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FUNCTIONALIZATION OF THE 3β-METHYL GROUP OF PENICILLIN

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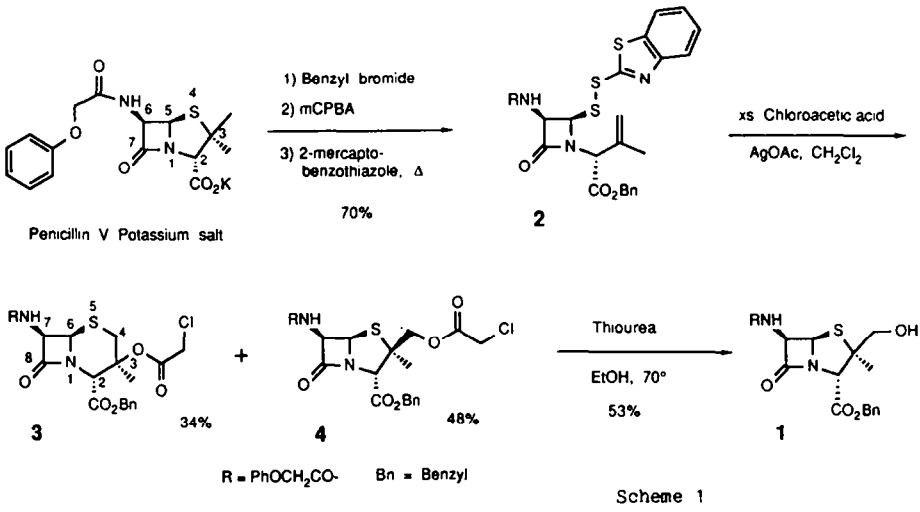
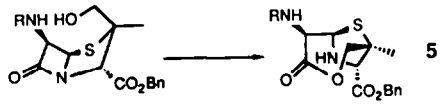
Abstract: A number of penicillins functionalized at the 3β-methyl position have been synthesised. The progenitor of these compounds is the 3β-hydroxymethyl penicillin 1.

We wish to report that the 3β-hydroxymethyl penicillin 1 is the progenitor of a number of 3β-functionalized penicillins. The synthesis of this compound which is strictly analogous to that reported earlier[1] is shown in Scheme 1. Compound 1 is a challenging synthetic intermediate as it



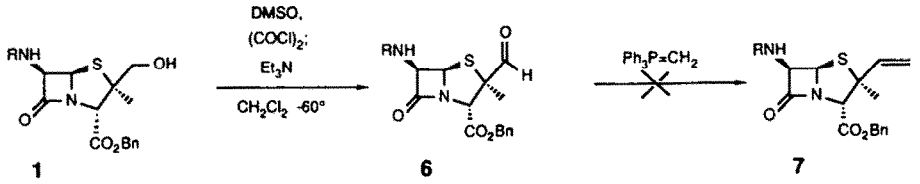
Scheme 1

requires little provocation[1a,2] to convert to the lactone 5. The ease of this transformation is no doubt due to the enforced proximity of the hydroxyl group to the β-lactam carbonyl. Fortunately 1 could be isolated as a stable crystalline solid.



In connection with our biosynthetic studies the 3β-vinyl penicillin 7 was sought. This material seemed to be accessible from the aldehyde 6. Attempted oxidation of 1 with the usual

coterie of chromium reagents (PCC, PDC, or $CrO_3 \cdot 2py$) produced extensive decomposition with no sign of formation of the desired aldehyde. Use of Fetizon's reagent[3] only served to induce lactonization. Fortunately, use of the Swern procedure[4] cleanly provided 6 in quantitative yield. Like the alcohol 1, this aldehyde could not be purified by silica gel chromatography. Analytically pure material, however, was obtained by crystallization.



1 6 7

Unfortunately, treatment of 6 with methylenetriphenylphosphorane under a variety of temperatures and solvents led only to substrate destruction. Use of $(CH_3)_3SiCH_2MgCl$[5] gave similarly unfavourable results. As both of these reactions proceed through an alkoxide intermediate it may be that lactonization (as seen with 1) is favoured over olefin formation. On the other hand the hindered, neopentyl aldehyde moiety may not be the primary locus of reagent attack in this highly functionalized molecule.

The aldehyde 6 did, however, react efficiently with stabilized ylides.[6] A number of these reactions are shown in Table 1. The lessened reactivity of these reagents with respect to methylenetriphenylphosphorane may account for their more favourable results.

Reduction of 3 With Stabilized Ylides

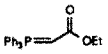
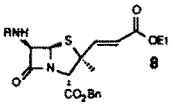
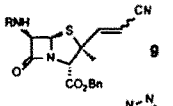
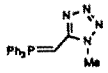
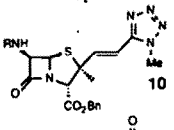
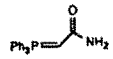
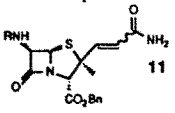
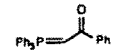
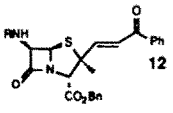
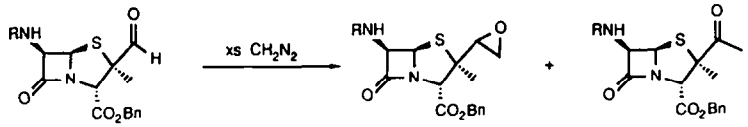
Ylide	Conditions	Product	Yield	E:Z
	Benzene, 60°	 **8**	95%	>95:5
	Benzene, 60°	 **9**	79%	9:1
	CH_2Cl_2, 25°	 **10**	82%	>95:5
	Benzene, 60°	 **11**	51%	6:1
	Benzene, 80°	 **12**	81%	>95:5

Table 1

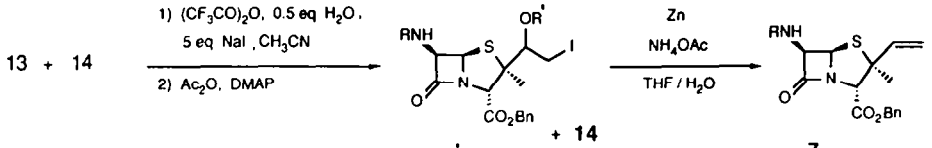
The success of the stabilized ylides spurred us to investigate the reaction of 6 with the dipolar reagent - diazomethane. In short, treatment of 6 with an excess of diazomethane gave a 92% yield of an inseparable mixture (1.5:1) of epoxide 13 and methyl ketone 14.[7] Treatment of this mixture with Zn in HOAc followed by chromatography allowed for the isolation of 13 as a single[8]



6 13 14

epimer of unknown stereochemistry. It is more efficient, however, to use the mixture in subsequent transformations. The epoxide 13 was not formed when 6 was treated with dimethyloxosulfonium methylide.[9] This reagent, instead, produces an intractable mixture.

Although there exists a number of methods[10] for the deoxygenation of epoxides only the following sequence was found to be efficacious for the conversion of 13 to the vinyl penicillin 7. Submission of epoxide 13 to conditions (trifluoroacetic anhydride, NaI, CH_3CN) which are reported[11] to convert epoxides to olefins via a β-iodo trifluoroacetate gave, instead, the iodohydrin 15. Traces of H_2O in the reaction solution promoted iodohydrin formation; in fact this reaction works best when a half equivalent of H_2O is added! The trifluoracetate is only seen when the reaction is run under rigorously anhydrous conditions. It, however, is an undesirable product due to its lability on silica gel. Only one regioisomer was noted for the epoxide opening. Presumably the regioselectivity was sterically controlled.

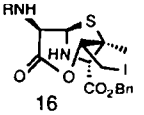


15 R' = H

17 R' = Ac

7

Replacement of trifluoroacetic anhydride with trifluoroacetic acid also produced 15 but at the expense of partial lactonisation to 16. The labile iodohydrin 15 is immediately acetylated to give 17. The epoxide 13 is not converted to 17 with Ac_2O/NaI.



16

The vinyl penicillin 7 was produced from 17 by reductive elimination with zinc metal. The overall conversion of aldehyde to olefin is 45%.

