Electronic Supplementary Information

Chemoenzymatic synthesis of (2*S*)-2-arylpropanols through a dynamic kinetic resolution of 2-arylpropanals with alcohol dehydrogenases.

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Synthesis and spectroscopic data of 2-arylpropanals 1b-f

Representative procedure for **1b** synthesis.

Method 1: racemic 2-(4-isobutylphenyl)-propanoic acid, Ibuprofen, (30 mmol, 6.2 g) was refluxed in EtOH (50 mL) in the presence of a catalytic amount of $BF_3.Et_2O$ (0.5 mL). At disappearance of the starting carboxylic acid, the solvent was concentrated, the crude dissolved in EtOAc (50 mL) and washed with aqueous $NaHCO_3$, the organic phase was concentrated furnishing ethyl 2-(4-isobutylphenyl)-propanoate[1] in 80% yield. The ethyl ester (25 mmol, 5.9 g) was then dissolved in Et_2O (100 mL) at -78°C, then iBu_2AlH (1M solution in hexane, 36 mL, 36 mmol) was added dropwise. Conversion was followed by GC, at completion the reaction mixture was poured into a 2M aqueous solution of potassium sodium tartrate, diluted with Et_2O (100 mL), vigorously shaken until phase separation and re-extracted with Et_2O (3× 50 mL). The combined organic phases were dried and concentrated under vacuum. **2b** is obtained as over-reduction-by-product in the same reaction. **1b** and **2b** can be easily separated by flash-chromatography and were obtained in 65% and 15% yield respectively.

Method 2: racemic 2-(4-isobutylphenyl)-propanoic acid, Ibuprofen, (10 mmol, 2.06 g) was dissolved in Et_2O (50 mL) at 0°C, then the complex $BH_3.Me_2S$ (49 mmol, 4.6mL) was added dropwise. Conversion was followed by TLC, at completion the $BH_3.Me_2S$ in excess was carefully quenched with H_2O, NaOH 2N (50 mL) was added and the mixture was extracted with EtOAc (3× 50 mL) and concentrated affording **2b** in 98% yield. In a flask charged with a solution of oxalyl chloride (12 mmol, 1mL) in CH_2Cl_2 (100 mL) at -78°C, DMSO (22 mmol, 1.56 mL) was added dropwise. After 10 minutes **2b** (10 mmol, 1.9 g) was added and the mixture is stirred at -78°C for 1h then TEA was added (40 mmol, 5.58 mL). Conversion was followed by TLC, the reaction was quenched with a saturated solution of NH_4Cl, extracted with CH_2Cl_2 and washed with $NaHCO_3$. The organic phase was concentrated and **1b** was obtained after purification by flash-chromatography in 80% yield.

2-(4-isobutylphenyl)-propanal (Ibuprofenal) **1b:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, *J* = 6.6 Hz, 6H, $(CH_3)_2CH$), 1.46 (d, *J* = 7.2 Hz, 3H, CH_3CH), 1.89 (m, 1H, $(CH_3)_2CHCH_2$), 2.50 (d, *J* = 6.6 Hz, 2H, CH_2), 3.64 (q, *J* = 7.2 Hz, 1H, CH_3CH), 7.10-7.21 (m, 4H, arom), 9.73 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3, 22.1, 29.9, 44.8, 52.3, 127.8, 129.5, 134.6, 140.6, 200.8; IR: ν = 3433, 2950, 1722; elemental analysis calcd (%) for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 82.01, H 9.58.

2-(2-Fluoro-biphenyl-4-yl)-propionaldehyde (Flurbiprofenal) **1c**. Obtained in 70% overall yields following method A. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (d, *J* = 7.4 Hz, 3H, CH_3), 3.70 (dq, *J* = 1.4, 7.4 Hz, 1H, CH), 7.01-7.11 (m, 2H, arom), 7.34-7.59 (m, 6H, arom), 9.73 (d, *J* = 1.4 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): 14.2, 51.1, 115.8 (d, *J*(C,F) = 27 Hz), 124.1 (d, *J*(C,F) = 3 Hz), 127.7, 127.9, 128.4, 128.7 (d, *J*(C,F) = 3 Hz), 131.1 (d, *J*(C,F) = 4 Hz), 135.1, 139.9 (d, 1C, *J*(C,F) = 8 Hz), 159.8 (d, 1C, *J*(C,F) = 248 Hz), 200.2; IR: ν = 3433, 3080, 3030, 1727; elemental analysis calcd (%) for $C_{15}H_{13}FO$: C 78.93, H 5.74; found: C 78.92, H 5.81.

