Synthesis of Novel 2-Oxo-4-thia-1-azabicyclo[3.3.0]oct-7-ene-8-carboxylic Acid Derivatives

Steven Coulton* and Robert Southgate
SmithKline Beecham Pharmaceuticals, Research Division, Brockham Park, Betchworth, Surrey, RH3 7AJ, UK

The bicyclic thiazolidinone-carbapenem analogues, **18**, **19** and **37** have been prepared from thioglycolamide **5** and 3-triphenylmethoxypropionaldehyde **7**, *via* 2-(2-triphenylmethoxyethyl)thiazolidin-4-one **8**.

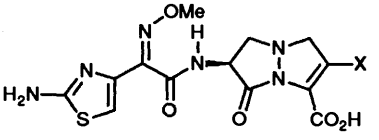
Elaboration of the thiazolidin-4-one **8** to the phosphorane **11**, followed by detritylation, oxidation, and cyclization provided the bicyclic ester **14**, which could be oxidized to the sulfoxide **15**.

Functionalization at the C-5 position of the thiazolidin-4-one required protection as the tetrahydrothiazolo-1,3-oxazine **22**, which upon reaction with lithium diisopropylamide, toluene-*p*-sulfonyl azide and acetic acid provided the azido derivative **23** in 76% yield. Reduction and acylation, followed by acid catalysed hydrolysis gave 2-(2-hydroxyethyl)-5-phenylacetamidothiazolidin-4-one **28**, which was oxidized to the aldehyde **29**. The aldehyde functionality was masked as the α,β-unsaturated ester **31** during the process of ylide construction. Regeneration of the aldehyde moiety could then be achieved by selective ozonolysis of phosphorane **34**. The phosphorane-aldehyde **35** thus formed spontaneously cyclized to the bicyclic thiazolidinone ester **36**.

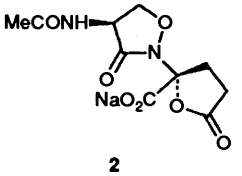
Removal of the carboxylate protecting groups of the bicyclic thiazolidinone derivatives **14**, **15** and **36** then provided the sodium salts of the carboxylic acids **18**, **19** and **37**, respectively.

The recent discovery of the antibacterially active bicyclic pyrazolidinone derivatives **1**[1] and lactivicin **2**[2] has signalled a resurgence of interest in the synthesis of novel, non-β-lactam compounds which may inhibit bacterial transpeptidase enzymes. Much of the recent attention has focused upon the replacement of the β-lactam ring of the β-lactam antibiotic with another functionality, such as a γ-lactam ring, with a view to developing new families of antibacterial agents.[3]

The reported microbiological activity of the monocyclic thiazolidin-4-one **3**[4] prompted us to prepare bicyclic thiazolidinone analogues of the carbapenem[5] family of antibiotics. The present paper describes their preparation from thioglycolamide **5** and 3-triphenylmethoxypropionaldehyde **7**, *via* 2-(2-triphenylmethoxyethyl)thiazolidin-4-one **8**.



1 X = COMe, CO_2Me



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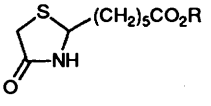


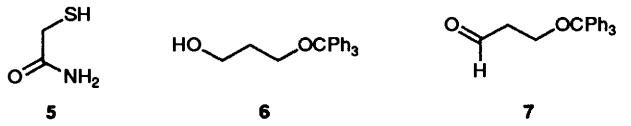
3 R = H
4 R = Me

Results and Discussion

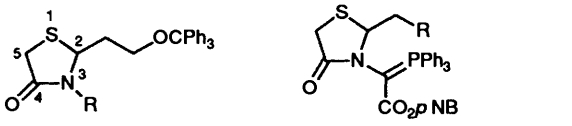
The 2-(5-carboxypentyl)thiazolidin-4-one **3** was prepared by Pennington *et al.*,[4] using the acid catalysed condensation of thioglycolamide with methyl 7-oxoheptanoate in refluxing benzene, followed by basic hydrolysis of the resulting ester **4**. We have adopted this procedure to prepare a thiazolidin-4-one derivative suitably functionalized at the C-2 position for subsequent elaboration of the second ring and which would permit the introduction of other functional groups at the C-5 position. To this end, acid catalysed condensation of thioglycolamide **5** with 3-triphenylmethoxypropionaldehyde **7** in refluxing benzene, with the provision for the continuous removal of water, provided the 2-(2-triphenylmethoxyethyl)-thiazolidin-4-one **8** in 30% yield.

The bicyclic ring system was then constructed by means of the well established intramolecular Wittig cyclization reaction, first reported by R. B. Woodward.[6] Condensation of the thiazolidinone **8** with *p*-nitrobenzyl glyoxylate afforded a diastereoisomeric mixture of hydroxyacetates **9**, which upon treatment with thionyl chloride and 2,6-lutidine gave the chloroacetates **10**. Compared to chloroacetates of azetidinone derivatives, the chloroacetate **10** was remarkably unreactive. Indeed, it required quite forceful conditions for conversion to the phosphorane **11**; reaction of the chloroacetate **10** with triphenylphosphine and 2,6-lutidine in a concentrated solution of 1,4-dioxane at 85 °C for 18 hours gave the phosphorane **11** in 65% yield. The preparation of azetidinone phosphoranes required much lower temperatures and reaction times. With the phosphorane **11** in hand, detritylation in aqueous acetic acid at 95 °C gave the phosphorane alcohol **12** in 60% yield. Oxidation of the alcohol **12** to the aldehyde **13** was achieved by reaction with sulfur trioxide–pyridine complex and triethylamine in dimethyl sulfoxide (DMSO); the aldehyde **13** cyclized spontaneously to the bicyclic thiazolidinone derivative **14**, which was isolated in 50% yield.

Attempts to oxidize the sulfide **14** to the sulfone **16** were unsuccessful. The sulfone spontaneously ring opened to the *N*-acetylpyrrole **17**, presumably with the liberation of sulfur dioxide. The sulfoxide **15** could however be prepared in

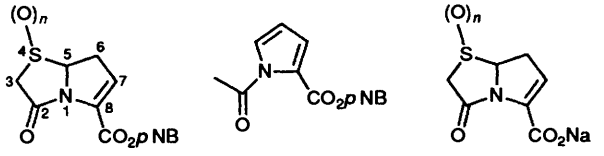


5 6 7



8 R = H
9 R = 
10 R = 
11 R = 

12 R = CH_2OH
13 R = CHO



14 n = 0
15 n = 1
16 n = 2

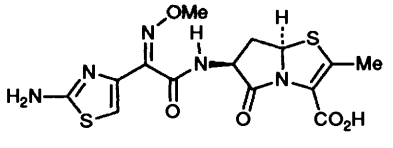
17

18 n = 0
19 n = 1

pNB = p-nitrobenzyl

quantitative yield by the oxidation of the bicyclic sulfide **14** with 1 equivalent of *m*-chloroperoxybenzoic acid.

