Wittig Reactions with β-Lactam Carbonyl Functions. The Effect of C-7 Substitution on the Chemistry of Penicillins and Clavulanic Acid Derivatives.

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The Wittig reaction of phosphoranes and phosphonates with the carbonyl function of mono- and bicyclic β-lactams has been studied and the influence of phosphorane and β-lactam reactivities on the outcome of the reaction noted. The utility and general chemistry of the Wittig products from penicillins and clavulanic acid esters is also reported.

An earlier communication [1] illustrated the reactions of penicillin V benzyl ester (**1a**) and benzyl clavulanate (**7a**)[2,3] with stabilised phosphoranes. We now wish to report further examples of Wittig reactions on β-lactam carbonyl functions and to amplify the chemistry of this interesting series of compounds.

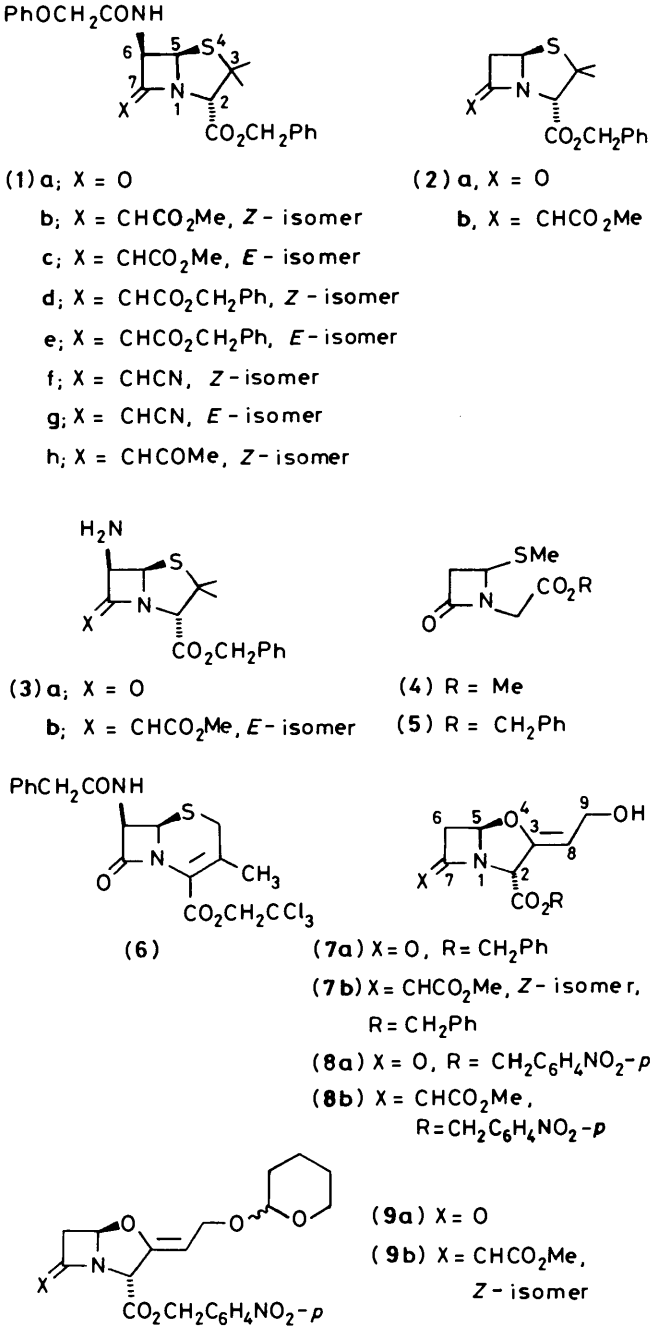
The Effect of Phosphorane Stability.—The reaction products of phosphoranes and phosphonates with various mono- and bicyclic β-lactams, under a variety of conditions, are listed in Table 1. Penicillin V benzyl ester (**1a**) was not converted into a Wittig product by either an unstabilised phosphorane (entry vi) or a phosphonate (entry vii), an observation which may be explained by the basic nature of these reagents and the lability of the C-2† proton of penicillins.

It has already been established by Fliszar *et al.*,[4] that the rate of nucleophilic attack of a stabilised phosphorane with a carbonyl compound is proportional to the pK_a of the conjugate acid. The pK_a values[4,5] of the stabilised phosphoranes used in the present study are indicated in Table 2. Thus, whilst methoxycarbonylmethylene-, benzyloxycarbonylmethylene-, and cyanomethylenetriphenylphosphorane give good conversions with penicillin (**1a**) in toluene (entries i, ii, iii), only recovered penicillin was obtained with acetylmethylenetriphenylphosphorane (entry iv) under these conditions. Increasing the reaction temperature, by changing the solvent to xylene, led to extensive decomposition but a small amount of material was isolated that had an ^1H n.m.r. spectrum compatible with the desired olefin (**1h**) (entry v).

The Effect of β-Lactam Stability.—It would appear from a study of Table 1 that monocyclic β-lactams are not sufficiently reactive towards phosphoranes and phosphonates to undergo a Wittig reaction (entries xi and xii). The cephalosporin (**6**) and benzyl penicillanate (**2a**) also failed to yield Wittig products under the usual conditions (entries xiii and viii). However, at higher temperature benzyl penicillanate (**2a**) did afford a low yield of the desired olefin as an inseparable mixture of geometric isomers (entry ix). Presumably in these examples failure or reluctance to react with stabilised phosphoranes reflects the greater β-lactam stability to nucleophilic attack inherent in these systems when compared with penicillins.

Clavulanic acid derivatives (**7a**), (**8a**), and (**9a**)[2,3,6] were generally less stable to the reaction conditions and extensive decomposition was usually observed. However, a successful Wittig reaction was obtained with the more reactive methoxycarbonylmethylenetriphenylphosphorane (entries xiv

† The systematic numbering of penicillins, based on the bicyclo-[3.2.0]heptane unit, has been used throughout in order to accommodate the naming of the olefinic products.



Scheme 1.

Table 1. Reaction products of β-lactams with Wittig reagents

Entry no.	Starting material	Phosphorane or phosphonate	Solvent at reflux	Olefinic products (%)[a] Recovered starting material	*Z*-Isomer	*E*-Isomer
i	(**1a**)	$Ph_3P{=}CHCO_2Me$	Toluene	0	(**1b**) 35	(**1c**) 32
ii	(**1a**)	$Ph_3P{=}CHCO_2CH_2Ph$	Toluene	17	(**1d**) 35	(**1e**) 33
iii	(**1a**)	$Ph_3P{=}CHCN$	Toluene	8	(**1f**) 36	(**1g**) 26
iv	(**1a**)	$Ph_3P{=}CHCOMe$	Toluene	87		
v	(**1a**)	$Ph_3P{=}CHCOMe$	Xylene	25	(**1h**) 7	—
vi	(**1a**)	$Ph_3P{=}CH_2$	Ether/20 °C	0	0	0
vii	(**1a**)	$(MeO)_2P(O)CH_2COMe$/NaH	THF/20 °C	Mainly	0	0
viii	(**2a**)	$Ph_3P{=}CHCO_2Me$	Toluene	80	0	0
ix	(**2a**)	$Ph_3P{=}CHCO_2Me$	Xylene	Trace	(**2b**) 10	(**2b**) 6
x	(**3a**)	$Ph_3P{=}CHCO_2Me$	Toluene	0	Small amount	(**3b**) 12
xi	(**4**)	$Ph_3P{=}CHCO_2Me$	Toluene	70	0	0
xii	(**5**)	$(MeO)_2P(O)CH_2CO_2Me$/NaH	THF/20 °C	Mainly	0	0
xiii	(**6**)	$Ph_3P{=}CHCO_2CH_2Ph$	Toluene	Mainly	0	0
xiv	(**7a**)	$Ph_3P{=}CHCO_2Me$	Toluene	0	(**7b**) 7	0
xv	(**8a**)	$Ph_3P{=}CHCOMe$	Toluene	Trace	0	0
xvi	(**9a**)	$Ph_3P{=}CHCO_2Me$	Toluene	0	(**9b**) 31	0
xvii	(**9a**)	$Ph_3P{=}CHCN$	Toluene	8	0	0

[a] Geometries determined by comparison of the chemical shift of the 2-H in the ^1H n.m.r. spectrum with values found for compounds of known geometry, see ref. 1.