2-(3-Phenoxy-phenyl)-propionaldehyde (Fenoprofenal) **1d**. Obtained in 65% overall yields following method A. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (d, *J* = 7.2 Hz, 3H, CH_3), 3.62 (dq, *J* = 1.2, 7.2 Hz, 1H, CH), 6.91-6.98 (m, 3H, arom), 7.03-7.06 (m, 2H, arom), 7.12-7.17 (m, 1H, arom), 7.33-7.40 (m, 3H, arom), 9.69 (d, *J* = 1.2 Hz, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 52.7, 117.5, 118.5, 119.0, 122.9, 123.5, 129.7, 130.2, 139.6, 156.7, 157.9, 200.6; IR: ν = 3430, 3070, 3034, 1726, 1582, 1250; elemental analysis calcd (%) for $C_{15}H_{14}O_2$: C 79.62, H 6.24; found: C 79.71, H 6.28.

2-(6-Methoxy-naphthalen-2-yl)-propionaldehyde (Naproxenal) **1e**. Obtained in 80% overall yield following method A. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (d, *J* = 7.0 Hz, 3H, CH_3), 3.75 (dq, *J* = 1.0, 7.0 Hz, 1H, CH), 3.92 (s, 3H, OCH_3), 7.14-7.30 (m, 3H, arom), 7.60 (s, 1H, arom), 7.69-7.77 (m, 2H, arom), 9.74 (d, *J* = 1.2 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.5, 52.8, 55.2, 105.6, 119.2, 126.6, 126.9, 127.6, 129.0, 129.1, 132.7, 133.8, 157.8, 201.0; IR: ν = 3350, 1720, 1606; elemental analysis calcd (%) for $C_{14}H_{14}O_2$: C 78.48, H 6.59; found: C 78.35, H 6.70.

2-(3-Benzoyl-phenyl)-propionaldehyde (Ketoprofenal) **1f**: obtained in overall 50% yield following method B. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (d, *J* = 7.0 Hz, 3H, CH_3), 3.74 (dq, *J* = 1.0, 7.0 Hz, 1H, CH), 7.28-7.84 (m, 9H, arom), 9.74 (d, *J* = 1.0 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.7, 52.8, 128.4, 128.9, 129.3, 129.7, 130.1, 132.2, 132.7, 137.4, 138.3, 196.4, 200.5; ; IR: ν = 3400, 3060, 1730, 1658, 1596 1317, 1281; elemental analysis calcd (%) for $C_{16}H_{14}O_2$: C 80.65, H 5.92; found: C 80.58, H 5.96.

Oxidation of (2*S*)-arylpropanols 2c and 2d to (2*S*)-2-arylpropionic acids

Solid $KMnO_4$ (0.52 mmol, 82 mg) was added to a solution of (2*S*) - (2-Fluoro-biphenyl-4-yl)-propan-1-ol **2c** obtained from enzymatic reduction (0.13 mmol, 30 mg) in acetone (1.5 mL) and H_2SO_4 3N (1.5 mL) at 0°C under stirring. The solution was kept at 0° C for 4 more hours and at room temperature for 30 minutes. Conversion was followed by TLC. The reaction was diluted by adding 5 mL of HCl (1N) and solid Na_2SO_3 until the discolouring of the solution. The aqueous phase was extracted twice with EtOAc (2 x 10 mL), the organic phase was then extracted with a 2% NaOH solution (2 x 10 mL). The collected acqueos phase was acidified to pH 1 with HCl (2N) and extracted twice with CH_2Cl_2 (2 x 10 mL). The final organic phase was dried over Na_2SO_4 and concentrated in vacuo obtaining 15 mg of Flurbiprofen as a light yellow oil in 46 % yield. $[\alpha]^{20}_D$ = +37.2 (c = 1, $CHCl_3$); lit. data of (*S*)- Flurbiprofen $[\alpha]^{20}_D$ = +42 (c = 1, $CHCl_3$).[2]

