Synthesis of a Cyclobutanone Analogue of a β-Lactam Antibiotic

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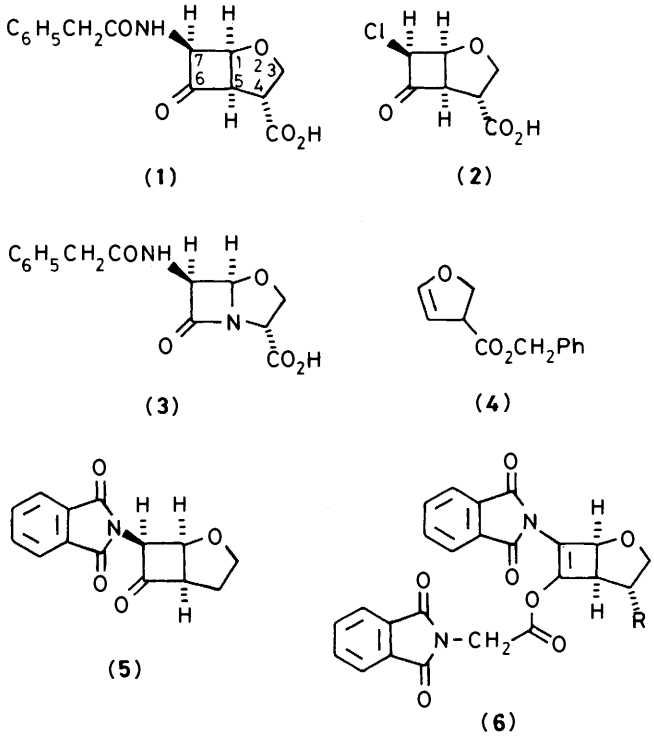
A route has been developed which allows cyclobutanone analogues of β-lactam antibiotics to be synthesized and is illustrated by the synthesis of 6-oxo-7β-phenylacetamido-2-oxabicyclo-[3.2.0]heptane-4α-carboxylic acid. Although this analogue (which contained some 7α-epimer) did not show significant antibacterial activity it was a weak inhibitor of *Streptomyces* R61 D,D-carboxypeptidase and a time-dependent inhibitor of *E.coli* R-TEM and *B. cereus* type I β-lactamases. 7β-Chloro-6-oxo-2-oxabicyclo[3.2.0]heptane-4α-carboxylic acid also exhibited time-dependent inhibition of these β-lactamases.

The extensive use of penicillins and other β-lactam antibiotics over the past forty years has led to an ever increasing number of resistant bacteria.[1] Bacterial resistance toward penicillin was first recognised even before the structure of the antibiotic had been elucidated,[2] and it was subsequently shown that with this and other β-lactam antibiotics resistance usually arises by the bacterium acquiring the ability to produce a β-lactamase either by mutation or by transfer of a plasmid-encoded gene from a resistant organism.[1,3] In order to combat resistant pathogenic bacteria three approaches have been adopted. First, the search for new β-lactam antibiotics has continued and by using ingenious assay techniques several new classes have been detected and isolated. Secondly, modification by chemical methods of natural antibiotics has given rise to a host of semisynthetic products. Thirdly, new classes of β-lactam antibacterial agents have been obtained by total synthesis.[4] All of these new antibacterial agents, however, retain the β-lactam ring and it seems almost inevitable that after extensive use of these new β-lactam antibacterial agents resistant bacteria will arise.

In an attempt to overcome this seemingly endless battle, we have initiated a programme designed to investigate the possibility of replacing the β-lactam ring in this class of antibacterial agents by some other functionality. In this our initial approach, reported previously in preliminary form,[5] we chose to synthesize analogues of the penicillins in which the β-lactam ring was replaced by cyclobutanone. The target molecules chosen for study were the 2-oxabicyclo[3.2.0]heptan-6-ones (**1**) and (**2**). The 7-phenylacetamido derivative (**1**) is a close analogue of 1-oxabisnorpenicillin G (**3**),[6] which is known to be an active antibiotic *in vivo*.

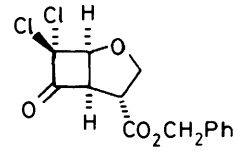
Cyclobutanones are very susceptible to nucleophilic addition, consequently, a cyclobutanone analogue of a β-lactam antibiotic should form a tetrahedral adduct with an active-site serine or cysteine residue. Thus if the cyclobutanone analogue (**1**) retains compatibility with the active site of the bacterial transpeptidases and D,D-carboxypeptidases involved in cell wall biosynthesis,[4] it would be expected to form a ketonic hemiacetal with the active-site functional group. Moreover this covalent adduct should be structurally similar to the tetrahedral intermediates that are likely to be formed when the nascent peptidoglycan chains of the natural substrate are cross-linked by the bacterial transpeptidases or trimmed by the bacterial D,D-carboxypeptidases. Since such intermediates are likely to be close in energy to the transition states leading to them, by Hammond's postulate they should be close in structure also. Now enzymes achieve catalysis, at least in part, by stabilizing transition states[7] and hence there is reason to expect that if a ketonic hemiacetal is formed between a cyclobutanone analogue and the bacterial transpeptidases and D,D-carboxypeptidases it will be stabilized by these enzymes. We considered



that the cyclobutanone analogue (**1**) might also, for similar reasons, form a tightly bound ketonic hemiacetal with the class A and C β-lactamases (that is those β-lactamases that are known to possess an essential active-site serine residue). The chlorocyclobutanone (**2**) might also inhibit bacterial transpeptidases and D,D-carboxypeptidases as well as β-lactamases in the same way. In addition it seemed possible that the chloroketone would react irreversibly with an active-site functional group, although it was recognised that nucleophilic substitution at carbon in a four-membered ring is generally unfavourable.

Our synthetic strategy to the cyclobutanone analogues (**1**) and (**2**) involved the cycloaddition of a suitably substituted ketene to the ketenophile 2,3-dihydro-3-furoic acid, protected as its benzyl ester (**4**). This ketenophile was readily prepared by the Birch reduction of 3-furoic acid using a modification of the method of Kinoshita *et al.*[8] Reduction with sodium in liquid ammonia in the presence of propan-2-ol, followed by alkylation of the sodium salt with benzyl bromide, gave the benzyl ester (**4**) in 83% yield.

Initially cycloaddition between nitrogen-functionalized ketenes and ketenophiles was investigated in an attempt to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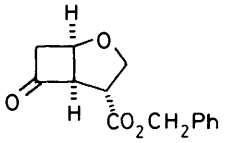
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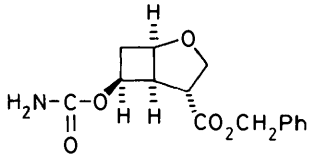
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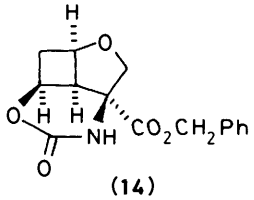
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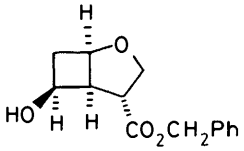
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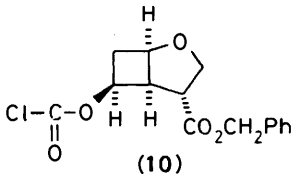
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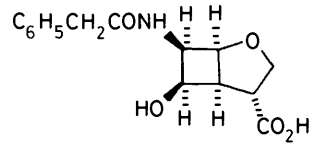
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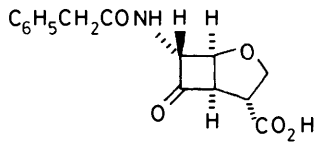
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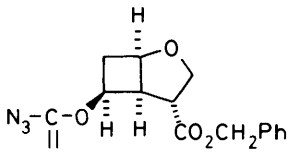
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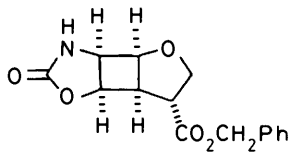
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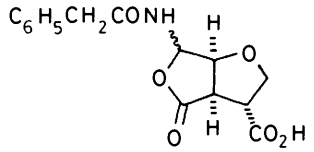
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introduce the amino group, required to form an acylamino side-chain, in a rather direct manner. However, azidoketene generated *in situ* from azidoacetyl chloride and triethylamine gave no detectable cycloadducts with either the model ketenophile, 2,3-dihydrofuran, or its 3-carboxylic ester (**4**), whereas with imines this often constitutes a good route to β-lactams.[9]

Phthalimidoketene, generated *in situ* from phthalimidoacetyl chloride and triethylamine, did react with 2,3-dihydrofuran at 0 °C in methylene dichloride to give the cyclobutanone adduct (**5**) in 40% yield together with 7% of the diphthaloyl adduct (**6**; R = H). The regiochemistry of the cycloaddition leading to the adduct (**5**) was confirmed by selective decoupling experiments and the configuration at C-7 was established by the coupling constants $J_{7,1}$ 5.8 Hz and $J_{7,5}$ 3.9 Hz.[10] The formation of (**6**; R = H) can be rationalized either by acylation of the enolate of adduct (**5**) by phthalimidoketene or phthalimidoacetyl chloride or by an 'ene'-type cycloaddition between (**5**) and phthalimidoketene.

