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Synthesis of Arylpropanoic Acids From Optically Active 2-(Iodophenyl)propanoic Acids

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Abstract: The coupling of organozinc compounds with homochiral 2-(3-iodophenyl)propanoic and 2-(4-iodophenyl)propanoic acids in the presence of palladium is a general method for the synthesis of optically active arylpropanoic acids.

One of the major groups of anti-inflammatory agents is the arylpropanoic acids where the activity resides predominantly in the (*S*) isomers. Both *meta* and *para* substituted derivatives are used clinically and, with the exception of naproxen, they are administered as racemates. Recent interest in the enantioselective synthesis of these compounds has led to the development of a variety of approaches.[1] An approach which we have developed for the synthesis of (*S*)-ibuprofen **1a** and (*S*)-ketoprofen **2a** involves a combination of Sharpless epoxidation, which induces the asymmetry followed by stereoselective catalytic hydrogenolysis of the introduced benzylic epoxide carbon-oxygen bond which establishes the stereogenic centre and then oxidative cleavage of the derived diol which gives the desired functionality.[2]

The key intermediates for those syntheses were the optically active diols **3a** and **4a**. We have now found that the diols **3a** and **4a** undergo electrophilic substitution with iodine monochloride to give the iodo diols **3b** and **4b** in high yields. On oxidation (ruthenium trichloride, sodium periodate) these diols give the corresponding optically active iodo acids **1b** and **2b** which have been found[3] to be suitable substrates for palladium catalysed coupling with a variety of organozinc compounds. Thus satisfactory coupling gives access to a range of homochiral arylpropanoic acid anti-inflammatory agents from a common precursor in each of the *meta* or *para* series.

In the present study we have coupled (*S*)-2-(4-iodophenyl)propanoic acid **1b** or its enantiomer with isobutyl, isobutenyl and phenyl zinc reagents and the *meta* isomer **2b** with phenyl, benzyl and phenylethynyl zinc derivatives to illustrate the generality of this approach for the introduction of alkyl, alkenyl, aryl, benzyl and alkynyl substituents. The zinc derivatives were made from the corresponding Grignard reagents in tetrahydrofuran by addition of anhydrous zinc chloride (1.05 equiv.). Coupling reactions between the organo zinc compounds and the iodo acids **1b** and **2b** occurred in tetrahydrofuran with bis(triphenylphospine)palladium (O) (from the Pd (II) salt by reduction with diisobutylaluminium hydride) as catalyst. In each case the optical purity of the arylpropanoic acid was determined by converting

it to the amide (thionyl chloride, (*S*)-1-phenylethylamine) followed by HPLC analysis of the resultant diastereoisomeric amides. The authentic racemic arylpropanoic acids, whose amides were required as standards for HPLC analysis, were made from the racemic *meta* and *para*[3,4] iodo acids or, in one example **2e**, from the protected precursor, (2R*,3S*)-3-(3-iodophenyl)butane-1,2-diyl diacetate **5**, followed by deacetylation and oxidation (ruthenium trichloride, sodium periodate).

The enantiomer of the iodo acid **1b** coupled with isobutylzinc to yield (*R*)-ibuprofen [**1a**, (*R*) isomer] in 75% yield, m.p. 50-52°C, with an optical purity of 96%. The spectral data were identical with those of authentic ibuprofen.[2,5] Similarly, the zinc reagent from 1-bromo-2-methyl-1-propene coupled with the (*S*) iodo acid **1b** to give the unsaturated analogue **1c** of ibuprofen, as an oil (84% yield). Its spectral data‡ were in agreement with the structure and the optical purity (98%) was determined after conversion into ibuprofen (PtO_2, H_2). When phenylzinc was used the (*S*) iodo acid **1b** gave (*S*)-2-(4-biphenylyl)propanoic acid **1d**[6], m.p. 158.5-160.5°C (62% yield; optical purity, 97%).

