Olivanic Acid Analogues. Part 4.[1] Cycloaddition Reactions of *p*-Nitrobenzyl 7-Oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate, and Synthesis of the 8-Oxo-1-azatricyclo[4.2.0.0^{2,4}]octane-2-carboxylate System

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p-Nitrobenzyl 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**1**) participated in Diels–Alder and 1,3-dipolar cycloaddition reactions, yielding a range of novel polycyclic azetidinone structures. The two 8-oxo-1-azatricyclo[4.2.0.0^{2,4}]octane-2-carboxylates (**21**) and (**24**) were prepared, and their cyclopropane stereochemistries assigned using nuclear Overhauser difference spectroscopy. Sodium (1′*RS*,2*SR*,4*RS*,6*RS*,7*SR*)-7-(1-hydroxyethyl)-8-oxo-1-azatricyclo[4.2.0.0^{2,4}]octane-2-carboxylate (**37**) was synthesised from compound (**1**) *via* *p*-nitrobenzyl (1′*RS*,5*RS*,6*SR*)-6-[1-(*p*-nitrobenzyloxycarbonyloxy)ethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**32**).

In the course of our recent studies on the synthesis of molecules related to the olivanic acid series of streptomycete metabolites,[2] we have described the preparation of some bicyclic azetidinone esters (**1**) and their derived sodium salt.[3,4] The latter compound constitutes the simplest of bicyclic β-lactam antibacterials, and may be regarded as the parent carbapenem nucleus of the olivanic acids. Recently, an optically active form of a compound (**1**) has been obtained[5] from bacterial sources; considerations of stability necessitated its isolation as the *p*-nitrobenzyl ester.

In order to incorporate into our synthesis a 3-sulphur substituent, a feature which is characteristic of the olivanate natural products, we have demonstrated that the double bond present in compound (**1**) reacts with thiols as a Michael acceptor.[6] Reintroduction of the double bond using (dichloroiodo)benzene gave access either to a Δ^2-3-sulphinyl derivative,[6] or to a mixture of the corresponding Δ^2-and Δ^3-sulphenyl compounds[7] [*e.g.* (**19**), (**20**)], according to the oxidative conditions employed.

In the context of our interest in reactions of the double bond of compound (**1**), we now describe our methodology whereby the 'acrylate' component of compound (**1**) may participate in cycloadditions, and thus provide a series of new polycyclic azetidinone systems.[8] In Diels–Alder reactions with reactive dienes the ester (**1**) functions as a dienophile. Thus, on heating compound (**1**) in toluene (80 °C; 6 h) with diphenylisobenzofuran (**2**), a single adduct (**3**)† (54%) was obtained. The observation of a considerable upfield shift [Δδ − 2.6 p.p.m.] in the 10a-H resonance of compound (**3**) (δ 1.8) relative to that of the corresponding 5-Hα in ester (**1**) (δ 4.4) permitted unambiguous structural assignment. Examination of Dreiding models indicates that only in the case of the adduct stereoisomer shown (Figure 1) will the 10a-H lie directly on the shielding axis of the aromatic ring.

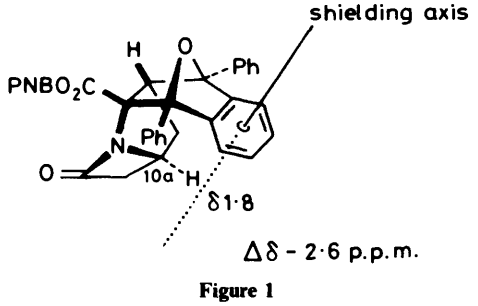
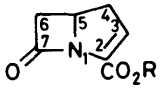
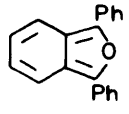


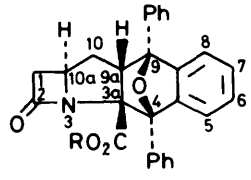
Figure 1



(**1**)



(**2**)



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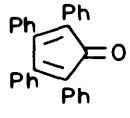
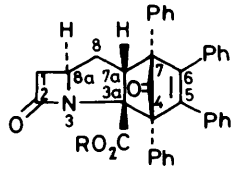


(**4**)



(**5**)

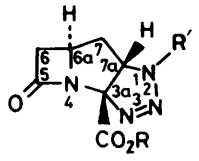
R = $CH_2C_6H_4NO_2$-*p*

The product is therefore the expected *endo*-adduct (with respect to the oxabicyclo[2.2.1]heptene unit present in the product) arising from attack of diene at the less hindered α-face of ester (**1**) (*exo*-face approach to dienophile). Azetidinone (**1**) also reacted with 'tetracyclone' (**4**) under more exacting conditions (toluene; 110 °C; 20 h) to give the tetracycle (**5**) (49%). Although the 8a-H in this compound is necessarily less dramatically shielded (δ 3.67) than the corresponding proton in pentacycle (**3**), by analogy we have assigned the stereochemistry of product (**5**) as shown. This adduct exhibited three i.r. carbonyl absorptions [$\nu_{max.}$(KBr) 1 775 (strained ketone), 1 760 (β-lactam), and 1 735 (ester)], indicating that cheletropic expulsion of carbon monoxide had not occurred.

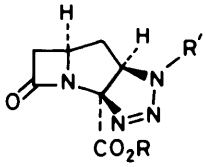
The higher temperatures required for reaction with more synthetically useful Diels–Alder dienes were incompatible with the stability of compound (**1**); polymerisation occurred. The lability of (**1**) to acid also precluded the use of proton or Lewis acid catalysis.

Several tricyclic azetidinones, including triazoles, have been prepared[9] in these laboratories by Pearson and his co-workers, using intramolecular 1,3-dipolar cycloadditions. We have explored the scope of ester (**1**) to participate as the dipolarophile component in a series of intermolecular 1,3-

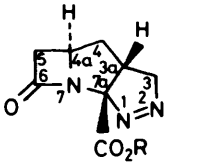
† All compounds prepared are racemic. Where it is necessary to specify relative stereochemistries, one enantiomer is depicted for convenience.



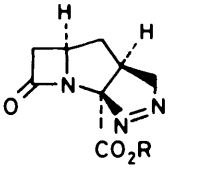
(6) R = $CH_2C_6H_4NO_2$-*p*, R' = Ph
(7) R = Na, R' = Ph
(8) R = $CH_2C_6H_4NO_2$-*p*, R' = CH_2Ph



(9) R = $CH_2C_6H_4NO_2$-*p*, R' = Ph
(10) R = Na, R' = Ph



(11) R = $CH_2C_6H_4NO_2$-*p*
(12) R = Me
(13) R = H



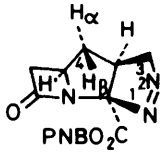
(14) R = $CH_2C_6H_4NO_2$-*p*
(15) R = Me
(16) R = H

dipolar cycloaddition reactions. These are exemplified by the reaction with phenyl azide[10] (90 °C; 12 h) which gave a major triazole (**6**) (47%) and a minor isomer (**9**) (18%). Closely similar in their n.m.r. spectral properties, these products' structures were assigned as those due to α- and β-face attack, respectively, at the double bond. We also consider that both adducts arise as a consequence of the regioselectivity which is favoured by Frontier Orbital theory predictions, and which is observed in the reaction of simple acrylates.[11] Indeed, examination of molecular models shows the alternative regiochemistry to be strongly disfavoured on steric grounds. The observation in the ^{1}H n.m.r. spectrum of compound (**6**) that $^3J_{7\alpha,7a\beta} \simeq 0$—1 Hz (requiring $\theta \simeq 90°$; Karplus equation), together with a long-range W-coupling ($^4J_{6a\alpha,7a\alpha} \simeq 1$ Hz) provided supporting evidence for the indicated geometry. Hydrogenolysis of the *p*-nitrobenzyl residues of compounds (**6**) and (**9**) by our usual procedure,[4,12] followed by treatment with sodium hydrogen carbonate, furnished aqueous solutions of their respective sodium salts (**7**) and (**10**). Reconstitution of the esters (see Experimental section) confirmed the integrity of these preparations.

Azetidinone (**1**) reacted similarly, albeit less cleanly, with benzyl azide to provide just one compound (57%). Closely similar in ^{1}H n.m.r. properties to the major phenyl azide adduct (**6**), its structure was assigned as (**8**) the product of α-face addition.

Reaction of compound (**1**) with the simple 1,3-dipole diazomethane occurred under much milder conditions (0 °C—room temperature; 1 h), providing two pyrazolines. Proof of their stereochemistries was ultimately obtained by correlation with the derived cyclopropanes (*vide infra*). The major isomer (**11**), resulting from α-face approach, was obtained as a gum (69%). The minor, β-face, adduct (**14**) was crystalline (20%). Each showed the expected weak u.v. ($\lambda_{max.}$ *ca.* 325 nm), and very weak i.r. ($\nu_{max.}$ *ca.* 1 550 cm^{-1}), absorptions which are characteristic of the pyrazoline azo moiety.[13–15] [These effects were more readily observed in the spectra of the corresponding methyl esters (**12**) and (**15**), which were produced by methanolysis of the *p*-nitrobenzyl esters.] The assigned stereochemistries are those expected from steric considerations, and were supported by the ^{1}H n.m.r. spectrum of the minor isomer (**14**) (Figure 2).

