Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 1, pp. 263-272, 1996

0957-4166/96 $15.00 + 0.00

0957-4166(95)00443-2

Enantioselective Synthesis of the Four Isomers of the Biologically Active Metabolite of the 2-Arylpropanoic Acid NSAID, Ximoprofen, and Assessment of Their Inhibitory Activity on Human Platelet Cyclo-oxygenase *in Vitro*

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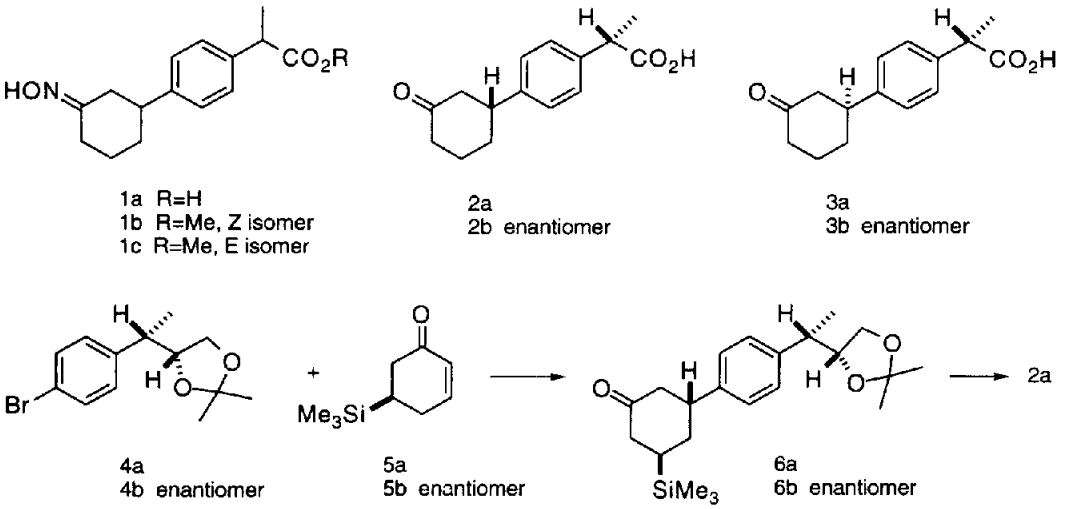
Abstract: The four stereoisomers of the parent keto acid of the oximino drug ximoprofen have been prepared in high enantiomeric purity. The stereochemistry in the propionic acid chain was established by the combination of Sharpless epoxidation followed by stereoselective hydrogenolysis of the benzylic carbon-oxygen bond with inversion of configuration. The stereochemistry of the centre in the cyclohexanone ring was controlled by the stereoselective conjugate addition of the arylpropanoic acid moiety to the enantiomers of 5-(trimethylsilyl)-2-cyclohexenone with subsequent removal of the trimethylsilyl group. The pharmacological activity of each of the four isomers of the keto acid parent of ximoprofen were assessed by their in vitro inhibition of human platelet cyclo-oxygenase. As expected, the (*S*) configuration of the propionic acid chain was essential for activity but it was also found that the stereochemistry in the cyclohexanone moiety was important. Attempts to separate the (*E*) and (*Z*) isomers of the oxime derivative from one of the stereoisomers were unsuccessful.

A paper on 2-[4'-(3"-{hydroxyimino}cyclohexyl)phenyl]propanoic acid (Ximoprofen) **1**, reported that this experimental non-steroidal anti-inflammatory agent was significantly more potent than 2-[4'-(2"-methylpropyl)phenyl]propanoic acid (Ibuprofen).[1] The active component was considered to be the precursor keto acid. Ximoprofen can exist as eight possible stereoisomers and the precursor keto acid can exist as four stereoisomers. No information has been reported either about the synthesis of the individual stereoisomers or of their pharmacological activity. It is assumed that a mixture of all possible stereoisomers has been used in these pharmacological studies. Because the importance of single enantiomers has now been recognised in the area of drug synthesis we have developed asymmetric syntheses which allow access to the four keto acid stereoisomers **2a**, **2b**, **3a** and **3b**. We present here the experimental details for a preliminary communication[2] concerning the enantioselective synthesis of these isomers and an attempt to isolate the pure (*E*) and (*Z*) oximes derived from one of them. Pharmacological aspects are discussed after the synthesis section.