The 2,3-dihydrofuran ester (**4**) failed to react with phthalimidoketene at 0 °C but did react in refluxing benzene–ether to give the diphthalimido adduct (**6**; R = CO_2CH_2Ph) as the sole product. We have noted that the ester (**4**) is generally less reactive than 2,3-dihydrofuran towards a variety of ketenes. This cannot be attributed to a steric factor since cycloaddition occurs at the unhindered face of the heterocycle. We suspect that it may be due to a homoallylic interaction between the olefin and the carbonyl group of the ester thus diminishing the electron density of the olefin at C-4. No trace of the required cyclobutanone could be detected. Attempts to cleave the enol phthalimidoacetate linkage back to the required cyclobutanone were unsuccessful. Presumably the acidity of the C(7)–H bond in the phthalimidocyclobutanone adducts makes them particularly susceptible to formation of these 2:1 adducts. In spite of these observations, the ketene cycloaddition reaction was still deemed to be the simplest route to the bicyclic framework of (**1**) and (**2**) and attention was consequently turned to the highly reactive dichloroketene. The acylamino side-chain would of course have to be introduced by an indirect method at a later stage.

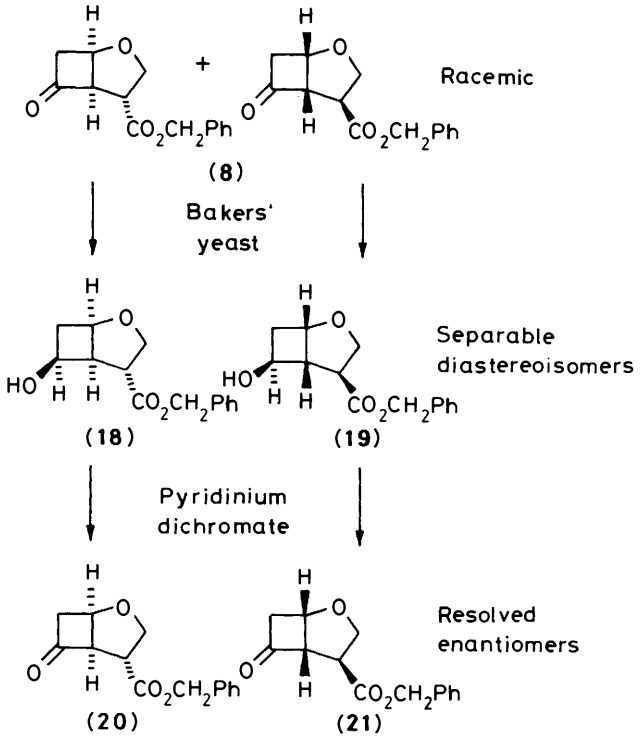
Cycloaddition of (**4**) with dichloroketene (generated *in situ* from dichloroacetyl chloride and triethylamine) in ether at −10 °C gave the required cyclobutanone (**7**) in 59% yield after chromatography and recrystallization. The stereochemistry at C-4 [numbering as in (**1**)] was confirmed by ^{1}H n.m.r. spectroscopy in which 4-H appears as a doublet, coupling only to the *endo* proton on C-3. The lack of any coupling between 4-H and 5-H established the stereochemistry at C-4 since the structure with the *exo* carboxylate is the only one where 4-H and 5-H can achieve a dihedral angle of 90°, consistent with zero coupling. Catalytic hydrogenolysis of (**7**) over palladium–charcoal gave the *endo*-chloroacid (**2**) in 51% isolated yield. The proton at C-7 showed two *cis* couplings to 1-H and 5-H in the ^{1}H n.m.r. spectrum, confirming that the least hindered chlorine atom had been removed selectively. This compound can be regarded as an analogue of the 6β-halogenopenicillanic acids which are known to be potent inactivators of bacterial β-lactamases.[11] Reduction of (**7**) with zinc and acetic acid removed both chlorine atoms, giving the adduct (**8**).

In order to introduce the acylamino side-chain into the cyclobutanone (**8**), a route was devised which involved an intramolecular insertion reaction of an O-acyl nitrene to provide a cyclic carbamate, capable of being hydrolysed to a *cis*-aminoalcohol. Aminoacylation followed by oxidation of the alcohol function should then provide the required acylaminocyclobutanone system. To this end, the cyclobutanone (**8**) was reduced stereospecifically with L-Selectride to provide the *endo*-alcohol (**9**). Treatment of this alcohol with phosgene furnished the chloroformate (**10**) which on reaction with sodium azide in dimethylformamide (DMF) gave the azidoformate (**11**). Azidoformates are known to decompose thermally or photochemically to yield acyl nitrenes capable of inserting into accessible C–H bonds.[12] Thermolysis of the azidoformate (**11**) in methylene dichloride in a sealed glass tube gave a mixture of products from which the desired cyclic carbamate (**12**) could be isolated chromatographically in 29% yield. Two other products were obtained as an inseparable mixture and their structures were assigned on the basis of i.r. and n.m.r. spectroscopy as the acyclic carbamate (**13**) and the six-membered cyclic carbamate (**14**).

Hydrolysis of the cyclic carbamate (**12**) was achieved by refluxing with potassium hydroxide in aqueous dioxane, which also effected the deprotection of the benzyl ester to the free

acid. Aminoacylation with phenylacetyl chloride *in situ* then provided the required 7-*endo*-acylaminoalcohol (**15**) in 52% yield. It is noteworthy that all of the asymmetric centres in (**15**) have been generated stereospecifically. Oxidation of (**15**) to the cyclobutanone proceeded efficiently with pyridine–sulphur trioxide in dimethyl sulphoxide (DMSO) and triethylamine.[13] However, epimerization of the side-chain could not be avoided and the product was a mixture of the epimers (**1**) and (**16**) in the ratio 66:34 as determined by ^{1}H n.m.r. and ^{13}C n.m.r. signal intensities. Attempts to separate the epimers by reverse-phase h.p.l.c. were unsuccessful. The product showed an i.r. band at 1 795 cm^{-1} and a pair of signals in the ^{13}C n.m.r. spectrum at 208.5 and 205.0 p.p.m., thus confirming that the required cyclobutanone system had been obtained. Oxidation of (**15**) with a variety of chromium-based reagents (Jones' reagent,[14] pyridinium dichromate,[15] pyridinium chlorochromate[16]) did not provide the required cyclobutanone, giving instead a mixture of the epimeric lactones (**17**) as the major isolable products. These showed an i.r. band at 1 778 cm^{-1} and a pair of signals in the ^{13}C n.m.r. spectrum at 176.5 and 177.9 p.p.m., corresponding to a γ-lactone carbonyl group. The formation of γ-lactones from the oxidation of cyclobutanols with chromium species is not without precedent,[17] although they are usually minor products unless forcing conditions are used. Moreover the cyclobutanol (**9**) gave no trace of any lactonic products on oxidation with pyridinium dichromate and thus it seems that the acylamino side-chain is assisting the formation of the lactone.

