Olivanic Acid Analogues. Part 6.[1] Biomimetic Synthesis of (±)-PS-5, (±)-6-*Epi*-PS-5, and (±)-Benzyl MM22381

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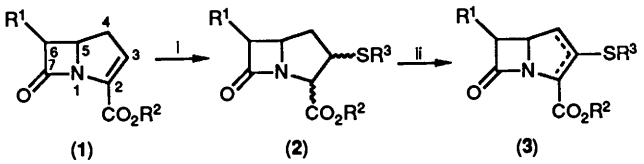
Michael addition of thiols to 6-substituted azabicyclo[3.2.0]hept-2-ene-2-carboxylates, followed by reintroduction of the double bond with iodobenzene dichloride–pyridine under anhydrous conditions, provides a biomimetic strategy for the synthesis of 3-alkylthio-substituted olivanic acids (carbapenems) and their derivatives. This is illustrated by syntheses of representatives of the PS-5 and MM22381 series of antibacterial natural products.

In our preceding paper we described[1] the stereochemical outcome of a series of Michael additions of thiols to carbapenems unsubstituted at the 3-position† [(**1**), Scheme]. Subsequently, reintroduction of the double bond, which is essential for antibacterial activity, into the resulting thiocarbapenams (**2**) was achieved by oxidation with iodobenzene dichloride (IBD).‡ The sulphenyl (**3**) or sulphinyl oxidation state was obtained, depending on the conditions employed. We now provide an account of the application of these mild methods[2,3] to the total synthesis[4–9] of some naturally occurring carbapenem antibiotics (*e.g.* the PS-5[10] and MM22381[11] families of streptomycete olivanic acids). Our methods also provide syntheses of close relatives, such as 6-*epi*-PS-5, which remains undetected as a natural product.

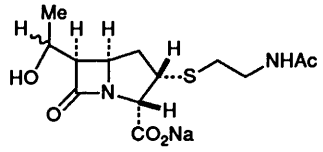


(1) (2) (3)

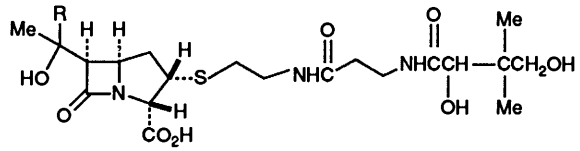
Scheme. *Reagents and conditions:* i, R^3SH, K_2CO_3, dimethylformamide (DMF); ii, IBD (1 mol equiv.), C_5H_5N (2 mol equiv.), CH_2Cl_2 or PhH, 5 °C, 2–3 h.

Retrospectively, we were intrigued by the similarity of aspects of our strategy in relation to emerging knowledge concerning the biosynthetic pathways leading to the carbapenem antibiotics.[12] The parallels in the sequence were particularly evident for the final oxidation of a substituted carbapenam to the corresponding carbapenem. Moreover, some of our synthetic intermediates (or variants thereof in similar oxidation states) have since been discovered as natural products in their own right. Ester (**1**; R^1 = H, R^2 = PNB),[13] § the 'carbapenem nucleus' is a key intermediate in many of our synthetic routes. The sodium salt (**1**; R^1 = H, R^2 = Na)[13] has been isolated[14] as its (+)-enantiomer from bacterial sources by the Squibb group, and represents the simplest of bicyclic β-lactam antibiotics. Studies to determine its biosynthetic role are at an early stage.[15]

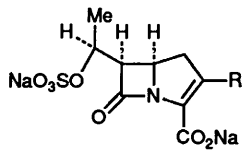
Furthermore, antibacterially inactive carbapenam molecules of structure (**2**), whose synthesis is a subject of this paper, are now known as natural products, occurring as co-metabolites of the carbapenems. Examples include the 3-(acetamidoethylthio)carbapenam 17927D (**4**)[16] and representatives (**5**) and (**6**)[17] from the Sanraku pantetheinyl series. The pantetheinyl residue has been demonstrated[18] to function as a possible precursor to the acetamidoethylthio side-chain, which is



(4)



(5) R = H OA - 6129D
(6) R = Me OA - 6129E



(7) R = $SOCH_2CH_2NHAc$ MM4550
(8) R = SO_3Na SF - 2103A

present in PS-5 and in many olivanic acids. Although the detailed mechanism of the initial stages of C-3 side-chain incorporation is not yet proven, some preliminary supporting evidence for the intermediary role of carbapenams has been reported.[16] A Michael process for the addition of thiol derivatives at C-3, followed by pyrrolidine ring oxidation, is implicated[15,19] (*cf.* the synthetic strategy of this paper). Later oxidative stages in the side-chain biosynthesis are represented by sulphoxide metabolites as in Beecham MM4550 (**7**),[20] and ultimately by the SF-2103A/pluracidomycin 3-sulphonic acids (**8**) and their co-metabolites.[21,22]

Biosynthetic studies by other groups have shown[23,24] that the 6-hydroxyethyl side-chain, which is present in many of the olivanic acids, arises in nature by a sequential one-carbon alkylation process. We have also obtained (*vide infra*)

† This paper employs systematic numbering based on the azabicyclo-[3.2.0]hept-2-ene system throughout. Trivial numbering in respect of the terms 'carbapenem' and 'carbapenam' does not apply.
‡ (Dichloroiodo)benzene.
§ PNB = *p*-nitrobenzyl.

molecules containing a one-carbon 6-substituent, which are related to the putative intermediates of this pathway. The 6-methylcarbapenems/carbapenams were synthesized in both 5,6-*trans* and 5,6-*cis* stereochemistries [*cf.* salts (**18b**) and (**28c**)].

Our route to *trans*-substituted systems is illustrated by a synthesis of (±)-PS-5 (**18a**) from (3*RS*,4*RS*)-4-allyl-3-ethylazetidin-2-one (**9a**).[25] Reaction of this versatile intermediate with glyoxylic acid hydrate in dimethylformamide (DMF) in the presence of molecular sieves, followed by alkylation *in situ* with *p*-nitrobenzyl bromide, gave glyoxylate ester (**10a**). Successive reaction with thionyl chloride–2,6-lutidine and with triphenylphosphine–2,6-lutidine according to our published procedures[13,25] provided the phosphorane (**11a**) [70% overall from (**9a**)]. Protonation of the ylide [trifluoroacetic acid (TFA)–ethyl acetate], followed by ozonolysis of the allyl group, produced an aldehyde-phosphonium salt. Neutralisation ($NaHCO_3$) generated the aldehyde-phosphorane which cyclised spontaneously to the 6-ethylcarbapenem ester (**12a**) (63%). A *trans*-arrangement of the C-5 and -6 protons was evident from the ^1H NMR spectrum (J 3 Hz). Michael addition of 2-acetamidoethanethiol[26] (DMF–potassium carbonate) led to an inseparable mixture of thiocarbapenam adducts (**13a**), (**14a**), and (**15a**) (5:3:2). In this case optimum yields (70%) were achieved when 2 mol equiv. of thiol were used. The C-2, C-3 stereochemistries of the three isomers were assigned on the basis of the chemical shifts of the C-2 proton resonances.[1] Treatment of the mixture in ethyl acetate with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) effected epimerisation of isomer (**15a**) to (**14a**).

(**9**) (**10**)

(**11**) (**12**)

(**13**) (**14**)

(**15**) (**16**)

(**17**) R^3 = PNB
(**18**) R^3 = Na
[(**18a**) = PS-5]

a; R^1 = Et, R^2 = CH_2CH_2NHAc
b; R^1 = Me, R^2 = Et
c; R^1 = $Me_2C(OH)$, R^2 = Et

PNB = $CH_2C_6H_4NO_2$-*p*

Reintroduction of the double bond was achieved by the method which we have found to be general for such thiocarbapenams.[1,2] The mixture of 2α-*p*-nitrobenzyl esters (**13a**) and (**14a**) was oxidised in methylene dichloride by means of IBD (1.1 mol equiv.) in the presence of pyridine (2.2 mol equiv.) under rigorously anhydrous conditions (5 °C; 3 h). This gave the Δ^3-ester (**16a**) (60%); no α-chloro sulphide was detected.[27] Ester (**16a**) exhibited the allylically coupled C-2 and C-4 proton resonances characteristic of this system ($^4J_{2\beta,4}$ 1 Hz). With other substrates this reaction sometimes also produced smaller amounts of the isomeric Δ^2-ester (*vide infra*). Equilibration of compound (**16a**) in methylene dichloride in the presence of a catalytic amount of DBU (20 °C; 5 h) followed by rapid chromatography on silica gel afforded recovered ester (**16a**) (45%) together with the *p*-nitrobenzyl ester of (±)-PS-5, compound (**17a**) (30%) [λ_{max}(EtOH) 317 nm; ν_{max}($CHCl_3$) 1 780 cm^{-1}]. This was identical in its spectral data (UV, IR, NMR, MS) with semisynthetic material derived[28] in these laboratories from the naturally occurring olivanic acid MM17880. Deprotection of compound (**17a**) by hydrogenolysis (i, H_2, Pd-C, 1,4-dioxane–water; ii, $NaHCO_3$) gave (±)-PS-5 (sodium salt) (**18a**) (63%) which was indistinguishable (UV, ^1H NMR) from an authentic sample kindly suplied by Sanraku-Ocean Co. Ltd.

In a parallel synthetic sequence starting from (3*RS*,4*RS*)-4-allyl-3-methylazatidin-2-one (**9b**),[25] we obtained the aforementioned *trans*-substituted 6-methyl analogue (**18b**). Addition of ethanethiol to the 6-methylcarbapenem (**12b**) gave adducts (**13b**), (**14b**), and (**15b**). IBD oxidation of the isomers (**13b**) and (**14b**) (2α-stereochemistry) afforded Δ^3-ester (**16b**) (56%), together with trace amounts of Δ^2-isomer (**17b**). DBU-catalysed equilibration of compound (**16b**) provided its isomer (**17b**) (30%) and hydrogenolysis, the sodium salt (**18b**).