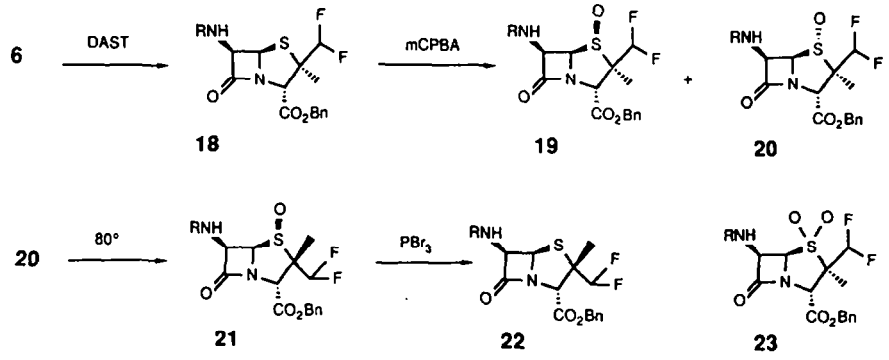
Fluorinated Derivatives

As substitution of hydrogen by fluorine in a molecule can lead to profound changes in its pharmacological action[12] it seemed interesting to synthesize and bioassay some fluorinated penicillins. The aldehyde 6 provided ready access to both 3β- and 3α-difluoromethyl penicillins.

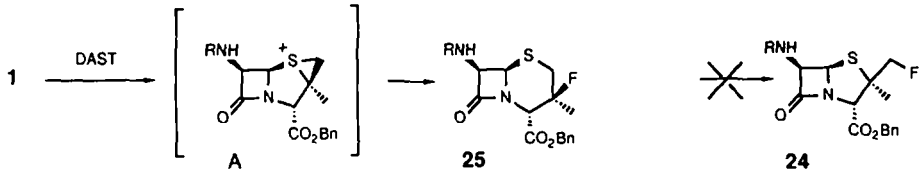
Thus, reaction of 6 with (diethylamino)sulfur trifluoride (DAST)[13] provided the 3β-difluoromethyl penicillin 18 in 90% yield. The presence of the difluoromethyl group was quite evident in the PMR spectrum as a triplet at δ 5.63 with a coupling constant of 56 Hz. Oxidation of 10 with 1.1 equivalents of mCPBA produced the β- and α-sulfoxides 19 and 20 in 45% and 25% yields respectively. The stereochemical assignments were based on their PMR and IR spectra.[14] The formation of the α-sulfoxide was somewhat surprising as the β-sulfoxide is usually the sole product[15] in mCPBA oxidation of penicillins containing a secondary amido group at C6. The amido group serves to steer the stereochemical course of the reaction by hydrogen bonding with the peracid. The appearance of the α-sulfoxide in the present case may be the result of an unfavourable dipole-dipole repulsion of the difluoromethyl dipole with the dipole of the developing sulfur-oxygen bond in the transition state leading to the β-sulfoxide. Any such repulsion would be less important during formation of the α-sulfoxide.

The α-sulfoxide 20 was thermally isomerized[15] to the 4β-oxo-3-α-difluoromethyl penicillin 21 in a 52% yield. Reduction with PBr_3,[16] gave the 3α-difluoromethyl penicillin 22.

Finally, oxidation of 18 with an excess of mCPBA provided the sulfone 23.



An attempt to produce the fluoromethyl penicillin 24 by treating 1 with DAST provided only the isomeric 3β-fluoro cepham 25 in 63% yield. This compound probably arises via the episulfonium ion A.



Assays for Antibiotic Activity

A number of the compounds reported here were hydrogenolyzed [10% Pd/C, $NaHCO_3$ (1 eq), H_2O/THF] and the resulting sodium carboxylates were assayed for antibiotic activity.

It is noteworthy that the vinyl moiety of 7 survived benzyl ester hydrogenolysis. It may be that the olefin, being situated on the concave face of the molecule, was inaccessible to the catalyst.

The antibiotic activities of these compounds are shown in Tables 2 and 3. Suffice to say that while all of these compound are biologically active their activity is less than or comparable to that of the parent compound - penicillin V.

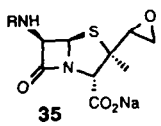
Agar Dilution Assay[17a,b]

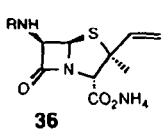
Results Given in Minimum Inhibitory Concentration (μg ml^{-1})

Compound	Test Organism: Bacillus subtilis (Gram-positive)	Escherichia coli 605 (Gram-negative)
Penicillin V K^+ Salt	≤ 0.001	>100
Hydrogenolysis product of:		
8 (26)	≤ 0.049	>100
9 (27)	≥ 0.098	>100
10 (28)	≤ 0.049	>100
11 (29)	0.049	>100
18 (30)	0.049	>100
19 (31)	1.562	>100
22 (32)	≤ 0.098	> 50
23 (33)	>100	>100
25 (34)	0.098	>100

Table 2

Well Diffusion Assay [18]





Organism	Penicillin	Mean Zone of Inhibition Diameters (mm)					
		Concentration of Pencillin in μg ml^{-1}					
		1	5	10	20	50	100
S.aureus	Pen V	*	34	35	36	38	39
	35	*	23	28	31	30	31
E.coli	Pen V	*	23	27	31	35	38
	35	*	-	-	-	trace	12
S.aureus$^{\Delta}$	Pen V	22.5	27.0	29.0	30.5	*	*
	36	*	28.0	30.0	31.5	32.5	*
E.coli$^{\Delta}$	Pen V	13.0	24.5	32.0	38.0	44.0	*
	36	12.0	21.0	27.0	35.0	43.0	*

Table 3

$^{\Delta}$ These runs were not done with the same culture batches as the above runs.

* Not done.

Acknowledgements

We thank the National Institutes of Health for a fellowship (J.E.C.) and the S.E.R.C. for a CASE studentship (L.N.S.) with Pfizer (Sandwich). Also we wish to thank Dr. S. Ray for helpful advice and for the biological testing.

EXPERIMENTAL

Reactions were run under a dry argon atmosphere at room temperature unless stated otherwise. Reactions were monitored by TLC using Merck Kiesegel 60 F_{254} aluminum backed plates (0.2 mm layer thickness). TLC plates were visualized using a UV lamp, iodine or charring with 10% ammonium molybdate in 1.0 N H_2SO_4. Reaction mixtures were evaporated at 25° on a Büchi rotovapor R110 followed by further evaporation at ≤ 1 mm Hg. Aqueous solutions were freeze dried. Melting points (m.p.) were determined on a Kofler hot stage and are uncorrected. Flash chromatography was carried out as described by Still.[19] Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 681 spectrophotometer, only weak (w), medium (m) or strong (s) bands were reported. ^{1}H NMR spectra were recorded on a Bruker WH300 MHz or AM250 NMR spectrometer. ^{1}H NMR spectra taken in $CDCl_3$ were referenced to residual $CHCl_3$ at δ 7.27; those taken in D_2O were referenced to DOH at δ 4.63. ^{19}F NMR spectra were taken at 84.6 MHz on a Perkin-Elmer R32 spectrometer and were referenced to external trifluoroacetic acid at 60.0. Multiplicities were reported as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Mass spectra were recorded on a V.G. Analytical Ltd. ZAB 1F spectrometer [for field desorption (FD), field ionization (F.I.), in beam electron impact (I.B.E.I.) or desorption chemical ionization (D.C.I.)] or a ZAB 16F spectrometer [for chemical ionization (C.I.)]. Microanalyses were recorded by the Microanalytical Laboratory, Dyson Perrins Laboratory, University of Oxford. All starting material reagents and solvents were purified[20] and dried before use.

Preparation of benzyl (2S,3R,5R,6R)-3-chloroacetoxy-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (4) and benzyl (2S,3S,6R,7R)-3-chloroacetoxy-3-methyl-8-oxo-7-phenoxyacetamido-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylate (3) (1a)

To a solution of silver acetate (1.67 g, 10 mmol) and chloroacetic acid (20 g, 212 mmol) in 75 ml CH_2Cl_2 was added 3.025 g (5 mmol) of the disulfide 2.[21] The resulting suspension was stirred for 4 hours and then filtered through a pad of silica gel (CH_2Cl_2 wash). The filtrate was neutralized with 5% $NaHCO_3$, washed with brine, dried over Na_2SO_4 and concentrated to 2.94 g of a yellow foam. Flash chromatography [EtOAc : petrol (1:3)] afforded the penam (1.273 g, 48%) and the cepham (913 mg, 34%) as white foams.