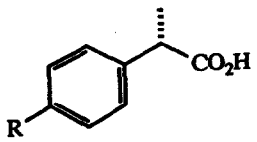
In the *meta* series, (*S*)-2-(3-biphenylyl)propanoic acid **2c** (racemate[7]), m.p. 72-75°C, was obtained from the (*S*) iodo acid **2b** and phenylzinc (74% yield; 98% optical purity). In a similar manner, the (*S*) iodo acid **2b** and phenylethynylzinc gave the acetylene derivative, (S)-2-[3-(phenylethynyl)phenyl]propanoic acid **2d**, m.p. 80-82°C in 72% yield (optical purity, 98%). Its 300 MHz ^1H n.m.r. spectrum‡ was identical with that of the racemic compound whose structure has been established by full spectral and microanalytical data. In the final example in the *meta* series, benzylzinc coupled smoothly with the (*S*) iodo acid **2b** to yield (*S*)-2-(3-benzylphenyl)propanoic acid **2e**[8], as an oil in 90% yield (97% optical purity). This compound has been converted into (*S*)-ketoprofen by oxidation with potassium permanganate.[8]

An important advantage of this method for the synthesis of enantiomers of the arylpropanoic acid group of anti-inflammatory agents is that the substituent is introduced into the phenyl ring in the final step. This allows easy access to compounds bearing the wide range of substituents which are compatible with palladium coupling conditions and in particular easily oxidisable side chains such as alkenyl and alkynyl groups which would not survive our earlier method. Because the stereochemistry of the iodo acids **1b** and **2b** is established by the combination of Sharpless epoxidation followed by heterogeneous catalytic hydrogenolysis[2] either enantiomer of the iodo acids can be equally easily prepared.

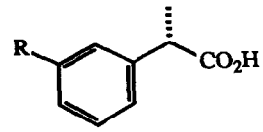
‡ 300 MHz ^1H n.m.r. data:

(*S*)-2-(4-Iodophenyl)propanoic acid **1b** δ ($CDCl_3/D_2O$): 1.49 (d, *J* 7.2 Hz, CH_3); 3.68 (q, *J* 7.2 Hz, H2); 7.07 (apparent d, *J* 8.3 Hz, 2H, ArH); 7.65 (apparent d, *J* 8.3 Hz, 2H, ArH). $[\alpha]_D^{20}$ +39.0° (c = 2.45, $CHCl_3$).

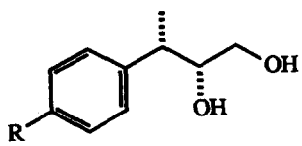
(*S*)-2-(3-Iodophenyl)propanoic acid **2b** δ ($CDCl_3/D_2O$): 1.50 (d, *J* 7.2 Hz, CH_3); 3.67 (q, J 7.2 Hz, H2); 7.07 (t, *J* 7.8 Hz, H5'), 7.29 (d, *J* 7.8 Hz, H6'), 7.61 (d, *J* 7.8, H4'), 7.67 (brs, H2'). $[\alpha]_D^{20}$ +43.4° (c = 1.20, $CHCl_3$).



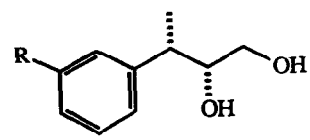
(1a) ; R = CH_2CHMe_2
(1b) ; R = I
(1c) ; R = $CH{=}CMe_2$
(1d) ; R = Ph



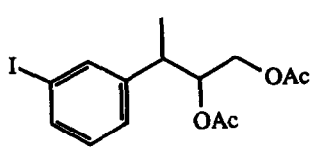
(2a) ; R = PhCO
(2b) ; R = I
(2c) ; R = Ph
(2d) ; R = $PhC{\equiv}C$
(2e) ; R = $PhCH_2$



(3a) ; R = $SiMe_3$
(3b) ; R = I



(4a) ; R = $SiMe_3$
(4b) ; R = I



(5)

(*S*)-2-(4'-[2"-Methyl-1"-propenyl]phenyl)propanoic acid **1c** δ ($CDCl_3$): 1.51 (d, *J* 7.1 Hz, C2-Me); 1.85 (d, *J* 1.1 Hz, C2"-Me); 1.89 (d, *J* 1.2 Hz, C2"-Me); 3.72 (q, *J* 7.1 Hz, H2); 6.23 (brs, H1"); 7.18 (apparent d, *J* 8.2 Hz, 2H, ArH); 7.26 (apparent d, *J* 8.2 Hz, 2H, ArH).

(*S*)-2-[3'-(Phenylethynyl)phenyl]propanoic acid **2d** δ ($CDCl_3$): 1.54 (d, *J* 7.2 Hz, CH_3); 3.75 (q, *J* 7.2 Hz, H2); 7.2-7.5 (complex, ArH).

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