(**19**) (**20**)

(**21**) (**22**)

(**23**)

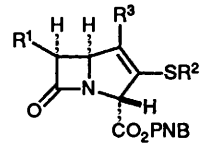
a; R = CHO
b; R = CH_2OH
c; R = $CH_2OS(O)_2Me$
d; R = Me
e; R = H

(**24**) R = Et, CH_2CH_2NHAc

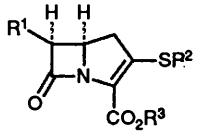
cis-Carbapenems are less synthetically accessible than their thermodynamically favoured *trans*-counterparts.[29] We have achieved the synthesis of the *cis*-carbapenem aldehyde (**20**) from the azabicyclo-octene (**19**) by an ozonolysis–cyclisation sequence,[25] a strategy which ensures a *cis*-disposition of C-5 and C-6 protons in the product (J 6 Hz). Addition of

acetamidoethanethiol to compound (**20**) provided the expected series of carbapenam adducts (**21a**)–(**23a**) (77%). Although we separated the individual isomers and subjected each of them, in turn, to the forthcoming reaction sequence, it was more convenient (see Experimental section) to progress a bulk sample containing all three isomers.

Reduction with sodium borohydride in aq. tetrahydrofuran (THF) gave the corresponding alcohols (**21b**)–(**23b**). On attempted purification these isomerised to the pyrrolidine-lactones (**24**; R = CH_2CH_2NHAc). This is analogous to a similar silica gel-catalysed rearrangement which we have observed in the parent, 3-unsubstituted series.[25] Immediate methanesulphonylation of the crude alcohol mixture gave mesyl esters (**21c**)–(**23c**) [81% overall from aldehydes (1:3:1 proportions)]. Reduction of a mixture of the 2α-carboxy mesylate isomers (**21c**) and (**22c**) in hexamethylphosphoric triamide (HMPT) with an excess of sodium cyanoborohydride (95 °C; 4.5 h) provided the *cis*-6-ethylcarbapenams (**21d**) and (**22d**) (71%). IBD oxidation in methylene dichloride as before gave Δ^3-ester (**25a**) (66%). On conducting the oxidation in anhydrous benzene, usually an equally effective solvent for such reactions,[1] poor substrate solubility resulted in over-chlorination of the double bond, leading to the formation of a substantial amount (15%) of the 4-chloro-Δ^3-ester (**26a**). DBU equilibration of ester (**25a**) provided the required Δ^2-isomer (**27a**) (14%). The yield was raised (25%) by recycling of the recovered Δ^3-substrate (**25a**). Hydrogenolysis yielded an aqueous solution of (±)-6-*epi*-PS-5 (**28a**) (45%). Utilisation of ethanethiol in the Michael addition step led to the corresponding 3-ethylthio sodium salt (**28b**).



(**25**) R^3 = H
(**26**) R^3 = Cl

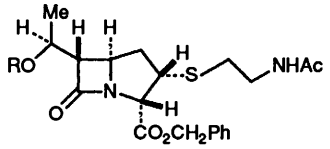


(**27**) R^3 = PNB
(**28**) R^3 = Na

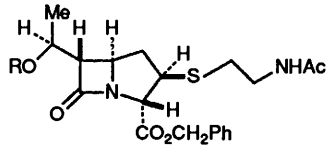
a; R^1 = Et, R^2 = CH_2CH_2NHAc
b; R^1 = R^2 = Et
c; R^1 = Me, R^2 = Et

In the latter series, we have also obtained *cis*-carbapenams/carbapenems containing a 6-methyl substituent. Decarbonylation of a mixture (*ca.* 1:1) of aldehyde isomers (**21a**) and (**22a**) (3-SEt substituent) of 'natural' C-2 stereochemistry by means of *tris*-(triphenylphosphine)rhodium(I) chloride[29] in refluxing acetonitrile gave the corresponding 6-methylcarbapenams (**21e**; 3-SEt) (35%) and (**22e**; 3-SEt) (25%). Similar attempts to transform the 2β,3β-isomer corresponding to aldehyde (**23a**) led to the unexpected recovery once more of the 2α,3β-product (**22e**; 3-SEt); concomitant C-2 epimerisation had occured during the course of the decarbonylation reaction. IBD oxidation and DBU isomerisation provided esters (**25c**) and (**27c**); deprotection gave the *cis*-6-methyl-substituted salt (**28c**). The integrity of the sodium salt preparations (**28a–c**) was confirmed by conversion into the *in vivo* hydrolysable phthalidyl esters.

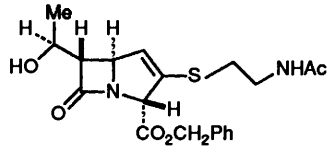
The anhydrous IBD–pyridine oxidation was also compatible with the presence of a 6-hydroxyethyl group in the carbapenam substrate.[1] However, initial oxidation attempts with 2-acetamidoethylthio derivatives (**29**) and (**31**)[1] were unsuccessful owing to their insolubility. Prior solubilisation by silylation of the hydroxy group [Me_3SiCl, $(Me_3Si)_2NH$, THF] gave silyl ethers (**30**) and (**32**). Subsequent IBD oxidation, followed by silyl ether hydrolysis (pH 2 with sodium phosphate buffer) provided, as anticipated, the same Δ^3-ester (**33**) (67 and 43%, respectively). This compound exhibited allylic coupling ($^4J_{2\beta,4}$ 2 Hz), together with the long-range coupling between the C-2 and C-5 protons which we have observed[1] previously in such systems ($^nJ_{2\beta,5\alpha}$ 3 Hz). DBU isomerisation gave the Δ^2-ester (**34**) in low equilibrium proportion (7%). This (±) sample was identical (^{1}H NMR spectrum) with the benzyl ester of the naturally occurring olivanic acid, MM22381.[11]



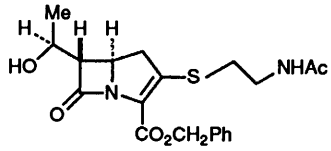
(**29**) R = H
(**30**) R = $SiMe_3$



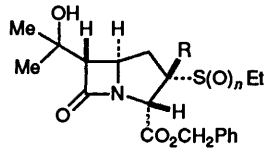
(**31**) R = H
(**32**) R = $SiMe_3$



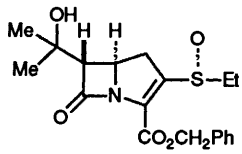
(**33**)



(**34**)



(**35**) R = H, *n* = 0
(**36**) R = Cl, *n* = 1



(**37**)

The presence of a *trans*-substituted 6-hydroxyisopropyl[6-(1-hydroxy-1-methylethyl)] substituent (carpetimycin[30]-type analogues) provided an unexpected limitation to our method. Anhydrous IBD oxidation of compound (**13c**) gave the Δ^3-ester (**16c**) (35%) (no Δ^2-isomer). However, on prolonged treatment with DBU, we could detect no equilibrium concentration of the required Δ^2-ester (**17c**). In contrast, with the corresponding benzyl ester as substrate, use of our alternative IBD oxidation conditions[1] gave a Δ^2-product at the sulphoxide oxidation level: reaction of compound (**35**) with IBD (2 mol equiv.) in the presence of pyridine (3 mol equiv.) and water led to α-chloro sulphoxide (**36**). Dehydrohalogenation wiith DBU (1 mol equiv.) then afforded the Δ^2-sulphoxide (**37**).

Experimental

The experimental techniques, materials, solvents, and spectroscopic instrumentation employed in this work were as described in Parts 2[25] and 4[31] of the series. Unless stated otherwise, IR spectra were recorded for chloroform solutions, and NMR spectra were obtained in $CDCl_3$. IBD was prepared[32] from chlorine gas and iodobenzene in chloroform. It was crystallised from chloroform–hexane, air dried, and stored in sealed vessels at 0 °C. Solvents for the anhydrous IBD oxidations were obtained as follows. Benzene was dried over sodium wire and distilled; methylene dichloride was passed through basic alumina, refluxed over BDH phosphorus pentaoxide–silica gel drying agent (Trockenmittel®), and distilled therefrom; pyridine was dried over potassium hydroxide and distilled. Biogel® P2 refers to 200–400 mesh grade. All compounds prepared are racemic; NMR stereochemical assignments refer to that enantiomer which is depicted.

Total Synthesis of (±)-PS-5

(3RS,4RS)-p-*Nitrobenzyl*[4-*Allyl*-3-*ethyl*-2-*oxoazetidin*-4-*yl*](*triphenylphosphoranylidene*)*acetate* (**11a**).—(3*RS*,4*RS*)-4-Allyl-3-ethylazetidin-2-one (**9a**)[25] (1.60 g) was converted into the title phosphorane (**11a**) *via* glyoxylate (**10a**) by use of our established procedures.[13,25] The phosphorane was obtained as a pale yellow foam [4.71 g, 70% overall from (**9a**)], ν_{max} 1 740, 1 730, 1 640–1 580, and 1 350 cm^{-1}.