In order to provide an entry into a possible chiral synthesis of (**1**), the reduction of (**8**) was investigated using actively fermenting bakers' yeast (*Saccharomyces cerevisiae*). This was prompted by a report in the literature[18] in which racemic bicyclo[3.2.0]hept-2-en-6-one was reduced in a substrate-non-enantiospecific and a product-enantioselective manner to give diastereoisomeric alcohols of high optical purity. Reduction of (**8**) by yeast proceeded smoothly to give a mixture of two alcohols in 59% isolated yield. [A small amount of 2-(4-hydroxyphenyl)ethanol was also isolated: presumably a product of yeast metabolism]. A portion of the alcohol mixture was separated by preparitive t.l.c. to give pure samples of both alcohols. The less polar alcohol had identical spectroscopic characteristics with those of the product obtained from the L-Selectride reduction of (**8**) and was thus assigned an *endo*-hydroxy group. The more polar alcohol had spectra consistent with the diastereoisomeric *exo*-alcohol. Assuming the yeast reduction gives the (*S*)-configuration at C-6 as precedent suggests,[18,19] the two alcohols can be assigned the structures (**18**) and (**19**) respectively (Scheme). Compound (**18**), which is the one required for subsequent synthesis, was shown to be > 95% optically pure by observation of its ^{1}H n.m.r. spectrum in the presence of the chiral shift reagent tris-(3-trifluoroacetyl-α-camphorato)europium(III).[20] To confirm that the yeast reduction had indeed given the (*S*)-configuration at C-6, the two alcohols (**18**) and (**19**) were oxidised with pyridinium dichromate to give the enantiomeric ketones (**20**) and (**21**). These had i.r. and ^{1}H n.m.r. spectra identical with those of authentic racemic ketone (**8**) but had nearly equal and opposite c.d. spectra; the oxidation product of the *endo*-alcohol (**18**) had a negative c.d. curve, $\Delta\varepsilon_{max.}$ −0.61 at 300 nm, and that of the *exo*-alcohol (**19**) a positive c.d. curve, $\Delta\varepsilon_{max.}$ +0.54 at 300 nm. Although the octant rule was developed in order to interpret the o.r.d. and c.d. spectra of chiral cyclohexanones,[21] application to the chiral cyclobutanones leads to the prediction that (**20**) should have a negative c.d. spectrum and (**21**) should have a positive c.d. spectrum. Thus the c.d. spectra support the assignment of the (1*R*,4*R*,5*R*)-configuration to (**20**) and the (1*S*,4*S*,5*S*)-configuration to (**21**). A chiral synthesis of (**1**) should thus be possible starting with (**18**) and following the route developed above.



Scheme. Microbial resolution of racemic (**8**)

The mixture of compounds (**1**) and (**16**), and compound (**2**), were tested against a number of bacteria (including a range of Gram-positives and Gram-negatives as well as *haemophilis*, *pseudomonads*, and *bacteriodes*) at a maximum concentration of 128 mg l^{-1}. No antibacterial activity was observed. The mixture (**1**) and (**16**) did, however, show weak inhibition of *Streptomyces* R61 D,D-carboxypeptidase with 50% inhibition (I_{50}) at approximately 260 mg l^{-1}. Both the chlorocyclobutanone (**2**) and the mixture of (**1**) and (**16**) show slow, time-dependent inhibition of the *E. coli* RTEM-2 β-lactamase and β-lactamase type I from *B. cereus* strain 568/H. Work is in progress to ascertain the nature of this inhibition.

In summary, a 66:34 epimeric mixture of the 7β- and 7α-phenylacetamido-substituted penicillin analogues (**1**) and (**16**) has been synthesized in ten steps from 3-furoic acid in 1.1% overall yield. Although synthetic approaches to similar target molecules have recently been reported,[22] this is the first example of an analogue of a β-lactam antibiotic which has a cyclobutanone ring, a suitably positioned acid group, and an acylamino side-chain.

Experimental

Where necessary, solvents were dried and purified according to recommended methods.[23] Light petroleum refers to the fraction boiling in the range 40—60 °C. Ether is diethyl ether. Organic solutions were routinely dried over $MgSO_4$ and evaporation refers to solvent removal on a rotary evaporator under reduced pressure. Preparative t.l.c. was performed on 1 mm thick layers of Merck silica gel HF_{254} coated on 20 × 20 cm glass plates. Flash chromatography refers to the method of Still *et al.*[24] The column internal diameters and eluants are as stated. M.p.s were determined on a Kofler block and are uncorrected. B.p.s were recorded as ranges during distillation. I.r. spectra were recorded on a Perkin-Elmer 297 grating spectrophotometer. Routine electron impact and ammonia chemical ionization mass spectra were recorded on a VG Micromass 16 F instrument. Field

desorption and high-resolution ammonia chemical ionization mass spectra were recorded on a VG Analytical ZAB 1F instrument. ^{1}H N.m.r. spectra were recorded on a Bruker WH 300 spectrometer (300 MHz). ^{13}C Spectra were recorded on a Bruker WH 400 (100 MHz), a Bruker WH 300 (75.5 MHz), or a Bruker AM 250 spectrometer (63 MHz). To aid annotation of the n.m.r. spectra, protons on the *exo* and *endo* faces of the bicyclic skeleton are distinguished by adding a prime to the H-atom on the *endo* face. Thus, for example, 3-H_{endo} is termed 3′-H and 3-H_{exo} simply 3-H.

Reaction of Phthalimidoacetyl Chloride with 2,3-Dihydrofuran.—To a stirred solution of phthalimidoacetyl chloride (6.71 g, 30 mmol) and 2,3-dihyrdofuran (2.10 g, 30 mmol) in dry methylene dichloride (30 ml) at 0 °C was added dropwise a solution of triethylamine (3.04 g, 30 mmol) in dry methylene dichloride (30 ml) during 1 h. The mixture was stirred at 0 °C for a further 1.5 h and at room temperature for 0.5 h. The solution was diluted with water (60 ml), the organic phase was separated, and the aqueous phase was extracted with methylene dichloride (60 ml). The combined organic phases were washed successively with saturated aqueous sodium hydrogen carbonate (3 × 50 ml), water (50 ml), and brine (50 ml) and the organic phase was dried and evaporated to give a yellow solid (7.72 g). One crystallization from chloroform–hexane gave a white solid (4.68 g). T.l.c. analysis [ethyl acetate–light petroleum (1:1 v/v)] showed two spots at R_F 0.30 and 0.35. Flash chromatography of a 350 mg portion [30 mm; ethyl acetate–light petroleum (1:1 v/v)] gave the *phthalimidoketone* (**5**) (230 mg, 40%) followed by the *diphthaloyl adduct* (**6**; R = H) (70 mg, 7%). Compound (**5**) had m.p. 157—160 °C (from benzene–hexane) (Found: C, 65.5; H, 4.4; N, 5.3. $C_{14}H_{11}NO_4$ requires C, 65.36; H, 4.31; N, 5.45%); $\nu_{max.}$($CHCl_3$) 1 725 and 1 780 (cyclic imide) and 1 805 cm^{-1} (cyclobutanone); δ_H (300 MHz; $CDCl_3$) 7.87 (2 H, m, ArH), 7.76 (2 H, m, ArH), 5.21 (2 H, br, 6 lines, 1- and 7-H), 4.27 (1 H, ddd, $J_{3',3}$ 9.5, $J_{3',4'}$ 7.7, and $J_{3',4'}$ 3.2 Hz, 3′-H), 4.10 (2 H, m, 3- and 5-H), 2.28 (1 H, m, 4′-H), and 2.13 (1 H, m, 4-H); δ_H (300 MHz; C_6D_6) includes 4.97 (1 H, dd, $J_{7,1}$ 5.8 and $J_{7,5}$ 3.9 Hz, 7-H) and 4.51 (1 H, dd, $J_{1,5}$ 9.9 and $J_{1,7}$ 5.8 Hz, 1-H); *m/z* (electron impact) 257 (M^+, 31%), 187 (69), 132 (48), 104 (82) and 69 (100). Compound (**6**; R = H) had m.p. 213—216 °C (from benzene–hexane) (Found: C, 65.0; H, 3.65; N, 6.1. $C_{24}H_{16}N_2O_7$ requires C, 64.86; H, 3.63; N, 6.31%); $\nu_{max.}$($CDCl_3$) 1 730br and 1 780br cm^{-1} (cyclic imides); δ_H (300 MHz; $CDCl_3$) 7.80 (8 H, m, ArH), 5.44 (1 H, d, $J_{1,5}$ 3.3 Hz, 1-H), 4.63 and 4.65 (2 H, ABq, *J* 17.6 Hz, O·CO·CH_2), 4.05 (2 H, m, 3- and 3′-H), 3.73 (1 H, dd, $J_{5,4}$ 7.3 and $J_{5,1}$ 3.3 Hz, 5-H), 2.05 (1 H, dd, $J_{4',4}$ 12.9 and $J_{4',3}$, 4.8 Hz, 4′-H), and 1.68 (1 H, m, 4-H); *m/z* (electron impact) 444 (M^+, 2%), 257 (8), and 200 (100).