Solid $KMnO_4$ (0.88 mmol, 139 mg) was added to a solution of (2*S*) -2-(3-phenoxy-phenyl)-propan-1ol **2d** obtained from enzymatic reduction (0.22 mmol, 50 mg) in acetone (2 mL) and H_2SO_4 3N (2 mL) at 0°C under stirring. The solution was kept at 0° C for 4 more hours and at room temperature for 30 minutes. Conversion was followed by TLC. The reaction was diluted by adding 5 mL of HCl (1N) and solid Na_2SO_3 until the discolouring of the solution. The aqueous phase was extracted twice with EtOAc (2 x 10 mL), the organic phase was then extracted with a 2% NaOH solution (2 x 10 mL). The collected aqueous phase was acidified to pH 1 with HCl (2N) and extracted twice with CH_2Cl_2 (2 x 10 mL). The final organic phase was dried over Na_2SO_4 and concentrated in vacuum obtaining 25 mg of Fenoprofen as a light yellow oil in 47 % yield. $[\alpha]^{20}_D$ = +36.5 (c = 2, $CHCl_3$); lit. data of (*S*)- Fenoprofen $[\alpha]^{20}_D$ = +46 (c = 1, $CHCl_3$).[3]

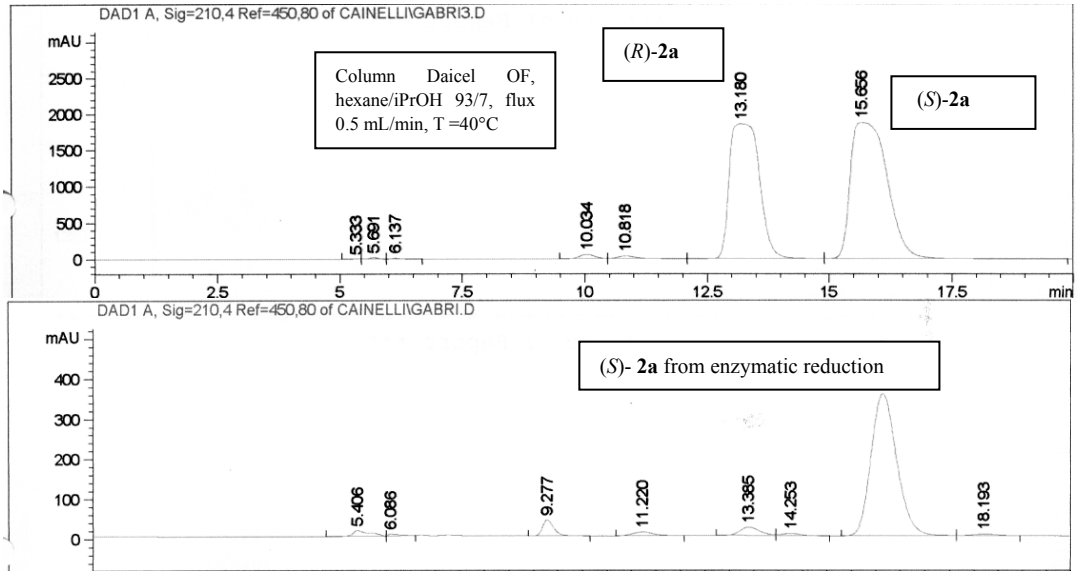
Determination of enantiomeric ratio and configurational assignment of major stereoisomers.

Enantiomeric ratios were determined by HPLC analysis on chiral columns. In the case of alcohols **2a**, **2b, 2e** and **2f** the (*S*) configuration of the major isomer was established by direct comparison with commercial (*S*) 2-phenylpropanol or (*S*) alcohols, obtained by reduction with $BH_3.Me_2S$ of the commercial (*S*) acids. For **2c** and **2d** the (*S*) configuration of the major isomer was established by converting the alcohols obtained in the semipreparative procedure into acids by oxidation with $KMnO_4$ and comparing the optical rotation with reported data.