(5RS,6RS)-p-*Nitrobenzyl* 6-*Ethyl*-7-*oxo*-1-*azabicyclo*-[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**12a**).—The title ester was prepared from the phosphorane (**11a**) (0.520 g) by an ozonolysis–cyclisation sequence in the manner which we have previously described.[13,25] Rapid chromatography on silica gel (Art. 9385) [elution with ethyl acetate–hexane (3:2)] provided pure ester (**12a**) as a gum (0.175 g, 63%); ν_{max} 1 775, 1 730, 1 610, 1 525, and 1 350 cm^{-1}; δ_H 1.04 (3 H, t, *J* 7 Hz, Me), 1.84 (2 H, dq, *J* 7.5 and 7 Hz, MeCH_2), 2.76 and 3.01 (each 1 H, ddd, *J* 19, 9, and 3 Hz) (together 4-H_2), 3.17 (1 H, td, *J* 7.5 and 3 Hz, 6-H), 4.03 (1 H, td, *J* 9 and 3 Hz, 5-H), 5.27 (1 H, *J* 14 Hz) and 5.44 (1 H, *J* 14 Hz) (together ABq, CH_2Ar), 6.55 (1 H, t, *J* 3 Hz, 3-H), and 7.62 (2 H, *J* 9 Hz) and 8.19 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

p-*Nitrobenzyl* 3-(2-*Acetamidoethylthio*)-6-*ethyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate*.—2-Acetamidoethanethiol[26] (0.55 g, 4.6 mmol, 2 mol equiv.) was added to a solution of ester (**12a**) (0.730 g, 2.3 mmol) in DMF (10 ml), followed by potassium carbonate (0.070 g, 0.5 mmol). The mixture was stirred at room temperature for 20 min, and then partitioned between ethyl acetate and brine. The organic layer was dried, evaporated, and the residue was chromatographed on silica gel (Art. 7729). Elution with ethanol–hexane–ethylene dichloride (3:3:14) gave an inseparable mixture of the isomeric *adducts* (0.700 g, 70%) (Found: M^+, 435.1505. $C_{21}H_{26}N_2O_6S$ requires *M*, 435.1544); ν_{max} 3 600–2 250, 1 760, 1 670, 1 610, 1 525 and 1 350 cm^{-1}. The (2*RS*,3*RS*,5*SR*,6*SR*)-isomer (**13a**), the (2*RS*,3*SR*,5*SR*,6*SR*)-isomer (**14a**), and the (2*RS*,3*RS*,5*RS*,6*RS*)-isomer (**15a**) were present in the proportions (5:3:2); δ_H *inter alia* 2-H signals at 4.76 (d, *J* 7 Hz), 4.41 (d, *J* 5 Hz), and 4.14 (d, *J* 8 Hz), respectively.

The mixture, in ethyl acetate, was treated with DBU (0.10 g) for 3 h to effect isomerisation of isomer (**15a**) to isomer (**14a**) HPLC monitoring).

(2RS,5RS,6SR)-p-*Nitrobenzyl* 3-(2-*Acetamidoethylthio*)-6-*ethyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**16a**).—A mixture of thiol adduct isomers (**13a**) and (**14a**) (1.50 g, 3.4 mmol) in dry methylene dichloride (100 ml) containing pyridine (0.59 g, 7.5 mmol, 2.2 mol equiv.) was cooled to −20 °C under argon. IBD (1.03 g, 3.7 mmol, 1.1 mol equiv.) was added. The solution was maintained at −20 °C for 5 min, and at 5 °C for 3 h. Evaporation, and chromatography of the residue on silica gel (Art. 9385) [elution with EtOH–EtOAc–hexane (3:12:5)] followed by crystallisation from ethyl acetate, gave the Δ^3-*ester* (**16a**) (0.90 g, 60%), m.p. 95–97 °C (Found: C, 55.2; H, 5.4; N, 9.5; S, 6.9%; M^+ 433.1331. $C_{20}H_{23}N_3O_6S$ requires C, 55.4; H, 5.4; N, 9.7; S, 7.4%; *M*, 433.1305); ν_{max} 3 450, 1 760, 1 670, 1 610, 1 575w (vinyl sulphide), 1 525, and 1 350 cm^{-1}; δ_H 1.05 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.85 (2 H, quin, *J* 7 Hz, MeCH_2), 1.97 (3 H, s, Ac), 2.85–3.15 (3 H, m, 6-H and SCH_2), 3.25–3.55 (2 H, m, NCH_2), 4.35 (1 H, m, 5-H), 5.12 (1 H, dd, *J* 3 and 1 Hz, 2-H), 5.28 (2 H, s, CH_2Ar), 6.11 (1 H, t, *J* 1 Hz, 4-H), 6.88 (1 H, t, *J* 5 Hz, NH), and 7.55 (2 H, *J* 9 Hz) and 8.20 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

(5RS,6RS)-p-*Nitrobenzyl* 3-(2-*Acetamidoethylthio*)-6-*ethyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**17a**).—A solution of Δ^3-ester (**16a**) (0.420 g) in dry methylene dichloride (20 ml) was kept at room temperature in the presence of DBU (0.065 g) under argon for 2 h. The solution was concentrated and chromatographed on silica gel (Art. 9385), and eluted rapidly with EtOH–EtOAc–hexane (3:3:14). Early fractions afforded recovered Δ^3-ester (0.190 g, 45%). Later fractions provided the Δ^2-*isomer* (**17a**) (0.125 g, 30%), m.p. 138–139 °C (from EtOAc) (Found: C, 55.45; H, 5.35; N, 9.45%; M^+, 433.1278); λ_{max} (EtOH) 317 and 268 nm; ν_{max} 3 450, 1 780, 1 700sh, 1 670, 1 610, 1 550sh (vinyl sulphide), 1 520, and 1 350 cm^{-1}; δ_H 1.07 (3 H, t, *J* 7.5 Hz, *Me*CH_2), 1.82 and 1.92 (each 1 H, quin, *J* 7.5 Hz, MeCH_2), 2.00 (3 H, s, Ac), 2.91 (1 H, ddd, *J* 14, 7, and 6.5 Hz, SCH), 3.05 (1 H, td, *J* 14 and 7 Hz, SCH), 3.10 (1 H, dd, *J* 18 and 8.5 Hz, 4-H), 3.15 (1 H, dt, *J* 7.5 and 2.5 Hz, 6-H), 3.39 (1 H, q, *J* 7 Hz, NCH), 3.45 (1 H, dd, *J* 18 and 10 Hz, 4-H), 3.46 (1 H, ddd, *J* 12, 7, and 6.5 Hz, NCH), 4.00 (1 H, ddd, *J* 10, 8.5, and 2.5 Hz, 5-H), 5.25 (1 H, *J* 14 Hz) and 5.51 (1 H, *J* 14 Hz) (together ABq, CH_2Ar), 5.89 (1 H, m, NH), and 7.67 (2 H, *J* 9 Hz) and 8.23 (2 H, *J* 9 Hz) (together AA′BB′, ArH). The UV, IR, NMR and mass spectral data of ester (**17a**) were identical with those of semi synthetic material derived[27] from the naturally occurring olivanic acid MM17880.

(5RS,6RS)-*Sodium* 3-(2-*Acetamidoethylthio*)-6-*ethyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**18a**).—A catalyst of 5% palladium–carbon (0.060 g) was suspended in dioxane–water (2:1) (15 ml) and the suspension was shaken under hydrogen for 30 min. A solution of Δ^2-ester (**17a**) (0.040 g) in dioxane (5 ml) was added, and hydrogenation was continued for 2.5 h. A solution of sodium hydrogen carbonate (0.007 g) in water (1 ml) was added, the mixture was filtered (Celite), and the filtrand was washed with dioxane–water. The combined filtrate and washings were evaporated and the aqueous solution was extracted with ethyl acetate. The aqueous layer was concentrated under reduced pressure and chromatographed on HP20SS. Elution with water–acetone mixtures (1:0–9:1) (UV monitoring) and lyophilisation afforded the sodium salt (**18a**) (0.0185 g, 63%); λ_{max}(water) 299 nm (ε 4 900); ν_{max}(KBr) 1 750 cm^{-1}; δ_H(250 MHz; D_2O) 0.78 (3 H, t, *J* 7.5 Hz, SCH_2*Me*), 1.56 (1 H) and 1.58 (1 H) (each quin., *J* 7.5 Hz, CH_2Me), 1.77 (3 H, s, Ac), 2.66 (1 H) and 2.78 (1 H) (each 5 lines, *J* 7 Hz, SCH_2), 2.84 (1 H) and 3.02 (1 H) (each dd, *J* 17 and 7 Hz, 4-H_2), 3.05 (1 H, td, *J* 7 and 2.5 Hz, 6-H), 3.18 (2 H, br t, *J* 7 Hz, CH_2N), and 3.79 (1 H, td, *J* 8 and 2.5 Hz, 5-H).

The (±)-synthetic material was indistinguishable by UV, IR, and ^{1}H NMR spectroscopy, and by HPLC, from authentic (+)-PS-5 (supplied by Sanraku-Ocean Co. Ltd).

In a parallel synthetic sequence, we obtained the corresponding 6-methyl compound bearing a 3-SEt group,

(**18b**). (3*RS*,4*RS*)-4-allyl-3-methylazatidin-2-one (**9b**)[25] was converted into the phosphorane (**11b**) and thence, by ozonolysis–cyclisation, into (5RS,6RS)-p-*nitrobenzyl*-6-*methyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**12b**) (67%), m.p. 128–130 °C (from EtOAc–hexane) (Found: C, 59.2; H, 4.7; N, 9.2%. M^+, 302.0905. $C_{15}H_{14}N_2O_5$ requires C, 59.6; H, 4.7; N, 9.3%; *M*, 302.0910); λ_{max}(EtOH) 267 nm (14 100); ν_{max} 1 780, 1 730, 1 610, 1 525, and 1 350 cm^{-1}; δ_H 1.45 (3 H, d, *J* 8 Hz, 6-Me), 2.74 (1 H) and 3.00 (1 H) (each ddd, *J* 19, 9, and 3 Hz, 4-H_2), 3.22 (1 H, dq, *J* 8 and 3 Hz, 6-H), 3.98 (1 H, dt, *J* 9 and 3 Hz, 5-H), 5.25 (1 H, *J* 14 Hz) and 5.47 (1 H, *J* 14 Hz) (together ABq, CH_2Ar), 6.53 (1 H, t, *J* 3 Hz, 3-H), and 7.62 (2 H, *J* 9 Hz) and 8.24 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

Addition of ethanethiol provided the expected adduct isomers, (**13b**) (61%), (**14b**) (11%), and (**15b**) (28%).

