-3}), *Klebsiella pneumoniae* E70 (128 μg cm^{-3}), *Proteus mirabilis* C889 (128 μg cm^{-3}), *Staphylococcus aureus* Oxford (4 μg cm^{-3}) and *Staphylococcus aureus* Russell (4 μg cm^{-3}).*

This, together with the report that the demethyl asparenomycin derivatives **39** displayed only low levels of antibacterial activity,[26] would imply that other factors are involved in the inhibition of transpeptidases and β-lactamases by the alkylidene carbapenems.

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 457 machine. ^{1}H NMR spectra were recorded at 90 MHz on a Perkin-Elmer R32 and at 250 MHz on a Bruker WM 250 instrument with tetramethylsilane as internal standard for spectra in $CDCl_3$ and $DCON(CD_3)_2$ ([$^2H_7$]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-focusing spectrometer, a VG TRIO-2 quadrupole spectrometer or a Finnigan MAT TSQ70 spectrometer. 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 (1:1 mixture of finer than 230 mesh and 230–400 mesh ASTM) by using the slightly increased pressure provided by a Medcalf Hy-flo pump. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Sodium salts were purified by column chromatography over Diaion HP-20SS resin, and elution with ethanol–water mixtures and monitoring of the column fractions by UV spectroscopy. THF was dried over sodium hydride and distilled immediately before use. Numbering of bicyclic compounds is based on the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene ring system according to IUPAC nomenclature.

(3R,4RS)-*Methyl* 2-(4′-*Acetoxy*-3′-*bromo*-2′-*oxoazetidin*-1′-*yl*)-3-*methylbut*-2-*enoate* **17**.—A solution of acetic anhydride (30 cm^3) and 1,2-dichloroethane (30 cm^3) was cooled to ice-bath temperature under nitrogen and treated with conc. sulphuric acid (0.3 cm^3). Fuming nitric acid (4.8 cm^3) was then added dropwise to the cooled, stirred solution during 1 h and the mixture was stirred at ice-bath temperature for 2.5 h. A solution of methyl 6α-bromopenicillanate **15**[16] (17.83 g, 60.6 mmol) in 1,2-dichloroethane (30 cm^3) was added and the mixture was stirred at ice-bath temperature for a further 3 h before being poured into ice–water (150 cm^3) and stirred for 16 h at room temperature. The organic phase was separated, washed successively with water and saturated brine, and cooled to ice-bath temperature. Triethylamine (30 cm^3) was added to the cooled solution during 2 h and the mixture was stirred for an additional 2 h. The solution was then washed successively with 1 mol dm^{-3} HCl, water and brine, dried ($MgSO_4$), and evaporated at reduced pressure. The crude product was chromatographed over silica gel. Elution with a gradient of 30–50% ethyl acetate–hexane provided the title compound **17** as a diastereoisomeric mixture (7.6 g, 39%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 1790, 1758, 1722 and 1635; $\delta_H(CDCl_3)$ 1.98 and 2.03 (3 H, 2 × s, C=CMe), 2.10 and 2.16 (3 H, 2 × s, C=CMe), 2.26 (3 H, s, OAc), 3.80 (3 H, s, CO_2Me), 4.80 (0.6 H, br s, *trans*-CH), 5.21 (0.4 H, d, *J* 3.5, *cis*-CH), 6.23 (0.6 H, br s, *trans*-CH) and 6.35 (0.4 H, d, *J* 3.5, *cis*-CH).

(3R,4RS)-4-*Acetoxy*-3-*bromoazetidin*-2-*one* **19**.—The diastereoisomeric mixture of acetates **17** (6.18 g, 19.3 mmol) was dissolved in ethyl acetate (150 cm^3) and the solution was cooled to −78 °C. A stream of ozonolysed oxygen was passed through the cooled solution until the solution was saturated (blue colour). The excess of ozone was then blown off with argon and the solution, after having warmed to room temperature, was evaporated at reduced pressure to yield the diastereoisomeric oxalimides **18** as an oil; $\nu_{max}(CHCl_3)$/cm^{-1} 1838, 1760 and 1723.

