Stereocontrolled ring-opening of some enantiomerically enriched epoxy ketones and epoxy alcohols using trimethylaluminium: synthesis of (*S*)-2-arylpropanoic acids

Lydia Carde,[a] D. Huw Davies[b] and Stanley M. Roberts[a]

[a] *Department of Chemistry, Liverpool University, Liverpool, UK L69 7ZD*
[b] *AstraZeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire, UK SK10 4TG*

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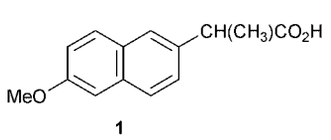
Poly-(D)-leucine-catalysed epoxidation of chalcone furnished epoxide (+)-**6**; treatment of this epoxide with trimethylaluminium followed by zinc borohydride reduction and oxidative cleavage furnished (*S*)-2-phenylpropanoic acid **11**. In a complementary sequence epoxy ketones (−)-**6** and **25** were converted into (*S*)-2-phenylpropanoic acid and (*S*)-fenoprofen **5** respectively by reduction with zinc borohydride, reaction with trimethylaluminium and oxidative cleavage. Similarly epoxy ketones (−)-**6**, **21** and **28** were treated with methylmagnesium iodide, trimethylaluminium and the resultant alcohols subjected to oxidative cleavage to afford (*S*)-2-phenylpropanoic acid (from the first two substrates) and (*S*)-naproxen **1**.

Introduction and background information

2-Arylpropionic acids are well known as anti-inflammatory agents and, as such, are widely used to control the symptoms of arthritis and related connective tissue disorders.[1] Typical examples of these non-steroidal anti-inflammatory agents include naproxen **1**, ibuprofen **2**, flurbiprofen **3**, ketoprofen **4**, and fenoprofen **5**.



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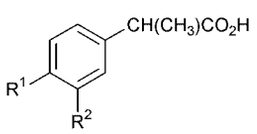

2 $R^1 = CH_2CH(CH_3)_2$; $R^2 = H$
3 $R^1 = C_6H_5$; $R^2 = F$
4 $R^1 = H$; $R^2 = COC_6H_5$
5 $R^1 = H$; $R^2 = OC_6H_5$

It is now well established that the major therapeutic activity of many, if not all, of these compounds resides in the (*S*)-enantiomer. For example, in the case of naproxen **1**, the (*S*)-enantiomer is twenty-eight times more potent than the (*R*)-enantiomer.[2] Several methods for obtaining the (*S*)-enantiomers of arylpropanoic acids, free of contaminating (*R*)-enantiomers, are known. These include asymmetric chemical synthesis as well as classical chemical resolutions and biocatalysis.[3]

Contemporaneously, there has been an increased interest in the chemistry surrounding the ring-opening of epoxides using trimethylaluminium (Fig. 1). In most cases ring-opening occurs with inversion of configuration[4] except when R^2 is an electron-donating unit capable of stabilising an intermediate carbocation (*e.g.*, R^2 = aryl) when retention of configuration at the reacting carbon centre can be observed.[5] It has been shown, moreover, that reaction of 2,3-epoxyalkan-1-ols with trialkylaluminium reagents proceeds regio- and stereo-selectively with inversion of configuration at the C-3 position.[6]

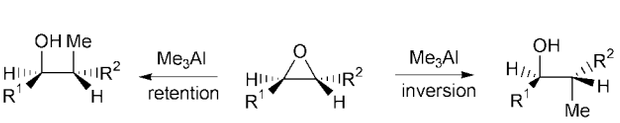

Fig. 1

We reasoned that if the ring-opening reaction with trimethylaluminium could extend to suitably substituted enantiopure 2,3-epoxy ketones, oxidative cleavage of the resultant vicinal hydroxy ketone unit would provide rapid access to (*S*)-arylpropionic acids (Fig. 2). The requisite optically active epoxy ketones were anticipated to be readily available by Juliá–Colonna asymmetric epoxidation[7] of the corresponding unsaturated ketones using, as the chiral catalyst, poly-(L)-leucine or poly-(D)-leucine (as appropriate to complement the stereochemistry of the epoxide-ring opening).

As described hereunder, after some modification, the above strategy did provide rapid, high yielding reactions leading to a small selection of (*S*)-arylpropanoic acids.[8]

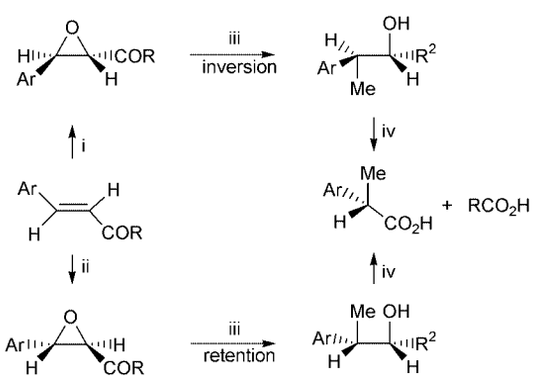

Fig. 2 *Reagents and conditions*: (i) [O], poly-(D)-leucine; (ii) [O], poly-(L)-leucine; (iii) Me_3Al; (iv) oxidative cleavage.

Results and discussion

Synthesis of (*S*)-2-phenylpropanoic acid

Exploratory studies focused on the synthesis of (*S*)-(+)-phenylpropanoic acid. Thus chalcone was converted into the epoxide (−)-**6** (95% ee) using poly-(L)-leucine adsorbed onto silica,[9] together with urea–hydrogen peroxide and diazabicycloundecene (DBU) in tetrahydrofuran (THF).

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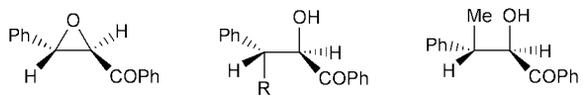
Alkylation with epoxide ring-opening was accomplished using trimethylaluminium under conditions recommended by Miyashita *et al.*[10,11] Thus trimethylaluminium (10 mol equiv.) was added dropwise to a stirred solution of epoxychalcone (−)-**6** (1 equiv.) in 1,2-dichloroethane at −30 °C and water (6 equiv.) was added to the reaction mixture. After reaction (30 min) and work-up a mixture of *anti*-**7** and *syn*-**9** alcohols was obtained in the ratio 3:1 and a combined yield of 66%. (The relative stereochemistry within **7** and **9** was ascertained by further experimentation, *vide infra*.) Optimisation of the reaction led to the employment of just two equiv. of trimethylaluminium with 1.2 equiv. of water in dichloromethane at −78 °C, reaction conditions which furnished hydroxy ketones **7** and **9** in the ratio 10:1 and a yield of 83%.

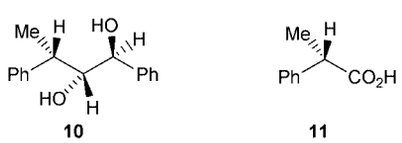
The presence of water was important, otherwise most of the epoxychalcone **6** was recovered unchanged with only small



amounts of unidentified materials being formed. It is mooted that the water probably reacts with Me_3Al to give species such as $R_2AlOAlR_2$ and R_3AlO which are potent methylating agents.[11] It should be noted that under these conditions the reaction occurred with inversion of configuration, predominantly.

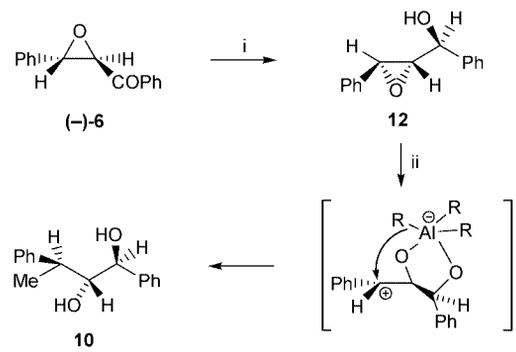
In passing it should be noted that triethylaluminium also reacted with racemic epoxide (±)-**6** under the same conditions to give only *anti*-2-hydroxy-1,3-diphenylpentan-1-one (±)-**8** in a highly respectable 85% yield. While the chemistry of the ethyl compound was not investigated further it is clear that, by analogy with the work described hereunder, such species, if prepared in single enantiomer form, could be converted into optically active α-arylbutanoic acids, for example indobufen[12] and analogues.

Notwithstanding literature precedent,[13] attempts to cleave the *anti*-**7** and *syn*-hydroxy ketone **9** (using sodium periodate on silica[14] followed by Jones oxidation) were disappointing, affording the desired arylpropanoic acid in very low yield. However, zinc borohydride reduction of the hydroxy ketone **9** gave the diol **10** (95% yield) which, in contrast, was readily cleaved



with periodate on silica; subsequent Jones oxidation furnished (+)-2(*S*)-phenylpropanoic acid **11** in 71% yield over two steps. The yield of the oxidative cleavage was relatively low because the desired product **11** could only be separated from the simultaneously formed benzoic acid by column chromatography. The absolute configuration of the acid **11** was ascertained by comparison of the optical rotation {$[a]_D^{20}$ +72.5 (*c* 1.0, $CHCl_3$) with the literature value ($[a]_D^{20}$ +72.8 (*c* 1.0, $CHCl_3$) for 99% ee (*S*)-acid[15]} and the enantiomeric excess was confirmed as 95% by conversion of the acid **11** into the corresponding methyl ester and then application of NMR spectroscopy using the chiral shift reagent $Eu(hfc)_3$.†

The diol **10** was obtained from chalcone epoxide by a second route, namely reduction of (−)-**6** using zinc borohydride, a reaction known to give only the epoxy alcohol **12**.[16] Treatment of **12** with trimethylaluminium in dry hexane at 0 °C gave diol **10** in 93% yield through a reaction involving essentially complete *retention* of configuration at C-3 (Scheme 1). It seems



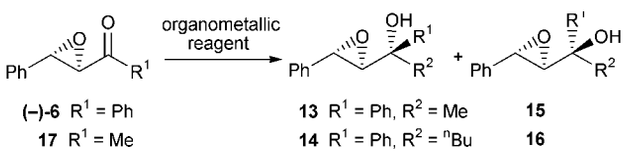
Scheme 1 *Reagents and conditions* (yields in parenthesis): (i) $Zn(BH_4)_2$ (0.3 equiv.), Et_2O, 0 °C, 30 min (95%); (ii) Me_3Al (3 equiv.), hexane, 0 °C (93%).

that the aluminium species, acting as a Lewis acid, coordinates to both oxygen atoms, creating a benzylic carbocation which allows delivery of the methyl group from the face previously occupied by the oxirane moiety.[5,6]

Thus (*S*)-phenylpropanoic acid **11** was available by oxidation of chalcone in the presence of poly-(L)-leucine to afford (−)-**6** and then either treatment with trimethylaluminium, separation of the minor component **9**, reduction to the diol **10** and oxidative cleavage (overall 4% yield) or zinc borohydride reduction of ketone (−)-**6** to give epoxy alcohol **12**, reaction with the alkylating agent and cleavage (overall yield from the epoxy ketone 57%).

