APPROACHES TO THE ASYMMETRIC SYNTHESIS OF 2-ARYLPROPANOIC ACIDS

A Thesis

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by

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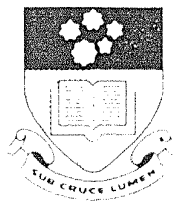

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ABSTRACT

(*S*)-2-(3'-Benzoylphenyl)propanoic acid (ketoprofen) and (*S*)-2-[4'-(2"-methylpropyl)phenylpropanoic acid (ibuprofen) were synthesised in 96%+ e.e. Control of stereochemistry was achieved by a combination of Sharpless epoxidation followed by catalytic hydrogenolysis of the introduced benzylic epoxide oxygen bond.

The coupling of organic compounds in the presence of palladium with enantiopure 2-(3'-iodophenyl)propanoic and 2-(4'-iodophenyl)propanoic acids, prepared by the methodology above, was shown to be a general method for the synthesis of optically active arylpropanoic acids.

The four stereoisomers of the parent keto acid of the oximino drug 2-[4'-(3"-{hydoxyimino}cyclohexyl)phenyl]propanoic acid (ximoprofen) were prepared in high optical purity. The stereochemistry in the propanoic acid chain was established by the methodology above. The configuration of the centre in the cyclohexanone ring was controlled by the stereoselective conjugate addition of the arylpropanoic acid moiety to the enantiomers of 5-(trimethylsilyl)-2-cyclohexenone with subsequent removal of the trimethylsilyl group. Attempts to separate the (*E*) and (*Z*) isomers of the oxime derivative of one of the stereoisomers were unsuccessful.

An alternative method for the preparation of (*S*)-ketoprofen in high optical purity was developed. The stereochemistry was controlled by a combination of Sharpless asymmetric dihydroxylation followed by catalytic hydrogenolysis of the introduced benzylic hydroxyl group.