Reductive removal of the *p*-nitrobenzyl protecting groups of the bicyclic esters **14** and **15** then provided the sodium salts **18** and **19**. Disappointingly, neither compound displayed antibacterial activity against a range of Gram-positive and Gram-negative organisms.



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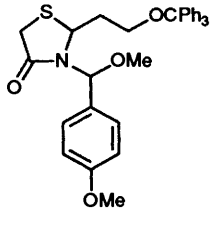


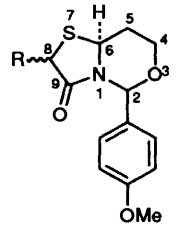
21

Morin and co-workers[7,8] established that the 7-acylamino side chain was necessary in order to confer antibacterial activity upon the γ-lactam analogues of the penems **20**. We therefore sought to prepare the analogous acylamino-substituted bicyclic thiazolidinone-carbapenem derivative.

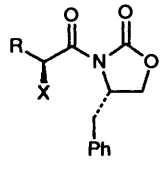
* All new compounds are racemic. Only one enantiomer is depicted for convenience.

Functionalization at the C-5 position of the monocyclic thiazolidin-4-one **8** required protection of the thiazolidinone NH atom. We and other workers have previously protected γ-lactam[9] and azetidin-2-one[10] derivatives as the *N*-α-methoxy-*p*-methoxybenzyl derivative.

Reaction of the thiazolidinone **8** with anisaldehyde dimethylacetal in the presence of boron trifluoride–diethyl ether gave, not the *N*-α-methoxy-*p*-methoxybenzyl thiazolidinone derivative **21**, but the tetrahydrothiazolo-1,3-oxazine **22** in 85% yield. This was not surprising since triphenylmethyl ethers are known to cleave under such conditions.[11] Nevertheless, the tetrahydrothiazolo-1,3-oxazine **22** was a suitably protected thiazolidinone derivative, which was compatible with the carbanion chemistry necessary for the introduction of the acylamino side chain.



22 R = H
23 R = N_3
24 R = NH_2
25 R = $NHCOCH_2Ph$



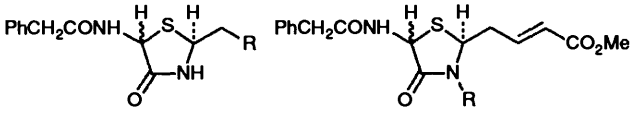
26 X = H
27 X = N_3

Electrophilic azide transfer was first reported by Kuhlein and Jensen[12] for the α-azidation of azetidin-2-ones. We applied their procedure to the α-azidation of the protected thiazolidinone **22**. Reaction of **22** with lithium diisopropylamide in THF at −78 °C, followed by toluene-*p*-sulfonyl azide (tosyl azide) and trimethylsilyl chloride gave the α-azido derivative **23** in consistently low yields (0–21%). In general, the reactions of enolates with arenesulfonyl azides are documented to give several types of products depending upon the course of fragmentation of the presumed intermediate 1:1 adduct.[13,14] According to the method of Kuhlein and Jensen, quenching the primary reaction product of the lithium enolate and tosyl azide with trimethylsilyl chloride is reported to promote azide transfer at the expense of diazo transfer. D. A. Evans and T. C. Britton[15] have systematically studied the reaction parameters and found that the optimum reagents for electrophilic azidation of *N*-acyloxazolidinones **26** were potassium hexamethyldisilazide, 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide) and acetic acid. They reported that the yield of azide transfer increased at the expense of competing diazo transfer as the enolate counterion became more electropositive (Li ≪ Na < K) and as the azide transfer reagent became more electron-rich and sterically demanding (*p*-nitrobenzenesulfonyl azide < tosyl azide < trisyl azide). In addition, the quench reagent was found to be an essential ingredient for successful azide transfer; acetic acid proved to be superior to trimethylsilyl chloride, trimethylsilyl triflate or TFA. Mechanistic studies revealed that the potassium acetate generated by the addition of acetic acid was highly

effective in promoting the decomposition of the intermediate triazine to the α-azidocarboximide **27**, whereas lithium acetate was ineffective in this respect.

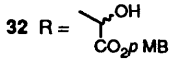
We investigated the use of these reagents in order to optimise the preparation of the azidothiazolidinone derivative **23**. Disappointingly, the use of potassium hexamethyldisilazide, trisyl azide or tosyl azide and acetic acid gave only unchanged starting material. The use of lithium diisopropylamide, tosyl azide and acetic acid meanwhile gave the desired azide **23** in consistently high yields (70–76%). It was therefore apparent that the critical reagent in this reaction was the acetic acid; merely replacing the trimethylsilyl chloride by acetic acid resulted in a much superior and efficient reaction. The product **23** was obtained as a diastereoisomeric mixture in the approximate ratio of 3:1. Since the tetrahydrothiazolo-1,3-oxazine **22** appeared to be diastereoisomerically pure by ^{1}H NMR spectroscopy, it was assumed that the product azides **23** were diastereoisomeric at the C-8 position.

Hydrogenation of **23** in the presence of 10% Pd/C catalyst gave the amine **24**, which was immediately acylated to provide the diastereoisomeric phenylacetamido derivatives **25** in 66% yield. Acid catalysed hydrolysis of the tetrahydrothiazolo-1,3-oxazine **25** then gave the 2,5-disubstituted thiazolidin-4-one **28** in 74% yield, again as a diastereoisomeric mixture. Oxidation of the alcohol **28** using water soluble carbodiimide, pyridine, and TFA (trifluoroacetic acid) in dimethyl sulfoxide–toluene gave the aldehyde **29** (30%), together with a small quantity of the thioether by-product **30** (11%).