Synthesis of the Isomers

Two particular challenges arise in the enantioselective synthesis of the isomeric keto acids: control of the stereochemistry at C-2 in the propionic acid chain and at the stereogenic center in the cyclohexanone unit. It was considered that the stereochemistry of these two centers could be controlled in the following way (see Scheme 1

for an outline of the synthesis, depicted for **2a**). The *R* or *S* configuration at C-2 can be established by the use of the enantiomeric bromoacetals, **4a** and **4b**, respectively. One of the acetals has been prepared earlier[3] as an intermediate for the synthesis of (*S*)-Ibuprofen (2-[4'-(2"-methylpropyl)phenyl]propanoic acid). The chemistry for this involved a combination of Sharpless epoxidation, which induces the asymmetry into the molecule, followed by stereoselective catalytic hydrogenolysis of the introduced benzylic carbon-oxygen bond with inversion of configuration which puts the required stereogenic center in place. Among various methods for the preparation of optically active 3-substituted cyclohexanones, the stereoselective 1,4-conjugate addition[4] of a Grignard reagent to (*R*)- or (*S*)-5-(trimethylsilyl)-2-cyclohexenone, **5a** or **5b**[5], in the presence of $CuBr.SMe_2$, Me_3SiCl and HMPA seemed to be appropriate for the introduction of **4a** and **4b** into the cyclohexanone ring with control of the stereochemistry at the stereogenic center. In addition, this method should allow the chromatographic removal of any minor *cis* diastereoisomer arising from the conjugate addition which would then ensure exclusive *R* or *S* configuration in the cyclohexanone moiety in the isomers **6a**, **6b**, **7a** and **7b** (assuming **4a**, **4b** and **5a**, **5b** are enantiomerically pure). The trimethylsilyl group can be replaced readily by hydrogen by the sequence of elimination and hydrogenation.[4] Further functional group manipulations and oxidation would then give the required keto acids.

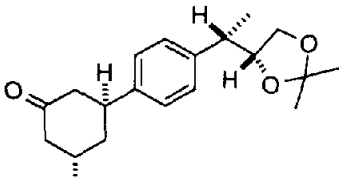


Scheme 1

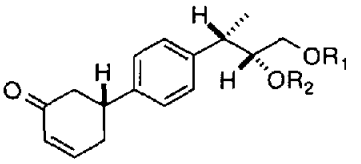
The starting material for the preparation of the (2*S*,1"*R*) keto acid **2a** was the acetal **4a**. The Grignard reagent from **4a** underwent 1,4-conjugate addition to **5a** in the presence of $CuBr.SMe_2/Me_3SiCl$/HMPA to give, after cleavage of the intermediate trimethylsilyl enol ether (KF/MeOH), *trans* ketone **6a** in 44% overall yield from the bromo diol precursor of **4a**. It has been established that conjugate addition to **5a** gives predominantly *trans* products.[4] A trace of the *cis* addition product was removed by chromatography along with some recovered enone **5a**. Since **5a** was enantiomerically pure the removal of the *cis* product ensured that there was only one stereoisomer present which was obtained as an oil. Reaction of **6a** with $CuCl_2$/DMF effected both elimination of the trimethylsilyl group and hydrolysis of the acetal to give a mixture of the required diol **8a** and the corresponding formates **8c** and **8d**. Hydrolysis of the formates (MeOH/HCl) gave more **8a** which was obtained

in 54 % overall yield from **6a**. Catalytic reduction (H_2/Pd/C) of the double bond in **8a** gave, after separation of some starting material by chromatography, **10a** in 62% yield. Oxidation of **10a** ($RuCl_3/NaIO_4$) then gave keto acid (2*S*, 1"*R*)-**2a**, mp 94.0-95.5°C, $[\alpha]_D^{20}$=52.2 (c=1.75, EtOH).

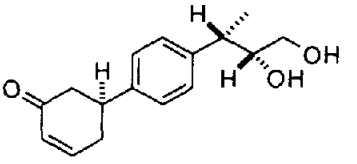
The enantiomeric acetal **4b** was prepared by the route used for **4a**[3] except that (-)-diethyl tartrate was used to establish the configuration in the Sharpless asymmetric epoxidation. Conjugate addition of the Grignard reagent derived from **4b** to enone **5b** and subsequent reactions as outlined above for the synthesis of **2a**, gave the (2*R*,1"*S*) enantiomer **2b**, mp 92-94°C, $[\alpha]_D$ -53.3 (c=1.75, EtOH). Both the enantiomers **2a** and **2b** and other enantiomeric intermediates in the sequence had identical spectral properties.



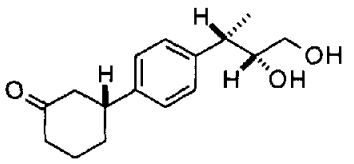
7a
7b enantiomer



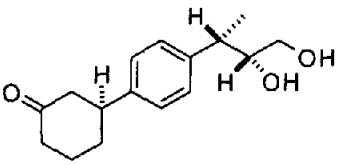
8a R_1=R_2=H
8b R_1=R_2=H, enantiomer
8c R_1=H, R_2=CHO
8d R_1=CHO, R_2=H



9a
9b enantiomer



10a
10b enantiomer



11a
11b enantiomer

The (2*S*,1"*S*) diastereoisomer **3a**, mp 132.0-133.5°C, $[\alpha]_D$ +48 (c=1.45, EtOH), and its (2*R*,1"*R*) enantiomer **3b**, mp 132-133.5°C, $[\alpha]_D$ -48 (c=0.51, EtOH) were prepared in a similar manner: **3a** from **4a** and **5b**; **3b** from **4b** and **5a**. The retention times of the stereoisomers of the keto acids on TLC were the same and the ^1H NMR (300 MHz, $CDCl_3$) spectra were indistinguishable. Although the ^{13}C NMR (75.1 MHz, $CDCl_3$) spectra of the isomers were also virtually indistinguishable, a spectrum of a mixture of diastereoisomers showed twinning of some peaks (see experimental section). The amides formed from (*S*)-a-methylbenzylamine separated by HPLC when the configuration differed at C2 but not when they differed only at C1".