The above oil was dissolved in methanol (100 cm^3) and treated with 2,6-lutidine (8 drops). The resulting solution was stirred at room temperature for 1 h, then was evaporated at reduced pressure, and the residual oil was chromatographed over silica gel. Elution with a gradient of 50–75% ethyl acetate–hexane gave a diastereoisomeric mixture of (3*R*,4*RS*)-4-acetoxy-3-bromoazetidin-2-one **19** as an oil (3.45 g, 86%); $\nu_{max}(CHCl_3)$/cm^{-1} 3410, 1800 and 1748; $\delta_H(CDCl_3)$ 2.18 (3 H, s, OAc), 4.78–4.83 (0.7 H, m, *trans*-4-CH), 5.21 (0.3 H, t, *J* 3.5, *cis*-4-CH), 5.89 (0.7 H, s, *trans*-3-CH), 6.10 (0.3 H, d, *J* 3.5, *cis*-3-CH) and 7.4–7.8 (1 H, br, NH). The diastereoisomers could be separated by repeated column chromatography over silica gel. They were, however, processed as a mixture.

(3R,4R)-4-*Allyl*-3-*bromoazetidin*-2-*one* **21**.—The diastereoisomeric mixture of 4-acetoxy-3-bromoazetidin-2-ones **19** (1.85 g, 8.85 mmol) was dissolved in dichloromethane (50 cm^3) and the solution was cooled to 5 °C. Allyltrimethylsilane (1.51 g, 13.28 mmol), followed by boron trifluoride–diethyl ether (1.51 g, 10.63 mmol), were added to the solution, which was then stirred at room temperature for 2 h before being diluted with dichloromethane (100 cm^3) and washed successively with water and brine, dried ($MgSO_4$), and evaporated at reduced pressure. The crude product was purified by column chromatography over silica gel. Elution with a gradient of 10–50% ethyl acetate–hexane furnished a single isomer of (3*R*,4*R*)-4-allyl-3-bromoazetidin-2-one **21** as an oil (1.19 g, 71%); $\nu_{max}(CHCl_3)$/cm^{-1} 3400 and 1700; $[\alpha]_D^{20}$ +39.6° (*c* 1.0, MeOH) {lit.,[19] $[\alpha]_D^{25}$ +38.6° (*c* 0.78, MeOH)}; $\delta_H(CDCl_3)$ 2.32–2.60 (2 H, m,

* Figures quoted are minimum inhibitory concentrations (MICs). The compounds were serially diluted in Tryptone Soya Broth using microtitre equipment. All microtitre trays were inoculated with a multipoint inoculator which delivered 0.001 cm^3 of a 1/10 dilution of an overnight broth culture of the test organism, an inoculum equivalent to 10^6 cfu cm^{-3}. The MIC was determined after incubation at 37 °C for 18 h as the lowest concentration of antibiotic preventing visible growth.

CH_2CH), 3.86 (1 H, dt, *J* 1.7 and 6.7, 4-H), 4.43 (1 H, t, *J* 2.1, 3-H), 5.14–5.21 (1 H, m, C=CH), 5.23 (1 H, d, *J* 1, C=CH), 5.7–5.88 (1 H, m, C=CH) and 6.4–6.55 (1 H, br, NH).

p-*Methoxybenzyl Glyoxylate Monohydrate*.—(*a*) Phosphorus tribromide (42 cm^3, 0.44 mol) was added dropwise to a stirred solution of *p*-methoxybenzyl alcohol (138 g, 1.0 mol) in dry diethyl ether (1.5 dm^3). During the addition the solution began to reflux gently. After the addition was complete, the reaction solution was heated to reflux for an additional 1 h. After cooling, the solution was washed successively with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to small volume. The resulting solution of *p*-methoxybenzyl bromide was added to a stirred solution of (±)-tartaric acid (75.0 g, 0.5 mol) and triethylamine (140 cm^3, 1.0 mol) in DMF (1.0 dm^3) at 5 °C. The resulting solution was stirred at room temperature for 16 h and then was evaporated to small volume, diluted with ethyl acetate, washed successively with water (× 2), aq. sodium hydrogen carbonate, and brine. The dried ($MgSO_4$) solution was evaporated to small volume at reduced pressure and the residue was triturated with hexane to yield bis-(*p*-methoxybenzyl) tartrate as a solid (87.9 g, 45%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3530, 1745 and 1615; $\delta_H(CDCl_3)$ 3.15–3.45 (2 H, br, 2 × OH), 3.75 (6 H, s, 2 × OMe), 4.52 (2 H, s, 2 × CH), 5.14 (4 H, s, 2 × CH_2Ar), 6.84 (4 H, d, *J* 9, ArH) and 7.25 (4 H, d, *J* 9, ArH).