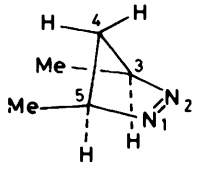
The '*syn*-fusion' of rings in this β-face pyrazoline adduct results in a shielding effect on the 4-H_β as a result of the diamagnetic anisotropy of the proximate N=N π-system. This



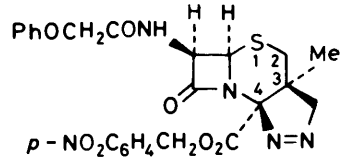
'syn'-fused cycloadduct (**14**)
H_β δ 1·03
H_α δ 2·51
Δδ 1·48 p.p.m.

cf. 'anti'-fused cycloadduct (**11**)
H_β δ 2·22
H_α δ 2·07
Δδ 0·15 p.p.m.

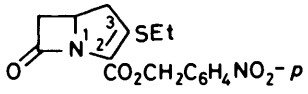
Figure 2



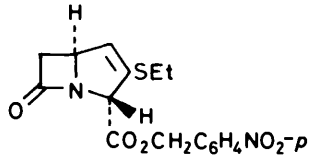
(**17**)



(**18**)



(**19**)

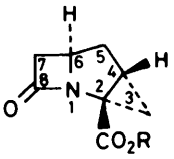


(**20**)

contributes to the large chemical-shift difference for the 4-H_2 protons, in contrast to the isomeric α-pyrazoline (**11**) (*cf.* Figure 2). Such shieldings are rarely documented. However, a comparable chemical-shift difference (Δδ 1.60 p.p.m.) has been reported[13] by Crawford *et al.* for the 4-H_2 proton resonances of the conformationally anchored, monocyclic system 3,5-dimethyl-Δ^1-pyrazoline (**17**).

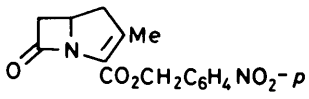
The pyrazolines show the same regiochemistry of addition as that found[16] by a Hungarian group in a related Δ^3-cephalosporin-derived system (**18**). Interestingly, subsequent n.m.r. studies revealed[17] a β-stereochemistry for their single adduct; *i.e.* opposite to that found for the major product in our experiment. Clearly, the cephalosporin 7β-phenoxyacetamido substituent exerts a β-face directing effect.[18] More recent studies from the same group report[19] the preparation of a 2,2'-spiropyrazoline from a 2-methylenecephem sulphoxide. 6,6'-Spiropyrazolinylcarbapenems have been synthesised in our own laboratories.[8,20] In all these examples, the dipolarophile double bond is in conjugation with a carbonyl group. Neither our Δ^3-3-ethylthio derivative (**20**), nor Jászbérenyi's Δ^2-cephem[16] reacted with diazomethane to give pyrazolines. The β-thioacrylate (**19**)[7] also failed to react.

Pyrazoline esters (**11**) and (**14**) were hydrogenolysed to give stable, aqueous solutions of the respective carboxylic acids (**13**) and (**16**). It is known that hydrogenation even of strained azo linkages requires forcing conditions.[21] Nonetheless, confirmation of the identity of the acids was achieved by methylation of an aliquot of each with diazomethane, yielding methyl esters (**12**) and (**15**). Attempts to prepare aqueous solutions of the corresponding sodium salts by addition of aqueous sodium hydrogen carbonate resulted in slow decomposition.

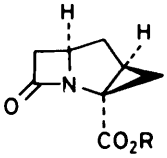


(21) R = $CH_2C_6H_4NO_2$-*p*

(22) R = Na



(23)



(24) R = $CH_2C_6H_4NO_2$-*p*

(25) R = Na

Thermolysis of the pyrazoline (**11**) in refluxing ethyl acetate gave the corresponding isomer of the new 8-oxo-1-azatricyclo[4.2.0.$0^{2,4}$]octane-2-carboxylate ring system, (**21**) (64%), together with a smaller amount (16%) of the Δ^2-3-methyl compound (**23**).[4] In contrast, the pyrazoline (**14**) yielded the cyclopropane (**24**) (87%) as the only product. Both *p*-nitrobenzyl esters (**21**) and (**24**) were deprotected, as before, to give sodium salts (**22**) and (**25**).

Final confirmation of the stereochemistry of esters (**21**) and (**24**) was obtained by application of ^{1}H n.m.r. techniques. For both isomers, a full chemical shift and coupling constant analysis was first performed by irradiating the protons along the carbon chain in double-resonance experiments. In the case of isomer (**24**) [derived from the minor pyrazoline adduct (**14**)] the use of the lanthanide shift reagent Eu([$^2H_9$]fod)$_3$* was required in order to separate the overlapping resonances subsequently assigned to 4-H_α and 5-H_α. In each isomer a 4-bond coupling (*ca.* 1 Hz) was observed between a 5-proton and one of the 3-protons. Models of compounds (**21**) and (**24**) showed the presence in each case of a planar W-type coupling pathway, from that 3-H which is *cis* to the 4-H to one of the 5-protons. At best, however, the coupling constant and chemical-shift data in support of the assignments was tentative, and corroborative only in the light of the proposed structures of their pyrazoline precursors.

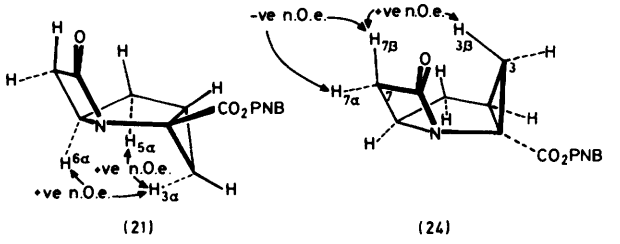
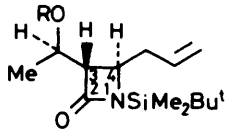


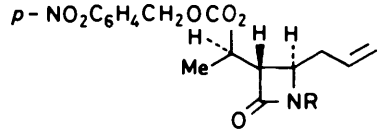
Figure 3

Conclusive evidence for the cyclopropane stereochemistries was obtained from their nuclear Overhauser difference spectra. For isomer (**21**), irradiation at the frequency of that 3-proton signal which, from the previous work, was expected to be due to 3-H_α produced an Overhauser enhancement (n.O.e.) (*ca.* 1—2%) in 6-H_α, together with a weaker response in the proton



(26) R = H

(27) R = $CO_2CH_2C_6H_4NO_2$-*p*

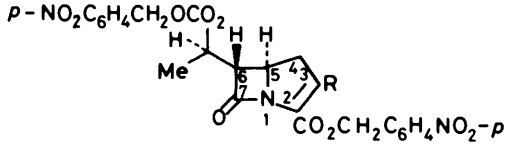


(28) R = H

(29) R = $CH(OH)CO_2CH_2C_6H_4NO_2$-*p*

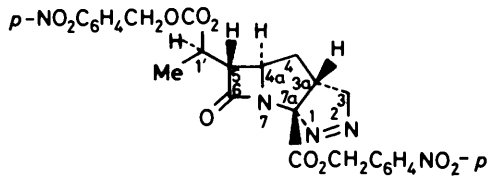
(30) R = $CH(Cl)CO_2CH_2C_6H_4NO_2$-*p*

(31) R = $C(=PPh_3)CO_2CH_2C_6H_4NO_2$-*p*



(32) R = H

(33) R = Me



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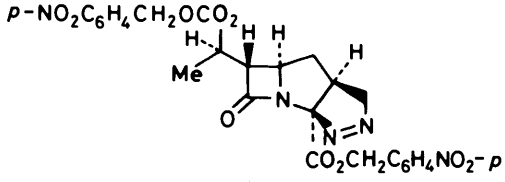

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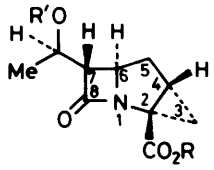

(36) R = $CH_2C_6H_4NO_2$-*p*, R' = $CO_2CH_2C_6H_4NO_2$-*p*

(37) R = Na, R' = H

resonance assigned to 5-H_α. Conversely, irradiation of 6-H_α led to a large positive response in 3-H_α, together with a smaller one in 5-H_α. These results agree totally with the initial assignment of the cyclopropyl group of compound (**21**) as being α-orientated (*cf.* Figure 3) (*i.e. anti*-fusion of the rings).

In the case of isomer (**24**), irradiation at the frequency of the 3-H_β resonance produced a very strong positive response at 7-H_β, an effect which is possible only where the cyclopropane ring is itself β-orientated. The concomitant observation of a weaker, indirect negative n.O.e.[22,23] in the 7-H_α signal (*cf.* Figure 4) emphasises the proximity[24,25] of the 3β- and 7β-protons and provides conclusive support for the structure (*syn*-fusion of rings).

As a final check, 6-H_α of isomer (**24**) was irradiated and, as expected, no response was detected in the cyclopropyl proton resonances.