(2RS,5RS,6SR)-p-*Nitrobenzyl* 3-*Ethylthio*-6-*methyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**16b**).—Ethanethiol adduct isomer (**13b**) (0.280 g) was dissolved in benzene (15 ml) and was then oxidised with IBD (0.250 g) in the presence of pyridine (0.130 g) to give Δ^3-*ester* (**16b**) (0.166 g, 60%), which was isolated as a gum (Found: M^+, 362.0932. $C_{17}H_{18}N_2O_5S$ requires *M*, 362.0936); ν_{max} 1 755, 1 610, 1 570 (vinyl sulphide), 1 525, and 1 350 cm^{-1}; δ_H 1.29 (3 H, t, *J* 7.5 Hz, CH_2*Me*), 1.43 (3 H, d, *J* 8 Hz, 6-Me), 2.83 (2 H, q, *J* 7.5 Hz, SCH_2), 3.07 (1 H, dq, *J* 8 and 2.5 H, 6-H), 4.31 (1 H, ddd, *J* 3.5, 2.5, and 2 Hz, 5-H), 5.14 (1 H, dd, *J* 3.5 and 2 Hz, 2-H), 5.28 (2 H, s, CH_2Ar), 5.83 (1 H, t, *J* 2 Hz, 4-H), and 7.55 (2 H, *J*, 9 Hz) and 8.22 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

(5RS,6RS)-p-*Nitrobenzyl* 3-*Ethylthio*-6-*methyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**17b**).—This was prepared by equilibration of Δ^3-ester (**16b**) (0.220 g, 0.6 mmol) in methylene dichloride (15 ml) in the presence of DBU (0.03 g, 0.2 mmol) (20 °C; 2 h). This gave recovered substrate (**16b**) (0.120 g, 55%) and the *title* Δ^2-*ester* (**17b**) (0.067 g, 30%) (Found: M^+, 362.0928); λ_{max}(EtOH) 315 and 267 nm; ν_{max} 1 775, 1 710, 1 610, 1 545sh (vinyl sulphide), 1 525, aand 1 350 cm^{-1}; δ_H 1.26 (3 H, t, *J* 7.5 Hz, CH_2*Me*), 1.44 (3 H, d, *J* 8 Hz, 6-Me), 2.7–3.3 (5 H, m, 4-H_2, 6-H, and SCH_2Me), 3.90 (1 H, td, *J* 9 and 2.5 Hz, 5-H), 5.21 (1 H, *J* 14 Hz) and 5.50 (1 H, *J* 14 Hz) (together ABq, CH_2Ar), and 7.65 (2 H, *J* 9 Hz) and 8.9 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

Hydrogenolysis of compound (**17b**) (0.035 g) (Biogel P2 purification) provided an aqueous solution of the sodium salt (**18b**), λ_{max}(water) 299 nm.

Total Synthesis of (±)-6-Epi-PS-5

p-*Nitrobenzyl* 3-(2-*Acetamidoethylthio*)-6-*formylmethyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**21a**)–(**23a**).—A solution of (5*RS*,6*SR*)-p-nitrobenzyl 6-formylmethyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**20**)[25] (0.934 g) in DMF (15 ml) was stirred with 2-acetamidoethanethiol (0.330 g) in the presence of potassium carbonate (0.034 g) at room temperature for 35 min. The reaction mixture was diluted with ethyl acetate (150 ml), washed well with brine (3 × 30 ml), and the aqueous phases were back-extracted with ethyl acetate. The organic phases were bulked, dried, and evaporated. The oily residue (1.15 g) was chromatographed on silica gel (1:1 ratio Art. 9385 and Art. 7729 grades; 20 × 3.5 cm). Elution with EtOH–EtOAc (1:19) gave a (1:3) mixture of the (2RS,3RS,5SR,6RS)-*isomer* (**21a**) and (2RS,3SR,5SR,6RS)-*isomer* (**22a**) of the *title carboxylate* as a gum (0.780 g, 61%). Rechromatography of an aliquot of the material afforded the pure components.

(2RS,3RS,5SR,6RS)-*isomer* (**21a**). A gum (Found: M^+, 449.1252. $C_{20}H_{23}N_3O_7S$ requires *M*, 449.1253); ν_{max} 3 450, 1 760, 1 745, 1 725sh, 1 670, 1 610, 1 525, and 1 350 cm^{-1}; δ_H 1.5–2.1 (2 H, m, CH_2CHO), 1.95 (3 H, s, Ac), 2.4–3.0 (4 H, m, 4-H_2 and SCH_2), 3.40 (2 H, q, *J* 6.5 Hz, NCH_2), 3.6–4.35 (3 H, m, 3-, 5-, and 6-H), 4.72 (1 H, d, *J* 7 Hz, 2-H), 5.27 (2 H, s, CH_2Ar), 5.88 (1 H, br s, NH), 7.53 (2 H, *J* 9 Hz) and 8.22 (2 H, *J* 9 Hz) (together AA′BB′, ArH), and 9.78 (1 H, s, CHO).

(2RS,3SR,5SR,6RS)-*isomer* (**22a**). A gum (Found: M^+, 449.1258); ν_{max} 3 450, 1 760, 1 745, 1 725sh, 1 670, 1 610, 1 525, and 1 345 cm^{-1}; δ_H 1.4–1.9 (2 H, m, CH_2CHO), 1.96 (3 H, s, Ac), 1.95–2.3 (4 H, m, 4-H_2 and SCH_2), 3.39 (2 H, q, *J* 6.5 Hz, NCH), 3.6–4.25 (3 H, m, 3-, 5-, and 6-H), 4.32 (1 H, d, *J* 6.5 Hz, 2-H), 5.29 (2 H, s, CH_2Ar), 6.04 (1 H, br s, NH), 7.54 (2 H, *J* 9 Hz) and 8.23 (2 H, *J* 9 Hz) (together AA′BB′, ArH), and 9.73 (1 H, s, CHO).

Further elution of the original column provided the (2RS,3RS,5SR,6SR)-*isomer* (**23a**), again as a gum (0.205 g, 16%) (Found: M^+, 449.1241); ν_{max} 3 450, 1 750, 1 725, 1 670, 1 610, 1 525, and 1 350 cm^{-1}; δ_H 1.56–2.20 (2 H, m, CH_2CHO), 1.94 (3 H, s), 2.57–2.86 (4 H, m, 4-H_2 and SCH_2), 3.35 (2 H, q, *J* 6.5 Hz, NCH_2), 3.35–4.1 (3 H, m, 3-, 5-, and 6-H), 4.27 (1 H, d, *J* 7 Hz, 2-H), 5.28 (2 H, s, CH_2Ar), 5.98 (1 H, br s, NH), 7.57 (2 H, *J* 9 Hz) and 8.22 (2 H, *J* 9 Hz) (together AA′BB′, ArH), and 9.73 (1 H, s, CHO).

p-*Nitrobenzyl* 3-(2-*Acetamidoethylthio*)-6-(2-*hydroxyethyl*)-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**21b**)–(**23b**).—A mixture of aldehyde isomers (**21a**)–(**23a**) (0.700 g) in THF (30 ml) was cooled to 0 °C. A solution of sodium borohydride (0.015 mg; 1 mol equiv., 0.25 molar ratio) in water (3 ml) was added dropwise during 5 min, and the mixture was stirred for a further 10 min. Water (10 ml) was added, the bulk of the THF was evaporated off at 0 °C, and the residue was diluted witth ethyl acetate (100 ml). The organic layer was separated, washed with brine, and dried. Evaporation provided the isomeric alcohols (**21b**)–(**23b**) as a gum (0.680 g, 98%) [Found: (EI) MH^+, 452.1493. $C_{20}H_{26}N_3O_7S$ requires *m/z*, 452.1488]; ν_{max} 3 450, 1 750, 1 725sh, 1 670, 1 610, 1 525, 1 350, and 1 290 cm^{-1}; the NMR spectrum, although very complex, showed features consistent with the proposed structures; the signals due to the aldehyde protons of the substrate aldehydes (**21a**)–(**23a**) were absent.

Considerations of stability precluded chromatographic separation of these isomers; the material was converted into the methanesulphonate esters immediately. On exposure to silica gel, alcohols (**21b**)–(**23b**) gave more polar pyrrolidine lactones (**24**; R = CH_2CH_2NHAc).

p-*Nitrobenzyl* 3-(2-*Acetamidoethylthio*)-6-(2-*methylsulphonyloxyethyl*)-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**21c**)–(**23c**).—A solution of the crude mixture of isomeric alcohols (**21b**)–(**23b**) (0.680 g) in pyridine (10 ml) at 0 °C was stirred with an excess of methanesulphonyl chloride (0.220 g). The mixture was allowed to warm to room temperature during 1.5 h, diluted with ethyl acetate (100 ml), and washed successively with 10% aq. citric acid and brine. The solution was dried, evaporated, and the residue wad chromatographed on silica gel [12 × 4 cm; (1:1) ratio Art. 9385 and Art. 7729 grades]. Elution with EtOH–EtOAc (1:9) gave the title methanesulphonate esters (**21c**)–(**23c**) as a gum (0.669 g, 81% overall from aldehydes) (1:3:1 proportions). Rechromatography [EtOH–EtOAc (1:19)] of an aliquot of the mixture gave, in order of elution.

