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Concerning the Enantioselective Synthesis of the Isomers of the Arylpropanoic Acid NSAID Ximoprofen.

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Abstract: All four stereoisomers of the parent ketone of the oximido drug ximoprofen have been prepared pure. An attempt to isolate the pure *E* and *Z* isomers of the oxime derivative from one of these stereoisomers was unsuccessful.

Ximoprofen **1** is an experimental non-steroidal anti-inflammatory drug, of the arylpropanoic acid class, which is reported[1] to be some 10-40 times more active than ibuprofen. With the two chiral centres and geometrical isomerism about the oxime, there are eight possible stereoisomers for this compound. Since it appears that this drug has neither been developed commercially, nor withdrawn, we considered that this might be because the individual isomers had not been prepared to allow full toxicological testing. We have extended chemistry which we developed recently[2], which has allowed the preparation of each of the four stereoisomers of the keto acid **2**. We disclose here an outline of the syntheses of these keto acids and preliminary results concerning the preparation of the oxime derivatives.

The *R*-2, *S*-3-bromodiol **3**[2], protected as the acetonide, was converted to the Grignard reagent and this reacted with *R*-5-trimethylsilylcyclohex-2-enone **4** in the presence of $CuBr.SMe_2$, Me_3SiCl and HMPA following the procedure developed[3] for the 1,4-conjugate addition reactions of this enone. The intermediate silyl enol ether was cleaved (KF, MeOH) to give, in 44% overall yield, the product **5**† arising from addition *anti* to the Me_3Si group. A trace of the *syn* addition product **6** was removed by chromatography along with some recovered starting enone. Since the starting bromodiol was optically pure, the removal of the *syn* product ensured that there was only one stereoisomer present which was obtained as an oil (the enantiomer was also an oil). Elimination of the Me_3Si group, following the procedure reported[3] ($CuCl_2$, DMF), gave a mixture of the required diol **7**† and the corresponding monoformates **8** and **9**. The formates were converted to the diol (MeOH, HCl) which was obtained in 54% yield overall. Because catalytic reduction (H_2/Pd/C) of the double bond of **7** was incomplete the product was obtained in only 62% yield by chromatography. Ruthenium tetroxide oxidation (cat. $RuCl_3$, $NaIO_4$, 82% yield) then gave the *S*-2, *R*-1"-keto acid **10**†, mp. 94-95.5°C, $[\alpha]_D$ +52° (c=1.75, EtOH).

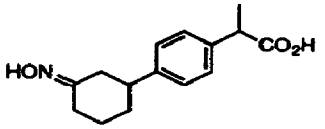
In a similar manner, but by the use of the enantiomer of the enone 4[3] and the acetonide of **3**, the diastereomer **11** was obtained crystalline, mp. 73.0-74.5°C (from EtOH) in 51% yield. Elimination of the Me_3Si group gave, in 53% yield, the corresponding enone diol. The ^1H NMR spectra of both **11** and the derived enone diol were indistinguishable fom those of the other diastereomers (5 and its enone diol). Catalytic reduction of this enone diol, followed by ruthenium tetroxide oxidation, gave in 78% overall yield, the *S*-2, *S*-1"-keto acid **12**, mp. 132-133.5°C, $[\alpha]_D$ +48° (c=1.45, EtOH).

The enantiomer (*S*-2, *R*-3-bromodiol) of the diol **3** was obtained as reported earlier[2] except that (-)-di-*iso*propyl tartrate was used in the Sharpless reaction employed in that procedure. By the use of this diol in place of its enantiomer, in the chemistry discussed above, the enantiomers of the acids already described were also obtained. The *R*-2, *S*-1"-keto acid **13** was identical to the isomer **10** in all respects except that it gave $[\alpha]_D$ -53° (c=1.75, EtOH). The *R*-2, *R*-1" isomer **14** was identical to the isomer **12** except that it gave $[\alpha]_D$ -48° (c=0.51, EtOH).

The retention times of the diastereomeric acids on TLC were the same and the ^1H NMR (300 MHz, $CDCl_3$) spectra were indistinguishable. The ^{13}C NMR (75.1 MHz, $CDCl_3$) spectra of the diastereomeric acids were also virtually indistinguishable, however a ^{13}C NMR spectrum of a mixture of the diastereomers showed twinning of several peaks. The *S*-1-phenylethylamine amides of the acids separated by HPLC when they differed at C-2 in the configuration of the acid. However, the amides of the acids which differed only at C-1" did not separate.

