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ASYMMETRIC SYNTHESIS OF IBUPROFEN AND KETOPROFEN

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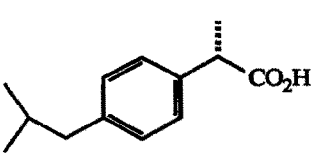
Abstract: (*S*)-2-[4'-(2"-Methylpropyl)phenyl]propanoic acid (ibuprofen) and (*S*)-2-(3'-benzoylphenyl)propanoic acid (ketoprofen) have been synthesised in high enantiomeric excess. Control of the stereochemistry was achieved by a combination of Sharpless epoxidation followed by catalytic hydrogenolysis of the introduced benzylic epoxide oxygen bond.

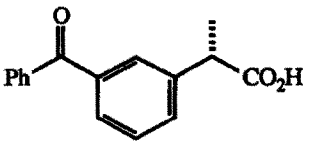
It is now recognised that enantiomers usually display different physiological activities. As a result, the asymmetric synthesis of drugs has received much attention. In particular, several methods have been reported[1] for the enantioselective synthesis of non-steroidal anti-inflammatory agents of the arylpropanoic acid class. We report the synthesis of two important members of this group, ibuprofen **1** and ketoprofen **2**, by a route we developed recently.[2] That approach employs a combination of Sharpless epoxidation followed by stereoselective hydrogenolysis of a benzylic carbon-oxygen bond to establish the stereochemistry.

The starting material for the ibuprofen synthesis was 4-trimethylsilylacetophenone **3a** which is easily prepared[3] from the reaction of chlorotrimethylsilane with the Grignard reagent derived from the ethylenedioxy acetal of 4-bromoacetophenone. Reaction of the ketone **3a** with triethyl phosphonoacetate in the presence of lithium ethoxide gave mainly the thermodynamically more stable (*E*) isomer **4a** together with a small amount of the (*Z*) isomer (17:1 ratio). Reduction of the mixture of esters with lithium aluminium hydride then yielded the allylic alcohols (**5a** and its (*Z*) isomer) (75% from **3a**) which were subjected to Sharpless epoxidation,[4] using (+) diisopropyl tartrate. The epoxide **6a** was obtained in 70% yield after chromatography. One crystallisation from pentane gave material which was greater than 98% optically pure, m.p. 41-43°C, $[\alpha]_D^{20}$ -20.0 (c = 2.86, CCl_4).

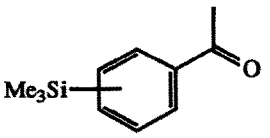
The structure of the epoxy alcohol **6a** was supported by microanalytical and spectral data. In particular the ^1H n.m.r. spectrum† showed H2 as a doublet of doublets at δ 3.10 (*J* 4.2, 6.5 Hz) and two doublets of doublets for the methylene protons at δ 3.83 (*J* 6.5, 12.2 Hz) and δ 3.97 (*J* 4.2, 12.2 Hz). The optical purity was determined on the acetate **6c**, $[\alpha]_D^{20}$ -47.0 (c = 1.33, CCl_4), by use of the chiral shift reagent, tris-[3-



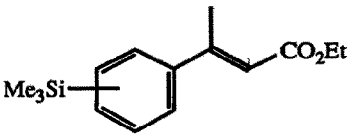
(1)



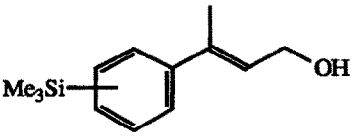
(2)