* Eu([$^2H_9$]fod)$_3$ = tris-(6,6,7,7,8,8,8-heptafluoro-2,2-di[$^2H_3$]methyl-[$^2H_3$]octane-3,5-dionato)europium.

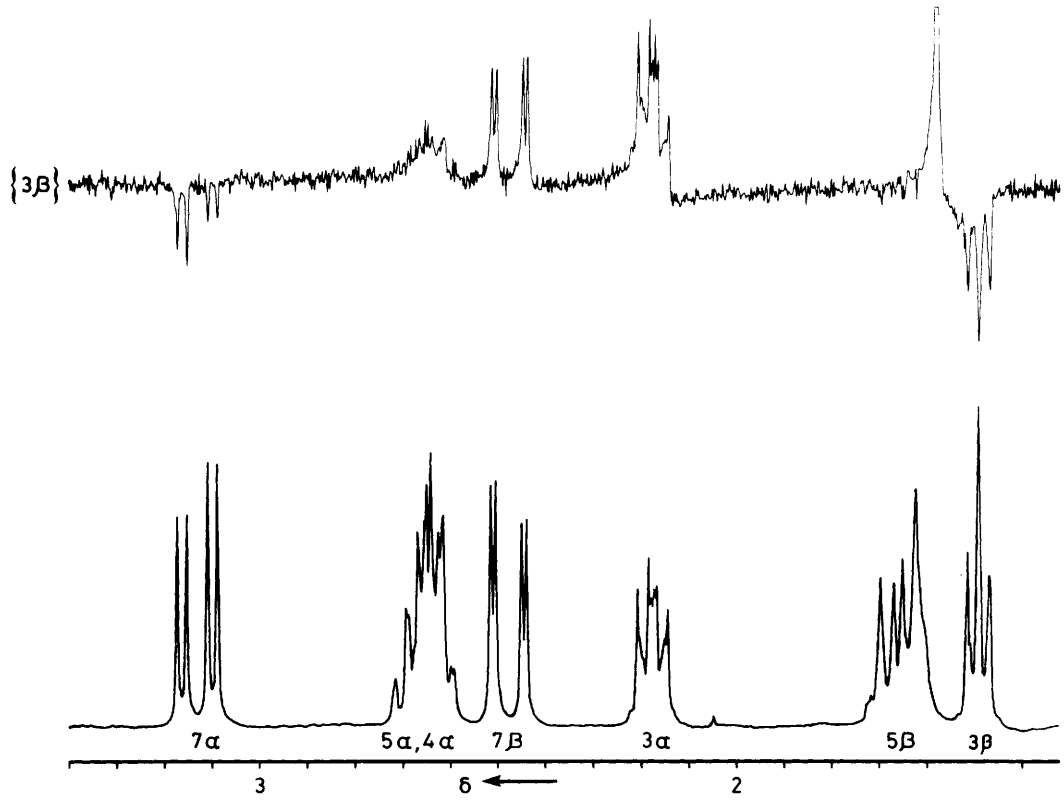

Figure 4. n.O.e. difference spectrum of compound (**24**)

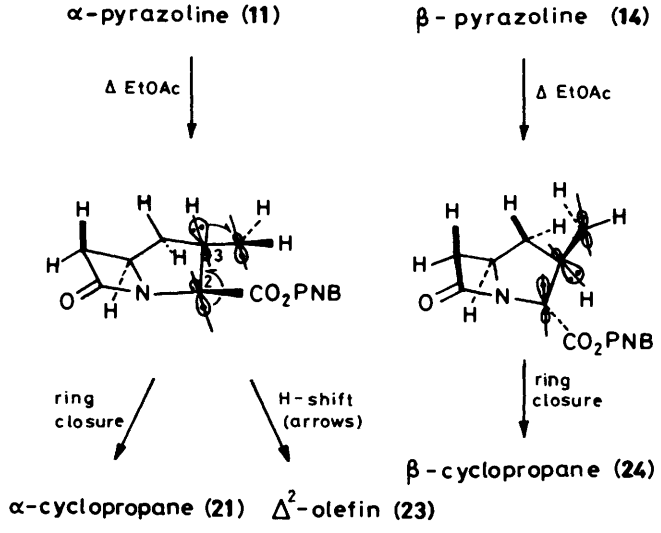

Figure 5

It remains for us to account for the appearance of an olefinic product (**23**) only during the formation of isomer (**21**) from pyrazoline (**11**). The classical view of pyrazoline pyrolyses to give cyclopropanes and/or their isomeric olefins favoured a single diradical intermediate. The large body of evidence has been reviewed by Mackenzie,[26] and is probably best represented by the researches of Crawford.[27] More recently, zwitterionic intermediates have once more found favour in studies on the thermolysis of model pyrazolines prepared from simple acrylates.[28] Other schools have argued for a duality of mechanism, or have shown that in protic solvents a two-step mechanism might occur, involving non-concerted breaking of the carbon–nitrogen bonds in the transition state.[29]

In the present work, a considerable steric constraint is imposed during the decomposition of the tricyclic pyrazolines (**11**) and (**14**). This controls the fate of the resulting reactive intermediates, favouring cyclopropane formation at the expense of olefinic products. Figure 5 shows the orbital alignments within hypothetical radical intermediates resulting from concerted loss of nitrogen. Consideration of models leads to the conclusion that only in the case of the intermediate derived from compound (**11**) can the resulting sp^3 orbitals be accommodated so as to be antiperiplanar to the 3-H bond. In contrast, the corresponding orbitals in the intermediate derived from isomer (**14**) are unable to give smooth overlap. Accordingly, only in the former case can the 1,2-hydrogen-shift mechanism (arrows), which is required for the formation of the 3-methyl-Δ^2-isomer (**23**), compete efficiently with cyclopropane ring closure.

We have applied the aforementioned procedures to provide a 7-(hydroxyethyl) derivative of the tricyclic cyclopropane (**22**). The *N*-silylated hydroxyethyl compound (**26**), prepared[12] from allylazetidinone, was protected with *p*-nitrobenzyl chloroformate. The carbonate product (**27**) was desilylated using potassium fluoride in methanol to give free azetidinone (**28**), and the required *N*-(triphenylphosphoranylidene)acetate unit was assembled *via* glyoxylate (**29**) and α-chloro ester (**30**) using our established methods.[4,12] The resulting phosphorane (**31**), in ethyl acetate–trifluoroacetic acid (TFA), was ozonolysed at −70 °C. Reduction of the ozonide with triphenylphosphine, neutralisation, and cyclisation of the resulting aldehyde-phosphorane afforded the *bis* protected (1′*RS*,5*RS*,6*SR*)-carbapenem derivative (**32**) (thienamycin stereochemistry). This reacted with diazomethane to give predominantly the pyrazoline (**34**) (63%), with reduced amounts of the isomer resulting from β-face attack (<3%), (**35**). Thermolysis of product (**34**) in ethyl acetate gave the cyclopropane (**36**) (79%),

together with (predictably) the isomeric Δ^2-3-methyl compound (**33**) (10%). Hydrogenolysis of compound (**36**) as before gave the sodium salt (**37**) (83%) whose ^{1}H n.m.r. spectrum was entirely consistent with the proposed structure. The spectra of esters (**32**)—(**36**) were also closely similar to those of their unsubstituted counterparts.

In contrast to the sodium salt corresponding to (**1**)[4], the sodium salts/carboxylic acids (**7**), (**10**), (**13**), (**16**), (**22**), (**25**), and (**37**) did not exhibit appreciable levels of antibacterial activity. Thus, the structural similarity between the Δ^2-double bond of simple olivanic acid derivatives and a conjoined cyclopropane ring is not reflected in their biological properties.

Experimental

The experimental techniques and spectroscopic instrumentation employed in the course of this work were as described in Part 2 of the series.[1,2] High-performance liquid chromatography (h.p.l.c.) was conducted using a Beckmann (Altex) system, employing a C-18μ-Bondpak reverse-phase column (Waters), with pH 4.7 0.05M-ammonium dihydrogen orthophosphate buffer containing acetonitrile as eluant, and employing u.v. detection at 300 nm.

All compounds prepared are racemic; n.m.r. spectral assignments refer to that enantiomer which is depicted.

p-*Nitrobenzyl* (3aRS,4RS,9SR,9aSR,10RS)-1,2,3a,4,9,9a,10,-10a-*Octahydro*-2-*oxo*-4,9-*diphenyl*-4,9-*epoxyazeto*[1,2-a]*benz*-[f]*indole*-3a-*carboxylate* (**3**).—*p*-Nitrobenzyl 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate[4] (**1**) (0.075 g) and 1,3-diphenylisobenzofuran (**2**) (0.075 g) were heated in toluene (10 ml) at 80 °C under argon for 6 h. The solution was filtered, the solvent was removed under reduced pressure, and the residue was crystallised from chloroform to give the *title adduct* (**3**) as off-white prisms (0.081 g, 56%), m.p. 203—204 °C (decomp.) (Found: C, 73.1; H, 4.75; N, 5.0. $C_{34}H_{26}N_2O_6$ requires C, 73.1; H, 4.7; N, 5.0%); $\lambda_{max.}$(MeOH) 266 nm (ε 14 000); $\nu_{max.}$($CHCl_3$) 1 765, 1 735sh, 1 605, 1 520, 1 350, and 1 210 cm^{-1}; δ (90 MHz) 1.65—2.05 (3 H, m, 10-H_2 and 10a-H_α), 2.52 (1 H, dd, *J* 16 and 2 Hz, 1-H_β), 2.87 (1 H, dd, *J* 16 and 4 Hz, 1-H_α), 4.21 (1 H, br d, *J* 7 Hz, 9a-H_β), 4.90 (1 H, *J* 13.5 Hz) and 5.12 (1 H, *J* 13.5 Hz) (ABq, ArCH_2), 6.9—7.7 (16 H, m, ArH), and 8.03 (2 H, d, *J* 8 Hz, BB′ of *p*-nitrobenzyl AA′BB′). Irradiation at the frequency of the 10-H_2 resonance caused the 9a-H signal to collapse to a singlet; irradiation, in turn, at the frequency of the 9a-H proton simplified each of the 1-H signals to a doublet, *J* 13.5 Hz, and located the 10-H resonance at δ 1.8.

