Olivanic Acid Analogues. Part 1. Total Synthesis of the 7-Oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate System and Some Related β-Lactams

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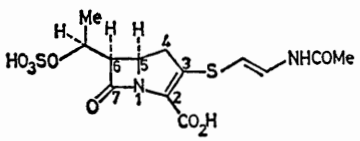
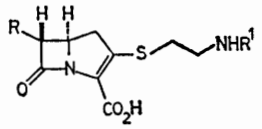
4-Allylazetidin-2-one, prepared from penta-1,4-diene and chlorosulphonyl isocyanate, has been used to synthesise the parent 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate system of the naturally occurring olivanic acids, using an intramolecular Wittig reaction to construct the 2,3-double bond. Cyclisation of ketones derived from the 4-allyl grouping produced 3-substituted derivatives, while use of the azetidin-2-one prepared from hexa-1,5-diene and chlorosulphonyl isocyanate has given the homologous 8-oxo-1-azabicyclo[4.2.0]oct-2-ene system.

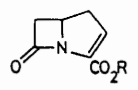
OLIVANIC acid derivatives [1] such as MM 13902 (1), together with thienamycin [2] (2), PS-5 [3] (3), and other related structures,[4] comprise a family of streptomycete metabolites characterised by the presence of the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid system (4; R = H). The novel chemical features, and potent antibacterial properties of these new bicyclic β-lactams, prompted us to undertake the synthesis of some representative structures related to the natural products. In this paper we report the methodology for the preparation of the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate nucleus [5] (4), some simple derivatives (5), and the homologous 8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate system (6).



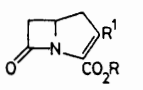
(1)



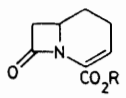
(2) R = MeCH(OH), R^1 = H
(3) R = $MeCH_2$, R^1 = COMe



(4)

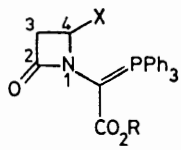


(5) a; R^1 = Me
b; R^1 = CH(Ph)CO_2Me

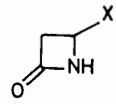


(6)

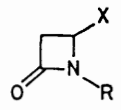
The intramolecular Wittig reaction of an azetidinylphosphorane grouping with an aldehyde or ketone has been widely used for the preparation of novel cephalosporins [6] and their 1-oxa counterparts.[7] Such an approach seemed attractive as an entry into the system (4), provided that it was possible to obtain the appropriately functionalised phosphorane (7). The preparation of (7) requires the elaboration of a suitable monocyclic precursor carrying a protected or potential oxoethyl group at the 4-position of the azetidin-2-one. Whereas a number of such derivatives having oxygen- or sulphur-linked substituents are available from penicillins, or by total synthesis from 4-acetoxyazetidin-2-one,[8] this was not the case with carbon-linked substituents. At the outset of this work only the 4-vinylazetidin-2-one [9] (14), prepared from buta-1,3-diene and



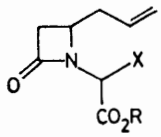
(7) X = CH_2CHO
(8) X = CH=CH–OAc
(9) X = CH_2–CH=CH_2
(10) X = CH_2COMe
(11) X = CH_2CO_2H
(12) X = $CH_2COCH(Ph)CO_2Me$
(13) X = $CH_2CH_2CH=CH_2$



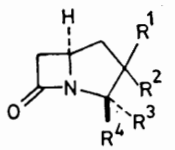
(14) X = $CH=CH_2$
(15) X = $CH_2CH=CH_2$
(16) X = CH=CH–OAc
(17) X = $CH_2CH_2CH=CH_2$
(18) X = CH_2COMe
(19) X = $CH_2CH(OH)Me$
(20) X = CH_2CO_2R



(21) X = O·CH_2·CH, R = H
(22) X = O·CH_2·CH, R = Me
(23) X = $CH(OH)CH_2I$, R = H
(24) X = CMe=$CHCO_2Me$, R = Me
(25) X = COMe, R = Me
(26) X = CH_2CHO, R = Me



(27) X = OH
(28) X = Cl



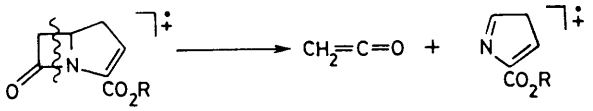
(29) R^1 = R^2 = R^3 = H, R^4 = CO_2CH_2Ph
(30) R^1R^2 = =C(Ph)CO_2Me, R^3 = CO_2CH_2Ph, R^4 = H

chlorosulphonyl isocyanate (CSI), seemed a possible synthon for use in the carbon series. We also undertook an examination of the cycloaddition reactions of CSI with a number of other dienes, which we felt could lead to better precursors of (4), (5), and (6). Thus, from penta-1,4-diene we obtained the 4-allylazetidin-2-one (15); 1-acetoxybuta-1,3-diene gave (16), and hexa-1,5-diene provided (17). The preparation and use of the latter two azetidin-2-ones has since been reported by other workers.[10,11] More recently other routes [12,13] to 4-allyl-substituted compounds have been described.

Initially the ready availability of the vinyl derivative (14) led us to undertake some experiments with a view to using the vinyl group as a precursor of the 4-substituent in (7). Epoxidation of the double bond in (14) or its

N-methyl derivative [14] occurred readily, but Lewis-acid-catalysed rearrangement of the epoxide in (21) or (22) to give the aldehyde was accompanied by much polymerisation. Ring opening of (21) using n-propyl iodide and sodium iodide [15] gave the iodohydrin (23). When the epoxide (22) was heated in benzene containing lithium bromide and methoxycarbonylmethylenetriphenylphosphorane,[16] the olefin (24) was isolated, indicative of the intermediacy of the ketone (25) rather than the aldehyde (26). Attempts to regenerate the aldehyde from the enol acetate (16) or the derived phosphorane (8; R = CH_2Ph) without disruption of the β-lactam were unsuccessful. The 4-acetoxyethyl derivative resulting from reduction of (16) has been used in another approach to (4) and related derivatives.[17]

Our preparation of the 4-allylazetidin-2-one (15) afforded a readily available intermediate for the preparation of (7), and the desired esters (4). Reaction of (15) with a glyoxylic ester followed by conversion of the mixture of α-hydroxy-esters (27) into the chlorides (28), and then into the phosphorane (9), followed the route originated by Woodward in the cephem field.[6] Selective oxidation of the terminal double bond in (9) in the presence of the phosphorane was achieved by ozonolysis in the presence of trifluoroacetic acid.[18] Reduction of the ozonide produced the trifluoroacetic acid salt of the phosphorane (7). When this was partitioned between ethyl acetate and aqueous sodium hydrogencarbonate, regeneration of the phosphorane moiety occurred to give the intermediate (7), which rapidly cyclised to the ester (4; R = Bu^t, Me, CH_2Ph, $CH_2C_6H_4NO_2$-*p*, or CH_2COMe). The esters (4) all showed the characteristic 1 780 cm^{-1} β-lactam carbonyl i.r. absorption, as found in esters of the natural olivanic acid derivatives.[1] N.m.r. and mass spectral data were consistent with structure (4), the fragmentation pattern (Scheme) showing the characteristic loss of keten.



SCHEME

Little degradation was apparent (t.l.c.) in the cyclisation sequence, but yields of isolated (4) were variable (45—70%). This was attributed to instability of the bicyclic material during the column chromatography required to remove unwanted triphenylphosphine oxide. We have found this to be the case with many simple derivatives of this system. Non-crystalline samples were also prone to decomposition unless kept in solution in an inert solvent.