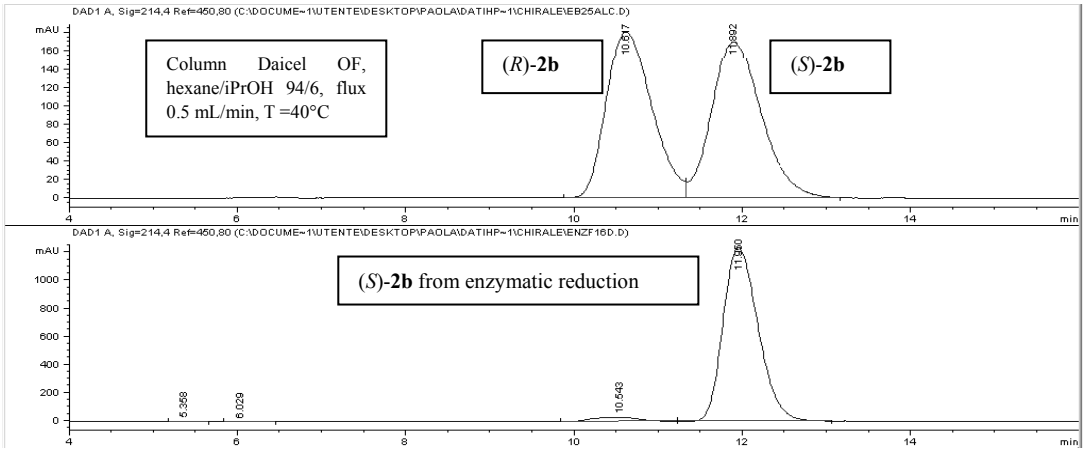
Table 6. HPLC conditions and retention times of enantiomers of alcohols **2a-f** on Daicel chiral columns.

	Rt(min)	Rt (min)	Column, hexane/iPrOH (0.5 mL/min)
2a	13.2 (*R*)	15.6 (*S*)	OF, 93/7 isocratic analysis
2a	38.2 (*R*)	39.4 (*S*)	OD, 99/1 isocratic analysis
2b	10.6 (*R*)	11.9 (*S*)	OF, 94/6 isocratic analysis
2c	13.9 *(S)*	16.5 (*R*)	OD, 89/11 isocratic analysis
2d	22.1 *(S)*	23.9 (*R*)	OF, 95/5 isocratic analysis
2e	16.4 (*S*)	17.3 (*R*)	OD, 94/6-80/20 in30 min
2f	43.6 (*S*)	44.8 (*R*)	OF, 97/3-93/7 in 20 min then 60/40 in 50 min

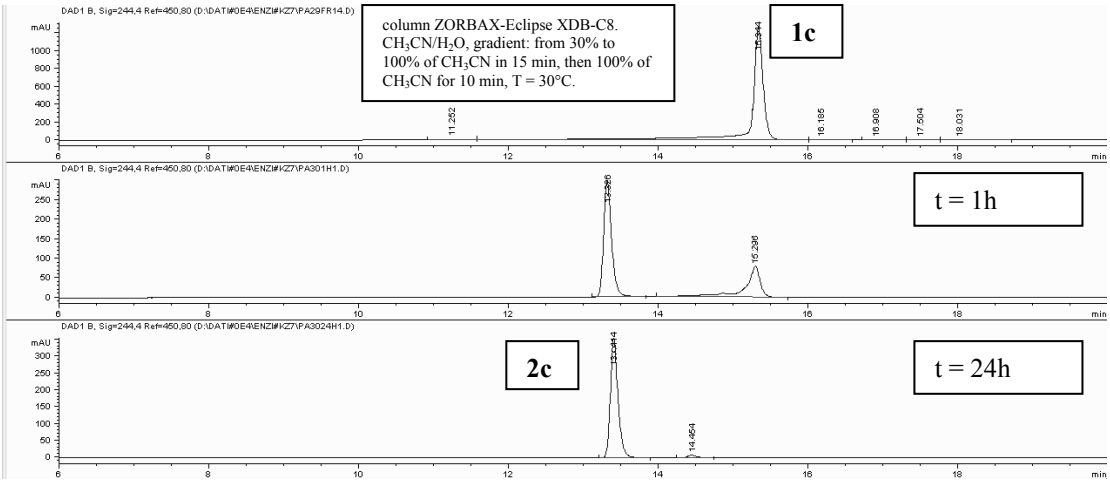
2-Phenylpropanol **2a** racemic mixture and (*S*)-2-phenylpropanol (*S*)-**2a** obtained as enzymatic reaction product