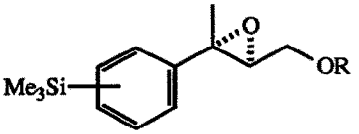
(3a) ; *p*
(3b) ; *m*



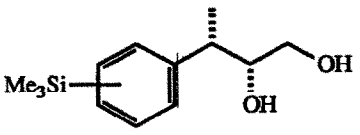
(4a) ; *p*
(4b) ; *m*



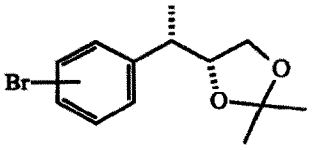
(5a) ; *p*
(5b) ; *m*



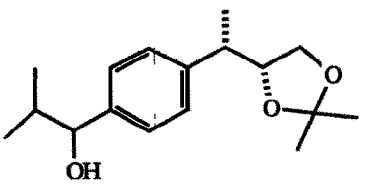
(6a) ; *p* ; R = H
(6b) ; *m* ; R = H
(6c) ; *p* ; R = Ac
(6d) ; *m* ; dinitrobenzoyl
(6e) ; *m* ; R = Ac



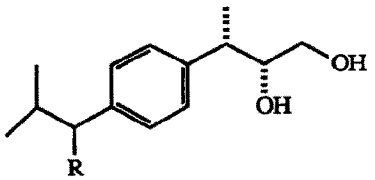
(7a) ; *p*
(7b) ; *m*



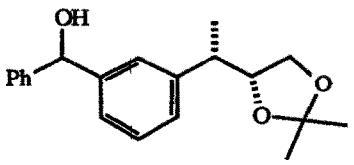
(8a) ; *p*
(8b) ; *m*



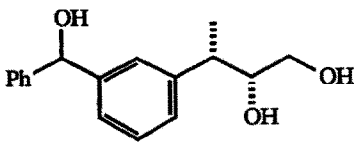
(9)



(10a) ; R = OH
(10b) ; R = H



(11)



(12)

(heptafluoropropylhydroxymethylene)-d-camphorato]europium (III) derivative, under conditions where good separation of the C3-methyl resonances was observed with the racemic epoxy alcohol.

Hydrogenolysis of the epoxy alcohol **6a** with 10% palladium on carbon at -60°C proceeded quantitatively with inversion of configuration to yield the diol **7a**, m.p. 84-86°, from pentane. Microanalytical and spectral data† were in agreement with the structure. In addition to the resonances expected for H1 and H2, the ^{1}H n.m.r. spectrum showed a doublet at δ 1.36 for the methyl group and a quintet for H3 at δ 2.79 (*J* 7 Hz). Inversion of configuration during hydrogenolysis has been established[2] with a related epoxy alcohol, 3-methyl-3-phenyloxiranemethanol, and in the present work, confirmation was obtained when the product **7a** was subsequently converted into (*S*)-ibuprofen.

After electrophilic substitution of the trimethylsilyl group in **7a** with bromine (91%, LiBr, N-chlorosuccinimide) and protection of the diol as the acetonide **8a**, the aryl lithium was prepared from the bromide **8a** by exchange with *tert*-butyllithium and added to 2-methylpropanal. Removal of the protecting group under acidic conditions, followed by hydrogenolysis of the triol **10a** with 10% palladium on carbon gave the diol **10b**. Oxidation (ruthenium trichloride/sodium periodate)[5,6] of the diol **10b** then gave (*S*)-ibuprofen in 90% yield, m.p. 50-52°C, from ethanol (lit.[7] 50-52°C). $[\alpha]_D^{20}$ +57 (c = 2.33, EtOH) [lit.[7] $[\alpha]_D^{20}$ +57 (95% optical purity)]. Analysis of the derived amide (thionyl chloride, (*S*)-phenylethylamine) by HPLC, compared with diastereoisomers as standards, showed the synthetic ibuprofen to have an optical purity of 96.4%.