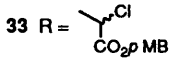


28 R = CH_2OH
29 R = CHO
30 R = $CH_2OCH_2SCH_3$

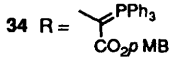
31 R = H



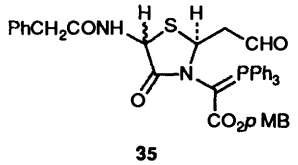
32 R =



33 R =



34 R =



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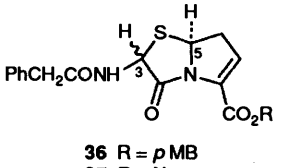

36 R = *p*MB
37 R = Na

*p*MB = *p*-methoxybenzyl

Masking of the aldehyde moiety during the construction of the thiazolidinone phosphorane was achieved by reaction of the aldehyde **29** with the stabilized Wittig reagent, methoxycarbonylmethylenetriphenylphosphorane,[16] the (*E*)-α,β-unsaturated aldehyde **31** being isolated in 87% yield as a 3:1 mixture of diastereoisomers. None of the (*Z*)-geometric isomer was evident by NMR spectroscopy. This ester **31** was then elaborated to the phosphorane **34** by the same procedure described for the C-5 unsubstituted phosphorane **11**. Condensation with *p*-methoxybenzyl glyoxylate in refluxing benzene furnished the diastereoisomeric hemiaminals **32**, which upon treatment with thionyl chloride and 2,6-lutidine gave the chloroacetates **33**. As in the case of the C-5 unsubstituted thiazolidinone series, the chloroacetates **33** were remarkably unreactive; reaction with triphenylphosphine and 2,6-lutidine under forceful conditions (80 °C, 16 h) provided the phosphorane **34** in 43% yield. Regeneration of the aldehyde moiety could then be achieved by ozonolysis in the presence of excess trifluoroacetic acid, the phosphorane functionality being protected against ozonolytic cleavage by reversible protonation.[17] Thus, ozonolysis of phosphorane **34** in ethyl acetate–trifluoroacetic acid (3.5:1) at −78 °C, followed by neutralization with sodium hydrogen carbonate, produced the aldehyde phosphorane **35**, which spontaneously cyclized to the bicyclic thiazolidinone **36** (35% yield). Again, ^{1}H NMR spectroscopy indicated a 3:1 mixture of diastereoisomers. Although not conclusive, nuclear Overhauser enhancement spectroscopy (NOESY) suggested that the major isomer was the C-3,5-*cis*-isomer. Irradiation at 5-H in the major isomer gave rise to a small enhancement (2%) at 3-H of the major isomer, whereas irradiation at 5-H in the minor isomer resulted in no enhancement whatsoever at 3-H.

Finally, Lewis acid-mediated deprotection[18] of the diastereoisomeric esters **36** using ethyl aluminium dichloride in anisole–dichloromethane gave the sodium salt of 2-oxo-3-phenylacetamido-4-thia-1-azabicyclo[3.3.0]oct-7-ene-8-carboxylic acid **37**, thereby completing the synthesis of the novel bicyclic thiazolidinone-carbapenem analogue from thioglycolamide and 3-triphenylmethoxypropionaldehyde.

Disappointingly, like the unsubstituted bicyclic thiazolidinones **18** and **19**, the 3-phenylacetamido derivative **37** was also devoid of both antibacterial activity and β-lactamase inhibitory activity.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. UV spectra were recorded on a Pye Unicam SP7-500 UV–VIS spectrophotometer. IR spectra were recorded on a Perkin-Elmer 197 or 983 machine. ^{1}H NMR spectra were recorded at 90 MHz on a Perkin-Elmer R32 and at 250 MHz on a Bruker WM250 instrument with tetramethylsilane as internal standard for spectra in $CDCl_3$ and [$^2H_7$]DMF, and acetonitrile as external standard for spectra in D_2O. *J* Values are given in Hz. Mass spectra were recorded on either a VG-ZAB double focussing spectrometer, a VG TRIO-2 quadrupole spectrometer or a Finnigan MAT TSQ70 spectrometer. Fast atom bombardment (FAB) mass spectra were recorded using either thioglycerol or 3-nitrobenzyl alcohol/sodium acetate (3-NOBA/NA) as matrix. The purity of all compounds was tested by TLC on Merck pre-coated silica gel 60 F_{254} plates. Preparative chromatography was carried out on columns of Merck silica gel 60, using the slightly increased pressure provided by a Medcalf Hyflo pump. Sodium salts were purified by column chromatography over Diaion HP-20SS resin, eluting with ethanol–water mixtures and monitoring the column fractions by UV spectroscopy. Tetrahydrofuran (THF) was dried over sodium hydride and distilled immediately before use. Iron powder was purchased from BDH chemicals and was used as supplied (prereduced with hydrogen). All compounds are racemic and are named according to IUPAC nomenclature.

3-*Triphenylmethoxypropan*-1-*ol* **6**.—Propane-1,3-diol (14.8 g, 0.195 mol) and triphenylmethyl chloride (20.0 g, 0.072 mol) were dissolved in dry DMF (*N*,*N*-dimethylformamide) (50 cm^3) and the solution was cooled to 5 °C. A solution of triethylamine (10 cm^3, 0.072 mol) and 4-dimethylaminopyridine (DMAP) (100 mg) in dry DMF (10 cm^3) was added dropwise to the above stirred solution and stirring was continued at room temp. for 64 h. The reaction solution was then partitioned between ethyl acetate and water. The organic solution was washed with 1 mol dm^{-3} hydrochloric acid, water, brine and dried ($MgSO_4$). The solvent was then evaporated at reduced

pressure and the residue applied to a column of silica gel. Elution wtih a gradient of 5 to 20% ethyl acetate–hexane gave 3-*triphenylmethoxypropan*-1-*ol* **6** as a white solid (16.1 g, 70%), m.p. 121–123 °C, $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3600, 3550, 1600, 1490 and 1445; $\delta_H(CDCl_3)$ 1.82 (2 H, m), 2.10 (1 H, br res., OH), 3.23 (2 H, t, *J* 6), 3.71 (2 H, t, *J* 6) and 6.90–7.80 (15 H, m) (Found: C, 82.9; H, 7.0. $C_{22}H_{22}O_2$ requires C, 80.3; H, 6.95%).

3-*Triphenylmethoxypropionaldehyde* **7**.—A solution of oxalyl chloride (5.06 cm^3, 55.72 mmol) in dichloromethane (250 cm^3) was cooled to −55 °C under an atmosphere of argon. A solution of dry dimethyl sulfoxide (DMSO) (9.1 cm^3, 111.25 mmol) in dichloromethane (50 cm^3) was added to the cooled, stirred solution over a period of 5 min. Stirring was continued at −55 °C for a further 15 min. A solution of the alcohol **6** (16.10 g, 53.31 mmol) in dichloromethane (100 cm^3) was then added over a period of 10 min and stirring was continued at −55 °C for an additional 15 min. Triethylamine (36 cm^3, 0.49 mol) was added and the solution allowed to warm up to room temp. The solution was then washed with water, 1 mol dm^{-3} hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, brine and dried ($MgSO_4$). The solvent was evaporated at reduced pressure and the residue chromatographed over silica gel. Elution with a gradient of 5 to 10% ethyl acetate–hexane afforded the *aldehyde* **7** as a white solid after crystallization from ethyl acetate–hexane (12.8 g, 80%), m.p. 97–98 °C, $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1725, 1600, 1492 and 1448; $\delta_H(CDCl_3)$ 2.52 (2 H, dt, *J* 2 and 6, CH_2CHO), 3.41 (2 H, t, *J* 6, CH_2O), 7.0–7.7 (15 H, m, Ar) and 9.64 (1 H, t, *J* 2, CHO) (Found: C, 83.45; H, 6.4. $C_{22}H_{20}O_2$ requires C, 83.5; H, 6.35%).