Table 2. pK_a Values of some phosphoranes in conjugate acid form

$Ph_3\overset{+}{P}{-}CH_2R$	pK_a
R=COMe	6.6
R=CN	7.5
$R=CO_2Me$	8.8

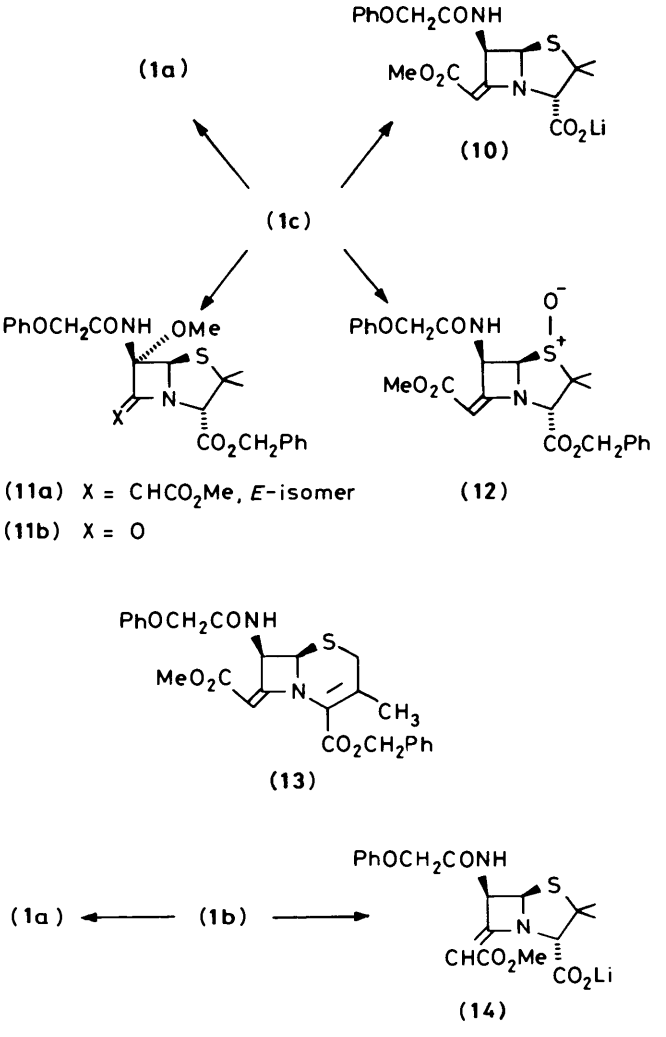
and xvi), a higher yield being obtained when the 9-hydroxy group was protected as an ether.

Further Modifications of Penicillin Wittig Products.— Ozonolysis of the *E*-(**1c**) and the *Z*-Wittig product (**1b**) in ethyl acetate at −78 °C regenerated penicillin V benzyl ester (**1a**) in yields of 69 and 95% respectively (Scheme 2). In order to demonstrate the utility of β-lactam regeneration the Wittig compound (**1c**) was treated with lithium methoxide and t-butyl hypochlorite in tetrahydrofuran (THF) at −70 °C in the manner of Koppel *et al.*,[7] to provide the 6α-methoxy derivative (**11a**), albeit in poor yield. The β-lactam was regenerated by treatment with ozone in the usual way to afford 6α-methoxypenicillin V benzyl ester (**11b**).

In another aspect of the work it was found that the *E*-isomer (**1c**) could be hydrogenolysed over palladised charcoal to afford, after neutralisation, the lithium salt (**10**) in 60% yield. ^1H N.m.r. examination of (**10**) indicated that no appreciable isomerisation of the double-bond had taken place. However, when the *Z*-isomer (**1b**) was similarly treated, the reaction was found to be substantially incomplete. The lithium salt (**14**), isolated in poor yield, was judged to be a mixture of geometric isomers.

A more convenient route to the salt (**10**) was by hydrolysis of the benzyl ester (**1c**) in dilute lithium hydroxide–THF at pH 13. By contrast, when a penicillin is subjected to such basic conditions β-lactam cleavage occurs before C-2 ester hydrolysis.[8] Thus, the conversion of β-lactams into Wittig products confers a considerable degree of stability to basic conditions and the above reactions amply demonstrate the use of the Wittig reaction in β-lactam protection.

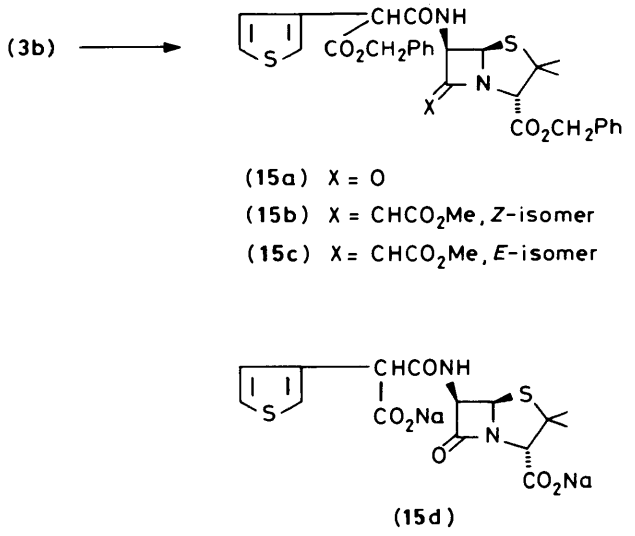
The modified behaviour of (**1c**) has been noted in another respect. Oxidation to the sulphoxide (**12**) with *m*-chloroperbenzoic acid followed by the standard ring-expansion



Scheme 2.

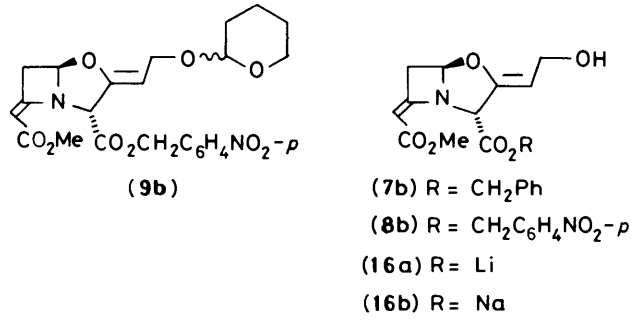
conditions of Morin *et al.*,[9] failed to give any of the expected cephalosporin derivative (**13**). Similarly, the conditions of Barton *et al.*[10] also failed to effect this reaction.

Benzyl 6β-aminopenicillanate (**3a**) reacts with methoxycarbonylmethylenetriphenylphosphorane to give essentially the *E*-isomer (**3b**) in 12% yield (entry x). Treatment of the amine (**3b**) with monobenzyl 3-thienylmalonic acid chloride and triethylamine gave a readily separable mixture of the *Z*- (**15b**) and the *E*-isomer (**15c**) in an 8:5 ratio (Scheme 3). Ozonolysis of this mixture at low temperature afforded ticarcillin dibenzyl ester (**15a**) in reasonable yield.



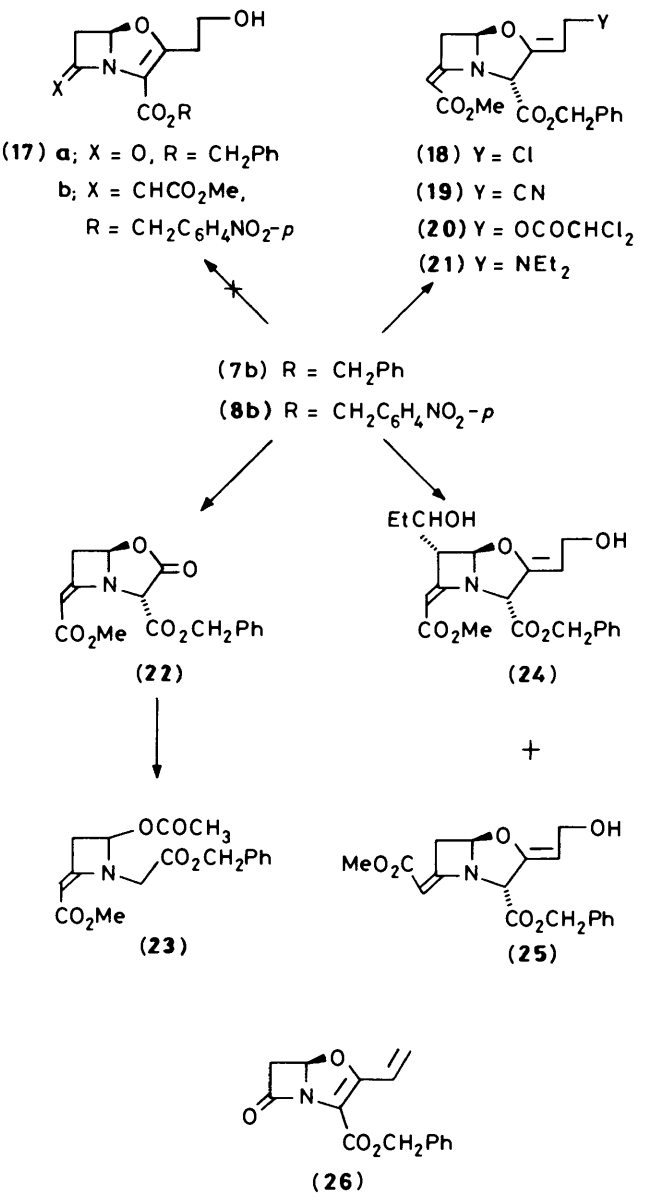
Scheme 3.