The mother liquors were chromatographed on silica gel 60 (Art. 9381; 7 × 2 cm) with ethyl acetate–light petroleum (3:7) as eluant to yield an unidentified, non-β-lactam by-product (0.032 g), m.p. 127—128 °C, together with a further amount of adduct (**3**) (0.010 g).

Recrystallisation of an aliquot of adduct (**3**) from chloroform–ethyl acetate furnished an *ethyl acetate solvate* m.p. 218—220 °C (decomp.) (Found: C, 70.5; H, 5.1; N, 4.4. $C_{38}H_{34}N_2O_8$ requires C, 70.6; H, 5.3; N, 4.3%).

p-*Nitrobenzyl* (3aRS,4RS,7SR,7aRS,8aRS)-1,2,3a,4,7,7a,8,8a-*Octahydro*-2,9-*dioxo*-4,5,6,7-*tetraphenyl*-4,7-*methanoazeto*[1,2-a]*indole*-3a-*carboxylate* (**5**).—The bicyclic azetidinone (**1**) (0.030 g) and tetraphenylcyclopentadienone (tetracyclone) (**4**) (0.040 g) were heated in toluene (2 ml) at 100 °C under argon for 20 h. The mixture was cooled (0 °C; 2 h) and the precipitated product was collected and washed well with ethyl acetate to give adduct (**5**) as an off-white solid (0.034 g, 49%), m.p. 238—240 °C (decomp.) (Found: C, 76.5; H, 4.8; N, 4.1. $C_{43}H_{32}N_2O_6$ requires C, 76.8; H, 4.8; N, 4.2%); $\lambda_{max.}$ (saturated solution in EtOH) 263 and 270sh nm; $\nu_{max.}$(KBr) 1 775sh, 1 760, 1 735, 1 650br, 1 605, 1 520, and 1 350 cm^{-1}; $\nu_{max.}$(Nujol) 1 780sh, 1 765, 1 750sh, 1 655br, 1 605, 1 520, and 1 345 cm^{-1}; δ (80 MHz) 2.0—2.45 (2 H, m, 8-H_2), 2.63 (1 H, dd, *J* 16 and 2 Hz, 1-H_β), 3.13 (1 H, dd, *J* 16 and 5 Hz, 1-H_α), 3.67 (1 H, m, $w_{\frac{1}{2}}$ *ca.* 10 Hz, 8a-H_α), 3.93 (1 H, br d, *J* 7 Hz, 7a-H_β), 5.24 (1 H, *J* 13 Hz) and 5.48 (1 H, d, *J* 13 Hz) (ABq, ArCH_2), 6.35—7.6 (22 H, m, ArH), and 8.17 (2 H, d, *J* 8 Hz, BB′ of *p*-nitrobenzyl AA′BB′).

p-*Nitrobenzyl* 3a,5,6,6a,7,7a-*Hexahydro*-5-*oxo*-1-*phenyl*-1H-*azeto*[1′,2′:1,5]*pyrrolo*[2,3-d]-1,2,3-*triazole*-3a-*carboxylate* (**6**) *and* (**9**).—Bicyclic azetidinone (**1**) (0.200 g) and phenyl azide[10] (1 ml) were stirred at 90 °C under argon for 12 h. The reaction mixture was chromatographed on silica gel 60 (Art.9385) (10 × 2 cm), with ethyl acetate–hexane mixtures (1:9—1:1) as eluant. Early fractions contained the major product, contaminated with phenyl azide. Rechromatography [ethyl acetate–light petroleum (1:1)], followed by crystallisation from chloroform–ether gave the (3aRS,6aRS,7aSR)-*isomer* (**6**) of the title compound as buff-coloured microcrystals (0.132 g, 47%), m.p. 148—150 °C (melt), 170—172 °C (gas evolution) (Found: C, 59.0; H, 4.2; N, 16.8. $C_{20}H_{17}N_5O_5$ requires C, 59.0; H, 4.2; N, 17.2%); $\lambda_{max.}$(EtOH) 268 (ε 16 400) and 287infl. nm (13 000); $\nu_{max.}$($CHCl_3$) 1 770, 1 745, 1 600, 1 520, 1 490, and 1 345 cm^{-1}; δ (250 MHz) 2.24 (1 H, ddd, *J* 13.5, 9.5, and 8 Hz, 7-H_β), 2.95 (1 H, dd, *J* 16 and 2.5 Hz, 6-H_β), 3.10 (1 H, ddd, *J* 13.5, 5.5, and 1 Hz, 7-H_α), 3.23 (1 H, dd, *J* 16 and 5 Hz, 6-H_α), 3.72 (1 H, ddddd, *J* 9.5, 5.5, 5, 2.5, and *ca.* 1 Hz, 6a-H_α), 5.23 (1 H, *J* 13 Hz) and 5.41 (1 H, *J* 13 Hz) (ABq, ArCH_2), 5.42 (1 H, br d, *J* 8 Hz, 7a-H_β), 7.1—7.55 (7 H, m, ArH), and 8.16 (2 H, *J* 8 Hz, BB′ of *p*-nitrobenzyl AA′BB′); irradiation at the frequency of the 7a-H_α proton simplified the 7-H_2 signals at δ 2.24 and 3.10. Sharpening of the 6a-H_α signal, δ 3.72, confirmed that $^4J_{6a,7a}$ ~ 1 Hz; *m/z* (e.i.) $(M - N_2)^+$, 379.

Later fractions from the original column gave the least polar, minor component. Rechromatography [elution with ethyl acetate–hexane (7:3)] afforded the (3aRS,6aSR,7aSR)-*isomer* (**9**) of the title compound as a pale orange gum (0.052 g, 18%) [Found: $(M - N_2)^+$, 379.1167. $C_{20}H_{17}N_3O_5$ requires *m/z* 379.1168]; $\lambda_{max.}$(EtOH) 266 (ε 17 000) and 290infl. nm (10 800); $\nu_{max.}$($CHCl_3$) 1 780, 1 760, 1 600, 1 520, 1 490, and 1 345 cm^{-1}; δ (250 MHz) 2.21 (1 H, ddd, *J* 14, 7, and 6 Hz, 7-H_β), 2.81 (1 H, ddd, *J* 16, 2, and *ca.* 0.5 Hz, 6-H_β), 3.02 (1 H, ddd, *J* 14, 9 and 7.5 Hz, 7-H_α), 3.38 (1 H, dd, *J* 16 and 5 Hz, 6-H_α), 4.06 (1 H, dddd, *J* 7.5, 7, 5, and 2 Hz, 6a-H_α), 4.97 (1 H, *J* 13 Hz) and 5.28 (1 H, *J* 13 Hz) (ABq, ArCH_2), 5.69 (1 H, br dd, *J* 9.5 and 6 Hz, 7a-H_α), 7.0—7.4 (7 H, m, ArH), and 8.02 (2 H, *J* 8 Hz, BB′ of *p*-nitrobenzyl AA′BB′); irradiation at the frequency of the 7a-H_α proton simplified the 7-H_2 signal. The broadening of the 6-H_β resonance was removed, indicating $^5J_{6\beta,7a}$ ~ 0.5 Hz.

Sodium 3a,5,6,6a,7,7a,-*Hexahydro*-5-*oxo*-1-*phenyl*-1H-*azeto*-[1′, 2′:1,5]*pyrrolo*[2,3-d]-1,2,3-*triazole*-3a-*carboxylate* (**7**) *and* (**10**).—(3aRS,6aRS,7aSR)-*isomer* (**7**). Ester (**6**) (0.020 g) was shaken in dioxane–water (3:1) (2 ml) under hydrogen in the presence of 5% palladium–carbon catalyst for 20 min. A solution of sodium hydrogen carbonate (0.003 g) in water (1 ml) was added, and the solution was filtered through Celite. The filtrate was evaporated to yield an aqueous residue, which was extracted with portions of ethyl acetate to give an aqueous solution of the sodium salt (**7**); $\lambda_{max.}$(H_2O) 230 and 290infl. nm. Evaporation of an aliquot, followed by esterification in dimethylformamide (DMF) with an excess of *p*-nitrobenzyl bromide, regenerated ester (**6**), identical (t.l.c. i.r.) with the previous sample.

