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Enantioselective Syntheses of 2-Arylpropanoic Acid Non-steroidal Anti-inflammatory Drugs and Related Compounds.

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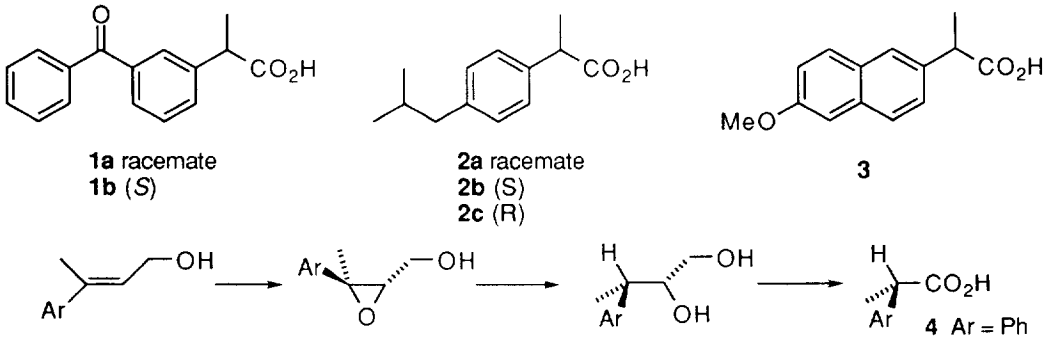
Abstract: (*S*)-2-[4'-(2"-Methylpropyl)phenylpropanoic acid (ibuprofen) and (*S*)-2-(3'-benzoylphenyl)propanoic acid (ketoprofen) have been synthesised in high enantiomeric excess. Control of stereochemistry was achieved by a combination of Sharpless epoxidation followed by catalytic hydrogenolysis of the introduced benzylic epoxide oxygen bond. Also, the coupling of organic compounds in the presence of palladium with enantiopure 2-(3-iodophenyl)propanoic and 2-(4-iodophenyl)propanoic acids, prepared by the methodology above, is a general method for the synthesis of optically active arylpropanoic acids.

It is recognised that enantiomers of biologically active compounds usually display different physiological activities. There has also been very rapid progress in asymmetric synthetic methods in recent years. As a result increasing attention is being paid to the synthesis of non-racemic chiral drugs[1]. One of the major groups of anti-inflammatory agents is the arylpropanoic acid class of non-steroidal anti-inflammatory drugs (NSAID) where the activity resides in the (*S*) isomers. Both *meta* and *para* substituted derivatives are used clinically, e.g. ketoprofen **1** and ibuprofen **2**, and with the exception of naproxen **3**, they are all currently administered as racemates. We sought to find synthetic methodology[2] which would provide a general method to introduce the stereogenic centre common to all of these NSAID's. We have developed a strategy (outlined) whereby asymmetry is introduced into the molecules by means of a Sharpless asymmetric epoxidation and then the required stereogenic centre is 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.



1a racemate
1b (*S*)

2a racemate
2b (S)
2c (R)

3

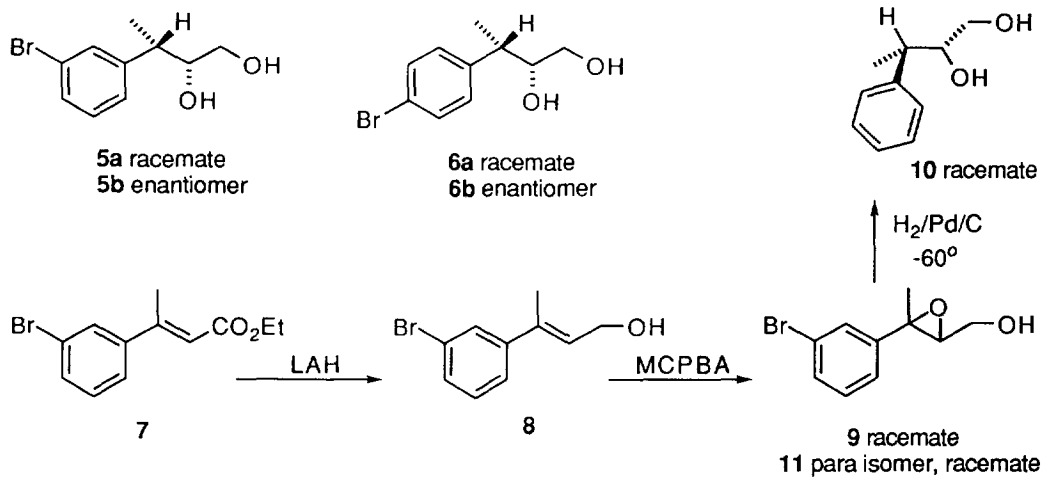
4 Ar = Ph

For pedagogical reasons we chose to demonstrate the strategy first[3] with an asymmetric synthesis of 2-phenylpropanoic acid **4.** Then, having established the viability of the route, we turned our attention to the application of this strategy to the synthesis of representative members of this class of drugs. We present here the details of work which has been described in outline earlier[4,5].

RESULTS AND DISCUSSION

In the planning stages it was deemed desirable to develop key intermediates which might allow the construction of a range of arylpropanoic acids substituted in either the *meta* or the *para* positions. To this end efforts were directed to the syntheses of the optically active bromo compounds **5b** and **6b.**

The *m*-bromo ester **7** was synthesized from *m*-bromoacetophenone by reaction with triethyl phosphonoacetate and *t*-BuOK[6]. The (*E*) isomer of ester **7** was separated by chromatography and it was reduced to the (*E*) allylic alcohol **8** by LAH. Epoxidation of this alcohol with *m*-CPBA gave the racemic epoxide **9.** Catalytic hydrogenolysis of this epoxide over Pd/C, even at -60°C, not only effected the required cleavage of the benzylic epoxide bond but also removed the bromine to give the diol **10.** There was no selectivity apparent in this process since the compounds isolated from an interrupted reaction were the starting material **9** and the product **10** only. A similar observation has been made also for the *p*-bromo epoxide **11**[7].



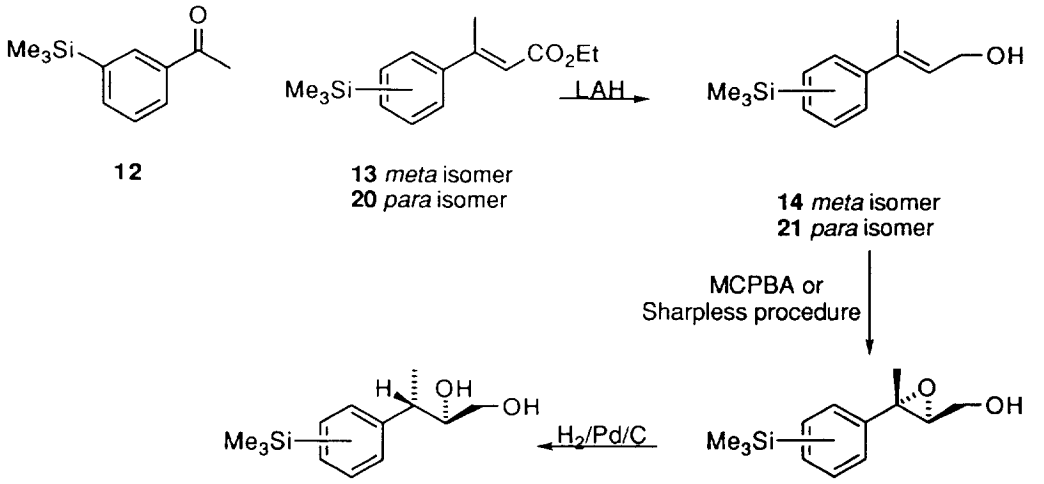
A Synthesis of (S)-Ketoprofen

The ease of hydrogenolysis of the aromatic bromine from the epoxide **9** required that the bromine should be introduced into the molecule after the hydrogenolysis step if the bromo compound **5** was to serve as a common intermediate for the synthesis of the *meta* substituted drugs. Although synthetically not the most desirable route, this was readily achieved by first taking out the bromine and then putting it back in later.

Conversion of *m*-bromoacetophenone to *m*-(trimethylsilyl)acetophenone **12** *via* a reaction between the Grignard reagent, formed from the corresponding bromo acetal, with chlorotrimethylsilane, followed closely the procedure described for the *para* derivative[8]. Reaction of the ketone **12** with triethyl phosphonoacetate and *t*-BuOK gave mainly the (*E*) ester **13** with a small amount of the (*Z*) isomer which was removed by chromatography. Reduction of the (*E*) isomer with LAH gave the (*E*) allylic alcohol **14.**

Epoxidation of this alcohol, with *m*-CPBA, gave the racemic epoxide **15a,** and by the catalytic Sharpless epoxidation procedure[9], with (+)-diisopropyl tartrate, gave the optically active epoxide **15b,** as an oil, approximately 90% optically pure. The 3,5-dinitrobenzoate derivative **15c** was crystalline and this could be recrystallized to enhance the optical purity, mp 90-92°C, $[\alpha]_D$ = -32 (c = 1.11, CCl_4). Hydrolysis of this purified derivative gave the epoxide **15b** which was estimated to be, at least, 98% optically pure. The determinations of the optical purities of these samples were made by use of a chiral NMR shift reagent on the derived acetate. The singlet resonances, at 300MHz, for the methyl groups on the epoxide rings of the two enantiomers **15d** were clearly discerned by this method. Under these conditions the methyl peak for only one enantiomer in the optically pure material **15e** was seen. At this stage the isomer was presumed to have the configuration (2*S*, 3*S*) on the

basis of the predictions which can be made for the Sharpless epoxidation procedure[10].



