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ENANTIOSELECTIVE SYNTHESES OF 2-ARYLPROPANOIC ACIDS: (S)-2-PHENYLPROPANOIC ACID

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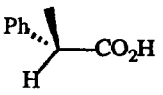
SUMMARY:

(S)-2-Phenylpropanoic acid, an intermediate for the preparation of optically active Ibuprofen, has been synthesized using, as the key steps, Sharpless epoxidation and benzylic hydrogenolysis

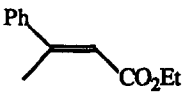
Among the non-steroidal antiinflammatory agents,[1] the 2-arylpropanoic acids are important pharmaceutical drugs and they are chiral All, except one (naproxen), of these drugs which are commercially available are sold as racemates One enantiomer gives the desired physiological response and although the other isomer is usually interconverted in the body the efficiency of this process varies between individuals.[2] The preparation of the active enantiomer is therefore desirable and a number of enantioselective syntheses of members of this class have appeared.[3] Many of these reported syntheses lack simplicity and high stereoselectivity We set out therefore to see if we could develop a route to such compounds which would introduce optical activity with high selectivity and which would have some generality for this class of compounds For pedagogical reasons we chose to demonstrate this first with an asymmetric synthesis of 2-phenylpropanoic acid (**1**) which could in turn be converted into Ibuprofen

The Sharpless procedure for the asymmetric epoxidation of allylic alcohols[4] is well known as a reliable method for obtaining optically active compounds Stereochemical control in the hydrogenolysis of benzylic groups has also been demonstrated and ranges from inversion to retention of configuration depending on the catalyst and the reaction conditions [5] However, the stereochemical outcome of the hydrogenolysis of epoxy alcohols has not been established The combination of the Sharpless epoxidation followed by hydrogenolysis of the epoxy alcohol constitutes the key steps in our synthetic route

A careful fractional distillation of the product obtained by the method of Lipkin and Stewart[6] gave essentially pure ethyl (E)-3-phenylbut-2-enoate (**2**) (>98% by g l.c) Reduction[7] of this ester by lithium aluminium hydride gave (E)-3-phenylbut-2-en-1-ol (**3**) Epoxidation of this allylic alcohol with



(1)



(2)

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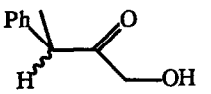
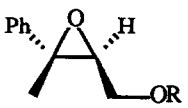
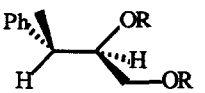


(8)



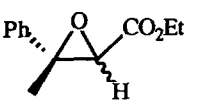
(4) R=H (±)

(5) R=H (-)

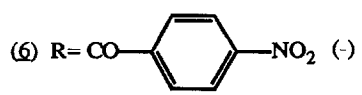


(7) R=H

(10) R=$COCH_3$



(9) (±)



(6) R= CO— —NO_2 (-)

m-chloroperoxybenzoic acid in dichloromethane gave racemic 2,3-epoxy-3-phenylbutan-1-ol (**4**) † Laevorotatory epoxy alcohol (**5**)† was obtained, by the use of (+) diisopropyl tartrate in the catalytic epoxidation procedure developed by Sharpless et al ,[8] as an oil (80% yield, 80-85% ee*) Conversion of the optically active epoxy alcohol into the p-nitrobenzoate ester and recrystallisation from ethanol gave the derivative (**6**)† m p 94-95° $[\alpha]_D$ - 10 2° (CH_2Cl_2, C = 1 26)(60% yield) Hydrolysis of this derivative with aqueous sodium hydroxide in ethanol regenerated the labile epoxy alcohol (**5**) as an oil (81% yield) This epoxy alcohol appeared to be optically pure** Hydrogenolysis of this epoxy alcohol (10% Pd/C, EtOH, NaOH) at -45° gave the diol (**7**)† contaminated with a small amount of the ketol (**8**) † This keto alcohol formed, presumably, by rearrangement of the epoxy alcohol on the catalyst [5] The diol was obtained pure by

