Synthesis of 7β-Phenylacetamido-6-oxo-2-oxabicyclo[3.2.0]heptane-4α-carboxylic acid, a Cyclobutanone Analogue of a β-Lactam Antibiotic

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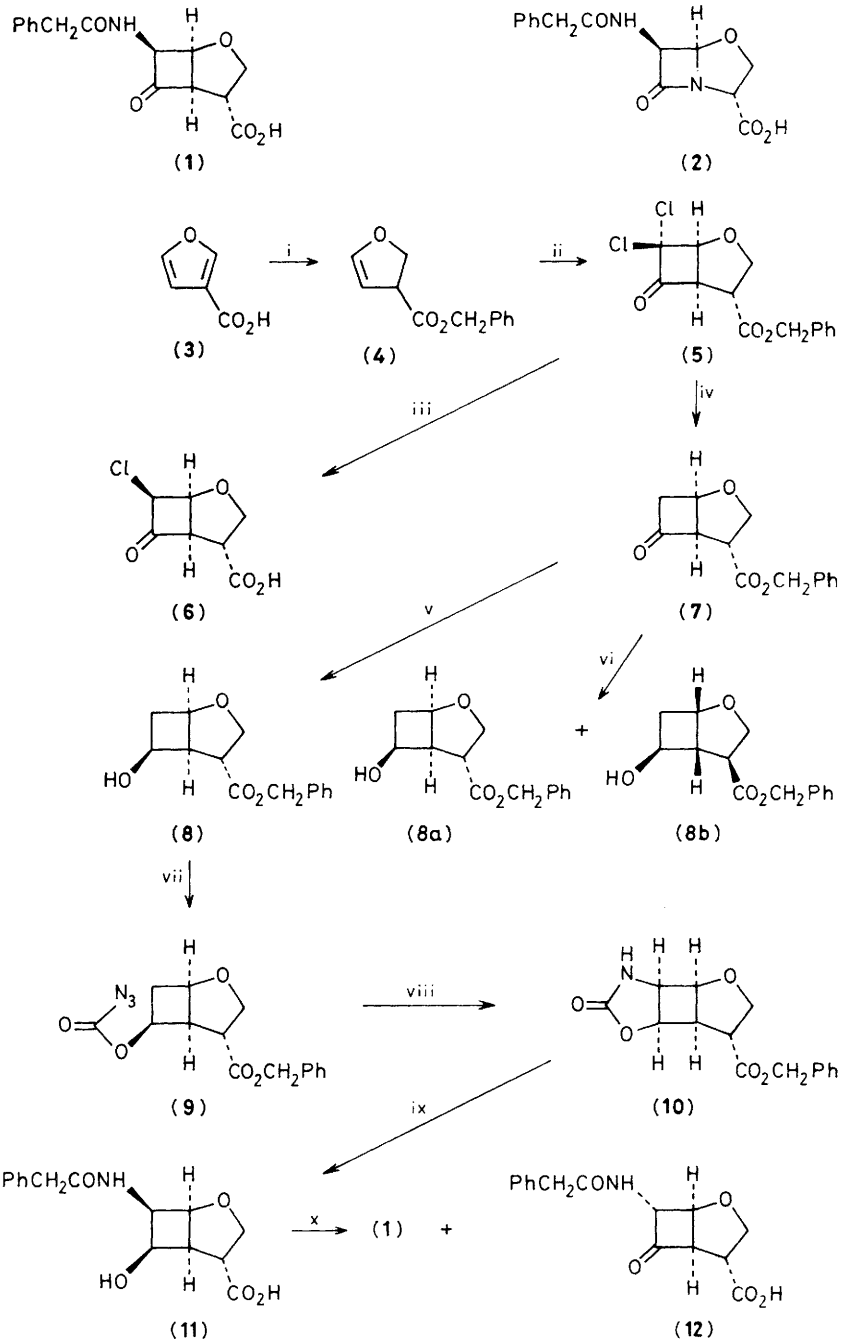
A route has been developed for the synthesis of cyclobutanone analogues of β-lactam antibiotics.

The β-lactam antibiotics constitute the most important class of antibacterial agents at the present time,[1] but owing to their widespread use an ever increasing number of resistant bacterial strains are evolving primarily due to the mutation and transfer of structural genes coding for β-lactamases.[2] Although the search for new microbial β-lactam antibiotics and their modification by chemical and enzymic methods has led to many highly potent therapeutic agents,[3] the Achilles



Scheme 1. *Reagents:* i, Na–liq. NH_3–Me_2CHOH then $PhCH_2Br$–K_2CO_3–dimethylformamide (DMF); ii, $Cl_2CHCOCl$–NEt_3; iii, H_2–Pd/C; iv, Zn–AcOH; v, $LiB[CHMeEt]_3H$; vi, *Saccharomyces cerevisiae*; vii, $COCl_2$–C_5H_5N then NaN_3–DMF; viii, 135 °C for 3.5 h, CH_2Cl_2 in a sealed tube; ix, aq. KOH–dioxane, then $PhCH_2COCl$; x, SO_3–C_5H_5N–Me_2SO–NEt_3.

heel of the β-lactam antibiotics remains the β-lactam ring itself. At the outset of this investigation structure–activity studies had been undertaken on all features of the penicillins except the β-lactam ring, and none had been found to be mandatory.[4] It has been widely assumed as the name suggests, that the β-lactam ring is an essential feature for antibacterial activity. If this assumption is incorrect it might be possible to synthesize analogues against which bacteria might find it difficult or impossible to develop resistance.