The (3aRS,6aSR,7aSR)-isomer (**10**) was similarly prepared from ester (**9**).

p-*Nitrobenzyl* 1-*Benzyl*-3a,5,6,6a,7,7a-*hexahydro*-5-*oxo*-1H-*azeto*[1′,2′:1,5]*pyrrolo*[2,3-d]-1,2,3-*triazole*-3a-*carboxylate*.—Bicyclic azetidinone (**1**) (0.150 g) and benzyl azide (0.5 ml) were heated in toluene (2 ml) in the dark at 110 °C for 6 h. The reaction mixture was chromatographed on silica gel 60 (Art.9385) (6 × 2 cm), with ethyl acetate–light petroleum (1:1) as eluant, to give *inter alia* the title *triazoline isomer* (**8**) (0.125 g, 57%), m.p. 148—151 °C (from Et_2O–hexane) (Found: C, 59.7; H, 4.3; N, 16.2. $C_{21}H_{19}N_5O_5$ requires C, 59.85; H, 4.5; N, 16.6%); $\nu_{max.}$($CHCl_3$) 1 775, 1 750sh, 1 605, 1 525, and 1 350 cm^{-1}; δ (80 MHz) 2.10 (1 H, ddd, *J* 13, 10 and 8 Hz, 7-H_β), 2.74 (1 H, dd, *J* 16 and 3 Hz, 6-H_β), 3.01 (1 H, br dd, *J* 13 and 6 Hz, 7-H_α), 3.18 (1 H, dd, *J* 16 and 5 Hz, 6-H_α), 3.49 (1 H, m, 6a-H_α), 4.83 (2 H, s, PhCH_2), 5.14 (1 H, *J* 13 Hz) and 5.31 (1 H, *J* 13 Hz) (ABq, *p*-$NO_2C_6H_4CH_2$), 5.36 (1 H, d, *J* 8 Hz, 7a-H_β), 7.05—7.65 (7 H, m, ArH), and 8.16 (2 H, *J* 8 Hz, BB′ of AA′BB′).

p-*Nitrobenzyl* 3a,4,4a,5,6,7a-*Hexahydro*-6-*oxo*-3H-*azeto*[1′,2′:1,5]*pyrrolo*[2,3-c]*pyrazole*-7a-*carboxylate* (**11**) *and* (**14**).—To a solution of the azetidinone (**1**) (0.500 g) in methylene dichloride (20 ml) at 0 °C was added an excess of ethereal diazomethane solution. The solution was stirred at 0 °C—room temperature for 1 h. Acetic acid was added, and the solvents were evaporated off to give a gummy residue, which was chromatographed on silica gel (Art.9385). Elution with ethyl acetate–hexane (1:1) gave the (3aRS,4aRS,7aRS)-*isomer* (**11**) of the title compound. The material remained as a gum (0.396 g, 69%) [Found: $(M - N_2)^+$, 302.0904. $C_{15}H_{14}N_2O_5$ requires *m/z* 302.0902]; $\lambda_{max.}$(EtOH) 263 (ε 12 900) and 326 infl. nm (490); $\nu_{max.}$($CHCl_3$) 1 775, 1 745, 1 605, 1 550w (N=N), 1 520, 1 450, and 1 345 cm^{-1}; δ (250 MHz) 2.07 (1 H, dt, *J* 13 and 9 Hz, 4-H_β), 2.22 (1 H, ddd, *J* 13, 6, and 1.5 Hz, 4-H_α), 2.78 (1 H, dd, *J* 15.5 and 2 Hz, 5-H_β), 3.28 (1 H, m, $w_{\frac{1}{2}}$ 12 Hz, 3a-H_β), 3.32 (1 H, dd, *J* 15.5 and 5 Hz, 5-H_α), 3.67 (1 H, m, 9 lines, *J* 8.5, 5, 5, and 2 Hz, 4a-H_α), 4.40 (1 H, dd, *J* 18.5 and 5 Hz, 3-H_α), 4.88 (1 H, dd, *J* 18.5 and 9.5 Hz, 3-H_β), 5.38 (1 H, *J* 13 Hz) and 5.51 (1 H, *J* 13 Hz) (ABq, ArCH_2), and 7.64 (2 H, *J* 9 Hz) and 8.24 (2 H, *J* 9 Hz) (AA′BB′); *m/z* (c.i.) (NH_3 gas) $(M + NH_4)^+$, 320 and $(M + H)^+$, 303.

Later fractions from the column afforded the minor product, the (3aRS,4aSR,7aRS)-*isomer* (**14**) as pale yellow needles (0.0112 g, 20%), m.p. 120 °C (gas evolution) (from EtOAc–hexane) [Found: C, 54.4; H, 4.5; N, 16.9%; *m/z*, 302.0880 $(M - N_2)^+$. $C_{15}H_{14}N_4O_5$ requires C, 54.6; H, 4.3; N, 17.0%; *m/z* 302.0902 $(M - N_2)^+$]; $\lambda_{max.}$(EtOH) 263 (ε 12 700) and 327 nm (430); $\nu_{max.}$($CHCl_3$) 1 775, 1 750sh, 1 610, 1 550w (N=N), 1 525, 1 450, and 1 350 cm^{-1}; δ (250 MHz) 1.03 (1 H, dt, *J* 12 and 10 Hz, 4-H_α), 2.51 (1 H, ddd, *J* 12, 7, and 5 Hz, 4-H_β), 2.68 (1 H, dd, *J* 15 and 2.5 Hz, 5-H_β), 3.22 (1 H, dd, *J* 15 and 5 Hz, 5-H_α), 3.31 (1 H, br dt, *J* 10 and 7 Hz, 3a-H_α), 3.90 (1 H, 10 lines, *J* 10, 5, 5, and *ca.* 2.5 Hz, 4a-H_α), 4.12 (1 H, dd, *J* 17 and 7 Hz, 3-H_α), 4.94 (1 H, br d, *J* 17 Hz, 3-H_β), 5.26 (1 H, *J* 13 Hz) and 5.34 (1 H, *J* 13 Hz) (ABq, ArCH_2), and 7.51 (2 H, *J* 9 Hz) and 8.23 (2 H, *J* 9 Hz) (AA′BB′); *m/z* (c.i.) (NH_3 gas) $(M + NH_4)^+$, 320 and $(M + H)^+$, 303.

Methyl 3a,4,4a,5,6,7a-*Hexahydro*-6-*oxo*-3H-*azeto*[1′,2′:1,5]-*pyrrolo*[2,3-c]-*pyrazole*-7a-*carboxylate*.—(3aRS,4aRS,7aRS)-*Isomer* (**12**). A solution of the *p*-nitrobenzyl ester (**11**) (0.040 g) in a mixture of methylene dichloride (1 ml) and methanol (1 ml) was stirred in the presence of potassium hydroxide (0.008 g) overnight. The solution was chromatographed through a short column of silica gel and evaporated; the product was crystallised from ethyl acetate–hexane to give the *methyl ester* (**12**) (0.025 g) as pale yellow rosettes, m.p. 119—120 °C (gas evolution) (Found: C, 51.4; H, 5.2; N, 20.2. $C_9H_{11}N_3O_3$ requires C, 51.7; H, 5.3; N, 20.1%); $\lambda_{max.}$(EtOH) 325 nm (ε 400); $\nu_{max.}$($CHCl_3$) 1 780, 1 745, and 1 550 w cm^{-1}; δ (90 MHz) 1.95—2.30 (2 H, m, 4-H_2), 2.74 (1 H, dd, *J* 16 and 2 Hz, 5-H_β), *ca.* 2.20 (1 H, m, $w_{\frac{1}{2}}$ 12 Hz, 3a-H_β), 3.26 (1 H, dd, *J* 16 and 4.5 Hz, 5-H_α), 3.63 (1 H, m, 4a-H_α), 3.90 (3 H, s), 4.29 (1 H, dd, *J* 19 and 5 Hz, 3-H_α), and 4.84 (1 H, dd, *J* 19 and 10 Hz, 3-H_β); *m/z* (e.i.) M^+, 209.

The (3a*RS*,4a*SR*,7a*RS*)-isomer (**15**), prepared from *p*-nitrobenzyl ester (**14**) in similar fashion, remained as a gum, $\lambda_{max.}$(EtOH) 327 nm (ε 390); $\nu_{max.}$($CHCl_3$) 1 775, 1 740, and 1 550 w cm^{-1}; δ (90 MHz) 0.95 (1 H, dt, *J* 13 and 10 Hz, 4-H_α), 2.44 (1 H, ddd, *J* 13, 7, and 5 Hz, 4-H_β), 2.58 (1 H, dd, *J* 15 and 2.5 Hz, 5-H_β), 3.15 (1 H, m, 3a-H_α), 3.19 (1 H, dd, *J* 15 and 5 Hz, 5-H_α), 3.75 (3 H, s), 3.81 (1 H, m, 4a-H_α), 4.35 (1 H, dd, *J* 18 and 7 Hz, 3-H_α), and 4.86 (1 H, dd, *J* 18 and 1 Hz, 3-H_β); *m/z* (e.i.) M^+, 209.