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* From the 300 MHz ^{1}H n m r spectrum of the derived MTPA ester[13] as compared with that from the racemic epoxy alcohol derivative

** Because of the labile nature of this epoxy alcohol it has not yet been obtained analytically pure, however, the derived MTPA ester[13] showed peaks for only one diastereomer in the 300 MHz ^{1}H n m r spectrum as compared with the spectrum for the racemic epoxy alcohol derivative

flash chromatography (70% yield) and appeared to be one diastereomer by 300 MHz ^{1}H n m r spectroscopy# The absolute configuration shown follows from the subsequent oxidation Thus oxidation of the diol with ruthenium tetroxide and sodium periodate[9] gave in 52% yield homochiral (S)-2-phenylpropanoic acid $[\alpha]_D$ = +76 3, $[\alpha]_{546}$ = +91.5 (CH_2Cl_2C=0 81) [Lit.[10] $[\alpha]_D$ = +76 2 ($CHCl_3$,C=3) $[\alpha]_D$= +74 8°, $[\alpha]_{546}$ +90 9° ($CHCl_3$,C=3)] The formation of (S)-2-phenylpropanoic acid in conjunction with the prediction of the stereochemistry of the Sharpless epoxidation[4] establishes that the hydrogenolysis of the epoxy alcohol (5) proceeded with inversion of configuration at the benzylic carbon [5]

As a model for the preparation of Ibuprofen by acylation of the diacetate of diol (7), (+)-2-phenylpropyl acetate has been acylated with 2-methylpropanoyl chloride without racemisation [11] However, a report of this approach to Ibuprofen from the diol (7) prepared by an alternative route, has recently appeared in the literature with details of the acylation procedures [12]

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† **300 MHz ^{1}H nmr data:**

Compound (4/5)($CDCl_3$) 1.64, s, (CH_3), 3 07, dd, 6 3 and 4 4 Hz (COCHC), 3 4, br s, (OH), 3 77, dd, 6 3 and 12 2 Hz and 3 90, dd, 4 4 and 12 2 Hz (diastereotopic CH_2O), 7 3 complex (ArH) Compound (6) ($CDCl_3$ 1 79, s, (CH_3), 2 36, dd, 6 6 and 4 2 Hz, (COCHC), 4 49, dd, 6 6 and 12 2 Hz, and 4 78, dd, 4 2 and 12 2 Hz, (diastereotopic CH_2O), 7 3 complex (ArH), 8 28, ABq, (ArH) Compound (7) ($CDCl_3$) 1 30, d, 6 9 Hz, (CH_3), 1 78, 2 10 br s, (2 x OH), 2 74, br quintet, ≡ 7 2 Hz, ($CHCH_3$), 3 31, dd, 7 5 and 11 1 Hz, and 3 40, dd, 3 1 and 11 1 Hz, (CH_2O), 3 70, appears as a dt, 3 1, 7 5, 7 9 Hz, (CCHORC), 7 2, complex (ArH) Compound (8) ($CDCl)_3$ 1 48, d, 7 0 Hz, (CH_3), 3 07, br s, (OH), 3 77, q, 7 O Hz, (CHPh), 4 20, s, (CH_2O), 7 3 complex (ArH) Compound (10) (CCl_4) 1 27, d, 7 0 Hz, (CH_3), 1 95, s and 2 04, s, (2 x CH_3CO), 2 96, dq, 7 0 and 9 3 Hz, (PhCH), 3 67, dd, 6 3 and 12 0 Hz and 4 09, dd, 2 7 and 12 0 Hz, (diastereotopic CH_2O), 5 15, ddd, 2 7, 6 3 and 9 3 Hz, (CCHORC), 7 2, complex, (ArH)

A mixture of the diastereomers has been made from the glycidic esters (9)[14] by hydrogenolysis followed by LAH reduction Doublets appear at δ 1 30 and 1 22 for the methyl groups in the 300 MHz ^{1}H spectrum of this mixture The above optically active diastereomer showed only the doublet at δ 1 30 The n m r spectrum of the diacetate derivative (10)† showed a similar pattern to that reported but the chemical shift values were somewhat different[15] for either diastereomer

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