The mixture of *E* and *Z* oximes prepared from **2a** ($HONH_2$.HCl, pyridine) could not be separated by chromatography on silica. However, the oxime isomers **1b** and **1c**, prepared from the corresponding methyl ester, could be separated by HPLC (SiO_2). The second eluting isomer showed in its ^1H NMR spectrum resonances for the methylene protons next to the oxime group which can be differentiated by a combination of chemical shift values and coupling to the adjacent benzylic protons as determined by a COSY experiment. The protons of the methylene group adjacent to the benzylic proton resonate at δ 1.94 (axial) and 3.47 (equatorial) whereas those in the other methylene group resonate at δ 2.11 (axial) and 2.44 (equatorial). The corresponding resonances in the other isomer were between δ 1.9-2.1 for both axial protons, 2.57 for the equatorial proton next

to the benzylic proton, and 3.37 for the other equatorial proton. Protons in methylene groups *syn* to the OH of an oxime group are deshielded and consequently resonate at lower field.[6] It follows, therefore, that the first eluting isomer has the (*E*) configuration **1c** and the second eluting isomer has the (*Z*) configuration **1b**. Unfortunately, hydrolysis of **1c** (LiOH, THF, H_2O) gave the carboxylic acid as a 1:1 mixture of the oximes. It was also found that **1b** isomerised to a mixture of **1b** and**1c** on standing in $CDCl_3$ solution.

ASSESSMENT OF PHARMACOLOGICAL ACTIVITY

Nonsteroidal anti-inflammatory drugs (NSAIDs), including congeners of the 2-arylpropanoic acid class, exert their predominant pharmacological effects via inhibition of prostanoid biosynthesis[7]. Specifically, NSAIDs act as competitive inhibitors of the cyclo-oxygenase subunit of prostaglandin synthetase whose inhibition is highly enantioselective with major or exclusive activity residing with the (*S*) isomers[8]. The four isomers of the keto acid precursor of ximoprofen were individually examined by measuring their effect on human platelet cyclo-oxygenase *in vitro*. Since ximoprofen is rapidly hydrolysed *in vivo* to the corresponding ketone[1], the isomeric keto acids, rather than the parent oximes, were studied pharmacologically. The amount of thromboxane B_2 (TxB_2) generated during the controlled clotting of whole blood from four healthy volunteers was used as an index of cyclo-oxygenase activity, relative to the arylpropanoic acid NSAID, ketoprofen[9].

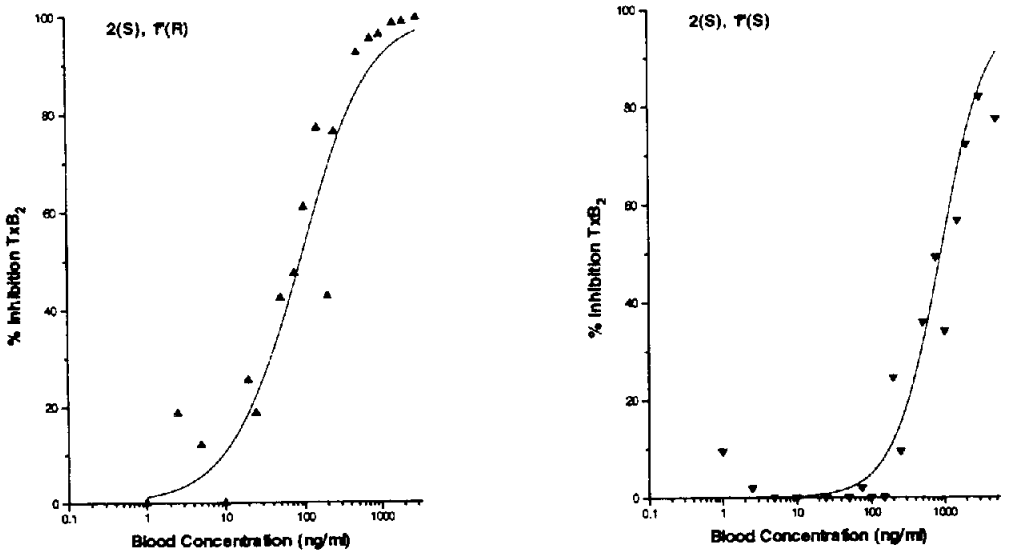


Fig.1. The *in vitro* relationships between the % inhibition of human platelet TxB_2 production and logarithmic blood concentrations of the pharmacologically active diastereomers of the keto acids of ximoprofen in a representative study volunteer (subject #2). The symbols are actual data points when the isomers were added to blood and the lines represent the predicted relationships, according to a sigmoidal E_{max} model, from least-squares regression analyses.