The (2RS,3SR,4SR,5RS)-*isomer* (**22c**), which crystallised from ethyl acetate–light petroleum as needles, m.p. 137–138 °C (Found: C, 47.6; H, 4.8; N, 7.7; S, 11.9. $C_{21}H_{27}N_3O_9S_2$ requires C, 47.6; H, 5.1; N, 7.9; S, 12.1%); ν_{max} 3 450, 1 765, 1 750, 1 670, 1 610, 1 520, 1 360sh, 1 350, and 1 175 cm^{-1}; δ_H 1.55–1.85 (1 H, m, 4-H), 1.96 (3 H, s, Ac), 1.90–2.3 (2 H, m, $CH_3SO_2CH_2CH_2$), 2.35–2.6 (1 H, m, 4-H), 2.6–2.8 (2 H, m, SCH_2), 3.00 (3 H, s,

$MeSO_2$), 3.39 (2 H, q, *J* 6.5 Hz, NCH_2), 3.5–4.2 (3 H, m, 3-, 5-, and 6-H), 4.30 (1 H, d, *J* 7 Hz, 2-H), 4.34 (2 H, t, *J* 6 Hz, $MeSO_2CH_2$), 5.28 (2 H, s, CH_2Ar), 5.94 (1 H, br s, NH), and 7.52 (2 H, *J* 9 Hz) and 8.23 (2 H, *J* 9 Hz) (together AA'BB', ArH).

The (2*RS*,3*RS*,5*SR*,6*RS*)-isomer (**21c**), which remained a gum, ν_{max} 3 450, 1 765, 1 750, 1 670, 1 605, 1 525, 1 360sh, 1 350, and 1 175 cm^{-1}; δ_H 1.7–2.4 (4 H, m, 4-H_2 and $MeSO_2CH_2CH_2$), 2.00 (3 H, s, Ac), 2.6–2.9 (2 H, m, SCH_2), 3.07 (3 H, s, $MeSO_2$), 3.44 (2 H, q, *J* 6.5 Hz, NCH_2), 3.5–4.2 (3 H, m, 3-, 5-, and 6-H), 4.38 (2 H, t, *J* 6 Hz, $MeSO_2CH_2$), 4.75 (1 H, d, *J* 7 Hz, 2-H), 5.28 (2 H, s, CH_2Ar), 6.10 (1 H, br s, NH), and 7.51 (2 H, *J* 9 Hz) and 8.22 (2 H, *J* 9 Hz) (together AA'BB', ArH).

The (2RS,3RS,5RS,6SR)-*isomer* (**23c**), which crystallised from chloroform–light petroleum as microcrystals, m.p. 148–150 °C (Found: C, 47.2; H, 5.0, N, 7.7; S, 11.8); ν_{max} 3 450, 1 765, 1 745, 1 670, 1 610, 1 520, 1 350sh, 1 345, and 1 170 cm^{-1}; δ_H 1.8–2.3 (4 H, m, 4-H_2 and $MeSO_2CH_2CH_2$), 1.96 (3 H, s, Ac), 2.55–2.8 (2 H, m, SCH_2), 2.99 (3 H, s, $MeSO_2$), 3.37 (2 H, q, *J* 6.5 Hz, NCH_2), 3.5–4.2 (3 H, m, 3-, 5-, and 6-H), 4.18 (1 H, d, *J* 7 Hz, 2-H), 4.25 (2 H, t, *J* 6 Hz, $MeSO_2CH_2$), 5.29 (2 H, s, CH_2Ar), 5.83 (1 H, br s, NH), and 7.58 (2 H, *J* 9 Hz) and 8.24 (2 H, *J* 9 Hz) (together AA'BB', ArH).

p-*Nitrobenzyl* 3-(2-*Acetamidoethylthio*)-6-*ethyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**21d**) *and* (**22d**).—A mixture of methanesulphonate isomers of 2α-configuration (**21c**) and (**22c**) (0.950 g, 1.8 mmol) in HMPT (15 ml) was heated with an excess of sodium cyanoborohydride (0.675 g, 10.7 mmol, 6 mol equiv.) at 95 °C for 4.5 h. The mixture was cooled, diluted with ethyl acetate, and washed successively with 0.5M-aq. hydrochloric acid and brine. The solution was dried and evaporated, and the residue was chromatographed on silica gel [16 × 3 cm, (1:1) mixture of Art. 9385 and Art. 7729 grades]. Elution with EtOH–EtOAc (1:19) gave two isomers of the *title ester* as a gum (0.560 g, 71%). Rechromatography, as before, afforded pure samples of the components.

(2*RS*,3*RS*,5*SR*,6*RS*)-*Isomer* (**21d**) was isolated as a gum (Found: M^+, $C_{20}H_{25}N_3O_6S$ requires *M*, 435.1461); ν_{max} 3 460, 1 760, 1 745, 1 670, 1 610, 1 525, 1 350, and 1 285 cm^{-1}; δ_H 1.01 (3 H, t, *J* 7 Hz, $MeCH_2$), 1.4–1.95 (4 H, m, 4-H_2 and $MeCH_2$), 1.95 (3 H, s, Ac), 1.57–1.78 (2 H, m, SCH_2), 3.37 (3 H, m, 6-H and NCH_2), 4.05–4.4 (2 H, m, 3- and 5-H), 4.70 (1 H, d, *J* 7 Hz, 2-H), 5.27 (2 H, s, CH_2Ar), 6.00 (1 H, br s, NH), and 7.53 (2 H, *J* 9 Hz) and 8.21 (2 H, *J* 9 Hz) (together AA'BB', ArH).

(2*RS*,3*SR*,5*SR*,6*RS*)-*Isomer* (**22d**) was obtained as microcrystals ($CHCl_3$–EtOAc–light petroleum), m.p. 127–129 °C (Found: C, 55.5; H, 5.7; N, 9.4%; M^+, 435.1485. $C_{20}H_{25}N_3O_6S$ requires C, 55.2; H, 5.8; N, 9.7%; *M*, 435.1461); ν_{max} 3 460, 1 765, 1 750, 1 670, 1 610, 1 525, 1 350, and 1 250 cm^{-1}; δ_H 1.97 (3 H, t, *J* 7 Hz, $MeCH_2$), 1.45–1.9 (3 H, m, 4-H and $MeCH_2$), 1.96 (3 H, s, Ac), 2.30–2.53 (1 H, m, 4-H), 2.6–2.9 (2 H, m, SCH_2), 3.2–3.6 (3 H, m, 6-H and NCH_2), 3.67–4.04 (2 H, m, 3- and 5-H), 4.25 (1 H, d, *J* 7 Hz, 2-H), 5.28 (2 H, s, CH_2Ar), 6.03 (1 H, br s, NH), and 7.53 (2 H, *J* 9 Hz) and 8.22 (2 H, *J* 9 Hz) (together AA'BB', ArH).

Reduction experiments with a corresponding series of toluene-*p*-sulphonate esters gave inferior results (50–55%, 6 h).

(2RS,5RS,6RS)-p-*Nitrobenzyl* 3-(2-*Acetamidoethylthio*)-6-*ethyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**25a**).—(i) *Anhydrous benzene as solvent.* A stirred mixture of 2α-carboxylate isomers (**21d**) and (**22d**) (0.075 g) was suspended in benzene (4 ml) under argon and cooled in an ice-bath. Pyridine (0.030 g, 2 mol equiv.) was added, followed by IBD (0.051 g, 1 mol equiv.). The mixture was left at 4 °C for 2 h. Chromatography on silica gel [13 × 2 cm, Art. 9385; elution with EtOH–EtOAc (3:97)] unexpectedly gave (2RS,5RS,6RS)-p-*nitrobenzyl* 3-(2-*acetamidoethylthio*)-4-*chloro*-6-*ethyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**26a**) as a gum (0.009 g, 15%), λ_{max}(EtOH) 264 nm; ν_{max} 3 450, 1 780, 1 755, 1 675, 1 610, 1 570w (vinyl sulphide), 1 525, and 1 350 cm^{-1}; δ_H 1.13 (3 H, t, *J* 7 Hz, $MeCH_2$), 1.55–1.95 (2 H, m, $MeCH_2$), 1.99 (3 H, s, Ac), 2.75–3.2 (2 H, m, SCH_2), 2.3–2.7 (3 H, m, 6-H and NCH_2), 4.66 (1 H, dd, *J* 6 and 4 Hz, 5-H), 5.31 (3 H, m, 2-H and CH_2Ar), 5.83 (1 H, br s, NH), and 7.55 (2 H, *J* 9 Hz) and 8.28 (2 H, *J* 9 Hz) (together AA'BB', ArH); *m/z* (EI) M^+, 467.469. $C_{20}H_{22}ClN_3O_6S$ requires *M*, 467.469; (NH_3 gas CI) MNH_4^+, 485.487.

Further elution afforded the desired *title* Δ^3-*ester* (**25a**) as microcrystals (from $CHCl_3$–Et_2O–light petroleum) (0.0165 g, 22%), m.p. 122–123 °C (Found: C, 55.1; H, 5.3; N, 9.5; S, 7.1%; M^+, 433.1313. $C_{20}H_{23}N_3O_6S$ requires C, 55.4; H, 5.3; N, 9.7; S, 7.4%; *M*, 433.1305); ν_{max} 3 450, 1 770, 1 750sh, 1 670, 1 610, 1 575 (vinyl sulphide) 1 525, and 1 350 cm^{-1}; δ_H 1.02 (3 H, t, *J* 7 Hz, $MeCH_2$), 1.4–1.75 (2 H, m, $MeCH_2$), 1.95 (3 H, s, Ac), 2.97 (2 H, br t, *J* 7 Hz, SCH_2), 3.32–3.56 (3 H, m, 6-H and NCH_2), 4.68 (1 H, 7 lines, *J* 6, 4 and 2 Hz, 5-H), 5.08 (1 H, dd, *J* 4 and 2 Hz, 2-H), 5.27 (2 H, s, CH_2Ar), 5.99 (1 H, t, *J* 2 Hz, 4-H), 6.20 (1 H, br s, NH), and 7.33 (2 H, *J* 9 Hz) and 8.22 (2 H, *J* 9 Hz) (together AA'BB', ArH).