Since the N-atom of the β-lactam is made pyramidal by ring fusion in the penicillins and cephalosporins, replacement with sp^3 hybridized carbon should retain stereochemical compatibility with the active site of the transpeptidases and D,D-carboxypeptidases involved in bacterial cell wall biosynthesis. Consequently a cyclobutanone analogue of a β-lactam antibiotic should be able to form a tetrahedral adduct with the active site functional group of a serine or cysteine residue or with enzyme bound water. All three types of D,D-carboxypeptidase are known to occur in bacteria.[5] The formation of such an adduct would be favoured both by release of angle strain when the sp^2 carbon atom of the cyclobutanone ring is converted into an sp^3 carbon centre and by enzymic stabilization since the adduct should be structurally similar to the transition state leading to the acylation of transpeptidases and D,D-carboxypeptidases by β-lactam antibiotics.[6] Likewise such isosteres should also be β-lactamase

inhibitors. We selected as our initial target the isostere (**1**) of the β-lactam (**2**) which is known to possess antibacterial activity.[7] During the course of this work two reports appeared with similar objectives but in neither case was an acylamino side chain incorporated.[8,9]

Reduction of 3-furoic acid (**3**) with sodium in liquid ammonia in the presence of propan-2-ol gave sodium 2,3-dihydro-3-furoate,[10] which was alkylated with benzyl bromide to give the benzyl ester (**4**) (83%).† [$_{s}2_{\pi}$ + $_{a}2_{\pi}$]-Cycloaddition reactions between olefins and ketenes are especially facile when the olefin is electron rich and the ketene possesses electron withdrawing groups.[11,12] Cycloaddition of the 2,3-dihydrofuroic ester (**4**) with dichloroketene (generated *in situ*) occurred both regio- and stereo-specifically as expected to give the adduct (**5**) (ν_{max} 1810 cm^{-1}; 59%). Catalytic hydrogenolysis of the adduct (**5**) gave 7β-chloro-6-oxo-2-oxabicyclo[3.2.0]heptane-4α-carboxylic acid (**6**) (ν_{max} 1800 cm^{-1}; 51%) whereas treatment with zinc in acetic acid gave the bicyclic ketone (**7**) (ν_{max} 1785 cm^{-1}; 88%). Introduction of the nitrogen function at the 7-position was investigated by a variety of methods, but the one which proved most satisfactory involved initial reduction of the ketone (**7**) stereospecifically to the alcohol (**8**) (59%) with L-Selectride; reduction could also be achieved with *Saccharomyces cerevisiae* (baker's yeast) which gave the enantiomerically pure diastereoisomers (**8a, b**). Treatment of the racemic alcohol (**8**) with phosgene gave the chloroformate quantitatively which was converted into the azidoformate (**9**) (65%) with sodium azide. Thermolysis of the azidoformate (**9**) led *via* nitrene insertion to the cyclic urethane (**10**) (29%) together with some acyclic urethane and other minor products. It is noteworthy that all the chiral centres were incorporated stereospecifically and since the enantiomer (**8a**) is available, the cyclic urethane (**10**) could be obtained as the pure enantiomer shown in Scheme 1. However, the synthesis was completed with the racemic cyclic urethane. Base catalysed hydrolysis to the amino acid was followed by acylation with phenylacetyl chloride *in situ* to give the phenylacetamido-derivative (**11**) (52%). Oxidation to the target molecule (**1**) with sulphur trioxide–pyridine in dimethyl sulphoxide containing triethylamine,[13] gave the epimeric ketones (**1**) and (**12**) (ν_{max} 1795 cm^{-1}; 48%) in the ratio 66:34, respectively (by ^{1}H and ^{13}C n.m.r. spectroscopy), which could not be separated. Not surprisingly the product is susceptible to further oxidation to the γ-lactone which could not be avoided with several other reagents investigated.

The mixture of epimeric ketones (**1**) and (**12**) showed inhibition of *Streptomyces* R61 D,D-carboxypeptidase only at 260 μg/ml and no significant activity against a range of bacteria at 128 μg/ml. The chloroketone (**6**) and the epimeric mixture of ketones (**1**) and (**12**), however, showed time dependent inhibition of *E. coli* R-TEM and *B. cereus* I β-lactamases which may be associated with the slow formation of a tetrahedral adduct between the inhibitor and the enzyme. Further studies are in progress to determine the nature of the enzyme–inhibitor adduct.

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† All new compounds gave satisfactory i.r. and ^{1}H n.m.r. (300 MHz) spectra, and microanalytical and/or mass spectral data in agreement with the assigned structures.

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