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A CHIRAL INTERMEDIATE FOR THIENAMYCIN ANALOGUE SYNTHESIS: (3S,4R)-4-(2-HYDROXYETHYL)-3-[(R)-1-(4-NITROBENZYLOXYCARBONYLOXY)ETHYL]AZETIDIN-2-ONE

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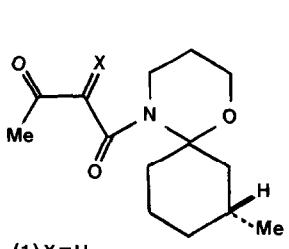
Abstract: Incorporation of a chiral ketone into the established tetrahydro-1,3-oxazine route to thienamycin analogues, has enabled the isolation of single enantiomers having the naturally occurring (R)-configuration at the bridgehead.

A number of enantiospecific syntheses of members of the "carbapenem" group of antibacterials have appeared. They have tended to fall into three main types: elaboration of a chiral starting material such as L-aspartic acid[1]; classical resolution using an optically active acid or base[2]; and an elegant enzymatic selection process[3,4]. These methods increase the length of the synthesis, but the tetrahydro-1,3-oxazine route that was described from these laboratories[5], has now been modified to provide (5R)-thienamycin analogues without any additional steps being added to the racemic route.

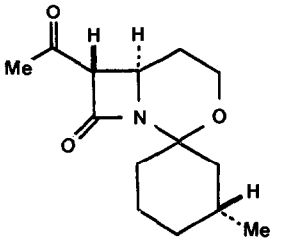
The key concept was the replacement of the cyclohexanone, used in the original synthesis, by a chiral ketone. Camphor, nopinone, menthone and carvomenthone were found to be unsuitable because none of them cleanly gave an oxazine on reaction with 3-aminopropan-1-ol. However, commercially available (R)-3-methylcyclohexanone reacted satisfactorily with the aminoalcohol (benzene, reflux, 24 h) to form a tetrahydro-1,3-oxazine. The unpurified product was acylated with diketene (benzene, 0°C, 3h) to produce the β-ketoamide (1)[6], which was isolated by chromatography in 68% yield. The proton and carbon n.m.r. spectra showed (1) to be slightly enolised, but surprisingly it was substantially a single isomer of unknown stereochemistry at the spiro centre. A diazo transfer to (1) utilising methanesulphonyl azide (NEt_3, benzene, 0°C for 2 h, 20°C for 18 h) then gave a quantitative yield of (2). This underwent a carbenoid insertion on treatment with rhodium (II) acetate (0.1 weight of substrate, benzene, 20°C, 20 h) to produce a 3:2 mixture of tricyclic compounds (3) and (4). Chromatography (silica gel 60, $CHCl_3$) followed by crystallisation of the slower fractions from hexane enabled isolation of pure (6R)-diastereoisomer (3) (22%), m.p. 82-84°C, $[\alpha]_D^{20}$ +25.3° (c 1 in $CHCl_3$).

The reduction of (3) with potassium tri-sec-butylborohydride[1] (THF, 0 to 20°C, 0.75 h) gave a 75% yield of the (R)-alcohol (5) [plus 10% of (S)-isomer], which was protected with 4-nitrobenzyloxycarbonylchloride (Bu^nLi, THF, -70 to 20°C, 0.75 h) to form (6). This was hydrolysed ($M.H_2SO_4$ in 10:1 Me_2CO/H_2O, 20°C, 2.5h) in 60% yield to the versatile intermediate (7), $[\alpha]_D^{20}$ +2.6°(c 1 in $CHCl_3$), which has all of the thienamycin asymmetric centres correctly set up. This compound has been previously made by the enzymatic route[4]. The utility of (7) was confirmed by employing existing methodology[7] to progress it to the

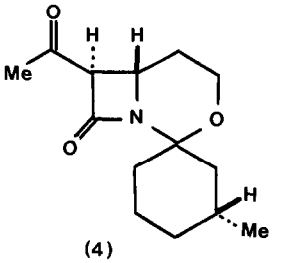
protected thienamycin analogue (8), $[\alpha]_D^{20}$ + 59.4° (c 1 in $CHCl_3$), which was in the bioactive naturally occurring series.



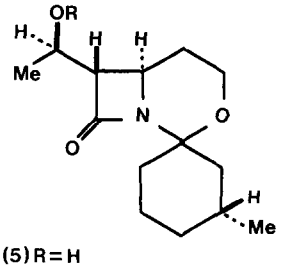
(1) X=H_2
(2) X=N_2



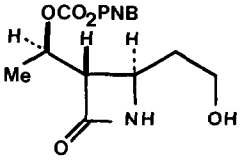
(3)



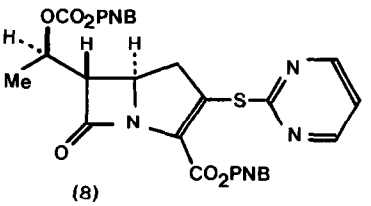
(4)



(5) R=H
(6) R=CO_2PNB



(7)



(8)

PNB=p-Nitrobenzyl

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References and notes

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5. R.J. Ponsford and R. Southgate, J. Chem. Soc., Chem. Commun., 1979, 846.
6. New compounds were characterised by infra-red and 250 MHz nuclear magnetic resonance spectra plus mass spectral and/or microanalytical evidence. Some selected physical data are as follows. (3): $\nu_{max.}$ ($CHCl_3$) 1740 and 1710 cm^{-1}; $\delta(CDCl_3)$ 0.89 (3 H, d, J 7 Hz, CH_3), 2.31 (3 H, s, $COCH_3$), 3.76 (1 H, ddd, J 13,5 and 3 Hz, 4-H), 3.83 (1 H, d, J 2 Hz, 7-H), 3.87 (1 H, ddd, J 13, 6 and 3 Hz, 4-H), and 4.02 (1 H, ddd, J 11, 5 and 2 Hz, 6-H). (7): $\nu_{max.}$ ($CHCl_3$) 3400, 3300 br, and 1745 cm^{-1}; $\delta(CDCl_3)$ 1.48 (3H, d, J 6 Hz, CH_3), 1.61 (1 H, s, OH), 3.06 (1 H, ddd, J 8, 2 and 1 Hz, 3-H), 5.13 (1 H, dq, J 8 and 6 Hz, CH-O), and 6.11 (1 H, br s, NH).
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