3a,4,4a,5,6,7a-*Hexahydro*-6-*oxo*-3H-*azeto*[1′,2′:1,5]*pyrrolo*-[2,3-c]*pyrazole*-7a-*carboxylic Acid*.—(3aRS,4aRS,7aRS)-*isomer* (**13**). A solution of the *p*-nitrobenzyl ester (**11**) (0.030 g) in a mixture of dioxane (5 ml) and phosphate buffer (2 ml; 0.05M) was shaken under hydrogen in the presence of a 5% palladium–carbon catalyst (0.010 g) for 10 min. The mixture was filtered through Celite, and the residue was washed with further portions of dioxane. Evaporation of the combined filtrate and washings, and extraction of the residue with ethyl acetate, gave the title carboxylic acid (**13**) which remained stable in aqueous solution. Evaporation of an aliquot gave an amorphous solid, $\nu_{max.}$($CHBr_3$) 1 740 cm^{-1}. Methylation of this material with an excess of ethereal diazomethane gave the methyl ester (**12**), identical [i.r., t.l.c. (R_F 0.37 in ethyl acetate)] with the sample previously prepared.

In a parallel experiment, attempts to isolate the acid (**13**) as its sodium salt, using aqueous sodium hydrogen carbonate solution, resulted in eventual decomposition of the material, with considerable yellowing of the aqueous solution.

(3aRS,4aSR,7aRS)-*isomer* (**16**). *p*-Nitrobenzyl ester (**14**) was hydrogenolysed similarly to give a stable aqueous solution of the corresponding carboxylic acid (**16**). Methylation of an aliquot with diazomethane afforded the methyl ester (**15**) (*vide supra*).

p-*Nitrobenzyl* (2RS,4SR,6SR)-8-*Oxo*-1-*azatricyclo* [4.2.0.-$0^{2,4}$]*octane*-2-*carboxylate* (**21**).—A solution of the pyrazoline (**11**) (0.165 g) in ethyl acetate (10 ml) was heated at reflux under argon for 3 h. Evaporation gave an oil (0.145 g) which was chromatographed on silica gel (Art.9385) (8 × 2 cm), with ethyl acetate–hexane (3:7) (5 ml fractions) as eluant. Fractions 9—12 gave *p*-nitrobenzyl 3-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate[4] (**23**) (0.024 g, 16%), identical (i.r., n.m.r., t.l.c.) with the sample prepared previously in these laboratories. Fractions 13—16 (0.020 g) contained ester (**23**), contaminated with *p*-nitrobenzyl alcohol. Fractions 17—28 crystallised from chloroform–hexane, giving the hemihydrate of the *title cyclopropane* (**21**) as rosettes of needles (0.099 g, 64%), m.p. 148 °C (Found: C, 57.35; H, 4.8; N, 9.0. $C_{15}H_{14}N_2O_5 \cdot \frac{1}{2}H_2O$ requires C, 57.9; H, 4.9; N, 9.0%). [An aliquot, dried *in vacuo* and analysed immediately, had m.p. 142 °C (Found: C, 59.6; H, 4.6, N, 9.25%; M^+, 302.0898. $C_{15}H_{14}N_2O_5$ requires C, 59.6; H, 4.7; N, 9.3%; *M*, 302.0902)]; $\nu_{max.}$($CHCl_3$) 1 765, 1 730, 1 610, 1 520, and 1 350 cm^{-1}; δ (250 MHz) 1.28 (1 H, t, *J* 6 Hz, 3-H_α), 1.38 (1 H, ddd, *J* 9, 6, and 1 Hz, 3-H_β), 1.60 (1 H, br s, H_2O), 1.92 (1 H, dddd, *J* 13, 8.5, 8, and 1 Hz, 5-H_β), 2.33 (1 H, dd, *J* 13 and 7 Hz, 5-H_α), 2.44 (1 H, dt, *J* 9 and 5.5 Hz, 4-H_β), 2.64 (1 H, dd, *J* 15.5 and 2 Hz, 7-H_β), 3.32 (1 H, dd, *J* 15.5 and 5.5 Hz, 7-H_α), 3.59 (1 H, m, *J* 8.5, 7, 5.5, and 2 Hz, 6-H_α), 5.29 (1 H, *J* 13.5 Hz) and 5.43 (1 H, *J* 13.5 Hz) (ABq, ArCH_2), and 7.67 (2 H, *J* 9 Hz) and 8.23 (2 H, *J* 9 Hz) (AA′BB′); irradiation at the frequency of the 4-H_β signal simplified the 3-H_2 signals to dd *J* 6 Hz each.

Sodium (2RS,4SR,6SR)-8-*Oxo*-1-*azatricyclo*[4.2.0.0^{2,4}]-*octane*-2-*carboxylate* (**22**).—A solution of the *p*-nitrobenzyl ester (**21**) (0.025 g) in a mixture of dioxane (5 ml) and water (1 ml) was shaken in the presence of 5% palladium–carbon catalyst (0.005 g) under hydrogen for 15 min. A solution of sodium hydrogen carbonate (0.007 g) in water (1 ml) was added, and the mixture was filtered through Celite, and the Celite was washed with aqueous dioxane. Evaporation of the dioxane from the combined filtrate and washings, folowed by extraction of the residue with ethyl acetate provided an aqueous solution of the sodium salt (**22**) as a single component (h.p.l.c.) containing no ester (t.l.c.). Evaporation of an aliquot gave a residue (0.004 g) which in DMF (1 ml), was re-esterified on being stirred with *p*-nitrobenzyl bromide (0.005 g) in the presence of molecular sieves for 1 h. Recovery in ethyl acetate, followed by chromatography [elution with ethyl acetate–hexane (1:3)], furnished ester (**21**) (0.0025 g), identical i.r., t.l.c.) with the previous sample.

p-*Nitrobenzyl* (2RS,4SR,6RS)-8-*Oxo*-1-*azatricyclo*[4.2.0.-0^{2,4}]*octane*-2-*carboxylate* (**24**).—A solution of the pyrazoline (**14**) (0.029 g) in ethyl acetate (5 ml) was heated at reflux under argon for 1.5 h. Chromatography as before [compound (**21**)], and crystallisation from ethyl acetate–hexane, gave the title *cyclopropane isomer* (**24**) as needles (0.023 g, 87%), m.p. 142—143 °C (Found: C, 59.6; H, 4.7; N, 9.4. $C_{15}H_{14}N_2O_5$ requires C, 59.6; H, 4.7; N, 9.3%); $\nu_{max.}$($CHCl_3$) 1 765, 1 730, 1 605, 1 520, and 1 350 cm^{-1}; δ (250 MHz) 1.49 (1 H, t, *J* 6 Hz, 3-H$_\beta$), 1.66 (1 H, br dd, *J* 12 and 6 Hz, 5-H$_\beta$), 2.18 (1 H, ddd, *J* 8, 6, and *ca.* 1 Hz, 3-H$_\alpha$), 2.48 (1 H, dd, *J* 15.5 and 2 Hz, 7-H$_\beta$), 2.62 (1 H, m, 4-H$_\alpha$), 2.68 (1 H, m, 5-H$_\alpha$), 3.13 (1 H, dd, *J* 15.5 and 5.5 Hz, 7-H$_\alpha$), 4.43 (1 H, m, *J* 7, 7, 5.5, and 2 Hz, 6-H$_\alpha$), 5.26 (2 H, s, ArC*H*$_2$), and 7.52 (2 H, *J* 9 Hz) and 8.24 (2 H, *J* 9 Hz) (AA′BB′) [Note: $J_{4\alpha.5\alpha}$ = 7 Hz, and $J_{4\alpha.5\beta} \simeq$ 1 Hz were obtained from the l.i.s. spectrum]; *m/z* (c.i.) (NH_3 gas) $(M + NH_4)^+$, 320 and $(M + H)^+$, 303.

Sodium (2RS,4SR,6RS)-8-*Oxo*-1-*azatricyclo*[4.2.0.0^{2,4}]-*octane*-2-*carboxylate* (**25**).—*p*-Nitrobenzyl ester (**24**) (0.010 g) was dissolved in a mixture of dioxane (2 ml) and water (0.5 ml) and hydrogenolysed as described above [compound (**22**)] to give an aqueous solution of the title sodium salt (**25**). As before, the integrity of the product was confirmed by the presence of a single peak on h.p.l.c. analysis, and by evaporation of an aliquot and re-esterification with *p*-nitrobenzyl bromide.