Data for 4 : TLC [EtOAc : petrol (1:2)] R_f 0.43; ν_{max} ($CHCl_3$) 3420 m, 1794 s (β-lactam C=O), 1750 s (ester C=O), 1697 s (amide C=O), 1601 m, 1593 m, 1521 s, 1496 s, 1443 m, 1306 m, 1080 m, 697 m and 690 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.42 (3H, s, $-CH_3$), 4.02 and 4.08 (2H, ABq, J 15 Hz, $-CH_2Cl$), 3.94 and 4.40 (2H, ABq, J 12 Hz, $-CH_2OCO-$), 4.55 and 4.59 (2H, ABq, J 15 Hz, $PhOCH_2-$), 4.74 (1H, s, 2-H), 5.22 (2H, s, $PhCH_2-$), 5.66 (1H, d, J 4 Hz, 5-H), 5.75 (1H, dd, J 4, 9 Hz, 6-H), and 6.92-7.40 (11H, m,); m/e (D.C.I. - NH_3) 550 (M + NH_4^+, 46%), 413 (49%), 342 (100%), 238 (53%), and 192 (50%).

Data for 3 : TLC [EtOAc : petrol (1:2)] R_f 0.36; ν_{max} ($CHCl_3$) 3420 m, 1784 s (β-lactam C=O), 1748 s (ester C=O), 1698 s (amide C=O), 1601 m, 1593 m, 1521 s, 1498 s, 1443 m, 1156 m, 1071 m, 695 m, and 690 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.52 (3H, s, $-CH_3$), 3.38 and 3.46 (2H, ABq, J 15 Hz, $4-CH_2$), 3.94 and 4.00 (2H, ABq, J 15 Hz, $-CH_2Cl$), 4.55 (2H, s, $PhOCH_2-$), 4.82 (1H, s, 2-H), 5.18 and 5.23 (2H, ABq, J 12 Hz, $PhCH_2-$), 5.33 (1H, d, J 4 Hz, 6-H), 5.67 (1H, dd, J 4, 10 Hz, 7-H) and 6.90-7.46 (11H, m,); m/e (D.C.I. - NH_3) 550 (M + NH_4^+, 100%).

Preparation of benzyl(2S,3R,5R,6R)-3-hydroxymethyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1)

A solution of the chloroacetate 4 (2.578 g, 4.84 mmol) and thiourea (1.84 g, 24.2 mmol) in 110 ml ethanol was warmed to 70° and stirred for 10 minutes. The temperature was reduced to 50° and the solution was stirred for 20 minutes. The solution was concentrated to dryness and the residue

was suspended in 75 ml CH_2Cl_2 and washed with 2 x 50 ml H_2O. The CH_2Cl_2 solution was then dried over Na_2SO_4 and concentrated to a yellow foam (2.468 g). Methanol (10 ml) was added to this material and the alcohol (1.18 g, 53%) precipitated as a white amorphous solid. Crystalline needles of 3 could be obtained by recrystallisation from iso-propanol; m.p. 158-161°; $[\alpha]_D^{\beta}$ +111° (c 0.45, $CHCl_3$); ν_{max} ($CHCl_3$) 3700 m, 3630 m, 3380 m, 1789 s (β-lactam C=O), 1750 s, (ester C=O), 1687 s (amide C=O), 1603 m, 1593 m, 1525 s, 1496 s, 1050 s and 931 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.32 (3H, s, $-CH_3$), 2.50 (1H, t, J 5 Hz, -OH), 3.44 (1H, dd, J 5, 11 Hz, $-CH_2OH$), 3.67 (1H, dd, J 5, 11 Hz, $-CH_2OH$), 4.54 (2H, s, $PhOCH_2-$), 4.73 (1H, s, 2-H), 5.20 (2H, s, $PhCH_2-$), 5.61-5.66 (2H, m, 5-H and 6-H), 6.90-7.38 (10H, m,), and 7.89 (1H, d, J 12 Hz, -NH-); m/e (I.B.E.I.) 456 (M^+); Found: C, 60.29%; H, 5.28%; N, 6.42%; S, 6.78%: $C_{23}H_{24}N_2O_6S$ requires C, 60.52%; H, 5.26%; N, 6.14%; S, 7.02%.

Preparation of benzyl (2S,3R,5R,6R)-3-formyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (6)

To a solution of 40 µl (0.46 mmol) of oxalyl chloride in 15 ml of CH_2Cl_2 stirring at -60° was added 34.7 µl (0.49 mmol) of DMSO. Ten minutes later a solution of 139.6 mg (0.31 mmol) of 1 in 4.5 ml of CH_2Cl_2 was added dropwise. One hour later triethylamine (149 µl, 1.07 mmol) was added. This solution was warmed to room temperature five minutes later and then poured into 50 ml of 0.2 M HCl. The aqueous layer was extracted with 2 x 50 ml of CH_2Cl_2. These extracts were washed with 50 ml of H_2O, dried over Na_2SO_4 and concentrated to 138.9 mg of 6 (100%) as a pale yellow foam. Crystals can be obtained from EtOAc/petrol; m.p. 118-9°; $[\alpha]_D^{\beta}$ +148.6° (c 0.50, $CHCl_3$); ν_{max} ($CHCl_3$) 3410 m, 1799 s (β-lactam C=O), 1749 s, (ester C=O), 1728 s (aldehyde C=O), 1691 s (amide C=O), 1601 m, 1592 m, 1520 s, 1497 s, 1442 m, 1294 m, 1068 m, 700 m, and 667 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.43 (3H, s, $-CH_3$), 4.56 (2H, s, $PhOCH_2$), 5.17 (1H, s, 2-H), 5.23 (2H, s, $-CH_2Ph$), 5.57 (1H, dd, J 4, 8 Hz, 6-H), 5.68 (1H, d, J 4 Hz, 5-H), 6.94-7.41 (11H, m), and 9.13 (1H, s, -CHO); m/e F.D. 454 (M^+); I.B.E.I. 454 (M^+, 3%), 264 (39%), 107 (28%), 91 (100%). Found C, 60.70%; H, 5.01%; N, 6.17%; S, 6.83%; (M^+) 454.1198. $C_{23}H_{22}N_2O_6S$ requires C, 60.79%, H, 4.85%; N, 6.17%; S, 7.05%; (M^+) 454.1199.

Preparation of benzyl (2S,3S,5R,6R)-3-[(E)-3-ethoxy-3-oxopropen-1-yl]-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (8)

To a solution of the aldehyde 6 (90.8 mg, 0.20 mmol) in 10 ml benzene was added (carbethoxymethylene)triphenylphosphorane (76.6 mg, 0.22 mmol). This solution was warmed to 60° and stirred for 1 hour. Concentration gave a white foam. Flash chromatography (acetone : chloroform, 1:49) afforded 8 (99.3 mg, 95%) as a white foam; $[\alpha]_D^{\beta}$ +94.9° (c 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3420 m, 1795 s (β-lactam C=O), 1750 s (ester C=O), 1715 s (α,β unsaturated ester C=O), 1697 s (amide C=O), 1601 m, 1592 m, 1519 s, 1495 s, 1441 m, 1299 s, 981 m, 699 m, and 691 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.25 (3H, t, J 7 Hz, $-CH_2CH_3$), 1.51 (3H, s, $3-CH_3$), 4.18 (2H, q, J 7 Hz, $-CH_2CH_2$), 4.55 (2H, s, $PhOCH_2-$), 4.74 (1H, s, 2-H), 5.18 and 5.24 (2H, ABq, J 12 Hz, $PhCH_2-$). 5.64 (1H, d, J 4 Hz, 5-H), 5.76 (1H, dd, J 4, 9 Hz, 6-H), 5.98 (1H, d, J 15 Hz, $=CH-CO_2Et$), 6.94-7.38 (11H, m), and 7.02 (1H, d, J 15 Hz, $-CH=CHCO_2Et$); m/e (F.D.) 525 ($M^+ + 1$), 524 (M^+). I.B.E.I. 524 (M^+, 0.8%) 334 (73%), 107 (13%), and 91 (100%). Found: (M^+) 524.1618, $C_{27}H_{28}N_2O_7S$ requires 524.1617.