In an alternative pathway chalcone was oxidised to (+)-**6** using poly-(D)-leucine on silica (92% yield, 97% ee). Treatment of (+)-**6** with trimethylaluminium, then zinc borohydride, followed by the usual oxidative cleavage protocol, gave (*S*)-2-phenylpropanoic acid[11] in 48% overall yield. Once again the overall yield was compromised by the mandatory separation of (+)-**11** from benzoic acid.

In order to overcome this separation problem trimethylaluminium-promoted ring-opening of some related epoxy tertiary alcohols was investigated. Reaction of epoxychalcone with organocerium reagents has been shown to result in tertiary alcohols with the major diastereoisomer being formed by nucleophilic attack on the carbonyl group from the *re*-face (Table 1: Entries 1,2).[17] Even better selectivity has now been obtained, simply by treating the epoxy ketone with methylmagnesium iodide (Entry 3) or *n*-butylmagnesium bromide (Entry 4), giving epoxy tertiary alcohols **13** and **14** as pure



single compounds. The epoxy alcohol **15** was available as the major product, but contaminated with diastereomer **13**, by reaction of epoxide **17** with phenylmagnesium bromide (Entry 5).[18]

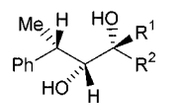
Treatment of the epoxy alcohol **13** with trimethylaluminium in hexane at −78 °C gave the diol **18** (the product of alkylation with retention of configuration) in 82% yield. Cleavage of the diol using sodium periodate–silica followed by Jones oxidation gave (*S*)-2-phenylpropanoic acid in 86% yield; the acid was readily separated from the acetophenone produced concurrently. Thus (*S*)-2-phenylpropanoic acid was prepared from chalcone in 58% overall yield.

† $Eu(hfc)_3$ = europium tris(heptafluorobutynylcamphorate).

Table 1 Reactions of some 2,3-epoxy ketones with organocerium and organomagnesium reagents

Entry	Substrate	Reagent	Reaction time (*t*/h)	Products (Ratio)	Yield (%)
1	(−)-**6**	MeLi–CeI_3	2	**13**,**15** (4:1)	91
2	(−)-**6**	BuLi–CeI_3	2	**14**,**16** (9:1)	80
3	(−)-**6**	MeMgI	1.5	**13**,**15** (>99:<1)	90
4	(−)-**6**	BuMgBr	4	**14**,**16** (>99:<1)	60
5	**17**	PhMgBr	1.5	**13**,**15** (1:6)	70

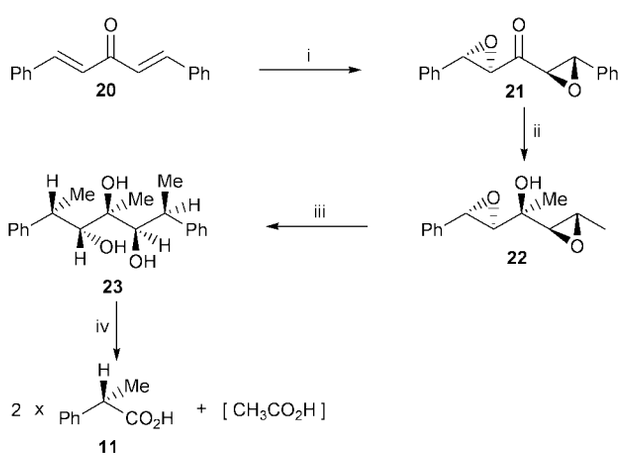
Similar treatment of the diastereoisomeric mixture rich in epoxy alcohol **15** (see Table 1, Entry 5) with trimethylaluminium gave the alcohol **19** as the major product (with



18 R^1 = Ph, R^2 = Me
19 R^1 = Me, R^2 = Ph

retention of configuration at the reacting carbon atom) since oxidative cleavage gave, once more, (*S*)-2-phenylpropanoic acid in 84% yield. Thus the configuration of the tertiary alcohol group had no bearing on the stereochemistry of the epoxide ring-opening reaction.

We were also minded to try to improve the atom efficiency in these new routes to optically active 2-arylpropanoic acids. To this end the dienone **20** was prepared from benzaldehyde and acetone and then the optically pure bis-epoxide **21** was prepared in 90% yield using poly-(L)-leucine on silica as the catalyst for the asymmetric epoxidation (Scheme 2).



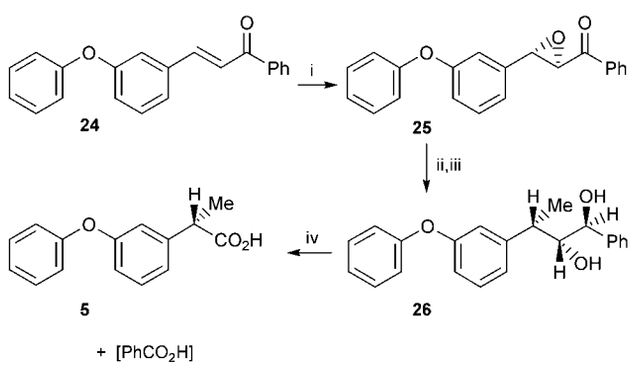
Scheme 2 *Reagents and conditions* (yields in parenthesis): (i) Poly-(L)-leucine adsorbed onto silica, *tert*-butyl methyl ether containing urea–hydrogen peroxide and DBU, −10 °C (90%); (ii) MeMgI, THF, Et_2O, −78 °C (88%); (iii) Me_3Al, hexane, −78 °C (71%); (iv) $NaIO_4/SiO_2$, CH_2Cl_2; then Jones oxidation (69%).

Reaction of the ketone **21** with methylmagnesium iodide gave the tertiary alcohol **22** which reacted with excess of trimethylaluminium so as to undergo a double alkylation reaction to give the triol **23**. Retention of configuration during alkylation was confirmed by oxidative cleavage to afford (*S*)-2-phenylpropanoic acid in 39% overall yield from dienone **20**; acetic acid (which was lost on work-up) was the only other product.

Synthesis of (*S*)-(+)-fenoprofen 5

After establishing viable routes to (*S*)-2-phenylpropanoic acid, attention was switched to the synthesis of two anti-inflammatory drugs in optically active form. The first target was (*S*)-(+)-fenoprofen **5**, a compound prepared by the Lilly group using (+)-α-methylbenzylamine to resolve, in classical fashion, the racemic carboxylic acid.[19]

Aldol condensation of 3-phenoxybenzaldehyde with acetophenone gave the *E*-enone **24** in 91% yield (Scheme 3).



Scheme 3 *Reagents and conditions* (yields in parenthesis): (i) Poly-(L)-leucine adsorbed onto silica, urea–hydrogen peroxide, DBU, THF, 2 h (98% yield, 94% ee); (ii) $Zn(NH_4)_2$ (0.3 equiv.), Et_2O, 0 °C, 3 h (95%); (iii) Me_3Al (3 equiv.), hexane, −78 °C, 2 h (85%); (iv) $NaIO_4/SiO_2$, CH_2Cl_2; then Jones oxidation (64%).

Polyleucine-catalysed asymmetric oxidation of **24** was highly efficient, furnishing the epoxy ketone **25** in 98% yield and 94% enantiomeric excess. Zinc borohydride reduction followed by treatment with trimethylaluminium gave diol **26** in 81% yield over the two steps. Oxidative cleavage gave (*S*)-(+)-fenoprofen **5**, $[a]_D^{20}$ +46 (*c* 1.0, $CHCl_3$) (identical to the literature value) in 64% yield. Thus (*S*)-(+)-fenoprofen is available from 3-phenoxybenzaldehyde in 46% overall yield.

Synthesis of (*S*)-(+)-naproxen 1

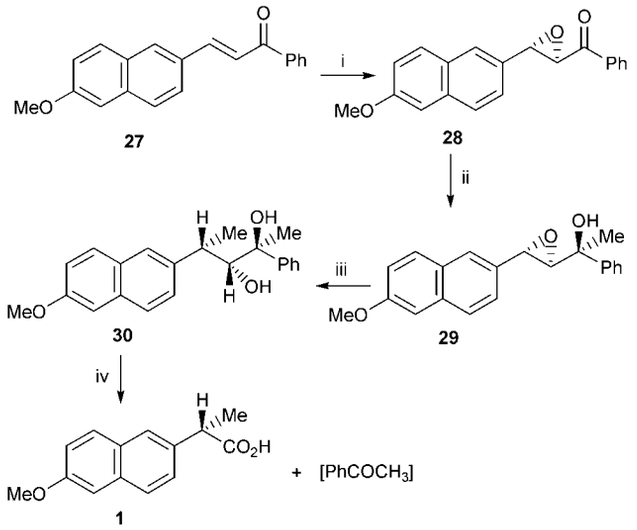
The synthesis of naproxen in its enantiomerically pure (*S*)-form has attracted considerable attention over the years[20] but we believe our new asymmetric synthesis, described below, is as efficient as any of the other, pre-existing methodologies.

Aldol condensation of 6-methoxy-2-naphthaldehyde with acetophenone gave the enone **27** in 90% yield (Scheme 4). Stereoselective epoxidation of this enone using poly-(L)-leucine on silica as the chiral catalyst furnished the epoxide **28** in 97% yield and 94% ee. Treatment of this epoxy ketone with methylmagnesium iodide formed the tertiary alcohol **29** which was ring-opened (with retention of configuration) using trimethylaluminium to give the diol **30** (66% yield over two steps). The diol was cleaved in the usual manner to give naproxen **1** (88% yield) and acetophenone.

