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Asymmetric dihydroxylation in an approach to the enantioselective synthesis of 2-arylpropanoic acid non-steroidal anti-inflammatory drugs

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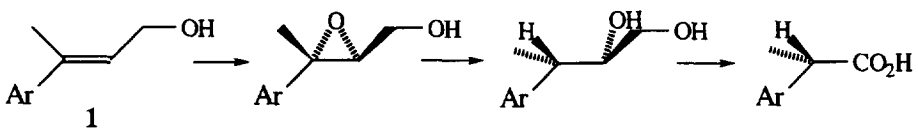
Abstract: Naproxen ((*S*)-2-(6-methoxy-2-naphthyl)propanoic acid) and flurbiprofen ((*S*)-2-(3-fluoro-4-phenylphenyl)propanoic acid) have been synthesised in high enantiomeric excess. The synthetic strategy employed was to introduce asymmetry into the molecules by Sharpless asymmetric dihydroxylation of the appropriate methyl styrenes. The resultant diols were then converted into optically active epoxides and the required stereogenic centre was assembled by catalytic hydrogenolysis of the introduced benzylic epoxide oxygen bond, followed by oxidation of the derived optically active primary alcohol. © 1997 Elsevier Science Ltd. All rights reserved.

Increasingly attention is being paid[1] to the problem of the manufacture of non-racemic chiral drugs and asymmetric synthesis may play an important role here. Certain arylpropanoic acids constitute one of the major classes of non-steroidal anti-inflammatory drugs (NSAID) and the physiological activity resides in the (*S*) isomer. We have already developed a strategy[2] for the synthesis of such compounds. Asymmetry is first introduced into the molecule by means of a Sharpless asymmetric epoxidation. The required stereogenic centre is then put in place by means of a highly stereoselective catalytic hydrogenolysis of the benzylic epoxide bond, followed by an oxidative cleavage of the resultant diol (Scheme 1). Although this strategy for the asymmetric construction is highly efficient, preparation of the requisite allylic alcohols **1** makes this overall approach less so. We have studied alternative chemistry in the hope that more efficient routes to enantiomerically pure NSAID can be invented.



Scheme 1.

Alkenes **2** are easier to prepare than the allylic alcohols **1** particularly since there is no requirement for stereochemical purity, therefore, a new strategy, in which asymmetry is introduced into the molecule by means of a Sharpless asymmetric dihydroxylation (AD) reaction, has been developed (Scheme 2). Direct hydrogenolysis[3] of the benzylic tertiary hydroxyl group in the intermediates **3** leading to ketoprofen, ibuprofen and naproxen was not very satisfactory. However, a modification of this approach, in which the diol is first converted to an epoxide and this is hydrogenolysed and the resultant primary alcohol is then oxidised, has led to the asymmetric synthesis of both naproxen and flurbiprofen in high enantiomeric purity. An outline of this chemistry is given in Scheme 2.

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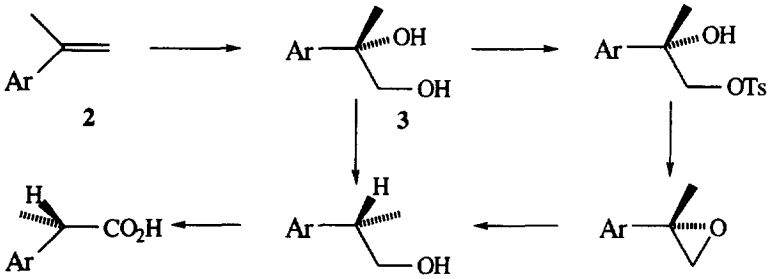
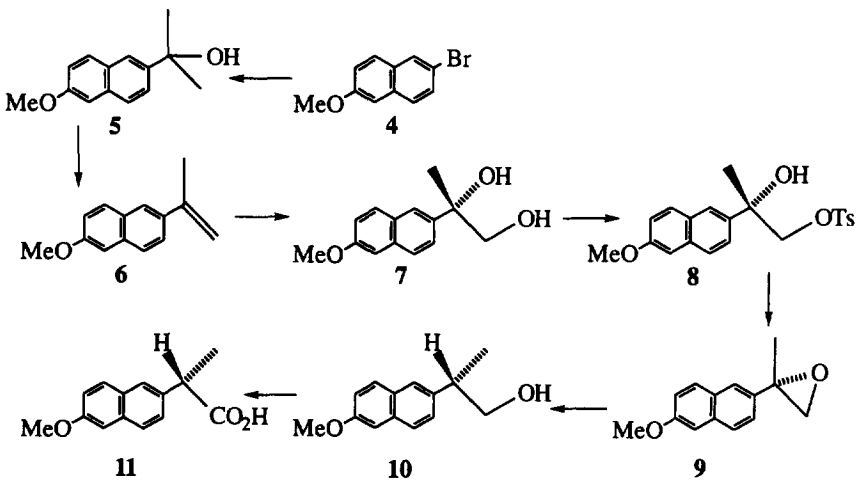


Scheme 2.

The asymmetric synthesis of naproxen

The alkene **6**,[4] mp 104–6°, was prepared from the bromo compound **4** *via* the tertiary alcohol **5**. Asymmetric dihydroxylation of this alkene was reported,[5] during studies on the development of ligands, to occur with 88% e.e. The use of AD mix α gave the optically active diol **7**, mp 107–8°, (98% e.e.) None of these compounds is particularly stable and isolation and purification, at each step, usually results in only medium yields. However, when these reactions are carried out without any attempt at purification, diol sufficiently pure for the next step is obtained in an overall yield of *ca.* 85%. The racemic diol, mp 110–1°, was obtained by OsO_4/NMMNO oxidation[6] of the alkene and the enantiomeric excess of the diol **7** was then determined by the use of chiral shift NMR experiments on the derived mono primary acetates. An attempt to prepare the epoxide **9** by the method developed by Sharpless[7] for less substituted diols was unsuccessful. However, conversion of the diol **7** to the monotosylate **8** and treatment of the crude derivative, which contains some epoxide, with sodium hydride gave the rather labile epoxide **9**, mp 86–8° (80%).