For the purpose of biological evaluation we required the parent acid (4; R = H) or carboxylate salt. Hydrolysis of the methyl ester (4; R = Me) led to rupture of the β-lactam, while the t-butyl ester (4; R = Bu^t) was rapidly degraded under the normal conditions of cleavage using trifluoroacetic acid. In the phosphorane (9; R = Bu^t) however, the t-butyl ester was stable in the presence of trifluoroacetic acid during the ozonolysis step. This is attributed to protonation of the ylide instead of the oxygen, as would be expected in a normal ester. Hydrogenolysis of the benzyl ester (4; R = CH_2Ph) and the *p*-nitrobenzyl ester (4; R = $CH_2C_6H_4NO_2$-*p*) was also investigated. In the latter case no discernible β-lactam product was isolated. From (4; R = CH_2Ph) the 1-azabicycloheptane benzyl ester (29) * was isolated, the relative stereochemistry at C(2) and C(5) being assigned by a comparison of n.m.r. data with those of related penam [19] and 1-oxadethiapenam [20] structures. A minor product was the 2-epimer of (29) having the ' natural ' penicillin stereochemistry of the carboxylate grouping. No β-lactam containing free acid was obtained. Clearly reduction of the double bond proceeds faster than ester hydrogenolysis. Further reaction of (29) with hydrogen over palladium catalyst led to gradual loss of the β-lactam.

The ester (4; R = $CH_2C_6H_4NO_2$-*p*) was also subjected to an electrochemical procedure [21] developed for deprotection of the carboxylate group of the natural products. In this case the free acid (4; R = H) was successfully extracted into aqueous solution as the lithium salt (4; R = Li), $\lambda_{max.}$ 262 nm. Attempted lyophilisation was accompanied by almost complete decomposition, a result paralleling that of Cama and Christensen [17] when using the photolabile *o*-nitrobenzyl protecting group in their preparation of this system. Hydrolysis of the acetonyl ester (4; R = CH_2COMe) as in the penem series [22] provided a solution of the sodium salt (4; R = Na), which again showed less stability than the more highly substituted natural products. A solution of (4; R = Na) was shown to inhibit the growth of a number of bacteria *in vitro*.

The intrinsic antibacterial activity associated with the parent olivanic acid nucleus (4; R = H) was also demonstrated in a model *in vivo* infection using the more readily handled, biologically labile, phthalidyl or pivaloyloxymethyl esters (4; R = phthalidyl or CH_2OCOBu^t). In these cases a variation of the normal procedure was used to introduce the potential C(2) ester grouping. Condensation of (15) with glyoxylic acid in the presence of molecular sieves, followed by successive treatment with potassium carbonate and bromophthalide or pivaloyloxymethyl bromide produced the α-hydroxy-esters (27; R = phthalidyl or CH_2OCOBu^t). The pivaloyloxymethyl derivative (28; R = CH_2OCOBu^t) was converted into the phosphorane (9; R = CH_2OCOBu^t) and then into the bicyclic ester (4; R = CH_2OCOBu^t). For the phthalidyl ester (27; R = phthalidyl), tris-(*p*-methoxyphenyl)phosphine was used to produce the phosphorane, the tris-(*p*-methoxyphenyl)-phosphine oxide formed in the cyclisation step, being more readily separated from the final product (4; R = phthalidyl). In this case brief heating (45 °C) was required to effect cyclisation.

Ketones similarly participated in the ring closure

* All compounds prepared are racemic; in this instance one enantiomer is depicted for convenience.

reaction, but required more vigorous conditions for cyclisation. This was demonstrated by the use of the methyl ketone (18) prepared from 4-allylazetidin-2-one (15). Oxymercuration [23] of (15) with mercury(II) acetate followed by reduction with sodium borohydride provided the secondary alcohol (19), which was oxidised with pyridinium chlorochromate to (18). Subsequently, using an oxypalladation procedure described by Rodeheaver,[24] the ketone (18) could be obtained from (15) in a single step. Conversion into the phosphorane (10; R = Bu^t) followed by heating in toluene at 100 °C for 1.5 h gave an 83% yield of the t-butyl ester of the 3-methyl-substituted bicyclic structure (5a; R = Bu^t). The influence of the ester grouping on the rate of cyclisation could be seen on comparison with the *p*-nitrobenzyl ester (10; R = $CH_2C_6H_4NO_2$-*p*), when heating at 100 °C for 10 h was required to produce a 64% yield of (5a; R = $CH_2C_6H_4NO_2$-*p*). Difficulties were again encountered in deprotection and the sodium salt corresponding to (5a; R = Na) was not isolated.

Oxidation by peroxy-acid of the ozonide derived from (9; R = CH_2Ph) afforded the 4-carboxymethylazetidin-2-one derivative (11; R = CH_2Ph). Conversion of the acid group in (11; R = CH_2Ph) into the diphenylphosphinic anhydride, followed by reaction with the lithium ester enolate derived from methyl phenylacetate and lithium hexamethyldisilazanide gave two isomers of the ketone (12; R = CH_2Ph). Heating (12; R = CH_2Ph) in toluene for 3 hours gave a low yield (*ca.* 15%) of product (5b; R = CH_2Ph), although some 50% of uncyclised phosphorane was recovered. Prolonged heating was accompanied by decomposition. Brief treatment of (5b; R = CH_2Ph) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the exocyclic double-bond isomer (30).

In preliminary experiments attempts to oxidise the allyl group of the *N*-unsubstituted azetidin-2-one (15) to give the acid (20; R = H) met with limited success. Use of potassium permanganate and a crown ether [25] or permanganate and a phase-transfer catalyst,[26] followed by esterification and isolation as the benzyl ester (20; R = CH_2Ph), was found to be best. Subsequent hydrogenolysis gave a quantitative conversion into the free acid (20; R = H). Whereas benzyl 3-methylbut-3-enoate reacts with CSI to give an azetidin-2-one,[27] attempts to obtain (20; R = CH_2Ph) by this method from benzyl but-3-enoate were unsuccessful.

We have also applied our methodology for the formation of the bicyclo[3.2.0] system to obtain the homologous bicyclo[4.2.0] system (6). The synthesis of acylamino derivatives of the latter using an intramolecular Wittig–Horner reaction for the cyclisation has been described previously.[28] Conversion of 4-(but-3-enyl)-azetidin-2-one (17) into the phosphorane (13; R = Bu^t) followed by cyclisation as for (9) gave the 8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate ester (6; R = Bu^t). It was expected that (6) would show a greater degree of stability to deprotection, but unlike conventional cephalosporins, removal of the t-butyl group with trifluoroacetic acid led to destruction of the β-lactam ring.

EXPERIMENTAL

U.v. spectra were recorded on a Pye-Unicam SP 8000 or a Perkin-Elmer 554 spectrophotometer. Unless stated otherwise i.r. spectra were recorded for solutions in chloroform on a Perkin-Elmer 197 or 457 machine. ^{1}H N.m.r. spectra were recorded at 60 MHz on a Varian EM 360, at 80 MHz on a Varian CFT 20, at 90 MHz on a Perkin-Elmer R32, and at 250 MHz on a Bruker WM 250 instrument, for solutions in $CDCl_3$ with tetramethylsilane as internal standard unless otherwise stated. Mass spectra were determined with an A.E.I. MS9 or VG 7070F instrument. The purity of all compounds was tested by t.l.c. on Merck precoated silica gel 60 F_{254} plates. Preparative chromatography was carried out on columns of Merck silica gel 60 (finer than 230 mesh or 230—400 mesh ASTM) with ethyl acetate–light petroleum (b.p. 60—80 °C) as eluant using the slightly increased pressure provided by a Medcalf Hy-flo pump. Solutions were dried with magnesium sulphate or sodium sulphate, and solvents were removed by evaporation under reduced pressure using a rotary evaporator. M.p.s were determined with a Kofler hot-stage apparatus. All compounds prepared are racemic.