Further Modifications of Wittig Products from Clavulanic Acid Derivatives.—The tetrahydropyranyl ether (**9b**) was readily cleaved with pyridinium toluene-*p*-sulphonate in ethanol[11] to give the free alcohol (**8b**) in good yield (Scheme 4). Hydrogenation of the *p*-nitrobenzyl ester (**8b**) over palladised charcoal and subsequent neutralisation with dilute lithium hydroxide solution afforded the salt (**16a**) in 67% yield. Surprisingly, the corresponding benzyl ester (**7b**) could not be hydrogenated in this way. However, (**7b**) was readily hydrolysed in the presence of dilute sodium hydroxide solution at pH 12.0 to furnish the salt (**16b**) in quantitative yield.



Scheme 4.

We were interested to know how the reactivity of clavulanates had been altered by C-7 modification and to this end we proceeded to apply some of the known reactions of clavulanic acid esters to the modified clavulanates (**7b**) and (**8b**). Benzyl clavulanate (**7a**) has been reported[2,12] to isomerise to the clavem (**17a**) on treatment with 1 equiv. of triethylamine in



Scheme 5.

dichloromethane (Scheme 5). However, similar treatment of the C-7 modified clavulanate (**8b**) failed to effect any isomerisation to (**17b**) and unchanged starting material was recovered as judged by ^{1}H n.m.r. This noticeable modification to the lability of the C-2 proton could be explained by the influence of the C-7 methoxycarbonylmethylene substituent acting in either an electronic or a steric manner.

Attempts at C-9 substitution in the clavulanic acid field have frequently led to 1,4-elimination to give the diene (**26**).[6,13] It occurred to us that it might be possible to carry out efficient C-9 substitution reactions on Wittig-modified clavulanates in view of the reduced lability of the C-2 proton in these cases.

To illustrate this the C-7 modified clavulanate (**7b**) was converted into the 9-chloro derivative (**18**) using thionyl chloride and pyridine. Subsequent reaction of (**18**) with sodium cyanide in dimethylformamide afforded the 9-cyano compound (**19**) in 37% yield overall. Similarly, on treatment of (**7b**) with dichloroacetyl chloride and pyridine the crude dichloroacetate (**20**) was isolated. Treatment of (**20**) with diethylamine gave the desired amine (**21**) in 51% yield overall.

The C-7 modified clavulanate (**7b**) can be alkylated in the C-6 position by treating with 3 equiv. of lithium bis(trimethylsilyl)-amide in dry THF and allowing the resulting trianion to react with propionaldehyde. In this way the derivative (**24**) was prepared in 14% yield as a mixture of diastereoisomers. The ^{1}H n.m.r. spectrum of this material indicated a coupling constant of <1 Hz between the C-5 and C-6 protons and on this basis a *trans* stereochemistry was assigned. A by-product of this reaction was the isomerised starting material (**25**) isolated in 7% yield. The expected upfield shift of the C-2 proton[1] for this isomer was observed in the ^{1}H n.m.r. spectrum of (**25**).

In order to achieve a selective ozonolysis of the Wittig adduct (**7b**) it was necessary to generate a saturated solution of ozone in dichloromethane at -70 °C and then to add an equivalent amount of this solution to the adduct (**7b**) also at -70 °C. In order to facilitate this approach a suitable apparatus was constructed, modelled on the design of Rubin.[14] With this technique it was possible to isolate the unstable lactone (**22**) in 44% yield after rapid chromatography. No trace of the β-lactam (**7a**) (from selective ozonolysis of the C-7 double-bond) could be detected in the reaction mixture but this is not altogether surprising in view of the expected lower reactivity of the C-7 double bond to electrophilic ozone.

Subsequent reaction of (**22**) with glacial acetic acid afforded the monocyclic derivative (**23**).

Conclusions

The Wittig reaction between a phosphorane ylide and a β-lactam appears to be finely balanced and a successful outcome depends critically on the nature of the reacting species. The more stable ylides are insufficiently reactive towards β-lactam carbonyls whilst ylides that are too basic lead to degradative side reactions. Similarly, β-lactams that are relatively stable fail to give a Wittig-type product whereas the chemically more sensitive examples degrade at a significant rate under the reaction conditions.

The formation of such olefinic products can be used as a form of β-lactam protection, something not otherwise possible, and the β-lactam carbonyl can be subsequently regenerated by ozonolysis. However, whilst this process is useful in the penicillin series it is of limited value in clavulanic acid chemistry due to the preferential ozonolysis of the C-3 double bond in the deprotection step.

The free acids of the Wittig products in the penicillin and clavulanic acid series showed very little antibacterial or β-lactamase inhibitory activity.

Experimental

M.p.s were determined using a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 197 spectrometer and u.v. spectra on a Pye Unicam SP7-500 instrument. ^{1}H N.m.r. spectra were recorded on either a Perkin-Elmer R32 (90 MHz) or a Bruker WM 250 (250 MHz) spectrometer and $CDCl_3$ solutions included tetramethylsilane as an internal standard. For D_2O solutions the HOD signal at δ 4.6 (90 MHz) or 4.8 p.p.m. (250 MHz) was used as an internal standard. Mass spectra were recorded on a double focusing VG 70-70F mass spectrometer coupled to a Multispec 8 data system. Merck silica gel 60 was used for t.l.c. and column chromatography with ethyl acetate–cyclohexane mixtures as eluant, unless otherwise stated. Solutions were dried over magnesium sulphate before evaporation.

Benzyl (2S,5R,6R)-(Z)-7-*Methoxycarbonylmethylene*-3,3-*dimethyl*-6-*phenoxyacetamido*-4-*thia*-1-*azabicyclo*[3.2.0]-*heptane*-2-*carboxylate* (**1b**) *and* E-*Isomer* (**1c**).—Penicillin V benzyl ester (**1a**) (200 mg, 0.454 mmol) and methoxycarbonylmethylenetriphenylphosphorane (167 mg, 0.50 mmol) in toluene (8 ml) were heated to reflux for 18 h. After this time further phosphorane (80 mg) was added and reflux maintained for a further 6 h. The solvent was then removed under reduced pressure and the residue chromatographed to give compound (**1b**) as a colourless oil (78 mg, 35%); $[\alpha]_D^{20}$ +56° (*c* 0.9, MeOH); $\lambda_{max.}$(EtOH) 268 nm (ε 14 400 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$($CHCl_3$) 1 745, 1 700, 1 690, 1 660, and 1 220 cm^{-1}; δ($CDCl_3$) 1.35 (3 H, s, Me), 1.57 (3 H, s, Me), 3.57 (3 H, s, OMe), 4.51 (2 H, s, OCH_2CO), 4.98 (1 H, s, 2-H), 4.99 (1 H, d, *J ca.* 0.5 Hz vinyl H), 5.21 (2 H, s, OCH_2), 5.42 (1 H, ddd, *J* 9, 5, and 0.5 Hz, 6-H), 5.78 (1 H, d, *J* 5 Hz, 5-H), 6.85—7.35 (10 H, 2 × ArH), and *ca.* 7.3 (1 H, d, *J* 9 Hz, NH); (Found: M^+ 496.1677. $C_{26}H_{28}N_2O_6S$ requires *M*, 496.1667). Further elution gave compound (**1c**) as a colourless oil (73 mg, 32%); $[\alpha]_D^{20}$ +342° (*c* 1.0, MeOH); $\lambda_{max.}$(EtOH) 269 nm (ε 17 800); $\nu_{max.}$($CHCl_3$) 1 745, 1 700, 1 690, 1 660, 1 240, and 1 150 cm^{-1}; δ($CDCl_3$) 1.35 (3 H, s, Me), 1.60 (3 H, s, Me), 3.60 (3 H, s, OMe), 3.91 (1 H, s, 2-H), 4.50 (2 H, s, OCH_2CO), 5.09 (1 H, d, *J* 1 Hz, vinyl H), 5.18 (2 H, s, OCH_2), 5.43 (1 H, ddd, *J* 5, 5, and 1 Hz, 6-H), 5.81 (1 H, d, *J* 5 Hz, 5-H), 6.86—7.35 (10 H, 2 × ArH), and 7.92 (1 H, d, *J* 5 Hz, NH); (Found: M^+ 496.1665).