5a ← LiBr, NCS — **16a** *meta* isomer, racemate
5b ← — **16b** *meta* isomer, enantiomer
16c *meta* isomer, diacetate, racemate

6a ← LiBr, NCS — **23a** *para* isomer, racemate
6b ← — **23b** *para* isomer, enantiomer

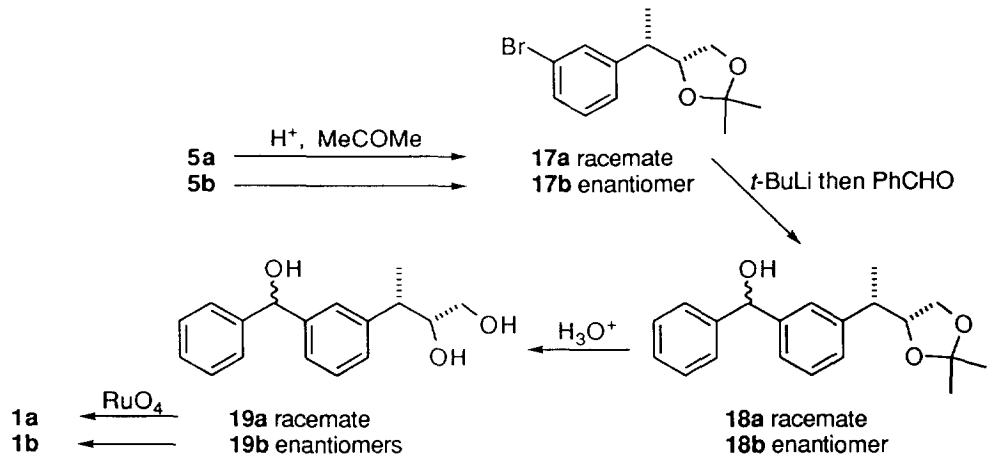
15a *meta* isomer, racemate
15b *meta* isomer, enantiomer
15c *meta* isomer, dinitrobenzoate
15d *meta* isomer, acetate, racemate
15e *meta* isomer, acetate, enantiomer
22a *para* isomer, racemate
22b *para* isomer, enantiomer
22c *para* isomer, acetate

Catalytic hydrogenolysis of both the racemic epoxide **15a** and the enantiomer **15b** at -60°C over Pd/C proceeded with almost complete inversion of stereochemistry. The ^{1}H NMR (300 MHz) spectrum of the (2*R*, 3*S*) isomer of the diol **16b** showed a doublet for the methyl peak at δ = 1.34 (J,7.1H). Another doublet, with an intensity comparable to the ^{13}C-H satellite peak for the first doublet, was seen at δ = 1.29 (J,7.1H). It was presumed that this minor doublet belonged to the (2*R*, 3*R*) diastereomer because it was found in greater abundance when the hydrogenolysis was run at rt. The configuration of the major diastereomer was confirmed by the eventual conversion of this material to ketoprofen of known configuration. Treatment of the diol **16b** with LiBr and NCS effected electrophilic substitution of the silyl moiety by bromine to give the key intermediate **5b.** An attempted Friedel-Crafts benzoylation[11] of the diacetate **16c** of the racemic silyl compound **16a** was not successful.

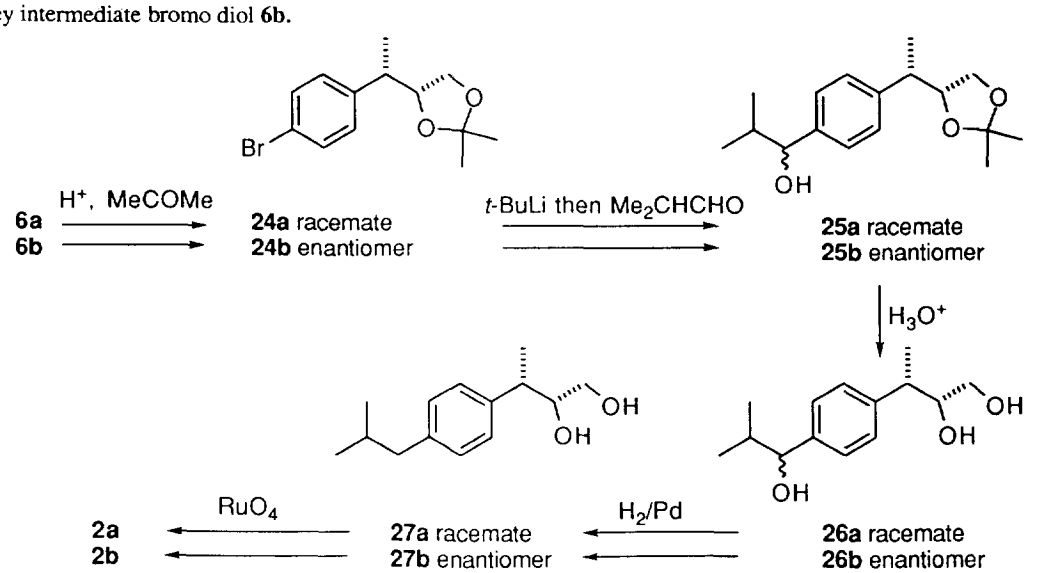
The bromo diol **5b** was protected as the acetal **17b** and this underwent a metal-halogen exchange with *t*-BuLi, at -78°C, and the resultant aryllithium derivative reacted with benzaldehyde to yield the alcohol **18b.** Hydrolysis of the acetal and oxidation of the triol **19b** with $RuO_4/NaIO_4$[12,13] gave (*S*)-ketoprofen **1b**, $[\alpha]_D$ +54.4 (c = 2.71,CH_2Cl_2 [lit.[14] +57.1, (c = 0.76, CH_2Cl_2)]; with spectral data identical with an authentic sample of racemic ketoprofen. HPLC analysis[15] of the amide derived from (*S*)-phenylethylamine showed that the optical purity was 98%.

A Synthesis of (S)-Ibuprofen

The bromo diol **6b** was made by a similar route to that used for bromo diol **5b**. The reaction between *p*-(trimethylsilyl)acetophenone[8], triethyl phosphonoacetate and *t*-BuOK gave, in 66% yield, a mixture of the *E* and *Z* isomers **20,** in the ratio of 8:1, from which the *E* isomer could be obtained pure by chromatography. However,



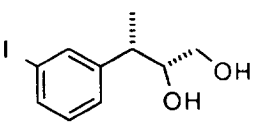
it was found that the use of EtOLi[7], as the base in this reaction, produced, in almost quantitative yield, mainly the *E* isomer (*E*/*Z* = 17:1) and this mixture was carried through to the subsequent steps. Reduction with LAH gave, in 75% overall yield from *p*-trimethylsilylacetophenone, the allylic alcohols **21** (isomer ratio unchanged). These allylic alcohols were epoxidised with MCPBA to give the racemic epoxide **22a**, and with the Sharpless procedure[9] to give the optically active epoxide **22b**. The epoxides **22a** and **22b**, derived from the (*E*) isomer, were obtained pure by chromatography and they were solids. The optical purity of **22b** was determined, on the derived acetate **22c**, by the chiral shift reagent method described above. The optical purity of the epoxide obtained directly from the asymmetric epoxidation was enhanced from 90% to greater than 98% by one recrystallization from pentane, mp 41-43°C, $[\alpha]_D$ = -20 (c = 2.86, CCl_4). Catalytic hydrogenolysis of the epoxides, **22a** or **22b**, over Pd/C at -60°C, proceeded, with inversion of configuration, to give the diols, **23a** or **23b**, which were at least 98% diastereomerically pure by ^1H NMR. The confirmation of the absolute configuration of the diol **23b**, mp 84-86°C, as (2*R*, 3*S*) was obtained when this diol was subsequently converted to (*S*)-ibuprofen. Replacement of the trimethylsilyl group with bromine, by electrophilic substitution, gave the key intermediate bromo diol **6b**.



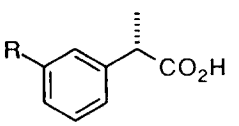
The bromo diol **6b** was protected as the acetal **24b** and this underwent a metal-halogen exchange with *t*-BuLi, at -78°C, and the resultant aryllithium derivative reacted with 2-methylpropanal to yield the alcohols **25b**. Removal of the protecting group, under acidic conditions, gave the triols **26b** which underwent hydrogenolysis, on Pd/C, to the diol **27b**. Oxidation of this diol, with $RuCl_3/NaIO_4$, gave, in 90% yield, (*S*)-ibuprofen, **2b**, mp 50-52°, $[\alpha]_D$ =+57 (c = 2.33, EtOH) [lit.[16] mp 50-52°, $[\alpha]_D$ =+57 (95% ee)]. Analysis, by HPLC, of the derived (*S*)-phenylethylamide, showed that the optical purity was 96% ee.

The synthesis of key intermediates and their conversion to arylpropanoic acids

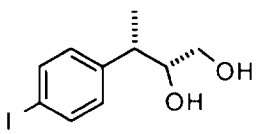
The realisation of the goal to make the key intermediates **5** and **6** led us to think about the possibility of making more generally useful key intermediates. It was considered that the silyl derivatives **16** and **23** could be converted first to the iodo diols **28** and **29** and that these then could be converted to the corresponding acids **30** and **31**. These iodo acids might well undergo Pd catalysed coupling[17] with a variety of organozinc reagents to give access to a range of actual or potential arylpropanoic acid anti-inflammatory agents from a common precursor for each of the *meta* or *para* series of such drugs. An important advantage of this method would be the fact that the substituent would be introduced into the phenyl ring as the final step. This should allow easy access to compounds bearing a wide range of substituents which are compatible with Pd coupling conditions and, in particular, easily oxidizable side chains such as alkenyl and alkynyl groups which would not survive the earlier method described above. Because the asymmetry of the iodo acids would be controlled by a Sharpless epoxidation either enantiomer of potential drugs would be readily available for pharmacological testing.



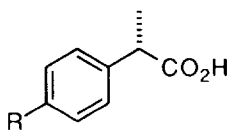
28a racemate
28b enantiomer



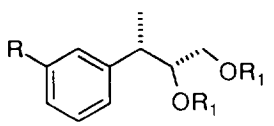
R = I	**30a** racemate **30b** enantiomer
R = Ph	**34a** racemate **34b** enantiomer
R = Ph—≡	**35a** racemate **35b** enantiomer
R = $PhCH_2$	**36a** racemate **36b** enantiomer



29a racemate
29b enantiomer



R = I	**31a** racemate **31b** enantiomer
R = CH=CMe_2	**32a** racemate **32b** enantiomer
R = Ph	**33a** racemate **33b** enantiomer



37a R = I, R_1 = Ac
37b R = $PhCH_2$, R_1 = Ac
37c R = $PhCH_2$, R_1 = H

The diols **16a**, **16b**, **23a** and **23b** undergo electrophilic substitution with ICl to give the iodo diols **28a**, **28b**, **29a** and **29b**, respectively, in high yield. Oxidation of these diols with $RuCl_3/NaIO_4$ give the corresponding racemic and optically active iodo acids **30a**, **30b**, **31a** and **31b** which have been found to be suitable substrates for Pd catalyzed coupling with a variety of organozinc compounds. By way of illustration we have coupled (*S*)-2-(4-iodophenyl)propanoic acid **31b**, or its enantiomer, with isobutyl, isobutenyl and phenylzinc reagents and the *meta* isomer, (*S*)-2-(3-iodophenyl)propanoic acid **30b**, with phenyl, benzyl and

phenylethynylzinc reagents. The structures of the arylpropanoic acids **2b** and **32-36** which were prepared in this manner are shown. The zinc derivatives were made from the corresponding Grignard reagents in THF by the addition of anhydrous $ZnCl_2$. Coupling reactions between the organozinc compounds and the iodo acids **30b** or **31b** occurred in THF with bis(triphenylphosphine)Pd[0] as catalyst, prepared *in situ* by DIBALH reduction of the Pd[II] salt. The optical purity of the arylpropanoic acids obtained was determined, in each case, by conversion to the (*S*)-1-phenylethylamide diastereomers followed by HPLC analysis on SiO_2. The racemic arylpropanoic acids, whose (*S*)-1-phenylethylamide diastereomers were required as standards for the HPLC analysis, were made, in a similar manner, from the racemic *meta* and *para* iodo acids **30a** and **31a**[17,18] or, in one example compound **36a**, from the protected precursor, (2*RS*, 3*SR*)-3-(3-iodophenyl)butane-1,2-diyl diacetate **37a**, followed by hydrolysis and oxidation.