4-*Allylazetidin-2-one* (15).—Penta-1,4-diene (30 g) and chlorosulphonyl isocyanate (35.4 ml) were mixed and kept at room temperature for 3 days in a pressure bottle. The thick dark syrup was diluted with methylene chloride (500 ml) and added dropwise to a stirred solution of sodium sulphite (66 g) in water (240 ml). The pH was maintained between 6.5 and 7.5 by the addition of aqueous 10% potassium hydroxide (600 ml in total). The organic phase was separated and the aqueous residue extracted (×2) with ethyl acetate. The combined organic phase was dried, filtered, and evaporated to give the *azetidin-2-one* (15) (16.05 g), as an oil, b.p. 76—80 °C at 0.2 mmHg, $\nu_{max.}$ 3 490, 1 770, and 1 650 cm^{-1}; δ 2.39 (2 H, t, *J* 6 Hz, CH_2–CH=CH_2), 2.61 (1 H, ddd, *J* 14, 2, and 1.5 Hz, collapsing on D_2O exchange to dd, *J* 14 and 2 Hz, 3-H), 3.10 (1 H, ddd, *J* 14, 5, and 2 Hz, collapsing on D_2O exchange to dd, *J* 14 and 5 Hz, 3-H), 3.55—3.91 (1 H, m, 4-H), 4.98—6.21 (3 H, m, CH=CH_2), and 6.67 (1 H, br s, exchangeable D_2O, NH) (Found: M^+, 111.0683. C_6H_9NO requires *M*, 111.0684).

4-(*But-3-enyl*)*azetidin-2-one* (17).—A mixture of hexa-1,5-diene (7.3 ml) and chlorosulphonyl isocyanate (5.4 ml) was kept at room temperature for 7 days. The syrupy product was dissolved in methylene chloride (20 ml) and added dropwise to a vigorously stirred mixture of sodium sulphite (10.5 g), water (50 ml), and methylene chloride (25 ml), while the pH was maintained at 7—9 by addition of aqueous 10% potassium hydroxide (*ca.* 100 ml). Ethyl acetate (100 ml) was then added and the organic phase separated. The aqueous solution was extracted with more ethyl acetate (3 × 50 ml) and the combined organic solutions were dried, concentrated, and then subjected to column chromatography to obtain the *azetidinone* (17) as a pale yellow oil (3.94 g), $\nu_{max.}$ 3 440, 1 755, and 1 640 cm^{-1}; δ 1.68 (2 H, br q, *J* 6.5 Hz, CH_2–CH_2–CH=CH_2), 2.09 (2 H, br q, *J* 7 Hz, CH_2–CH=CH_2), 2.49 (1 H, dd, *J* 14 and 2 Hz after D_2O exchange, 3-H), 3.00 (1 H, dd, *J* 14 and 5 Hz after D_2O exchange, 3-H), 3.56 (1 H, tdd, *J* 6, 5, and 2 Hz, 4-H), 4.8—5.2 (2 H, m, C=CH_2), 5.76 (1 H, ddt, *J* 17, 9, and 6 Hz,

CH=C), and 6.85 (1 H, br s, exchangeable, NH) (Found: M^+, 126.0909. $C_7H_{12}NO$ requires M, 126.0919).

4-(*Oxiranyl*)*azetidin*-2-*one* (21).—4-Vinylazetidin-2-one [9] (0.93 g) in anhydrous dichloromethane (10 ml) was treated dropwise over 5 min with a solution of *m*-chloroperbenzoic acid (2.23 g of 85% purity) in dichloromethane (25 ml). After heating at reflux temperature for 7 h the solution was evaporated to small volume and chromatographed to give the oily *epoxide* (21) (0.55 g), $\nu_{max.}$ 3 380 and 1 770 cm^{-1}; δ 2.50—3.72 (6 H, m) and 7.18 (1 H, br s, exchangeable D_2O, NH) [Found: $(M^+ + 1)$, 114.0555. $C_5H_8NO_2$ requires $(M + 1)$, 114.0555].

Similar reaction of 1-methyl-4-vinylazetidin-2-one [14] (1.66 g) with *m*-chloroperbenzoic acid (2.94 g) afforded the epoxide (22) (1.01 g), $\nu_{max.}$ 1 750 cm^{-1}; δ 2.30—3.61 (6 H, m) and 2.82 (3 H, s, NMe); M^+ 127.

4-(1-*Hydroxy*-2-*iodoethyl*)*azetidin*-2-*one* (23).—The epoxide (21) (0.395 g) was heated at 80 °C in *N*,*N*-dimethylformamide (50 ml) containing n-propyl iodide (1.7 ml) and sodium iodide (2.6 g). After 6 h the reddish solution was evaporated to dryness (high vacuum pump) and the residual gum triturated with toluene. The supernatant liquid was evaporated to dryness and the residue chromatographed to give the product as a gum (0.224 g). Crystallisation from ethyl acetate–light petroleum gave pure *iodohydrin* (23), m.p. 103—106 °C, $\nu_{max.}$ 3 480 and 1 760 cm^{-1}; δ[$(CD_3)_2CO$] 2.70—3.80 (6 H, m), 4.56 (1 H, d, *J* 6 Hz, exchangeable D_2O, OH), and 7.10 (1 H, br s, exchangeable D_2O, NH) (Found: M^+, 240.9606. $C_5H_8INO_2$ requires M, 240.9602).

Methyl (E)-3-(1-*Methyl*-2-*oxoazetidin*-4-*yl*)*but*-2-*enoate* (24).—Lithium bromide (0.087 g) and methoxycarbonylmethylenetriphenylphosphorane (0.334 g) in dry benzene (10 ml) were heated at reflux and the azetidin-2-one (22) (0.127 g) in benzene (2 ml) was added. Heating was continued for 22 h; then the solvent was removed and the residue chromatographed. Initially eluted was the minor (*Z*)-isomer (0.006 g) of (24), followed by the major product as the (E)-*isomer* of (24) (0.026 g), $\nu_{max.}$ 1 745, 1 715, and 1 650 cm^{-1}; δ 2.08 (3 H, d, *J ca.* 1 Hz, C=C–Me), 2.66 (1 H, dd, *J* 14 and 2 Hz, 3-H), 2.73 (3 H, s, NMe), 3.14 (1 H, dd, *J* 14 and 6 Hz, 3-H), 3.76 (3 H, s, OMe), 3.92 (1 H, m, 4-H), and 5.83 (1 H, s, slightly broadened, H–C=C) (Found: M^+, 183.0894. $C_9H_{13}NO_3$ requires M, 183.0895).

Esters (9) *of* (4-*Allyl*-2-*oxoazetidin*-1-*yl*)*triphenylphosphoranylideneacetic Acid*.—*t-Butyl ester* (9; R = Bu^t). t-Butyl glyoxylate hydrate (6.22 g) in benzene (120 ml) was heated at reflux for 1 h in a Dean–Stark apparatus. 4-Allylazetidin-2-one (15) (2.31 g) was then added and heating continued for 4 h. Evaporation and chromatography of the residual oil gave the alcohol (27; R = Bu^t), as a mixture of isomers (4.48 g), $\nu_{max.}$ 3 490, 1 755, and 1 640 cm^{-1}. A stirred solution of the alcohol (27; R = Bu^t) (4.20 g) in dry tetrahydrofuran (120 ml) under an argon atmosphere was cooled to −20 °C and treated with 2,6-lutidine (4.03 ml) in tetrahydrofuran (15 ml). Thionyl chloride (2.54 ml) in tetrahydrofuran (15 ml) was added dropwise over 5—10 min. The temperature was allowed to rise to 0 °C over 30 min; then the precipitated solid was removed by filtration, and the filtrate evaporated to dryness. Evaporation was repeated twice from toluene and the residue containing the crude α-chloro-ester (28; R = Bu^t) taken up into dry dioxan (100 ml) under argon. Triphenylphosphine (9.1 g) and 2,6-lutidine (4.03 ml) were added to the solution, which was stirred at room temperature overnight. 2,6-Lutidine hydrochloride was removed by filtration and the filtrate evaporated to dryness and chromatographed to give *t-butyl* (4-*allyl*-2-*oxoazetidin*-1-*yl*)*triphenylphosphoranylideneacetate* (9; R = Bu^t) (4.62 g), m.p. 188—189 °C (from diethyl ether); $\nu_{max.}$ 1 730, 1 638, and 1 610 cm^{-1} (Found: C, 74.1; H, 6.8; N, 3.0; P, 6.2. $C_{30}H_{32}NO_3P$ requires C, 74.2; H, 6.6; N, 2.9; P, 6.4%).