Benzyl (2S,5R,6R)-(Z)-7-*Benzyloxycarbonylmethylene*-3,3-*dimethyl*-6-*phenoxyacetamido*-4-*thia*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**1d**).—Penicillin V benzyl ester (**1a**) (0.88 g, 2.0 mmol) and benzyloxycarbonylmethylenetriphenylphosphorane (1.0 g, 2.4 mmol) in toluene (30 ml) were heated to reflux for 18 h. The solvent was removed under reduced pressure and the residue chromatographed to give compound (**1d**) as colourless needles (0.39 g, 35%) from ethyl acetate–light petroleum; m.p. 85—86 °C; $[\alpha]_D^{20}$ +54° (*c* 1.0, MeOH); $\lambda_{max.}$(EtOH) 270 nm (ε 18 700); $\nu_{max.}$($CHCl_3$) 1 740, 1 690, 1 660, and 1 600 cm^{-1}; δ($CHCl_3$) 1.35 (3 H, s, Me), 1.53 (3 H, s, Me), 4.50 (2 H, s, OCH_2CO), 5.05 (4 H, overlapping, CH_2Ph, 2-H, vinyl *H*), 5.19 (2 H, s, CH_2Ph), 5.41 (1 H, ddd, *J* 9, 5, and 1 Hz, 6-H), 5.79 (1 H, d, *J* 5 Hz, 5-H), and 6.85—7.35 (16 H, 3 × ArH and NH); (Found: C, 67.4; H, 5.8; N, 5.1; S, 5.7%; M^+ 572.2020. $C_{32}H_{32}N_2O_6S$ requires C, 67.1; H, 5.6; N, 4.9; S, 5.6%; *M* 572.1978). Further elution gave the *E*-isomer (**1e**) and recovered (**1a**) as an inseparable mixture (0.56 g). ^{1}H N.m.r. indicated that the ratio of (**1e**) to (**1a**) was approximately 2:1.

Benzyl (2S,5R,6R)-(Z)-7-*Cyanomethylene*-3,3-*dimethyl*-6-*phenoxyacetamido*-4-*thia*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**1f**) *and* E-*Isomer* (**1g**).—A solution of penicillin V benzyl ester (**1a**) (1.34 g, 3.04 mmol) and cyanomethylenetriphenylphosphorane (1.01 g, 3.38 mmol) in toluene (30 ml) was heated to reflux for 18 h. The solvent was then removed under reduced pressure. The residue was chromatographed to give recovered (**1a**) as an oil (0.10 g, 8%) followed by the *Z*-isomer (**1f**) as a colourless oil (0.51 g, 36%); $[\alpha]_D^{20}$ +35° (*c* 1.1, MeOH); $\lambda_{max.}$(EtOH) 260 nm (ε 12 700); $\nu_{max.}$($CHCl_3$) 2 210, 1 740, 1 685, 1 660, and 1 600 cm^{-1}; δ($CDCl_3$) 1.35 (3 H, s, Me), 1.60 (3 H, s, Me), 4.42 (1 H, d, *J* 1 Hz, vinyl H), 4.50 (2 H, s, OCH_2CO), 4.65 (1 H, s, 2-H), 5.10 and 5.25 (2 H, AB quartet, *J* 12 Hz, CH_2Ph), 5.40 (1 H, ddd, *J* 8.5, 4.5, and 1 Hz, 6-H), 5.79 (1 H, d, *J* 4.5 Hz, 5-H), 6.85—7.35 (11 H, Ar*H* and N*H*); (Found: M^+ 463.1541. $C_{25}H_{25}N_3O_4S$ requires *M*, 463.1563). Continued elution afforded the *E*-isomer (**1g**) as an oil (0.36 g, 26%); $[\alpha]_D^{20}$ +207° (*c* 0.7, MeOH); $\lambda_{max.}$(EtOH) 258 nm (ε 15 200); $\nu_{max.}$($CHCl_3$) 2 210, 1 740, 1 685, 1 660, and 1 600 cm^{-1}; δ($CDCl_3$) 1.35 (3 H, s, Me), 1.60 (3 H, s, Me), 3.87 (1 H, s, 2-H), 4.47 (1 H, d, *J* 1 Hz, vinyl H), 4.43 and 4.65 (2 H, AB quartet, *J* 16 Hz, OCH_2CO), 5.17 (2 H, s, CH_2Ph), *ca.* 5.70 (2 H, overlapping m, 5- and 6-H), and 6.90—7.35 (11 H, 2 × ArH and NH); (Found: M^+ 463.1565).

Reaction of Penicillin V Benzyl Ester (**1a**) *with Acetylmethylenetriphenylphosphorane.*—A solution of the penicillin (**1a**) (220 mg, 0.5 mmol) and the phosphorane (175 mg, 0.55 mmol) in xylene (15 ml) were heated to reflux for 18 h. The solvent was removed under reduced pressure and the residue carefully chromatographed to afford an oil (18 mg, 7%); $\nu_{max.}$($CHCl_3$) 1 730, 1 670, 1 590, and 1 200 cm^{-1}; δ($CDCl_3$) 1.33 (3 H, s, Me), 1.52 (3 H, s, Me), 2.03 (3 H, s, COMe), 4.53 (2 H, s, OCH_2CO), 5.12 and 5.26 (2 H, ABq, *J* 10 Hz, OCH_2), 5.22 (1 H, s, 2-H), 5.35 (1 H, s, vinyl H), 5.39 (1 H, dd, *J* 9 and 5 Hz, 6-H), 5.82 (1 H, d, *J* 5 Hz, 5-H), and 6.85—7.35 (11 H, 2 × ArH and NH). Although this material was never fully purified the above data are consistent with the structure (**1h**).

Reaction of Benzyl Penicillanate (**2a**) *with Methoxycarbonylmethylenetriphenylphosphorane.*—A solution of benzyl penicillanate (**2a**) (0.54 g, 1.86 mmol) and the phosphorane (2.0 g, 6.0 mmol) in xylene (20 ml) was heated to reflux for 24 h. The solvent was removed under reduced pressure and the residue chromatographed to give recovered (**2a**) (17 mg) followed by an oil (131 mg, 16%) $\nu_{max.}$($CHCl_3$) 1 740, 1 695, 1 640, 1 260, and 1 160 cm^{-1}; δ($CDCl_3$) (major isomer) 1.32 (3 H, s, Me), 1.63 (3 H, s, Me), 2.81 (1 H, ddd, *J* 17, 2.0, and 1.5 Hz, 6-H), 3.24 (1 H, ddd, *J* 17, 4.5, and 1.1 Hz, 6-H), 3.54 (3 H, s, OMe), 4.68 (1 H, s, 2-H), 4.80 (1 H, dd, *J* 1.5 and 1.1 Hz, vinyl H), 5.22 (2 H, s, OCH_2), 5.49 (1 H, dd, *J* 4.5 and 2.0 Hz, 5-H), 7.35 (5 H, s, ArH); (minor isomer) 1.32 (3 H, s, Me), 1.63 (3 H, s, Me), 3.20 (1 H, ddd, coupling constants not readily measurable, 6-H), 3.55 (1 H, ddd, 6-H), 3.60 (3 H, s, OMe), 3.96 (1 H, s, 2-H), 5.02 (1 H, dd, vinyl H), 5.18 (2 H, s, OCH_2), 5.49 (1 H, 5-H), and 7.35 (5 H, s, ArH). Although this material was never fully purified the spectroscopic data above is consistent with a 2:1 ratio of the *Z*-and *E*-isomers of compound (**2b**).

Benzyl (2S,5R,6R)-6-*Amino*-(E)-7-*methoxycarbonylmethylene*-3,3-*dimethyl*-4-*thia*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**3b**).—A solution of benzyl 6-aminopenicillanate (**3a**) (1.98 g, 6.46 mmol) and methoxycarbonylmethylenetriphenylphosphorane (2.38 g, 7.10 mmol) in toluene (50 ml) was stirred at reflux for 18 h. The solvent was then evaporated under reduced pressure and the residue chromatographed to afford (**3b**) as a pale oil (0.29 g, 12%); $[\alpha]_D^{20}$ +336° (*c* 1.0, MeOH); $\lambda_{max.}$(EtOH) 267 nm (ε 16 100); $\nu_{max.}$($CHCl_3$), 1 730, 1 700, and 1 645 cm^{-1}; δ($CDCl_3$) 1.40 (3 H, s, Me), 1.68 (3 H, s, Me), 2.15 (2 H, br s, NH_2), 3.66 (3 H, s, OMe), 3.90 (1 H, s, 2-H), 4.57 (1 H, d, *J* 5 Hz, 6-H), 5.00 (1 H, s, vinyl H), 5.20 (2 H, s, CH_2Ph), 5.76 (1 H, d, *J* 5 Hz, 5-H), and 7.38 (5 H, s, ArH); (Found: M^+ 362.1300. $C_{18}H_{22}N_2O_4S$ requires *M*, 362.1300).