(*b*) Lead tetraacetate (29.23 g, 66.0 mmol; pre-washed with hexane and dried *in vacuo*) was suspended in dry benzene (230 cm^3). Bis-(*p*-methoxybenzyl) tartrate (23.4 g, 60.0 mmol) was added and the resulting, stirred suspension was heated to reflux for 1.5 h, cooled, and filtered through Celite. The filtrate was evaporated to small volume and applied to a column of silica gel. Elution with 50% ethyl acetate–hexane provided *p*-methoxybenzyl glyoxylate hydrate as a semi-solid (22.09 g, 95%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3510, 1748, 1612 and 1515; $\delta_H(CDCl_3)$ 3.74 (3 H, s, OMe), 3.85–4.20 (2 H, br, 2 × OH), 5.11 (2 H, ABq), CH_2Ar), 5.33 (1 H, br s, CH), 6.83 (2 H, d, *J* 9, ArH) and 7.24 (2 H, d, *J* 9, ArH).

(3′R,4′R)-p-*Methoxybenzyl* (4′-*Allyl*-3′-*bromo*-2′-*oxoazetidin*-1′-*yl*)(*triphenylphosphoranylidene*)*acetate* **24**.—A solution of *p*-methoxybenzyl glyoxylate monohydrate (2.12 g, 10 mmol) in benzene (150 cm^3) was heated to reflux with the provision for the removal of water (Dean and Stark apparatus) for 1 h. After the mixture had cooled to room temperature, a solution of (3*R*,4*R*)-4-allyl-3-bromoazetidin-2-one **21** (1.88 g, 9.89 mmol) in benzene (20 cm^3) containing triethylamine (0.14 cm^3) was added and the mixture was stirred for 16 h before being evaporated at reduced pressure to yield the diastereoisomeric mixture of hydroxyacetates **22** as an oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3500, 1780, 1745, 1610 and 1510.

The hemiaminal **22** was dissolved in dry THF (75 cm^3) and the solution was cooled to −20 °C, under argon. To the stirred solution were added 2,6-lutidine (1.73 cm^3) and thionyl chloride (1.09 cm^3) and the mixture was stirred at −20 °C for 15 min. The resulting suspension was filtered and the filtrate was evaporated at reduced pressure to yield the diastereomeric chloroacetates **23** as a foam; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1790, 1755, 1615 and 1515.

The mixture of chloroacetates **23** was dissolved in 1,4-dioxane (100 cm^3) and the solution was stirred with triphenylphosphine (10.36 g) until homogeneous. The solution was then evaporated to low volume (~ 20 cm^3) and heated to 50 °C under argon for 2.5 h with 2,6-lutidine (1.39 cm^3). The solution was then diluted with ethyl acetate and washed successively with water, 5% aq. citric acid, and brine, and dried ($MgSO_4$). After evaporation at reduced pressure, the crude phosphorane was chromatographed over silica gel. Elution with a gradient of 10–50% ethyl acetate–hexane gave the pure *phosphorane* **24** as a foam (3.78 g, 61%) (Found: M^+, 627.1185. $C_{34}H_{31}BrNO_4P$ requires M, 627.1174); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1760, 1640sh, 1618 and 1510.