(ii) *Anhydrous methylene dichloride as solvent.* The reaction was repeated with esters (**21d**) and (**22d**) (0.614 g) in methylene dichloride (4 ml) containing pyridine (0.225 g, 2 mol equiv.) and IBD (0.390 g, 1 mol equiv.), the mixture being stirred at 0–5 °C for 6 h, and then at room temperature for 0.5 h. Chromatography produced the title Δ^3-ester (**25a**) (0.401 g, 66%). It was identical with the sample described above (TLC, IR, NMR spectra).

(5RS,6SR)-p-*Nitrobenzyl* 3-(2-*Acetamidoethylthio*)-3-*ethyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**27a**).—A solution of Δ^3-ester (**25a**) (0.397 g) in methylene dichloride (3 ml) was stirred in the presence of DBU (0.042 g, 0.3 mol equiv.) at room temperature under argon for 3.5 h. Rapid chromatography of the reaction mixture on silica gel (Art. 9385, 10 × 3 cm), and elution with EtOH–EtOAc (3:97), gave recovered Δ^3-ester (**25a**) (0.28 g, 72%). Rapid elution with EtOH–EtOAc (1:9) provided the isomeric *title* Δ^2-*ester* (**27a**) (0.054 g, 14%) as off-white needles, m.p. 144–145 °C (from EtOAc–light petroleum) (Found: C, 55.2; H, 5.3; N, 9.4%; M^+, 433.1314. $C_{20}H_{23}N_3O_6S$ requires C, 55.2; H, 5.3; N, 9.7%; *M*, 433.1305); λ_{max}(EtOH) 317 (12 000) and 266 nm (11 400); ν_{max} 3 450, 1 775, 1 700sh (unsaturated ester), 1 670, 1 610, 1 550 (vinyl sulphide), 1 520, 1 350, and 1 330 cm^{-1}; δ_H 1.05 (3 H, t, *J* 7.5 Hz, $MeCH_2$), 1.4–2.1 (2 H, m, $MeCH_2$), 1.99 (3 H, s, Ac), 2.9–3.1 (2 H, m, SCH_2), 3.10 (1 H, dd, *J* 18 and 10 Hz) and 3.22 (1 H, dd, *J* 18 and 11 Hz) (together 4-H_2), 3.38–3.64 (3 H, m, 6-H and NCH_2), 4.31 (1 H, td, *J ca.* 10.5 and 6 Hz, 5-H), 5.23 (1 H, *J* 14 Hz) and 5.51 (1 H, *J* 14 Hz) (together ABq, CH_2Ar), 5.88 (1 H, br s, NH), and 7.65 (2 H, *J* 9 Hz) and 8.23 (2 H, *J* 9 Hz) (together AA'BB', ArH).

Re-equilibriation of the recovered Δ^3-ester (**25a**) permitted the isolation of further quantities of the required Δ^2-isomer (**27a**) (0.44 g). Total yield 0.098 g (25%).

(5RS,6SR)-*Sodium* 3-(2-*Acetamidoethylthio*)-3-*ethyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**28a**).—A catalyst of 5% palladium–carbon (0.080 g) was suspended in dioxane–water (2:1) (10 ml) and shaken under hydrogen for 10 min. A solution of the Δ^2-ester (**27a**) (0.060 g) in dioxane (8 ml) was added and hydrogenolysis was continued for 2.25 h. A solution of sodium hydrogen carbonate (0.012 g) in water (5 ml) was added, and the solution was filtered through Celite; the filtrand was washed well with dioxane–water. After removal of the dioxane under reduced pressure, the filtrate and washings were chromatographed on a column of Biogel P2 (15 × 2 cm) to give an aqueous solution of the title sodium salt (**28a**) (6-*epi*-PS-5) (*ca.* 45%). Evaporation of the solution (0 °C), followed by

trituration and evaporation successively from ethanol and toluene, gave a hygroscopic, white solid, λ_{max}(water) 298 nm; ν_{max}(KBr) 1 750 cm^{-1}; $\delta_H(D_2O)$ 0.88 (3 H, t, *J* 7 Hz, *Me*CH_2) 1.4–1.8 (2 H, m, MeCH_2), 1.94 (3 H, s, Ac), 2.7–3.1 (2 H, m, SCH_2), 2.85–3.05 (2 H, m, 4-H_2), 3.25–3.70 (3 H, m, 6-H and NCH_2), and 4.36 (1 H, m, 5-H). The *phthalidyl ester* of compound (**28a**) was prepared by methods which we have described,[1] m.p. 165–169 °C (Found: C, 58.4; H, 5.3; N, 6.3. $C_{21}H_{22}N_2O_6S$ requires 58.6; H, 5.15; N, 6.5%).

Utilisation of ethanethiol in the Michael addition step provided a comparable series of adducts. Stepwise reduction of the 6-(formylmethyl) function (*vide supra*) provided a series of *S*-ethylcarbapenams corresponding to esters (**21d**)–(**23d**). As before, unless alcohols (**21b**)–(**23b**) (3-SEt) were rapidly converted into their mesyl derivatives, isomerisation to pyrrolidine lactones occurred; *e.g.*, alcohol (**21b**) (3-SEt) (0.040 g) gave *compound* (**24**; R = Et) as a gum (0.035 g, 88%) (Found: *M*H$^+$, 395.1257. $C_{18}H_{23}N_2O_6S$ requires *M*H, 395.1276); ν_{max} 1 765 (lactone), 1 745, 1 610, and 1 350 cm^{-1}; δ_H 1.19 (3 H, t, *J* 7 Hz, CH_2*Me*), 1.8–2.8 [8 H, m, including 2.54 (2 H, q, *J* 7 Hz, SCH_2Me), NH, 4-H_2, 3′-H, and 4′-H_2], 3.50 (1 H, q, *J* 7 Hz, 3-H), 4.0–4.5 (4 H, m, 5′-H_2, 5-H, and 2-H), 5.27 (2 H, s, CH_2Ar), and 7.55 (2 H, *J* 9 Hz) and 8.20 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

IBD oxidation of the 2α,3α-isomer (**21d**) (3-SEt) (0.360 g) in benzene gave (2RS,5RS,6RS)-p-*nitrobenzyl* 6-*ethyl*-3-*ethylthio*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**25b**) as a gum (0.182 g, 50%) (Found: M^+, 376.1117. $C_{18}H_{20}N_2O_5S$ requires *M*, 376.1093); ν_{max} 1 770, 1 750, 1 610, 1 570, 1 525, and 1 350 cm^{-1}; δ_H 1.00 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.30 (3 H, t, *J* 7 Hz, SCH_2*Me*), 1.4–1.85 (2 H, m, MeCH_2), 2.83 (2 H, q, *J* 7 Hz, SCH_2Me), 3.44 (1 H, ddd, *J* 8, 7, and 6 Hz, 6-H), 4.70 (1 H, 7 lines, *J* 6, 4 and 2 Hz, 5-H), 5.08 (1 H, dd, *J* 4 and 2 Hz, 2-H), 5.27 (2 H, s, CH_2Ar), 5.72 (1 H, t, *J* 2 Hz, 4-H), and 7.54 (2 H, *J* 9 Hz) and 8.21 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

Further elution of the column provided (5RS,6SR)-p-*nitrobenzyl* 6-*ethyl*-3-*ethylthio*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**27b**). Crystallisation (from chloroform–acetone) gave pale needles (0.054 g, 15%), m.p. 144–146 °C (Found: C, 57.0; H, 5.3; N, 7.1%; M^+, 376.1107. $C_{18}H_{20}N_2O_5S$ requires C, 57.4; H, 5.4; N, 7.4%; *M*, 376.1093); λ_{max}(EtOH) 317 (10 800) and 264 nm (10 900); ν_{max} 1 780, 1 705, 1 610, 1 550, 1 525, and 1 350 cm^{-1}; δ_H 1.02 (3 H, t, *J* 7 Hz), 1.33 (3 H, t, *J* 7 Hz), 1.45–1.95 (2 H, m), 2.88 (2 H, q, *J* 7 Hz), 3.01 (2 H, d, *J* 10 Hz, 4-H_2), 3.52 (1 H, ddd, *J* 8, 7, and 6 Hz, 6-H), 4.25 (1 H, td, *J* 10 and 6 Hz, 5-H), 5.17 (1 H, *J* 14 Hz) and 5.47 (1 H, *J* 14 Hz) (together ABq, CH_2Ar), and 7.60 (2 H, *J* 9 Hz) and 8.17 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

Further quantities of compound (**27b**) (33%) were obtained by DBU-catalysed equilibration of its isomer (**25b**).