Similarly from methyl glyoxylate was prepared the *methyl ester* (9; R = Me), m.p. 208—212 °C (Found: C, 72.6; H, 5.9; N, 3.0. $C_{27}H_{26}NO_3P$ requires C, 73.1; H, 5.9; N, 3.2%); from benzyl glyoxylate the *benzyl ester* (9; R = CH_2Ph), m.p. 158—159 °C (Found: C, 76.1; H, 5.8; N, 2.6. $C_{33}H_{30}NO_3P$ requires C, 76.3; H, 5.8; N, 2.7%); from *p*-nitrobenzyl glyoxylate [19] the p-*nitrobenzyl ester* (9; R = $CH_2C_6H_4NO_2$-*p*), m.p. 182—183 °C (Found: C, 70.3; H, 5.3; N, 4.8. $C_{33}H_{29}N_2O_5P$ requires C, 70.2; H, 5.1; N, 5.0%), and from acetonyl glyoxylate [22] the *acetonyl ester* hemi-hydrate (9; R = CH_2COMe), m.p. 197—200 °C (Found: C, 69.9; H, 5.7; N, 2.7. $C_{29}H_{28}NO_4P{\cdot}0.5H_2O$ requires C, 70.4; H, 5.9; N, 2.8%).

Pivaloyloxymethyl ester (9; R = CH_2OCOBu^t). Glyoxylic acid monohydrate (1.75 g) and 4-allylazetidin-2-one (15) (2.00 g) were stirred together in dry *N*,*N*-dimethylformamide (10 ml) in the presence of 4 A molecular sieves (*ca.* 0.5 g) for 6 h. The mixture was cooled to 0 °C, treated with powdered potassium carbonate (1.31 g), and then allowed to warm to room temperature once more. Pivaloyloxymethyl bromide (5.30 g) was then added and the mixture stirred overnight. The product was poured into a mixture of 0.1N-hydrochloric acid (80 ml) and ethyl acetate (80 ml). The ethyl acetate layer was separated; the aqueous layer was extracted with ethyl acetate (50 ml); the combined extracts were washed with saturated aqueous sodium hydrogencarbonate and then brine, and finally dried and concentrated to give the ester (27; R = CH_2OCOBu^t) as a yellow oil (4.77 g), $\nu_{max.}$ 3 500 and 1 755 cm^{-1}. This material was converted into the chloride (28; R = CH_2OCOBu^t) and then the phosphorane (9; R = CH_2OCOBu^t) by the methods used for the corresponding t-butyl ester. Chromatography of the final product followed by crystallisation from diethyl ether gave *pivaloyloxymethyl* (4-*allyl*-2-*oxoazetidin*-1-*yl*)*triphenylphosphoranylideneacetate* (9; R = CH_2OCOBu^t) (3.06 g), m.p. 140—142 °C; $\nu_{max.}$ 1 740 and 1 635 cm^{-1} (Found: C, 70.8; H, 6.7; N, 2.6. $C_{32}H_{34}NO_5P$ requires C, 70.7; H, 6.3; N, 2.6%).

Phthalidyl ester (9; R = $\overline{C_6H_4{-}CO{-}O{-}CH}$). Glyoxylic acid monohydrate (5.52 g) and 4-allylazetidin-2-one (15) (6.3 g) in dry *N*,*N*-dimethylformamide (30 ml) containing 4 A molecular sieves (*ca.* 1.5 g) were treated as for the pivaloyloxymethyl ester. The crude mixture of alcohols (27; R = $\overline{C_6H_4{-}CO{-}O{-}CH}$) (10 g) was similarly converted into the phosphorane (9; R = $\overline{C_6H_4{-}CO{-}O{-}CH}$), except that tris-(*p*-methoxyphenyl)phosphine (15 g) was substituted for triphenylphosphine. Chromatography of the final product and crystallisation from ethyl acetate–light petroleum gave as a dihydrate *phthalidyl* (4-*allyl*-2-*oxoazetidin*-1-*yl*)-*tris*-(p-*methoxyphenyl*)*phosphoranylideneacetate* (9; R = $\overline{C_6H_4{-}CO{-}O{-}CH}$) (6.25 g), m.p. 136—139 °C; $\nu_{max.}$ 1 780, 1 745, and 1 650 cm^{-1} (Found: C, 65.0; H, 5.2; N, 2.1. $C_{37}H_{34}NO_8P{\cdot}2H_2O$ requires C, 64.7; H, 5.5; N, 2.0%. M^+, 651.2033. $C_{37}H_{34}NO_8P$ requires M, 651.2081).

Esters (4) *of* 7-*Oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxy*-

lic Acid.—t-Butyl ester (4; R = Bu^t). The phosphorane (9; R = Bu^t) (0.242 g) in ethyl acetate (15 ml) was treated at room temperature with trifluoroacetic acid (0.4 ml) and the solution cooled to −70 °C. Ozone was passed through the solution until it became pale blue; then the solution was purged with argon to remove the excess of ozone (negative starch–iodide). Triphenylphosphine (0.131 g) in ethyl acetate (1 ml) was added to the solution; after 5 min the reaction vessel was transferred to an ice-bath and the solution neutralized by the addition of saturated aqueous sodium hydrogencarbonate (20 ml). The organic phase was separated, washed with brine, dried and evaporated to small volume, then the residue was rapidly chromatographed (in this case using finer than 230 mesh silica gel 60; subsequently 230—400 mesh ASTM was used) to give *t-butyl 7-oxo-1-azabicyclo*[3.2.0]*hept-2-ene-2-carboxylate* (4; R = Bu^t) (0.05 g) as an oil, $\nu_{max.}$ 1 780, 1 710, and 1 610 cm^{-1}; δ 1.49 (9 H, s, Bu^t), 2.70 (1 H, ddd, *J* 19, 10, and 2 Hz, 4-H), 2.87 (1 H, ddd, *J* 19, 9, and 2 Hz, 4-H), 2.86 (1 H, dd, *J* 14 and 2.5 Hz, 6-H), 3.40 (1 H, dd, *J* 14 and 5 Hz, 6-H), 3.99—4.33 (1 H, 5-H), and 6.26 (1 H, t, *J* 2 Hz, 3-H) (Found: M^+, 209.1050. $C_{11}H_{15}NO_3$ requires *M*, 209.1052).

Similarly, the phosphorane (9; R = Me) (0.886 g) in ethyl acetate (60 ml) and trifluoroacetic acid (1.5 ml) gave the *methyl ester* (4; R = Me) (0.15 g), m.p. 72—72.5 °C, $\lambda_{max.}$ (EtOH) 272 nm (ε 4 500); $\nu_{max.}$ 1 785, 1 738, and 1 610 cm^{-1}; δ 2.66 (1 H, ddd, *J* 19, 8.5, and 3 Hz), 3.04 (1 H, ddd, *J* 19, 11.5, and 3 Hz), 2.90 (1 H, dd, *J* 16.5 and 3 Hz), 3.45 (1 H, dd, *J* 16.5 and 5.5 Hz), 3.79 (3 H, s), 4.23 (1 H, m), and 6.43 (1 H, t, *J* 3 Hz) (Found: C, 57.5; H, 5.6; N, 8.2%; M^+, 167.0589. $C_8H_9NO_3$ requires C, 57.5; H, 5.4; N, 8.4%; *M*, 167.0582). The phosphorane (21; R = CH_2Ph) (2.0 g) in ethyl acetate (140 ml) and trifluoroacetic acid (6 ml) gave the *benzyl ester* (4; R = CH_2Ph) (0.7 g) as an oil, $\lambda_{max.}$ (EtOH) 270 nm (ε 4 250); $\nu_{max.}$ 1 780, 1 725, and 1 610 cm^{-1}; δ 2.68 (1 H, ddd, *J* 16, 9, and 3 Hz), 2.90 (1 H, ddd, *J* 16, 9, and 3 Hz), 2.92 (1 H, dd, *J* 16 and 3.5 Hz), and (3.45, 1 H, dd, *J* 16 and 5.5 Hz) (collapsing to ABq *J* 16 Hz on irradiation at δ 4.24), 4.24 (1 H, m, collapsing to d, *J* 5.5 Hz on irradiation at δ 2.80), 5.20 (2 H, s) 6.44 (1 H, t, *J* 3 Hz, collapsing to singlet on irradiation at δ 2.80), and 7.30 (5 H, s) (Found: M^+, 243.0883. $C_{14}H_{13}NO_3$ requires *M*, 243.0895).