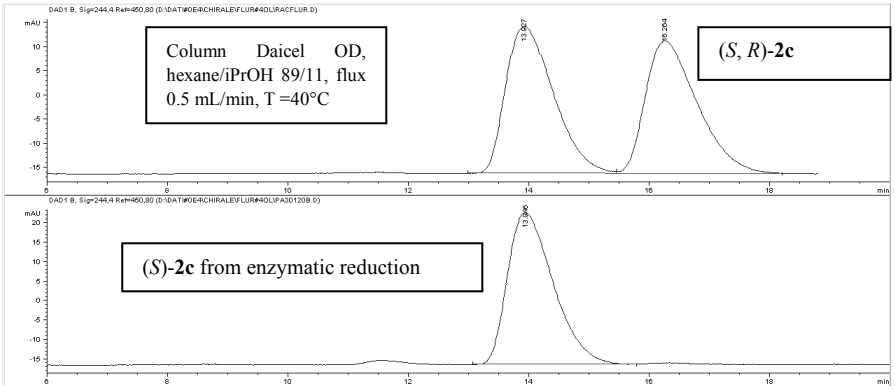
Ibuprofenol **2b** racemic mixture and (*S*)-Ibuprofenol (*S*)-**2b** obtained as enzymatic reaction product



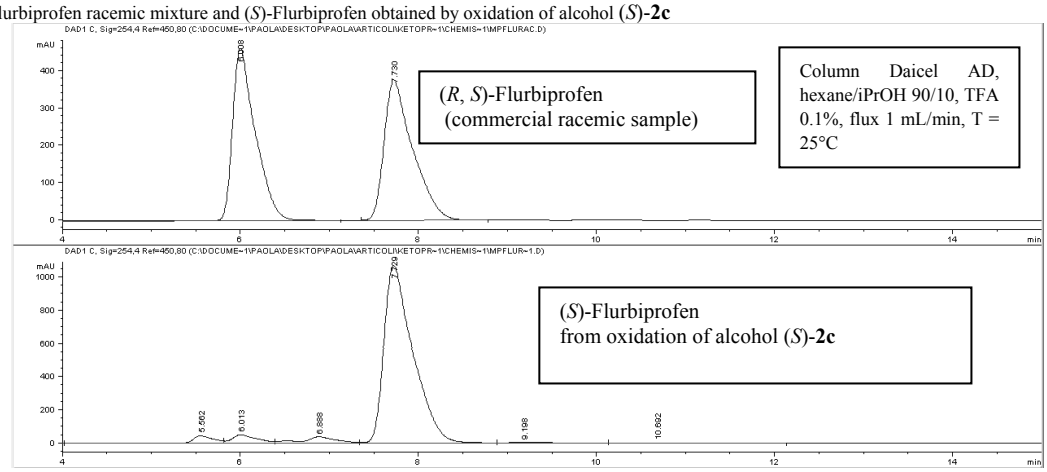
Representative HPLC analysis for Flurbiprofenal **1c** enzymatic reduction at different reaction times: t = 1h, t = 24h