(5R,6R)-p-*Methoxybenzyl* 6-*Bromo*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **26**.—The phosphorane **24** (1.56 g) was dissolved in ethyl acetate (30 cm^3) and the solution was cooled to 0 °C. TFA (10 cm^3) was added to the stirred solution. After 15 min at 0 °C the solution was cooled to −78 °C and a stream of ozonolysed oxygen was passed through the solution until a blue colour appeared (*ca.* 6 min). The excess of ozone was immediately blown off with argon and a solution of triphenylphosphine (0.651 g) in ethyl acetate (5 cm^3) was added. The solution was allowed to reach room temperature and was then carefully neutralised with aq. sodium hyrogen carbonate. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was chromatographed over silica gel (40 g). Elution with a gradient of 10–30% ethyl acetate–hexane provided the pure (5R,6R)-p-*methoxybenzyl* 6-*bromo*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **26** as a crystalline solid (from diethyl ether) (0.563 g, 64%), m.p. 104–105 °C (Found: C, 51.2; H, 4.0; N, 4.0; Br, 22.75%; M^+, 351.0098. $C_{15}H_{14}BrNO_4$ requires C, 51.15; H, 4.0; N, 4.0; Br, 22.7%; M, 351.0106); λ_{max}(EtOH)/nm 280 (ε 5395), 274 (5340), 250 (6060) and 226 (14 920); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1799, 1725, 1612 and 1512; $\delta_H(CDCl_3)$ 2.84 (1 H, ddd, *J* 2.7, 8.3 and 19.7, 4-H^a), 3.05 (1 H, ddd, *J* 2.9, 10.3 and 19.7, 4-H^b), 3.82 (3 H, s, OMe), 4.41 (1 H, ddd, *J* 2.8, 8.3 and 10.7, 5-H), 4.73 (1 H, d, *J* 2.7, 6-H), 5.20 (1 H, d, *J* 12, C*H*^{a}Ar), 5.25 (1 H, d, *J* 12, C*H*^{b}Ar), 6.48 (1 H, t, *J* 2.8, 3-H), 6.90 (2 H, d, *J* 8.7, ArH) and 7.38 (2 H, d, *J* 8.7, ArH).

Sodium Salt of (5R,6R)-6-*Bromo*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylic Acid* **27**.—Anhydrous aluminium trichloride (0.067 g, 0.5 mmol) was dissolved in a dry mixture of anisole (0.8 cm^3) and dichloromethane (1 cm^3) and the solution was cooled to −40 °C under argon. To the stirred solution was added a solution of the 6α-bromocarbapenem ester **26** (0.070 g, 0.20 mmol) in dichloromethane (3 cm^3) and the mixture was stirred at −40 °C for 20 min. A 0.5 mol dm^{-3} solution of disodium hydrogen orthophosphate buffer (6.77 cm^3) was added to the rapidly stirred solution, which was then allowed to reach room temperature. The resulting suspension was filtered through Celite, washing well with water. The aq. layer was washed with dichloromethane, concentrated to low volume, and applied to a column of Diaion HP-20SS. The column was eluted with water and the column fractions were monitored by UV spectroscopy. Those fractions possessing the desired UV chromophore were combined and lyophilised to yield the sodium salt of (5R,6R)-6-bromo-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid **27** as a solid (0.035 g, 69%); $[\alpha]_D^{20}$ +93° (*c* 0.5, water); λ_{max}(water)/nm 275 (ε 1440) and 237 (2120); ν_{max}(KBr)/cm^{-1} 3414br, 1763, 1620, 1598 and 1408; $\delta_H(D_2O)$ 2.85 (1 H, ddd, *J* 2.6, 8.5 and 19.3, 4-H^a), 2.98 (1 H, ddd, *J* 2.9, 10.0 and 19.3, 4-H^b), 4.43 (1 H, ddd, *J* 2.4, 8.7 and 9.8, 5-H), 5.07 (1 H, d, *J* 2.5, 6-H) and 6.25 (1 H, dd, *J* 2.4 and 2.9, 3-H).

(5R)-p-*Methoxybenzyl* 6-[(E)-(1-*Methyl*-1H-1,2,3-*triazol*-4-*yl*)*methylene*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **29** *and* (5R)-p-*Methoxybenzyl* 6-[(-Z)-(1-*Methyl*-1H-1,2,3-*triazol*-4-*yl*)*methylene*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **31**.—Butyllithium (1.41 mol solution in hexane; 0.4 cm^3, 0.578 mmol) was added to a stirred solution of diphenylamine (105 mg, 0.620 mmol) in dry THF (5 cm^3) at −20 °C, under argon. The mixture was stirred at −20 °C for 5 min, then was cooled to −78 °C, and a solution of (5*R*,6*R*)-*p*-methoxybenzyl 6-bromo-7-oxo-1-azabicylo[3.2.0]hept-2-ene-2-carboxylate **26** (0.200 g, 0.568 mmol) in dry THF (4 cm^3) was