Thus in the *para* series the enantiomer of the iodo acid **31b** coupled with isobutylzinc to give, in 75% yield and 96% optical purity, (*R*)-ibuprofen (**2c**), m.p. 50-52°C. The spectral data were identical with those of authentic ibuprofen.[16] Similarly, the zinc reagent from 1-bromo-2-methyl-1-propene coupled with the (*S*) iodo acid **31b** to give, in 84% yield, the unsaturated analogue of ibuprofen **32b**, as an oil . The spectral data for analogue **32b** were in agreement with the structure and its optical purity was determined to be 98% after reduction to ibuprofen. When phenylzinc was used the (*S*) iodo acid **31b** gave, in 62% yield and 97% optical purity, (*S*)-2-(4-biphenylyl)propanoic acid **33b**[19], m.p. 158.5-160.5°C. In the *meta* series, (*S*)-2-(3-biphenylyl)propanoic acid **34b** (racemate reported[20]), m.p. 72-75°C, was obtained, in 74% yield and 98% optical purity, from the (*S*) iodo acid **30b** and phenylzinc. In a similar manner, the (*S*) iodo acid **31b** and phenylethynylzinc gave, in 72% yield and 98% optical purity, the acetylene derivative, (S)-2-[3-(phenylethynyl)phenyl]propanoic acid **35b**, m.p. 80-82°C. Its 300 MHz ^{1}H n.m.r. spectrum was identical with that of the racemic compound **35a** 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 **30b** to give, in 90% yield and 97% optical purity, (*S*)-2-(3-benzylphenyl)propanoic acid **36b**[14], as an oil. This compound has been converted into (*S*)-ketoprofen **1b** by oxidation with $KMnO_4$.[14]

Acknowledgements

We wish to thank the Australian Research Council for financial support and Mr P J Hayball (Repatriation General Hospital, Daw Park, Australia) for the determination of enantiomeric purity of the arylpropanoic acids.

EXPERIMENTAL SECTION

General Procedure. Melting points were taken on a Kofler hot stage apparatus under a Reichert microscope and are uncorrected. ^{1}H spectra were recorded on Bruker CXP-300 or ACP-300 (or 60 MHz on Varian T60) instruments. TMS (δ 0.00 ppm) was used as internal reference. Optical rotations were measured with a Perkin-Elmer 141MC Polarimeter at 20°C in the solvents specified. MS were obtained at an ionisation potential of 70 eV. Elemental analyses were carried out by the Canadian Microanalytical Service Ltd., New Westminster, Canada. Flash chromatography[21] was performed with Merck Kieselgel 60 (230-400 mesh). TLC was done with Merck DC-Alufolien Kieselgel 60 F_{254} plates which were visualized either with UV light or by immersion in acidic ammonium molybdate solution. All solvents were distilled before use. Anhyd Et_2O and THF were distilled from Na/benzophenone. Other anhyd solvents and reagents were prepared according to standard laboratory procedures[22].

2-Methyl-2-[3'-(trimethylsilyl)phenyl]-1,3-dioxolane. To 3-bromoacetophenone (25.6 g, 0.13 mol) in benzene (130 mL) were added ethylene glycol (9.3 g, 0.15 mol) and TsOH (0.1 g). The flask was fitted with a Dean-Stark trap and the mixture refluxed for 20 h. After cooling to rt the mixture was washed with Na_2CO_3 solution then H_2O. The organic phase was dried with Na_2SO_4 and the solvent removed. Distillation gave 2-(3'-bromophenyl)-2-methyl-1,3-dioxolane as a colourless oil (31.1 g, 98%): bp 82°C/0.3 mm Hg (lit[23]: bp 128-130°C/12 mm Hg). A dry flask was charged with Mg turnings (2.29 g, 94.1 mmol), anhyd THF (110 mL) and a flake of I_2. The flask was heated to 60°C and the bromo dioxolane (22.2 g, 91.5 mmol) in THF (25 mL) was added over 2 h. After a further 4 h at 60°C, TMSCl (14.4 g, 133 mmol) was added and the mixture stirred

overnight. THF was removed in vacuo and the residue dissolved in CH_2Cl_2, washed with H_2O and dried with Na_2SO_4. The solvent was removed to give a white crystalline solid (19.42 g, 90%). Recrystallization from MeOH gave the silyl dioxolane: mp 119-120°C; bulb-to-bulb distilled at 85-95°C/0.1 mm Hg (heated block); ^1H NMR (60 MHz, CCl_4) δ 0.31 (s, 9H), 1.59 (s, 3H), 3.50-4.17 (m, 4H), 7.17-7.60 (m, 4H). Anal. Found: C, 65.60; H, 8.27%. Calcd for $C_{13}H_{20}O_2Si$: C, 66.05; H, 8.53%.

3-(Trimethylsilyl)acetophenone (12). The acetal above (6.2 g, 26.3 mmol) was dissolved in MeOH (25 mL), H_2O (5 mL), and 10% HCl (1.5 mL). After 1 h at rt the MeOH was removed in vacuo, the residue dissolved in CH_2Cl_2 and washed with $NaHCO_3$ solution. The organic phase was dried with Na_2SO_4 and the solvent removed. Distillation of the residue gave the silyl ketone as a colourless oil (4.9 g, 97%): bp 68°C/0.1 mm Hg; ^1H NMR (60 MHz, CCl_4) d 0.29 (s, 9H), 2.50 (s, 3H), 7.21-8.14 (m, 4H) (lit[24]: no data reported).

Ethyl (*E*)-3-[3'-(Trimethylsilyl)phenyl]-2-butenoate (13). To *t*-BuOK (11.37 g, 101 mmol) in anhyd THF (100 mL) at 0°C in a N_2 atm, was added triethyl phosphonoacetate (21.1 g, 90.5 mmol). After 30 min at rt, **12** (17.38 g, 90.5 mmol) in THF (20 mL) was added and the mixture stirred overnight at rt. Further triethyl phosphonoacetate (2.8 g, 14.5 mmol) was added and the reaction mixture stirred for 24 h. The THF was removed in vacuo and the residue dissolved in CH_2Cl_2, washed with dilute HCl and dried with Na_2SO_4. The solvent was removed and the residue purified by chromatography with hexane/CH_2Cl_2 as eluant to give **13** (10.0 g, 42%): bp 107°C/0.05 mm Hg; ^1H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 9H), 1.32 (t, 3H, J=7.1 Hz), 2.59 (d, 3H, J=1.2 Hz), 4.22 (q, 2H, J=7.1 Hz), 6.12 (q, 1H, J=1.2 Hz), 7.25-7.59 (m, 4H). Anal. Found: C, 68.50; H, 8.43%. Calcd for $C_{15}H_{22}O_2Si$: C, 68.66; H, 8.45%.

(*E*)-3-[3'-(Trimethylsilyl)phenyl]-2-buten-1-ol (14). To LAH (1.2 g, 31.6 mmol) in anhyd Et_2O (30 mL) at -78°C was added **13** (7.4 g, 28.2 mmol), and the mixture stirred at -78°C for 6 h. After *cautious* addition of EtOAc and 10% HCl the ethereal layer was decanted and the aqueous layer extracted with three portions of Et_2O. The organic fractions were combined, dried with Na_2SO_4 and the solvent removed. Residual **13** (2.6 g, 9.9 mmol) was removed by chromatography with a gradient of hexane/EtOAc as eluant to give **14** as a colourless oil (3.6 g, 58%): bp 130°C/0.1 mm Hg; ^1H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 1.55 (br s, 1H), 2.09 (d, 3H, J=1.3 Hz), 4.37 (d, 2H, J=6.9 Hz), 5.96 (dt, 1H, J= 1.3 Hz and 6.8 Hz), 7.25-7.55 (m, 4H). HRMS 222.0681, calculated for ($C_{13}H_{20}OSi$) 222.0681.

(2*RS*,3*RS*)-3-Methyl-3-[3'-(trimethylsilyl)phenyl]oxiranemethanol (15a). To **14** (1.00 g, 4.55 mmol) in CH_2Cl_2 (15 mL) at 0°C was added *m*-CPBA (80%, 1.08g, 5.00 mmol) and the mixture was stirred at 0°C for 40 min. This mixture was then added dropwise to a vigorously stirred excess of 10% NaOH/NaCl solution, then 0.1 M $Na_2S_2O_3$ solution (50 mL) was added. The organic layer was dried with $MgSO_4$ and the solvent removed. Flash chromatography with CH_2Cl_2/EtOAc (90/10, v/v) as eluant gave **15a** as a colourless oil (1.0 g, 93%): bp 102°C/0.05 mm Hg; ^1H NMR (300 MHz, $CDCl_3$, D_2O) δ 0.27 (s, 9H), 1.71 (s, 3H), 3.11 (dd, 1H, J=6.5 Hz and 4.2 Hz), 3.82 (dd, 1H, J=6.6 Hz and 12.2 Hz), 3.98 (dd, 1H, J= 4.2 Hz and 12.2 Hz), 7.25-7.48 (m, 4H). Anal. Found: C, 65.38; H, 8.40%. Calcd for $C_{13}H_{20}O_2Si$: C, 66.06; H, 8.53%.