The phosphorane (9; R = $CH_2C_6H_4NO_2$-*p*) (1.0 g) in ethyl acetate (50 ml) and trifluoroacetic acid (1.5 ml) gave, after 2.5 h at room temperature, the p-*nitrobenzyl ester* (4; R = $CH_2C_6H_4NO_2$-*p*) (0.21 g), m.p. 144—147 °C; $\lambda_{max.}$ (EtOH) 270 nm (ε 13 550); $\nu_{max.}$ 1 780, 1 730, 1 610, 1 525, and 1 350 cm^{-1}; $\nu_{max.}$ (KBr) 1 770, 1 715, 1 602, 1 545, and 1 350 cm^{-1}; δ 2.55—3.15 (2 H, m), 2.95 (1 H, dd, *J* 16 and 3 Hz), 3.50 (1 H, dd, *J* 16 and 6 Hz), 4.10—4.40 (1 H, m), 5.21 and 5.41 (2 H, ABq, *J* 12 Hz), 6.53 (1 H, t, *J* 2.5 Hz), 7.55 (2 H, d, *J* 8 Hz), and 8.15 (2 H, d, *J* 8 Hz) (Found: C, 58.2; H, 4.2; N, 9.5%; M^+, 288.0773. $C_{14}H_{12}N_2O_5$ requires C, 58.3; H, 4.2; N, 9.5%; *M*, 288.0773).

The phosphorane (9; R = CH_2COMe) (0.5 g) in ethyl acetate (50 ml) containing trifluoroacetic acid (5 ml) gave, after 1 h at room temperature, the *acetonyl ester* (4; R = CH_2COMe) (0.092 g), which crystallised (ethyl acetate, diethyl ether, hexane) as the hemi-hydrate, m.p. 92 °C, $\lambda_{max.}$ (EtOH) 271 nm (ε 4 645); $\nu_{max.}$ 1 780, 1 735sh, 1 725, and 1 610 cm^{-1}; δ 2.23 (3 H, s), 2.80 (1 H, ddd, *J* 19, 8, and 3 Hz), 3.00 (1 H, ddd, *J* 19, 10, and 3 Hz), 3.01 (1 H, dd, *J* 17 and 3 Hz), 3.53 (1 H, dd, *J* 17 and 6 Hz), 4.32 (1 H, m), 4.74 and 4.83 (2 H, ABq, *J* 17 Hz), and 6.65 (1 H, t, *J* 3 Hz) (Found: C, 55.0; H, 5.6; N, 6.4%; M^+ 209.0671. $C_{10}H_{11}NO_4 \cdot 0.5H_2O$ requires C, 55.0; H, 5.5; N, 6.4%. $C_{10}H_{11}NO_4$ requires *M*, 209.0687).

Ozonolysis of the phosphorane (9; R = CH_2OCOBu^t) (0.50 g) in ethyl acetate (15 ml) and trifluoroacetic acid (3 ml) gave the *pivaloyloxymethyl ester* (4; R = CH_2OCOBu^t) after 3 h at room temperature. This compound was very unstable to chromatography; after rapid short column chromatography on silica gel 60 and Florisil it was obtained as a colourless gum in very low yield (0.022 g); $\nu_{max.}$ 1 790, 1 750, and 1 610 cm^{-1}; δ 1.20 (9 H, s, Bu^t), 2.69 (1 H, ddd, *J* 19, 9, and 3 Hz, 4-H), 2.90 (1 H, dd, *J* 17 and 3 Hz, 6-H), 2.97 (1 H, ddd, *J* 19, 9, and 3 Hz, 4-H), 3.46 (1 H, dd, *J* 17 and 5.5 Hz, 6-H), 4.22 (1 H, tdd, *J* 9, 5.5, and 3 Hz, 5-H), 5.76 and 5.85 (2 H, ABq, *J* 5.5 Hz, OCH_2O), and 6.49 (1 H, t, *J* 3 Hz, 3-H) (Found: M^+, 267.1118. $C_{13}H_{17}NO_5$ requires *M*, 267.1107).

Ozonolysis of the phosphorane (9; R = $\overset{1}{C_6H_4}$–CO–O–$\overset{1}{CH}$) (0.82 g) in ethyl acetate (100 ml) and trifluoroacetic acid (15 ml) followed the normal course, except tris-(*p*-methoxyphenyl)phosphine (0.445 g) was used to reduce the ozonide. Cyclisation was completed by heating the final ethyl acetate solution at 45 °C for 1.5 h. After evaporation and purification by rapid chromatography the product was obtained as a 2 : 1 mixture of epimers (n.m.r.) of the *phthalidyl ester* hemi-hydrate (9; R = $\overset{1}{C_6H_4}$–CO–O–$\overset{1}{CH}$) (0.14 g), m.p. 152—157 °C (decomp.) (microcrystals from ethyl acetate–diethyl ether); $\lambda_{max.}$ (EtOH) 280, 274, and 224 nm; $\nu_{max.}$ 1 795, 1 750, and 1 610 cm^{-1}; δ 2.45—2.95 (2 H, m, 4-H_2), 2.94 (1 H, dd, *J* 17 and 4 Hz, 6-H), 3.78 (1 H, s, H_2O), 4.23 (1 H, m, 5-H), 6.49 (t, *J* 3 Hz, minor epimer) and 6.62 (t, *J* 3 Hz, major epimer) (together 1 H, 3-H), 7.45 (s, major epimer) and 7.51 (s, minor epimer) (together 1 H, phthalidyl CH), and 7.55—7.96 (4 H, m, Ar) (Found: C, 60.9; H, 4.1; N, 4.5%; M^+, 285.0644. $C_{15}H_{11}NO_5 \cdot 0.5H_2O$ requires C, 61.2; H, 4.1; N, 4.8%. $C_{15}H_{11}NO_5$ requires *M*, 285.0636).

Benzyl 7-Oxo-1-azabicyclo[3.2.0]*heptane-2-carboxylate* (29).—The ester (4; R = CH_2Ph) (0.102 g) was hydrogenated over 10% Pd–C (0.035 g) in tetrahydrofuran (10 ml) for 0.5 h. The catalyst was removed by filtration through Kieselguhr and the filtrate divided into two equal portions: one half was evaporated to dryness, suspended in chloroform (*ca.* 2 ml) and treated with triethylamine (0.025 g). Evaporation and trituration with diethyl ether gave an insoluble fraction (0.014 g) and a non-polar (t.l.c.) ether-soluble fraction (0.030 g). The insoluble material was not the triethylamine salt of the acid (4; R = H) nor of the saturated acid corresponding to (29). The other half of the reaction solution was also evaporated to dryness and in this case treated with sodium hydrogencarbonate (0.017 g) in the minimum volume of water. Evaporation from toluene–ethanol gave a solid, which could be separated into a chloroform-insoluble (0.014 g) and a chloroform-soluble fraction, which was identical (t.l.c.) with the non-polar component from the first half of the solution. The insoluble material did not correspond to the sodium salt of (4; R = Na) nor to the saturated system (29). The fractions containing the non-polar material were combined, evaporated, and chromatographed to give as major product (0.030 g) the oily *1-azabicycloheptane ester* (29), $\nu_{max.}$ 1 760 and 1 740 cm^{-1}; δ 1.50—2.41 (4 H, m, 3-H_2 and 4-H_2), 2.68 (1 H, dd, *J* 15 and 2.5 Hz, 6-H), 3.06 (1 H, dd, *J* 15 and

4 Hz with further fine splitting, 6-H), 3.66 (1 H, m, 5-H), 3.87 (1 H, t, *J* 4.5 Hz, 2-H), 5.12 (2 H, s, CH_2Ph), and 7.29 (5 H, s, Ph) (Found: M^+, 245.1057. $C_{14}H_{15}NO_2$ requires *M*, 245.1052).