added. After 2 min at −78 °C the mixture was treated with a solution of 1-methyl-1*H*-1,2,3-triazole-4-carbaldehyde[23] (0.750 g, 0.675 mmol) in dry THF (4 cm^3), immediately followed by a solution of acetic anhydride (0.2 cm^3) in THF (1 cm^3). The reaction solution was allowed to reach room temperature and was stirred for an additional 10 min before being diluted with ethyl acetate (50 cm^3). The organic solution was washed successively with dil. aq. sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was chromatographed over silica gel (10 g), and eluted with a gradient of 10–75% ethyl acetate–hexane. The first eluted component was unchanged starting material **26** (0.071 g). Continued elution gave a diastereoisomeric mixture of acylated bromohydrins **28** (proportions 5:2:1) as a foam (0.160 g, 56%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1792, 1753, 1721, 1608 and 1510; $\delta_H(CDCl_3)$ *inter alia* 1.94 (s, minor isomer) and 2.18 (s, major isomer) (3 H, OAc), 2.95 (ddd, major isomer, *J* 2.9, 11.1 and 20.7) and 3.07 (ddd, minor isomer, *J* 2.8, 11.2 and 20.7) (1 H, 4-H[a]), 3.47 (ddd, major isomer, *J* 2.7, 8.5 and 20.7) and 3.80 (ddd, minor isomer, *J* 2.7, 8.5 and 20.7) (1 H, 4-H[b]), 3.82 (3 H, s, OMe), 4.10 (3 H, s, triazole Me), 4.64 (dd, major isomer, *J* 8.5 and 11.0) and 4.90 (dd, minor isomer, *J* 8.7 and 11.1) (1 H, 5-H), 5.15–5.30 (2 H, m, CH_2Ar), 6.28 (s, minor isomer) and 6.58 (s, major isomer) (1 H, 8-H), 6.45 (0.12 H, t, *J* 2.8) and 6.52 (0.62 H, t, *J* 2.8) and 6.60 (0.23 H, t, *J* 2.8) (3-H), 6.90 (2 H, d, *J* 8.7, ArH), 7.3–7.42 (2 H, m, ArH) and 7.68 (s, major isomer) and 7.72 (s, minor isomer) (1 H, triazole CH).

The isomeric mixture of acylated bromohydrins **28** (0.150 g) was dissolved in THF (10 cm^3) and the solution was stirred at room temperature for 30 min with glacial acetic acid (0.2 cm^3) and activated zinc powder (250 mg). The reaction solution was then diluted with ethyl acetate (50 cm^3) and filtered through Celite. The filtrate was washed successively with aq. sodium hydrogen carbonate, water, and brine, dried ($MgSO_4$), and evaporated at reduced pressure. The reaction product was chromatographed over silica gel (5 g) and eluted with 75% ethyl acetate–hexane. The first eluted component was the (Z)-*isomer* of (5R)-p-*methoxybenzyl* 6-[(1-*methyl*-1H-1,2,3-*triazol*-4-*yl*)-*methylene*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **31**, obtained as a foam (0.014 g, 13%) (Found: M^+, 366.1327. $C_{19}H_{18}N_4O_4$ requires M, 366.1326); λ_{max}(10% MeCN in EtOH)/nm 280 (14 260) and 225 (16 980); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1758, 1720, 1610 and 1515; $\delta_H(CDCl_3)$ 2.89 (1 H, ddd, *J* 2.7, 7.9, and 19.3, 4-H[a]), 2.99 (1 H, ddd, *J* 2.9, 9.8 and 19.1, 4-H[b]), 3.82 (3 H, s, OMe), 4.13 (3 H, s, NMe), 4.94 (1 H, br t, 5-H), 5.23 (2 H, s, CH_2Ar), 6.50 (1 H, t, *J* 2.8, 3-H), 6.88 (1 H, d, *J* 0.9, 8-H), 6.90 (2 H, d, *J* 8.7, ArH), 7.37 (2 H, d, *J* 8.6, ArH) and 8.76 (1 H, s, triazole CH).