Confirmation of the absolute stereochemistry of compound **1** was provided by comparison of the optical activity {$[a]_D^{20}$ +68 (*c* 1.0 ($CHCl_3$)} with data published previously {$[a]_D^{20}$ +67.5 (*c* 1.0 ($CHCl_3$)}.[21] Thus (*S*)-(+)-naproxen **1** is available from 6-methoxy-2-naphthaldehyde in six steps (five-pots) in a non-optimised overall yield of 51%.

Conclusions

The routes to (*S*)-2-phenylpropanoic acid **11**, (*S*)-fenoprofen **5** and (*S*)-naproxen **1**, described in Schemes 2, 3 and 4 respectively, are efficient and high yielding. The fact that polyleucine-



Scheme 4 *Reagents and conditions* (yields in parenthesis): (i) Poly-(L)-leucine adsorbed onto silica, urea–hydrogen peroxide, DBU, THF, 1.5 h (97% yield, 94% ee); (ii) MeMgI, THF, Et_2O, −78 °C, 2.5 h (85%); (iii) Me_3Al (3 equiv.), hexane, −78 °C, 4 h (78%); (iv) $NaIO_4/SiO_2$, CH_2Cl_2; then Jones oxidation (88%).

catalysed asymmetric oxidations of enones can be applied so as to match the retention or inversion of configuration in the subsequent alkylation process allows a small portfolio of routes to these important compounds to be constructed. Obviously (*R*)-arylpropanoic acids could be made available, if and when required, by application of the same technologies. To the chemical purist some of the transformations (for example conversion of triol **23** into the acid **11** and acetic acid) may seem wasteful in terms of the loss of well defined stereogenic centres, so it is also of interest to us to use such 2,4,6-trisubstituted heptane-3,4,5-triols in synthetic sequences where the array of contiguous stereogenic centres is not subsequently lost. These later studies will be the subject of another full paper.

Experimental

Diethyl ether and THF were distilled over sodium metal and benzophenone. Petroleum spirit (distillation range 40–60 °C) and dichloromethane were distilled over calcium hydride. Other reagents and solvents were obtained commercially and used as received without further purification. Reactions were monitored by TLC, performed on glass-backed silica plates coated with Merck 60F-254. Visualisation was achieved either by treatment with potassium permanganate, cerium(IV) ammonium molybdate (CAM), or *p*-anisaldehyde, followed by heating and/or UV light (254 nm). Flash column chromatography was performed using Merck 60 silica gel (40–63 μm). Mps were measured on a Gallenkamp melting point apparatus, and are uncorrected. IR spectra were recorded on a Perkin-Elmer 881 infrared spectrometer. Low-resolution EI mass spectra were measured on a Fisons Trio 1000 instrument; CI and accurate mass spectra were measured on a VG Analytical 7070E double-focusing mass spectrometer. ^{1}H NMR spectra were measured [$CDCl_3$ as a solvent using tetramethylsilane (TMS) as internal reference] with a Brucker AC200 instrument at 200 MHz or a Varian Gemini 300 at 300 MHz. ^{13}C NMR spectra were recorded on a Varian Gemini 3000 at 75 MHz. All chemical shifts are quoted in ppm relative to TMS (0.0 ppm) and to residual $CHCl_3$ (77.0 ppm) for ^{13}C analysis. Optical rotations were measured on an Optical Activity Ltd. AA-1000 polarimeter, and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}.

Synthesis of (*S*)-2-phenylpropanoic acid 11

(2*R*,3*S*)-2,3-Epoxy-1,3-diphenylpropan-1-one (−)-6. (*E*)-Chalcone (180 mg, 0.9 mmol), urea–hydrogen peroxide (100 mg, 1 mmol) and poly-(L)-leucine adsorbed onto silica [1:3 ratio poly-(L)-leucine to silica][9] (1.5 g) were stirred with exclusion of light in THF (10 cm^3) and DBU (0.15 cm^3, 1 mmol) was added. After 30 min, the reaction mixture was filtered and the filtrate was diluted with ethyl acetate (100 cm^3) and washed successively with aq. sodium sulfite (20%) (2 × 20 cm^3) and brine (20 cm^3). The organic layer was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. Purification by flash column chromatography (SiO_2; petroleum spirit–ethyl acetate, 9:1) afforded the pure *trans*-epoxychalcone (−)-**6** (191 mg, 95%, 97% ee), mp 61–62 °C (from diethyl ether); $[\alpha]_D$ −205 (*c* 1.0, $CHCl_3$) (Found: C, 80.2; H, 5.3. $C_{15}H_{12}O_2$ requires C, 80.35; H, 5.4%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1690 (C=O), 1292, 835 (C–O, epoxide); δ_H (400 MHz; $CDCl_3$) 4.08 (1H, d, *J* 1.9, H-3), 4.25 (1H, d, *J* 1.9, H-2), 7.15–8.10 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 59.4 and 61.1 (C-2 and -3), 125.9, 128.4, 128.8, 128.9 and 129.1 (C-1^2, -1^3, -1^4, -3^2, -3^3 and -3^4), 134.0 and 135.1 (C-1^1 and -3^1), 186.0 (C-1); *m*/*z* (EI) 224 (M^+, 11%), 105 (PhC=O, 100).

***anti*-(2*R*,3*R*)- and *syn*-(2*R*,3*S*)-2-Hydroxy-1,3-diphenylbutanone 7 and 9.** To a solution of epoxychalcone (−)-**6** (200 mg, 0.89 mmol) in dichloromethane (35 cm^3) under an argon atmosphere at −78 °C was added dropwise a solution of trimethylaluminium (2 M solution in hexane; 0.9 cm^3, 1.78 mmol) followed by water (19.2 × 10^{-3} cm^3, 0.373 mmol). After 30 min, the reaction was quenched by slow addition of water and the resulting mixture was filtered over a pad of Celite® and washed with dichloromethane. The aqueous layer was extracted with dichloromethane (3 × 20 cm^3) and the combined organic layers were washed successively with water (2 × 15 cm^3) and brine (2 × 15 cm^3), dried over magnesium sulfate, filtered and evaporated under reduced pressure to afford a yellow oil. Purification by flash column chromatography [SiO_2; petroleum spirit–ethyl acetate, 9:1) yielded the *syn-hydroxy ketone* **9** as an oil (18 mg, 8%), R_f (isohexane–ethyl acetate, 9:1) 0.26 (Found: C, 80.0, H, 6.8. $C_{16}H_{16}O_2$ requires C, 80.0; H, 6.7); ν_{max}(NaCl)/cm^{-1} 3470 (OH), 3060, 3025 (=CH), 1687 (C=O), 1595, 1580 (C=C, Ar); δ_H (300 MHz; $CDCl_3$) 1.15 (3H, d, *J* 7.1, H_3-4), 3.12 (1H, qd, *J* 7.1 and 0.1, H-3), 3.80 (1H, d, *J* 6.0, OH), 5.23 (1H, m, H-2), 7.15–7.65 (8H, m, ArH), 7.85–8.12 (2H, m, ArH); δ_C (75 MHz; $CDCl_3$) 13.1 (C-4), 43.5 (C-3), 76.7 (C-2), 126.9 (C-3^4), 127.8, 128.6, 128.7 and 129.0 (C-1^2, -1^3, -3^2 and -3^3), 133.8 (C-1^4), 134.0 and 144.1 (C-1^1 and -3^1), 201 (C=O); *m*/*z* (EI) 105 (PhC=O, 100%), 77 (Ph, 35); followed by its major diastereoisomer *anti-hydroxy ketone* **7** as an oil (163 mg, 75%), R_f (isohexane–ethyl acetate, 9:1) 0.21 (Found: C, 80.2, H, 6.6%) ν_{max}(NaCl)/cm^{-1} 3480 (OH), 3090, 3072 (=CH), 1685 (C=O), 1600, 1580 (C=C, Ar); δ_H (300 MHz; $CDCl_3$) 1.52 (3H, d, *J* 7.2, H_3-4), 3.32 (1H, qd, *J* 7.2 and 2.7, H-3), 3.50 (1H, d, *J* 7.0, OH), 5.20 (1H, dd, *J* 7.0 and 2.7, H-2), 6.88–7.60 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 18.1 (C-4), 44.2 (C-3), 76.6 (C-2), 127.0 (C-3^4), 127.9, 128.2, 128.5, 128.7 and 128.9 (C-1^2, -1^3, -3^2 and -3^3), 133.7 (C-1^4), 134.8 and 139.8 (C-1^1 and -3^1), 201.0 (C=O); *m*/*z* (EI) 105 (PhC=O, 100%), 77 (Ph, 39). Diastereoisomer ration (dr) of the crude mixture (determined by NMR analysis), **7**:**9**, 10:1.

***anti*-(2*R*,3R)-2-Hydroxy-1,3-diphenylpentan-1-one *rac*-8.** The same procedure as above was followed using (±)-epoxychalcone (±)-**6** (200 mg, 0.89 mmol) in dichloromethane (35 cm^3) with triethylaluminium (1 M solution in hexane; 1.78 cm^3, 1.78 mmol) and water (19.2 × 10^{-3} cm^3, 0.373 mmol). After 1 h, the reaction was complete and quenched as for the alkylation with trimethylaluminium (see above). Purification by flash column chromatography (SiO_2; petroleum spirit–ethyl acetate, 9:1) afforded the hydroxy ketone (±)-**8** (193 mg, 85%) as a white solid, mp 85–87 °C (from hexane); R_f (isohexane–ethyl acetate, 9:1) 0.35 (Found: C, 80.15, H, 7.0. $C_{17}H_{18}O_2$ requires C, 80.3; H, 7.0); ν_{max}(NaCl)/cm^{-1} 3480 (OH), 3075, 3072, 3030 (=CH),

1685 (C=O), 1600, 1575 (C=C, Ar); δ_H (300 MHz; $CDCl_3$) 0.96 (3H, t, *J* 8.0, H_3-5), 2.10 (2H, m, H_2-4), 2.96 (1H, dt, *J* 2.5 and 3.2, H-3), 3.58 (1H, d, *J* 7.0, OH), 5.33 (1H, dd, *J* 7.0 and 2.5, H-2), 6.98–7.63 (8H, m, ArH), 7.8–7.92 (2H, m, H-1^2); δ_C (75 MHz; $CDCl_3$) 12.0 (C-5), 25.3 (C-4), 51.6 (C-3), 75.5 (C-2), 126.8 (C-3^4), 127.7–128.7 (C-3^2, -3^3, -1^2 and -1^3), 133.6 (C-1^4), 134.4 and 138 (C-1^1 and -3^1), 200.9 (C=O); *m*/*z* (EI) 105 (Ph-C=O, 100%), 77 (Ph, 29).