A second product (0.007 g) was the more polar 2-epimer of (29) obtained only as a mixture with the major product, $\nu_{max.}$ 1 760 and 1 740 cm^{-1}; δ (by difference) 1.60—2.60 (4 H, m), 2.56 (1 H, dd, *J* 16 and 2 Hz), 3.25 (1 H, dd, *J* 16 and 4.5 Hz), 3.85 (1 H, m), 4.40 (1 H, t, *J* 8 Hz, 2-H), 5.10 (2 H, s), and 7.28 (5 H, s); M^+ 245. Further hydrogenolysis of the ester (29) led to gradual decomposition of the β-lactam.

Lithium 7-Oxo-1-azabicyclo[3.2.0]*hept-2-ene-2-carboxylate* (4; R = Li).—Cleavage of the *p*-nitrobenzyl ester was effected by reduction at a mercury cathode (−1.3 V *vs.* standard calomel electrode) in a divided cell with a platinum anode using 0.1M-$Bu^n_4N^+BF_4^-$ in *N*,*N*-dimethylformamide as electrolyte. The ester (4; R = $CH_2C_6H_4NO_2$-*p*) (0.11 g) in electrolyte solution (1 ml) was added to the cathode; the total volume of electrolyte was 25 ml. After completion of reduction the catholyte was evaporated to dryness, and the residue in dichloromethane (10 ml) was extracted with water (2 ml) containing lithium iodide (0.070 g). The aqueous phase was chromatographed on Biogel P2 (elution with water containing 1% n-butyl alcohol) to give the lithium salt (4; R = Li), $\lambda_{max.}$ 262 nm. Attempted lyophilization for further characterisation led to decomposition with loss of the chromophore.

Sodium 7-Oxo-1-azabicyclo[3.2.0]*hept-2-ene-2-carboxylate* (4; R = Na).—The ester (4; R = CH_2COMe) (0.028 g) in tetrahydrofuran (6 ml) and water (2 ml) was cooled in an ice-bath. Aqueous 0.1N-sodium hydroxide (1.3 ml) was added dropwise over 2 min. After a further 5 min in the cold, the solution was diluted with water (5 ml) and washed with dichloromethane (2 × 15 ml). The aqueous solution containing the bioactive sodium salt (4; R = Na), $\lambda_{max.}$ 262 nm (*ca.* 0.014 g based on ε 4 500) was not purified further.

4-(2-Hydroxypropyl)azetidin-2-one (19).—The azetidin-2-one (15) (0.2 g) in tetrahydrofuran (1 ml) was added to mercury(II) acetate (0.6 g) in tetrahydrofuran (1 ml) and water (2 ml). The mixture was stirred at ambient temperature for 2.5 h. Aqueous saturated sodium hydrogen carbonate solution was added to neutralize the acetic acid, followed by sodium borohydride (0.08 g). Hydrogen was evolved and mercury deposited from the solution. The solution was saturated with sodium chloride, filtered through Kieselguhr, and extracted with ether. The dried organic phase was evaporated and chromatographed to give pure *alcohol* (19) (0.036 g), δ 1.27 (3 H, d, *J* 7 Hz, Me), 1.60—1.85 (2 H, m, CH_2CH–OH), 2.60 (1 H, dd, *J* 16 and 2 Hz, 3-H), 3.15 (1 H, dd, *J* 15 and 5 Hz, 3-H), 3.40—4.10 (3 H, m, 4-H and CHOH), and 7.18 (1 H, br d, NH) (Found: M^+, 129.0786. $C_6H_{11}NO_2$ requires *M*, 129.0790). Further extraction of the aqueous layer with ethyl acetate was subsequently found to give more (19).

4-(2-Oxopropyl)azetidin-2-one (18).—The azetidin-2-one (15) (0.22 g) and mercury(II) acetate (0.64 g) were stirred in methanol (6 ml) for 2 h at room temperature. The solution was added to a mixture of copper(II) chloride dihydrate (1.03 g) and palladium(II) chloride (0.034 g) in methanol (6 ml) and the product heated for 1 h at 60 °C. After cooling, saturated aqueous sodium hydrogencarbonate was added until the solution was at pH 9. The mixture was filtered and the methanol removed by evaporation. The aqueous residue was extracted with ethyl acetate (3 × 25 ml), and the organic phase dried, evaporated, and chromatographed to give the *ketone* (18) (0.17 g), m.p. 77—78 °C (from ethyl acetate–light petroleum), $\nu_{max.}$ 3 420, 3 000, 1 760, and 1 720 cm^{-1}; δ 2.14 (3 H, s, Me), 2.40—3.40 (4 H, m, 3-H_2 and CH_2CO), 3.86 (1 H, m, 4-H), and 6.75 (1 H, br s, NH) (Found: C, 56.7; H, 7.4; N, 10.9%; M^+, 127.0628. $C_6H_9NO_2$ requires C, 56.7; H, 7.1; N, 11.0%; *M*, 127.0634). Oxidation of the alcohol (19) (0.036 g) with pyridinium chlorochromate (0.09 g) in dichloromethane (2 ml) for 3 h at room temperature also gave the ketone (18).

Esters of [4-(2-*Oxopropyl*)-2-*oxoazetidin*-1-*yl*]*triphenylphosphoranylideneacetate* (10).—t-Butyl glyoxylate hydrate (0.3 g) was heated at reflux in benzene (10 ml) for 1 h in a Dean–Stark apparatus to remove water. The ketone (18) (0.14 g) in dry benzene (3 ml) was added and heating continued at reflux for 4 h. Removal of solvent and chromatography gave the α-hydroxy-ester (0.196 g), which was dissolved in dry tetrahydrofuran (5 ml). The solution was cooled to −20 °C and treated with 2,6-lutidine (0.163 g) followed by thionyl chloride (0.181 g). After 20 min the mixture was filtered, and the filtrate evaporated to dryness; the residue was dissolved in dry dioxan (7 ml). Triphenylphosphine (0.4 g) and 2,6-lutidine (0.163 g) were added and the solution stirred under argon at room temperature for 16 h. Filtration and evaporation left a residue which was chromatographed to give *t-butyl* [4-(2-*oxopropyl*)-2-*oxoazetidin*-1-*yl*]-*triphenylphosphoranylideneacetate* (10; R = Bu^t) (0.255 g), m.p. 176.5—177.5 °C (from diethyl ether), $\nu_{max.}$ 1 740, 1 720, and 1 640 cm^{-1} (Found: C, 71.8; H, 6.4; N, 2.7%. $C_{30}H_{32}NO_4P$ requires C, 71.8; H, 6.4; N, 2.7%).