A relationship between the percentage inhibition of TxB_2 generation and the whole blood concentration of each keto acid isomer was modelled for each volunteer according to a sigmoidal E_{max} equation. Consistent with activity data obtained from other 2-arylpropanoic acid NSAID isomer studies[9], each of the two keto acid isomers with the (*R*) configuration in the propanoic acid moiety, **2b** and **3b**, were inactive at the highest blood concentration examined (3000 ng/mL, data not shown). Figure 1 depicts the concentration-effect data for the two active isomers in a representative volunteer. Interestingly, while both isomers in which the propanoic acid moiety has the (*S*) configuration were active, the isomer possessing the (*R*) configuration in the cyclohexanone moiety, (2*S*,1"*R*)-**2a**, was approximately an order of magnitude more active than the epimeric (2*S*,1"*S*) diastereomer as shown in Table 1 ($P < 0.01$). Table 1 consists of computer generated sigmoidal E_{max} model parameters describing the relationship between blood concentrations of 2(*S*), 1"(*R*) and 2(*S*), 1"(*S*) keto acid diastereomers of ximoprofen and % inhibition of TxB_2 generation (EC_{50}: the drug concentration required to cause 50% of E_{max}). To our knowledge, these data describe for the first time the influence of stereochemistry on the pharmacological activity of an NSAID possessing more than one chiral centre.

Table 1. Computer Generated Sigmoidal E_{max} model parameters.

Subject	EC50 ± S.E.[a] (ng/ml) 2(S), 1"(R)	EC50 ± S.E.[a] (ng/ml) 2(S), 1"(S)
#1	84.5 ± 8.9	786.1 ± 93.1
#2	89.7 ± 10.8	892.5 ± 324.2
#3	174.6 ± 24.4	1345.4 ± 269 8
#4	61.3 ± 17.8	1226.0 ± 254.4
Mean	102.5	1062.5[b]
S.D.	49.6	265.9

[a] S.E., standard error of the model parameter estimate. [b] Statistically different EC_{50} value between isomers ($P < 0.01$)

EXPERIMENTAL SECTION

Melting points were determined using a Kofler hot stage apparatus under a Reichert microscope and are uncorrected. NMR spectra were recorded on a Bruker ACP-300 spectrometer relative to Me_4Si as internal standard. IR spectra were recorded on a Hitachi 270-30 spectrophotometer. Elemental analyses were carried out by the Canadian Microanalytical Service Ltd., New Westminster, Canada. Mass specra were recorded on an AEI MS-30 double focussing mass spectrometer. Optical rotations were measured using a Perkin-Elmer 141MC

MS-30 double focussing mass spectrometer. Optical rotations were measured using a Perkin-Elmer 141MC Polarimeter. Flash chromatography[10] was performed on Merck Kieselgel 60 (230-400 mesh ASTM). Thin layer chromatography (TLC) was performed with Merck DC-Alufolien Kieselgel 60 F_{254} Art. 5554. TLC plates were visualized with acidic ammonium molybdate solution followed by heating. All solvents were distilled before use. Dry Et_2O and THF were distilled from sodium/benzophenone. Other dry solvents and reagents were prepared according to standard laboratory procedures.[11]

To monitor the effects of the ximoprofen keto acid isomers on platelet cyclo-oxygenase, the amount of TxB_2 generated was assessed by measuring its concentration (radioimunoassay) in harvested serum as described[12]. Blood was collected by venepuncture from four young healthy volunteers (equal gender numbers) none of whom were taking any medication. For a given subject, 1 mL of blood was immediately transferred to a series of borosilicate tubes (10 x 75mm) containing a range of amounts of separate isomers to give final isomer concentrations in blood from zero (control samples) to 3000 ng/mL (18 individual drug concentrations over this range). The tube contents were incubated under controlled conditions (37°C, 1 h) and the sample was centrifuged (2000*g*, 10 min) to enable harvesting of serum for subsequent quantification of TxB_2. For samples containing drug, the inhibition of TxB_2 production for each isomer blood concentration was calculated as the percentage decrease in the serum concentration of TxB_2, relative to the control concentration (in the absence of drug isomer). The relationship between the particular isomer blood concentration and the percentage inhibition of TxB_2 generation was examined by fitting separate isomer data for individual subjects according to a standard sigmoidal E_{max} equation with an extended least-squares modelling computer program (Origin 2.8, Microcal Software Inc., Northampton, MA). Several weighting schemes were explored with the least-squares analysis, the most appropriate being the reciprocal of % TxB_2 inhibition. From the modelled data, the concentration of isomer required to cause 50% inhibition of TxB_2 production by platelets (EC_{50}) was compared between isomers with (*R*) and (*S*) configurations in the cyclohexanone moiety using Welch's alternate *t*-test.