(2*S*,3*S*)-3-Methyl-3-[3'-(trimethylsilyl)phenyl]oxiranemethanol (15b). Following the procedure of Sharpless[9], a flask was charged with (L)-(+)-diisopropyl tartrate (65 mg, 0.28 mmol) and anhyd CH_2Cl_2 (35 mL) and cooled to -20°C. To the flask were added activated, powdered 4A sieves (0.20 g), Ti(O*i*Pr)4 (53 mg, 0.19 mmol), *t*-BuOOH (1.55 mL of a 4.8 M CH_2Cl_2 solution, 7.44 mmol) and, after 1 h, **14** (0.88 g, 4.0 mmol) in CH_2Cl_2 (2mL). After 3.5 h at -20°C, 10% aqueous NaCl/NaOH solution (0.32 mL) and Et_2O (3.6 mL) were added and the mixture was allowed to warm to 10°C and remain there for 10 min. $MgSO_4$ (0.32 g) and Celite (0.04 g) were added and the reaction stirred for 15 min. Unreacted *t*-BuOOH was removed from the filtered solution by azeotropic distillation with toluene. Flash chromatography with CH_2Cl_2/EtOAc (95/5, v/v) as eluant gave **15b** as a colourless oil (0.88 g, 94%): ^1H NMR (300 MHz, $CDCl_3$) spectrum identical to that of

15a.

Preparation and Hydrolysis of (2*S*,3*S*)-3-Methyl-3-[3'-(trimethylsilyl)phenyl]oxiranemethyl 3,5-Dinitrobenzoate (15c). To **15b** (0.68 g, 2.88 mmol) in anhyd CH_2Cl_2 (11 mL) at 0°C in a N_2 atm, were added 3,5-dinitrobenzoyl chloride (0.69 g, 2.97 mmol) and triethylamine (350 mg, 3.46 mmol) and the mixture was stirred overnight at rt, then 10% NaOH solution (10 mL) was added and the organic phase washed with H_2O and dried with Na_2SO_4. Removal of the solvent and flash chromatography, with hexane/EtOAc (85/15, v/v) as eluant, gave the 3,5-dinitrobenzoate as a white crystalline solid (0.97 g, 84%): mp 85.5-90°C which was recrystallized from EtOH (x2): mp 90-92°C; $[\alpha]_D^{20}$=-32.0 (c=1.11, CCl_4). The ester (1.66 g, 4.17 mmol) was hydrolysed with K_2CO_3 (0.63 g, 4.59 mmol) in MeOH (25 mL). After 2 h at rt, the MeOH was removed in vacuo and the residue dissolved in CH_2Cl_2, washed with H_2O and dried with $MgSO_4$. Removal of the solvent and flash chromatography with CH_2Cl_2/EtOAc (90/10, v/v) as eluant gave enantiomerically enriched **15** (0.73 g, 75%).

(2*S*,3*S*)-3-Methyl-3-[3'-(trimethylsilyl)phenyl]oxiranemethyl Acetate (15e). To **15b** (71 mg, 0.30 mmol) in pyridine (0.7 mL) was added Ac_2O (0.4 mL). After 16 h at rt the mixture was diluted with CH_2Cl_2, washed with H_2O, 5% HCl until acidic, 5%$NaHCO_3$ solution and H_2O. Removal of the solvent and flash chromatography with hexane/EtOAc (90/10, v/v) as eluant gave **15e** as a colourless oil (70 mg, 82%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 9H), 1.71 (s, 3H), 2.10 (s, 3H), 3.09 (dd, 1H, J=4.3 Hz and 6.7 Hz), 4.18 (dd, 1H, J=6.75 Hz and 12.2 Hz), 4.45 (dd, 1H, J=4.3 Hz and 12.2 Hz), 7.35 (m, 4H).

(2*RS*,3*RS*)-3-Methyl-3-[3'-(trimethylsilyl)phenyl]oxiranemethyl Acetate (15d). Racemic **15d** was obtained similarly to **15e** from **15a**. ^1H NMR ($CDCl_3$) spectrum identical to that of **15e**.

(2*RS*,3*SR*)-3-[3'-(Trimethylsilyl)phenyl]butane-1,2-diol (16a). Pd on carbon (10%, 0.77 g), EtOH (30 mL) and 1M NaOH solution (1.0 mL) were stirred in a H_2 atm for 1.5 h, then cooled to -60°C. **15a** (0.58 g, 2.46 mmol) in EtOH (10 ml) was added over 10 min and the mixture stirred at -60°C for 6 h, then warmed to rt and filtered through Celite. Removal of the solvent and flash chromatography with CH_2Cl_2/EtOAc (90/10, v/v) gave **16a** as a colourless oil (0.56 g, 97%): ^1H NMR (300 MHz, $CDCl_3$, D_2O) δ 0.26 (s, 9H), 1.36 (d, 3H, J=7.0 Hz), 2.78 (quint, 1H, J=7.1 Hz), 3.35 (dd, 1H, J=7.7 Hz and 11.2 Hz), 3.45 (dd, 1H, J=3.1 Hz and 11.2 Hz), 3.76 (dt, 1H, J=3.1 Hz and 7.7 Hz), 7.16-7.40 (m, 4H). This product was characterised as the diacetate **16c**.

(2*R*,3*S*)-3-[3'-(Trimethylsilyl)phenyl]butane-1,2-diol (16b). In a similar manner **16b** was obtained from **15b**. ^1H NMR ($CDCl_3$, D_2O) spectrum identical to that of **16a**.

(2*RS*,3*SR*)-3-[3'-(Trimethylsilyl)phenyl]butane-1,2-diyl Diacetate (16c). Diol **16a** (30 mg) was dissolved in pyridine (0.75 mL) and Ac_2O (0.5 mL). After 16 h at rt, CH_2Cl_2 was added to the mixture and it was washed with H_2O, 5% HCl until acidic, 5% $NaHCO_3$ solution and H_2O. Removal of the solvent and flash chromatography with CH_2Cl_2 as eluant gave **16c** (38 mg, 95%) as a solid after bulb-to-bulb distillation: 120-125°C/0.04 mm Hg (heated block); mp 52-53°C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9H), 1.30 (d, 3H, J=6.9 Hz), 2.02 (s, 3H), 2.11 (s, 3H), 3.04 (quint, 1H, J=7.0 Hz), 3.79 (dd, 1H, J=6.4 Hz and 12.0 Hz), 4.12 (dd, 1H, J=2.8 Hz and 12.0 Hz), 5.24 (m, 1H), 7.19-7.40 (m, 4H). Anal. Found: C, 63.60; H, 8.13%. Calcd for $C_{17}H_{26}SiO_4$: C, 63.32; H, 8.13%.

(2*RS*,3*SR*)-3-(3'-Bromophenyl)butane-1,2-diol (5a). Following the procedure of Wilbur[25], **16a** (364 mg, 1.53 mmol) was dissolved in MeOH (3 mL), LiBr (160 mg, 1.84 mmol) and NCS (246 mg, 1.84 mmol) were added and the mixture stirred at rt for 1 h. The MeOH was removed in vacuo, the residue dissolved in CH_2Cl_2, washed with H_2O and dried over $MgSO_4$. Flash chromatography with EtOAc/hexane (50/50, v/v) as eluant gave **5a** as a colourless oil (334 mg, 89%): ^1H NMR (300 MHz, $CDCl_3$, D_2O) δ 1.29 (d, 3H, J=7.1 Hz), 2.71 (quint, 1H, J=7.3 Hz), 3.25 (dd, 1H, J=7.8 Hz and 11.3 Hz), 3.37 (dd, 1H, J=2.8 Hz and 11.3 Hz), 3.64 (dt, 1H, J=2.8 Hz and 7.8 Hz), 7.09-7.37 (m, 4H).

(2*R*,3*S*)-3-(3'-Bromophenyl)butane-1,2-diol (5b). The optically active diol **5b** was prepared in a similar manner from **16b**. ^{1}H NMR ($CDCl_3$, D_2O) spectrum identical to that of **5a**.

(4*RS*,1'*SR*)-4-[1'-(3''-Bromophenyl)ethyl]-2,2-dimethyl-1,3-dioxolane (17a). Racemic diol **5a** (420 mg, 1.71 mmol) in anhyd acetone (18 mL) and TsOH (7 mg) were stirred at rt in a N_2 atm for 5 h. Saturated $NaHCO_3$ solution was added and the acetone removed in vacuo. The residue was dissolved in CH_2Cl_2, washed with H_2O and dried with $MgSO_4$. Removal of the solvent, flash chromatography with hexane/EtOAc (90/10, v/v) as eluant and bulb-to-bulb distillation gave **17a** (385mg, 79%): 125°C/0.1 mm Hg (heated block); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, 3H, J=6.4 Hz), 1.37 (s, 3H), 1.41 (s, 3H), 2.77 (quint, 1H, J=7.0 Hz), 3.51 (dd, 1H, J=6.9Hz and 8.2 Hz), 3.75 (dd, 1H, J=6.2Hz and 8.3 Hz), 4.14 (m, 1H), 7.11-7.37 (m, 4H). HRMS 284.0418, calcd for ($C_{13}H_{17}BrO_2$) 284.0418.
(4*R*, 1'*S*)-4-[1'-(3''-Bromophenyl)ethyl]-2,2-dimethyl-1,3-dioxolane (17b). The optically active acetal **17b** was obtained in a similar manner from **5b**. ^{1}H NMR ($CDCl_3$) spectrum identical to that of **17a**.

(4'''*RS*,1''*SR*, 1*RS*)- and (4'''*RS*,1''*SR*,1*SR*)-{3'-[1''-(2''',2'''-Dimethyl-1''',3'''-dioxolan-4'''-yl)ethyl]phenyl}phenylmethanol (18a). Bromo compound **17a** (338 mg, 1.19 mmol) was dissolved in anhyd Et_2O and cooled to -78°C under N_2. *t*-BuLi (1.42 mL of a 1.75 M hexane solution, 2.49 mmol) was added and these reagents were stirred at - 78°C for 1.75 h before benzaldehyde (297 mg, 2.8 mmol) was added. After the mixture had warmed to rt, it was diluted with CH_2Cl_2, washed with H_2O and dried with $MgSO_4$. Removal of the solvent and flash chromatography with hexane/EtOAc (80/20, v/v) as eluant gave **18a** as a colourless oil (280 mg, 76%): ^{1}H NMR (60 MHz, $CDCl_3$, D_2O) δ 1.30 (d, 3H, J=7 Hz), 1.35 (s, 3H), 1.40 (s, 3H), 2.75 (quint, 1H, J=7 Hz), 3.30-4.40 (complex, 3H), 5.80 (s, 1H), 6.92-7.43 (m, 9H).
(4'''*R*,1''*S*,1*RS*)-{3'-[1''-(2''',2'''-Dimethyl-1''',3'''-dioxolan-4'''-yl)ethyl]phenyl}phenylmethanol (18b). The optically active intermediate **18b** was obtained in a similar manner from **17b**. ^{1}H NMR ($CDCl_3$) spectrum identical to that of **18a**.

