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SYNTHESIS OF 6-ALK-1'-ENYL PENICILLANIC ACIDS; DOUBLE BOND ISOSTERES OF THE SIDE-CHAIN AMIDE LINKAGE IN PENICILLINS

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Summary Two penicillin analogues have been prepared which incorporate C=C bonds at $C_6\alpha$ and $C_6\beta$ respectively, in place of the normal side-chain NHCO group.

The concept of isosteric replacement of an amide function by a carbon-carbon double bond has recently been exemplified in the synthesis of active enkephalin analogues.[1,2] The application of this concept to the synthesis of new penicillin analogues appears attractive, particularly in view of recent interest in all-carbon side-chains stimulated by the discovery of thienamycin.[3-6] We report the first examples of 6-alk-1'-enyl penicillanic acids, formed by a unique, selective, 1,6-reduction of a specific dienamide stereoisomer.

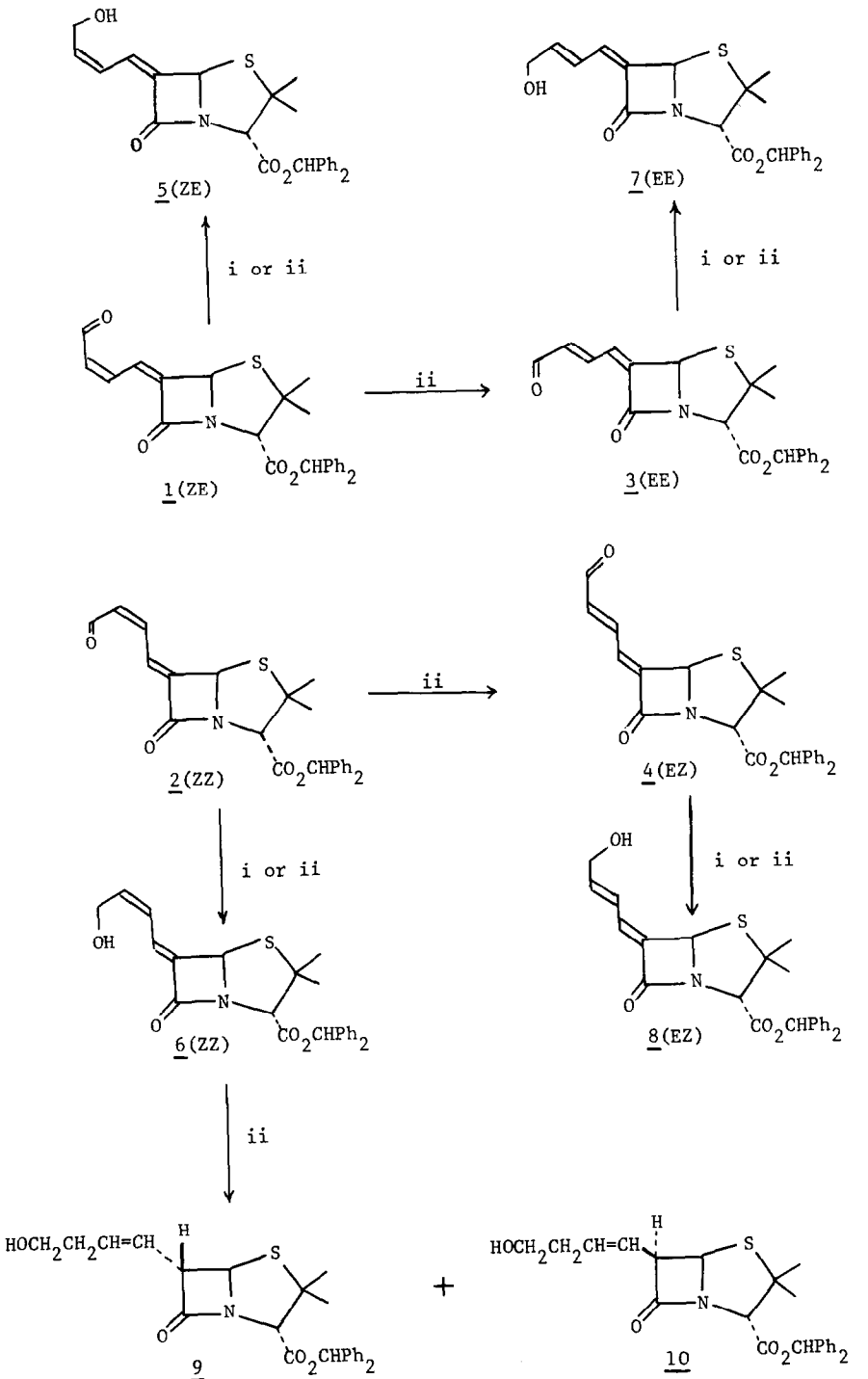
The dienals (1) and (2) are obtained[7] quantitatively in a 2:1 ratio by the rhodium-catalysed addition of benzhydryl 6-diazopenicillanate to furan.[8] Reduction of the dienals by $NaBH_4$ was expected to give simply the corresponding dienyl alcohols, but proved to be more complicated. By monitoring the reaction products by HPLC (Hypersil 5μm SiO_2, MeCN-CH_2Cl_2 7:93) it was established that the ZE and ZZ dienals (1) and (2) each undergo two competing reactions with $NaBH_4$ in wet acetonitrile - isomerisation of the Z double bond adjacent to the aldehyde function and reduction of the aldehyde to primary alcohol. The isomeric EE and EZ dienals (3) and (4) were themselves rapidly reduced to the corresponding dienyl alcohols.[9] The isomerisations and carbonyl group reductions are all fast processes: all the dienals (1) - (4) were consumed within 1-2min. of mixing with excess $NaBH_4$. At a slower rate (10-20 min. reaction time), the ZZ dienyl alcohol (6) was reduced to a 6:4 mixture of α and β 6-(4'-hydroxybut-1'-enyl) penicillanates (9) and (10). The ZE isomer (5) was not significantly reduced under these conditions, but it was subsequently shown that with a large excess of $NaBH_4$ in wet acetonitrile there was some reduction to alkenols (9) and (10) after 2h. The remaining two isomer (7) and (8) showed no conversion at all to alkenols.