(*R*)-5-(Trimethylsilyl)-2-cyclohexenone (5a): **5a** was prepared according to the literature procedure[5]. Isomerisation of the intermediate non-conjugated ketone to the conjugated ketone with DBU was complete after 2 days. Kinetic resolution gave, after several recrystallizations from EtOH or hexane, enantiomerically pure (3*S*, 5*S*)-3-(4'-methylbenzenethio)-5-(trimethylsilyl)cyclohexanone: mp 114-115°C; $[\alpha]_D^{20}$= +35.5 (c=1.00, $CHCl_3$), lit[5]: $[\alpha]_D^{20}$= +35.5 (c=1.08, $CHCl_3$). ^1H NMR ($CDCl_3$) δ -0.04 (s, 9H, $SiMe_3$), 1.66 (m, 1H, SiCH), 1.81-2.68 (methylene envelope), 2.31 (s, 3H, CH_3), 3.87 (m, 1H, SCH), 7.10 (d, 2H, Ar-H, J=8.0 Hz), 7.31 (d, 2H, Ar-H, J=8.0 Hz). The thioether was treated with DBU and the product distilled to give **5a** as a colourless oil in quantitative yield: ^1H NMR ($CDCl_3$) δ -0.01 (s, 9H, $SiMe_3$), 1.40 (m, 1H, SiCH), 2.09-2.42 (methylene Hs), 5.96 (dt, 1H, H2, J=1.3 Hz and 10.1 Hz), 7.00 (m, 1H, H3).

(*S*)-5-(Trimethylsilyl)-2-cyclohexenone (5b): **5b** was obtained according to the literature procedure[5]. Recrystallization of (3*R*, 5*R*)-3-(4'-methylbenzenethio)-5-(trimethylsilyl)cyclohexanone from EtOH gave enantiomerically pure material: mp 113-114.5°C; $[\alpha]_D^{20}$= -35.7 (c=1.04, $CHCl_3$), lit[5]: $[\alpha]_D^{20}$= -35.5 (c=1.00, $CHCl_3$), which was treated with DBU to give **5b**: ^1H NMR ($CDCl_3$) spectrum identical to **5a**.

(4*S*,1'*R*)-4-[1'-(4''-Bromophenyl)ethyl]-2,2-dimethyl-1,3-dioxolane (4b): This was prepared by the sequence of reactions described for its enantiomer[3] except that (-)-diethyl tartrate was used in the Sharpless

asymmetric epoxidation. The epoxy alcohol was estimated to be >98% ee from NMR analysis of the acetate derivative (prepared with Ac_2O in pyridine) with the optically active shift reagent, tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium (III) derivative. Spectral data for the intermediate compounds were identical with those reported for the enantiomers[3].

(3*S*,5*R*,1'*S*,4''*R*)-3-(4-[1'-{2'',2''-Dimethyl-1,3-dioxolan-4''-yl}ethyl]phenyl)-5-(trimethylsilyl)cyclohexanone (6a). Following the procedure of Asaoka et al[4], **5a** (574 mg, 3.42 mmol), dry THF (55 mL), CuBr.SMe_2 complex (66mg), HMPA (1.25 g, 6.9 mmol) and Me_3SiCl (1.07 g, 9.85 mmol) were cooled to -78° C and the Grignard reagent from **4a** (1.46 g, 5.13 mmol) in THF (6 mL) was added. The reaction mixture was allowed to warm to room temperature and hexane (170 mL) was added. After washing with water then brine, and removal of solvent, the residue was dissolved in MeOH (47 mL), treated with KF (1.3 g), and allowed to stand for 15 min. Water (330 mL) was added and the aqueous mixture extracted thrice with CH_2Cl_2. Flash chromatography with Et_2O/hexane (25/75, v/v) as eluant gave **6a** as a colourless oil (560 mg, 44%): ^{1}H NMR ($CDCl_3$) δ -0.06 (s, 9H, $SiMe_3$), 1.13 (m, 1H, H5), 1.33 (d, CH_3CH, J=6.6 Hz), 1.33 and 1.37 (each s, 3H, C2''Me), 1.95-2.75 (complex, 8H, ring Hs and CH_3CH), 3.49 (dd, 1H, H5'', J=6.9 Hz and 8.3 Hz), 3.69 (dd, 1H, H5'', J=6.1 Hz and 8.3 Hz), 4.10 (dt, 1H, H4'', J=6.7 Hz and 8.1 Hz), 7.09 (apparent s, 4H, Ar-H). Anal. Found: C, 70.71; H, 8.98 %. $C_{22}H_{33}SiO_2$ requires C, 70.54; H, 9.15%.
The other stereoisomers were obtained similarly.