(2*RS*,3*SR*,1''*RS*)- and (2*RS*,3*SR*,1''*SR*)-3-[3'-(Hydroxyphenylmethyl)phenyl]butane-1,2-diol (19a). The intermediate **18a** (68 mg, 0.22 mmol) was dissolved in MeOH (1 mL), H_2O (0.2 mL) and 5% HCl (0.06 mL) and allowed to stand at rt for 8 h then at -20°C for 16 h. The MeOH was removed in vacuo and the residue dissolved in CH_2Cl_2, washed with H_2O and dried with $MgSO_4$. Flash chromatography with EtOAc/hexane (70/30, v/v) as eluant gave **19a** as a colourless oil (55 mg, 93%): ^{1}H NMR (300 MHz, $CDCl_3$, D_2O) δ 1.28 (d, 3H, J=7.0 Hz), 2.75 (quint, 1H, J=6.9 Hz), 3.23 (dd, 1H, J=7.5 Hz and 11.3 Hz), 3.37 (dd, 1H, J=2.8 Hz and 11.3 Hz), 3.64 (dt, 1H, J=2.5 Hz and 7.4 Hz), 5.74 (s, 1H), 7.03-7.32 (m, 9H).
(2*R*,3*S*,1''*RS*)-3-[3'-(Hydroxyphenylmethyl)phenyl]butane-1,2-diol (19b). The optically active triol **19b** was obtained in a similar manner from **18b**. ^{1}H NMR ($CDCl_3$, D_2O) spectrum identical to that of **19a**.
(*RS*)-2-(3'-Benzoylphenyl)propanoic acid (1a). Following the procedure of Sharpless[12], **19a** (55 mg, 0.20 mmol) was dissolved in CCl_4 (1.1 mL), CH_3CN (1.1 mL) and H_2O (1.7 mL) and treated with $RuCl_3.H_2O$ (1.1 mg, 0.005 mmol) and $NaIO_4$ (225 mg, 1.0 mmol). The mixture was stirred vigorously at rt for 1.25 h, then diluted with CH_2Cl_2, washed with H_2O and dried with $MgSO_4$. Flash chromatography with hexane/EtOAc (1/1, v/v) gave **1a** as a colourless oil (37 mg, 72%) which had spectral data identical with those of an authentic sample of ketoprofen.
(*S*)-2-(3'-Benzoylphenyl)propanoic acid (1b). (*S*)-Ketoprofen was obtained in a similar manner from **19b**, as a colourless oil, which had spectral data identical with those of racemic ketoprofen. $[\alpha]_D^{20}$=+54.4 (c=2.71, CH_2Cl_2) [lit[8]: $[\alpha]_D^{20}$=+57.1 (c=0.76, CH_2Cl_2)].

2-(4'-Bromophenyl)-2-methyl-1,3-dioxolane. A mixture of 4-bromoacetophenone (51.2 g, 0.26 mol), benzene (250 mL), ethylene glycol (18.6 g, 0.30 mol) and TsOH (0.2 g) was azeotroped for 16 h. The benzene was removed, the residue dissolved in CH_2Cl_2 and washed with saturated Na_2CO_3 solution then H_2O. The

solution was dried and the solvent removed to give, after distillation, the dioxolane as a colourless oil (61.0g, 97%) which still contained 5% ketone: bp 80-85°C/0.2 mm Hg; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.60 (s, 3H), 3.88 (m, 4H), 7.50 (m, 4H) (lit[8]: bp 175-180°C/20-30 mm Hg; mp 44-45°C; no NMR data reported).

2-Methyl-2-[4'-(trimethylsilyl)phenyl]-1,3-dioxolane. The bromo dioxolane (52.7 g, 0.217 mol) in THF (140 mL) was added to Mg turnings (10.55g, 0.434 mol) in THF (40 mL) at a rate which maintained gentle reflux. The mixture was stirred for 1 h at reflux. TMSCl (26.1 g, 0.24 mol) was added and the reaction stirred for 16 h at rt. THF and unreacted TMSCl were removed in vacuo, and the residue dissolved in CH_2Cl_2. The solution was washed with H_2O and the solvent removed. Distillation of the residue gave the bromo acetal as a white crystalline solid (38.4g, 75%): bp 85-90°C/0.22mm Hg; mp 57-59°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9H), 1.65 (s, 3H), 3.77 (m, 2H), 4.03 (m, 2H), 7.48 (m, 4H) (lit[8]: product not isolated).

4-(Trimethylsilyl)acetophenone. The bromo acetal (72.0 g, 0.305 mol) in MeOH (200 mL), H_2O (40 mL) and 10% HCl (5.5 mL) was heated at 60°C for 1 h. The MeOH was removed in vacuo and the residue dissolved in CH_2Cl_2, washed with $NaHCO_3$ solution and dried with $MgSO_4$ to give 4-(trimethylsilyl)acetophenone as a colourless oil (lit[8]: mp 41°C) which was used without further purification (57.6g, 98%): ^{1}H NMR ($CDCl_3$) δ 0.29 (s, 9H), 2.60 (s, 3H), 7.62 (d, 2H, J=8.2 Hz), 7.92 (d, 2H, J=8.2 Hz) (NMR data in agreement with lit[26] values).

Ethyl (*E*)-3-[4'-(Trimethylsilyl)phenyl]-2-butenoate (20). To anhyd EtOH (600 mL) was added Li in small pieces (2.78 g, 0.402 mol). After the Li had dissolved, triethyl phosphonoacetate (64.3 g, 0.287 mol) was added, and these reagents stirred at rt for 30 min. 4-(Trimethylsilyl)acetophenone (55.1 g, 0.287 mol) in EtOH (200 mL) was added and the reaction stirred at rt for 2 days, after which time further triethyl phosphonoacetate (12.9g, 57 mmol) was added. The mixture was stirred for 16 h at rt and 4 h at reflux, the EtOH was removed in vacuo and the residue dissolved in CH_2Cl_2, washed with H_2O and dried with $MgSO_4$. The solvent was removed to give **20** (80.0 g) which was used without further purification. A sample was purified by flash chromatography with hexane/EtOAc (97/3, v/v) as eluant, and bulb to bulb distillation: 120°/0.07 mm Hg (heated block); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 9H) 1.32 (t, 3H, J=7.1Hz), 2.57 (d, 3H, J=1.2 Hz), 4.21 (q, 2H, J=7.1 Hz), 6.15 (d, 1H, J=1.3 Hz), 7.45 (d, 2H, J=8.2 Hz), 7.53 (d, 2H, J=8.2 Hz). Anal. Found: C, 68.66; H, 8.48%. Calcd for $C_{15}H_{22}SiO_2$: C, 68.73; H, 8.31%.

(*E*)-3-[4'-(Trimethylsilyl)phenyl]-2-buten-1-ol (21). To LAH (7.4 g, 0.195 mol) in anhyd Et_2O (450 mL) was added crude **20** (66.5 g, 0.254 mol) in Et_2O (350 mL) at a rate which maintained gentle reflux. The mixture was stirred for 40 min at rt, then EtOAc was cautiously added followed by dilute HCl. The ethereal layer was decanted and the aqueous layer extracted with Et_2O. The organic fractions were combined, dried, and the solvent removed. Fractional distillation gave **21** as a colourless oil (41.4 g, 74%): bp 114-120°C/0.07 mm Hg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 9H), 2.07 (s, 3H), 4.35 (d, 2H, J=6.7 Hz), 5.99 (t, 1H, J=6.7 Hz), 7.39 (d, 2H, J=8.1 Hz), 7.49 (d, 2H, J=8.1 Hz). Anal. Found: C, 70.86; H, 9.15%. Calcd for $C_{13}H_{20}OSi$: C, 70.26; H, 8.95%.

(2*S*,3*S*)-3-Methyl-3-[4'-(trimethylsilyl)phenyl]oxiranemethanol (22b). According to the method of Sharpless[9], a flask was charged with (L)-(+)- diisopropyl tartrate (877 mg, 3.74 mmol) and anhyd CH_2Cl_2 (480 mL), and cooled to -20°C. To the flask were added powdered, activated 4A sieves (2.7 g), Ti(O*i*Pr)4 (731 mg, 2.58 mmol), *t*-BuOOH (25.7 mL of a 3.95M CH_2Cl_2 solution, 102 mmol) and, after 1.25 h, **21** (12.0 g, 54.5 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at -20°C for 3 h and then the reaction was quenched with 10% NaCl/NaOH solution (4.4 mL) and Et_2O (49 mL). After the reaction mixture had warmed to 10°C and remained there for 10 min, $MgSO_4$ (4.9 g) and Celite (0.6 g) were added and the mixture stirred for 15 min. Unreacted *t*-BuOOH was removed from the filtered solution by azeotroping with toluene. Flash chromatography with CH_2Cl_2/EtOAc (95/5, v/v) as eluant gave **22b** as a white crystalline solid (9.0 g, 70%). Recrystallization from pentane gave enantiomerically enriched **22b** (6.0 g): mp 41-43°C, 98%+ ee; ^{1}H NMR (300 MHz, $CDCl_3$)

δ 0.26 (s, 9H), 1.70 (s, 3H), 3.10 (dd, 1H, J=4.2 Hz and 6.5 Hz), 3.83 (dd, 1H, J=6.5Hz and 12.2 Hz), 3.97 (dd, 1H, J=4.2 Hz and 12.2 Hz), 7.33 (d, 2H, J=8.1 Hz), 7.51 (d, 2H, J=8.1 Hz). Anal. Found: C, 65.67; H, 8.26%. Calcd for $C_{13}H_{20}O_2Si$: C, 66.06; H, 8.53%.

(2*RS*,3*RS*)-3-Methyl-3-[4'-(trimethylsilyl)phenyl]oxiranemethanol (22a). To **21** (3.87 g, 17.6 mmol) in CH_2Cl_2 (60 mL) at 0°C was added *m*-CPBA (80%, 4.2 g, 19.3 mmol) and the mixture was stirred at 0°C for 20 min, then it was added dropwise to a vigorously stirred excess of 10% NaOH/NaCl solution and then 0.1M $Na_2S_2O_3$ solution (200 mL) was added. The organic layer was dried and the solvent removed to give **22a** as a white crystalline solid (4.15 g, 100%): mp 34-39°C; ^{1}H NMR ($CDCl_3$) spectrum identical to that of **22b**.