Similarly, reaction of (18) (0.8 g) with *p*-nitrobenzyl glyoxylate monohydrate (2.61 g) gave the *p*-nitrobenzyl α-hydroxy-ester (1.39 g) as a colourless oil, $\nu_{max.}$ 3 450, 1 760, 1 715, 1 605, 1 520, and 1 345 cm^{-1}. This ester (0.611 g) gave p-*nitrobenzyl* [4-(2-*oxopropyl*)-2-*oxoazetidin*-1-*yl*]*triphenylphosphoranylideneacetate* (10; R = $CH_2C_6H_4NO_2$-*p*) (0.73 g) as a yellow crystalline solid, m.p. 185—187 °C; $\nu_{max.}$ 1 740, 1 715, 1 630, 1 610, 1 520, and 1 350 cm^{-1} (Found: C, 67.1; H, 5.15; N, 4.75. $C_{33}H_{29}N_2O_6P \cdot 0.5H_2O$ requires C, 67.2; H, 5.1; N, 4.75%).

t-Butyl 7-*Oxo*-3-*methyl*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (5a; R = Bu^t).—The phosphorane (10; R = Bu^t) (0.062 g) was heated in dry toluene (5 ml) under argon for 1.5 h at 100 °C. Evaporation to dryness and chromatography of the residue gave the *ester* (5a; R = Bu^t) as an oil (0.023 g), $\lambda_{max.}$ (EtOH) 272 nm (ε 4 000); $\nu_{max.}$ 1 775, 1 700, and 1 635 cm^{-1}; δ 1.59 (9 H, s, Bu^t), 2.05 (3 H, t, *J* 1 Hz, Me), 2.73 (2 H, br d, *J* 9 Hz, 4-H_2), 2.77 (1 H, dd, *J* 16 and 3 Hz, 6-H), 3.34 (1 H, dd, *J* 16 and 6 Hz, 6-H), and 4.04 (1 H, m, 5-H) (Found: M^+, 223.1212. $C_{12}H_{17}NO_3$ requires *M*, 223.1208).

p-*Nitrobenzyl 7-Oxo*-3-*methyl*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (5a; R = $CH_2C_6H_4NO_2$-*p*).—The phosphorane (10; R = $CH_2C_6H_4NO_2$-*p*) (0.2 g) was heated in dry toluene (10 ml) under argon for 10 h at 100 °C. Evaporation and chromatography gave the bicyclic ester (5a; R = $CH_2C_6H_4NO_2$-*p*) (0.05 g) as needles, m.p. 116—118 °C (from ethyl acetate–light petroleum), $\lambda_{max.}$ (EtOH) 270 nm (ε 14 940); $\nu_{max.}$ 1 785, 1 725, 1 635, 1 610, 1 525, and 1 350 cm^{-1}; $\nu_{max.}$ (KBr) 1 775, 1 715, 1 610, 1 605, 1 510, and 1 380 cm^{-1}; δ 2.12 (3 H, t, *J* 1 Hz, Me), 2.80 (2 H, br d, *J* 9 Hz, 4-H_2), 2.87 (1 H, dd, *J* 16 and 3 Hz, 6-H), 3.42 (1 H, dd, *J* 16 and 6 Hz, 6-H), 4.13 (1 H, m, 5-H), 5.17 and 5.42 (2 H, ABq, *J* 14 Hz, $CH_2C_6H_4NO_2$-*p*), 7.56 (2 H, d, *J* 8 Hz,

Ar), and 8.14 (2 H, d, *J* 8 Hz, Ar) (Found: C, 59.8; H, 4.7; N, 9.1. $C_{15}H_{14}N_2O_5$ requires C, 59.6; H, 4.7; N, 9.3%). Unchanged phosphorane (10; R = $CH_2C_6H_4NO_2$-*p*) (0.05 g) was also recovered.

1-[(*Benzyloxycarbonyl*)(*triphenylphosphoranylidene*)-*methyl*]-2-*oxoazetidin*-4-*ylacetic acid* (11; R = CH_2Ph).—The allyl-substituted phosphorane (9; R = CH_2Ph) (0.15 g) in dichloromethane (5 ml) containing trifluoroacetic acid (1 ml) was ozonolysed at −60 °C. The solution was purged with argon, *m*-chloroperbenzoic acid (0.05 g) was added, and stirring continued at ambient temperature for 16 h. Removal of the solvents, followed by trituration and evaporation (×4) with portions of toluene, gave an oil which was chromatographed. Elution with ethyl acetate removed *m*-chlorobenzoic acid. Subsequent elution with ethanol–ethyl acetate (1 : 19) afforded the carboxylic acid (11; R = CH_2Ph) as a foam (0.092 g), $\nu_{max.}$ ($CHCl_3$) 3 250br, 1 735, and 1 580br cm^{-1}.

The carboxylic acid was characterised by conversion into the methyl ester. The acid (11; R = CH_2Ph) in dimethylformamide (2 ml) was treated successively with triethylamine (100 μl) and an excess of methyl iodide (200 μl). Stirring was continued at room temperature for 2 h. The mixture was diluted with ethyl acetate, washed with brine and dried. Evaporation and chromatography of the residue gave a foam (0.101 g). Trituration with diethyl ether–hexane (1 : 1) yielded *methyl* 1-[(*benzyloxycarbonyl*)(*triphenylphosphoranylidene*)*methyl*]-2-*oxoazetidin*-4-*ylacetate* as microcrystals (0.083 g), m.p. 112—113 °C, $\nu_{max.}$ 1 740 and 1 610br cm^{-1} (Found: C, 71.8; H, 5.7; N, 2.3; P, 5.5. $C_{33}H_{30}NO_5P$ requires C, 71.9; H, 5.5; N, 2.5; P, 5.6%).

Benzyl 7-*Oxo*-3-[(*methoxycarbonyl*)(*phenyl*)*methyl*]-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (5b; R = CH_2Ph).—The phosphorane-acid (11; R = CH_2Ph) (1.16 g) in dry tetrahydrofuran (20 ml) was treated with triethylamine (0.5 ml) and left at room temperature for 0.5 h. The solution was cooled (−20 °C) and diphenylphosphinyl chloride (0.75 g) in dry tetrahydrofuran (5 ml) was added, and the mixture was stirred at −20 °C for 0.5 h.

A solution of hexamethyldisilazane (0.68 g) in dry tetrahydrofuran (20 ml) at 0 °C was treated with n-butyl-lithium (1.87 ml of a 2.5M-solution in hexane). The solution was cooled to −70 °C and treated with methyl phenylacetate (0.318 g) in dry *N*,*N*-dimethylformamide (1 ml). After 5 min the previously prepared solution of the diphenylphosphinic anhydride was added to this solution, which was left at −70 °C for 2.5 h. The reaction mixture was then diluted with ethyl acetate and washed with brine, and the dried organic phase was evaporated. Chromatography of the residue gave the amorphous phosphorane (12; R = CH_2Ph) (0.556 g), $\nu_{max.}$ 1 740br and 1 640br cm^{-1}.

The phosphorane (12; R = CH_2Ph) (0.328 g) in dry toluene (60 ml) was heated at reflux temperature for 3 h. Evaporation and chromatography (silica gel; finer than 230 mesh) gave a 1 : 1 mixture of the epimers of the *ester* (5b; R = CH_2Ph) (0.025 g), $\lambda_{max.}$ (EtOH) 282 nm (ε 10 000); $\nu_{max.}$ 1 780, 1 730, and 1 610 cm^{-1}; δ 2.24—3.51 (4 H, m, 4-H_2 and 6-H_2), 3.67 (3 H, s, OMe), 3.77—4.31 (1 H, m, 5-H), 5.29 (2 H, s, CH_2Ph), 5.84 (s) and 5.89 (s) (together 1 H, PhC*H*CO_2Me), and 7.10—7.35 (10 H, m, aromatic) (Found: M^+, 391.1378. $C_{23}H_{21}NO_5$ requires *M*, 391.1420). Further elution gave unchanged phosphorane (12; R = CH_2Ph) (0.162 g) which could be recycled.