(3*R*,5*S*,1'*R*,4''*S*)-3-(4-[1'-{2'',2''-Dimethyl-1,3-dioxolan-4''-yl}ethyl]phenyl)-5-(trimethylsilyl)cyclohexanone (6b) from **4b** and **5b** as a colourless oil in 93% yield: ^{1}H NMR ($CDCl_3$) spectrum identical to **6a**.

(3*S*,5*R*,1'*R*,4''*S*)-3-(4-[1'-{2'',2''-Dimethyl-1,3-dioxolan-4''-yl}ethyl]phenyl)-5-(trimethylsilyl)cyclohexanone (7b) from **4b** and **5a** as a white solid which was recrystallised from EtOH in 71% yield: mp 73-74°C; ^{1}H NMR ($CDCl_3$) δ -0.06 (s, 9H, $SiMe_3$), 1.13 (m, 1H, H5), 1.33 (d, CH_3CH, J=6.6 Hz), 1.33 and 1.37 (each s, 3H, C2''Me), 1.95-2.75 (complex, 8H, ring Hs and CH_3CH), 3.49 (dd, 1H, H5'', J=6.9 Hz and 8.3 Hz), 3.69 (dd, 1H, H5'', J=6.1 Hz and 8.3 Hz), 4.10 (dt, 1H, H4'', J=6.7 Hz and 8.1 Hz), 7.09 (apparent s, 4H, Ar-H). Anal. Found: C, 70.72; H, 8.93 %. $C_{22}H_{33}SiO_2$ requires C, 70.54; H, 9.15%.

(3*R*,5*S*,1''*S*,4''*R*)-3-(4-[1'-{2'',2''-Dimethyl-1,3-dioxolan-4''-yl}ethyl]phenyl)-5-(trimethylsilyl)cyclohexanone (7a) from **4a** and **5b** as a white crystalline solid in 51% yield, which was recrystallised from EtOH: mp 73-74°C; ^{1}H NMR ($CDCl_3$) spectrum identical to **7a.**

(5*R*,1''*S*,2''*R*)-5-(4'-[2'',3''-Dihydroxy-1''-methylpropyl]phenyl)-2-cyclohexenone (8a). Ketone **6a** (550 mg, 1.47 mmol) and anhydrous $CuCl_2$ (576 mg) in anhydrous DMF (5.9 mL) were stirred at 70°C for 30 min. The DMF was removed in vacuo and the residue was dissolved in MeOH and 10% HCl (1mL). After 3 h at room temperature the MeOH was removed, the residue dissolved in CH_2Cl_2 and washed with water. Flash chromatography with EtOAc/hexane (70/30, v/v) gave **8a** (205 mg, 54%) as a white crystalline solid. A sample was recrystallised from EtOH/hexane: mp 114-115°C; ^{1}H NMR ($CDCl_3$) δ 1.34 (d,

3H, CH_3, J=7.1 Hz), 2.46-2.71 (complex, 4H, ring CH_2s), 2.78 (apparent quint, 1H, **CH**CH_3, J=7.1 Hz), 3.32 (dd, 1H, **CH**$_2$OH, J=7.7 Hz and 11.2 Hz), 3.33 (m, 1H, H5), 3.44 (dd, 1H, **CH**$_2$OH, J=3.0 Hz and 11.2 Hz), 3.73 (dt, 1H, **CH**OH, J=3.0 Hz and 7.7 Hz), 6.12 (dd, 1H, H2, J=2.2 Hz and 10.1 Hz), 7.06 (m, 1H, H3), 7.17 (s, 4H, Ar-H). Anal. Found: C, 73.82; H, 7.74%. $C_{16}H_{20}O_3$ requires C, 73.53; H, 7.58%.
The other stereoisomers were obtained similarly.

(5*S*,1''*R*,2''*S*)-5-(4'-[2'',3''-Dihydroxy-1''-methylpropyl]phenyl)-2-cyclohexenone (8b) from **6b** in 45% yield: ^{1}H NMR ($CDCl_3$) spectrum identical to **8a**.

(5*R*,1''*R*,2''*S*)-5-(4'-[2'',3''-Dihydroxy-1''-methylpropyl]phenyl)-2-cyclohexenone (9b) from **7b** as a colourless oil in 53% yield: ^{1}H NMR ($CDCl_3$) δ 1.34 (d, 3H, CH_3, J=7.1 Hz), 2.46-2.71 (complex, 4H, ring CH_2s), 2.78 (apparent quint, 1H, **CH**CH_3, J=7.1 Hz), 3.32 (dd, 1H, **CH**$_2$OH, J=7.7 Hz and 11.2 Hz), 3.33 (m, 1H, H5), 3.44 (dd, 1H, **CH**$_2$OH, J=3.0 Hz and 11.2 Hz), 3.73 (dt, 1H, **CH**OH, J=3.0 Hz and 7.7 Hz), 6.12 (dd, 1H, H2, J=2.2 Hz and 10.1 Hz), 7.06 (m, 1H, H3), 7.17 (s, 4H, Ar-H).
(5*S*,1''*S*, 2''*R*)-5-(4'-[2'',3''-Dihydroxy-1''-methylpropyl]phenyl)-2-cyclohexenone (9a) from **7a** in 54% yield: ^{1}H NMR ($CDCl_3$) spectrum identical to **9b**.