(2*R*,3*S*)-3-Methyl-3-[4'-(trimethylsilyl)phenyl]oxiranemethyl Acetate (22c). Alcohol **22b** (50 mg) was treated with Ac_2O (0.5 mL) in pyridine (0.75 mL). After 16 h at rt CH_2Cl_2 was added to the mixture and it was washed with H_2O, 5% HCl until acidic, 5% $NaHCO_3$ and H_2O. Removal of the solvent and flash chromatography with hexane/EtOAc (90/10, v/v) as eluant gave **22c**: $[\alpha]_D^{20}$=-47.0° (c=1.33, CCl_4), 98%+ ee; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9H), 1.71 (s, 3H), 2.11 (s, 3H), 3.09 (dd, 1H, J=4.6 Hz and 6.4 Hz), 4.20 (dd, 1H, J=6.4 Hz and 12.1 Hz), 4.42 (dd, 1H, J=4.6 Hz and 12.1 Hz), 7.33 (d, 2H,, J=8.1 Hz), 7.51 (d, 2H, J=8.1 Hz).

(2*R*,3*S*)-3-[4'-(Trimethylsilyl)phenyl]butane-1,2-diol (23b). Pd on carbon (10%, 2.5 g), EtOH (100 mL) and 1M NaOH solution (5 mL) were stirred in a H_2 atm for 1.5 h, then cooled to -60°C. Epoxide **22b** (2.9 g, 12.3 mmol) in EtOH (20 mL) was added over 10 min and the reaction was stirred at -60°C for 5 h. After filtration through Celite and removal of solvent, the crude product was purified by flash chromatography with hexane/EtOAc (50/50, v/v) as eluant to give **23b** as a white crystalline solid (2.9 g, 100%) which was recrystallized from pentane: mp 84.0-86.0°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 9H), 1.36 (d, 3H, J=7.0 Hz), 2.79 (quint, 1H, J=7.2 Hz), 3.35 (dd, 1H, J=7.7 Hz and 11.2 Hz), 3.46 (dd, 1H, J=3.0 Hz and 11.2 Hz), 3.75 (dt, 1H, J=3.0 Hz and 7.7 Hz), 7.18 (d, 2H, J=7.9 Hz), 7.45 (d, 2H, J=7.9 Hz). Anal. Found: C, 65.5; H, 9.30%. Calcd for $C_{13}H_{22}O_2Si$: C, 65.76; H, 9.00%.

(2*RS*,3*SR*)-3-[4'-(Trimethylsilyl)phenyl]butane-1,2-diol (23a). In a similar manner **23a** was obtained from **22a**, as a white crystalline solid which was recrystallized from pentane: mp 79.5-80.5°C. ^{1}H NMR ($CDCl_3$) spectrum identical to that of **23b**.

(2*R*,3*S*)-3-(4'-Bromophenyl)butane-1,2-diol (6b). The diol **23b** (3.86 g, 16.2 mmol), MeOH (32 mL), LiBr (1.70 g, 20.5 mmol) and NCS (2.61 g, 19.6 mmol) were stirred at rt for 1.25 h. The MeOH was removed in vacuo, the residue dissolved in CH_2Cl_2, washed with H_2O and dried with $MgSO_4$. Removal of solvent and flash chromatography with hexane/EtOAc (50/50, v/v) as eluant gave **6b** as a colourless oil (3.6g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, 3H, J=7.1 Hz), 2.71 (quint, 1H, J=7.3 Hz), 3.25 (dd, 1H, J=7.8 Hz and 11.3 Hz), 3.37 (dd, 1H, J=2.8 Hz and 11.3 Hz), 3.64 (dt, 1H, J=2.8 Hz and 7.8 Hz), 7.05 (d, 2H, J=8.3 Hz), 7.41 (d, 2H, J=8.3 Hz). Anal. Found: C, 49.00; H, 5.35%. Calcd for $C_{10}H_{13}BrO_2$: C, 48.88; H, 5.52%.

(2*RS*,3*SR*)-3-(4'-Bromophenyl)butane-1,2-diol (6a). In a similar manner **6a** was obtained from **23a**, as a colourless oil: ^{1}H NMR ($CDCl_3$) spectrum identical to that of **6b**.

(4*R*, 1'*S*)-4-[1'-(4''-Bromophenyl)ethyl]-2,2-dimethyl-1,3-dioxolane (24b). Diol **6b** (3.6 g, 14.7 mmol) in anhyd acetone (146 mL) and TsOH (40 mg) were stirred at rt in a N_2 atm for 5 h. Saturated $NaHCO_3$ solution (3 mL) was added and the acetone removed in vacuo. The residue was dissolved in CH_2Cl_2, washed with H_2O, dried with $MgSO_4$ and the solvent removed to give, after distillation, **24b** as a colourless oil (2.9 g, 73%): bulb-to-bulb distillation at 120°C/0.05 mm Hg (heated block); [a]$_D^{20}$=- 7.4° (c=3.07, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, 3H, J=7.0 Hz) 1.39 (s, 3H), 1.41 (s, 3H), 2.77 (quint, 1H, J=6.9 Hz), 3.51 (dd, 1H, J=6.8Hz and 8.3 Hz), 3.74 (dd, 1H, J=5.9Hz and 8.3 Hz), 4.13 (dt, 1H, J=6.5 Hz and 8.3

Hz), 7.08 (d, 2H, J=13.3 Hz), 7.42 (d, 2H, J=13.3 Hz). HRMS 284.0421, calcd for ($C_{13}H_{17}BrO_2$) 284.0394.

(4*RS*, 1'*SR*)-4-[1'-(4''-Bromophenyl)ethyl]-2,2-dimethyl-1,3-dioxolane (24a). In a similar manner **24a** was obtained from **6a**, as a colourless oil: ^{1}H NMR ($CDCl_3$) spectrum identical to that of **24b**.

(4'''*RS*,1'''*SR*, 1*RS*)- and (4'''*RS*, 1'''*SR*, 1*SR*)-1-{4'-[1''-(2''',2'''-Dimethyl-1''',3'''-dioxolan-4'''-yl)ethyl]phenyl}-2-methyl-1-propanol (25a). In a dry flask, **24a** (443 mg, 1.55 mmol) was dissolved in anhyd Et_2O (7mL) and cooled to -78°C in a N_2 atm. *t*-BuLi (1.86 mL of a 1.75 M hexane solution, 3.26 mmol) was added, these reagents stirred at -78°C for 1.75 h and then isobutyraldehyde (259 mg, 3.60 mmol) was added. The mixture was allowed to warm to rt, the Et_2O was removed and the residue dissolved in CH_2Cl_2 and washed with H_2O. The aqueous phase was extracted with CH_2Cl_2 and the organic fractions combined and dried with $MgSO_4$. Removal of the solvent and flash chromatography with hexane/EtOAc (80/20, v/v) as eluant gave **25a** as a colourless oil (370 mg, 86%): ^{1}H NMR (60 MHz, $CDCl_3$, D_2O) δ 0.69-1.60 (complex, 15H), 1.92 (m, 1H), 2.79 (quint, 1H, J=7 Hz), 3.30-4.20 (complex, 3H), 4.26 (d, 1H, J=7 Hz), 7.0-7.4 (m, 4H).

(4'''*R*,1''*S*,1*RS*)-1-{4'-[1''-(2''',2'''-Dimethyl-1''',3'''-dioxolan-4'''-yl)propyl)ethyl]phenyl}-2-methyl-1-propanol (25b). In a similar manner **25b** was obtained from **24b**. ^{1}H NMR ($CDCl_3$) spectrum identical with that of **25a**.

(2*RS*,3*SR*,1''*RS*)- and **(2*RS*,3*SR*,1''*SR*)-3-[4'-(1''-Hydroxy-2''-methylpropyl)phenyl]butane-1,2-diol (26a).** The alcohol **25a** (370 mg, 1.33 mmol) was dissolved in MeOH (7.5 mL), H_2O (1.5 mL) and 5% HCl (0.6 mL). After 16 h at rt the MeOH was removed in vacuo, the residue dissolved in CH_2Cl_2, washed with H2O and dried with $MgSO_4$. Flash chromatography with EtOAc/hexane (75/25, v/v) as eluant gave **26a** as a colourless oil (270 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$, D_2O) δ 0.76 (d, 3H, J=6.8 Hz), 0.99 (d, 3H, J=6.7 Hz), 1.31 (d, 3H, J=7.0 Hz), 1.92 (octet, 1H, J=6.8 Hz), 2.74 (quint, 1H, J=7.3 Hz), 3.23 (dd, 1H, J=7.8 Hz and 11.3 Hz), 3.34 (dd, 1H, J=2.8 Hz and 11.3 Hz), 3.64 (dt, 1H, J=2.8 Hz and 7.8 Hz), 4.28 (d, 1H, J=7.0 Hz), 7.12 (d, 2H, J=8.1 Hz), 7.22 (d, 2H, J=8.1 Hz).

(2*R*,3*S*,1''*RS*)-3-[4'-(1''-Hydroxy-2''-methylpropyl)phenyl]butane-1,2-diol (26b). In a similar manner **26b** was obtained from **25b**, as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, D_2O) spectrum identical to that of **25a**.

(2*RS*,3*SR*)-3-[4'-(2''-Methylpropyl)phenyl]butane-1,2-diol (27a). Pd on carbon (10%, 55 mg) and CH_2Cl_2 (2 mL) were stirred at rt in a H_2 atm for 1 h, then **26a** (47 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added and the mixture stirred in a H_2 atm overnight. The H_2 was cautiously replaced with air, the solution filtered through Celite and the solvent removed to give **27a** as a colourless oil (35 mg, 79%): ^{1}H NMR (300 MHz, $CDCl_3$, D_2O) δ 0.89 (d, 6H, J=6.7 Hz), 1.35 (d, 3H, J=6.9 Hz), 1.84 (m, 1H, J=6.8 Hz), 2.44 (d, 2H, J=7.2 Hz), 2.78 (quint, 1H, J=7.0 Hz), 3.36 (dd, 1H, J=7.7 Hz and 11.2 Hz), 3.46 (dd, 1H, J=3.0 Hz and 11.2 Hz), 3.74 (dt, 1H, J=3.2 Hz and 7.7 Hz), 7.09 (m, 4H). Anal. Found: C, 75.33; H, 9.55%. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%.

(2*R*,3*S*)-3-[4'-(2''-Methylpropyl)phenyl]butane-1,2-diol (27b). In a similar manner **27b** was obtained from **26b**, as a white crystalline solid which was recrystallized from pentane: mp 62.0-65.5°C; ^{1}H NMR (300 MHz, $CDCl_3$, D_2O) spectrum identical to that of **27a**.