Preparation of benzyl (2S,3S,5R,6R)-3-[(E)-2-cyanoethenyl]-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (9)

To a solution of the aldehyde 6 (90.8 mg, 0.20 mmol) in 10 ml benzene was added cyanomethylene triphenylphosphorane (72.2 mg, 0.24 mmol). This solution was warmed to 60° and stirred for 45 minutes. Concentration gave an orange foam. Flash chromatography (ethyl acetate, petrol, 1:4) afforded 9 (75.4 mg, 79%) as a white foam, $[\alpha]_D^{\beta}$ +103.3° (c 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3420 m, 2230 w (C≡N), 1795 s (β-lactam C=O), 1750 s (ester C=O), 1693 s (amide C=O), 1629 w, 1601 m, 1592 m, 1518 s, 1494 s, 1441 m, 965 m, 698 m, and 690 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.45 (3H, s, $-CH_3$), 4.54 and 4.56 (2H, ABq, J 15 Hz, $PhOCH_2-$), 4.72 (1H, s, 2-H), 5.18 and 5.24 (2H, ABq, J 12 Hz, $PhCH_2-$), 5.47 (1H, d, J 16 Hz, =CHCN), 5.63-5.70 (2H, m, 5-H, 6-H), 6.76 (1H, d, J 16 Hz $-CH=CHCN$), and 6.93-7.43 (11H, m); m/e (I.B.E.I.) 477 (M^+, 0.7%), 287 (48%). 107 (24%) and 91 (100%). Found: (M^+) 477.1359, $C_{25}H_{23}N_3O_5S$ requires 477.1358.

Preparation of benzyl(2S,3S,5R,6R)-3-methyl-3-[2-(1-methyl-1-H-tetrazol-5-yl)-(E)-ethenyl]-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (10)

A solution of the aldehyde 6 (90.8 m, 0.20 mmol) and (1-methyl-1H-tetrazol-5-yl)methylene triphenylphosphorane[22] (94.7 mg, 0.26 mmol) in 10 ml CH_2Cl_2 was stirred at room temperature for 1 hour. Concentration gave a yellow foam. Flash chromatography (ethyl acetate : petrol, 3:7) afforded 10 (87.1 mg, 82%) as a white foam, $[\alpha]_D^{\beta}$ +70.1° (c 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3420 m 1794 s (β-lactam C=O), 1750 s (ester C=O), 1697 s (amide C=O), 1601 m, 1594 m, 1517 s, 1496 s, 1440 m, 1298 m, 968 m, and 694 m cm^{-1}, δ_H (300 MHz, $CDCl_3$), 1.60 (3H, s, $3-CH_3$), 3.87 (3H, s, $-NCH_3$), 4.51 (2H, s, $PhOCH_2-$), 4.89 (1H, s, 2-H), 5.19 and 5.25 (2H, ABq, J 12 Hz, $PhCH_2-$), 5.68-5.73 (2H, m, 5-H and 6-H). 6.42 (1H, d, J 16 Hz, =CH-tetrazole), 6.80-7.39 (11H, m), and 7.11 (1H, d, J 16 Hz, -CH=CH-tetrazole); m/e (I.B.E.I.) 344 (3%), 107 (30%), 94 (43%), 91 (100%).

Preparation of benzyl (2S,3S,5R,6R)-3-[3-amino-3-oxopropen-1-yl]-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (11)

A solution of the aldehyde 6 (90.8 mg, 0.20 mmol) and carbamoylmethylenetriphenylphosphorane (95.7 mg, 0.30 mmol) in 10 ml benzene was warmed to 60° and stirred for 45 minutes. Concentration gave a yellow foam. Flash chromatography (ethyl acetate : chloroform, 1:2) afforded (Z) - 11 (7.3 mg, 7%) as a white foam and (E) - 11 (43.1 mg, 44%) as a white foam.

Data for (Z) - 11 : $[\alpha]_D^{\beta}$ +26.5° (c 0.36, $CHCl_3$); ν_{max} ($CHCl_3$) 3530 m, 3410 m, 1790 s (β-lactam C=O), 1749 s (ester C=O), 1687 s (amide C=O's), 1601 m, 1592 m, 1520 s, 1495 s, 1441 m, 1299 m, 1238 m, 1060 m, and 697 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.71 (3H, s, $-CH_3$), 4.55 (2H, s, $PhOCH_2-$), 5.14 (1H, s, 2-H), 5.21 (2H, s, $PhCH_2-$), 5.33 (1H, br s, $-CONH_2$), 5.61 (1H, d, J 4 Hz, 5-H), 5.65 (1H, d, J 12 Hz, $=CHCONH_2$), 5.70 (1H, dd, J 4, 9 Hz, 6-H), 6.10 (1H, d, J 12 Hz,

-CH=CH$_2$CONH$_2$), 6.92-7.40 (10H, m), and 7.45 (1H, d, J 9 Hz, -NH-); m/e (I.B.E.I.) 305 (29%), 151 (15%), 107 (22%), and 91 (100%).

Data for (E) - 11 : $[\alpha]_D^{\beta}$ +95.3° (c 1.54, $CHCl_3$); ν_{max} ($CHCl_3$) 3530 m, 3420 m, 1791 s (β-lactam C=O), 1751 s (ester C=O), 1691 s (amide C=O's), 1647 m, 1601 m, 1593 m, 1520 s, 1496 s, 1441 m, 1375 m, 976 m, and 698 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.49 (3H, s, -CH$_3$), 4.53 (2H, s, PhOCH$_2$-), 4.78 (1H, s, 2-H), 5.18 and 5.22 (2H, ABq, J 12 Hz, PhCH$_2$-), 5.63-5.69 (2H, m, 5, 6-H), 5.76 (1H, br s, CONH$_2$), 5.97 (1H, d, J 15 Hz, =CHCONH$_2$), 6.03 (1H, br s, -CONH$_2$), 6.87-7.40 (10 H, m), 6.89 (1H, d, J 15 Hz, -CH=CHCONH$_2$), and 7.48 (1H, d, J 8 Hz, -NH-); m/e (I.B.E.I.) 495 (M^+, 0.4%), 305 (39%), 107 (19%), and 91 (100%). Found: (M^+) 495.1465, $C_{23}H_{25}N_3O_6S$ requires 495.1464.

Preparation of benzyl (2S,3S,5R,6R)-3-methyl-7-oxo-3-[(E)-3-oxo-phenylpropen-1-yl]-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (12)

A solution of the aldehyde 6 (90.8 mg, 0.20 mmol) and benzoylmethylenetriphenylphosphorane (91.2 mg, 0.24 mmol) was warmed to 80° and stirred for 3 hours. Concentration gave a white foam. Flash chromatography (ethyl acetate : petrol, 1:3) afforded 12 (90.2 mg, 81%) as a white foam, $[\alpha]_D^{\beta}$ +110.5° (c 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3420 m, 1792 s (β-lactam C=O), 1751 s (ester C=O), 1693 s (amide C=O), 1680 s (α,β unsaturated ketone C=O), 1618 m, 1601 m, 1592 m, 1520 s, 1497 s, 1450 m, 1441 m, 1297 s, 1174 m, and 697 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.59 (3H, s, -CH$_3$), 4.51 (2H, s, PhOCH$_2$-), 4.88 (1H, s, 2-H), 5.20 and 5.26 (2H, ABq, J 12 Hz, PhCH$_2$-), 5.68 (1H, d, J 4 Hz, 5-H), 5.76 (1H, dd, J 4, 9 Hz, 6-H), 6.83-7.89 (11H, m), 6.94 (1H, d, J 15 Hz, olefinic H), and 7.04 (1H, d, J 15 Hz, olefinic H); m/e (F.D.) 556 (M^+). I.B.E.I. 556 (M^+, 1%), 366 (31%), and 91 (100%). Found: (M^+) 556.1669, $C_{31}H_{28}N_2O_6S$ requires 556.1669.

Preparation of benzyl (2S,3R,5R,6R)-3-methyl-3-oxiranyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (13) and benzyl (2S,3R,5R,6R)-3-acetyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (14)

To a solution of the aldehyde 6 (227.5 mg, 0.501 mmol) in 5 ml EtOAc maintained at 0° was codistilled diazomethane (generated from 15 mmol Diazald) and ether (30 ml). The resulting solution was allowed to stand at 0° for 5 hours and then at room temparature for 12 hours. This solution was concentrated to a yellow oil. Flash chromatography (EtOAc : petrol, 1:2) afforded 215.4 mg (92%) of a colourless oil. 300 MHz NMR indicated that this was a 1.5:1 mixture of 13 and 14 (vide infra for spectral details). These compounds were inseparable by silica gel chromatography.