A mixture of the oximes **15** of the *S*-2, *R*-1"-keto acid **10** was prepared ($HONH_2.HCl$, pyridine) but the isomers could not be separated by chromatography on silica. The oximes **16** and **17** of the corresponding methyl ester were prepared and they could be separated by HPLC (SiO_2, hexane/ethyl acetate). The second eluting isomer showed in its ^1H NMR (300MHz, $CDCl_3$) 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 proton as determined by a COSY experiment. The protons for the methylene group adjacent to the benzylic proton resonate at δ = 1.94 (axial) and 3.47 (equatorial). The protons for 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. It has been shown[4] that protons in methylene groups *syn* to the OH of an oxime group are deshielded and therefore resonate at lower field. It follows, therefore, that the first eluting isomer has the *E* configuration **17** and the other isomer has the *Z* configuration **16.**

The *Z* compound isomerised to a mixture of *E* and *Z* isomers on standing as a solution in $CDCl_3$. Hydrolysis of the *E* isomer (LiOH, THF, H_2O) gave the carboxylic acid as a 1:1 mixture of the oxime diastereomers **15.**



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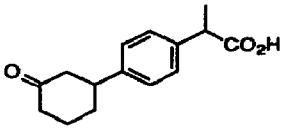

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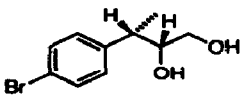

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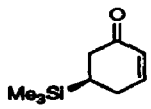

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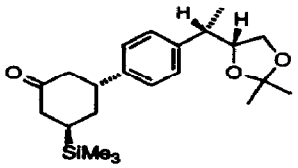

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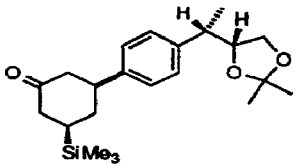

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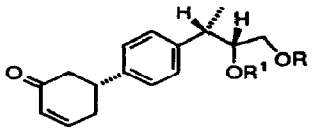
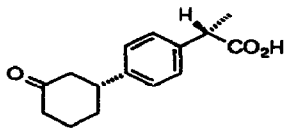


7 R = R^1 = H
8 R = H, R^1 = CHO
9 R = CHO, R^1 = H



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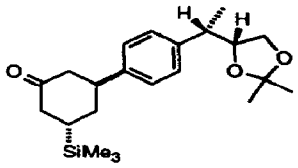

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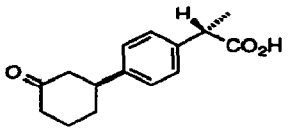

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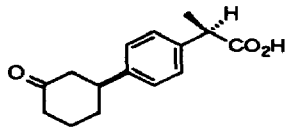

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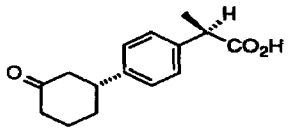

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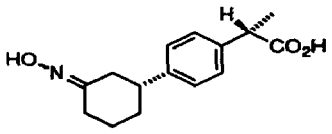

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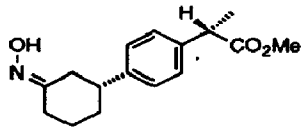

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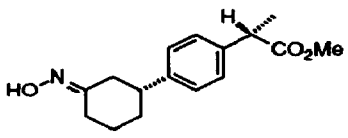

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† Acceptable analytical data obtained. ^{1}H NMR (300 MHz, $CDCl_3$)

(3S, 5R, 1'S, 4''R)-3-[4-(1'-[2'',2''-dimethyl-1'',3''-dioxolan-4''-yl]ethyl)phenyl]-5-(trimethylsilyl) cyclo-hexanone (5) δ -0.06 (s, $SiMe_3$), 1.13 (m, H5), 1.33 (d, J 6.6, CH_3CH), 1.33 and 1.37 (each s, 3H, CH_3CCH_3), 1.95-2.75 (complex, 8H), 3.49 (dd, J 6.9, 8.3, 1H) and 3.69 (dd, J 6.1, 8.3, 1H)(CH_2O), 4.10 (dt, J 6.7, 8.1, CHO), 7.09 (single peak, 4H, ArH).

(5R, 1'S, 2'R)-5-[4-(2',3'-dihydroxy-1'-methylpropyl)phenyl]-2-cyclohexen-1-one (7) δ 1.34 (d, J 7.1 CH_3), 2.46-2.71 (complex, 4H), 2.78 (quint., J .7.1, H1'), 3.32 (dd, J 7.7, 11.2, 1H, CH_2O), 3.33 (m, H5), 3.44 (dd, J 3.0, 11.2, 1H CH_2O), 3.73 (dt, J 3.0, 7.7, 1H, CHO), 6.12 (dd, J 10.1, 2.2, H2), 7.06 (m, H3), 7.17 (single peak, 4H, ArH).

(2S, 1''R)-2-[4'-(3''-oxocyclohexyl)phenyl]propanoic acid (10) δ 1.50 (d, J 7.1, CH_3), 1.73-1.90 (complex, 2H) and 2.05-2.18 (complex 2H) and 2.32-2.45 (m, 2H), 2.49-2.61 (m, 2H, CH_2CH), 2.99 (tt, J 4.2, 11.6, H1''), 3.73 (q, J 7.1, H2), 7.18 and 7.28 (each d, J 8.1, ArH).

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