Reduction of hydroxy ketone 9. *Preparation of zinc borohydride [Zn(BH$_4$)$_2$].* An ethereal solution of zinc chloride (5 g, 36 mmol) and distilled diethyl ether (70 cm^3) was added dropwise to a stirred suspension of sodium borohydride (3.375 g, 90 cm^3) in distilled diethyl ether (180 cm^3). The mixture was stirred at room temperature under argon atmosphere for 12 h. The solid formed (NaCl) was allowed to settle and the liquid was removed and stored in a stoppered bottle under an argon atmosphere at −18 °C and was used as a 0.144 M $Zn(BH_4)_2$ solution in diethyl ether.

(1S,2R,3S)-1,2-Dihydroxy-1,3-diphenylbutane ***10****.* To an ice-cold solution of the hydroxy ketone **9** (200 mg, 0.83 mmol) in diethyl ether (5 cm^3) was added, dropwise, a solution of zinc borohydride (0.144 M in diethyl ether; 1.75 cm^3, 0.25 mmol). After 1 h, the reaction was quenched with water (1 cm^3). The solution was then stirred for another 30 min. The aqueous layer was extracted with diethyl ether (3 × 15 cm^3) and the combined organic layers were dried over magnesium sulfate and filtered under reduced pressure to afford a yellow oil. Purification by flash column chromatography (SiO_2; petroleum spirit–ethyl acetate, 9:1) furnished the pure *diol* **10** as a white solid (194 mg, 95%), mp 90–92 °C (from ethyl acetate–hexane); $[a]_D$ +63.5 (*c* 1.04, $CHCl_3$); R_f (petroleum spirit–ethyl acetate, 4:1) 0.18 (Found: C, 79.2; H, 7.3. $C_{16}H_{18}O_2$ requires C, 79.3; H, 7.4%); ν_{max}(NaCl)/cm^{-1} 3609 (OH), 1602, 1644 (C=C, Ar); δ_H (300 MHz; $CDCl_3$) 1.33 (3H, d, *J* 6.9, H_3-4), 1.85 (1H, s, OH), 2.22 (1H, s, OH), 2.82 (1H, quint, *J* 6.9, H-3), 4.02 (1H, t, *J* 6.9, H-2), 4.53 (1H, d, *J* 6.9, H-1), 7.09–7.29 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 16.6 (C-4), 41.5 (C-3), 75.2 (C-2), 78.8 (C-1), 126.6 and 128.2 (C-1^4 and -3^4), 127.7, 128.0, 128.4 and 128.6 (C-1^2, -1^3, -3^2 and -3^3), 140.7 and 144.7 (C-1^1 and -3^1); *m*/*z* (EI) 135 (M − PhCOH, 13%), 108 [M − PhCH(CH$_3$)COH, 100], 105 (PhC=O, 91), (Ph, 40).

***anti*-(1*S*,2*S*,3*S*)-2,3-Epoxy-1,3-diphenylpropan-1-ol 12.** To an ice-cold solution of epoxychalcone (−)-**6** (1 g, 4.46 mmol) in distilled diethyl ether (20 cm^3) was added dropwise a cold solution of $Zn(BH_4)_2$ (0.144 M solution in diethyl ether; 9.3 cm^3, 1.34 mmol). After 30 min, the reaction was quenched with water (5 cm^3) and stirred vigorously for another 30 min. The aqueous layer was extracted with diethyl ether (3 × 15 cm^3) and the combined organic phases were dried over magnesium sulfate, filtered and evaporated under reduced pressure. Crystallisation of the crude compound from hexane afforded the *epoxy alcohol* **12** as a white solid (0.96 g, 95%), mp 114–115 °C (from ethyl acetate–hexane); $[a]_D$ −12.65 (*c* 1.0, $CHCl_3$); R_f (petroleum spirit–ethyl acetate 4:1) 0.37 (Found: C, 79.8; H, 6.1. $C_{15}H_{14}O_2$ requires C, 79.6; H, 6.2%); ν_{max}(NaCl)/cm^{-1} 3430 (OH), 1220, 870, (C–O, epoxide); δ_H (300 MHz; $CDCl_3$) 2.54 (1H, d, *J* 2.0, OH), 3.28 (1H, dd, *J* 1.65 and 2.75, H-2), 4.13 (1H, d, *J* 1.65, H-3), 4.98 (1H, d, *J* 2.75, H-1), 7.23–7.44 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 55.0 (C-2), 64.9 (C-3), 71.3 (C-1), 125.8, 126.5, 128.5 and 128.7 (C-1^2, -1^3, -3^3 and -3^2), 128.2 and 128.3 (C-1^4 and -3^4), 136.5 and 139.2 (C-1^1 and -3^1); *m*/*z* (EI) 118 (M − PhCHCOH,81%), 105 (PhC=O, 91), 91 (C_7H_7, 100), 77 (Ph, 55).

Alkylation of epoxy alcohol 12 with trimethylaluminium. A solution of epoxy alcohol **12** (1 g, 4.42 mmol) in hexane (20 cm^3) was added dropwise to a solution of trimethylaluminium (2 M solution in hexane, 6.6 cm^3, 13.27 mmol) at 0 °C under an argon atmosphere. After stirring of the solution for 1 h at 0 °C, the resulting mixture was diluted with dichloromethane (45 cm^3), and treated with sodium fluoride (5.5 g, 0.13 mol) and water (2.5 cm^3). Vigorous stirring of the resulting suspension was continued at room temperature for another 30 min. The semi-solid was filtered off and washed with diethyl ether (3 × 30 cm^3). The filtrate and washings were dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; petroleum spirit–ethyl acetate, 4:1) furnished the diol **10** as a white solid (0.94 g, 93%), $[a]_D$ +63.47 (*c* 1.05, $CHCl_3$); mp 90–91 °C (from ethyl acetate–hexane).

Oxidative cleavage of diol 10. Synthesis of (2*S*)-2-phenylpropanoic acid 11. To a solution of diol **10** (400 mg, 1.65 mmol) in dichloromethane (9 cm^3) was added sodium periodate supported on silica gel (1.2 mmol g^{-1}; 4.96 mmol, 4.13 g). After 1 h, the reaction was complete and the mixture was filtered through sodium sulfate and concentrated under reduced pressure to give a mixture of phenylpropanal and benzaldehyde which was used without any further purification for the next step. To a solution of the crude product (380 mg) in acetone (15 cm^3) at 0 °C was added dropwise a solution of Jones reagent (2.7 M; 0.76 cm^3). After 1 h the reaction was judged to be complete and the excess of oxidant was destroyed by addition of propan-2-ol (10 cm^3). The solid residue was filtered off, and washed with acetone (3 × 5 cm^3). The combined filtrates were diluted with water (20 cm^3) and concentrated to *ca.* 20 cm^3. The remaining aqueous residue was extracted with ethyl acetate (5 × 10 cm^3). The combined organic extracts were washed with 1 M $NaHCO_3$ (3 × 10 cm^3). The combined aqueous extracts were acidified with a solution of hydrochloric acid (1 M) and re-extracted with ethyl acetate (3 × 10 cm^3). The combined organic extracts were dried over sodium sulfate and evaporated under reduced pressure to give a mixture of benzoic acid and phenylpropanoic acid. Purification by flash column chromatography (SiO_2; dichloromethane–methanol, 49:1) furnished (2*S*)-phenylpropanoic acid **11** as a colourless liquid (176 mg, 71%), $[a]_D$ +72.5 (*c* 1.0, $CHCl_3$) {lit.,[14] $[a]_D$ +72.8 (*c* 1.0, $CHCl_3$), 99% ee}; R_f (dichloromethane–methanol, 97:3) 0.23 (Found: M^+, 150.06813; C, 72.3; H, 6.9. $C_9H_{10}O_2$ requires *M*, 150.06808; C, 72.0; H, 6.7%); ν_{max}(NaCl)/ cm^{-1} 2600–3600 (OH), 1705 (CO); δ_H (300 MHz; $CDCl_3$) 1.60 (3H, d, *J* 5.8, H_3-3), 3.82 (1H, q, *J* 5.8, H-2), 7.35–7.43 (5H, m, ArH), 11.90 (1H, br s, COOH); δ_C (75 MHz, $CDCl_3$) 18.2 (C-3), 45.55 (C-2), 127.6 (C-2^4), 127.8 and 128.9 (C-2^2 and -2^3), 139.9 (C-2^1), 181.9 (COOH); *m*/*z* (EI).

Synthesis of (2*S*)-2-phenylpropanoic acid 11 from epoxychalcone (+)-6

In parallel experiments to those described above the epoxychalcone (+)-**6** was prepared from chalcone using poly-(D)-leucine on silica as the catalyst. Treatment of (+)-**6** with trimethylaluminium, reduction using zinc borohydride, separation of the major diastereoisomer and two-step oxidative cleavage gave the desired product **11** in 48% overall yield. The physical properties of product **11** were found to be exactly the same as those described above.