Purification of 13:

To a solution of 13 and 14 (1:1, 200 mg, 427 μmol) in HOAc was added an excess of zinc dust. The resulting suspension was rapidly stirred for 20 minutes. The reaction was quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. These extracts were washed with brine, dried over Na_2SO_4 and concentrated to 184 mg of a white foam. Flash chromatography (acetone : chloroform, 3:97) afforded 83.8 mg (84%) of the oxirane 13 as a white foam; TLC [EtOAc : petrol (1:1)] R_f 0.54; ν_{max} ($CHCl_3$) 3380 m, 1792 s (β-lactam C=O), 1743 s (ester C=O), 1685 s (amide C=O), 1601 m, 1522 s, 1494 s, 1441 m, 1299 m, 1081 m, and 908 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.38 (3H, s, -CH$_3$), 2.56 (1H, dd, J 2.6, 4.6 Hz), 2.63 (1H, t, J 4.3 Hz), 3.12 (1H, dd, J 2.6, 3.9 Hz), 4.56 (2H, s, PhOCH$_2$-), 4.88 (1H, s, 2-H), 5.20 and 5.24 (2H, ABq, J 12 Hz, PhCH$_2$-), 5.55 (1H, d, J 4 Hz, 5-H), 5.73 (1H, dd, J 4, 10 Hz, 6-H), 6.92-7.38 (10 H, m), and 8.13 (1H, d, J 10 Hz, -NH-); m/e (F.D.) 468 (M^+). Found: (M^+) 468.1355, $C_{24}H_{24}O_6N_2S$ requires 468.1355.

Preparation of benzyl (2S,3R,5R,6R)-3-(1-acetyloxy-2-iodoethyl)-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (17)

To a solution of 222 mg (1.48 mmol, dried overnight at 100°) NaI and 2.7 μl (0.15 mmol) H_2O in 3 ml CH_3CN was added 42 μl (0.30 mmol) trifluoroacetic anhydride. The resulting yellow solution was stirred for five minutes and cooled to 0°. A solution of 163.3 mg of a 58:42 mixture of 13 and 14 in 4.5 ml CH_3CN was then added via cannula (followed by a 1 ml CH_3CN rinse). The resulting solution was warmed to room temperature and stirred for one hour. The reaction was quenched with the addition of 5 ml of pH 7 phosphate buffer. This solution was extracted with 2 x 40 ml EtOAc. These extracts were washed with 25 ml each of 1% $NaHSO_3$ and H_2O, dried over Na_2SO_4 and concentrated to 187 mg of a pale yellow foam. 250 MHz NMR indicates that this is a mixture of unreacted methyl ketone 14 and iodohydrin 15. (Selected NMR Data for 15 : δ(250 MHz, $CDCl_3$) 3.01 (1H, t, J 10 Hz, -CH$_2$I), 3.36 (1H, dd, J 1.6, 10 Hz, -CH$_2$I), and 3.97 (1H, dd, J 1.6, 10 Hz, -CHOH). A solution of this mixture in 5 ml CH_2Cl_2 was treated with 1 mmol each of Ac_2O (94 μl) and 4-dimethylaminopyridine (122 mg). This solution was stirred for 2.5 hours and then loaded directly onto a column of 20 g of silica gel (40-63μm). Elution with 2:1 petrol : EtOAc afforded 98.0 mg (76% based on epoxide) of the iodide 17 as a pale yellow oil and 63.6 mg (93%) of recovered methyl ketone 14 as a pale yellow oil.

Data for 17 : TLC [EtOAc : petrol (2:3)] R_f 0.43; $[\alpha]_D^{\beta}$ +84.3° (c 1.34, $CHCl_3$); ν_{max} ($CHCl_3$) 3400 m, 1792 s (β-lactam C=O), 1748 s (ester C=O), 1692 s (amide C=O), 1602 m, 1524 m, 1498 m, 1442 m, 1372 m, 1303 m, 1232 m, and 700 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.40 (3H, s, -CH$_3$), 2.09 (3H, s, -COCH$_3$), 3.14 (1H, t, J 10.6 Hz, -CH$_2$I), 3.40 (1H, dd, J 2.1, 10.9 Hz, -CH$_2$I), 4.57 and 4.61 (2H, ABq, J 15.3 Hz, PhOCH$_2$-), 4.72 (1H, s, 2-H), 5.21 (2H, s, PhCH$_2$), 5.31 (1H, dd, J 2.2, 10.4 Hz, -CHOAc), 5.64 (1H, d, J 4.0 Hz, 5-H), 5.84 (1H, dd, J 4.0, 10.1 Hz, 6-H), 7.02-7.07 (3H, m,), 7.32-7.40 (7H, m), and 7.74 (1H, d, J 10.1 Hz, -NH-); m/e (C.I.-NH_3) 639 (M^+ + 1, 0.6%), 511 (2.7%), 91 (100%).

Data for 14 : TLC [EtOAc : petrol (2:3)] R_f 0.31; ν_{max} ($CHCl_3$) 3410 m, 1795 s (β-lactam C=O), 1743 s (ester C=O), 1707 m (ketone C=O), 1687 s (amide C=O), 1601 m, 1520 s, 1496 s, 1443 m, 1293 m, 1175 m, and 908 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.53 (3H, s, -CH$_3$), 2.27 (3H, s, -COCH$_3$), 4.55 (2H, s, PhOCH$_2$-), 5.22 (2H, s, PhCH$_2$-), 5.32 (1H, s, 2-H), 5.60 (1H, dd, J 4, 9 Hz, 6-H), 5.65 (1H, d, J 4 Hz, 5-H), 6.93-7.38 (10H, m), and 7.60 (1H, d, J 9 Hz, -NH-); m/e (F.I.) 468 (M^+). Found: (M^+) 468.1355, $C_{24}H_{24}N_2O_6S$ requires 468.1355.

Preparation of benzyl (2S,3S,5R,6R)-3-ethenyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (7)

To a solution of iodide 17 (96.2 mg, 0.15 mmol) in 3 ml THF containing 100 μl HOAc was added 100 mg freshly activated zinc shavings. The resulting suspension was vigorously stirred for 45 minutes and then loaded directly onto a column of 20 g silica gel (40-63 μm). Elution with 2:1 petrol : EtOAc afforded 69.1 mg (100%) of the olefin 7; TLC [petrol : EtOAc (2:1)] R_f 0.36; $[\alpha]_D^{\beta}$ +101.8° (c 1.35, $CHCl_3$); ν_{max} ($CHCl_3$) 3410 m, 3030 m, 1791 s (β-lactam C=O), 1748 s (ester C=O), 1692 (amide C=O), 1602 m, 1522 s, 1497 s, 1443 m, 1295 m, 1238 s, 1083 m, 1066 m, and 699 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.48 (3H, s, $-CH_3$), 4.57 (2H, s, $PhOCH_2$-), 4.72 (1H, s, 2-H), 5.15 (1H, d, J 10.4 Hz, $=CH_2$ (Z)), 5.21 (2H, s, $PhCH_2$-), 5.39 (1H, d, J 16.8 Hz, $=CH_2$ (E)), 5.62 (1H, d, J 4.2, 5-H), 5.73 (1H, dd, J 4.2, 9.3 Hz, 6-H), 6.01 (1H, dd, J 10.4, 16.8, $-CH=CH_2$), 6.91-7.08 (3H, m), and 7.31-7.38 (8H, m); m/e (D.C.I.-NH_3) 470 ($M + NH_4^+$, 8%), 453 ($M + H^+$, 8%), 262 (100%). Found C, 63.85%; H, 5.51%; N, 6.00%; $C_{24}H_{24}O_5N_2S$ requires C, 63.70%; H, 5.35%; N, 6.19%.