Benzyl (2R5R)-(Z)-3-(β-*Hydroxyethylidene*)-(Z)-7-*methoxycarbonylmethylene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**7b**).—Benzyl clavulanate (**7a**) (2.89 g, 10.0 mmol) and methoxycarbonylmethylene triphenylphosphorane (3.35 g, 10.0 mmol) in toluene (40 ml) were heated to reflux for 18 h. Evaporation of the solvent under reduced pressure gave a dark gum which was chromatographed to afford (**7b**) as colourless needles (0.23 g, 7%) from ether; m.p. 85—87 °C; $[\alpha]_D^{20}$ −129° (*c* 0.1; MeOH); $\lambda_{max.}$(EtOH) 257 nm (ε 10 200); $\nu_{max.}$($CHCl_3$) 1 745, 1 710, 1 665, and 1 170 cm^{-1}; δ($CDCl_3$) 2.14 (1 H, br s, OH), 2.80 (1 H, ddd, *J* 17, 1.5, and 1.0 Hz, 6-H), 3.17 (1 H, ddd, *J* 17, 3.1, and 1.4 Hz, 6-H), 3.56 (3 H, s, OMe), 4.16 (2 H, d, *J* 7 Hz, 9-H), 4.83 (1 H, dt, *J* 7 and 0.9 Hz, 8-H), 5.02 (1 H, dd, *J* 1.4 and 1.5 Hz, vinyl H), 5.20 (2 H, s, OCH_2), 5.29 (1 H, d, *J* 0.9 Hz, 2-H), 5.69 (1 H, dd, *J* 3.1 and 1.0 Hz, 5-H), and 7.33 (5 H, s, ArH); (Found: C, 62.9; H, 5.6; N, 4.1%; M^+ 345.1191. $C_{18}H_{19}NO_6$ requires C, 62.6; H, 5.5; N, 4.1%; *M*, 345.1212).

p-*Nitrobenzyl* (2R,5R)-(Z)-7-*Methoxycarbonylmethylene*-(Z)-3-[β-(*tetrahydropyran*-2′-*yl*)*oxyethylidene*]-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**9b**).—The clavulanate (**9a**)[10] (2.19 g, 5.25 mmol) and methoxycarbonylmethylenetriphenylphosphorane (1.76 g, 5.25 mmol) in toluene (50 ml) were heated to reflux for 18 h. The solvent was then removed under reduced pressure and the residue chromatographed to give (**9b**) as an oil (0.76 g, 31%); $[\alpha]_D^{20}$ −121° (*c* 0.8, MeOH); $\lambda_{max.}$(EtOH) 258 nm (ε 19 800); $\nu_{max.}$($CHCl_3$) 1 750, 1 710, 1 665, 1 525, and 1 350 cm^{-1}; δ($CDCl_3$) 1.5—1.8 (6 H, m, CH_2), 2.85 (1 H, d, *J* 17 Hz, 6-H), 3.23 (1 H, dd, *J* 17 and 2 Hz, 6-H), 3.63 (3 H, s, OMe), 3.4—3.8 (2 H, m, OCH_2), 4.1—4.4 (2 H, m, 9-H), 4.6 (1 H, m, OCHO), 4.85 (1 H, t, *J* 7 Hz, 8-H), 5.09 (1 H, m, 10-H), 5.33 (2 H, s, CH_2Ar), 5.39 (1 H, s, 2-H), 5.73 (1 H, d, *J* 2 Hz, 5-H), 7.52 (2 H, d, *J* 9 Hz, ArH), and 8.20 (2 H, d, *J* 9 Hz, ArH); (Found: M^+ 474.1637. $C_{23}H_{26}N_2O_9$ requires *M*, 474.1617).

Ozonolysis of Compound (**1c**).—A stirred solution of the diester (**1c**) (191 mg, 0.39 mmol) in ethyl acetate (25 ml) was cooled (−70 °C) and ozonised oxygen passed through the solution for about 5 min until a pale blue colour was just detectable. Argon was then bubbled through the solution for 30 min. Triphenylphosphine (100 mg, 0.39 mmol) was added and the solution allowed to warm to room temperature over the next 1 h. Evaporation of the solvent afforded crude product which was chromatographed to give penicillin V benzyl ester (**1a**) as an oil (117 mg, 69%), identical to authentic material (t.l.c., i.r., n.m.r.).

Ozonolysis of Compound (**1b**).—A stirred solution of the diester (**1b**) (168 mg, 0.34 mmol) in ethyl acetate (20 ml) was treated as above to afford penicillin V benzyl ester (**1a**) as an oil (142 mg, 95%), identical with authentic material.

Benzyl (2S,5R,6S)-6-*Methoxy*-7-*methoxycarbonyl*-(E)-*methylene*-3,3-*dimethyl*-6-*phenoxyacetamido*-4-*thia*-1-*azabicyclo*-[3.2.0]*heptane*-2-*carboxylate* (**11a**).—A solution of Analar methanol (0.053 ml, 1.55 mmol) in dry THF (40 ml) was cooled, under nitrogen, to −70 °C. A solution of butyl-lithium (1.55 mmol) in hexane was then added and stirring continued at −70 °C for 20 min. The diester (**1c**) (221 mg, 0.445 mmol) in dry THF (5 ml) was now added dropwise but rapidly to the lithium methoxide solution. After 1 min a solution of t-butyl hypochlorite (58 mg, 20% excess) in dry THF (2 ml) was added rapidly and stirring at −70 °C continued for a further 15 min. Glacial acetic acid (1 ml) was then added and the reaction mixture allowed to reach room temperature. Extraction with ethyl acetate and thorough washing with water afforded a crude extract which was chromatographed to afford compound (**11a**) as an oil (38 mg, 16%); $\lambda_{max.}$(EtOH) 276 nm (ε 13 200); $\nu_{max.}$($CHCl_3$) 3 300, 1 740, 1 690, 1 650, 1 600, 1 150, and 1 080 cm^{-1}; δ($CDCl_3$) 1.26 (3 H, s, Me), 1.33 (3 H, s, Me), 3.41 (3 H, s, OMe), 3.68 (3 H, s, COOMe), 3.88 (1 H, s, 2-H), 4.52 (2 H, s, CH_2CO), 5.06 (1 H, s, vinyl H), 5.20 (2 H, s, OCH_2), 5.75 (1 H, s, 5-H), 6.90—7.35 (10 H, 2 × ArH), and 9.65 (1 H, br s, N*H*) (Found: M^+, 526.1740. $C_{27}H_{30}N_2O_7S$ requires *M*, 526.1771).

Ozonolysis of Compound (**11a**).—The methoxy compound (**11a**) (34 mg, 0.065 mmol) in ethyl acetate (10 ml) was stirred at 70 °C and ozone passed slowly through the solution until a pale blue colour was detected. Argon was then passed through the solution for *ca.* 1 h at −70 °C. Triphenylphosphine (20 mg) was now added and the solution allowed to reach room temperature. Stirring was continued for a further 1 h and the solvent evaporated to give an oil. Chromatography afforded benzyl 6α-methoxy-6β-phenoxyacetamidopenicillanate (**11b**) as an oil (10 mg, 33%). I.r. and n.m.r. were identical to literature.[15]

Lithium (2S,5R,6R)-7-*Methoxycarbonyl*-(E)-*methylene*-3,3-*dimethyl*-6-*phenoxyacetamido*-4-*thia*-1-*azabicyclo*[3.2.0]-*heptane*-2-*carboxylate* (**10**).—(a) *By hydrogenation of* (**1c**). The diester (**1c**) (26 mg) in THF (20 ml) was hydrogenated over 10% palladium–charcoal (35 mg) for 5—6 h at ambient temperature and pressure. The mixture was filtered through Celite and some of the THF evaporated under reduced pressure. An equal volume of water was added and the resulting suspension titrated to pH 7 by addition of dilute lithium hydroxide solution. The solvents were then removed under reduced pressure. The resulting oil was triturated with diethyl ether containing a little acetone, to afford lithium salt as a white solid (13 mg, 60%); $[\alpha]_D^{20}$ +289° (*c* 0.4, H_2O); $\lambda_{max.}$(H_2O) 274 nm (ε 18 500); $\nu_{max.}$(KBr) 1 700, 1 640, 1 240 cm^{-1}; δ(D_2O) 1.37 (3 H, s, Me), 1.48 (3 H, s, Me), 3.40 (3 H, s, OMe), 3.70 (1 H, s, 2-H), 4.37 (2 H, s, OCH_2CO), 5.02 (1 H, s, vinyl H), 5.45 (1 H, d, *J* 5 Hz, 6-H), 5.67 (1 H, d, *J* 5 Hz, 5-H), and 6.6—7.1 (5 H, m, ArH). A sample of the salt (9 mg) in dry dimethylformamide (DMF) (0.5 ml) was treated with benzyl bromide (0.010 ml) and stirred for 18 h. After removal of the solvent at reduced pressure the residue was chromatographed to give the benzyl ester (**1c**) as an oil (2 mg), identical to an authentic sample (t.l.c., i.r., n.m.r.).