2-(2-*Triphenylmethoxyethyl*)*thiazolidin*-4-*one* **8**.—The aldehyde **7** (10 g, 33.33 mmol), thioglycolamide **5**[19] (10 g, 109.9 mmol) and toluene-*p*-sulfonic acid monohydrate (0.2 g) were suspended in dry benzene (1.5 dm^3) and heated to reflux, with stirring and the azeotropic removal of water (Dean and Stark apparatus), for 24 h. After cooling, the solvent was evaporated at reduced pressure and the residue digested in dichloromethane. The resulting suspension was applied to a column of silica gel, which was eluted with a gradient of 10–75% ethyl acetate–hexane to provide the *thiazolidin*-4-*one* **8** as a white solid from ethyl acetate–hexane (3.64 g; 30%), m.p. 189–191 °C, $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3380 and 1680; $\delta_H(CDCl_3)$ 1.80–2.20 (2 H, m, CH_2CH_2O), 3.15–3.40 (2 H, m, CH_2O), 3.45 (2 H, s, CH_2S), 4.82 (1 H, br t, *J* 6.5, CHN), 6.45 (1 H, br s, NH) and 7.1–7.5 (15 H, m, Ar) (Found: C, 73.9; H, 5.75; N, 3.65; S, 8.2. $C_{24}H_{23}NO_2S$ requires C, 74.0; H, 5.95; N, 3.6; S, 8.25%).

p-*Nitrobenzyl*[4-*Oxo*-2-(2-*triphenylmethoxyethyl*)*thiazolidin*-3-*yl*]*triphenylphosphoranylideneacetate* **11**.—A solution of *p*-nitrobenzyl glyoxylate monohydrate (0.440 g, 1.938 mmol) in benzene (100 cm^3) was heated to reflux with the provision for the removal of water (Dean and Stark apparatus) for 30 min. After cooling to room temperature, a solution of 2-(2-triphenylmethoxyethyl)thiazolidin-4-one **8** (0.500 g, 1.285 mmol) in benzene was added and the solution heated to reflux for a further 2 h. After cooling to room temp., triethylamine (4 drops) was added and stirring continued at room temp. for 4 h. The solution was then evaporated at reduced pressure to yield the diastereoisomeric mixture of hydroxyacetates **9** as a colourless oil; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3520, 1758, 1692, 1608, 1525 and 1350.

The hemiaminal **9** was dissolved in dry THF (50 cm^3) and cooled to −20 °C under an atmosphere of argon. To the stirred solution was added 2,6-lutidine (0.225 cm^3) and thionyl chloride (0.141 cm^3) and stirring was continued at −20 °C for 15 min. The resulting suspension was filtered and the filtrate evaporated at reduced pressure. The resulting oil was chromatographed rapidly over coarse grade silica gel, eluting with 25, 50 and 100% ethyl acetate–hexane to provide the diastereoisomeric chloroacetates **10** as a foam; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1762, 1700, 1605, 1522 and 1350.

The mixture of chloroacetates **10** was dissolved in 1,4-dioxane (50 cm^3) and stirred with triphenylphosphine (1.34 g) until the solution was homogeneous. The solution was then evaporated to small volume (*ca.* 10 cm^3) and heated to 85 °C under an atmosphere of argon for 18 h with 2,6-lutidine (0.182 cm^3). The solution, after cooling, was diluted with ethyl acetate and washed with water, 5% citric acid solution, brine and dried ($MgSO_4$). After evaporation at reduced pressure, the crude phosphorane was chromtographed over silica gel. Elution with a gradient of 50–100% ethyl acetate–hexane gave the phosphorane **11** as a white foam (0.703 g; 65%), $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1680, 1650, 1620, 1608, 1522 and 1348; *m/z* (3-NOBA/Na, FAB) 865 (MNa^+).

p-*Nitrobenzyl* [2-(2-*Hydroxyethyl*)-4-*oxothiazolidin*-3-*yl*]*triphenylphosphoranylideneacetate* **12**.—The trityl derivative **11** (0.550 g, 0.653 mmol) was dissolved in 10% aqueous acetic acid (20 cm^3) and heated to 90 °C for 3.5 h. After cooling, the reaction solution was partitioned between ethyl acetate and water. The organic solution was washed with saturated aqueous sodium hydrogen carbonate (×3), brine, dried ($MgSO_4$) and evaporated at reduced pressure. The residue was then chromatographed over silica gel. Elution with a gradient of 50–100% ethyl acetate–hexane provided the phosphorane **12** as a white foam (0.235 g, 60%), $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3320, 1682, 1622, 1610sh, 1522 and 1350; *m/z* (thioglycerol, FAB) 601 (MH^+).

p-*Nitrobenzyl* 2-*Oxo*-4-*thia*-1-*azabicyclo*[3.3.0]*oct*-7-*ene*-8-*carboxylate* **14**.—The alcohol **8** (0.220 g, 0.367 mmol) was dissolved in dry dimethyl sulfoxide (5 cm^3) and stirred at room temp. for 1 h with triethylamine (0.253 cm^3, 1.835 mmol) and sulfur trioxide–pyridine complex (0.350 g, 2.20 mmol). The reaction solution was then partitioned between ethyl acetate and 1 mol dm^{-3} hydrochloric acid. The organic solution was washed with water, aqueous sodium hydrogen carbonate, brine, dried ($MgSO_4$) and evaporated at reduced pressue. The crude product was chromatographed over silica gel (5 g). Elution with a gradient of 10–50% ethyl acetate–hexane provided the *ester* **14** as a white solid after crystallisation from ethyl acetate–hexane (0.058 g; 50%), m.p. 128–130 °C, $\lambda_{max}(EtOH)/nm$ 265 (ε 16 547); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1742, 1702, 1610, 1522 and 1350; $\delta_H(CDCl_3)$ 2.80–3.05 (2 H, m, 6-CH_2), 3.53 (1 H, d, *J* 15, 3-CHa), 4.08 (1 H, d, *J* 15, 3-CHb), 5.35 (1 H, d, *J* 13.5, C*H*aAr), 5.42 (1 H, d, *J* 13.5, C*H*bAr), 5.67 (1 H, t, *J* 9.5, 5-CH), 6.47 (1 H, t, *J* 3, 7-CH), 7.60 (2 H, d, *J* 8.5, Ar) and 8.23 (2 H, d, *J* 8.5, Ar) (Found: C, 52.6; H, 3.5; N, 8.7; S, 9.85%; M^+, 320.0467. $C_{14}H_{12}N_2O_5S$ requires: C, 52.5; H, 3.75; N, 8.75; S, 10.0%; *M*, 320.0467).