Synthesis of tertiary epoxy alcohols

Alkylation of epoxychalcone (−)-6 with MeMgI. Synthesis of (2*S*,3*R*,4*S*)-3,4-epoxy-2,4-diphenylbutan-2-ol 13. Diethyl ether (10 cm^3) and THF (7 cm^3) were added to a nitrogen-filled flask and the vessel was cooled to −78 °C. Epoxychalcone (448 mg, 2 mmol) as a solution in THF (2 cm^3) was then added, followed by methylmagnesium iodide (2 M solution in diethyl ether; 1.6 cm^3, 3.2 mmol). After 1.5 h, the reaction was quenched with saturated aq. ammonium chloride and extracted with diethyl ether (3 × 50 cm^3). The combined organic layers were washed

successively water (50 cm^3) and brine (50 cm^3), dried over magnesium sulfate and evaporated under reduced pressure. Purification by flash column chromatography (SiO_2; petroleum spirit–diethyl ether, 6:1) afforded the diastereomerically pure *epoxy alcohol* **13** (432 mg, 90%) as white crystals, mp 101–102 °C (from hexane); [*a*] −47 (*c* 0.5, $CHCl_3$); R_f (petroleum spirit–diethyl ether, 3:1) 0.3 (Found: C, 79.9; H, 6.7. $C_{16}H_{16}O_2$ requires C, 80.0; H, 6.7%); ν_{max}(NaCl)/cm^{-1} 3495 (OH), 1630, 1212, 981, 870 (C–O, epoxide); δ_H(400 MHz; $CDCl_3$) 1.70 (3H, s, H_3-1), 2.84 (1H, s, OH), 3.25 (1H, d, *J* 2.2, H-3), 4.05 (1H, d, *J* 2.2, H-4), 7.18–7.50 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 27.8 (C-1), 55.8 (C-3, 68.3 (C-4), 71.3 (C-2), 128.6–125.2 (CH, Ar), 136.9 (C, Ar), 143.8 (C, Ar); *m*/*z* (EI) 121 (M − PhCHOCH, 36%), 120 ($PhCHOCH_2$, 86), 105 (PhC=O, 91), 91 (C_7H_7, 100), 77 (Ph, 53).

Alkylation of epoxychalcone (−)-6 with ″BuMgBr. Synthesis of (1*S*,2*R*,3*S*)-1,2-epoxy-1,3-diphenylheptan-3-ol 14. To a stirred suspension of magnesium turnings (108 mg, 4.46 mmol) in diethyl ether (10 cm^3) was added 1-bromobutane (0.48 cm^3, 4.5 mmol) under a nitrogen atmosphere at such a rate as to maintain reflux. After complete reaction of the magnesium, THF (10 cm^3) was added and the contents of the flask were cooled to −78 °C. *trans*-Epoxychalcone (−)-**6** (500 mg, 2.23 mmol) was added *via* a solid-addition tube. After 4 h, the reaction was quenched by addition of saturated aq. ammonium chloride (10 cm^3), allowed to warm to room temperature and extracted with diethyl ether (3 × 50 cm^3). The combined organic extracts were washed successively with water (50 cm^3) and brine (50 cm^3) and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a crude reaction mixture which contained the desired tertiary alcohol with a diastereomeric ratio of >99:1. Purification by flash column chromatography (SiO_2; petroleum ether spirit–diethyl ether, 6:1) and recrystallisation from hexane afforded the *alcohol* **14** (378 mg, 60%) as white crystals, mp 81–83 °C (from hexane); $[a]_D$ −51.0 (*c* 1.0, $CHCl_3$); R_f (petroleum spirit–Et_2O, 3:1) 0.4 (Found: C, 80.8; H, 7.8. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.9%); ν_{max} (KBr)/cm^{-1} 3495 (OH), 1210, 961 and 881; δ_H (300 MHz; $CDCl_3$) 0.88 (3H, m, H-7), 1.18–1.48 (2 × 2H, m, H-5 and H-6), 1.94–2.09 (2H, m, H-4), 2.36 (1H, s, OH), 3.36 (1H, d, *J* 2.2, H-2), 3.92 (1H, d, *J* 2.2, H-1), 7.17–7.47 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 14.6 (C-7), 23.7 and 25.9 (C-6 and -5), 41.7 (C-4), 55.7 (C-2), 68.6 (C-1), 73.9 (C-3), 125.7, 126.4, 127.7, 128.8, 129.0 and 129.0 and 136.8 142.6 (Ar); *m*/*z* (EI) 163 (20%), 120 (83), 105 (100), 91 (81), 77 (59).

(3*R*,4*S*)-3,4-Epoxy-4-phenylbutan-2-one 17. (*E*)-4-Phenylbut-3-en-2-one (180 mg, 0.9 mmol), urea–hydrogen peroxide (100 mg, 1 mmol) and poly-(L)-leucine on silica (1.550 g) were stirred in *tert*-butyl methyl ether (10 cm^3) at −10 °C, and DBU (150 × 10^{-3} cm^3, 1 mmol) was added. After 10 h, the reaction was complete and the solution was filtered (glass sinter, porosity 3) and the residue was rinsed with ethyl acetate (3 × 50 cm^3). The filtrate was washed successively with aq. sodium sulfite (20%; 20 cm^3) and brine (20 cm^3), dried over magnesium sulfate and evaporated under reduced pressure**.** Purification by flash column chromatography (SiO_2; petroleum spirit–ethyl acetate, 9:1) followed by crystallisation from hexane afforded the pure enantiomeric *trans-epoxide* **17** (124 mg, 85%), mp 42–43 °C; $[a]_D$ −203 (*c* 1.0, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1712 (C=O), 1203 and 886 (C–O, epoxide), 1411, 1368 (Found: C, 74.2; H, 6.25. $C_{10}H_{10}O_2$ requires C, 74.1; H, 6.2%); δ_H (300 MHz; $CDCl_3$) 2.16 (3H, s, H_3-1), 3.47 (1H, d, *J* 2.2, H-2), 3.99 (1H, d, *J* 2.2, H-3), 7.23–7.27 (5H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 24.7 (C-1), 57.7 (C-2), 63.5 (C-3), 125.8 and 128.8 (C-4^2 and -4^3), 129.1 (C-4^4), 135.2 (C-4^1), 204.1 (C-4); *m*/*z* (EI) 162 (M^+, 19%), 91 (C_7H_7, 100). ee > 90% determined by NMR spectroscopy [chiral shift reagent Eu(hfc)$_3$].

Reaction of epoxy ketone 17 with PhMgBr. Synthesis of (2*R*,3*R*,4*S*)-3,4-epoxy-2,4-diphenylbutan-2-ol 15. To a stirred suspension of magnesium turnings (77.8 mg, 3.2 mmol) in diethyl ether (10 cm^3) was added bromobenzene (0.337 cm^3, 3.2 mmol) under a nitrogen atmosphere at such a rate as to maintain reflux. After complete reaction of the magnesium, THF (10 cm^3) was added and the contents of the flask were cooled to −78 °C. *trans*-Epoxy ketone **17** (324 mg, 2 mmol) was added *via* a solid-addition tube. After 2 h the reaction had gone to completion and was quenched with saturated aq. ammonium chloride before being extracted with dichloromethane (3 × 50 cm^3). The combined organic layers were washed successively with water (2 × 25 cm^3) and brine (2 × 25 cm^3), then dried over sodium sulfate, filtered, and evaporated under reduced pressure. Purification by flash column chromatography (SiO_2; petroleum spirit–diethyl ether, 8:2) afforded an inseparable mixture of **13** and **15** as a white solid (336 mg, 70%), mp 102–103 °C; R_f (petroleum spirit–diethyl ether, 3:1) 0.35 (Found: C, 79.8; H, 6.6. $C_{16}H_{16}O_2$ requires C, 80.0; H, 6.7%); ν_{max}(NaCl)/cm^{-1} 3497 (OH), 1212, 991, 881 (C–O, epoxide). The diastereomeric ratio determined by ^{1}H NMR analysis was found to be **13**:**15**, 1:6.

Synthesis of (2*S*,3*R*,4*S*)-2,3-dihydroxy-2,4-diphenylpentane 18

To a solution of tertiary epoxy alcohol **13** (500 mg, 2.08 mmol) in hexane (10 cm^3) was added dropwise a solution of trimethylaluminium (2 M solution in hexane; 3.12 cm^3, 6.24 mmol) at −78 °C under an argon atmosphere. After stirring for 1 h at −78 °C, the resulting mixture was diluted with dichloromethane (25 cm^3), and treated with sodium fluoride (2.75 g, 65 mmol) and water (1.25 cm^3). Vigorous stirring of the resulting suspension was continued at room temperature for another 30 min. The semi-solid was filtered off and washed with diethyl ether (3 × 20 cm^3). The filtrate and washings were dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; petroleum spirit–ethyl acetate, 4:1) furnished the *diol* **18** as an oil (454. mg, 82%) $[a]_D$ +36 (*c* 1.0, EtOH); R_f (petroleum spirit–ethyl acetate, 9:1) 0.18 (Found: C, 79.5; H, 7.9. $C_{17}H_{20}O_2$ requires C, 79.7; H, 7.8%); ν_{max}(NaCl)/cm^{-1} 3619 (OH), 1602, 1654 (C=C, Ar); δ_H (300 MHz; $CDCl_3$) 1.17 (3H, d, *J* 6.9, H_3-5), 1.56 (3H, s, H_3-1), 2.16 (1H, br s, OH), 2.44 (1H, br s, OH), 2.59–2.68 (1H, dq, *J* 6.9 and 3.0, H-4), 3.88 (1H, d, *J* 3.0, H-3), 7.04–7.48 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 14.25 (C-5), 29.05 (C-1), 40.45 (C-4), 60.15 (C-2), 81.1 (C-3), 125.1, 127.4, 128.3 and 128.5 (C-4^2, -4^3, -2^2 and -2^3), 126.2 and 126.9 (C-4^4 and -2^4), 145 and 146.5 (C-4^1 and -2^1), *m*/*z* (CI) (Found: $[M + NH_4]^+$, 274.18052, $C_{17}H_{24}NO_3$ requires *m*/*z*, 274.18071), 121 ($PhCCH_3OH$, 100%), 105 (PhCO, 45), 91 (C_7H_7, 21), 43 (CH_3CO, 83).

(2*R*,3*R*,4*S*)-2,3-Dihydroxy-2,4-diphenylpentane 19

The mixture of epoxy alcohols **13** and **15** (500 mg, 2.08 mmol; **15**:**13**. 6:1) was alkylated as above with a solution of trimethylaluminium (2 M solution in hexane; 3.12 cm^3, 6.24 mmol). Purification by flash column chromatography (SiO_2; petroleum spirit–ethyl acetate, 4:1) furnished an inseparable mixture of the diastereomers **19** and **18** whose ratio was found to be **19**:**18**, 6:1. Crystallisation, from hexane, of the resulting solid furnished the two diastereomers **19** and **18** in a 12:1 ratio (393 mg, 71%). Diol **19**: δ_H (300 MHz; $CDCl_3$) 1.30 (3H, d, *J* 7.0, H_3-5), 1.49 (3H, s, H_3-1), 2.20 (1H, br s, OH), 2.26 (1H, br s, OH), 3.03 (1H, dq, *J* 7.0 and 4.1, H-4), 3.94 (1H, d, *J* 4.1, H-3), 7.04–7.48 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 16.4 (C-5), 25.1 (C-1), 40.6 (C-4), 60.5 (C-2), 81.3 (C-3), 125.1–128.5 (CH, Ar), 146.5 and 146.7 (C-4^1 and -2^1).