(1′RS,3SR,4RS)-4-*Allyl*-1-(*dimethyl*-t-*butylsilyl*)-3-[1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]*azetidin*-2-*one* (**27**).—(1′RS,-3SR,4RS)-4-Allyl-1-(dimethyl-t-butylsilyl)-3-(1-hydroxyethyl)-azetidin-2-one (**26**), (0.70 g), prepared[12] from allylazetidinone as previously described, was dissolved in tetrahydrofuran (THF) (15 ml) and the solution was cooled to −70 °C under argon. n-Butyl-lithium (1.7 ml of a 1.55M solution in hexane) was added, and the mixture was stirred for 10 min. A solution of *p*-nitrobenzyl chloroformate (0.615 g, 1.1 equiv.) in THF (5 ml) was added, and the solution was allowed to warm to 0 °C. Saturated aqueous ammonium chloride was added, and the mixture was diluted with ethyl acetate. The aqueous phase was extracted with further portions of ethyl acetate, and the combined organic layers were washed with brine and dried. Evaporation afforded the *carbonate* (**27**) as an oil (0.725 g, 62%) [Found: $(M + H)^+$, 449.2129. $C_{22}H_{33}N_2O_6Si$ requires *m/z* 449.2106]; $\nu_{max.}$ 1 740, 1 640, 1 610, 1 525, and 1 350 cm^{-1}; δ (250 MHz) 0.21 (3 H, s) and 0.28 (3 H, s) (2 × SiC*H*$_3$), 0.97 (9 H, s, Bu^{t}Si), 1.39 [3 H, d, *J* 6.5 Hz, C*H*$_3$CH(OR)], 2.22 (1 H, m) and 2.59 (1 H, m) (C*H*$_2$CH=CH$_2$), 3.01 (1 H, dd, *J* 6 and 2 Hz, 3-H$_\beta$), 3.62 (1 H, ddd, *J* 9, 3, and 2 Hz, 4-H$_\alpha$), 5.05—5.2 [3 H, m, CH=C*H*$_2$ and CH$_3$C*H*(OR)], 5.24 (2 H, s), 5.72 (1 H, ddt, *J* 17, 11, and 7 Hz, C*H*=CH$_2$), and 7.53 (2 H, *J* 8 Hz) and 8.25 (2 H, *J* 8 Hz) (AA′BB′).

(1′RS,3SR,4RS)-4-*Allyl*-3-[1-(p-*nitrobenzyloxycarbonyloxy*)-*ethyl*]*azetidin*-2-*one* (**28**).—A solution of the *N*-silylated carbonate (**27**) (0.700 g) in methanol (12 ml) was stirred with an excess of potassium fluoride (0.110 g, 1.2 equiv.) at room temperature for 5 min. The methanol was evaporated off and the residue was partitioned between ethyl acetate and brine. The organic layer was dried and evaporated, and the residue was chromatographed on silica gel (Art. 9385) (10 × 3 cm). Elution with ethyl acetate–hexane (7:3) gave the azetidinone (**28**) as a gum (0.460 g, 88%), $\nu_{max.}$($CHCl_3$) 3 420, 1 765, 1 750sh, 1 640, 1 610, 1 525, and 1 350 cm^{-1}; δ (90 MHz) 1.41 [3 H, d, *J* 6.5 Hz, C*H*$_3$CH(O)], 2.37 (2 H, br t, *J* 7 Hz, C*H*$_2$CH=CH$_2$), 2.97 (1 H, br dd, *J* 6.5 and 2.5 Hz, 3-H), 3.67 (1 H, td, *J* 7 and 2.5 Hz, 4-H), 5.03—5.19 (2 H, m, =C*H*$_2$), 5.23 (2 H, s, ArC*H*$_2$), 5.74 (1 H, ddt, *J* 17, 11, and 7 Hz, C*H*=CH$_2$), 6.13 (1 H, br s, D_2O exch., NH), and 7.53 (2 H, *J* 9 Hz) and 8.22 (2 H, *J* 9 Hz) (AA′BB′); irradiation at the frequency of the NH signal sharpened the dd due to the 3-H resonance, demonstrating the presence of ^4J long-range coupling; *m/z* (c.i.) (NH_3 gas) $(M + NH_4)^+$, 352 and $(M + H)^+$, 335.

p-*Nitrobenzyl* (1′RS,3SR,4RS)-{4-*Allyl*-3-[1-(p-*nitrobenzyl-oxycarbonyloxy*)*ethyl*]-2-*oxoazetidin*-1-*yl*}*hydroxyacetate* (**29**).—A solution of the azetidinone (**28**) (0.450 g) in benzene (25 ml) was heated in a Dean–Stark apparatus in the presence of *p*-nitrobenzyl glyoxylate hydrate (0.290 g) at reflux under argon for 6 h. The mixture was cooled, diluted with ethyl acetate, washed well with brine, dried, and evaporated. The residue was chromatographed on silica gel (Art. 9385) (8 × 4 cm). Elution with ethyl acetate–hexane (1:1) furnished the epimeric hydroxy esters (**29**) as a gum (0.684 g, 93%), $\nu_{max.}$($CHCl_3$) 3 530, 1 760, 1 755, 1 640, 1 610, 1 525, and 1 350 cm^{-1}; δ (90 MHz) 1.40 [3 H, d, *J* 6.5 Hz, C*H*$_3$CH(OR)], 2.49 (2 H, t, *J* 7 Hz, C*H*$_2$CH=CH$_2$), 3.13 (1 H, dd, *J* 7 and 2 Hz, 3-H$_\beta$), 3.85 (1 H, m, 4-H$_\alpha$), 4.6—5.1 [*ca.* 5 H m, C*H*(OH), CH=C*H*$_2$, CH$_3$C*H*(OR), and OH], 5.20 (2 H, s), 5.30 (2 H, s), 5.77 (1 H, m, C*H*=CH$_2$), and 7.61 (2 H, *J* 8 Hz) and 8.27 (2 H, *J* 8 Hz) (2 × AA′BB′). The material was transformed into the phosphorane (**31**) without further purification.

p-*Nitrobenzyl* (1′RS,3SR,4RS)-{4-*Allyl*-3-[1-(p-*nitrobenzyl-oxycarbonyloxy*)*ethyl*]-2-*oxoazetidin*-1-*yl*}(*triphenylphosphor-anylidene*)*acetate* (**31**).—The dry, crude α-hydroxy esters (**29**) (0.675 g) were dissolved in THF (15 ml) and the solution was treated successively with lutidine (0.270 g, 300 μl) and thionyl chloride (0.300 g, 180 μl) at −20 °C under argon for 1 h. The mixture was filtered, the filter was washed with cold THF, the combined filtrate and washings were evaporated, and toluene was added and evaporated from the resulting oil (× 2) to give the α-chloro ester (**30**) (0.723 g), $\nu_{max.}$($CHCl_3$) 1 775, 1 760, 1 610, 1 525, and 1 350 cm^{-1}.

A solution of the crude material in dry dioxane (15 ml) was stirred with lutidine (300 μl) in the presence of triphenylphosphine (0.651 g) at room temperature for 1.5 h. The dioxane was removed under reduced pressure and the residue was partitioned between ethyl acetate and brine. The organic layer was dried and evaporated, and the resulting oil was chromatographed on silica gel (Art. 9385) (8 × 4 cm). Elution with ethyl acetate–hexane (1:1) provided the *title phosphorane* (**31**) as a white foam [0.601 g, 61% overall from (**29**)] (Found: C, 65.2; H, 5.3; N, 5.1; P, 3.5. $C_{43}H_{38}N_3O_{10}P$ requires C, 65.6; H, 4.9; N, 5.3; P, 3.9%); $\nu_{max.}$($CHCl_3$) 1 740, 1 640sh, 1 610sh, 1 605br (phosphorane), 1 525, and 1 350 cm^{-1}.

p-*Nitrobenzyl* (1′RS,5RS,6SR)-6-[1-(p-*Nitrobenzyloxycarb-onyloxy*)*ethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxy-late* (**32**).—(With M. Finn).—A solution of the phosphorane (**31**) (0.6 g) in ethyl acetate (30 ml) containing TFA (6 ml)

was ozonolysed according to our established procedure.[4,12] Neutralisation at 0 °C with saturated aqueous sodium hydrogen carbonate (20 ml), followed by portionwise addition of solid sodium hydrogen carbonate, effected spontaneous cyclisation of the intermediate aldehyde-phosphorane. The ethyl acetate layer was washed with brine, dried, and evaporated to give a gum which was chromatographed rapidly on silica gel 60 (Art. 9385) (10 × 3 cm). Elution with ethyl acetate–hexane (7:3) gave the title azabicycloheptene (**32**) as a white foam (from $CHCl_3$) (0.252 g, 65%), $\lambda_{max.}$(EtOH) 266 nm (ε 22 075); $\nu_{max.}$($CHCl_3$) 1 785, 1 745, 1 610, 1 525, and 1 350 cm^{-1}; δ (250 MHz) 1.49 [3 H, d, *J* 6.5 Hz, $CH_3CH(O)$], 2.83 (1 H, ddd, *J* 19.5, 8.5, and 3 Hz, 4-H), 3.00 (1 H, ddd, *J* 19.5, 10, and 3 Hz, 4-H), 3.42 (1 H, dd, *J* 7 and 3 Hz, 6-H_β), 4.29 (1 H, ddd, *J* 10, 8.5, and 3 Hz, 5-H_α), 5.18 [1 H, quintet, *J* 6.5 Hz, $CH_3CH(O)$], 5.26 (2 H, s, $ArCH_2OCO_2$), 5.29 (1 H, *J* 13 Hz) and 5.45 (1 H, *J* 13 Hz) (ABq, $ArCH_2O$), 6.57 (1 H, t, *J* 3 Hz, 3-H), and 7.55, 7.60, 8.23, and 8.24 (each 2 H, d, *J* 9 Hz) (2 × AA′BB′). Crystallisation from ethyl acetate–light petroleum furnished the ethyl acetate *monosolvate*, m.p. 77—83 °C (Found: C, 56.0; H, 4.7; N, 7.5. $C_{28}H_{29}N_3O_{12}$ requires C, 56.1; H, 4.9; N, 7.0%). The n.m.r. spectrum of the analytical sample included signals arising from the presence of ethyl acetate in stoicheiometric quantity.