Sodium 2-*Oxo*-4-*thia*-1-*azabicyclo*[3.3.0]*oct*-7-*ene*-8-*carboxylate* **18**.—The ester **14** (0.035 g, 0.109 mmol) was dissolved in THF (3 cm^3) and aqueous 1 mol dm^{-3} ammonium chloride solution (2 cm^3) and cooled to 5 °C. Iron powder (0.40 g) was added and the resulting suspension was stirred at 5 °C for 5 min and room temp. for 2 h. The solution was then diluted with ethyl acetate and water, and acidified (pH 2) by the addition of 1 mol dm^{-3} hydrochloric acid. The resulting suspension was filtered through Celite, washing well with ethyl acetate. The organic solution was separated and the aqueous layer extracted with ethyl acetate. The combined organic solutions were evaporated at reduced pressure and the residue dissolved in aqueous THF. The solution was adjusted to pH 7.0 by the addition of 1 mol dm^{-3} sodium hydroxide solution, and then evaporated to low volume at reduced pressure. The resulting aqueous solution was

applied to a column of Diaion HP 20SS, which was eluted with water. The column fractions were monitored by UV spectroscopy and those possessing the desired UV chromophore were combined and lyophilized to yield the sodium salt **18** as a white solid (0.012 g), λ_{max}/nm 251 (ε 6068); ν_{max}(KBr)/cm^{-1} 3400br, 1675, 1630, 1594 and 1387; δ_H(D_2O) 2.72 (1 H, ddd, *J* 2.5, 9.5 and 17.5, 6-CHa), 2.86 (1 H, ddd, *J* 3.5, 8.5 and 17.5, 6-CHb), 3.52 (1 H, d, *J* 15.5, 3-CHa), 4.16 (1 H, dd, *J* 1.5 and 15.5, 3-CHb), 5.69 (1 H, t, *J* 9, 5-CH) and 6.06 (1 H, t, *J* 3, 7-CH).

p-*Nitrobenzyl* 2,4-*Dioxo*-4-*thia*-1-*azabicyclo*[3.3.0]*oct*-7-*ene*-8-*carboxylate* **15**.—The ester **14** (0.073 g, 0.228 mmol) was dissolved in dichloromethane (5 cm^3) and cooled to 5 °C with stirring. *m*-Chloroperbenzoic acid (0.051 g; 85% pure, 0.251 mmol) was added and stirring continued at 5 °C for 1.5 h. The reaction solution was then diluted with dichloromethane, washed with 2% aqueous potassium carbonate, water and brine and dried ($MgSO_4$). Evaporation of the solvent provided the diastereoisomeric sulfoxides **15** as a white foam (0.074 g; 97%); ν_{max}(CH_2Cl_2)/cm^{-1} 1745, 1721, 1610, 1522 and 1350; δ_H($CDCl_3$) 2.85 (0.75 H, ddd, *J* 3.0, 10.5 and 19.0, 6-CHa of major isomer), 3.15–3.40 (2 × 0.25 H, m, 6-CH_2 of minor isomer), 3.46 (0.75 H, ddd, *J* 2.5, 9.5 and 19.0, 6-CHb of major isomer), 3.69 (0.75 H, d, *J* 16, 3-CHa of major isomer), 4.01 (0.75 H, d, *J* 16, 3-CHb of major isomer), 4.12 (2 × 0.25 H, s, 3-CH_2 of minor isomer), 5.21 (0.25 H, t, *J* 10, 5-CH of minor isomer), 5.28–5.43 (2 H, m, CH_2Ar of major and minor isomers), 5.50 (0.75 H, t, *J* 10, 5-CH of major isomer), 6.37 (0.25 H, t, *J* 3, 7-CH of minor isomer), 6.41 (0.75 H, t, *J* 2.5, 7-CH of major isomer), 7.59 (2 H, d, *J* 8.5, Ar) and 8.24 (2 H, d, *J* 8.5, Ar); *m*/*z* (thioglycerol FAB) 337 (MH^+) and 354 (MNH_4^+).

Sodium 2,4-*Dioxo*-4-*thia*-1-*azabicyclo*[3.3.0]*oct*-7-*ene*-8-*carboxylate* **19**.—The ester **15** (0.035 g, 0.104 mmol) was dissolved in THF (3 cm^3) and aqueous 1 mol dm^{-3} ammonium chloride solution (2 cm^3) and cooled to 5 °C. Iron powder (0.400 g) was added and the resulting suspension was stirred at 5 °C for 5 min and room temp. for 2 h. The solution was then diluted with ethyl acetate and water and acidified (pH 2) by the addition of 1 mol dm^{-3} hydrochloric acid. The resulting suspension was filtered through Celite, washing well with ethyl acetate. The organic solution was separated and the aqueous layer extracted with ethyl acetate. The combined organic solutions were evaporated at reduced pressure and the residue dissolved in aqueous THF. The solution was adjusted to pH 7.0 by the addition of 1 mol dm^{-3} sodium hydroxide solution, and then evaporated to low volume at reduced pressure. The resulting aqueous solution was applied to a column of Diaion HP20SS, which was eluted with water. The column fractions were monitored by UV spectroscopy and those possessing the desired UV chromophore were combined and lyophilized to yield the sodium salt **19** as a white solid (0.020 g), λ_{max}(H_2O)/nm 252 (ε 5800); ν_{max}(KBr)/cm^{-1} 3400br, 1685, 1635sh, 1600, 1578sh, 1410 and 1398.