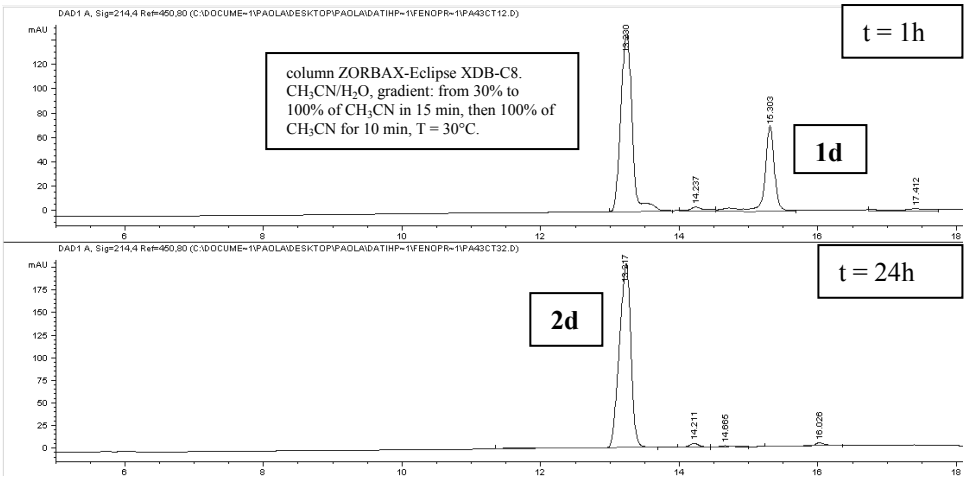
Flurbiprofenol **2c** racemic mixture and (*S*)-Flurbiprofenol (*S*)-**2c** obtained as enzymatic reaction product



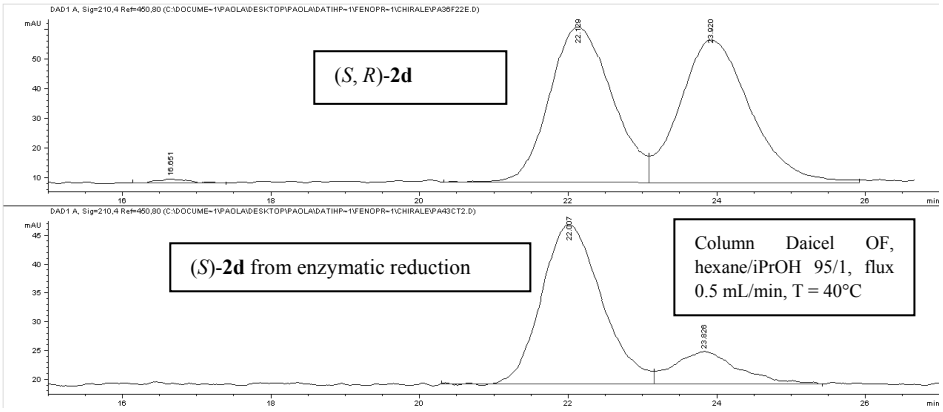
Flurbiprofen racemic mixture and (*S*)-Flurbiprofen obtained by oxidation of alcohol (*S*)-**2c**



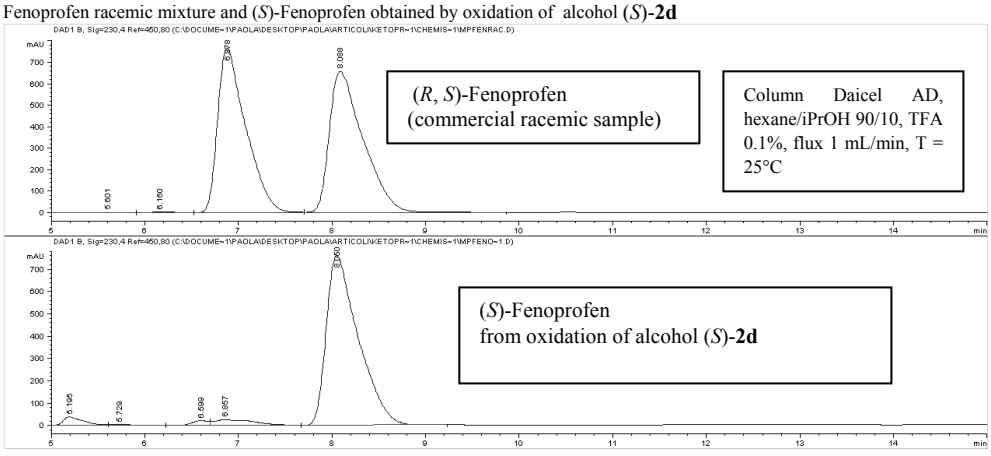
Representative HPLC analysis for Fenoprofenal **(1d)** enzymatic reduction at different reaction times: t = 1h, t = 24h