Although isomerisation of the dienals (1) and (2) has been noted previously under acid-catalysed conditions,[7] its observation in the present reaction was unexpected. It was initially suspected that interaction between sodium ions and the dienals was responsible, but whereas addition of aq. NaCl to the dienals (1) and (2) in acetonitrile caused no change, addition of aq. NaOH resulted in rapid appearance of the isomers (3) and (4). Thus, it is the high pH of the $NaBH_4$ solution which is responsible for the isomerisation. Two mechanisms were considered for the base-catalysed process, one involving enolisation towards C_5 and the other a conjugate addition-elimination pathway. It was observed that on treatment of the dienals (1) and (2) with $NaOD/D_2O$, rapid isomerisation to dienals (3) and (4) occurred without any D-incorporation at C_5, a result which is inconsistent with enolisation towards C_5.

When reductions of the ZE and ZZ dienals (1) and (2) were carried out in aq. MeCN buffered to pH 7.0, there was no isomerisation observed and only the corresponding ZE and ZZ dienyl alcohols, (5) and (6) respectively, were formed. Even on prolonged exposure to $NaBH_4$, the ZZ isomer (6) did not suffer appreciable reduction to the alkenols (9) and (10) under the buffered conditions. The formation of the alkenols appears to be a unique example of the selective reduction of one of a set of four isomeric 2,4-dienyl carbonyl compounds, the reaction occuring only under alkaline conditions. The reason for this selectivity and the role which pH plays remain to be elucidated.

Optimisation of the synthesis of the alkenols (9) and (10) requires a combination of buffered and unbuffered reductions. Thus, treatment of the readily prepared 2:1 mixture of dienals (1) and (2) with buffered $NaBH_4$, to avoid isomerisation, afforded a 2:1 mixture of dienols (5) and (6) which was further treated with unbuffered $NaBH_4$ to give a mixture of unreacted dienol (5) and alkenols (9) and (10). The latter isomers were isolated in a combined, overall yield of 35% based on benzhydryl 6-diazopenicillanate and were separated by preparative HPLC.

The orientations of the side-chains at C_6 in the two isomers (9) and (10) were apparent from the H_5-H_6 couplings in their ^1H nmr spectra (1.5Hz in the α isomer and 4.5Hz in the β isomer). The geometries of the double bonds in the two isomers were not immediately apparent, since in each case the ^1H nmr spectrum showed a deceptively simple pattern due to accidental magnetic equivalence of the two vinyl protons.[10] However, addition of $Eu(fod)_3$ led to a good separation of the chemical shifts of the vinyl protons in each of the two compounds, allowing the vicinal olefinic couplings to be measured. Both of the isomers (9) and (10) showed a coupling of 15Hz, demonstrating that both possess the trans configuration in their side-chains.



i. $NaBH_4$ in aq. MeCN buffered to pH 7.0

ii. $NaBH_4$ in aq. MeCN

Deprotection of each of the benzhydryl esters (9) and (10) was readily accomplished by brief contact with trifluroacetic acid-anisole, Neither compound underwent isomerisation under these conditions and the corresponding carboxylic acids could be isolated in yields of 70-80%. Both of these were found to be devoid of antibacterial activity against a standard series of laboratory strains.

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