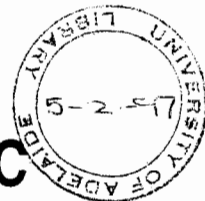


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APPROACHES TO THE ASYMMETRIC SYNTHESIS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

A Thesis
Submitted Towards the
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Doctor of Philosophy

by

Robert Christian Griesbach

B. Sc. (Hons.)



Organic Chemistry Department
The University of Adelaide
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ABSTRACT

The aryl propanoic acid ibuprofen ((*S*)-2-[4-(2-methylpropyl)phenyl]propanoic acid) was synthesized in 96% e.e. Control of stereochemistry was achieved by use of the Sharpless epoxidation reaction, followed by reduction of the product epoxide by complex hydride with assistance by titanium tetrakisopropoxide acting as a Lewis acid.

The final step was the coupling of an optically active carboxylic acid intermediate with the *iso*-butyl side chain to give (*S*)-ibuprofen. This intermediate is a bromo arene and could potentially be coupled to various side chains to give different members of the aryl propanoic acid family.

The synthesis of naproxen ((*S*)-2-(6-methoxy-2-naphthyl)propanoic acid) was also completed, in 96% e.e. Asymmetry was introduced with the Sharpless asymmetric dihydroxylation reaction followed by formation of the corresponding optically active epoxide. This epoxide was reduced by catalytic hydrogenolysis of the benzylic C-O bond to give the stereogenic centre with the correct configuration. The final step was oxidation to give naproxen.

The synthesis of ketorolac ((*S*)-5-benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid) was attempted. A target intermediate was sought, from which the methodology established above, for the synthesis of naproxen, could be used to establish the stereogenic centre adjacent to the carboxylate group. This intermediate, from which point asymmetric chemistry would be attempted, was a diketone, which had two carbonyl groups in direct conjugation with the pyrrole ring. Many problems were experienced in the preparation of this intermediate, in attempts to attach the second carbonyl group, due to the deactivating nature of the already attached, electron withdrawing, carbonyl group. The intermediate was not obtained in workable quantities.

Another route was attempted, in which the intermediates were not stabilized by the benzoyl group, however these intermediates were too unstable to ~~work with~~ ^{be useful.} It was not realised at the start ~~of this work~~ ^{that} ~~that~~ ^{with} these pyrrole compounds would be so difficult ~~to work with.~~