(*RS*)-2-[4'-(2''-Methylpropyl)phenyl]propanoic acid (2a). Following the procedure of Sharpless[12], **27a** (32 mg, 0.14 mmol) was dissolved in CCl_4 (1.1 mL), CH_3CN (1.1 mL) and H_2O (1.7 mL). $RuCl_3.H_2O$ (1.1 mg, 0.005 mmol) and $NaIO_4$ (180 mg, 0.84 mmol) were added and the mixture stirred vigorously at rt for 1.25 h. Then it was diluted with CH_2Cl_2, washed with H_2O and dried with $MgSO_4$. The solution was passed down a column of charcoal (2 cm) and the solvent removed to give **2a** as a colourless oil (27 mg, 90%): lit[11] mp 75-77°C. Spectral data identical with those of authentic ibuprofen.

(*S*)-2-[4'-(2''-Methylpropyl)phenyl]propanoic acid (2b). In a similar manner **2b** was obtained from **27b**. Distillation facilitated crystallization: mp 49-51°C (lit[16]: 50-52°C); $[\alpha]_D^{20}$=+57° (c=2.33, EtOH), [lit[27]: $[\alpha]_D^{20}$=+60° (c=2.95, EtOH)].

(2*R*,3*S*)-3-(3'-Iodophenyl)butane-1,2-diol (28b). To the silyl diol **16b** (400 mg, 1.68 mmol) in CH_2Cl_2 (20 mL) was added ICl (273 mg, 1.68 mmol). After 1 h at rt the reaction mixture was diluted with CH_2Cl_2 and washed with 10% $Na_2S_2O_3$ solution until colourless. The aqueous phase was extracted with CH_2Cl_2 , the combined organic fractions dried over $MgSO_4$ and the solvent removed in vacuo. Flash chromatography with hexane/EtOAc (50/50, v/v) as eluant gave **28b** as a colourless oil (400 mg, 82%) which was used without further purification. A sample was subjected to bulb to bulb distillation at 140°C/0.05 mm Hg (heated block); ^{1}H NMR (300 MHz, $CDCl_3$, D_2O) δ 1.30 (d, 3H, CH_3, J=7.0 Hz), 2.69 (quint, 1H, H3, J=7.0 Hz), 3.29 (dd, 1H, H1, J=7.7 Hz and 11.3 Hz), 3.42 (dd, 1H, H1, J=2.7 Hz and 11.3 Hz), 3.68 (dt, 1H, H2, J=2.7 Hz and 7.7 Hz), 7.00-7.56 (m, 4H, Ar-H).
(2*RS*,3*SR*)-3-(3'-Iodophenyl)butane-1,2-diol (28a). In a similar mannner **28a** was obtained from **16a**, as a colourless oil in 98% yield. ^{1}H NMR data identical to those of **28b**.

(2*R*,3*S*)-3-(4'-Iodophenyl)butane-1,2-diol (29b). To the silyl diol **23b** (200 mg, 0.84 mmol) in CH_2Cl_2 (6 mL) was added ICl (142 mg, 0.87 mmol) and the mixture stirred for 30 min at rt. It was then diluted with CH_2Cl_2 and washed with 10% $Na_2S_2O_3$ solution until colourless. The aqueous phase was extracted with CH_2Cl_2, the combined organic fractions dried over $MgSO_4$ and the solvent removed in vacuo. Flash chromatography with hexane/EtOAc (50/50, v/v) as eluant gave **29b** as a white crystalline solid (220 mg, 90%): mp 77.0- 78.5°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, 3H, CH_3, J=7.0 Hz), 1.85-2.70 (br, 2H, OH), 2.75 (quint, 1H, H3, J=7.2 Hz), 3.32 (dd, 1H, H1, J=7.5 Hz and 11.1 Hz), 3.45 (dd, 1H, H1, J=3.0 Hz and 11.1 Hz), 3.70 (dt, 1H, H2, J=3.0 Hz and 7.6 Hz), 6.95 (d, 2H, Ar-H, J=8.2 Hz), 7.66 (d, 2H, Ar-H, J=8.2 Hz).
(2*RS*,3*SR*)-3-(4'-Iodophenyl)butane-1,2-diol (29a). In a similar manner **29a** was obtained from **23a**, as a colourless oil in 95% yield. ^{1}H NMR data identical to those of **29b**.

(*S*)-2-(3'-Iodophenyl)propanoic Acid (30b). To the iodo diol **28b** (490 mg, 1.68 mmol) dissolved in CCl_4 (6 mL), CH_3CN (6 mL) and H_2O (9 mL), were added $RuCl_3.H_2O$ (9.7 mg, 0.037 mmol) and $NaIO_4$ (1.51 g, 7.06 mmol). The reaction was stirred vigorously at rt for 1.25 h, diluted with CH_2Cl_2 and washed with H_2O. The aqueous phase was extracted with CH_2Cl_2, the organic fractions combined, dried over $MgSO_4$ and the solvent removed in vacuo. Flash chromatography with hexane/EtOAc (50/50, v/v) as eluant gave **30b** as a white crystalline solid (320 mg, 69%) which was used without further purification. A sample was recrystallized from hexane: mp 49-52°C; $[\alpha]_D^{20}$=+43.4° (c=1.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, D_2O) δ 1.50 (d, 3H, CH_3, J=7.2 Hz), 3.67 (q, 1H, H2, J=7.2 Hz), 7.04-7.67 (m, 4H, Ar-H). Found: C: 39.41%, H: 3.37%, $C_9H_9IO_2$ requires C: 39.15%, H: 3.29%.
(*RS*)-2-(3'-Iodophenyl)propanoic Acid (30a). In a similar manner **30a** was obtained from **16a**, as a white crystalline solid which was used without further purification. A sample was recrystallized from hexane: mp 48.0-50.5°C. ^{1}H NMR data identical to those of **30b**.

(*S*)-2-(4'-Iodophenyl)propanoic Acid (31b). To the iodo diol **29b** (220mg, 0.75 mmol) in CCl_4 (3.0 mL), CH_3CN (3.0 mL) and H_2O (4.5 mL), were added $RuCl_3.H_2O$ (4.3 mg, 0.021 mmol) and $NaIO_4$ (674 mg, 3.2 mmol). The reaction was stirred vigorously at rt for 1.25 h, diluted with CH_2Cl_2 and washed with H_2O. The aqueous phase was extracted with CH_2Cl_2, the organic fractions combined, dried over $MgSO_4$ and the solvent removed in vacuo. Flash chromatography with hexane/EtOAc (50/50, v/v) as eluant gave **31b** as a white crystalline solid (157 mg, 75%) which was used without further purification. A sample was recrystallized from hexane: mp 139-140°C; $[\alpha]_D^{20}$=+39.0° (c=2.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$ D_2O) δ 1.49 (d, 3H, CH_3, J=7.2 Hz), 3.68 (q, 1H, H2, J=7.2 Hz), 7.07 (d, 2H, Ar-H, J=8.3 Hz), 7.65 (d, 2H, Ar-H, J=8.3 Hz). Found: C: 39.15%, H: 3.17%, $C_9H_9IO_2$ requires C: 39.15%, H: 3.29%.

(*RS*)-2-(4'-Iodophenyl)propanoic Acid (31a). In a similar manner **31a** was obtained from **29a**, as a white crystalline solid which was used without further purification. A sample was recrystallized from hexane: mp 100-102°C (lit[17], no data). ^{1}H NMR data identical to those of **31b**.

Palladium Catalysed Coupling Reaction - General Procedure.

a) Formation of Alkylzinc or Arylzinc Reagent. Grignard reagents were prepared from alkyl or aryl halides (redistilled) in either anhyd THF or ether and the concentration of each Grignard reagent was determined. In a separate, flame dried flask, anhyd $ZnCl_2$ (1.05 equivalents relative to the Grignard reagent) was dissolved in THF (0.15-0.20 g/mL) under N_2 (exothermic). To this was added the Grignard reagent via syringe, and immediate formation of a white precipitate was observed. The mixture was stirred at rt for at least 10 min.

b) Coupling Reaction. A flame dried, 2-necked flask was flushed with N_2 and charged with dichlorobis(triphenylphosphine)palladium(II) (0.14 equiv), anhyd THF (1 mL/50 mg iodo acid) and DIBALH (0.28 equiv). The iodo acid (1.0 equiv) in THF (1 mL/50 mg) was added, followed by the alkylzinc or arylzinc reagent (5.0 equiv), including the precipitate and supernatant. The reaction mixture was stirred at rt in an N_2 atmosphere for at least 1.5 h, the THF was removed in vacuo and the residue dissolved in CH_2Cl_2. The solution was washed with 10% HCl and the aqueous layer extracted with CH_2Cl_2. The organic fractions were combined, washed with saturated $NaHCO_3$ solution and the aqueous phase acidified by adding concd HCl dropwise and extracted with CH_2Cl_2. This fraction was dried with $MgSO_4$ and the solvent removed in vacuo.

c) Determination of the Optical Purity of Products followed a general procedure.[15]

(*S*)-2-(3'-Biphenylyl)propanoic Acid (34b). The Grignard reagent (1.53 M), from bromobenzene in ether was converted to the corresponding arylzinc reagent and the coupled to the iodo acid **30b** (41 mg, 0.15 mmol) following the general procedure. The acid **34b** was obtained as a colourless oil at rt (exists as a white crystalline solid at -20°C) (25 mg, 74%): ^{1}H NMR (300 MHz, $CDCl_3$, D_2O) δ 1.56 (d, 3H, CH_3, J=7.2 Hz), 3.81 (q, 1H, H2, J=7.2 Hz), 7.25-7.59 (m, 4H, Ar-H) (data in agreement with literature values for the racemate[20]). The optical purity (96% ee) was determined by the general procedure.

(*RS*)-2-(3'-Biphenylyl)propanoic Acid (34a). In a similar manner **34a** was obtained from **30a**, as a white crystalline solid in 83% yield: mp 64-68°C (lit[20] mp 64 °C). After recrystallization from hexane: mp 49-51 °C; ^{1}H NMR data identical to those of **34b**.

(*S*)-2-(3'-Benzylphenyl)propanoic Acid (36b). The Grignard reagent (0.966 M), from benzyl chloride in ether, was converted to the corresponding alkylzinc reagent, and coupled to **30b** (48 mg, 0.174 mmol) by the general procedure to give **36b** as a colourless oil (38 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, 3H, H3, J=7.2 Hz), 3.69 (q, 1H, H2, J=7.2 Hz), 3.97 (s, 2H), 7.06-7.30 (m, 9H, Ar-H). These data are in agreement with those reported[14] for product with mp 58-59°C. Optical purity (94% ee) was determined by the general procedure.