Benzyl 2,3-Dihydro-3-furoate (**4**).—The title compound was prepared by modification of the method of Kinoshita, Miyano, and Miwa.[8]

To freshly distilled, stirred pre-dried ammonia (350 ml) under reflux was added sequentially 3-furoic acid (3.50 g, 40 mmol), propan-2-ol (19.2 g, 320 mmol) and sodium (2.76 g, 120 mg-atom) in the form of small pellets. The mixture was stirred for 2 h by which time the initially formed deep-blue colour was discharged. Following evaporation of the ammonia at room temperature overnight, the residue was taken up in water (100 ml) and extracted with ether (3 × 50 ml). The aqueous phase was adjusted to pH 8 by bubbling through it a stream of carbon dioxide gas, and was then evaporated to dryness. The solid residue was taken up in DMF (50 ml) and water (15 ml) and potassium carbonate (8.29 g, 60 mmol) were added. A solution of freshly distilled benzyl bromide (6.18 g, 36 mmol) in DMF (60 ml) and water (10 ml) was then added in one portion and the mixture was stirred for 48 h. The solvents were evaporated under reduced pressure and the residue was partitioned between water (100 ml) and ether (3 × 75 ml). The combined ethereal extracts were washed with brine (100 ml), dried, and evaporated to yield the title compound (**4**) (6.13 g, 83% based on benzyl bromide) as a pale yellow mobile oil which was sufficiently pure for the next stage of the synthesis, b.p. 98—101 °C at 0.3 mmHg (Found: C, 70.5; H, 6.0. $C_{12}H_{12}O_3$ requires C, 70.57; H, 5.92%); $\nu_{max.}$($CHCl_3$) 1 735 (ester C=O) and 1 620 cm^{-1} (C=C); δ_H (300 MHz; $CDCl_3$) 7.37 (5 H, m, ArH), 6.43 (1 H, t, $J_{5,4}$ and $J_{5,3}$ 2.6 Hz, 5-H), 5.17 (2 H, q, *J* 11 Hz, $PhCH_2$), 5.07 (1 H, t, $J_{4,5}$ and $J_{4,3}$ 2.6 Hz, 4-H), 4.71 (1 H, dd, $J_{2',2}$ 9.2 and $J_{2',3}$ 6.7 Hz, 2′-H), 4.43 (1 H, dd, $J_{2,2'}$ 9.2 and $J_{2,3}$ 10.8 Hz, 2-H), and 3.86 (1 H, ddt, $J_{3,2}$ 10.8, $J_{3,2'}$ 6.7, $J_{3,4}$ and $J_{3,5}$ 2.6 Hz, 3-H).

Reaction of Phthalimidoacetyl Chloride with Benzyl 2,3-Dihydro-3-furoate (**4**).—To a stirred, refluxing solution of phthalimidoacetyl chloride (1.118 g, 5 mmol) and benzyl 2,3-dihydro-3-furoate (**4**) (1.021 g, 5 mmol) in benzene (25 ml) and ether (25 ml) was added a solution of triethylamine (0.506 g, 5 mmol) in ether (30 ml) dropwise during 0.5 h, during which time a fine white precipitate was deposited. The mixture was diluted with water (50 ml), the organic phase was separated, and the aqueous phase was extracted with ether (50 ml). The combined organic phases were washed successively with saturated aqueous sodium hydrogen carbonate (3 × 50 ml), water (50 ml), and brine (50 ml), and the organic phase was dried and evaporated to give a yellow oil (1.30 g). T.l.c. analysis [ethyl acetate–light petroleum, (6:4 v/v)] showed one major new component plus baseline material. Flash chromatography of 500 mg [30 mm; ethyl acetate–light petroleum (6:4 v/v)] gave the *diphthaloyl adduct* (**6**; R = CO_2CH_2Ph) (305 mg, 28%), m.p. 173—175 °C (from ethyl acetate–hexane) (Found: C, 66.1; H, 3.9; N, 4.6. $C_{32}H_{22}N_2O_9$ requires C, 66.43; H, 3.83; N, 4.84%); $\nu_{max.}$($CHCl_3$) 1 725, 1 735sh, 1 775, and 1 785sh cm^{-1} (cyclic imides); δ_H (300 MHz; $CDCl_3$) 7.80 (8 H, m, phthaloyl aromatics), 7.35 (5 H, m, benzyl aromatics) 5.37 (1 H, d, $J_{1,5}$ 3.1 Hz, 1-H), 5.16 (2 H, s, $PhCH_2$), 4.66 (2 H, s, O·CO·CH_2), 4.46 (1 H, d, $J_{3,3'}$ 9.7 Hz, 3-H), 4.25 (1 H, dd, $J_{3',3}$ 9.7 and $J_{3',4'}$ 5.7 Hz, 3′-H), 4.12 (1 H, d, $J_{5,1}$ 3.1 Hz, 5-H), and 3.25 (1 H, d, $J_{4',3'}$ 5.7 Hz, 4′-H); *m/z* (field desorption) 578 (M^+).

(1α,4α,5α)-4-*Benzyloxycarbonyl*-7,7-*dichloro*-2-*oxabicyclo*-[3.2.0]*heptan*-6-*one* (**7**).—To a stirred solution of dichloroacetyl chloride (6.63 g, 45 mmol) and benzyl 2,3-dihydro-3-furoate (**4**) (6.13 g, 30 mmol) in dry ether (150 ml) at −10 °C was added dropwise a solution of triethylamine (4.55 g, 45 mmol) in dry ether (100 ml) during 2 h. The mixture was stirred for 1 h below 0 °C, the precipitated salts were removed by filtration, and the filter cake was washed with ether (100 ml). The combined ethereal solution was washed successively with water (100 ml), saturated aqueous sodium hydrogen carbonate (2 × 100 ml), and brine (100 ml), dried, and evaporated to give a brown oil (10.46 g). Flash chromatography [50 mm; light petroleum–methylene dichloride (1:1 v/v)] gave the title compound (**7**) (7.05 g) as a pale-yellow oil, which crystallized with time. Recrystallization from hexane gave *white needles* (4.97 g, 53%), m.p. 63 °C. The concentrated mother liquors gave a second crop (0.56 g, 6%), m.p. 63 °C (Found: C, 53.4; H, 3.7; Cl, 22.3. $C_{14}H_{12}Cl_2O_4$ requires C, 53.35; H, 3.84; Cl, 22.50%); $\nu_{max.}$($CHCl_3$) 1 735 (ester) and 1 810 cm^{-1} (cyclobutanone); δ_H (300 MHz; $CDCl_3$) 7.38 (5 H, m, ArH), 5.18 (2 H, s, $PhCH_2$), 4.95 (1 H, d, $J_{1,5}$ 5.9 Hz, 1-H), 4.69 (1 H, d, $J_{5,1}$ 5.9 Hz, 5-H), 4.53 (1 H, d, $J_{3,3'}$ 9.9 Hz, 3-H), 4.11 (1 H, dd, $J_{3',3}$ 9.9 and $J_{3',4'}$ 6.3 Hz, 3′-H), and 3.47 (1 H, d, $J_{4',3'}$ 6.3 Hz, 4′-H); δ_C (75.5 MHz; $CDCl_3$) 194.6 (s, C-6), 169.9 (s, ester C=O), 134.9, 128.7, and 128.3 (aromatics), 87.2 (s, C-7), 82.7 (d, C-1), 72.5 (t, C-3), 67.7 (t, $PhCH_2$), 63.9 (d, C-5), and 46.9 (d, C-4); *m/z* (ammonia chemical ionization) 332, 334, and 336 [$(M + NH_4)^+$, chlorine isotopes].

(1α,4α,5α,7β)-4-*Carboxy*-7-*chloro*-2-*oxabicyclo*[3.2.0]*heptan*-6-*one* (**2**).—A 500 ml round-bottomed hydrogenation flask with a side-arm inlet was charged with 10% palladium–charcoal dry powder (1.0 g) and ethyl acetate (50 ml). The suspension was stirred, degassed with a water aspirator, and flushed with hydrogen gas (5 ×). A solution of the dichloroketone (**7**) (9.45 g, 30 mmol) in ethyl acetate (100 ml) was added *via* the side-arm and the hydrogenation was allowed to proceed at room temperature, under a slight positive pressure of hydrogen, while the solution was vigorously stirred. When 2 equiv. of hydrogen (60 mmol, 1 344 cm^3 at S.T.P.) had been taken up (about 4 h) the hydrogenation was stopped and the mixture was filtered through a Whatman GF/C glass microfibre filter paper. The clear filtrate was evaporated and the clear, oily residue was dissolved in ether (100 ml) and light petroleum (100 ml). The solution was kept at 4 °C overnight to give the *title compound* (**2**) (2.93 g, 51%) as white needles, m.p. 125—131 °C (decomp.) (Found: C, 43.9; H, 3.8; Cl, 18.5. $C_7H_7ClO_4$ requires C, 44.11; H, 3.70; Cl, 18.6%); $\nu_{max.}$(CH_3CN) 2 800—3 500br (acid OH), 1 800 (cyclobutanone), and 1 740 cm^{-1} (acid); δ_H (300 MHz; CD_3CN) 5.12 (1 H, dd, $J_{7,1}$ 5.9 and $J_{7,5}$ 4.5 Hz, 7-H), 4.99 (1 H, t, $J_{1,7}$ and $J_{1,5}$ 5.9 Hz, 1-H), 4.33 (1 H, dd, $J_{3,3'}$ 9.7 and $J_{3,4'}$ 1.0 Hz, 3-H), 4.27 (1 H, ddd, $J_{5,1}$ 5.9, $J_{5,7}$ 4.5, and $J_{5,4'}$ 1.0 Hz, 5-H), 3.92 (1 H, dd, $J_{3',3}$ 9.7 and $J_{3',4'}$ 6.1 Hz, 3′-H), and 3.34 (1 H, br d, $J_{4',3'}$ 6.1, $J_{4',3}$, and $J_{4',5}$ 1.0 Hz, 4′-H); δ_C (63 MHz; CD_3CN) 204.0 (s, C-6), 172.5 (s, CO_2H), 74.7 (d, C-1), 72.7 (t, C-3), 65.7 (d, C-5 or C-7), 64.1 (d, C-7 or C-5), and 48.0 (d, C-4); *m/z* (overloaded electron impact) 190 and 192 (M^+, chlorine isotopes); *m/z* (electron impact) 127 (20%), 113 (55), and 69 (100).