2-(4-*Methoxyphenyl*)-3-*oxa*-7-*thia*-1-*azabicyclo*[4.3.0]*nonan*-9-*one* **22**.—Boron trifluoride–diethyl ether (3.60 cm^3, 29.25 mmol) was added dropwise to a stirred, cooled suspension of the thiazolidinone **8** (16.9 g, 43.44 mmol) and anisaldehyde dimethylacetal (8.86 g, 48.68 mmol) in dry dichloromethane (350 cm^3). The resulting solution was then stirred at room temp. for 1 h before diluting with dichloromethane (250 cm^3) and washing with water, dilute sodium bisulfite solution and brine. The organic solution was dried ($MgSO_4$) and evaporated to yield an oil which was chromatographed over silica gel. Elution with a gradient of 10–50% ethyl acetate–hexane provided the *title compound* **22** as a white solid after crystallization from ethyl acetate–hexane (9.75 g; 85%), m.p. 112–113 °C; ν_{max}(CH_2Cl_2)/cm^{-1} 1685, 1615 and 1510; δ_H($CDCl_3$) 1.78–1.90 (1 H, m, 5-CHa), 2.02–2.22 (1 H, m, 5-CHb), 3.65–3.95 (7 H, 2 × s + m, OMe + 8-CH_2 + 4-CH_2), 4.85 (1 H, dd, *J* 3.5 and 11.5, 6-CH), 6.72 (1 H, s, 2-CH), 6.93 (2 H, d, *J* 8.5, Ar) and 7.22 (2 H, d, *J* 8.5, Ar) (Found: C, 58.9; H, 5.7; N, 5.35; S, 12.1. $C_{13}H_{15}NO_3S$ requires C, 58.85; H, 5.7; N, 5.3; S, 12.1%); *m*/*z* (FAB, thioglycerol) 266 (MH^+).

8-*Azido*-2-(4-*methoxyphenyl*)-3-*oxa*-7-*thia*-1-*azabicyclo*[4.3.0]*nonan*-9-*one* **23**.—Lithium diisopropylamide (3.03 cm^3 of a 2 mol dm^{-3} solution in heptane–tetrahydrofuran–ethylbenzene, 6.06 mmol) was added to a stirred solution of the tetrahydrothiazolo-1,3-oxazine **22** (1.337 g, 5.05 mmol) in dry THF (100 cm^3) at −78 °C under an atmosphere of argon. Stirring was continued at this temperature for 30 min. This solution was then added, by means of a cannula and a positive pressure of argon, to a solution of toluene-*p*-sulfonyl azide (1.39 g, 7.05 mmol) in dry THF (100 cm^3) at −78 °C. The solution was stirred at − 78 °C under an atmosphere of argon for 5 min. Acetic acid (1.39 g, 23.17 mmol) was then added and the reaction solution allowed to warm up to room temp. Stirring was continued at room temp. for 4 h. Ethyl acetate was then added and the organic solution was washed with saturated aqueous sodium hydrogen carbonate and water, and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure gave the crude product which was purified by silica gel column chromatography. Elution with a gradient of 5–20% ethyl acetate–hexane furnished an inseparable mixture of diastereoisomeric *azides* **23** as a white solid (1.17 g; 76%), m.p. 110–112 °C (ethyl acetate–hexane), ν_{max}($CHCl_2$)/cm^{-1} 2110, 1698, 1612 and 1510; δ_H($CDCl_3$) 1.88–2.25 (2 H, m, 5-CH_2), 3.70–4.0 (5 H, s + m, OMe + 4-CH_2), 4.81 (0.75 H, dd, *J* 3.5 and 11.5, 6-CH of major isomer), 4.98 (0.25 H, dd, *J* 3.5 and 10, 6-CH of minor isomer), 5.38 (0.25 H, d, *J* 1, 8-CH of minor isomer), 5.42 (0.75 H, s, 8-CH of major isomer), 6.73 (1 H, s, 2-CH), 6.95 (2 H, d, *J* 8.5, Ar), 7.21 (2 H, d, *J* 8.5, Ar) (Found: C, 50.95; H, 4.6; N, 18.05; S, 10.45%; M^+, 306.0786. $C_{13}H_{14}N_4O_3S$ requires: C, 50.95; H, 4.6; N, 18.3; S, 10.45%; *M*, 306.0787).

8-*Phenylacetamido*-2-(4-*methoxyphenyl*)-3-*oxa*-7-*thia*-1-*azabicyclo*[4.3.0]*nonan*-9-*one* **25**.—The diastereoisomeric mixture of azides **23** (0.84 g, 2.75 mmol) was dissolved in ethanol (150 cm^3) and shaken for 2 h at ambient temperature and pressure with hydrogen in the presence of 10% palladium on carbon catalyst (1.2 g). The suspension was filtered over Celite and evaporation at reduced pressure provided the amine **24** as a white foam.

This foam was then dissolved in dry dichloromethane (50 cm^3) and cooled to 5 °C. Phenylacetyl chloride (0.850 g, 5.50 mmol) was added to the stirred solution, followed by diisopropylethylamine (0.355 g, 2.75 mmol). Stirring was continued at 5 °C for 1 h. The solution was diluted with dichloromethane and the organic solution was washed with 5% citric acid solution, brine and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure gave the crude product, which was purified by silica gel column chromatography. Elution with a gradient of 10–100% ethyl acetate–hexane, followed by 50% dichloromethane–ethyl acetate (due to crystallization of product on the column) provided the pure *amide* **25** as a diastereoisomeric mixture and a white solid (0.719 g; 66%), m.p. 190–198 °C, ν_{max}(CH_2Cl_2)/cm^{-1} 3420, 1692, 1615 and 1510; δ_H($CDCl_3$) 1.78–1.95 (1 H, m, 5-CHa), 1.98–2.20 (1 H, m, 5-CHb), 3.69 (2 H, s, CH_2Ph), 3.72–3.92 (5 H, s + m, OMe + 4-CH_2), 4.81 (0.9 H, dd, *J* 3.5 and 11.5, 6-CH of major isomer), 4.98 (0.1 H, br d, 6-CH of minor isomer), 5.53 (0.1 H, dd, *J* 2.0 and 7.0, 8-CH of minor isomer), 5.94 (0.9 H, d, *J* 7.5, 8-CH of major isomer), 6.30 (1 H, br d, *J* 7.5, NH), 6.68 (0.1 H, s, 2-CH of minor isomer), 6.71 (0.9 H, s, 2-CH of major isomer), 6.95 (2 H, d, *J* 8.5, Ar),

7.17 (2 H, d, *J* 8.5, Ar) and 7.25–7.45 (5 H, m, Ar) (Found: C, 63.4; H, 5.55; N, 7.1; S, 8.05. $C_{21}H_{22}N_2O_4S$ requires: C, 63.3; H, 5.55; N, 7.05; S, 8.05%), *m/z* (FAB, 3-NOBA/Na) 421 (MNa^+).