The 1-azabicycloheptene (5b; R = CH_2Ph) (0.022 g) in dry chloroform (1 ml) was treated with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (0.008 g) for 15 min at room temperature. After dilution with more chloroform the solution was washed with water, dried, and evaporated to dryness. Chromatography of the residue gave benzyl 7-oxo-3-[(methoxycarbonyl)(phenyl)methylene]-1-azabicyclo[3.2.0]heptane-2-carboxylate (30) (0.010 g) as a gum, $\nu_{max.}$ 1 775, 1 738, and 1 718 cm^{-1}; δ 2.10—3.35 (4 H, m, 4-H_2 and 6-H_2), 3.55 (3 H, s, OMe), 3.65—3.95 (1 H, m, 5-H), 5.20 (2 H, s, CH_2-Ph), 5.75 (1 H, s, slightly broadened, 2-H), and 7.35 (10 H, s, Ph) [Found (no M^+): $M^+ - CO_2CH_2Ph$, 256.0983. $C_{15}H_{14}NO_3$ requires 256.0974; $C_{15}H_{14}NO_3 - 42$, 214.0868. $C_{13}H_{12}NO_2$ requires 214.0868].

Benzyl 2-*Oxoazetidin*-4-*ylacetate* (20; R = CH_2Ph).—Potassium permanganate (2.11 g) and 18-crown-6 (0.146 g) were stirred in benzene (20 ml). 4-Allylazetidin-2-one (15) (0.555 g) was added and the reaction left overnight at room temperature. The mixture was filtered and the residual solid carefully treated with a small volume of water to dissolve the potassium salt (20; R = K). Manganese dioxide was separated by filtration and the aqueous filtrate evaporated to dryness and dissolved in *N*,*N*-dimethylformamide (3 ml). Benzyl bromide (0.59 ml) was added and after stirring overnight the mixture was diluted with ethyl acetate and with water. The dried organic phase was evaporated to an oil which was chromatographed to give the *benzyl ester* (20; R = CH_2Ph) (0.154 g), m.p. 93—94 °C (from diethyl ether), $\nu_{max.}$ 3 450, 1 760, and 1 740 cm^{-1}; δ 2.50—2.91 (2 H, m, CH_2CO_2Ph), 2.65 (1 H, dd, *J* 14 and 3 Hz after D_2O exchange, 3-H), 3.18 (1 H, dd, *J* 14 and 6 Hz after D_2O exchange, 3-H), 3.80—4.20 (1 H, m, 4-H), 5.17 (2 H, s, CH_2Ph), 6.30 (1 H, br s, D_2O exch, NH), and 7.36 (5 H, s, Ar) (Found: C, 65.9; H, 6.0; N, 6.4%; M^+ 219.0873. $C_{12}H_{13}NO_4$ requires C, 65.8; H, 5.8; N, 6.4%; *M*, 219.0896).

Potassium permanganate (2.11 g) in water (15 ml) was stirred vigorously with benzene (15 ml), benzyltriethylammonium chloride (0.15 g) and 4-allylazetidin-2-one (0.555 g). After 2 h the mixture was filtered and the residue washed with a little water. The aqueous phase was separated and evaporated to dryness, and the residue dissolved in *N*,*N*-dimethylformamide (3 ml) together with benzyl bromide (0.59 g). After stirring overnight, work-up and chromatography gave crystalline ester (20; R = CH_2Ph) (0.14 g), identical with the material from the previous oxidation.

2-*Oxoazetidin*-4-*ylacetic Acid* (20; R = H).—The benzyl ester (20; R = CH_2Ph) (1.0 g) was hydrogenated over 10% Pd–C (0.01 g) in ethanol (25 ml) for 2 h. The catalyst was removed by filtration through Kieselguhr and the filtrate evaporated to yield the *acid* (20; R = H) (0.6 g), m.p. 120—126 °C, $\nu_{max.}$ (KBr) 3 230, 3 000br, 1 745, and 1 690 cm^{-1}; δ[$(CD_3)_2SO$] 2.51 (2 H, d, *J* 6 Hz, CHCH_2CO_2H), 2.48 (1 H, dd, *J* 14 and 2 Hz, 3-H), 2.93 (1 H, dd, *J* 14 and 5 Hz after D_2O exchange, 3-H), 3.55—3.85 (1 H, m, 4-H), and 7.85 (1 H, br s, NH, exchangeable) (Found: C, 46.9; H, 5.9; N, 10.5. $C_5H_7NO_2$ requires C, 46.5; H, 5.4; N, 10.9%).

t-Butyl [4-(*But*-3-*enyl*)-2-*oxoazetidin*-1-*yl*]*triphenylphosphoranylideneacetate* (13; R = Bu^t).—A solution of 4-(but-3-enyl)azetidin-2-one (17) (3.5 g) and t-butyl glyoxylate (8.3 g) in dry benzene (60 ml) was heated at reflux in an apparatus with provision for water removal for 4 h. The product was concentrated and then chromatographed to give the alcohol as a gum, $\nu_{max.}$ 3 500, 1 755, 1 730, and 1 640 cm^{-1}. This was dissolved in dry tetrahydrofuran (200 ml) and cooled

to −20 °C under argon. It was treated successively with pyridine (6.6 ml) and thionyl chloride (5.8 ml) and a period of 1 h was allowed for reaction. The resulting mixture was filtered and the filtrate concentrated and re-evaporated from toluene to produce the chloride as a yellow gum, $\nu_{max.}$ 1 760 and 1 635 cm^{-1}. This was put under high vacuum for 0.5 h and then immediately dissolved in dry dioxan (150 ml) and stirred under argon. Triphenylphosphine (21.0 g) and 2,6-lutidine (9.6 ml) were added and the mixture maintained at room temperature for 20 h. The product was concentrated and chromatographed to give a material which was crystallised from ethyl acetate–light petroleum. The crystalline solid (4.77 g) was a 2 : 1 mixture of the phosphorane (13) and triphenylphosphine oxide, $\nu_{max.}$ 1 730 and 1 635 cm^{-1}. This contaminated phosphorane was suitable for further manipulations.

t-Butyl 8-Oxo-1-azabicyclo[4.2.0]*oct-2-ene-2-carboxylate* (6; R = Bu^t).—An ethyl acetate (50 ml) solution of the impure phosphorane (13; R = Bu^t) (1.00 g) was cooled to 0 °C and treated with trifluoroacetic acid (1.5 ml). It was then stirred and cooled to −70 °C and ozone was bubbled through until the solution just became blue. The excess of ozone was blown off in a stream of argon and the ozonide reduced by addition of triphenylphosphine (0.53 g) in ethyl acetate (2 ml). After 0.5 h the reaction flask was transferred to an ice-bath and the reaction neutralised by addition of saturated aqueous sodium hydrogencarbonate (45 ml). The organic phase was then separated, washed with brine, dried, concentrated, and chromatographed to provide the *azabicyclo-octene* (6; R = Bu^t) (0.16 g), m.p. 109—110 °C (from ethyl acetate–light petroleum); $\lambda_{max.}$ (ethanol) 263 nm (ε 8 530); $\nu_{max.}$ 1 760, 1 710, and 1 630 cm^{-1}; δ_H 1.50 (9 H, s, Bu^t), 1.2—2.4 (4 H, m, 4-H_2 and 5-H_2), 2.56 (1 H, dd, *J* 15 and 2 Hz, 7-H), 3.24 (1 H, dd, *J* 15 and 5 Hz, 7-H), 3.3—3.6 (1 H, m, 6-H), and 6.13 (1 H, dd, *J* 6 and 2.5 Hz, 3-H); δ_C 22.6 (t, C-4 or C-5), 25.9 (t, C-4 or C-5), 28.0 (q, methyls of Bu^t), 44.2 (t, C-7), 46.1 (d, C-6), 82.0 (s, O–C of Bu^t), 121.0 (d, C-3), 130.1 (s, C-2), 161.2 (s, ester C=O), and 164.5 (s, C-8) (Found: C, 64.7; H, 7.7; N, 6.2%; M^+, 223.1207. $C_{12}H_{17}NO_3$ requires C, 64.6; H, 7.7; N, 6.3%; *M*, 223.1208).

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