(1α,4α,5α)-4-*Benzyloxycarbonyl*-2-*oxabicyclo*[3.2.0]*heptan*-6-*one* (**8**).—The dichloroketone (**7**) (8.32 g, 26.4 mmol) was dissolved in glacial acetic acid (100 ml) and the solution was stirred in a preheated oil-bath at 50 °C. Zinc powder (8.63 g, 132 mg-atom) was added portionwise during 5 min and the mixture was stirred at 50 °C for 45 min and at room temperature for 15 min. The excess of zinc and zinc salts were filtered off and washed with glacial acetic acid (50 ml). The filtrate was evaporated under reduced pressure and the residue was taken up in ethyl acetate (200 ml). This solution was washed successively with water (100 ml), saturated aqueous sodium hydrogen carbonate (3 × 100 ml), and brine (100 ml), dried and evaporated to yield a colourless oil (6.50 g). Flash chromatography [50 mm; ethyl acetate–light petroleum (5:95 v/v)] gave the *title compound* (5.70 g, 88%) as an oil after being dried *in vacuo* over phosphorus pentaoxide. The product crystallized overnight at −20 °C, but melted on rewarming to room temperature [Found: C, 68.1; H, 5.85% ($M + 1$)$^+$ (ammonia chemical ionization mass spectrum), 247.0969. $C_{14}H_{14}O_4$ requires C, 68.28; H, 5.73%; ($M + 1$), 247.0970]; $\nu_{max.}$($CDCl_3$) 1 785 (cyclobutanone) and 1 735 cm^{-1} (ester); δ_H (300 MHz; $CDCl_3$) 7.25 (5 H, m, ArH), 5.14 (2 H, s, PhCH_2), 5.00 (1 H, dt, $J_{1,5}$ and $J_{1,7}$ 5.9 Hz and $J_{1,7'}$ 2.2 Hz, 1-H), 4.36 (1 H, dd, $J_{3,3'}$ 9.7 and $J_{3,4'}$ 2.7 Hz, 3-H), 4.23 (1 H, m, 5-H), 4.12 (1 H, dd, $J_{3',3}$ 9.7 and $J_{3',4'}$ 6.4 Hz, 3′-H), 3.34 (1 H, dd, $J_{4',3}$ 6.4 and $J_{4',3}$ 2.7 Hz, 4′-H), 3.28 (1 H, ddd, $J_{7,7'}$ 18.9, $J_{7,1}$ 5.9, and $J_{7,5}$ 5.0 Hz, 7-H), and 2.93 (1 H, ddd, $J_{7',7}$ 18.9, $J_{7',5}$ 2.9, and $J_{7',1}$ 2.2 Hz, 7′-H); δ_C (75.5 MHz; $CDCl_3$) 207.3 (s, C-6), 170.9 (s, ester C=O), 135.3, 128.6, 128.4, and 128.1 (aromatics), 70.9 (t, C-3), 70.6 (d, C-1), 67.6 (d, C-5), 67.1 (t, $PhCH_2$), 52.8 (t, C-7), and 46.6 (d, C-4); *m/z* (ammonia chemical ionization) 247 [($M + H$)$^+$] and 264 [(M + NH_4^+)].

(1α,4α,5α,6β)-4-*Benzyloxycarbonyl*-2-*oxabicyclo*[3.2.0]-*heptan*-6-*ol* (**9**).—To a stirred solution of lithium tri-s-butylborohydride ('L-Selectride') [1M solution in tetrahydrofuran (THF); 26.4 mmol] at −78 °C was added a solution of the cyclobutanone (**8**) (3.24 g, 13.2 mmol) in THF (50 ml) dropwise during 0.5 h, under nitrogen. The mixture was stirred at −78 °C for 45 min and 2.5M aqueous sodium hydroxide (16 ml) was then added, followed immediately by 30% aqueous hydrogen peroxide (16 ml). The cooling bath was removed, and the mixture was stirred vigorously and allowed to warm up for 20 min. 1M Hydrochloric acid (160 ml) was added, followed by ether (150 ml), and the mixture was stirred for 5 min. The ethereal layer was separated and the aqueous layer was re-extracted with ether (150 ml). The combined ethereal extracts were washed with brine (150 ml), dried, and evaporated to leave a colourless oil (2.793 g). Flash chromatography [50 mm, ethyl acetate–methylene dichloride (3:7 v/v)] gave the *title compound* (1.940 g, 59%) as an oil after being dried *in vacuo* over phosphorus pentaoxide [Found: ($M + 1$)$^+$ (ammonia chemical ionization mass spectrum), 249.1124. $C_{14}H_{16}O_4$ requires (M + 1), 249.1127]; $\nu_{max.}$($CHCl_3$) 3 610 (OH) and 1 730 cm^{-1} (ester); δ_H (300 MHz; $CDCl_3$) 7.35 (5 H, m, ArH), 5.12 (2 H, s, PhCH_2), 4.46 (1 H, br q, 1-H), 4.38 (1 H, dd, $J_{3,3'}$ 9.5 and $J_{3,4'}$ 2.3 Hz, 3-H), 4.26 (1 H, m, simplified with D_2O to a br q, 6-H), 4.13 (1 H, dd, $J_{3',3}$ 9.5 and $J_{3',4'}$ 6.6 Hz, 3′-H), 3.44 (1 H, m, 5-H), 3.43 (1 H, dd, $J_{4',3'}$ 6.6 and $J_{4',3}$ 2.3 Hz, 4′-H), 2.66 (1 H, dddd, $J_{7,7'}$ 14.3, J 8.1, 6.2, and 3.2 Hz, 7-H), 2.52 (1 H, d, removed with D_2O, $J_{OH,6}$ 4.1 Hz, OH), and 1.88 (1 H, dddd, $J_{7',7}$ 14.3, J 5.9, 3.9, and 1.3 Hz, 7′-H); δ_C (75.5 MHz; $CDCl_3$) 173.7 (s, C=O), 135.7, 128.6, 128.3, and 128.1 (aromatics), 73.1 (d, C-1), 70.0 (t, C-3), 66.7 (t, $PhCH_2$), 60.2 (d, C-6), 50.1 (d, C-4 or C-5), 42.7 (d, C-5 or C-4), and 37.5 (t, C-7); *m/z* (ammonia chemical ionization) 249 [(M + H)$^+$] and 266 [(M + NH_4)$^+$].

