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SYNTHESIS OF *THREO*-3-ARYL-2,3-DIHYDROXYPROPANOIC ACID DERIVATIVES WITH HIGH OPTICAL PURITY

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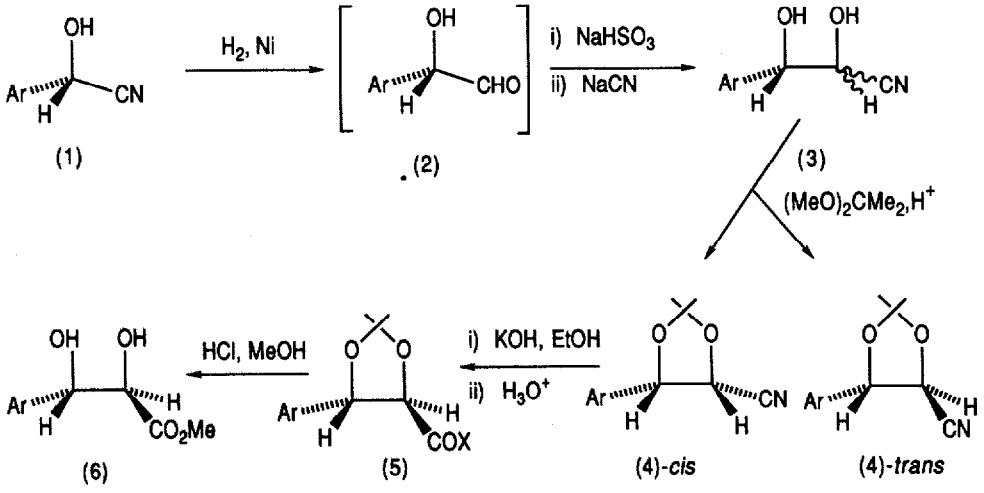
Summary
Cyanohydrins of arylaldehydes can be obtained in high optical purity using the 'Inoue' dipeptide catalyst system and converted into enantiomerically and diastereochemically pure *threo*-3-aryl-2,3-dihydroxypropanoic acid derivatives using a route which involves a novel base-catalysed equilibration of the acetonides of the cyanodiols.

Cyanohydrins from arylaldehydes are now readily available in a high degree of optical purity either by use of 'Inoue' type dipeptide catalysts[1] or by the use of immobilised enzyme extracts.[2] In this communication we describe their conversion to optically and stereochemically pure *threo*-3-aryl-2,3-dihydroxypropanoic acid derivatives which are useful synthetic intermediates for the preparation of the important cardiac drug, diltiazem, and its derivatives.[3]



Hydrogenation of the cyanohydrins (1) in strongly acidic solution over Raney nickel gave a hydroxyaldehydes (2) which were immediately converted into their cyanohydrins (3) *via* their bisulfite compounds following procedures described by Tinapp.[4] The cyanohydrins (3) were shown to be a mixture of *erythro*- and *threo*-diastereoisomers in ratio 56:44 by ^{1}H n.m.r. spectroscopy as well as by conversion to the cyclic dioxolanes (4)[5].

Reaction of the mixture of dioxolane-nitriles (4) with potassium hydroxide in aqueous ethanol under reflux for fifteen hours gave the pure *trans*-dioxolane acid (5; X = OH) in good yield. No trace of the *cis*-dioxolane acid could be detected by high field ^{1}H n.m.r. Equilibration involved epimerisation only at C2 as no loss of optical activity occurred when an optically pure sample of (R)-(+)- cyanohydrin (1; Ar = 4-MeOPh) was used in the above reaction sequence. The product (5; X = OH, Ar = 4-MeOPh), $[a]_D^{18}$ +12.2° was converted into an ester with (S)-(+)-octan-2-ol and signals due to only one diastereoisomer were observed in the ^{1}H n.m.r. (300 MHz) spectra under conditions where several peaks due to the other diastereoisomer were clearly resolved. Treatment of the dioxolane acid with methanolic hydrogen chloride gave enantiomerically pure diolester (6) which has been prepared by other methods.[6] This material was successfully converted into the cardiac drug Diltiazem (Cardizem).[7]

The epimerisation appears to involve removal of the H2 proton by the strong base at the amide stage of the hydrolysis for reaction of a mixture of the diastereoisomeric nitriles (4) (1:1) with potassium carbonate in methanol at ambient temperature or under reflux gave a mixture of the corresponding iminomethyl ethers in good yield but still with the same diastereoisomeric ratio. Reaction of the same mixture of diastereoisomers with potassium hydroxide in absolute ethanol gave a product containing the pure *trans*-amide (5; X = NH_2) together with a small amount of the iminoethers which were still present in an equimolar mixture of *cis*- and *trans*-isomers. The reaction product also contained traces of phenylacetic (3%) and benzoic acids (3%).

The formation of these unwanted biproducts could be suppressed by the use of aqueous ethanol as the reaction medium which led to the formation of the *trans*-acetonide acids (5; X = OH) as described above. The detailed mechanism of the equilibration reaction is not yet known and may involve bulky alcohol adducts of the amide as was proposed for the epimerisation of the dioxolane derivatives of *erythro*- and *threo*-aldoses.[8] However, the free amide may well be involved, as equilibration of the aldehydes of the closely related aryl dioxolane system (5; X = H) has been shown to involve the free aldehydes.[6]

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