***trans, trans*-(1*S*,2*R*,4*R*,5*S*)-1,2,4,5-Diepoxy-1,5-diphenylpentan-3-one 21**

(*E*,*E*)-1,5-Diphenylpenta-1,4-dien-3-one **20** (600 mg, 2.56 mmol), urea–hydrogen peroxide (289 mg, 3.1 mmol) and poly-

(L)-leucine on silica (2 g, 0.5 g of polymer) were stirred at −10 °C in *tert*-butyl methyl ether (90 cm^3) with exclusion of light, and DBU (464 × 10^{-3} cm^3, 3.1 mmol) was added. After 1 h the reaction was complete, the solution was filtered (glass sinter, porosity 3) and the residue rinsed with ethyl acetate (3 × 20 cm^3). The filtrate was washed successively with aq. sodium sulfite (20%; 20 cm^3) and brine (20 cm^3), dried over magnesium sulfate and evaporated under reduced pressure. Purification by flash column chromatography (SiO_2; petroleum spirit–ethyl acetate, 9:1) followed by crystallisation from hexane, afforded the pure bis-epoxide **21** as white needles (613 mg, 90%), mp 117–119 °C (from hexane) [lit.,[22] 118–118.5 °C (from ethanol)] $[\alpha]_D$ −253 (*c* 1.0, EtOH); R_f (petroleum spirit–ethyl acetate, 4:1) 0.56 (Found: C, 76.7; H, 5.3. $C_{17}H_{14}O_3$ requires C, 76.7; H, 5.3%); ν_{max}(NaCl)/cm^{-1} 1220, 870 (C–O, epoxide); δ_H (300 MHz; $CDCl_3$) 3.80 (2H, d, *J* 1.65, H-1 and -5), 4.08 (2H, d, *J* 1.65, H-2 and -4), 7.24–7.37 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 59.0 (C-1 and -5), 61.0 (C-2 and -4), 125.9 and 128.9 (C-1^2, -1^3, -5^2 and -5^3), 129.4 (C-1^4 and -5^4), 134.4 (C-1^1 and -5^1), 199.4 (C-3); *m*/*z* (EI) 180 ($PhCHOCH_2$, 40%), 105 (PhC=O, 43), 77 (Ph, 77). ee 99%, de 95% (before crystallisation), de 99% (after crystallisation).

Synthesis of (1*S*,2*R*,4*R*,5*S*)-1,2,4,5-diepoxy-3-methyl-1,5-diphenylpentan-3-ol 22

To a solution of the diepoxy ketone **21** (500 mg, 1.879 mmol) in freshly distilled diethyl ether (25 cm^3) and THF (20 cm^3) was added dropwise a solution of methylmagnesium iodide (3 M solution in diethyl ether; 2 cm^3, 6 mmol) under a nitrogen atmosphere at −78 °C. After 1 h, the reaction mixture was quenched with saturated aq. ammonium chloride and the solution extracted with diethyl ether (3 × 50 cm^3). The combined organic layers were washed successively with water (30 cm^3) and brine (30 cm^3), dried over magnesium sulfate and evaporated under reduced pressure. Purification by flash column chromatography (SiO_2; petroleum spirit–ethyl acetate, 9:1) followed by crystallisation from hexane–ethyl acetate, 10:1, furnished the *diepoxy alcohol* **22** (466 mg, 88%). $[\alpha]_D$ 93 (*c* 1.0, EtOH); mp 116–118 °C (from ethyl acetate–hexane); R_f (petroleum spirit–ethyl acetate, 9:1) 0.15 (Found: C, 76.55; H, 6.35. $C_{18}H_{18}O_3$ requires C, 76.6; H, 6.4%); ν_{max}($CHCl_3$)/cm^{-1} 3625 (OH), 3025 (ArH), 1205, 905 and 849 (C–O, epoxide); δ_H (300 MHz; $CDCl_3$) 1.41 (3H, s, CH_3), 2.24 (1H, br s, OH), 3.12 and 3.15 (each 1H, d, *J* 2.2, H-1 and -5), 3.95 and 4.02 (each 1H, d, *J* 2.2, H-2 and H-4), 7.33–7.37 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 20.2 (CH_3), 54.3 and 55.8 (C-1 and -5), 65.2 and 66.3 (C-2 and -4), 125.8 (C-1^4 and -5^4), 128.5 and 128.6 (C-1^2, -1^3, -5^2 and -5^3), 136.4 (C-1^1 and -5^1); *m*/*z* (CI) (Found: $[M + NH_4]^+$, 300.15997. $C_{18}H_{22}NO_3$ requires *m*/*z* 300.15997); *m*/*z* (EI) 147 (PhCHOCHCO, 77%), 105 (PhC=O, 14), 91 (C_7H_7, 84), 43 (CH_3CO, 100).

Synthesis of (2*S*,3*R*,5*R*,6*S*)-3,4,5-trihydroxy-4-methyl-2,6-diphenylheptane (23)

Diepoxy tertiary alcohol **22** was alkylated with a solution of trimethylaluminium as described above. Purification by flash column chromatography (SiO_2; petroleum spirit–ethyl acetate, 4:1) furnished the *triol* **23** as a colourless oil (446 mg, 71%); $[\alpha]_D$ +12 (*c* 1.0, EtOH); R_f (petroleum spirit–ethyl acetate, 4:1) 0.12 (Found: C, 76.5; H, 8.25. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%); ν_{max}(NaCl)/cm^{-1} 3455 (OH), 1320 (OH); δ_H (300 MHz; $CDCl_3$) 0.84 (3H, s, 4-CH_3), 1.31 and 1.34 (each 3H, d, *J* 7.2, H-1 and -7), 2.55 (1H, br s, 4-OH), 2.89 (1H, quint, *J* 7.2, H-2 or -6), 2.97 (2H, br s, 3-OH and -OH), 3.06 (1H, dq, *J* 7.2 and 3.3, H-6 or -2), 3.6 (1H, d, *J* 7.2, H-3 or -5), 4.0 (1H, d, *J* 3.3, H-5 or -3), 7.17–7.36 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 14.8 (4-*C*H_3), 18.9 and 22.5 (C-1 and -7), 40.7 and 42.1 (C-2 and -6), 76.2 and 78.3 (C-3 and -5), 83.75 (C-4), 126.5 and 126.6 (C-2^4 and -6^4), 127.7 and 128.7 (C-2^2, -2^3, -6^2 and -6^3), 145.9 and 146.1 (C-2^1 and -6^1); *m*/*z* (CI) (Found: $[M + NH_4]^+$, 332.22288. $C_{20}H_{30}NO_3$ requires *m*/*z*, 332.22288), 147 (23%), 105 (PhC=O, 100), 91 (C_7H_7, 20), 77 (Ph, 15), 43 (CH_3CO, 46.5).

Cleavage of triol 23. Synthesis of (*S*)-2-phenylpropanoic acid 11

The usual 2-step oxidative cleavage procedure was carried out on triol **23**. Purification by flash column chromatography (SiO_2; dichloromethane–methanol, 49:2) furnished (2*S*)-2-phenylpropanoic acid **11** as a colourless liquid (314 mg, 69%), $[\alpha]_D$ +72.5 (*c* 1.0, $CHCl_3$).

Synthesis of (*S*)-(+)-fenoprofen 5

(*E*)-3-(3-Phenoxyphenyl)-1-phenylpropenone 24. To a solution of acetophenone (0.9 cm^3, 7.56 mmol) and 3-phenoxybenzaldehyde (1.5 g, 7.65 mmol) in absolute methanol (7.6 cm^3; 1 cm^3 per mmol of ketone), under an argon atmosphere, were added 3 pellets of sodium hydroxide and the mixture was stirred vigorously. The reaction was monitored by TLC (petroleum spirit–ethyl acetate, 4:1) and visualised by UV light and CAM. A yellow precipitate was formed during the reaction which appeared to be complete after 24 h. The reaction mixture was evaporated under reduced pressure and the yellow solid obtained was washed successively with cold ethanol and water. Crystallisation from hexane–ethyl acetate, (10:1) afforded the pure (*E*)-*enone* **24** as a yellow solid (2.6 g, 91), mp 62–64 °C (from hexane–ethyl acetate); R_f (petroleum spirit–ethyl acetate, 9:1) 0.24 (Found: M^+, 300.11477; C, 84.1 H, 5.4. $C_{21}H_{16}O_2$ requires *M*, 300.11505; C, 84.0; H, 5.35%); ν_{max}($CHCl_3$)/cm^{-1} 3060, 1615, 1581, 980 (C=C), 1690 (C=O); δ_H (300 MHz; $CDCl_3$) 6.88–8.0 (16H, m, ArH, H-2 and -3; δ_C (75 MHz; $CDCl_3$) 106.15, 119.6, 121.3, 124.5, 127.6, 128.56, 128.66, 130.3, 132.7, 136.0, 138.6, 145.3, 156.9, 159.1, (C-2, -3 and Ar), 191.5 (C-1); *m*/*z* (EI) 300 (M^+, 100%), 207 (M − OPh, 60.2), 105 (PhC=O, 35), 77 (Ph, 67).