(1α,4α,5α,6β)-4-*Benzyloxycarbonyl*-2-*oxabicyclo*[3.2.0]-*heptan*-6-*yl Chloroformate* (**10**).—The cyclobutanol (**9**) (1.94 g, 6.24 mmol) and pyridine (1.20 ml, 14.8 mmol) were dissolved in benzene (100 ml) and the solution was stirred at room temperature. Phosgene gas was bubbled through the solution for 1.5 h during which time a precipitate of pyridine hydrochloride was formed. The mixture was quickly washed successively with water (2 × 75 ml) and brine (75 ml) and the organic solution was dried and evaporated to give the title compound (**10**) (2.348 g, 97%) as a white, crystalline solid after being dried *in vacuo* over phosphorus pentaoxide. The material was used without further purification for the next stage of the synthesis. The product had m.p. 57—58 °C (from methylene dichloride–hexane) (Found: C, 58.25; H, 4.9. $C_{15}H_{15}ClO_5$ requires C, 57.98; H, 4.87%); $\nu_{max.}$($CHCl_3$) 1 770 (chloroformate) and 1 735 cm^{-1} (ester); δ_H (300 MHz; $CDCl_3$) 7.35 (5 H, m, ArH), 5.15 (2 H, s, PhCH_2), 5.10 (1 H, m, 6-H), 4.57 (1 H, m, 1-H), 4.44 (1 H, dd, $J_{3,3'}$ 9.5 and $J_{3,4'}$ 2.3 Hz, 3-H), 4.18 (1 H, dd, $J_{3',3}$ 9.5 and $J_{3',4'}$ 6.6 Hz, 3′-H), 3.77 (1 H, m, 5-H), 3.27 (1 H, dt, $J_{4',3'}$ 6.6, $J_{4',3}$ and $J_{4',5}$ 2.3 Hz, 4′-H), 2.86 (1 H, dddd, $J_{7,7'}$ 15.1, J 8.1, 6.1, and 3.3 Hz, 7-H), and 2.19 (1 H, dddd, $J_{7',7}$ 15.1, J 5.9, 3.9, and 1.3 Hz, 7′-H); *m/z* (ammonia chemical ionization) 311 [(M + H)$^+$] and 328 and 330 [(M + NH_4)$^+$, chlorine isotopes].

(1α,4α,5α,6β)-4-*Benzyloxycarbonyl*-2-*oxabicyclo*[3.2.0]-*heptan*-6-*yl Azidoformate* (**11**).—To a stirred solution of the chloroformate (**10**) (2.348 g, 7.55 mmol) in dry DMF (50 ml) was added sodium azide (2.348 g, 36.1 mmol) in one portion at room temperature. After 2 h the mixture was diluted with water (150 ml) and extracted with ether (2 × 100 ml). The combined ethereal extracts were washed successively with water (75 ml) and brine (2 × 75 ml), dried, and evaporated to give a pale-yellow oil (2.215 g). T.l.c. analysis [ethyl acetate–methylene dichloride (5:95 v/v)] showed 2 well separated spots. Flash chromatography [50 mm; ethyl acetate–methylene dichloride (5:95 v/v, followed by 2:8 v/v)] gave the title compound (**11**)

(1.550 g, 65%) as an oil, followed by the cyclobutanol (**9**) (413 mg, 22%) also as an oil. The cyclobutanol (**9**) had identical t.l.c., i.r., and ^{1}H n.m.r. characteristics with those of an authentic sample. The azidoformate (**11**) had $\nu_{max.}$($CHCl_3$) 2 135 and 2 185 (azide), 1 730 and 1 735sh cm^{-1} (azidoformate and ester); δ_H (300 MHz; $CDCl_3$) 7.35 (5 H, m, ArH) 5.15 (2 H, s, PhCH_2), 5.03 (1 H, m, 6-H), 4.56 (1 H, m, 1-H), 4.41 (1 H, dd, $J_{3,3'}$ 9.5 and $J_{3,4'}$ 2.3 Hz, 3-H), 4.15 (1 H, dd, $J_{3',3}$ 9.5 and $J_{3',4'}$ 6.6 Hz, 3'-H), 3.75 (1 H, m, 5-H), 3.23 (1 H, dt, $J_{4',3'}$ 6.6, $J_{4',3}$ and $J_{4',5}$ 2.3 Hz, 4'-H), 2.84 (1 H, dddd, $J_{7,7'}$ 14.9, J 8.4, 6.1, and 3.3 Hz, 7-H), and 2.12 (1 H, dddd, $J_{7',7}$ 14.9, J 5.9, 3.8, and 1.3 Hz, 7'-H); *m/z* (ammonia chemical ionization) 318 [$(M + H)^+$] and 335 [$(M + NH_4)^+$].

(1α,4α,5α,6β,7β)-7-*Amino*-4-*benzyloxycarbonyl*-2-*oxabicyclo*[3.2.0]*heptan*-6-*ol Cyclic Carbamate* {(1α,2α,6α,7α,10α)-10-*Benzyloxycarbonyl*-3,8-*dioxa*-5-*azatricyclo*[5.3.0.$0^{2,6}$]*decan*-4-*one*} (**12**).—The azidoformate (**11**) (223 mg) was dissolved in dry methylene dichloride (12 ml) and introduced into a Carius tube (1 cm internal diameter, 20 ml capacity). The tube was sealed with a septum cap and the solution was purged with dry nitrogen for 15 min. The contents were then frozen in liquid nitrogen and the tube was sealed in a hot flame. The mixture was thermolysed in a Carius oven at 130—135 °C for 3.5 h and allowed to cool overnight. The resulting pale-brown solution was evaporated to give a brown oil (220 mg) which t.l.c. analysis [ethyl acetate-methylene dichloride (1 : 1 v/v)] indicated to be 3 major components plus baseline material and minor shadows. The three major resolved spots had R_F 0.69, 0.40, and 0.34. Flash chromatography [20 mm; ethyl acetate–methylene dichloride (1 : 1 v/v)] gave the following fractions: (A) a pale-brown oil (53 mg), R_F 0.69; (B) a pale-yellow oil (32 mg), R_F 0.40; (C) a pale-yellow oil (79 mg), R_F 0.40 and 0.34; this was separated by preparative t.l.c. [ethyl acetate–methylene dichloride (3 : 7 v/v), 3 elutions] into distinct bands which were isolated to give (D) an oil (19 mg), R_F 0.40 and (E) another oil, which solidified with time (59 mg), R_F 0.34. Fraction A was identified as a mixture of unchanged azidoformate (**11**) and a small amount of the cyclobutanone (**8**) by comparative t.l.c., i.r., and ^{1}H n.m.r. spectroscopy. Fractions B and D appeared identical and homogeneous on t.l.c. However, they gave similar but complex spectra, thus indicating 2 components to be present in the approximate proportions 3:1; $\nu_{max.}$($CHCl_3$) 3 540, 3 430, 1 735sh, and 1 730 cm^{-1}; δ_H (300 MHz; $CDCl_3$) very complex but includes 4.39 (dd, J 9.2 and 2.1 Hz), 4.17 (d, J 10 Hz), 4.14 (dd, J 9.2 and 6.7 Hz), 4.03 (d, J 10 Hz), 2.88 (m), 2.78 (m), and 1.05 (m). These data are consistent with the 2 products being the acyclic carbamate (**13**) and the cyclic carbamate (**14**) from nitrene insertion into the C(4)–4'-H bond. Fraction E was homogeneous on t.l.c. and gave clean spectra indicative of the *title cyclic carbamate* (**12**) (59 mg, 29%), m.p. 87—88 °C (from methylene dichloride–hexane) (Found: C, 61.9; H, 5.3; N, 4.8. $C_{15}H_{15}NO_5$ requires C, 62.28; H, 5.23; N, 4.84%); $\nu_{max.}$($CHCl_3$) 3 460 (NH), 1 760 (cyclic carbamate), and 1 735 cm^{-1} (ester); δ_H* (300 MHz; $CDCl_3$) 7.35 (5 H, m, ArH), 5.88 (1 H, br s, NH), 5.14 (2 H, s, PhCH_2), 5.05 (1 H, ddd, J 7.1, 6.0, and 2.7 Hz, 1-H or 6-H), 4.62 (1 H, br quintet, $J \sim 6$, 3, and 3 Hz, 6-H or 1-H), 4.41 (1 H, dd, $J_{3',3}$ 9.5 and $J_{3',4'}$ 7.6 Hz, 3'-H), 4.34 (1 H, dd, $J_{3,3'}$ 9.5 and $J_{3',4'}$ 4.1 Hz, 3-H), 4.31 (1 H, m, simplified on decoupling at δ_H 5.88, 7-H), 3.69 (1 H, m, 5-H), and 3.60 (1 H, ddd, $J_{4',3'}$ 7.6, $J_{4',3}$ 4.1, and $J_{4',5}$ 2.1 Hz, 4'-H); δ_C (63 MHz; $CDCl_3$) 172.2 (s, ester C=O), 160.5 (s, cyclic carbamate C=O), 135.3, 128.6, 128.4, and 128.1 (aromatics), 79.2 (d, C-6 or C-1), 75.2 (t, C-3), 72.7 (d, C-1 or C-6), 67.1 (t, PhCH_2), 54.2 (d, C-7), 48.2 (d, C-4), and 43.7 (d, C-5); *m/z* (ammonia chemical ionization) 290 [$(M + H)^+$] and 307 [$(M + NH_4)^+$].

* Numbering scheme is the same as for previous compounds.