(b) *By hydrolysis of* (**1c**). A solution of the benzyl ester (**1c**) (0.27 g, 0.545 mmol) in aqueous THF (1:1; 10 ml) was stirred at 20 °C during the addition of 1M aqueous lithium hydroxide. The pH of the solution was kept at 13.0 for 2 h. After this time the solution was neutralised to pH 7.0 by addition of dilute hydrochloric acid and the solvents evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water and the aqueous layer re-evaporated. Chromatography, eluting with butanol–ethanol–water (4:1:1), afforded (**10**) as a pale solid (110 mg, 50%).

Hydrogenation of (**1b**).—A solution of the benzyl ester (**1c**) (182 mg) in THF (20 ml) was hydrogenated over 10% palladium–charcoal (270 mg) for 6 h at ambient temperature and pressure. The reaction mixture was filtered through Celite and the filtrate evaporated to small bulk (10 ml). Water (10 ml) was now added and the pH adjusted to 7.0 by addition of dilute aqueous lithium hydroxide. The solvents were evaporated and the residue triturated with ether–acetone. The organic layer contained mainly starting material (**1b**) (110 mg, 60%). The mixture of salts (**14**) was isolated as a white solid (57 mg, 38%); $\nu_{max.}$(KBr) 1 700, 1 650, 1 240, and 1 210 cm^{-1}; δ(D_2O) (major isomer) 1.43 (3 H, s, Me), 1.53 (3 H, s, Me), and 3.55 (3 H, s, OMe), other signals overlapping with minor isomer; (minor isomer) identical to (**10**). Isomer ratio 3:2.

Oxidation of Benzyl Ester (**1c**) *with* m-*Chloroperbenzoic Acid*.—A stirred solution of the diester (**1c**) (283 mg, 0.57 mmol) in dichloromethane (10 ml) was cooled to 0 °C and treated with *m*-chloroperbenzoic acid (108 mg, 0.63 mmol). After 2 h the solvent was evaporated and the residue partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate. The organic layer was evaporated to afford the sulphoxide (**12**) as a pale solid (300 mg); $\nu_{max.}$($CHCl_3$) 1 740, 1 690, 1 660, 1 230, and 1 140 cm^{-1}; δ($CDCl_3$) 1.08 (3 H, s, Me), 1.65 (3 H, s, Me), 3.52 (3 H, s, OMe), 4.30 (1 H, s, 2-H), 4.51 (2 H, s, OCH_2CO), 5.04 (1 H, d, *J* 1.4 Hz, vinyl H), 5.18 and 5.33 (2 H, ABq, CH_2Ph), 5.20 (1 H, d, *J* 5.2 Hz, 5-H), 6.00 (1 H, ddd, *J* 8.6, 5.2, and 1.4 Hz, 6-H), 6.9—7.35 (10 H, 2 × ArH), and 8.40 (1 H, d, *J* 8.6 Hz, NH) (Found: M^+, 512.1584. $C_{26}H_{28}N_2O_7S$ requires *M*, 512.1616).

Benzyl (2S,5R,6R)-6-[*Benzyloxycarbonyl*-(3-*thienyl*)-*acetamido*]-7-*methoxycarbonyl*-(Z)-*methylene*-3,3-*dimethyl*-4-*thia*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**15b**) *and* E-*Isomer* (**15c**).—A stirred solution of 3-thienylmalonic acid monobenzyl ester (276 mg, 1.0 mmol) in THF (5 ml), containing DMF (1 drop), was cooled to 0 °C and treated with oxalyl chloride (0.13 ml, 1.50 mmol). The mixture was stirred at 20 °C for 1 h and the solvent evaporated under reduced pressure. A stirred solution of the amine (**3b**) (207 mg, 0.57 mmol) in THF (5 ml) at 0 °C was treated with triethylamine (100 mg, 1.0 mmol) followed by a solution of the acid chloride in THF (2 ml) added dropwise over 2 min. After being stirred at 20 °C for 2 h, the reaction mixture was diluted with ethyl acetate, washed with water and saturated aqueous sodium hydrogencarbonate, dried, and evaporated to afford a gum which was chromatographed to give the mixture of diastereomers (**15b**) as an oil (145 mg, 41%); $[\alpha]_D^{20}$ +61° (*c* 1.0, MeOH); $\lambda_{max.}$(EtOH) 270 nm (ε 13 900); $\nu_{max.}$($CHCl_3$) 1 740, 1 700, 1 660, and 1 160 cm^{-1}; δ($CDCl_3$) 1.30 (3 H, s, Me), 1.49 and 1.52 (3 H, s, Me), 3.54 and 3.56 (3 H, s, OMe), 4.70 (1 H, s), 4.87 and 4.98 (1 H, s), 4.95 (1 H, s), 5.17 (4 H, s, CH_2Ph), 5.29 (1 H, dd, *J* 9 and 5 Hz 6-H), 5.69 (1 H, m, 5-H), and 7.00—7.40 (14 H, Ar*H* and N*H*); (Found: M^+, 620.1668. $C_{32}H_{32}N_2O_7S_2$ requires *M*, 620.1651). Continued elution afforded the *E*-isomer (**15c**) as an oil (93 mg, 26%); $[\alpha]_D^{20}$ +254° (*c* 1.1, MeOH); $\lambda_{max.}$(EtOH) 266 nm (ε 17 100); $\nu_{max.}$($CHCl_3$) 1 740, 1 700, 1 660, and 1 160 cm^{-1}; δ($CDCl_3$) 1.30 (3 H, s, Me), 1.53 (3 H, s, Me), 3.45 and 3.52 (3 H, s, OMe), 3.86 (1 H, s, 2-H), 4.70 (1 H, s, CH), 5.02 (1 H, m, vinyl H), 5.15 and 5.17 (4 H, s, CH_2Ph), 5.31 (1 H, m, 6-H), 5.72 (1 H, m, 5-H), and 7.0—7.35 (14 H, Ar*H* and N*H*); (Found: M^+, 620.1653).

Benzyl 6β-[*Benzyloxycarbonyl*(3-*thienyl*)*acetamido*]*penicillanate* (**15a**).—(a) *By ozonolysis of* (**15b**) *and* (**15c**). A solution of the isomeric mixture (**15b**) and (**15c**) (0.41 g, 0.66 mmol) in ethyl acetate (20 ml) was cooled (−70 °C) and ozonised oxygen passed through the solution for *ca.* 5 min. The system was then flushed with argon for 30 min and triphenylphosphine (350 mg) added. The solution was then stirred for 1 h at room temperature. Evaporation of the solvent afforded an oil which was chromatographed to give compound (**15a**) as an oil (180 mg, 49%), the i.r. and ^1H n.m.r. of which were identical with those of authentic material (see below).