(5RS,6SR)-*Sodium* 6-*Ethyl*-3-*ethylthio*-7-*oxo*-1-*azabicyclo*-[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**28b**).—Hydrogenolysis of ester (**27b**) (Biogel P2 purification) provided an aqueous solution of the title salt (**28b**), λ_{max} 300 nm. Evaporation provided a solid (27%), λ_{max}(EtOH) 291 nm; ν_{max}($CHCl_3$) 1 760, 1 740sh, and 1 600 cm^{-1}; ν_{max}(KBr) 1 750 and 1 590br cm^{-1}. The *phthalidyl ester*[1] was obtained as needles (from EtOAc–light petroleum), m.p. 132–138 °C (Found: M^+, 373.0983. $C_{19}H_{19}NO_5S$ requirees *M*, 373.0984); λ_{max}(EtOH) 325 (8 700), 280 (2 700), 270 (2 500), and 227 nm (10 800); ν_{max} 1 785, 1 725br, 1 600, 1 545 (vinyl sulphide), and 975 cm^{-1}; δ_H 1.01 (3 H, t, *J* 7 Hz), 1.37 (3 H, t, *J* 7 Hz), 1.5–2.1 (2 H, m), 2.7–3.2 (4 H, m, SCH_2Me and 4-H_2), 3.52 (1 H, ddd, *J* 8, 7, and 6 Hz, 6-H), 4.25 (1 H, dt, *J* 10 and 6 Hz, 5-H), 7.45 (major) and 7.50 (minor) (together 1 H, *ca.* 3:2, phthalidyl methine H), and 7.6–8.0 (4 H, m, ArH).

p-*Nitrobenzyl* 3-*Ethylthio*-6-*methyl*-7-*oxo*-1-*azabicyclo*-[3.2.0]*heptane*-2-*carboxylate*.—Decarbonylation of a mixture of aldehyde isomers (**21a**) and (**22a**) (3-SEt substituent) (0.814 g, *ca.* 1:1) of 'natural' C-2 stereochemistry was effected by heating of the mixture with tris(triphenylphosphine)rhodium(I) chloride (1.90 g, 1 mol equiv.) in methylene dichloride at reflux temperature under argon for 20 h. The mixture was cooled, filtered, and the insoluble $(Ph_3P)_2Rh(CO)Cl$ (1.02 g) was washed well with methylene dichloride. The filtrate and washings were evaporated, and the red gum (0.525 g) was chromatographed on Kieselgel 60 (1:1 mixture of Art. 9385 and 7729 grades). Elution with ethyl acetate–light petroleum (1:3) gave the (2RS,3RS,5SR,6RS)-*isomer* of the *title ester* (**21e**; 3-SEt) as a gum (0.266 g, 35%) (Found: M^+, 364.1092. $C_{17}H_{20}N_2O_5S$ requires *M*, 364.109); ν_{max} 1 765, 1 745, 1 610, and 1 345 cm^{-1}; δ_H 1.15 (3 H, d, *J* 7.5 Hz, 6-Me), 1.19 (3 H, t, *J* 8 Hz, SCH_2*Me*), 1.94 (1 H, ddd, *J* 14, 10.5, and 7.5 Hz, 4-H), 2.24 (1 H, ddd, *J* 14, 8, and 3.5 Hz, 4-H), 2.57 (2 H, q, *J* 8 Hz, SCH_2Me), 3.39 (1 H, ddd, *J* 10.5, 8, and 7.5 Hz, 3-H), 3.53 (1 H, dq, *J* 7.5 and 6 Hz, 6-H), 4.17 (1 H, ddd, *J* 7.5, 6, and 3.5 Hz, 5-H), 4.72 (1 H, d, *J* 7.5 Hz, 2-H), 5.27 (2 H, s, CH_2Ar), and 7.55 (2 H, *J* 9 Hz) and 8.21 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

Further elution provided the (2RS,3SR,5SR,6RS)-*isomer* (**22e**; 3-SEt), again as a gum (0.189 g, 25%) (Found: M^+, 364.1109); ν_{max} 1 765, 1 745, 1 610, 1 520, and 1 345 cm^{-1}; δ_H 1.20 (3 H, d, *J* 7.5 Hz), 1.24 (3 H, t, *J* 8 Hz), 1.66 (1 H, ddd, *J* 13.5, 10, and 8.5 Hz, 4-H), 2.40 (1 H, dt, *J* 13.5 and 6.5 Hz, 4-H), 2.57 (2 H, q, *J* 8 Hz), 3.53 (1 H, dq, *J* 7.5 and 5.5 Hz, 6-H), 3.78 (1 H, dt, *J* 10 and 7 Hz, 3-H), 3.96 (1 H, dt, *J* 8.5 and 6 Hz, 5-H), 4.26 (1 H, d, *J* 7 Hz, 2-H), 5.29 (2 H, s, CH_2Ar), and 7.54 (2 H, *J* 9 Hz) and 8.22 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

Attempts to transform the remaining aldehyde isomer (**23a**; 3-SEt) led to the isolation once more of isomer (**22e**; 3-SEt); epimerisation at C-3 had occurred.

(2RS,5RS,6RS)-p-*Nitrobenzyl* 3-*Ethylthio*-6-*methyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**25c**).—This was obtained as a gum (0.117 g, 55%) from IBD oxidation of a (1:1) mixture of sulphides (**21e**) and (**22e**) (3-SEt) (0.320 g) (Found: M^+, 362.0953. $C_{17}H_{18}N_2O_5S$ requires *M*, 362.0936); ν_{max} 1 775, 1 755, 1 610, 1 570, 1 525, and 1 350 cm^{-1}; δ_H 1.14 (3 H, d, *J* 7.5 Hz), 1.29 (3 H, t, *J* 7 Hz), 2.83 (2 H, q, *J* 7 Hz, CH_2Me), 3.59 (1 H, dq, *J* 7.5 and 5.5 Hz, 6-H), 4.71 (1 H, 7 lines, *J* 5.5, 3.5, and 2 Hz, 5-H), 5.10 (1 H, dd, *J* 3.5 and 2 Hz, 2-H), 5.27 (2 H, s, CH_2Ar), 5.70 (1 H, t, *J* 2 Hz, 4-H), and 7.54 (2 H, *J* 9 Hz) and 8.22 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

The reaction also provided (5RS,6SR)-p-*nitrobenzyl* 3-*ethylthio*-6-*methyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**27c**) (0.40 g), which was crystallised (from EtOAc–light petroleum) as pale-yellow needles (0.028 g, 18%), m.p. 136 °C (Found: C, 56.0; H, 5.2; N, 7.6%; M^+, 362.0915. $C_{17}H_{18}N_2O_5S$ requires C, 56.3; H, 5.1; N, 7.7%; *M*, 362.0936); λ_{max}(EtOH) 318 (11 900), 266 (11 700), and 216 nm (infl); ν_{max} 1 780, 1 700, 1 605, 1 550, 1 520, and 1 345 cm^{-1}; $\delta_H[(CD_3)_2CO]$ 1.24 (3 H, d, *J* 7.5 Hz, 6-Me), 1.29 (3 H, t, *J* 7 Hz, CH_2*Me*), 2.97 (2 H, q, *J* 7 Hz, CH_2Me), 2.19 (2 H, d, *J* 10 Hz, 4-H_2), 3.74 (1 H, dt, 7.5 and 6 Hz, 6-H), 4.33 (1 H, dt, *J* 10 and 6 Hz, 5-H), 5.25 (1 H, *J* 14 Hz) and 5.52 (1 H, *J* 14 Hz) (together ABq, CH_2Ar), and 7.78 (2 H, *J* 9 Hz) and 8.24 (2 H, *J* 9 Hz) (together AA′BB′, ArH).

DBU-catalysed isomerisation of Δ^3-ester (**25c**) (0.160 g) provided further quantities of Δ^2-isomer (**27c**) (0.020 g).

(5RS,6SR)-*Sodium* 3-*Ethylthio*-6-*methyl*-7-*oxo*-1-*azabicyclo*-[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**28c**).—Hydrogenolysis of ester (**27c**) (Biogel P2 purification) as previously described gave an aqueous solution of the title salt, λ_{max} 300 nm. Evaporation of the solvent from an aliquot of the solution, followed by evaporation and trituration from ethanol and toluene, gave a

solid, $\nu_{max}(CHCl_3)$ 1 760, 1 745sh, and 1 600 cm^{-1}. The *phthalidyl ester*[1] had m.p. 126–130 °C (Found: C, 60.1; H, 4.9; N, 3.8. $C_{18}H_{17}NO_5S$ requires C, 60.15; H, 4.8; N, 3.9%).

Synthesis of Benzyl (±)-MM22381

(2RS,5RS,6RS,1'RS)-*Benzyl* 3-(2-*Acetamidoethylthio*)-6-(1-*hydroxyethyl*)-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**33**).—(i) *From sulphide isomer* (**31**)[1]. Initial attempts at IBD oxidation in benzene were unsuccessful owing to substrate insolubility. Solublisation using an excess of pyridine (25 mol equiv.) resulted in low yields of Δ^3-ester (**33**) (4%). The problem was overcome by silylation of the hydroxy group in the starting sulphides.

To a solution of sulphide (**31**) (0.140 g) in dry THF (10 ml) under argon was added hexamethyldisilazane (1.8 ml), followed by chlorotrimethylsilane (0.6 ml). The mixture was stirred at room temperature for 2 h, centrifuged, and the supernatant solution was concentrated under reduced pressure (1.5 h). The residue in benzene (10 ml) was centrifuged again to remove further solid. To the supernatant solution, containing silyl ether (**32**), were added pyridine (0.081 g) and IBD (0.100 g) and the mixture was stirred at 5 °C under argon for 18 h. The solution was filtered and evaporated. A solution of the residue in ethyl acetate (10 ml) was stirred vigorously with pH 2 aq. sodium phosphate buffer (10 ml) for 4 h. The organic phase was washed successively with aq. sodium hydrogen carbonate and brine, and dried. Evaporation gave a residue, which was chromatographed on silica gel (Art. 7729). Elution with EtOH–$CHCl_3$ (1:19) provided the Δ^3-*ester* (**33**) as a gum (0.060 g, 43%) (Found: M^+, 404.1388. $C_{20}H_{24}N_2O_4S$ requires M, 404.1405); ν_{max} 3 460, 2 980, 1 770, 1 750sh, 1 670, 1 570 (vinyl sulphide), and 1 510 cm^{-1}; δ_H 1.34 [3 H, d, J 6 Hz, *Me*CH(OH)], 1.92 (3 H, s, Ac), 2.6–3.0 (3 H, m, SCH_2 and OH), 3.15 (1 H, dd, J 5 and 3 Hz, 6-H), 3.39 (2H, q, J 6 Hz, CH_2NH), 4.19 [1 H, br quin, J 6 Hz, MeC*H*(OH)], 4.54 (1 H, ddd, J 3, 3, and 2 Hz, 5-H), 5.09 (1 H, dd, J 3 and 2 Hz, 2-H), 5.19 (2 H, s, CH_2Ph), 6.00 (1 H, t, J 2 Hz, 4-H), 6.12 (1 H, br s, NH), and 2.65 (5 H, s, Ph).