(1α,4α,5α,6β,7β)-4-*Carboxy*-7-(*phenylacetamido*)-2-*oxabicyclo*[3.2.0]*heptan*-6-*ol* (**15**).—A solution of the cyclic carbamate (**12**) (226 mg, 0.781 mmol) and potassium hydroxide (438 mg, 7.81 mmol) in dioxane (10 ml) and water (10 ml) was heated under gentle reflux under nitrogen for 23 h. The resulting buff-coloured solution was extracted with ether (2 × 20 ml), diluted with water (5 ml), and cooled to 0 °C. To the cold, vigorously stirred aqueous solution was added phenylacetyl chloride (155 mg, 1.0 mmol) in three portions at 1 min intervals, and the mixture was stirred at 0 °C for 1 h and at room temperature for 0.5 h. The mixture was acidified to pH 1 with 10M hydrochloric acid and extracted with ethyl acetate (5 × 20 ml). The combined EtOAc extracts were washed with brine (30 ml), dried, and evaporated to give an off-white, semi-solid residue. This residue was triturated with dry ether (4 × 10 ml) which removed substantial quantities of phenylacetic acid. The residue was dried *in vacuo* to leave a white solid (170 mg). Flash chromatography [20 mm; glacial acetic acid–ethyl acetate (5:95 v/v); sample applied in acetonitrile] gave a small amount of phenylacetic acid followed by the *title compound* (**15**) (118 mg, 52%), m.p. 148—152 °C (from acetone–hexane) after being dried *in vacuo* (Found: 61.9; H, 5.9; N, 4.6. $C_{15}H_{17}NO_5$ requires C, 61.84; H, 5.88; N, 4.81%); $\nu_{max.}$(CH_3CN) 3 620 (OH), 1 735 (acid), 1 670 (amide I), and 1 510 cm^{-1} (amide II); δ_H (300 MHz; CD_3CN) 7.30 (5 H, m, ArH), 6.35 (1 H, br s, NH), 4.47 (2 H, m, 1-H and 7-H), 4.35 (1 H, m, 6-H), 4.17 (1 H, dd, $J_{3,3'}$ 8.8 and $J_{3,4'}$ 2.6 Hz, 3-H), 3.96 (1 H, dd, $J_{3',3}$ 8.8 and $J_{3',4'}$ 7.0 Hz, 3'-H), 3.55 (2 H, s, PhCH_2), 3.33 (1 H, m, 5-H), and 3.22 (1 H, m, 4'-H); *m/z* (ammonia chemical ionization) 292 [$(M + H)^+$].

Oxidation of Amidoalcohol (**15**) *with Jones' Reagent*.—Stock Jones' reagent was prepared by dissolving chromium(VI) oxide (2.50 g) in conc. sulphuric acid (specific gravity 1.84) (2.15 ml) and diluting to 10 ml with water, giving a 2.5M solution.[14]

To a stirred solution of the amidoalcohol (**15**) (36 mg, 0.124 mmol) in acetone (4 ml) was added Jones' reagent (75 μl, 0.188 mmol) at room temperature during 15 s and the mixture was stirred for a further 30 sec. Propan-2-ol (0.5 ml) was then added to destroy excess of oxidant and the mixture was filtered through a glass sinter. The acetone was evaporated off and the residue was taken up in ethyl acetate (20 ml). This solution was washed successively with water (4 × 10 ml) and brine (10 ml), dried, and evaporated to give an oil (25 mg). T.l.c. analysis [glacial acetic acid–ethyl acetate (1:99 v/v)] indicated one major new component to be present at R_F 0.45, plus a trace of the more polar starting material. Flash chromatography [10 mm; glacial acetic acid–ethyl acetate (1:99 v/v)] of a portion (20 mg) gave a semi-solid product (11 mg) after being dried *in vacuo*, which gave one spot on t.l.c. The product was identified as a 4:1 mixture of the two epimeric bicyclic lactones (**17**), $\nu_{max.}$ (CH_3CN) 1 778 (lactone), 1 740 (acid), 1 700 (amide I), and 1 510 cm^{-1} (amide II); δ_H (300 MHz; CD_3CN) the major epimer had 7.3 (6 H, m, ArH and NH), 6.18 (1 H, dd, $J_{8,NH}$ 9.3 and $J_{8,1}$ 4.0 Hz, 8-H) 4.65 (1 H, dd, $J_{1,5}$ 5.7 and $J_{1,8}$ 4.0 Hz, 1-H), 4.13 (1 H, dd, $J_{3,3'}$ 9.3 and $J_{3,4'}$ 3.5 Hz, 3-H), 4.02 (1 H, dd, $J_{3',3}$ 9.3 and $J_{3',4'}$ 6.6 Hz, 3'-H), 3.76 (1 H, dd, $J_{5,1}$ 5.7 and $J_{5,4'}$ 1.8 Hz, 5-H), 3.63 (2 H, s, PhCH_2), and 3.48 (1 H, ddd, $J_{4',3'}$ 6.6, $J_{4',3}$ 3.5, and $J_{4',5}$ 1.8 Hz, 4'-H); the minor epimer had 7.6 (1 H, br, NH), 7.3 (5 H, m, ArH), 5.52 (1 H, d, $J_{8',NH}$ 7.9 Hz, 8'-H), 4.61 (1 H, d, $J_{1,5}$ 6.2 Hz, 1-H), 4.24 (1 H, dd, $J_{3,3'}$ 9.7 and $J_{3,4'}$ 4.4 Hz, 3-H), 4.06 (1 H, dd, $J_{3',3}$ 9.7 and $J_{3',4'}$ 7.1 Hz, 3'-H), 3.82 (1 H, dd, $J_{5,1}$ 6.2 and $J_{5,4'}$ 2.2 Hz, 5-H), 3.54 (2 H, s, PhCH_2), and 3.23 (1 H, m, 4'-H); δ_C (100 MHz; CD_3CN) the major epimer had 176.5 (s, C-6), 173.5 (s, acid or amide C=O), 173.3 (s, amide or acid C=O), 136.7 (s) and 130.9—128.5 (doublets, 3 signals, aromatics), 84.9 (d, C-1 or C-7), 80.2 (d, C-7 or C-1), 72.3 (t, C-3), 51.4 (d, 4-C or C-5), 49.6 (d, C-5 or C-4) and 43.8 (t, PhCH_2); the minor epimer had 177.9 (s, C-6), 173.6 (s, acid or amide C=O), 173.4 (s, amide or

acid C=O), 136.5 (s) and 130.9—128.5 (doublets, 3 signals, aromatics), 87.9 (d, C-1 or C-7), 83.1 (d, C-7 or C-1), 72.0 (t, C-3), 50.2 (d, C-4 or C-5), 49.5 (d, C-5 or C-4) and 44.0 (t, $PhCH_2$); *m/z* (ammonia chemical ionization) 306 [$(M + H^+]$ and 323 [$(M + NH_4)^+$].

Other oxidations with chromium-containing oxidising agents led to very similar results. Reactions were attempted with (a) chromic acid–ether, 2-phase system, using the method of Brown *et al*;[25] (b) pyridinium dichromate in DMF, using the method of Corey and Schmidt;[15] (c) pyridinium chlorochromate in methylene dichloride–acetone, buffered with sodium acetate, using the method of Corey and Suggs;[16] (d) 2,2′-bipyridinium chlorochromate in acetone, using the method of Guziec and Luzzio.[26]