p-*Nitrobenzyl* (1′*RS*,3a*RS*,4a*RS*,5*SR*,7a*RS*)-3a,4,4a,5,6,7a-*Hexahydro*-5-[1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]-6-*oxo*-3H-*azeto*[1,2′:1,5]*pyrrolo*[2,3-c]*pyrazole*-7a-*carboxylate* (**34**).—A solution of the azetidinone (**32**) (0.257 g) in methylene dichloride (5 ml) was stirred with an excess of ethereal diazomethane solution at 0 °C. The mixture was allowed to warm to room temperature, and was then stirred for 1 h. Evaporation, and chromatography of the residue on silica gel 60 (Art.9385) (8 × 2 cm) (elution with ethyl acetate), gave a mixture of pyrazoline isomers (0.218 g). Careful rechromatography (Art. 7729 containing 10% Art.9385) (15 × 2 cm) [elution with ethyl acetate–hexane (1:1)] afforded the title isomer (**34**) as a gum (0.177 g, 64%), $\nu_{max.}$ ($CHCl_3$) 1 780, 1 745, 1 605, 1 545w (N=N), 1 525, and 1 350 cm^{-1}; δ (250 MHz) 1.43 (3 H, d, *J* 6.5 Hz), 2.10 (1 H, dt, *J* 13 and 8.5 Hz, 4-H_β), 2.20 (1 H, ddd, *J* 13, 6, and 2 Hz, 4-H_α), 3.19 (1 H, dd, *J* 7.5 and 2 Hz, 5-H_β), 3.24 (1 H, m, $w_{\frac{1}{2}}$ 15 Hz, 3a-H_β), 3.66 (1 H, ddd, *J* 9, 6, and 2 Hz, 4a-H_α), 4.37 (1 H, dd, *J* 19 and 5 Hz, 3-H_α), 4.89 (1 H, dd, *J* 19 and 10 Hz, 3-H_β), 5.11 [1 H, quintet, *J* 6.5 Hz, $CH_3CH(O)$], 5.23 (2 H, s, $ArCH_2OCO_2$), 5.38 (1 H, *J* 13 Hz) and 5.49 (1 H, *J* 13 Hz) (ABq, $ArCH_2O$), and 7.53, 7.61, 8.23, and 8.24 (each 2 H, *J* 9 Hz) (2 × AA′BB′); *m/z* (c.i.) (NH_3 gas) $(M + NH_4)^+$, 571, $(M + H)^+$, 554.

Later fractions contained a second component, believed to be the (1′*RS*,3a*SR*,4a*RS*,5*SR*,7a*SR*) isomer (**35**) (0.008 g, <3%), $\nu_{max.}$($CHCl_3$) 1 775, 1 745, 1 605, 1 545w (N=N), 1 520, and 1 345 cm^{-1}. Although impure, the ^1H n.m.r. spectrum of the material contained features similar to those exhibited by pyrazoline (**14**).

p-*Nitrobenzyl* (1′*RS*,2*SR*,4*RS*,6*RS*,7*SR*)-7-[1-(p-*Nitrobenzyloxycarbonyloxy*)*ethyl*]-8-*oxo*-1-*azatricyclo*[4.2.0.0^{2,4}]*octane*-2-*carboxylate* (**36**).—A solution of pyrazoline (**34**) (0.115 g) in ethyl acetate (5 ml) was heated at reflux temperature under argon for 2 h. The mixture was evaporated, and the residue, in toluene, was applied to a column of silica gel 60 (Art. 9385) (6 × 2 cm). Elution with ethyl acetate–hexane (1:1) (4 ml fractions) gave (fractions 4—11) the *title cyclopropane* (**36**) as a gum (0.086 g, 79%), which slowly deposited as microcrystals from chloroform–hexane, m.p. 89—91 °C (Found: C, 56.8; H, 4.3; N, 7.7. $C_{25}H_{23}N_3O_{10}$ requires C, 57.1; H, 4.4; N, 8.0%); $\nu_{max.}$($CHCl_3$) 1 765, 1 740sh, 1 605, 1 520, and 1 345 cm^{-1}; δ (250 MHz) 1.28 (2 H, m, 3-H_2), 1.44 (3 H, d, *J* 6.5 Hz, CH_3CH), 1.93 (1 H, ddd, *J* 13, 9, and 5 Hz, 5-H_β), 2.31 (1 H, dd, *J* 13 and 7 Hz, 5-H_α), 2.42 (1 H, dt, *J* 9 and 6 Hz, 4-H_β), 3.02 (1 H, dd, *J* 7.5 and 2 Hz, 7-H_β), 3.54 (1 H, td, *J ca.* 6 and 2 Hz, 6-H_α), 5.11 [1 H, qd, *J* 7.5 and 6.5 Hz, $CH_3CH(O)$], 5.25 (2 H, s, $ArCH_2OCO_2$), 5.28 (1 H, *J* 13 Hz) and 5.40 (1 H, *J* 13 Hz) (ABq, $ArCH_2O$), and 7.54 and 7.65 (each 2 H, *J* 9 Hz) and 8.23 (4 H, *J* 9 Hz) (2 × AA′BB′).

Fractions 12—14 yielded an isomeric second component, identical in R_F value (0.64 in EtOAc) with the cyclopropane (**36**). It oxidised more rapidly when sprayed with dil. aqueous potassium permanganate solution, and proved to be *p*-nitrobenzyl 3-methyl-6-[1-(*p*-nitrobenzyloxycarbonyloxy)ethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**33**). It remained as a gum (0.011 g, 10%), $\lambda_{max.}$(EtOH) 267 nm (ε 23 000); $\nu_{max.}$($CHCl_3$) 1 785, 1 730, 1 635, 1 610, 1 520, and 1 350 cm^{-1}; δ (250 MHz) 1.48 (3 H, d, *J* 6.5 Hz, CH_3CH), 2.07 (1 H, br s, 3-CH_3), 2.87 (1 H, br d, *J* 9.5 Hz, 4-H_2), 3.33 (1 H, dd, *J* 8 and 3 Hz, 6-H_β), 4.13 (1 H, td, *J* 9.5 and 3 Hz, 5-H_α), 5.12 [1 H, m, $CH_3CH(O)$], 5.26 (2 H, s, $ArCH_2OCO_2$), 5.25 (1 H, *J* 14 Hz) and 5.48 (1 H, *J* 14 Hz) (ABq, $ArCH_2O$), and 7.56 and 7.64 (each 1 H, *J* 9 Hz) and 8.23 (4 H, *J* 9 Hz) (2 × AA′BB′); irradiation at the frequency of the 3-CH_3 resonance sharpened the 4-H_2 resonance, and *vice-versa*; *m/z* (c.i.) (NH_3 gas) $(M + NH_4)^+$, 543, $(M + H)^+$, 526.

Sodium (1′*RS*,2*SR*,4*RS*,6*RS*,7*SR*)-7-(1-*Hydroxyethyl*)-8-*oxo*-1-*azatricyclo*[4.2.0.0^{2,4}]*octane*-2-*carboxylate* (**37**).—A solution of the *p*-nitrobenzyl ester (**36**) (0.030 g) in dioxane–water (3:1) (3 ml) was shaken under hydrogen in the presence of a 10% palladium–carbon catalyst (0.003 g) for 30 min. A solution of sodium hydrogen carbonate (0.005 g) in water (1 ml) was added, the mixture was filtered through Celite, and the filter was washed with further portions of dioxane. The combined filtrate and washings were evaporated to give an aqueous residue, which was extracted with ethyl acetate (× 2) to leave the sodium salt (**37**) as a stable, aqueous solution, showing a single component [h.p.l.c.; retention time 1.4 min on elution with acetonitrile–0.05M-$NH_4H_2PO_4$ buffer (1:4)]. Evaporation gave a solid (0.011 g, 83%), $\nu_{max.}$($CHBr_3$) 3 400, 1 745, and 1 590 cm^{-1}; δ (250 MHz) 1.11—1.25 (2 H, m, 3-H_2), 1.24 [3 H, d, *J* 6.5 Hz, $CH_3CH(OH)$], 1.94 (1 H, ddd, *J* 13, 8, and 5 Hz, 5-H_β), 2.18 (1 H, dt, *J* 9 and 5.5 Hz, 4-H_β), 2.27 (1 H, dd, *J* 13 and 7 Hz, 5-H_α), 2.96 (1 H, dd, *J* 6.5 and 2 Hz, 7-H_β), 3.55 (1 H, ddd *J* 8, 7, and 7.65 (each 2 H, *J* 9 Hz) and 8.23 (4 H, *J* 9 Hz) (2 × AA′BB′).

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