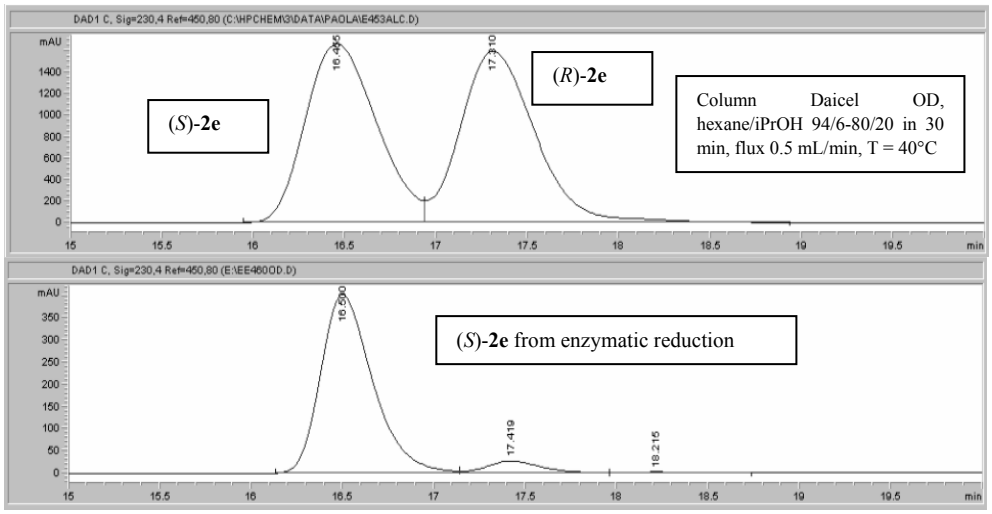
Fenoprofenol **2d** racemic mixture and (*S*)-Fenoprofenol (*S*)-**2d** obtained as enzymatic reaction product



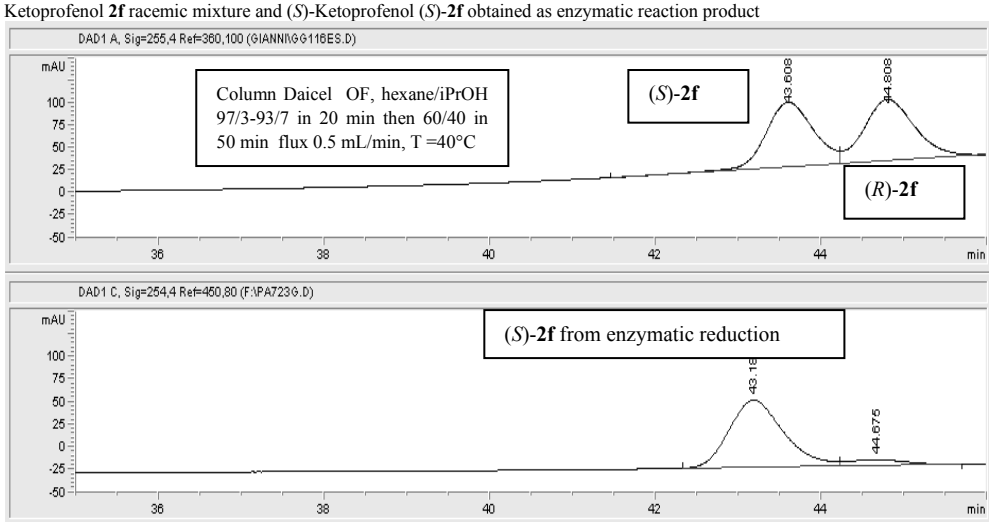
Fenoprofen racemic mixture and (*S*)-Fenoprofen obtained by oxidation of alcohol (*S*)-**2d**



Naproxenol **2e** racemic mixture and (*S*)-Naproxenol (*S*)-**2e** obtained as enzymatic reaction product



Ketoprofenol **2f** racemic mixture and (*S*)-Ketoprofenol (*S*)-**2f** obtained as enzymatic reaction product



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