(1α,4α,5α,7β)- *and* (1α,4α,5α,7α)-4-*Carboxy*-7-(*phenylacetamido*)-2-*oxabicyclo*[3.2.0]*heptan*-6-*one* (**1**) *and* (**16**).—To a stirred solution of the amidoalcohol (**15**) (88 mg, 0.302 mmol) in dry DMSO (1 ml) and triethylamine (458 mg, 4.53 mmol) under nitrogen was added a solution of pyridine–sulphur trioxide complex (144 mg, 0.906 mmol) in DMSO (2 ml) dropwise during 2 min. The mixture was stirred at room temperature for 1 h, cooled in ice, and acidified to pH 2 with 2M hydrochloric acid. The solution was diluted with water (15 ml) and extracted with ethyl acetate (3 × 25 ml) and the combined organic extracts were washed with brine (30 ml), dried, and evaporated to give a pale-brown oil (70 mg). T.l.c. analysis [glacial acetic acid–ethyl acetate (1:99 v/v)] indicated one major new component to be present at R_F 0.45. Flash chromatography [10 mm; glacial acetic acid–ethyl acetate (1:99 v/v)] gave the title compound [42 mg, 48%; 66:34 mixture of the two epimers (**1**) and (**16**) at C-7] as a white semi-solid after being dried *in vacuo*, which gave one spot on t.l.c. The product was dissolved in water (25 ml) and freeze-dried to give a white, fluffy powder; $\nu_{max.}(CH_3CN)$ 1 795 (cyclobutanone), 1 740 (acid), 1 680 (amide I), and 1 515 cm^{-1} (amide II); δ_H (300 MHz; CD_3CN) the major epimer had 7.3 (5 H, m, ArH), 7.05 (1 H, br d, NH), 5.31 (1 H, ddd, $J_{7,NH}$ 8.7, $J_{7,1}$ 5.8, and $J_{7,5}$ 3.8 Hz, 7-H), 4.89 (1 H, t, $J_{1,7}$ and $J_{1,5}$ 5.8 Hz, 1-H) 4.23 (1 H, dd, $J_{3,3'}$ 9.5 and $J_{3,4'}$ 3.6 Hz, 3-H), 4.10 (2 H, obscured by overlapping, 3′-H and 5-H), 3.54 (2 H, s, $PhCH_2$), and 3.30 (1 H, m, 4′-H); the minor epimer had 7.3 (5 H, m, ArH), 7.15 (1 H, br d, NH), 4.92 (1 H, dd, $J_{1,5}$ 6.6 and $J_{1,7}$ 3.0 Hz, 1-H), 4.31 (1 H, dd, $J_{3,3'}$ 9.8 and $J_{3,4'}$ 2.8 Hz, 3-H), 4.28 (1 H, obscured, 7′-H), 4.10 (2 H, obscured by overlapping, 3′-H and 5-H), 3.53 (2 H, s, $PhCH_2$), and 3.23 (1 H, m, 4′-H); δ_C (75.5 MHz; CD_3CN) the major epimer had 208.5 (s, C-6), 173.1 (s, acid or amide C=O), 171.6 (s, amide or acid C=O), 136.7(s) and 130.2—127.8 (doublets, 3 signals, aromatics), 76.0 (d, C-1), 73.4 (t, C-3), 65.6 (d, C-5 or C-7), 64.2 (d, C-7 or C-5), 47.2 (d, C-4), and 42.9 (t, $PhCH_2$); the minor epimer had 205.0 (s, C-6), 173.3 (s, acid or amide C=O), 172.5 (s, amide or acid C=O), 136.5(s) and 130.2—127.8 (doublets, 3 signals, aromatics), 79.3 (d, C-1), 71.9 (t, C-3), 70.7 (d, C-5 or C-7), 64.4 (d, C-7 or C-5), 45.9 (d, C-4) and 42.3 (t, $PhCH_2$); *m/z* (ammonia chemical ionization) 290 [$(M + H)^+$].

Asymmetric Reduction of the Cyclobutanone (**8**) *with Baker's Yeast* (Saccharomyces cerevisiae).—Active dried baker's yeast (Distillers Co. Ltd.) (100 g) was suspended in water (600 ml) at 37 °C and the mixture was kept for 5 min and occasionally shaken. Sucrose (200 g) was then added and the mixture was kept at room temperature until vigorous gas evolution ensued (about 15 min). The cyclobutanone (**8**) (758 mg) was then added and was washed in with ethanol (3 ml). The mixture was shaken manually several times and kept at room temperature for 4 h and subsequently at 37 °C for 36 h. More sucrose was added at intervals when gas evolution slowed appreciably. The mixture was filtered through a Celite pad and the filtrate was extracted with ethyl acetate (300 ml). The organic solution was dried and evaporated to give a yellow oil (830 mg) which smelled of yeast. T.l.c. analysis [methanol–methylene dichloride (6:94 v/v)] showed 3 products at R_F 0.50, 0.40, and 0.27, plus base-line material. Flash chromatography [40 mm; methanol–methylene dichloride (6:94 v/v)] gave the following fractions: (A) a pale-yellow oil (150 mg), R_F 0.50 and 0.40, but with the R_F 0.50 spot significantly enriched; (B) a pale-yellow oil (303 mg), R_F 0.50 and 0.40, and (C) a pale-yellow solid (17 mg), R_F 0.27. Fraction (C) had m.p. 89—90 °C; $\nu_{max.}(CH_3CN)$ 3 520 and 3 400 cm^{-1}; δ_H [60 MHz; $(CD_3)_2CO$] 7.0 (4 H, A_2B_2q), 3.8 (2 H, t), and 2.8 (2 H, t) which suggests 2-(4-hydroxyphenyl)ethanol (lit.,[27] m.p. 92—93 °C) as the correct structure. Fraction A was separated by preparative t.l.c. [2 plates ethyl acetate–methylene dichloride (2:8 v/v); elutions] into 2 homogeneous fractions. The less polar fraction was isolated to give (1*R*,4*R*,5*S*,6*S*)-4-benzyloxycarbonyl-2-oxabicyclo[3.2.0]heptan-6-ol (**18**) (70 mg) as an oil, $[\alpha]_D^{20}$ + 38.9 ± 2° (*c* 0.01 in chloroform). The product ran coincidentally on t.l.c. with the authentic racemic 6β-alcohol (**9**) and its i.r. and ^1H n.m.r. spectra were identical with those of (**9**). The optical purity of the product was estimated to be > 95% by comparison of its ^1H n.m.r. spectrum with that of racemic material in the presence of the chiral shift reagent tris-(3-trifluoroacetyl-α-camphorato)europium(III). The more polar fraction was isolated to give (1*S*,4*S*,5*R*,6*S*)-4-benzyloxycarbonyl-2-oxabicyclo[3.2.0]heptan-6-ol (**19**) (16 mg) as an oil, $\nu_{max.}$ ($CHCl_3$) 1 730 cm^{-1} (ester); δ_H (300 MHz; $CDCl_3$) 7.4 (5 H, m, ArH), 5.12 (2 H, s, $PhCH_2$), 4.76 (1 H, dt, *J* 6.4 and 2.2 Hz, 1-H), 4.33 (1 H, dd, $J_{3,3'}$ 9.3 and $J_{3,4'}$ 2.2 Hz, 3-H), 4.15 (1 H, m, 6-H), 4.05 (1 H, dd, $J_{3',3}$ 9.3 and $J_{3',4}$ 6.2 Hz, 3′-H), 3.22 (1 H, m, 5-H), 3.03 (1 H, dd, $J_{4',3}$ 6.2 and $J_{4',3}$ 2.2 Hz, 4′-H), 2.34 (1 H, m, 7-H), and 2.18 (2 H, m, 7′-H and OH).

Oxidation of the Racemic Cyclobutanol (**9**).—To a stirred solution of the racemic cyclobutanol (**9**) (275 mg, 1.108 mmol) in dry DMF (10 ml) was added pyridinium dichromate (1.60 g, 4.25 mmol) in one portion and the mixture was stirred at room temperature for 6 h. The reaction mixture was poured into water (90 ml) and extracted with ether (2 × 50 ml). The extract was washed with brine (50 ml), dried, and evaporated to yield an oil (258 mg). Flash chromatography [ethyl acetate–methylene dichloride (5:95 v/v)] gave the racemic cyclobutanone (**8**) (244 mg, 90%) as an oil. The product had identical t.l.c., i.r., and ^1H n.m.r. characteristics with authentic (**8**).

(1*R*,4*R*,5*R*)-4-*Benzyloxycarbonyl*-2-*oxabicyclo*[3.2.0]*heptan*-6-*one* (**20**).—The (1*R*,4*R*,5*S*,6*S*) alcohol (**18**) (60 mg) was oxidized as in the previous experiment to give the title compound (47 mg, 79%) as an oil, c.d. (methanol; *c* 0.728 g l^{-1}): $\lambda_{max.}$ (Δε) 300 nm (−0.61); t.l.c., i.r., and ^1H n.m.r. date were identical with those of racemic ketone (**8**).

(1*S*,4*S*,5*S*)-4-*Benzyloxycarbonyl*-2-*oxabicyclo*[3.2.0]*heptan*-6-*one* (**21**).—The (1*S*,4*S*,5*R*,6*S*) alcohol (**19**) (16 mg) was oxidized as above to give the title compound (10.5 mg, 66%) as an oil, c.d. (methanol; *c* 0.506 g l^{-1}): $\lambda_{max.}$ (Δε) 300 nm (+0.54); t.l.c., i.r., and ^1H n.m.r. data were identical with those of racemic ketone (**8**).

Acknowledgements

We are grateful to the S.E.R.C. and I.C.I. Pharmaceuticals Division for financial support through a CASE studentship. We also thank Dr. P. M. Scopes for the c.d. spectra, Dr. T. D. Hennessey and his staff for antibacterial testing, and Dr. R. H. B. Galt for many helpful discussions.

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Received 12*th June* 1984; *Paper* 4/982