2*R*,3*S*)-2,3-Epoxy-3-(3-phenoxyphenyl)-1-phenylpropan-1-one 25. To a solution of enone **24** (2.0 g, 6.67 mmol) in THF (100 cm^3) were added urea–hydrogen peroxide (753 mg, 8 mmol), poly-(L)-leucine on silica (6 g, (1.39 g of PLL)) and DBU (1.2 cm^3, 8 mmol). After 1 h, the reaction was complete, the mixture was filtered and the solid residue washed with ethyl acetate (5 × 20 cm^3). The filtrate was quenched with aq. sodium sulfite (20%). The organic phase was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. Crystallisation from hexane–ethyl acetate, 10:1, afforded the pure *epoxide* **25** as a white solid (2 g, 98%, 94% ee), $[\alpha]_D$ −223 (*c* 1.0, $CHCl_3$); mp 74–76 °C (from hexane–ethyl acetate); R_f (petroleum spirit–ethyl acetate, 9:1) 0.19 (Found: M^+, 316.10995; C, 79.85; H, 5.1. $C_{21}H_{16}O_3$ requires *M*, 316.11000; C, 79.75; H, 5.05%); ν_{max}($CHCl_3$)/cm^{-1} 3012 (ArH), 1691 (C=O), 1204 and 831 (C–O, epoxide); δ_H (300 MHz; $CDCl_3$) 4.05 (1H, d, *J* 1.9, H-2), 4.25 (1H, d, *J* 1.9, H-3), 6.99–8.0 (14 H, m, ArH); δ_C (75 MHz; $CDCl_3$) 60.9 (C-3), 58.75 (C-2), 115.5–133.8 (Ar); *m*/*z* (EI) 105 (PhC=O, 100%), 77 (Ph, 67).

(1*S*,2*R*,3*S*)-1,2-Dihydroxy-3-(3-phenoxyphenyl)-1-phenylbutane 26. The usual reduction procedure with $Zn(BH_4)_2$ was carried out on epoxy ketone **25** to afford (1*S*,2*S*,3*S*)-2,3-*epoxy*-3-(3-*phenoxyphenyl*)-1-*phenylpropan*-1-*ol* as an oil (382 mg, 95%), $[\alpha]_D$ −15.2 (*c* 1.0, $CHCl_3$); R_f (petroleum spirit–ethyl acetate, 8.5:1.5) 0.22 (Found: M^+, 318.12502; C, 79.3; H, 5.8. $C_{21}H_{18}O_3$ requires *M*, 318.12558; C, 79.25; H, 5.7%); ν_{max}(NaCl)/cm^{-1} 3425 (OH), 1220, 890 (C–O epoxide); δ_H (300 MHz; $CDCl_3$) 2.33 (1H, br s, OH), 3.25 (1H, dd, *J* 2.98 and 2.0, H-2), 4.1 (1H, d, *J* 2.0, H-3), 4.94 (1H, d, *J* 2.98, H-1), 6.87–7.93 (14H, m, ArH); δ_C (75 MHz; $CDCl_3$) 54.8 (C-2), 64.97 (C-3), 71.3 (C-1), 116.0, 118.6, 120.6, 123.6, 126.6, 128.5, 128.8 and 129.9 (CH, Ar), 138.8, 138.9, 156.9 and 157.8 (C, Ar); *m*/*z* (EI)

212 (M − PhCOH, 58%), 183 (M − PhCHOHCO, 61.4), 105 (PhC=O, 60.4), 77 (Ph, 100).

Alkylation of the epoxy alcohol with trimethylaluminium gave *diol* **26** as a colourless oil (85%); $[\alpha]_D$ +63.46 (*c* 1.04, $CDCl_3$); R_f (petroleum spirit–ethyl acetate, 4:1) 0.18 (Found: M^+, 334.15695; C, 79.2; H, 6.3. $C_{22}H_{22}O_3$ requires *M*, 334.15689; C, 79.0; H, 6.6%); ν_{max}(NaCl)/cm^{-1} 3612 (OH), 3075, 3030 (=CH), 1602, 1654 (C=C, Ar); δ_H (300 MHz; $CDCl_3$) 1.28 (3H, d, *J* 7.15, H_3-4), 1.85 (1H, br s, OH), 2.21 (1H, br s, OH), 2.70 (1H, m, H-3), 3.95 (1H, dd, *J* 6.6 and 5.3, H-2), 4.50 (1H, d, *J* 5.3, H-1), 6.8–7.30 (14H, m, ArH); δ_C (75 MHz; $CDCl_3$) 16.6 (C-4), 41.4 (C-3), 75.1 (C-2), 78.5 (C-1), 116.9, 118.7, 118.9, 122.8, 123.3, 127.6, 128.3, 128.5 and 129.8 (CH, Ar), 140.5, 146.9, 157.4 and 157.5 (C, Ar); *m*/*z* (EI) 227 (M − PhCHOH, 22%), 197 (M − PhCHOHCHOH, 22.3), 108 (PhCHOH, 100), 77 (Ph, 44.3).

(*S*)-(+)-Fenoprofen 5. The usual oxidative cleavage procedure was carried out on diol **26**. Purification of the residue by flash column chromatography (SiO_2; dichloromethane–methanol, 49:1) afforded (*S*)-fenoprofen **5** as a colourless liquid (64%), $[\alpha]_D$ +46 (*c* 1.0, $CHCl_3$) {lit.,[19] $[\alpha]_D$ +45.7 (*c* 1.0, $CHCl_3$)}; R_f (dichloromethane–methanol, 49:1) 0.17 (Found: C, 74.5; H, 5.8. Calc. for $C_{15}H_{14}O_3$: C, 74.4; H, 5.75); ν_{max}(NaCl)/cm^{-1} 2700–3100 (OH), 1720 (C=O); δ_H (300 MHz; $CDCl_3$) 1.36 (3H, d, *J* 7, -3), 3.50 (1H, q, *J* 7, H-2), 6.79–7.31 (9H, m, ArH_3), 8.40 (1H, br s, COOH); δ_C (75 MHz; $CDCl_3$) 18.2 (C-3), 45.75 (C-2), 117.3, 118.5, 118.9, 122.5, 123.3 and 129.8 (CH, Ar), 142.5, 157.2 and 157.4 (C, Ar), 180.75 (COOH).

Synthesis of (*S*)-naproxen 1

(*E*)-3-(6-Methoxynaphthalen-2-yl)-1-phenylpropenone 27. To a stirred solution of acetophenone (2.1 cm^3, 16.11 mmol) and 6-methoxy-2-naphthaldehyde (3 g, 15.3 mmol) in absolute methanol (16 cm^3; 1 cm^3 per mmol of ketone) were added 3 pellets of sodium hydroxide. After 20 h, the resulting yellow solid was washed successively with cold ethanol and water and was then crystallised from hexane–ethyl acetate, 10:1 to afford (*E*)-*enone* **27** (4.10 g, 90%) as a colourless crystalline solid, mp 148–149 °C (from ethyl acetate–hexane); R_f (petroleum spirit–ethyl acetate, 9:1) 0.24 (Found: M^+, 300.11477; C, 84.05 H, 5.4. $C_{21}H_{16}O_2$ requires *M*, 300.11505; C, 84.0; H, 5.35.); ν_{max}($CHCl_3$)/cm^{-1} 3060, 1615, 1581, 980 (C=C), 1690 (C=O); δ_H (300 MHz; $CDCl_3$) 3.94 (3H, s, CH_3) 6.88–8.0 (13H, m, ArH, H-2 and -3); δ_C (75 MHz; $CDCl_3$) 55.3 (CH_3, OCH_3), 106.2, 119.4, 121.3, 124.5, 127.6, 128.6, 128.8, 130.3, 130.4, 130.4, 132.7, 136.0, 138.6, 145.3 (C-2, -3, C-Ar and CH-Ar), 159 (C-3[6]) 190.7 (C-1); *m*/*z* (EI) 300 (M^+, 100%), 207 (M − OPh, 60.2), 105 (PhC=O, 35), 77 (Ph, 67).

(2*R*,3*S*)-2,3-Epoxy-3-(6-methoxynaphthalen-2-yl)-1-phenylpropan-1-one 28. To a solution of enone **27** (2.0 g, 6.94 mmol) in THF (80 cm^3) were added urea–hydrogen peroxide (784 mg, 8.34 mmol), poly-(L)-leucine adsorbed onto silica (6.4 g, 1.44 g of polymer) and DBU (1.25 cm^3, 8.34 mmol). After 1.5 h the reaction mixture was filtered and the solid residue washed with ethyl acetate (5 × 20 cm^3). The filtrate was quenched with aq. sodium sulfite (20%). The organic phase was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. Crystallisation from hexane–ethyl acetate, 10:1, afforded the pure *epoxy ketone* **28** as a white solid (2.0 g, 97%, 94% ee). $[\alpha]_D$ −310 (*c* 1.0, $CHCl_3$); mp 101–103 °C (from hexane–ethyl acetate); R_f (petroleum spirit–ethyl acetate, 9:1) 0.35 (Found: M^+, 304.11101; C, 78.9; H, 5.3. $C_{20}H_{16}O_3$ requires *M*, 304.10995; C, 78.95; H, 5.25%); ν_{max}($CHCl_3$)/cm^{-1} 3011 (Ar-H), 1691 (C=O), 1269 and 854 (C–O, epoxide); δ_H (300 MHz; $CDCl_3$) 3.90 (3H, s, OMe), 4.39 (1H, d, *J* 1.8, H-2), 4.20 (1H, d *J* 1.8, H-3), 7.15–8.0 (11 H, m, ArH); δ_C (75 MHz; $CDCl_3$) 55.4 (OMe), 59.8 (C-3), 61.25 (C-2), 105.95, 119.6, 123.2, 125.8, 127.6, 128.4, 128.7, 128.9 and 129.5 (CH, Ar), 130.6, 134.0, 135.0 and 135.7 (C-3[2], -3[4a] and -3[8a]), 158.4 (C-3[6]), 193.3 (C-1); *m*/*z* (EI) 304 (M^+, 37%), 171 ($MeOC_8H_6CHOH$, 62), 105 (PhC=O, 100), 77 (Ph, 47.4).