2-(2-*Hydroxyethyl*)-5-*phenylacetamidothiazolidin*-4-*one* **28**.—The tetrahydrothiazolo-1,3-oxazine **25** (0.45 g, 1.13 mmol) was suspended in 30% aqueous 1,4-dioxane (20 cm^3) and heated to 65 °C for 1.5 h in the presence of conc. sulfuric acid (0.7 cm^3). After cooling, the solution was neutralized by the addition of solid sodium hydrogen carbonate. The reaction solution was then diluted with ethyl acetate and washed with brine, and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure afforded the pure *thiazolidin*-4-*one* **28** as a white solid, which was collected by trituration with ethyl acetate–hexane (0.220 g, 70%), m.p. 147–151 °C; ν_{max}(KBr)/cm^{-1} 3465, 3276, 1690, 1649 and 1529; δ_H($CDCl_3$) 1.82–2.10 (2 H, m, CH_2CH_2OH), 3.65 (2 H, s, CH_2Ph), 3.68–4.00 (2 H, m, CH_2OH), 4.81 (1 H, dd, *J* 3.5 and 8.0, 2-CH), 5.71 (1 H, d, *J* 7.5, 5-CH), 6.32 (1 H, br d, NH), 7.02 (1 H, br s, OH) and 7.2–7.45 (5 H, m, Ar) (Found: C, 55.7; H, 5.75; N, 9.9; S, 11.4%; M^+, 280.0882. $C_{13}H_{16}N_2O_3S$ requires: C, 55.7; H, 5.75; N, 10.0; S, 11.45%; *M*, 280.0882).

An additional quantity (0.015 g; 4%) of pure thiazolidin-4-one **28** was obtained by silica gel column chromatography of the mother liquors. The column was eluted with a gradient of 50–100% ethyl acetate–hexane followed by 10% ethanol–ethyl acetate.

(4-*Oxo*-5-*phenylacetamidothiazolidin*-2-*yl*)*acetaldehyde* **29**.—The alcohol **28** (0.125 g, 0.446 mmol) was dissolved in dry dimethylsulfoxide (2 cm^3) and toluene (4 cm^3) and stirred at room temp. for 4 h with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.257 g, 1.34 mmol), pyridine (0.123 g, 1.56 mmol) and trifluoroacetic acid (0.026 g, 0.223 mmol). The reaction solution was partitioned between ethyl acetate and water and the organic solution washed with 2 mol dm^{-3} hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate and brine. The solution was dried ($MgSO_4$) and evaporated to yield an oil, which was chromatographed over silica gel. Elution with 75% ethyl acetate–hexane gave the thioether **30** (0.016 g; 11%); δ_H($CDCl_3$) 1.85–2.12 (2 H, m, CH_2CH_2O), 2.13 (3 H, 2 × s, major and minor isomers of SMe), 3.52–3.92 (4 H, m + s, CH_2CH_2O + CH_2Ph), 4.60 (2 H, ABq, CH_2S), 4.76 (0.75 H, dd, *J* 3.5 and 8.5, 2-CH of major isomer), 4.92 (0.25 H, m, 2-CH of minor isomer), 5.45 (0.25 H, m, 5-CH of minor isomer), 5.74 (0.75 H, d, *J* 7.5, 5-CH of major isomer), 6.18 (1 H, br d, NH), 6.72 and 6.77 (1 H, 2 × br s, NH of major and minor isomers) and 7.25–7.45 (5 H, m, Ar); *m/z* (FAB, 3-NOBA/NA) 363 (MNa^+).

Continued elution with ethyl acetate followed by 10% ethanol–ethyl acetate provided the pure aldehyde **29** as a white foam (0.037 g; 30%); ν_{max}(CH_2Cl_2)/cm^{-1} 3400, 1708, 1685sh and 1498; δ_H($CDCl_3$) 2.94 (0.5 H, d, *J* 6.5, CH_2CHO of minor isomer), 3.03 (dd, *J* 4.5 and 19.0, C*H*aCHO of major isomer) and 3.20 (dd, *J* 7.5 and 19.0, C*H*bCHO of major isomer (all 1.5 H), 3.60 (2 H, s, CH_2Ph), 4.92 (0.75 H, dd, *J* 4.5 and 7.0, 2-CH of major isomer), 5.07 (0.25 H, br t, *J* 6, 2-CH of minor isomer), 5.48 (0.75 H, d, *J* 7, 5-CH of major isomer), 5.53 (0.25 H, dd, *J* 1.5 and 7.0, 5-CH of minor isomer), 6.64 (d, *J* 7, minor isomer) and 6.71 (d, *J* 7, major isomer) (all 1 H, NH), 7.1–7.45 (5 H, m, Ar), 9.67 (s, major isomer) and 9.68 (s, minor isomer) (all 1 H, CHO); *m/z* 278.0733 ($C_{13}H_{14}N_2O_3S$ requires *M*, 278.0725).

Methyl (2E)-4-(4-*Oxo*-5-*phenylacetamidothiazolidin*-2-*yl*)-*but*-2-*enoate* **31**.—The aldehyde **29** (0.074 g, 0.266 mmol) and methoxycarbonylmethylenetriphenylphosphorane (0.134 g, 0.4 mmol) were dissolved in dry benzene (20 cm^3) containing dry *tert*-butanol (2 cm^3) and heated to 90 °C for 6 h. The solvent was then evaporated at reduced pressure and the residue was chromatographed over silica gel. Elution with a gradient of 50–75% ethyl acetate–hexane gave the α,β-unsaturated ester **31** as a white crystalline solid (0.077 g; 87%); ν_{max}(KBr)/cm^{-1} 3265, 3185, 1718, 1699, 1653 and 1525; δ_H([$^2H_6$]DMSO) 2.55–2.87 (2 H, m, CH_2CH=C), 3.49 and 3.47 (2 H, 2 × s, CH_2Ph of major and minor isomers), 3.68 (3 H, s, CO_2Me), 4.80 (0.75 H, t, *J* 6.0, 2-CH of major isomer), 4.92 (0.25 H, t, 2-CH of minor isomer), 5.48 (0.25 H, dd, 5-CH of minor isomer), 5.56 (0.75 H, d, *J* 8.5, 5-CH of major isomer), 5.96 and 5.99 (1 H, 2 × d, *J* 15.5, C=C*H*CO_2Me of major and minor isomers), 6.83 (1 H, dt, *J* 7.0 and 15.5, CH_2CH=C), 7.18–7.40 (5 H, m, Ar) 9.05–9.25 (2 H, m, 2 × NH) (Found: M^+, 334.1004. $C_{16}H_{18}N_2O_4S$ requires *M*, 334.0987).

p-*Methoxybenzyl* [2-(3-*Methoxycarbonylprop*-2E-*en*-1-*yl*)-4-*oxo*-5-*phenylacetamidothiazolidin*-3-*yl*]*triphenylphosphoranylideneacetate* **34**.—The thiazolidinone **31** (0.060 g, 0.18 mmol) and *p*-methoxybenzyl glyoxylate monohydrate (0.049 g, 0.233 mmol) were suspended in benzene (50 cm^3) and heated to reflux for 2 h, with the provision for the removal of water (Dean and Stark apparatus). After cooling, triethylamine (2 drops) was added and the solution was stirred at room temp. for 1.5 h. The solution was then evaporated at reduced pressure to yield the diastereoisomeric hydroxyacetates **32** as an oil.