(ii) *From sulphide isomer* (**29**).[1] The isomer (**29**) (0.122 g) was subjected to the same sequence of reactions as described for isomer (i). This gave Δ^3-ester (**33**) (0.078 g, 64%) as the sole product, identical (IR, NMR) with the previous sample.

(5RS,6SR,1'SR)-*Benzyl* 3-(2-*Acetamidoethylthio*)-6-(1-*hydroxyethyl*)-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**34**).—A solution of the Δ^3-ester (**33**) (0.078 g) in dry methylene dichloride (10 ml) was stirred with DBU (0.08 g) at room temperature under argon for 4 h. The solution was concentrated and chromatographed on silica gel (Art. 9385). Elution with EtOH–$CHCl_3$ (1:9) gave recovered Δ^3-ester (**33**) (0.051 g, 65%). Continued elution with EtOH–$CHCl_3$ (1:4) afforded Δ^2-*ester* (**34**) (0.006 g, 7%) (Found: M^+, 404.1398. $C_{20}H_{24}N_2O_5S$ requires M, 404.1405); λ_{max}(EtOH) 318 nm (10 100); ν_{max} 3 470, 3 370, 1 780, 1 670, 1 550 (vinyl sulphide), and 1 515 cm^{-1}; δ_H(250 MHz) 1.35 [3 H, d, J 6 Hz, *Me*CH(OH)], 1.96 (3 H, s, Ac), 2.8–3.1 (2 H, m, SCH_2), 3.2 (1 H, br, m, 6-H), 3.24 (2 H, d, J 8 Hz, 4-H_2), 3.39 (2 H, q, J 6 Hz, NCH_2), 4.12 (1 H, td, J 8 and 3 Hz, 5-H), 4.0–4.3 [1 H, m, $CH_3CH(OH)$], 5.29 (1 H, J 12 Hz) and 5.37 (1 H, J 12 Hz) (together ABq, CH_2Ph), 6.05 (1 H, br s, NH), and 7.2–7.5 (5 H, m, Ph). The material was identical (TLC, IR, NMR) with the benzyl ester (**34**) prepared from naturally occurring (+)-MM22381,[11] m.p. 139–141 °C (Found: C, 59.1; H, 6.0; N, 6.9%; M^+ 404.1407. $C_{20}H_{24}N_2O_4S$ requires C, 59.4; H, 6.0; N, 6.9%).

(2RS,5RS,6RS)-p-*Nitrobenzyl* 3-*Ethylthio*-6-(1-*hydroxy*-1-*methylethyl*)-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**16c**).—The bicyclohept-2-ene ester (**12c**)[25] was prepared from the phosphorane (**11c**). Addition of ethanethiol provided the three carbapenam isomers (**13c**)–(**15c**). The major component, (2RS,3RS,5SR,6RS)-p-*nitrobenzyl* 3-*ethylthio*-6-(1-*hydroxy*-1-*methylethyl*)-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**13c**), was crystallised from ethyl acetate–hexane, m.p. 133 °C (Found: C, 56.1; H, 5.9; N, 6.9; S, 7.7%; M^+, 408.1365. $C_{19}H_{24}N_2O_6S$ requires C, 55.9; H, 5.9; N, 6.9; S, 7.9%; M, 408.1355); ν_{max} 3 020, 1 765sh, 1 750, 1 610, and 1 525 cm^{-1}; δ_H 1.21 (3 H, t, J 7 Hz, CH_2Me), 1.33 (3 H, s) and 1.39 (3 H, s) [together $Me_2C(OH)$], 1.64 (1 H, s, OH, D_2O exch.), 2.19 (1 H, ddd, J 13, 11, and 8 Hz, 4-H), 2.28 (1 H, ddd, J 13, 9, and 3 Hz, 4-H), 2.60 (2 H, m, CH_2S), 3.04 (1 H, d, J 3 Hz, 6-H), 3.55 (1 H, ddd, J 11, 9, and 7 Hz, 3-H), 4.10 (1 H, td, J 8 and 3 Hz, 5-H), 4.83 (1 H, d, J 7 Hz, 2-H), 5.27 (2 H, s, CH_2Ar), and 7.56 (2 H, J 9 Hz) and 8.24 (2 H, J 9 Hz) (together AA'BB', ArH).

IBD oxidation of carbapenam (**13c**) (1.20 g) in the manner previously described gave the title Δ^3-*ester* (**16c**) as a gum (0.420 g, 35%) (Found: M^+, 406.1201. $C_{19}H_{22}N_2O_6S$ requires M, 406.1198); ν_{max} 3 600–2 800, 1 760, 1 615, 1 525, and 1 355 cm^{-1}; δ_H 1.28 (3 H, t, J 7.5 Hz, CH_2Me), 1.35 (3 H, s) and 1.39 (3 H, s) [together $Me_2C(OH)$], 2.1–2.6 (1 H, br s, D_2O exch.), 2.82 (2 H, q, J 7.5 Hz, CH_2Me), 3.08 (1 H, d, J 2.5 Hz, 6-H), 4.58 (1 H, m, 5-H), 5.13 (1 H, dd, J 3 and 2 Hz, 2-H), 5.27 (2 H, s, CH_2Ar), 5.80 (1 H, t, J *ca.* 1.5 Hz, 4-H), and 7.55 (2 H, J 9 Hz) and 8.22 (2 H, J 9 Hz) (together AA'BB', ArH). No Δ^2-ester (**17c**) was produced either in the oxidation, or in substituent equilibration in the presence of DBU.

(5RS,6SR)-*Benzyl* 3-[(RS)-*Ethylsulphinyl*]-6-(1-*hydroxy*-1-*methylethyl*)-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**37**).—A mixture of 2α,3α- (**35**) and 2α,3β-adduct isomers (3:1) was obtained similarly in the Michael addition of ethanethiol to benzyl 6-(1-hydroxy-1-methylethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.[25] To a solution of this mixture of benzyl esters of 'natural' 2-carboxylate configuration (0.040 g) in chloroform (3 ml) under argon at 0 °C were added water (0.004 g), pyridine (0.026 g, 3 mol equiv.), and IBD (0.061 g, 2 equiv.).[1] After being stirred for 2 h, the solution was evaporated, and the residue was chromatographed on silica gel (Art. 7729). Elution with ethyl acetate–light petroleum (4:1) gave (2*RS*,3*SR*,5*SR*,6*RS*)-benzyl 3-chloro-3-[(SR)-ethylsulphinyl]-6-(1-hydroxy-1-methylethyl)-7-oxo-1-azabicyclo-[3.2.0]heptane-2-carboxylate isomer (**36**) as the major product (retention of configuration at C-3)[1] as a gum (0.031 g, 68%), ν_{max} 3 450, 1 775, and 1 750sh cm^{-1}; δ_H 1.31 [3 H, s, *Me*CMe(OH)], 1.34 (3 H, t, J 7 Hz, CH_2Me), 1.38 [3 H, s, MeC*Me*(OH)], 2.03 (1 H, br s, OH), 2.36 (1 H, dd, J 15 and 1 Hz, 4-H), 3.08 (1 H, dd, J 15 and 8 Hz, 4-H), 2.7–3.3 (2 H, m, SCH_2), 3.49 (1 H, d, J 3 Hz, 6-H), 4.27 (1 H, ddd, J 8, 3, and 1 Hz, 5-H), 5.03 (1 H, s, 2-H), 5.12 (2 H, s, CH_2Ph), and 7.29 (5 H, s, Ph).

A solution of the α-chloro sulphoxide (**36**) (0.030 g) in ethyl acetate (2 ml) was stirred with DBU (0.011 g, 1 mol equiv.) at 20 °C under argon for 30 min.[1] The solution was washed with brine and dried. Evaporation gave a gum which was crystallised from chloroform–light petroleum to give the title Δ^2-3-*ethylsulphinyl ester* (**37**) (0.017 g, 62%), m.p. 146–149 °C (decomp.) (Found: C, 60.1; H, 6.3; N, 3.6. $C_{19}H_{23}NO_5S$ requires C, 60.5; H, 6.1; N, 3.7%); λ_{max}(EtOH) 308 nm; ν_{max} 3 400, 1 790, 1 720, and 1 595 cm^{-1}; δ_H 1.28 (3 H, t, J 7 Hz, CH_2Me), 1.30 (3 H, s) and 1.41 (3 H, s) (together Me_2C), 2.15 (1 H, br s, OH), 7.15 (2 H, q, J 7 Hz, SCH_2), 3.18 (2 H, d, J 9 Hz, 4-H_2), 3.34 (1 H, d, J 3 Hz, 6-H), 4.28 (1 H, td, J 9 and 3 Hz, 5-H), 5.14 (1 H, J 12 Hz) and 5.32 (1 H, J 12 Hz) (together ABq, CH_2Ph), and 7.31 (5 H, s, Ph).

Acknowledgements

We thank Mr. J. W. Tyler for the NMR spectra. Mass spectral

measurements were obtained by Dr. J. L. Gower and Mr. G. Risbridger. Mr. G. Powell is thanked for providing the microanalytical data.

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Paper 9/05476F
Received 22*nd December* 1989
Accepted 24*th January* 1990