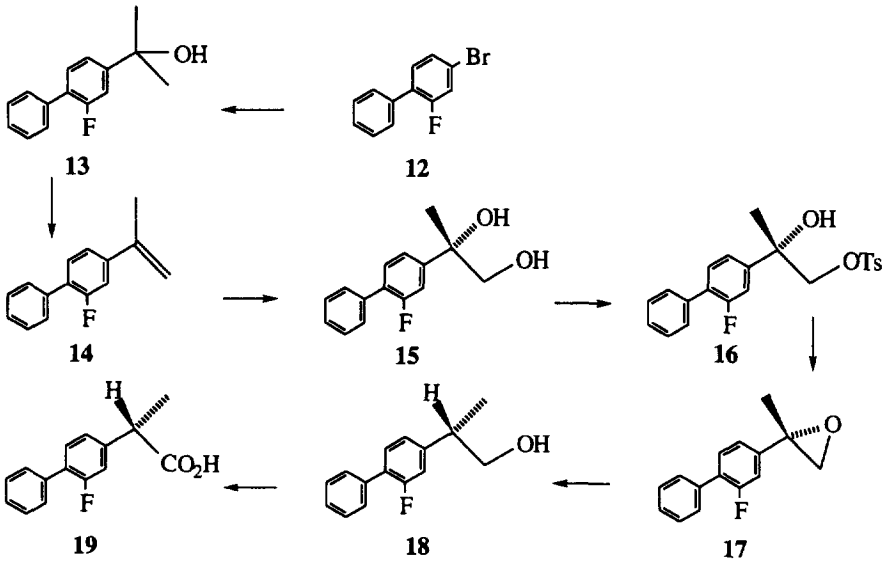


Catalytic hydrogenolysis (10%Pd/C/EtOH/trace OH^-) of the epoxide **9**, at room temp., gave the required primary alcohol **10** (92%), mp 82–4° (lit.[8] 88–9°). A ^1H NMR spectrum of the Mosher ester of this alcohol allowed a determination of the enantiomeric excess as *ca.* 90%. The drop in enantiomeric purity, from that of the diol **7**, could be due to partial racemisation of intermediates *en route* or due to poor stereochemical control in the hydrogenolysis step. Repetition of the hydrogenolysis at −40° and determination of the enantiomeric purity of the derived alcohol gave an enantiomeric excess of *ca.* 97%. Jones oxidation of the primary alcohol **10** gave (*S*) naproxen **11** in good chemical yield, mp 151–3° (lit.[8] 152–4°). The enantiomeric excess of the acid **11** was determined as *ca.* 96% from

the methyl resonances in a ^{1}H NMR spectrum of the salts derived from commercial cinchonidine (assumed to be enantiomerically pure).

The asymmetric synthesis of flurbiprofen

The aryl bromide **12** was converted to the Grignard reagent and this reacted with acetone to give the alcohol **13**[9] (75%). Dehydration of this alcohol with $MeSO_2Cl/Et_3N$ gave the alkene **14**[9] (83%). Asymmetric dihydroxylation of this alkene was achieved by the use of AD α mix to give the diol **15** mp 81–3° (93%, 98% e.e.). The racemic diol, mp 129–30°, was obtained by OsO_4/NMMNO oxidation of the alkene and the enantiomeric excess of the diol **15** was then determined by the use of chiral shift NMR experiments on the derived mono primary acetates. Conversion of the diol **15** to the monotosylate **16**, mp 111–2°, and then treatment of the tosylate with sodium hydride, gave the epoxide **17**[10] (76%). Catalytic hydrogenolysis (10%Pd/C/EtOH/trace OH^-) at −40° gave the alcohol **18**, mp 59–60° (lit.[11] rac. 61–3°) (90%).



Jones oxidation of the primary alcohol **18** gave (*S*)-(+)-flurbiprofen **19**, mp 108–10° (lit.[11] rac. 110–1°), (56%, 98% e.e.). The enantiomeric excess of flurbiprofen **19** could not be determined from its cinchonidine salt. Instead it was converted to the methyl ester and chiral shift NMR experiments[1] [12] on this derivative allowed the determination to be made.

Monoacetate of diol 7

^{1}H NMR (300 MHz, 15% C_6D_6 in CCl_4): δ 1.63 (s, 3H, CH_3), 2.03 (s, 3H, $COCH_3$), 2.7 (br s, OH), 3.91 (s, 3H, Ar–OCH_3), 4.29 (d, *J*=11.3 Hz, 1H, OCH_2), 4.39 (d, *J*=11.3 Hz, 1H, OCH_2), 7.11–7.87 (6H, Ar). The acetate methyl resonances were used for the determination.

Monoacetate of diol 15

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.59 (s, 3H, CH_3), 2.08 (s, 3H, $COCH_3$), 2.66 (br s, OH), 4.27 and 4.30 (ABq, J 11.4Hz, 2H, OCH_2), 7.2–7.6 (8H, ArH). The acetate methyl resonances were used for the determination.

Acknowledgements

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[1] All chiral shift NMR experiments were run in 15% C_6D_6 in CCl_4 with $Eu(hfc)_3$.

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