(3*R*,1''*S*, 2''*R*)-3-(4'-[2'',3''-Dihydroxy-1''-methylpropyl]phenyl)cyclohexanone (10a). Pd on carbon (10%, 220 mg) and **8a** (220 mg, 0.85 mmol) in EtOAc (29 mL) were stirred in a H_2 atmosphere for 1.5 h. Flash chromatography with EtOAc/hexane (70/30, v/v) as eluant separated unreacted **8a** from **10a**, which was obtained as a white crystalline solid (136 mg, 62%): mp 93-96°C; ^{1}H NMR ($CDCl_3$) δ 1.34 (d, 3H, CH_3, J=7.0 Hz), 1.82 (complex, 2H, $H4_{ax}$ and $H5_{ax}$), 1.95 (br s, 1H, OH), 2.11 (complex, 2H, $H4_{eq}$ and $H5_{eq}$), 2.39 (m, 2H, H6), 2.55 (m, 2H, H2), 2.68 (br s, 1H, OH), 2.78 (apparent quint, 1H, **CH**CH_3, J=7.0 Hz), (2.98, tt, 1H, H3, J=4.6 Hz and11.6 Hz), 3.33 (dd, 1H, **CH**$_2$OH, J=7.6 Hz and 11.2 Hz), 3.45 (dd, 1H, **CH**$_2$OH, J=3.0 Hz and 11.2 Hz), 3.73 (dt, 1H, **CH**OH, J= 3.0 Hz and 7.7 Hz), 7.15 (s, 4H, Ar-H).
The other stereoisomers were prepared similarly.

(3*S*,1''*R*,2''*S*)-3-(4'-[2'',3''-Dihydroxy-1''-methylpropyl]phenyl)cyclohexanone (10b) from **8b** in 70% yield as a white crystalline solid; ^{1}H NMR ($CDCl_3$) spectrum identical to enantiomer **10a**.

(3*R*, 1''*R*, 2''*S*)-3-(4'-[2'',3''-Dihydroxy-1''-methylpropyl]phenyl)cyclohexanone (11b) from **9b** as a white crystalline solid in 94% yield: mp 70-72°C; [^{1}H NMR ($CDCl_3$) δ 1.34 (d, 3H, CH_3, J=7.0 Hz), 1.82 (complex, 2H, $H4_{ax}$ and $H5_{ax}$), 1.95 (br s, 1H, OH), 2.11 (complex, 2H, $H4_{eq}$ and $H5_{eq}$), 2.39 (m, 2H, H6), 2.55 (m, 2H, H2), 2.68 (br s, 1H, OH), 2.78 (apparent quint, 1H, **CH**CH_3, J=7.0 Hz), (2.98, tt, 1H, H3, J=4.6 Hz and11.6 Hz), 3.33 (dd, 1H, **CH**$_2$OH, J=7.6 Hz and 11.2 Hz), 3.45 (dd, 1H, **CH**$_2$OH, J=3.0 Hz and 11.2 Hz), 3.73 (dt, 1H, **CH**OH, J= 3.0 Hz and 7.7 Hz), 7.15 (s, 4H, Ar-H). Anal. Found: C,72.96; H, 8.34%. $C_{16}H_{22}O_3$ requires C, 73.25, H, 8.45%.

(3*S*,1''*S*, 2''*R*)-3-(4'-[2'',3''-Dihydroxy-1''-methylpropyl]phenyl)cyclohexanone (11a) from **9a** in 76% yield as a white crystalline solid, mp 70-72°C; ^{1}H NMR ($CDCl_3$) spectrum identical to enantiomer **11b**.

(2*S*, 1''*R*)-2-(4'-[3''-Oxocyclohexyl]phenyl)propanoic acid (2a). Following the procedure of Sharpless[12], **10a** (135 mg, 0.51 mmol) was dissolved in CCl_4 (1.8 mL), acetonitrile (1.8 mL) and water (2.7 mL) and treated with $RuCl_3.H_2O$ (2.7 mg) and $NaIO_4$ (414 mg, 1.94 mmol). The reaction mixture was stirred vigorously at room temperature for 1.25 h. CH_2Cl_2 and water were added, the organic phase washed with saturated $NaHCO_3$ solution and the aqueous phase acidified and extracted with CH_2Cl_2. The solvent was removed in vacuo to give **2a** (104 mg, 82%). Recrystallization from EtOH/hexane (1:1) gave pure material: mp 94.0-95.5 °C, $[\alpha]_D^{20}$= +52 (c=1.75, EtOH); υ_{max} (CH_2Cl_2) 1225, 1710, 1720, 2950 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.50 (d, 3H, CH_3, J=7.1Hz), 1.73-1.90 (complex, 2H, H5 and H6), 2.05-2.18 (complex, 2H, H5 and H6), 2.32-2.45 (m, 2H, H4), 2.49-2.61 (m, 2H, H2), 2.99 (tt, 1H, H1, J=4.2 Hz and 11.6 Hz), 3.73 (q, 1H, $CHCH_3$, J=7.1 Hz), 7.18 (d, 2H, Ar-H, J=8.3 Hz), 7.28 (d, 2H, Ar-H, J=8.1 Hz). Anal. Found: C, 73.26; H, 7.37%. $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.37%.
The other stereoisomers were prepared similarly.