Continued elution afforded the (E)-*isomer* of (5R)-p-*methoxybenzyl* 6-[(1-*methyl*-1H-1,2,3-*triazol*-4-*yl*)*methylene*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **29** as a crystalline solid (from ethyl acetate–diethyl ether) (0.049 g, 45%); m.p. 115–117 °C (Found: C, 61.9; H, 4.8; N, 15.05%; M^+, 366.1327. $C_{19}H_{18}N_4O_4$ requires C, 62.3; H, 4.95; N, 15.3%; M, 366.1326); $[\alpha]_D^{20}$ +253° (*c* 1.0, CH_2Cl_2); λ_{max}(10% MeCN in EtOH)/nm 272.5 (15 390) and 225 (11 925); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1768, 1721, 1692sh, 1612 and 1512; $\delta_H(CDCl_3)$ 2.91 (1 H, ddd, *J* 2.7, 7.9 and 19.8, 4-H[a]), 3.13 (1 H, ddd, *J* 3.0, 10.7 and 19.8, 4-H[b]), 3.81 (3 H, s, OMe), 4.15 (3 H, s, NMe), 5.15–5.32 (3 H, m, CH_2Ar + 5-H), 6.48 (1 H, t, *J* 2.8, 3-H), 6.89 (2 H, d, *J* 8.7, ArH), 7.04 (1 H, d, *J* 1.7, 8-H), 7.38 (2 H, d, *J* 8.7, ArH) and 7.67 (1 H, s, triazole CH).

Sodium Salt of (5R)-6-[(E)-(1-*Methyl*-1H-1,2,3-*triazol*-4-*yl*)*methylene*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylic Acid* **30**. Aluminium trichloride (0.447 g) was dissolved in a dry mixture of anisole (0.8 cm^3) and dichloromethane (1 cm^3) and the solution was cooled to −40 °C under argon. A solution of (5*R*)-*p*-methoxybenzyl 6-[(*E*)-(1-methyl-1*H*-1,2,3-triazol-4-yl)methylene]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate **29** (0.049 g) in dichloromethane (2 cm^3) was added and the solution was stirred at −40 °C for 15 min. Aq. disodium hydrogen orthophosphate (4.6 cm^3, 0.5 mol dm^{-3}) was then added and the resulting suspension was allowed to warm up to room temperature before being filtered through Celite, and the filter was washed well with water and dichloromethane. The aq. layer was separated, washed with dichloromethane, concentration to small volume, and applied to a column of Diaion HP 20SS. The column was eluted with water and the column fractions were monitored by UV spectroscopy. Those fractions exhibiting the desired chromophore were combined and lyophilised to yield the sodium salt of (5*R*)-6-[(*E*)-(1-methyl-1*H*-1,2,3-triazol-4-yl)methylene]-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid **30** as a pale yellow, fluffy solid (0.025 g, 68%); $[\alpha]_D^{20}$ +224° (*c* 0.25, water); λ_{max}(water)/nm 278 (9530); ν_{max}(KBr)/cm^{-1} 3400br, 1744, 1684, 1620, 1594 and 1413; $\delta_H(D_2O)$ 2.75 (1 H, ddd, *J* 2.6, 7.9, and 18.9, 4-H[a]), 3.02 (1 H, ddd, *J* 3.0, 10.5 and 18.9, 4-H[b]), 4.12 (3 H, s, NMe), 5.05–5.15 (1 H, m, 5-H), 6.22 (1 H, t, *J* 2.7, 3-H), 7.18 (1 H, d, *J* 1.5, 8-H) and 8.11 (1 H, s, triazole CH).