(b) *By esterification of ticarcillin disodium salt* (**15d**). A stirred solution of (**15d**) (50 mg, 0.117 mol) in DMF (1 ml) was treated with benzyl bromide (0.035 ml, 0.30 mmol) and left for 18 h. The solvent was then removed under reduced pressure and the residue chromatographed to give the diester (**15a**) as an oil (40 mg, 61%); $[\alpha]_D^{20}$ +166° (*c* 0.5, MeOH); $\nu_{max.}$($CHCl_3$) 1 790, 1 740, 1 680, and 1 160 cm^{-1}; δ($CDCl_3$) 1.38, 1.48, and 1.53 (6 H, 2 × Me), 4.42 and 4.45 (1 H), 4.71 and 4.74 (1 H), 5.15 and 5.18 (4 H, CH_2Ph), 5.45—5.68 (2 H, m, 5- and 6-H), 7.1—7.35 (14 H, ArH + NH) (Found: C, 61.4; H, 5.0; N, 4.8; S, 11.0%; M^+, 564.1400. $C_{29}H_{28}N_2O_6S_2$ requires C, 61.7; H, 5.0; N, 5.0; S, 11.3%; *M*, 564.1389).

p-*Nitrobenzyl* (2R,5R)-(Z)-3-(β-*Hydroxyethylidene*)-7-*methoxycarbonyl*-(Z)-*methylene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**8b**).—A stirred solution of the tetrahydropyranyl ether (**9b**) (234 mg, 0.5 mmol) in ethanol (4 ml) at 55 °C was treated with pyridinium toluene-*p*-sulphonate (13 mg, 0.05 mmol). The solvent was then removed under reduced pressure and the residue chromatographed to give recovered (**9b**) (63 mg, 27%) followed by (**8b**) (120 mg, 62%) as needles from ethyl acetate–cyclohexane; m.p. 88—89 °C; $[\alpha]_D^{20}$ −120° (*c* 1.1, MeOH); $\lambda_{max.}$(EtOH) 258 nm (ε 19 200); $\nu_{max.}$($CHCl_3$) 1 750, 1 700, 1 660, 1 520, and 1 340 cm^{-1}; δ($CDCl_3$) 1.63 (1 H, br s, OH), 2.88 (1 H, d, *J* 17 Hz, 6-H), 3.24 (1 H, dd, *J* 17 and 3 Hz, 6-H), 3.64 (3 H, s, OMe), 4.24 (2 H, d, *J* 7 Hz, 9-H), 4.90 (1 H, t, *J* 7 Hz, 8-H), 5.10 (1 H, m, vinyl H), 5.33 (2 H, s, CH_2Ar), 5.39 (1 H, s, 2-H), 5.75 (1 H, d, *J* 3 Hz, 5-H), 7.54 (2 H, d, *J* 9 Hz, ArH), and 8.21 (2 H, d, *J* 9 Hz, ArH); (Found: C, 55.5; H, 4.8; N, 7.2%; M^+, 390.1066. $C_{18}H_{18}N_2O_8$ requires C, 55.4; H, 4.7; N, 7.2%; *M*, 390.1036).

Lithium (2R,5R)-(Z)-3-(β-*Hydroxyethylidene*)-7-*methoxycarbonyl*-(Z)-*methylene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**16a**).—A solution of the *p*-nitrobenzyl ester (**9b**) (93 mg, 0.24 mmol) in THF (20 ml) was hydrogenated over 10% palladium–charcoal (30 mg) at ambient temperature and pressure for 15 min. The suspension was then filtered and the filtrate diluted with an equal volume of water. The stirred solution was then neutralised to pH 7.0 by addition of dilute aqueous lithium hydroxide and the solvents evaporated under reduced pressure. Trituration of the residue with diethyl ether afforded (**16a**) as a pale solid (42 mg, 67%) the i.r. and ^{1}H n.m.r. spectra of which were identical with those of the sodium salt (**16b**) (see below).

Sodium (2R,5R)-(Z)-3-(β-*Hydroxyethylidene*)-7-*methoxycarbonyl*-(Z)-*methylene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**16b**).—A stirred solution of the ester (**7b**) (104 mg, 0.30 mmol) in aqueous THF (20 ml, 1:1) was maintained at pH 12.0—12.5 by addition of 1M aqueous sodium hydroxide dispensed from an automatic burette. After 1 h the pH of the solution was brought to 7.0 by addition of dilute hydrochloric acid and the solvents evaporated under reduced pressure. The residue was chromatographed eluting with butanol–ethanol–water (4:1:1) to give (**16b**) as a white solid (83 mg, 100%); $[\alpha]_D^{20}$ −151° (*c* 0.8, H_2O); $\lambda_{max.}$(H_2O) 265 nm (ε 12 100); $\nu_{max.}$(KBr) 1 700, 1 650, 1 600, and 1 200 cm^{-1}; δ(D_2O) 2.98 (1 H, d, *J* 17 Hz, 6-H), 3.30 (1 H, dd, *J* 17 and 5 Hz, 6-H), 3.67 (3 H, s, OMe), 4.17 (2 H, d, *J* 8 Hz, 9-H), 4.85 (1 H, m, vinyl H), 4.88 (1 H, t, *J* 8 Hz, 8-H), 5.09 (1 H, s, 2-H), and 5.72 (1 H, d, *J* 5 Hz, 5-H). A sample of the salt (**16b**) (38 mg, 0.137 mmol) in DMF (1 ml) was stirred and treated with benzyl bromide (0.020 ml, 0.168 mmol). The reaction mixture was stirred overnight and the solvent then removed under reduced pressure. The residue was chromatographed to afford the benzyl ester (**7b**) as a solid (30 mg, 64%) the t.l.c., i.r., and ^{1}H n.m.r. spectra of which were identical with those of an authentic sample.

Benzyl (2R,5R)-(Z)-3-(β-*Cyanoethylidene*)-7-*methoxycarbonyl*-(Z)-*methylene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**19**).—A solution of the hydroxy compound (**7b**) (217 mg, 0.63 mmol) in ethyl acetate (5 ml) was stirred and cooled to −60 °C. Pyridine (0.068 ml, 0.84 mmol) was added followed by thionyl chloride (0.055 ml, 0.76 mmol) and the resulting suspension allowed to warm to 20 °C over the next 30 min. The suspension was diluted with diethyl ether and washed with 10% aqueous citric acid, saturated aqueous sodium hydrogencarbonate, and finally with water. Evaporation of the solvent afforded the chloro derivative (**18**) as an unstable oil. A solution of (**18**) (0.63 mmol) in dry DMF (2 ml) at −10 °C was treated with sodium cyanide (60 mg, 1.2 mmol) and stirred for 30 min. The temperature was then allowed to rise to 0 °C and stirring was continued for a further 30 min. The resulting dark solution was diluted with ethyl acetate and washed with water. The solution was dried ($MgSO_4$) and evaporated and the residue chromatographed to afford (**19**) as colourless needles (82 mg, 37%) from chloroform–ethyl acetate–cyclohexane; m.p. 123—125 °C; $[\alpha]_D^{20}$ −164 °C (*c* 0.3, MeOH); $\lambda_{max.}$(EtOH) 257 nm (ε 12 900); $\nu_{max.}$($CHCl_3$) 2 250, 1 740, 1 700, and 1 660 cm^{-1}; δ($CDCl_3$) 2.84 (1 H, d, *J* 17 Hz, 6-H), 3.08 (2 H, d, *J* 7 Hz, 9-H), 3.25 (1 H, dd, *J* 17 and 3 Hz, 6-H), 3.60 (3 H, s, OMe), 4.57 (1 H, t, *J* 7 Hz, 8-H), 5.07 (1 H, t, *J* 0.5 Hz vinyl H), 5.23 (2 H, s, CH_2Ph), 5.37 (1 H, s, 2-H), 5.76 (1 H, d, *J* 3 Hz, 5-H), and 7.34 (5 H, s, ArH) (Found: C, 64.4; H, 5.1; N, 8.0%; M^+, 354.1204. $C_{19}H_{18}N_2O_5$ requires C, 64.4; H, 5.1; N, 7.9%; *M*, 354.1216).

Benzyl (2R,5R)-(Z)-3-(β-*Dichloroacetoxyethylidene*)-7-*methoxycarbonyl*-(Z)-*methylene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**20**).—A solution of the hydroxy compound (**7b**) (181 mg, 0.53 mmol) in dichloromethane (5 ml) was stirred and cooled to 0 °C. Pyridine (0.043 ml, 42 mg, 0.53 mmol) was added followed by dichloroacetyl chloride (0.050 ml, 78 mg, 0.53 mmol) and stirring at 0 °C was maintained for a further 30 min. The reaction mixture was diluted with dichloromethane and washed successively with aqueous citric acid, water, and brine to afford, after evaporation of the solvent, the desired product (**20**) as an oil (260 mg); $\nu_{max.}$($CHCl_3$) 1 740, 1 700, and 1 660 cm^{-1}; δ($CDCl_3$), 2.87 (1 H, d, *J* 17 Hz, 6-H), 3.23 (1 H, dd, *J* 17 and 3 Hz, 6-H), 3.60 (3 H, s, OMe), 4.82 (3 H, 8- and 9-H), 5.08 (1 H, t, *J* 1 Hz, vinyl H), 5.22 (2 H, s, CH_2Ph), 5.38 (1 H, s, 2-H), 5.77 (1 H, d, *J* 3 Hz, 5-H), 5.89 (1 H, s, $CHCl_2$), 7.35 (5 H, s, ArH) (Found: M^+, 455.0521. $C_{20}H_{19}Cl_2NO_7$ requires *M*, 455.0538).