(2*R*,1''*S*)-2-(4'-[3''-Oxocyclohexyl]phenyl)propanoic acid (2b) from **10b** as a white crystalline solid in 82% yield, which was recrystallised from CCl_4: mp 92-94°C; $[\alpha]_D^{20}$= -53 (c=1.75, EtOH): ^1H NMR ($CDCl_3$) spectrum identical to **2a**.

(2*S*,1''*S*)-2-(4'-[3''-Oxocyclohexyl]phenyl)propanoic acid (3a) from **11a** as a white crystalline solid in 83% yield: mp 132.0-133.5° C; $[\alpha]_D^{20}$= +48 (c=1.45, EtOH): ^1H NMR ($CDCl_3$) δ 1.50 (d, 3H, CH_3, J=7.1Hz), 1.73-1.90 (complex, 2H, H5 and H6), 2.05-2.18 (complex, 2H, H5 and H6), 2.32-2.45 (m, 2H, H4), 2.49-2.61 (m, 2H, H2), 2.99 (tt, 1H, H1, J=4.2 Hz and 11.6 Hz), 3.73 (q, 1H, $CHCH_3$, J=7.1 Hz), 7.18 (d, 2H, Ar-H, J=8.3 Hz), 7.28 (d, 2H, Ar-H, J=8.1 Hz). Anal. Found: C, 72.81; H, 7.37%. $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.37%.

(2*R*,1''*R*)-2-(4'-[3''-Oxocyclohexyl]phenyl)propanoic acid (3b) from **11b** as a white crystalline solid in 79% yield: mp 132-133.5°C; $[\alpha]_D^{20}$= -48 (c=0.51, EtOH): ^1H NMR ($CDCl_3$) spectrum identical to **3a**.

(*Z*,2*S*,1''*R*)- and (*E*,2*S*,1''*R*)-Methyl 2-[4'-(3''-{hydroxyimino}cyclohexyl)phenyl]propanoate (1b) and (1c). To **2a** (34 mg, 0.13 mmol) in Et_2O (1 mL) was added an ethereal diazomethane solution until the yellow colour persisted. A drop of acetic acid was added and the solvent removed in vacuo. The crude keto ester (79 mg, 0.32 mmol) in pyridine (1.25 mL) was treated with hydroxylamine hydrochloride (112 mg, 1.61 mmol) for 16 h at room temperature under N_2. The pyridine was removed, the residue dissolved in CH_2Cl_2 and washed with dilute HCl. The solvent was removed to give **1b** and **1c** which were separated by HPLC. Data for **1b**: ^1H NMR ($CDCl_3$) δ 1.49 (d, 3H, CH_3, J=7.1 Hz), 1.54-2.01 (complex, 4H, H5 and H6), 1.94 (dd, 1H, $H2_{ax}$, J=13.9 Hz and 12.5 Hz), 2.11 (d, 1H, $H4_{ax}$, J=13.6 Hz and 4.5 Hz), 2.44 (d, complex small coupling, 1H, $H4_{eq}$, J=13.5 Hz), 2.73 (tt, 1H, H1, J=11.7 Hz and 3.5 Hz), 3.47 (d, complex small coupling, 1H, $H2_{eq}$, J=13.9 Hz), 3.67 (s, 3H, OCH_3), 3.71 (q, 1H, $CHCH_3$, J=7.1 Hz), 7.17-7.25 (m, 4H, Ar-H), 7.33 (br s, 1H, NOH). Data for **1c**: ^1H NMR ($CDCl_3$) δ 1.49 (d, 3H, CH_3, J=7.2 Hz), 1.54-1.83 (complex, 4H, H5 and H6), 1.98-2.05 (complex, 2H, $H2_{ax}$ and $H4_{ax}$), 2.57 (d, complex small coupling, 1H, $H2_{eq}$, J=13.6 Hz), 2.75 (tt,

1H, H1, J=11.9 Hz and 3.4 Hz), 3.37 (d, 1H, $H4_{eq}$, J=14.1 Hz), 3.67 (s, 3H, OCH_3), 3.71 (q, 1H, $CHCH_3$, J=7.2 Hz), 7.13-7.24 (m, 4H, Ar-H), 7.41 (br s, 1H, NOH).

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(*Received in UK* 27 *October* 1995)