(5R)-p-*Methoxybenzyl* 6-(E)-*Ethylidene*-7-*oxo*-1-*azabicyclo*-[3.2.0]*hept*-2-*ene*-2-*carboxylate* **41** *and* (5R)-p-*Methoxybenzyl* 6-(Z)-*Ethylidene*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **42**.—(5R,6*R*)-*p*-Methoxybenzyl 6-bromo-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate **26** (0.250 g, 0.71 mmol) was dissolved in dry THF (25 cm^3) and the solution was cooled to −78 °C under argon. A solution of LDA (2.0 mol dm^{-3} solution in heptane–THF–ethylbenzene; 0.39 cm^3, 0.78 mmol) was added and the solution was stirred at −78 °C for 1 min. A solution of acetaldehyde (0.038 g, 0.825 mmol) in dry THF (2 cm^3) was then added, immediately followed by acetic anhydride (0.2 cm^3). The reaction vessel was removed from the cooling bath and the reaction mixture was stirred at ambient temperature for 30 min, before dilution with ethyl acetate. The organic solution was washed successively with aq. sodium hydrogen carbonate, water and brine, and was then dried ($MgSO_4$). The solvent was evaporated off at reduced pressure and the crude reaction product was applied to a column of silica gel (10 g). Elution with a gradient of 10–40% ethyl acetate–hexane gave unchanged 6α-bromocarbapenem **26** (0.048 g). Continued elution provided a diastereoisomeric mixture of *acylated bromohydrins* **40** as a pale yellow oil (0.142 g) (Found: M^+, 437.0475. $C_{19}H_{20}BrNO_6$ requires M, 437.0474); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1795, 1742, 1715, 1612 and 1515; $\delta_H(CDCl_3)$ *inter alia* 1.36 (d, *J* 6.8, minor isomer), 1.43 (d, *J* 6.3, major isomer) and 1.50 (d, *J* 6.5, minor isomer) (all 3 H, Me), 2.06 (s, major isomer) and 2.12 (s, minor isomer) (all 3 H, COMe), 2.75–2.92 (2 H, m, 4-H_2), 3.81 (3 H, s, OMe), 4.59 (1 H, t, *J* 9.7, 5-H), 5.12–5.34 (3 H, m, CH_2Ar + 8-H), 6.46 (1 H, t, *J* 2.8, 3-H), 6.89 (2 H, d, *J* 8.6, ArH) and 7.36 (2 H, d, *J* 8.6, ArH).

The diastereoisomeric mixture of acylated bromohydrins **40** (0.130 g) was dissolved in THF (20 cm^3) and the solution was stirred at room temperature for 30 min with activated zinc powder (0.250 g) and glacial acetic acid (0.2 cm^3). The reaction solution was then diluted with ethyl acetate (50 cm^3) and filtered through Celite. The organic solution was washed successively with aq. sodium hydrogen carbonate, water, and brine, and was then dried ($MgSO_4$). The solvent was evaporated off at reduced pressure and the residue was applied to a column of silica gel (5 g). Elution with a gradient of 10–35% ethyl acetate–hexane furnished the (Z)-*isomer* of (5R)-p-*methoxybenzyl* 6-*ethylidene*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **42** as an oil (0.029 g, 14%) (Found: M^+, 299.1152. $C_{17}H_{17}NO_4$ requires M, 299.1158); λ_{max}(EtOH)/nm 305 and 263; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1768, 1721, 1611 and 1515; $\delta_H(CDCl_3)$ 2.07 (3 H, dd, *J* 1.0 and 7.3, *Me*CH), 2.78 (1 H, ddd, *J* 2.7, 7.9 and 19.1, 4-H[a]), 2.86

(1 H, ddd, *J* 2.8, 9.7 and 19.1, 4-H^b), 3.80 (3 H, s, OMe), 4.72 (1 H, br t, 5-H), 5.18 (d, *J* 12.1) and 5.24 (d, *J* 12.1) (2 H, CH_2Ar), 5.95 (1 H, dq, *J* 1.1 and 7.2, 8-H), 6.43 (1 H, t, *J* 2.8, 3-H), 6.89 (2 H, d, *J* 8.7, ArH) and 7.38 (2 H, d, *J* 8.7, ArH).

Continued elution provided the (E)-*isomer* of (5R)-p-*methoxybenzyl* 6-*ethylidene*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* **41** as an oil (0.019 g, 9%) (Found: M^+, 299.1152); λ_{max}(EtOH)/nm 298sh, 278sh and 263; ν_{max}(CH_2Cl_2)/cm^{-1} 1778, 1720, 1612 and 1515; δ_H($CDCl_3$) 1.82 (3 H, d, *J* 7.4, *Me*CH), 2.80 (1 H, ddd, *J* 2.8, 7.9 and 19.0, 4-H^a), 2.90 (1 H, ddd, *J* 2.9, 10.1 and 19.0, 4-H^b), 3.81 (3 H, s, OMe), 4.82 (1 H, br t, *J* 9, 5-H), 5.18 (d, *J* 12.1) and 5.27 (d, *J* 12.1) (2 H, CH_2Ar), 6.43 (dq, *J* 1.6 and 7.2, 8-H) and 6.45 (t, *J* 2.6, 3-H) (all 2 H), 6.90 (2 H, d, *J* 8.6, ArH) and 7.38 (2 H, d, *J* 8.6, ArH).

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