Preparation of benzyl (2S,3R,5R,6R)-3-difluoromethyl-3-methyl-7-oxo-6-phenoxyacetamido-1-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (18)

To a solution of 1.00 g (2.203 mmol) of 6 in 20 ml CH_2Cl_2 was added dropwise a solution of 443 mg (2.75 mmol) of diethylaminosulfur trifluoride in 15 ml CH_2Cl_2. The resulting solution was stirred for 30 minutes at room temperature. This solution was diluted with 150 ml CH_2Cl_2 and washed with 50 ml $NaHCO_3$ and 30 ml of H_2O. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated to 1.076 g of a white foam. Flash chromatography with EtOAc : petrol (1:4) gave 945 mg (90%) of 18 as a white foam; $[\alpha]_D^{\beta}$ +104.8° (c 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3420 m, 1801 s (β-lactam C=O), 1750 s (ester C=O), 1694 s (amide C=O), 1601 m, 1593 m, 1520 s, 1495 s, 1441 m, 1303 s, 1173 s, 1088 s, 1058 m, 697 m, and 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.38 (3H, s, $-CH_3$), 4.54 (2H, s, $PhOCH_2$-), 4.91 (1H, s, 2-H), 5.21 (2H, s, $-CH_2Ph$), 5.63 (1H, t, J 56 Hz, $-CHF_2$), 5.64-5.68 (2H, m, 5-H, 6-H), and 6.90-7.40 (11H, m); $\delta^{19}F$ (84.6 MHz, $CDCl_3$) -44.5 (d, J 56 Hz); m/e (I.B.E.I.) 476 (M^+, 5%), 286 (43%), 176 (14%), 107 (20%), 91 (100%). Found: (M^+) 476.1216, $C_{23}H_{22}F_2N_2O_5S$ requires 476.1217.

Preparation of benzyl (2S,3R,4S,5R,6R)-3-difluoromethyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4-oxide (19) and benzyl (2S,3R,4R,5R,6R)-3-difluoromethyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4-oxide (20)

To a solution of 190.4 mg (0.40 mmol) 18 in 10 ml CH_2Cl_2 stirred at 0° was added dropwise a solution of m-chloroperbenzoic acid (87.3 mg (85%), 0.44 mmol) in 20 ml CH_2Cl_2. The resulting solution was warmed to room temperature. After 15 minutes this solution was washed with 15 ml 5% $NaHCO_3$ and 20 ml H_2O, dried over Na_2SO_4 and concentrated to 210.3 mg of a white foam. Flash chromatography (acetone : CH_2Cl_2, 1:99-3:97) gave 11.9 mg (6%) of recovered 18, 87.7 mg (45%) of 19 as a white foam and 49.0 mg (25%) of 20 as a white foam.

Data for 19: $[\alpha]_D^{\beta}$ +133.7° (c 1.23, $CHCl_3$); ν_{max} ($CHCl_3$) 3390 m, 1810 s (β-lactam C=O), 1751 s (ester C=O), 1697 s (amide C=O), 1600 m, 1592 m, 1515 s, 1496 s, 1441 m, 1172 s , 1079 s (S=O), 694 m, 688 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.17 (3H, s, $-CH_3$), 4.53 (2H, s, $PhOCH_2$), 5.07 (1H, d, J 4 Hz, 5-H), 5.08 (1H, s, 2-H), 5.17 and 5.25 (2H, ABq, J 12 Hz, $-CH_2Ph$), 6.16 (1H, dd, J 4, 11 Hz, 6-H), 6.23 (1H, t, J 55 Hz, $-CHF_2$), 6.89-7.40 (10H, m), and 8.10 (1H, d, J 10 Hz, -NH-); m/e (I.B.E.I.) 492 (M^+, 4%), 224 (18%), 107 (23%), 91 (100%). Found: (M^+) 492.1167, $C_{23}H_{22}F_2N_2O_6S$ requires 492.1167.

Data for 20: $[\alpha]_D^{\beta}$ +82.7° (c 0.95, $CHCl_3$); ν_{max} ($CHCl_3$) 3420 m, 1806 s (β-lactam C=O), 1750 s (ester C=O), 1698 (amide C=O), 1601 m, 1592 m, 1519 s, 1496 s, 1441 m, 1078 s (S=O), 952 m, 695 m and 688 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.28 (3H, s, $-CH_3$), 4.55 (2H, s, $PhOCH_2$-), 4.93 (1H, s, 2-H), 4.96 (1H, d, J 4 Hz, 5-H), 5.22 and 5.26 (2H, ABq, J 12 Hz, $-CH_2Ph$), 5.40 (1H, dd, J 4, 8 Hz, 6-H), 6.22 (1H, t, J 56 Hz, $-CHF_2$), 6.89-7.39 (10H, m), 7.45 (1H, d, J 8 Hz, -NH-); m/e (I.B.E.I.) 474 ($M^+ - H_2O$, 6%), 175 (24%), 107 (18%), 91 (100%). Found ($M^+ - H_2O$) 474.1059, $C_{23}H_{20}F_2N_2O_5S$ requires 474.1061.

Preparation of benzyl (2S,3S,4S,5R,6R)-3-difluoromethyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4-oxide (21)

A solution of sulfoxide 20 (49.0 mg, 0.10 mmol) in 5 ml benzene was refluxed for 45 minutes. Concentration gave a white foam which was flash chromatographed (acetone : petrol, 1:99) to afford 27.0 mg (55%) of the sulfoxide 21 as a white foam; $[\alpha]_D^{\beta}$ +133.6° (c 1.35, $CHCl_3$); ν_{max} ($CHCl_3$) 3390 m, 1808 s (β-lactam C=O), 1764 m (ester C=O), 1697 s (amide C=O), 1601 m, 1592 s, 1517 s, 1496 s, 1441 m, 1062 s (S=O), 947 m, 695 m, and 688 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 1.80 (3H, s, $-CH_3$), 4.55 (2H, s, $PhOCH_2$-), 4.75 (1H, s, 2-H), 5.12 (1H, d, J 4 Hz, 5-H), 5.23 and 5.27 (2H, ABq, J 12 Hz, $PhCH_2$-), 5.94 (1H, t, J 54 Hz, $-CHF_2$), 6.15 (1H, dd, J 4, 10 Hz, 6-H), 6.91-7.41 (10 H, m), and 8.13 (1H, d, J 10 Hz, -NH-); m/e I.B.E.I. 474 ($M^+ - H_2O$, 5%), 107 (19%), 91 (100%). Found: ($M^+ - H_2O$) 474.1059, $C_{23}H_{20}F_2N_2O_5S$ requires 474.1061.

Preparation of benzyl (2S,3S,5R,6R)-3-difluoromethyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (22)

To a solution of the sulfoxide 21 (21.4 mg, 43.5 μmol) in 0.6 ml DMF stirred at -5° to 0° was added dropwise 0.20 ml (2.12 mmol) freshly distilled phosphorous tribromide. After 30 minutes the resulting viscous suspension was added to ice-cold 5% $NaHCO_3$. This solution was extracted with 50 ml CH_2Cl_2. The extract was washed with 15 ml H_2O, dried over Na_2SO_4 and concentrated to an orange oil. Flash chromatography (EtOAc : petrol, 1:4) afforded 5.5 mg (27%) of 22; ν_{max} ($CHCl_3$) 3420 m, 1799 s (β-lactam C=O), 1750 s (ester C=O), 1698 s (amide C=O), 1601 m, 1592 m, 1521 s, 1497 s, 1442 m, 1081 m, 1060 m, 697 m, and 690 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.64 (3H, s, $-CH_3$), 4.55 and 4.57 (2H, ABq, J 15 Hz, $PhOCH_2$-), 4.60 (1H, s, 2-H), 5.20 (2H, s, $PhCH_2$-), 5.55 (1H, d, J 4 Hz, 5-H), 5.77 (1H, dd, J 4, 9 Hz, 6-H), 5.87 (1H, t, J 56 Hz, $-CHF_2$), and 6.91-7.42 (11H, m); m/e (I.B.E.I.) 476 (M^+, 4%), 286 (38%), 176 (19%), 107 (24%), 91 (100%). Found: (M^+) 476.1219, $C_{23}H_{22}F_2N_2O_5S$ requires 476.1217.

Preparation of benzyl (2S,3R,5R,6R)-3-difluoromethyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide (23)

To a solution of 18 (95.2 mg, 0.20 mmol), in 5 ml CH_2Cl_2 stirred at 0° was added dropwise a solution of m-chloroperbenzoic acid (119 mg (85% pure), 0.60 mmol) in 10 ml CH_2Cl_2. This solution was warmed to room temperature and stirred for 75 minutes. This solution was then washed with 15 ml of 5% $NaHCO_3$ and 10 ml H_2O, dried over Na_2SO_4 and concentrated to 150.6 mg of a colourless gum. Flash chromatography (EtOAc : petrol, 1:3-3:7) afforded 62.1 mg (61%) of the sulfone 23 and 26.5 mg (27%) of the sulfoxide 19.