(2*S*,3*R*,4*S*)-3,4-Epoxy-4-(6-methoxynaphthalen-2-yl)-2-phenylbutan-2-ol 29. To a solution of epoxy ketone **28** (1.5 g, 4.9 mmol) in freshly distilled diethyl ether (40 cm^3) and THF (32 cm^3) was added dropwise a solution of methylmagnesium iodide (3 M solution in diethyl ether; 2.6 cm^3, 7.84 mmol) at −78 °C under an argon atmosphere. After 2.5 h, the reaction mixture was quenched with saturated aq. ammonium chloride and extracted with diethyl ether (3 × 50 cm^3). The combined organic layers were washed successively with water (50 cm^3) and brine (50 cm^3), dried over magnesium sulfate and evaporated under reduced pressure. Purification of the residue by flash column chromatography (SiO_2; petroleum spirit–diethyl ether, 9:1) furnished the diastereomerically pure *epoxy alcohol* **29** as a white solid (1.3 g, 85%); $[\alpha]_D$ −38 (*c* 1.0, $CHCl_3$); mp 130–132 °C (from hexane); R_f (petroleum spirit–diethyl ether, 4:1) 0.31 (Found: M^+, 320.14158; C, 78.8; H, 6.4. $C_{21}H_{20}O_3$ requires *M*, 320.1421; C, 78.75; H, 6.25%); ν_{max}($CHCl_3$)/cm^{-1} 3495 (OH), 1210, 975 and 875 (C–O, epoxide); δ_H (300 MHz; $CDCl_3$) 1.78 (3H, s, H_3-1), 2.33 (1H, s, OH), 3.80 (1H, d, *J* 2.1, H-3), 3.90 (3H, s, OMe), 4.17 (1H, d, *J* 2.1, H-4), 7.09–7.69 (11H, m, Ar); δ_C (75 MHz; $CDCl_3$) 27.85 (C-1), 55.3 (OMe), 56.2 (C-4), 68.4 (C-3), 105.8, 119.3, 123.6, 125.1, 125.3, 127.2, 127.6, 128.5, 129.1, 131.8, 134.0, 141.8, 144.0 and 157.5 (Ar); *m*/*z* (EI) 200 (M − Ph $COCH_3$, 26%), 171 [M − $PhC(OH)CH_3CO$, 100], 105 (PhC=O, 85), 77 (Ph, 47).

(2*S*,3*R*,4*S*)-2,3-Dihydroxy-4-(6-methoxynaphthalen-2-yl)-2-phenylpentane 30. Tertiary epoxy alcohol **29** was alkylated in the usual manner with a solution of trimethylaluminium. Purification of the residue by flash column chromatography (SiO_2; petroleum spirit–ethyl acetate, 9:1) furnished the *diol* **30** as a colourless oil (815 mg, 78%); $[\alpha]_D$ +68 (*c* 1.0, $CHCl_3$); R_f (petroleum spirit–ethyl acetate, 4:1) 0.14 (Found: M^+, 336.17298; C, 78.65; H, 7.1. $C_{22}H_{24}O_3$ requires *M*, 336.17255; C, 78.6; H, 7.15%); ν_{max}(NaCl)/cm^{-1} 3400 (OH), 1320 (OH); δ_H (300 MHz; $CDCl_3$) 1.24 (3H, d, *J* 7.0, H_3-5), 1.53 (3H, s, H_3-1), 2.01 (1H, s, OH), 2.35 (1H, s br, OH), 2.76 (1H, dq, *J* 7.0 and 3.3, H-4), 3.87 (3H, s, OMe), 3.93 (1H, d, *J* 3.3, H-3), 7.07–7.64 (11H, m, ArH); δ_C (75 MHz; $CDCl_3$) 14.4 (C-5), 29.2 (C-1), 40.5 (C-4), 55.3 (C-2), 81.05 (C-3), 105.8 , 118.8, 125.25, 125.5, 127.0, 127.0 and 128.4, 129.2 (CH, Ar), 133.4, 141.7 and 145.2 (C-4[8a], -4[2] and -4[4a]); *m*/*z* (EI) 185 [M − PhC(Me)(OH)CHOH, 76%], 122 [$PhC(CH_3)OH$, 100], 77 (Ph, 44.3%).

(*S*)-Naproxen 1. The usual 2-step oxidative cleavage was carried out on diol **30**. Purification by flash column chromatography (SiO_2; dichloromethane–methanol, 98:2) afforded (*S*)-naproxen **1** as a white solid (88%, mp 154–156 °C (from hexane–ethyl acetate) (lit.,[21] 154–157 °C); $[\alpha]_D$ +68 (*c* 1.0, $CHCl_3$) {lit.,[21] $[\alpha]_D$ +67.5 (*c* 1.0, $CHCl_3$)} (Found: M^+, 230.094 31; C, 73.1; H, 6.1, $C_{14}H_{14}O_3$ requires *M*, 230.9428; C, 73.05; H, 6.1%); ν_{max}(NaCl)/cm^{-1} 2750–3100 (OH), 1780 (C=O); δ_H (300 MHz; $CDCl_3$) 1.57 (3H, d, *J* 7.0, H_3-3), 3.87 (1H, q, *J* 7.0, H-2), 3.90 (3H, s, OMe), 7.09–7.17 (2H, m, ArH), 7.40 (1H, m, ArH), 7.63–7.78 (3H, m, ArH); δ_C (75 MHz; $CDCl_3$) 18.1 (C-3), 45.3 (OMe), 55.3 (C-2), 105.7, 119.2, 126.3, 127.3 and 129.4 (CH, ArH), 129.0 and 133.9 (C-2[4a] and -2[8a]), 135.0 and 157.9 (C-2[2] and -2[6]), 180.5 (COOH); *m*/*z* (EI) 230 (M^+, 40%), 185 (M − COOH, 100), 170 ($MeOC_8H_6CH$, 18).

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References

1 K. M. Williams, R. O. Day and S. N. Breit, in *Biochemical Actions and Clinical Pharmacology of Anti-inflammatory Drugs*, Academic Press, 1993, pp. 121–198.

2 H. R. Sonawane, N. S. Bellur, J. R. Ahuja and D. G. Kulkarni, *Tetrahedron: Asymmetry*, 1992, **3**, 163.

3 V. N. Charushin, V. P. Krasnov, G. L. Levit, M. A. Korolyova, O. N. Chupakin, M. H. Kim, H. S. Lee and Y. J. Park, *Tetrahedron: Asymmetry*, 1999, **10**, 2691; A. C. Chen, L. Ren and C. M. Crudden, *Chem. Commun.*, 1999, 611; H. Ishibashi, M. Maeki, J. Yagi, M. Ohba and T. Kanai, *Tetrahedron*, 1999, **55**, 6075; C. S. Chang, S. W. Tsai and L. N. Lin, *Tetrahedron: Asymmetry*, 1998, **9**, 2799; B. H. Xie, C. G. Xia, S. J. Lu, K. J. Chen, J. Kou and Y. Q. Yin, *Tetrahedron Lett.*, 1998, **39**, 7365; J. B. H. Warneck and R. A. Wisdom, *Eur. Pat.* EP 0687305BI, 1997; J. J. Lalonde, C. Govardhan, N. Khalaf, A. G. Martinez, K. Visuri and A. L. Margolin, *J. Am. Chem. Soc.*, 1995, **117**, 6856 and references therein.

4 See, for example, T. Oka and A. Murai, *Tetrahedron*, 1998, **54**, 1; N. Ishibashi, M. Miyazawa and M. Miyashita, *Tetrahedron Lett.*, 1998, **39**, 3775.

5 M. Fukumasa, K. Furakashi, J. Umezawa, O. Takahashi and T. Hirai, *Tetrahedron Lett.*, 1991, **32**, 1059.

6 T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1982, **23**, 3597.

7 For reviews of this technology see M. J. Porter, S. M. Roberts and J. Skidmore, *Bioorg. Med. Chem.*, 1999, **7**, 2145; L. Pu, *Tetrahedron: Asymmetry*, 1998, **9**, 1457; S. Ebrahim and M. Wills, *Tetrahedron: Asymmetry*, 1997, **8**, 3163.

8 Initial investigations have been reported in a communication: L. Carde, H. Davies, T. P. Geller and S. M. Roberts, *Tetrahedron Lett.*, 1999, **40**, 5421.

9 T. P. Geller and S. M. Roberts, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 1397.

10 M. Miyashita, T. Shiratani, K. Kawamine, S. Hatakeyama and H. Irie, *Chem. Commun.*, 1996, 21.

11 M. Miyashita, K. Yoshihara, K. Kawamine, M. Hoshino and H. Irie, *Tetrahedron Lett.*, 1993, **34**, 6285; M. Miyashita, M. Hoshino and A. Yoshikoshi, *J. Org. Chem.*, 1991, **56**, 6483.

12 F. K. Glowka, *Chirality*, 2000, **12**, 38; C. Cerletti, S. Manarini, M. Colombo and A. Tavani, *J. Pharm. Pharmacol*, 1990, **42**, 885.

13 M. Kirihara, S. Takizawa and T. Momose, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 7.

14 Y. L. Zhong and T. K. M. Shing, *J. Org. Chem.*, 1997, **62**, 2622.

15 C. H. Senanayake, T. J. Bill, R. D. Larsen, J. Leazer and P. J. Reider, *Tetrahedron Lett.*, 1992, **33**, 5901.

16 S. Banfi, S. Colonna, H. Molinari and S. Juliá, *Synth. Commun.*, 1983, **13**, 901.

17 P. A. Bentley, S. Bergeron, M. W. Cappi, D. E. Hibbs, M. B. Hursthouse, T. C. Nugent, R. Pulido, S. M. Roberts and L. E. Wu, *Chem. Commun.*, 1997, 739.

18 For other examples of Grignard reactions with epoxy ketones in this series, see A. T. Gillmore, S. M. Roberts, M. B. Hursthouse and K. M. Malik, *Tetrahedron Lett.*, 1998, **39**, 3315.

19 W. J. Marshall, Eli Lilly and Company, *Fr. Demande* 2 015 728; 1970 (*Chem. Abstr.*, 1971, **75**, 48707m).

20 See, for example, T. Ohta, H. Takaya, K. Kitamura, K. Nagai and R. Noyori, *J. Org. Chem.*, 1987, **52**, 3174; J. K. Stille and G. Parrinello, *J. Am. Chem. Soc.*, 1987, **109**, 7122; T. Manimaran, T.-C. Wu, W. D. Klobucar, C. H. Kolich and G. P. Stahly, *Organometallics*, 1993, **12**, 1467.

21 F. J. Lopez, S. A. Ferrino, M. S. Reyes and R. Roman, *Tetrahedron: Asymmetry*, 1997, **8**, 2497; see also F. Effenberger, B. W. Graef and S. Osswald, *Tetrahedron: Asymmetry*, 1997, **8**, 2749 and references therein.

22 E. Hasegawa, K. Ishiyama, T. Kato, T. Haraguchi and T. Shimizu, *J. Org. Chem.*, 1992, **57**, 5352.