The mixture of hydroxyacetates **32** was dissolved in dry THF (15 cm^3) and cooled to −20 °C under an atmosphere of argon. To the stirred solution was added 2,6-lutidine (0.032 cm^3) and thionyl chloride (0.020 cm^3) and stirring was continued at −20 °C for 15 min. The resulting suspension was filtered and the filtrate was evaporated at reduced pressure to yield the diastereoisomeric chloroacetates **33** as a foam.

The mixture of chloroacetates **33** was dissolved in 1,4-dioxane (25 cm^3) and stirred with triphenylphosphine (0.188 g) until the solution was homogeneous. The solution was then evaporated to small volume (*ca.* 5 cm^3) and heated to 80 °C under an atmosphere of argon for 16 h with 2,6-lutidine (0.026 cm^3). The solution, after cooling, was diluted with ethyl acetate and washed with water, 2% citric acid solution, brine and dried ($MgSO_4$). After evaporation at reduced pressure, the crude product was chromatographed over silica gel. Elution with a gradient of 50–75% ethyl acetate–hexane gave the pure phosphorane **34** as a white foam (0.060 g; 43%); ν_{max}(CH_2Cl_2)/cm^{-1} 3400, 1720, 1690, 1642 and 1612; *m/z* (FAB, 3-NOBA/NA) 795 (MNa^+).

p-*Methoxybenzyl* 2-*Oxo*-3-*phenylacetamido*-4-*thia*-1-*azabicyclo*[3.3.0]*oct*-7-*ene*-8-*carboxylate* **36**.—The phosphorane **34** (0.060 g, 0.078 mmol) was dissolved in ethyl acetate (7 cm^3) and cooled to −20 °C under an atmosphere of argon. Trifluoroacetic acid (2 cm^3) was added to the stirred solution and the solution was then immediately cooled to −78 °C. A stream of ozonized oxygen was passed through the solution until a blue colouration appeared. The excess ozone was blown off with argon and a solution of triphenylphosphine (0.023 g, 0.086 mmol) in ethyl acetate (2 cm^3) was added. Saturated aqueous sodium hydrogen carbonate (50 cm^3) was then added and the reaction vessel was removed from the cooling bath. After reaching room temp., the reaction solution was diluted with ethyl acetate and the organic solution washed with an additional quantity of aqueous sodium hydrogen carbonate, brine and dried ($MgSO_4$). The solvent was evaporated at reduced pressure and the crude product was chromatographed over silica gel. Elution with a gradient of 25–75% ethyl acetate–hexane furnished the pure ester **36** as a white solid (0.012 g; 35%), λ_{max}(10% MeCN in EtOH)/nm 263 (ε 9429) and 224 (ε 22 421); ν_{max}(CH_2Cl_2)/cm^{-1} 3406, 1736, 1710, 1682, 1614 and 1516; δ_H($CDCl_3$) 2.20–3.0 (2 H, m, 6-CH_2), 3.66 and 3.62

(2 H, 2 × s, CH_2Ph of major and minor isomers in 2:1 ratio), 3.81 (3 H, s, OMe), 5.20 (2 H, ABq, CH_2Ar), 5.41 (0.67 H, t, *J* 9.0, 5-CH of major isomer), 5.67 (0.33 H, t, *J* 9.0, 5-CH of minor isomer), 5.82 (0.33 H, d, *J* 8.0, 3-CH of minor isomer), 6.15 (0.67 H, d, *J* 7.0, 3-CH of major isomer), 6.22 (0.67 H, d, *J* 7.0, NH of major isomer), 6.37 (0.33 H, d, *J* 8.0, NH of minor isomer), 6.40 (1 H, t, *J* 3.0, 7-CH), 6.88 (2 H, d, *J* 8.5, Ar) and 7.2–7.60 (7 H, m, Ar); *m/z* (FAB 3-NOBA/NA) 461 (MNa^+).

Sodium 2-Oxo-3-phenylacetamido-4-thia-1-azabicyclo[3.0]-*oct-7-ene-8-carboxylate* **37**.—The ester **36** (0.007 g, 0.016 mmol) was dissolved in dichloromethane (5 cm^3) containing anisole (1 cm^3) and the solution was cooled to −20 °C under an atmosphere of argon. A solution of ethyl aluminium dichloride in toluene (1.8 mol dm^{-3} solution; 0.026 cm^3, 0.047 mmol) was added to the stirred solution and stirring was continued at −20 °C for 20 min. Disodium hydrogen orthophosphate solution (0.5 mol dm^{-3} solution; 0.55 cm^3, 0.275 mmol) was added and the rapidly stirred solution was allowed to warm up to room temp. The suspension was filtered through Celite, washing well with water. The aqueous phase was separated, washed with diethyl ether, concentrated to small volume and applied to a column of Diaion HP20SS, which was eluted with a gradient of 0–10% ethanol–water. Column fractions were monitored by UV spectroscopy and those possessing the λ_{max}/nm 251 chromophore were combined. Concentration and lyophilization of the resulting solution provided the sodium salt **37** as a white solid (0.006 g); $\lambda_{max}(H_2O)$/nm 251 (ε 3900); ν_{max}(KBr)/cm^{-1} 3400br, 1684, 1640sh and 1610; $\delta_H(D_2O)$ 2.6–2.9 (2 H, m, 6-CH_2), 3.64 (2 H, s, CH_2Ph), 5.48 (0.67 H, t, *J* 9.0, 5-CH of major isomer), 5.73 (0.33 H, s, 3-CH of minor isomer), 5.78 (0.33 H, t, 5-CH of minor isomer), 6.12 (1 H, t, *J* 2.5, 7-CH), 6.20 (0.67 H, s, 3-CH of major isomer) and 7.22–7.45 (5 H, m, Ar).

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