Data for 23: $[\alpha]_D^{\circ}$ +65.1° (c 1.08, $CHCl_3$); ν_{max} ($CHCl_3$) 3420 m, 1820 s (β-lactam C=O), 1760 s (ester C=O), 1708 s and 1700 s (amide C=O), 1601 m, 1594 m, 1519 s, 1497 s, 1442 m, 1342 s (SO_2), 1159 (SO_2), and 1081 s cm^{-1}; δ_H (300 MHz, $CDCl_3$), 1.36 (3H, s, $-CH_3$), 4.53 and 4.54 (2H, ABq, J 15 Hz, $PhOCH_2$-), 4.81 (1H, d, J 4 Hz, 5-H), 5.06 (1H, s, 2-H), 5.18 and 5.26 (2H, ABq, J 12 Hz, $-CH_2Ph$), 6.16 (1H, t, J 54 Hz, $-CHF_2$), 6.23 (1H, dd, J 4, 11 Hz, 6-H), 6.88-7.40 (10H, m), and 8.15 (1H, d, J 11 Hz, -NH-); m/e (I.B.E.I.) 508 (M^+, 3%), 107 (28%), 91 (100%). Found: (M^+) 508.1112, $C_{23}H_{22}F_2N_2O_7S$ requires 508.1116.

Preparation of benzyl (2S,3S,6R,7R)-3-fluoro-3-methyl-8-oxo-7-phenoxyacetamido-5-thia-1-azabicyclo-[4.2.0]octane-2-carboxylate (25)

To a solution of 136.8 mg (0.30 mmol) 1 in 3 ml CH_2Cl_2 stirred at -78° was added dropwise 72.5 mg (0.45 mmol) of diethylaminosulfur trifluoride in 6 ml CH_2Cl_2. The resulting solution was allowed to warm to room temperature over a 30 minute period. This solution was then diluted with 30 ml CH_2Cl_2, washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to 125 mg of an orange foam. Flash chromatography (EtOAc : petrol, 3:17-1:4) gave 86.1 mg (63%) of 25 as a white foam; $[\alpha]_D^{\circ}$ +76.2° (c 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3420 m, 1781 s (β-lactam C=O), 1746 s (ester C=O), 1694 s (amide C=O), 1601 m, 1592 m, 1520 s, 1497 s, 1441 m, 1330 m, 1154 m, 1081 m, 697 m, and 690 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.35 (3H, d, J 21 Hz, $-CH_3$) 2.74 (1H, ddd, J 0.9, 4, 14 Hz, 4β-H), 3.34 (1H, dd, J 15, 32 Hz, 4α-H), 4.54 (2H, s, $PhOCH_2$-) 4.70 (1H, dd, J 0.9, 12 Hz, 2-H), 5.17 and 5.21 (2H, ABq, J 12 Hz, $-CH_2Ph$), 5.29 (1H, d, J 4 Hz, 6-H), 5.72 (1H, dd, J 4, 10 Hz, 7-H), 6.90-7.42 (10H, m), and 7.54 (1H, d, J 10 Hz, -NH-); $\delta^{19}F$ (84.6 MHz; $CDCl_3$) -70.0 (m); m/e (I.B.E.I.) 458 (M^+, 5%), 268 (53%), 176 (21%), 107 (18%), 91 (100%). Found: (M^+) 458.1309, $C_{23}H_{23}FN_2O_5S$ requires 458.1312.

A General Procedure for Benzyl Ester Hydrogenolysis:

A solution of the benzyl ester and 1 equivalent of $NaHCO_3$ in aqueous THF (1:1, 1 ml solvent per 20 μmol substrate) was added dropwise to a suspension of 10% Pd/C (equal in weight to the benzyl ester and presaturated with H_2) in an equal volume at the same solvent. The resulting suspension was stirred for 3 hours under 1 atmosphere of H_2. The product was obtained by filtration through a pad of Celite (aqueous wash) followed by freeze-drying of the filtrate.

Data for the Hydrogenolysis Products:

Sodium (2S,3S,5R,6R)-3-[(E)-3-ethoxy-3-oxopropen-1-yl]-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylate (26)

(80% yield); ν_{max} (Nujol) 3380 m, 1782 (β-lactam C=O), 1714 s (α,β unsaturated ester C=O), 1696 s (amide C=O), 1602 s (CO_2^- C=O), 1521 m, 1304 s, and 719 s cm^{-1}; δ_H (300 MHz, D_2O), 0.99 (3H, t, J 7 Hz, CH_2CH_3), 1.47 (3H, s, 3-CH_3), 3.90 (2H, q, J 7 Hz, $-CH_2CH_3$), 4.36 (1H, s, 2-H); 4.42 and 4.46 (2H, ABq, J 16 Hz, $PhOCH_2$-), 5.33 (1H, d, J 4 Hz, 5-H or 6-H), 5.53 (1H, d, J 4 Hz, 5-H or 6-H), 5.85 (1H, d, J 15 Hz, $=CHCO_2Et$), and 6.77-7.17 (6H, m).

Sodium (2S,3S,5R,6R)-3-[(E)-2-cyanoethenyl]-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-aza-bicyclo[3.2.0]heptane-6-carboxylate (27)

(89% yield); ν_{max} (Nujol) 3360 m, 3180 m, 2220 w (C≡N), 1780 s (β-lactam C=O), 1671 s (amide C=O), 1601 s (CO_2^- C=O), 1518 s, 1240 m, 1170 m, 1158 m, and 968 m cm^{-1}; δ_H (300 MHz, D_2O) 1.43 (3H, s, $-CH_3$), 4.33 (1H, s, 2-H), 4.51 and 4.55 (2H, ABq, J 15 Hz, $PhOCH_2$-) 5.30 (1H, d, J 4 Hz, 5-H or 6-H), 5.49 (1H, d, J 16 Hz, =CHCN), 5.51 (1H, d, J 4 Hz, 5-H or 6-H), 6.76 (1H, d, J 16 Hz, $-CH=CHCN$), and 6.84-7.24 (5H, m).

Sodium (2S,3S,5R,6R)-3-methyl-3-[2-[1-methyl-1H-tetrazol-5-yl]-(E)-ethenyl]-7-oxo-6-phenoxy-acetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (28)

(72% yield); ν_{max} (Nujol) 3370 m, 3180 m, 1774 s (β-lactam C=O), 1680 s (amide C=O), 1600 s (CO_2^- C=O), 1170 m, and 970 m cm^{-1}; δ_H (300 MHz, D_2O) 1.57 (3H, s, $-CH_3$), 3.76 (3H, s, $-NCH_3$), 4.41 and 4.47 (2H, ABq, J 15 Hz, $PhOCH_2$-), 4.46 (1H, s, 2-H), 5.29 (1H, d, J 4 Hz, 5-H or 6-H), 5.59 (1H, d, J 4 Hz, 5-H or 6-H), 6.36 (1H, d, J 16 Hz, =CH-tetrazole), 6.64-7.04 (5H, m), and 6.76 (1H, d, J 16 Hz, -CH=CH-tetrazole).

Sodium (2S,3S,5R,6R)-3-[(E)-3-amino-3-oxopropen-1-yl]-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (29)

(77% yield); δ_H (300 MHz, D_2O), 1.46 (3H, s, $-CH_3$), 4.35 (1H, s, 2-H), 4.53 and 4.57 (2H, ABq, J 15 Hz, $PhOCH_2$-), 5.32 (1H, d, J 4 Hz, 5-H or 6-H), 5.51 (1H, d, J 4 Hz, 5-H or 6-H), 5.94 (1H, d, J 15 Hz, $=CHCONH_2$), 6.63 (1H, d, J 15 Hz, $-CH=CHCONH_2$), and 6.81-7.23 (5H, m).

Sodium (2S,3R,5R,6R)-3-difluoromethyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate (30)

(100% yield); ν_{max} (Nujol) 3390 m, 1773 s (β-lactam C=O), 1681 s, (amide C=O), 1601 (CO_2^- C=O), 1533 s, 1242 m, 1082 m, 720 m cm^{-1}; δ_H (300 MHz, D_2O) 1.32 (3H, s, $-CH_3$), 4.47 (1H, s, 2-H); 4.54 (2H, s, $PhOCH_2$-), 5.28 (1H, d, J 4 Hz, 5-H or 6-H), 5.53 (1H, d, J 4 Hz, 5-H or 6-H), 5.70 (1H, t, J 56 Hz, $-CHF_2$), and 6.84-7.23 (5H, m).