Benzyl (2R,5R)-(Z)-3-(β-*Diethylaminoethylidene*)-7-*methoxycarbonyl*-(Z)-*methylene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**21**).—A solution of the dichloroacetate (**20**) (260 mg, 0.53 mmol) in DMF (5 ml) was treated with diethylamine (0.11 ml, 78 mg, 1.06 mmol) and stirred at room temperature for 2 h. The solution was diluted with ethyl acetate, washed with water, dried ($MgSO_4$), and evaporated and the residue chromatographed. Elution with ethyl acetate–methanol (1:1) afforded compound (**21**) as a yellow oil (108 mg, 51%); $[\alpha]_D^{20}$ −118° (*c* 0.1, $CHCl_3$); $\lambda_{max.}$(EtOH) 257 nm (ε 11 400); $\nu_{max.}$($CHCl_3$) 1 740, 1 700, 1 660, and 1 620 cm^{-1}; δ($CDCl_3$) 1.00 (6 H, t, *J* 7 Hz, 2 × CH_2CH_3), 2.43 (4 H, q, *J* 7 Hz, 2 × CH_2CH_3), 2.78 (1 H, d, *J* 17 Hz, 6-H), 3.20 (1 H, dd, *J* 17 and 3 Hz, 6-H), 3.25 (2 H, d, *J* 7 Hz, 9-H), 3.59 (3 H, s, OMe), 4.69 (1 H, t, *J* 7 Hz, 8-H), 5.05 (1 H, t, *J* 0.5 Hz, vinyl H), 5.22 (2 H, s, CH_2Ph), 5.30 (1 H, s, 2-H), 5.71 (1 H, d, *J* 3 Hz, 5-H), and 7.33 (5 H, s, ArH) (Found: M^+, 400.2013. $C_{22}H_{28}N_2O_5$ requires *M*, 400.1998).

Benzyl (2R,5R,6R)-(Z)-3-(β-*Hydroxyethylidene*)-6-(1-*hydroxypropyl*)-7-*methoxycarbonyl*-(Z)-*methylene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**24**) *and Benzyl* (2R,5R)-Z-3-(β-*Hydroxyethylidene*)-7-*methoxycarbonyl*-(E)-*methylene*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**25**).—A stirred solution of hexamethyldisilazane (1.77 g, 11.0 mmol) in dry THF (60 ml) in a nitrogen atmosphere was cooled to −20 °C and treated with butyl-lithium (2.4M solution in hexane; 4.6 ml, 11.0 mmol). The temperature was maintained at −20 °C for 20 min and then allowed to cool to −78 °C. A solution of the diester (**7b**) (1.26 g, 3.66 mmol) in dry THF (10 ml) was now added dropwise, but rapidly, to the cooled solution. After a further 20 min, redistilled propionaldehyde (212 mg, 3.66 mmol) in dry THF (2 ml) was added dropwise to the stirred solution and the temperature maintained at −78 °C for a further 2 h. The reaction was quenched with 10% aqueous citric acid and the temperature allowed to reach 20 °C. The resulting mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water and brine, dried ($MgSO_4$), and evaporated to afford the crude product. Chromatography afforded (**25**) as an oil (91 mg, 7%); $\lambda_{max.}$(EtOH) 254 nm (ε 11 600); $\nu_{max.}$($CHCl_3$) 1 740, 1 700, 1 660, and 1 600 cm^{-1}; δ($CDCl_3$) 1.90 (1 H, br s, OH), 3.18 (1 H, d, *J* 17 Hz, 6-H), 3.45 (1 H, ddd, *J* 17, 3, and 1 Hz, 6-H), 3.65 (3 H, s, OMe), 4.22 (2 H, m, 9-H), 4.56 (1 H, s, 2-H), 4.84 (1 H, t, *J* 7 Hz, 8-H), 5.19 (2 H, s, OCH_2Ph), 5.31 (1 H, m, vinyl H), 5.77 (1 H, d, *J* 3 Hz, 5-H), 7.36 (5 H, s, ArH) (Found: M^+, 345.1224. $C_{18}H_{19}NO_6$ requires *M*, 345.1210). Continued elution afforded recovered (**7b**) (212 mg, 17% followed by a 1:2 mixture of diastereoisomers (**24**) as an oil (212 mg, 14%); $\lambda_{max.}$(EtOH) 263 nm (ε 11 600); $\nu_{max.}$($CHCl_3$) 3 400, 1 740, 1 700, and 1 660 cm^{-1}; δ($CDCl_3$) 0.97 (3 H, t, *J* 7 Hz, CH_2Me), 1.58 (2 H, m, CH_2Me), 2.70 (2 H, br s, 2 × OH), 3.10 (1 H, d, *J* 6 Hz, 6-H), 3.57 and 3.62 (3 H, s, OMe), 3.8 (1 H, m, CHOH), 4.15 (2 H, d, *J* 7 Hz, 9-H), 4.82 (1 H, t, *J* 7 Hz, 8-H), 5.05 and 5.15 (1 H, d, *J* 1 Hz vinyl H), 5.21 (2 H, s, CH_2Ph), 5.25 (1 H, s, 2-H), 5.60 and 5.70 (1 H, s, 5-H), 7.33 (5 H, s, ArH) (Found: M^+, 403.1611. $C_{21}H_{25}NO_7$ requires *M*, 403.1627).

Benzyl (2S,5R)-(Z)-7-*Methoxycarbonylmethylene*-3-*oxo*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**22**).—A solution of the benzyl ester (**7b**) (508 mg, 1.47 mmol) in dichloromethane (20 ml) was stirred at −70 °C and treated rapidly with a saturated solution (at −70 °C) of ozone in dichloromethane (45 ml, *ca.* 1.8 mmol of ozone) also at −70 °C. The solution was stirred at this temperature for 15 min, triphenylphosphine (400 mg) in dichloromethane solution was added, and the resulting solution was allowed to reach 20 °C over the next 1 h. The solvent was evaporated and the residue rapidly chromatographed to afford the unstable lactone (**22**) as an oil (202 mg, 44%); $[\alpha]_D^{20}$ +57° (*c* 0.2, $CHCl_3$); $\lambda_{max.}$(EtOH) 261 nm (ε 10 700); $\nu_{max.}$($CHCl_3$) 1 810, 1 790, 1 745, 1 700, and 1 660 cm^{-1}; δ($CDCl_3$) 3.03 (1 H, dd, *J* 17 and 1 Hz 6-H), 3.37 (1 H, ddd, *J* 17, 3, and 1 Hz, 6-H), 3.60 (3 H, s, OMe), 5.17 (2 H, s, 2-H and vinyl H), 5.28 (2 H, s, CH_2Ph), 5.85 (1 H, d, *J* 3 Hz, 5-H), and 7.35 (5 H, s, ArH); (Found: M^+, 317.0903. $C_{16}H_{15}NO_6$ requires *M*, 317.0899).

2-*Acetoxy*-1-*benzyloxycarbonylmethyl*-4-*methoxycarbonyl*-(Z)-*methyleneazetidine* (**23**).—A solution of the lactone (**22**) (32 mg) in glacial acetic acid (1 ml) was stirred at 20 °C for 1 h. The solution was diluted with ethyl acetate and washed with saturated aqueous sodium hydrogencarbonate and water. The solution was dried and evaporated and the residue chromatographed to give the azetidine (**23**) as colourless plates (16 mg, 48%) from ethyl acetate–cyclohexane, m.p. 95—98 °C; $[\alpha]_D^{20}$ −17° (*c* 0.1, $CHCl_3$); $\lambda_{max.}$(EtOH) 260 nm (ε 21 300); $\nu_{max.}$($CHCl_3$) 1 740, 1 700, 1 640, 1 230, and 1 180 cm^{-1}; δ($CDCl_3$) 2.03 (3 H, s, Me), 3.14 (1 H, dd, *J* 17 and 2 Hz, 3-H), 3.50 (1 H, dd, *J* 17 and 5 Hz, 3-H), 3.60 (3 H, s, OMe), 3.92 (2 H, s, NCH_2), 4.70 (1 H, s, vinyl H), 5.16 (2 H, s, CH_2Ph), 6.16 (1 H, dd, *J* 5 and 2 Hz, 2-H), 7.34 (5 H, s, ArH) (Found: C, 61.5; H, 6.0; N, 4.3%; M^+, 333.1234. $C_{17}H_{19}NO_6$ requires C, 61.3; H, 5.7; N, 4.2%; *M*, 333.1212).

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