(2*RS*,3*SR*)-3-[3'-(Trimethylsilyl)phenyl]butane-1,2-diyl Diacetate (16c). To the silyl diol **16a** (554 mg, 2.33 mmol) in pyridine (5 mL) was added Ac_2O (3 mL), and the reaction mixture allowed to stand at rt overnight. CH_2Cl_2 was added to the mixture and it was washed with water, 5% HCl until acidic, 5% $NaHCO_3$ solution and H_2O. The solution was dried with $MgSO_4$ and the solvent removed in vacuo. Flash chromatography with CH_2Cl_2 as eluant, followed by bulb to bulb distillation at 122°C/0.04 mm Hg (heated block) gave **16c** as a white crystalline solid (710 mg, 95%): mp 52-53°C; ^{1}H NMR (60 MHz, $CDCl_3$) d 0.35 (s, 9H, $(CH_3)_3$), 1.33 (d, 3H, H4, J=7 Hz), 2.03 (s, 3H, $COCH_3$), 2.18 (s, 3H, $COCH_3$), 3.00 (m, 1H, H3), 3.82 (dd, 1H, H1, J=6 Hz and 12 Hz), 4.21 (dd, 1H, H1, J=3 Hz and 12 Hz), 5.25 (m, 1H, H2), 7.18-7.50 (m, 9H, Ar-H).

(2*RS*,3*SR*)-3-(3'-Iodophenyl)butane-1,2-diyl Diacetate (37a). In a procedure similar to that for the formation of the iodo diol **29b**, the silyl diacetate **16c** (267 mg, 0.83 mmol) in CH_2Cl_2 (10 mL) was treated with ICl (135 mg, 0.83 mmol). TLC showed the reaction to be complete after 20 min, and work up gave **37a** as a colourless oil (304 mg, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, 3H, H4, J=7.0 Hz), 2.03 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.98 (m, 1H, H3), 3.79 (dd, 1H, H1, J=6.4 Hz and 12.0 Hz), 4.13 (dd, 1H,

H1, J=3.0 Hz and 12.0 Hz), 5.20 (m, 1H, H2), 7.04-7.60 (m, 9H, Ar-H).

(2*RS*,3*SR*)-3-(3'-Benzylphenyl)butane-1,2-diyl Diacetate (37b). The Grignard reagent (0.954 M) from benzyl chloride in ether was converted to the corresponding alkylzinc reagent, and coupled to **37a** (128 mg, 0.34 mmol) by the general procedure to give **37b** as a colourless oil (100 mg, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, H4, J=7.0 Hz), 1.98 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.98 (m, 1H, H3), 3.77 (dd, 1H, H1, J=6.4 Hz and 12.0 Hz), 3.96 (s, 2H, CH_2Ar), 4.11 (dd, 1H, H1, J=2.9 Hz and 12.0 Hz), 5.22 (m, 1H, H2), 7.04-7.34 (m, 9H, Ar-H). Found: C: 73.49%, H: 7.07%. $C_{21}H_{24}O_4$ requires C: 74.09%, H: 7.11%.

(2*RS*,3*SR*)-3-(3'-Benzylphenyl)butane-1,2-diol (37c) from Hydrolysis of Diacetate. To the diacetate **37b** (80 mg) in MeOH (1.5 mL) was added K_2CO_3 (30 mg), and the reaction mixture was allowed to stand at rt for 2 h, at which time TLC showed **37b** to have been consumed and a single product formed. The MeOH was removed in vacuo, the residue dissolved in CH_2Cl_2 and washed with H_2O. The aqueous phase was extracted with CH_2Cl_2 and the organic phase dried with $MgSO_4$. Removal of the solvent in vacuo gave **37c** as a colourless oil: ^{1}H NMR (60 MHz, $CDCl_3$, D_2O) δ 1.32 (d, 3H, CH_3, J=7 Hz), 2.72 (quint, 1H, H3, J=7 Hz), 3.30-3.95 (complex, 3H, H1, H2), 3,99 (s, 2H, CH_2Ar), 6.95-7.60 (m, 9H, Ar-H). This product was used directly for oxidation to **36a**

(*RS*)-2-(3'-Benzylphenyl)propanoic Acid (36a). By the procedure for formation of the iodo acid **30a**, the diol **37c** (45 mg, 0.18 mmol) in CCl_4 (1.0 mL), CH_3CN (1.0 mL) and H_2O (1.5 mL) was treated with $RuCl_3.H_2O$ (1.0 mg, 0.004 mmol) and $NaIO_4$ (162 mg, 0.76 mmol). Work up gave **36a** as a colourless oil (37 mg, 86%): ^{1}H NMR data identical to those of **36b** and similar to that reported[14] for compound with mp 60-61°C.

(*S*)-2-[3'-(Phenylethynyl)phenyl]propanoic Acid (35b). In a flame dried flask under N_2 phenylacetylene (1.0 g, 9.79 mmol) was added to a stirred solution of anhyd THF (5 mL) and *n*-BuLi (4.20 mL of a 2.33 M hexane solution, 9.79 mmol). After 30 min at rt, anhyd $ZnCl_2$ (1.40 g, 10.3 mmol) in THF (5mL) was added to the deep purple solution, whereupon the colour changed to bright orange. This alkylzinc reagent was coupled to the iodo acid **30b** (46 mg, 0.17 mmol) by the general procedure. Flash chromatography with hexane/EtOAc (70/30, v/v) as eluant gave **35b** as a white crystalline solid (30 mg, 71%) which was recrystallized from hexane: mp 80-82°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, 3H, CH_3, J=7.2 Hz), 3.75 (q, 1H, H2, J=7.2 Hz), 7.30-7.55 (m, 9H, Ar-H). The optical purity (96% ee) was determined by the general procedure.

(*RS*)-2-[3'-(Phenylethynyl)phenyl]propanoic Acid (35a). In a similar manner **35a** was obtained from **30a**, as a white crystalline solid in 77% yield: mp 72-75°C. ^{1}H NMR data identical to those of **35b**. Found C: 81.55%, H: 5.86%, $C_{17}H_{14}O_2$ requires C: 81.58%, H: 5.64%.

(*S*)-2-(4'-Biphenylyl)propanoic Acid (33b). The Grignard reagent (0.76 M) from bromobenzene in ether was converted to the corresponding arylzinc reagent, and coupled to the iodo acid **31b** (26 mg, 0.09 mmol) by the general procedure and **33b** was obtained as a white crystalline solid (13 mg, 62%): mp 159-161°C; ^{1}H NMR (300 MHz, $CDCl_3$) d 1.56 (d, 3H, CH_3, J=7.2 Hz), 3.80 (q, 1H, H2, J=7.2 Hz), 7.34-7.59 (m, 4H, Ar-H). (Values same as in lit.[28]). The optical purity (94% ee) was determined by the general procedure.

(*RS*)-2-(4'-Biphenylyl)propanoic Acid (33a). In a similar manner **33a** was obtained from **31a**, as a white crystalline solid in 67% yield: mp 147-149°C (lit.[29] mp 146°C). ^{1}H NMR data identical to those of **33b**.

(*S*)-2-[4'-(2''-Methyl-1''-propenyl)phenyl]propanoic Acid (32b). The Grignard reagent (1.15 M) from 1-bromo-2-methyl-1-propene in THF was converted to the corresponding alkylzinc reagent, and coupled to the iodo acid **31b** (26 mg, 0.09 mmol) by the general procedure and **32b** was obtained as a colourless oil (17 mg, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) d 1.51 (d, 3H, CH_3, J=7.1 Hz), 1.85 (d, 3H, C2"CH_3, J=1.1 Hz), 1.89 (d, 3H, H3", J=1.2 Hz), 3.72 (q, 1H, H2, J=7.1 Hz), 6.23 (br s, 1H, H1"), 7.18 (d, 2H, Ar-H, J=8.2 Hz), 7.26 (d, 2H, Ar-H, J=8.2 Hz).

(*S*)-2-[4'-(2''-Methylpropyl)phenyl]propanoic Acid (2b) via Hydrogenation of Alkene (32b). To the alkene **32b** (9mg, 0.04 mmol) in EtOAc (2.5 mL) was added Pd on carbon (10%, 10 mg) and the reaction mixture was stirred in a H_2 atmosphere at rt for 1.5 h. The H_2 was replaced with air and the catalyst removed by filtration through cotton wool. Flash chromatography with hexane/EtOAc (50/50, v/v) as eluant did not remove a

lower Rf impurity. A CH_2Cl_2 solution of the residue was washed with $NaHCO_3$ solution. The aqueous phase was acidified by adding concd HCl dropwise and extracted with CH_2Cl_2. The organic phase was dried with $MgSO_4$ and the solvent removed in vacuo to give **2b** (6 mg, 69%). ^1H NMR data identical to those below. The optical purity was determined by the general procedure and found to be 96% ee.

(*S*)-2-[4'-(2''-Methylpropyl)phenyl]propanoic Acid (2b). The Grignard reagent (1.60 M) from 1-chloro-2-methylpropane in ether was converted to the corresponding alkylzinc reagent, and coupled to the iodo acid **31b** (54 mg, 0.20 mmol) by the general procedure. Acid **2b** was obtained as a white crystalline solid (31 mg, 77%): mp 49-51°C. It was recrystallized from EtOH: mp 50-52°C (lit[16] mp 49-51°C, 95% optically pure); ^1H NMR (300 MHz, $CDCl_3$, D_2O) δ 0.89 (d, 6H, $(CH_3)_2CH$, J=6.7 Hz), 1.50 (d, 3H, H3, J=7.0 Hz), 1.84 (m, 1H, H2", J=6.7 Hz), 2.44 (d, 2H, H1", J=7.1 Hz), 3.70 (q, 1H, H2, J=7.0 Hz), 7.10 (d, 2H, Ar-H, J=7.8 Hz), 7.22 (d, 2H, Ar-H, J=7.8 Hz) (data in agreement with literature values). The optical purity was determined by the general procedure and found to be 92% ee.

(*RS*)-2-[4'-(2''-Methylpropyl)phenyl]propanoic Acid (2a) In a similar manner **2a** was obtained from **31a**, as a white crystalline solid in 75% yield: mp 76-77°C (lit[30] mp 74°C). ^1H NMR data identical to those of **2b**.

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