Sodium (2S,3R,4S,5R,6R)-3-difluoromethyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate-4-oxide (31)

(90% yield); ν_{max} (Nujol) 3370 m, 3180 m, 1787 s (β-lactam C=O), 1682 s (amide C=O), 1617 s (CO_2^- C=O), 1516 s and 1059 s (S=O) cm^{-1}; δ_H (300 MHz, D_2O), 1.15 (3H, s, $-CH_3$), 4.54 (2H, s, $PhOCH_2-$), 4.77 (1H, s, 2-H), 5.23 (1H, d, J 4 Hz, 5-H or 6-H), 5.89 (1H, d, J 4 Hz, 5-H or 6-H), 6.20 (1H, t, J 54 Hz, $-CHF_2$), and 6.83-7.26 (5H,m).

Sodium (2S,3S,4S,5R,6R)-3-difluoromethyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate (32)

(88% yield); ν_{max} (Nujol) 3360 m, 3180 m, 1788 s (β-lactam C=O), 1698 s (amide C=O), 1617 s (CO_2^- C=O), 1517 s, 1167 m, 1154 m, and 1047 m cm^{-1}; δ_H (300 MHz, D_2O), 1.46 (3H, s, $-CH_3$), 4.26 (1H, s, 2-H), 4.58 and 4.60 (2H, ABq, J 15 Hz, $PhOCH_2-$), 5.34 (1H, d, J 4 Hz, 5-H or 6-H), 5.39 (1H, d, J 4 Hz, 5-H or 6-H), 5.94 (1H, t, J 56 Hz, $-CHF_2$) and 6.84-7.26 (5H, m).

Sodium (2S,3R,5R,6R)-3-difluoromethyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate-4,4-dioxide (33)

(97% yield); ν_{max} (D_2O) 1800 s (β-lactam C=O), 1677 s (amide C=O), 1628 (CO_2^- C=O), 1601 m, 1490 m, 1461 s, 1436 m, 1388 m, 1330 s (SO_2) cm^{-1}; δ_H (300 MHz, D_2O), 1.40 (3H, s, $-CH_3$), 4.57 (2H, s, $PhOCH_2-$), 4.77 (1H, s, 2-H), 5.05 (1H, d, J 4 Hz, 5-H or 6-H), 5.84 (1H, d, J 4 Hz, 5-H or 6-H), 6.21 (1H, t, J 54 Hz, $-CHF_2$), and 6.82-7.24 (5H, m).

Sodium (2S,3S,6R,7R)-3-fluoro-3-methyl-8-oxo-7-phenoxyacetamido-5-thia-1-azabicyclo[4.2.0]-octane-2-carboxylate (34)

(100% yield); ν_{max} (Nujol) 3400 m, 3190 m, 1759 s (β-lactam C=O), 1681 s (amide C=O), 1616 s (CO_2^- C=O), 1528 s, 1241 s, 1171 m, 1080 m, 751 s, and 720 s cm^{-1}; δ_H (300 MHz, D_2O), 1.36 (3H, d, J 23 Hz, $-CH_3$), 2.67 (1H, d, J 15 Hz, 4β-H), 3.31 (1H, dd, J 15, 34 Hz, 4α-H), 4.25 (1H, d, J 14 Hz, 2-H), 4.40 (2H, s, $PhOCH_2$), 5.27-5.29 (2H, m, 6-H and 7-H), and 6.74-7.17 (5H, m).

Sodium (2S,3R,5R,6R)-3-methyl-3-oxiranyl-7-oxo-6-phenoxyacetamide-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate (35)

(52% yield); δ_H (300 MHz, D_2O), 1.27 (3H, s, $-CH_3$), 2.38 (1H, t, J 3 Hz, $-CHOCH_2$), 2.50 (1H, t, J 4Hz, $-CHOCH_2$), 3.09 (1H, t, J 3 Hz, $-CHOCH_2$), 4.44 (1H, s, 2-H), 4.50 (2H, s, $PhOCH_2-$), 5.37 (1H, d, J 4 Hz, 5-H or 6-H), 5.42 (1H, d, J 4 Hz, 5-H or 6-H), and 6.86-7.25 (5H, m).

Ammonium (2S,3S,5R,6R)-3-ethenyl-3-methyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate (36)

(94% yield); The crude hydrogenolysis product was purified by reverse-phase HPLC (ODS column, 10mM NH_4HCO_3 : CH_3CN (3:1)), δ_H (300 MHz, D_2O), 1.37 (3H, s, $-CH_3$), 4.22 (1H, s, 2-H), 4.55 (2H, s, $PhOCH_2-$), 4.91 (1H, d, J 10.6 Hz, (Z) $=CH_2$), 5.12 (1H, d, J 17.1 Hz, (E) $=CH_2$), 5.33 (1H, d, J 4.2 Hz, 5-H or 6-H), 5.41 (1H, d, J 4.0 Hz, 5-H or 6-H), 5.85 (1H, dd, J 10.5, 16.9 Hz, $-CH=CH_2$), 6.81-6.92 (3H, m), and 7.16-7.22 (2H, m).

REFERENCES

1. a) D.O. Spry, J.Org.Chem., 1979, 44, 3084.
   b) J.E. Baldwin, and P. Singh, Tetrahedron Lett., 1979, 3757.
2. Silica gel chromatography or heat was sufficient to carry out this transformation.
3. M. Fetizon, and M. Golfier, C.R.Acad.Sci., serie C 1968, 267, 900.
4. S.L. Huang, K. Omura, and D. Swern, J.Org.Chem., 1976, 41, 3329.
5. D.J. Peterson, J.Org.Chem., 1968, 33, 780.
6. The benzyl ester of penicillin V has been reported to react with stabilized ylides at the β-lactam carbonyl. M.L. Gilpin, J.B. Harbridge, T.T. Howarth, and T.J. King, Chem.Commun., 1981, 929.
7. A discussion of the reaction of diazomethane with aldehydes and ketones can be found in "Heterocyclic Compounds With Three- and Four-Membered Rings Part One", A. Weissberger, Ed., Interscience Publishers, London, 1964, pp.158-171.
8. The PMR spectrum of the crude CH_2N_2 products suggests that a small amount of an epimeric epoxide is present. This compound has not been isolated, however.
9. E.J. Corey, and M. Chaykovsky, J.Am.Chem.Soc., 1965, 87, 1353.
10. For a leading reference see: A. Ogawa, J. Miyake, S. Murai, and N. Sonoda, Tetrahedron Lett., 1985, 26, 669.
11. P.E. Sonnet, J.Org.Chem., 1978, 43, 1841.
12. M. Schlosser, Tetrahedron, 1978, 34, 3.
13. R.A. Sharma, I. Kavai, Y.L. Fu, and M. Bobek, Tetrahedron Lett., 1977, 3433.
14. "Cephalosporins and Penicillins - Chemistry and Biology", E.H. Flynn, Ed., Academic Press, London, 1972, pp.349-358.
15. R.D.G. Cooper, L.D. Hatfield, and D.O. Spry, Acc.Chem.Res., 1973, 6, 32.
16. S. Kukolja, S.R. Lammert, M.R.B. Gleissner, and A.I. Ellis, J.Am.Chem.Soc., 1976, 98, 5040.
17. a) F.J. Baker, and M.R. Breach, 'Medical Microbiological Techniques', Butterworths, London, 1980, pp.343-359.
    b) These assays were carried out by Pfizer Central Research, Sandwich, Kent.
18. B.C. Stratford, 'An Atlas of Medical Microbiology', Blackwells Scientific Publications, Oxford, 1977, pp.131-142.
19. W.C. Still, M. Kahn, and A. Mitra, J.Org.Chem., 1978, 43, 2923.
20. D.D. Perrin, W.L.F. Armarego and D.R. Perrin, Purification of Laboratory Chemicals, 1st Edn., Pergamon Press, London (1966).
21. R.B. Woodward and H. Bickel Ger.Offen., 2,506,330 (Chem.Abstracts, 84 : 1739p).
22. T. Hashimoto, Y. Kawano, S. Natsume, T. Tanaka, T. Watanabe, M. Nagano, S.-I. Sugawara, and T. Miyadera, Chem.Pharm.Bull., 1978, 26, 1803.