Similar reactions on the *meta* substituted analogues **3b**-**7b** gave the protected bromide **8b**. In this series, the epoxy alcohol **6b** (94% from the Sharpless epoxidation) was esterified with 3,5-dinitrobenzoyl chloride for purification. The ester **6d**, on recrystallisation from ethanol, had m.p. 90-92°C $[\alpha]_D^{20}$ -32.0 (c = 1.11, CCl_4). After hydrolysis of this ester **6d**, the epoxy alcohol **6b** was converted into the acetate **6e**. When this acetate was analysed in the presence of the chiral shift reagent above, under conditions where the two enantiomers of the racemate could be observed, only one isomer could be detected. It is therefore concluded that **6b**, after recovery from the 3,5-dinitrobenzoate, has an optical purity >98%. Analytical and spectral data† for **6b** were consistent with the structure. Again, hydrogenolysis of **6b** in the presence of 10% palladium on carbon yielded the diol **7b** quantitatively with inversion of configuration. Analytical and spectral data allowed confirmation of the structure and the minor diastereoisomer, which could have arisen by hydrogenolysis with retention of configuration, could not be detected by 300 MHz ^{1}H n.m.r. spectroscopy. The two diastereoisomers have distinct ^{1}H n.m.r. spectra with the methyl doublets clearly resolved.

The diol **7b** was then protected by conversion into the acetal **8b** which in turn was treated with *tert*-butyllithium to yield the aryllithium. Addition to benzaldehyde then gave the alcohol **11** which was hydrolysed under acidic conditions to the triol **12**. Oxidation ($RuCl_3$, $NaIO_4$) of triol **12** then gave (*S*)-ketoprofen **2** in 72% yield, $[\alpha]_D^{20}$ +54.4 (c = 2.71, CH_2Cl_2) [lit.[8] +57.1 , (c = 0.76, CH_2Cl_2)] with spectral data identical with those of an authentic sample. HPLC analysis of its amide ($SOCl_2$, (*S*)-phenylethylamine) showed an optical purity of 98%.

All reactions in both the *para* and *meta* series proceed in good yields and intermediate compounds have been fully characterised.

Acknowledgement

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† 300 MHz ^1H n.m.r. data:

(2*S*,3*S*)-3-Methyl-3-(4'-trimethylsilylphenyl)oxiranemethanol **6a** δ ($CDCl_3$, D_2O): 0.26 (s, $(CH_3)_3Si$); 1.70 (s, CH_3); 3.10 (dd, 4.2 and 6.5 Hz, H2); 3.83 (dd, 6.5 and 12.2 Hz, CH_2OH); 3.97 (dd, 4.2 and 12.2 Hz, CH_2OH); 7.33 (d, 8.1 Hz, 2H, ArH); 7.51 (d, 8.1 Hz, 2H, ArH).

(2*R*,3*S*)-3-(4'-Trimethylsilylphenyl)butane-1,2-diol **7a** δ ($CDCl_3$, D_2O): 0.25 (s, $(CH_3)_3Si$); 1.36 (d, 7.0 Hz, CH_3); 2.79, (br quint, 7 Hz, H3); 3.35 (dd, 7.7 and 11.2 Hz, H1); 3.46 (dd, 3.0 and 11.2 Hz, H1); 3.75 (dt, 3.0 and 7.7 Hz, H2); 7.18 (d, 7.9 Hz, 2H, ArH); 7.45 (d, 7.9 Hz, 2H, ArH).

(2*S*,3*S*)-3-Methyl-3-(3'-trimethylsilylphenyl)oxiranemethanol **6b** δ ($CDCl_3$, D_2O): 0.27 (s, $(CH_3)_3Si$); 1.71 (s, CH_3); 3.11 (dd, 4.2 and 6.6 Hz, H2); 3.82 (dd, 6.6 and 12.2 Hz, CH_2OH); 3.98 (dd, 4.2 and 12.2 Hz, CH_2OH); 7.3-7.5 (ArH).

(2*R*,3*S*)-3-(3'-Trimethylsilylphenyl)butane-1,2-diol **7b** δ ($CDCl_3$, D_2O): 0.26 (s, $(CH_3)_3Si$); 1.36 (d, 7.0 Hz, CH_3); 2.78 (br quint, 7 Hz, H3); 3.35 (dd, 7.7 and 11.2 Hz, H1); 3.45 (dd, 3.1 and 11.2 Hz, H1); 3.76 (dt, 3.1 and 7.7 Hz, H2); 7.1-7.5 (ArH).

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