Fast Attrition Enhanced Deracemization of Naproxen Through a Gradual \textit{in-situ} Feed

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Methyl (RS)-2-(6-methoxynaphthalen-2-yl)propanoate (methyl ester of naproxen) 1
To a methanol solution (250 mL) of (RS)-2-(6-methoxynaphthalen-2-yl)propanoic acid (naproxen, 2.0 g, 8.81 mmol) was added 0.4 g of conc. H$_2$SO$_4$ and the reaction mixture was stirred for overnight before it was diluted with CH$_2$Cl$_2$ (ca. 50 mL), washed with sat. NaHCO$_3$ aq. solution and dried over sodium sulfate. Solvent evaporation gave the title methyl ester quantitatively.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.62 (s, 1H), 7.57 (d, 1H, J = 8.5 Hz), 7.48-7.45 (m, 2H), 7.18 (d, 1H, J = 2.6 Hz), 6.89 (d, 1H, J = 2.4 Hz), 3.71 (q, 1H, J = 7.1 Hz), 3.36 (s, 3H), 3.28 (s, 3H), 1.52 (d, 3H, J = 7.1 Hz).

Methyl (S)-2-(6-methoxynaphthalen-2-yl)propanoate (methyl ester of (S)-naproxen) (S)-1
To a methanol solution (250 mL) of (S)-2-(6-methoxynaphthalen-2-yl)propanoic acid (naproxen, 6.13 g, 27.0 mmol) was added 1.0 g of conc. H$_2$SO$_4$ and the reaction mixture was stirred for overnight before it was diluted with CH$_2$Cl$_2$ (ca. 50 mL), washed with sat. NaHCO$_3$ aq. solution and dried over sodium sulfate. Solvent evaporation gave the title methyl ester quantitatively.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.62 (s, 1H), 7.57 (d, 1H, J = 8.5 Hz), 7.48-7.45 (m, 2H), 7.18 (d, 1H, J = 2.6 Hz), 6.89 (d, 1H, J = 2.4 Hz), 3.71 (q, 1H, J = 7.1 Hz), 3.36 (s, 3H), 3.28 (s, 3H), 1.52 (d, 3H, J = 7.1 Hz).

Ethyl (RS)-2-(6-methoxynaphthalen-2-yl)propanoate (ethyl ester of naproxen) 2
Following the procedure of (RS)-1, however with ethanol instead of methanol, (RS)-2-(6-methoxynaphthalen-2-yl)propanoic acid (naproxen, 5.74 g, 27.0 mmol) in 250mL ethanol with ca. 1.2 g concentrated H$_2$SO$_4$ was converted to the title product quantitatively.

$^1$H NMR (300 MHz, CDCl$_3$): δ = 7.72-7.67 (m, 3H), 7.41 (dd, 1H, J = 1.8 Hz, J = 8.4 Hz), 7.16-7.12 (m, 2H), 4.21-4.05 (m, 2H), 3.91 (s, 3H), 3.83 (q, 3H, J = 7.2 Hz), 1.55 (d, 2H, J = 3.0 Hz), 1.20 (t, 3H, J = 8.1 Hz).

Ethyl (S)-2-(6-methoxynaphthalen-2-yl)propanoate (ethyl ester of (S)-naproxen) (S)-2
Following the procedure of (S)-1, however with ethanol instead of methanol, (S)-2-(6-methoxynaphthalen-2-yl)propanoic acid (naproxen, 10.25 g, 48.2 mmol) in 350 mL ethanol with ca. 2.0 g concentrated H$_2$SO$_4$ was converted to the title product quantitatively.

$^1$H NMR (300 MHz, CDCl$_3$): δ = 7.72-7.67 (m, 3H), 7.41 (dd, 1H, J = 1.8 Hz, J = 8.4 Hz), 7.16-7.12 (m, 2H), 4.21-4.05 (m, 2H), 3.91 (s, 3H), 3.83 (q, 3H, J = 7.2 Hz), 1.55 (d, 2H, J = 3.0 Hz), 1.20 (t, 3H, J = 8.1 Hz).

Deracemization of methyl (RS)-2-(6-methoxynaphthalen-2-yl)propanoate 1
In a standard 10 mL sample vial were added 8.7 g glass beads, 0.7553 g (RS)-1, 0.0030 g (S)-1 and 6.302 g of a 13.6 wt% solution of NaMeO in MeOH (from stock: 2.2g Na dissolved in 45 mL MeOH). The sample vial was closed with a septum, and placed on an Elma Transsonic T470/H ultrasonic bath. The bath was kept at a constant temperature of 23 °C using a cooling spiral that was attached to a Julabo F25 thermostat bath. For sampling, 0.3 mL of the slurry was taken using a syringe, filtered on a P4 glass filter and washed with ca. 2mL MeOH. The chemical and enantiomeric purity was measured using chiral HPLC, $^1$H-NMR and XRPD. HPLC analysis was performed on Chiralcel-OJ (250x4.6 mm ID) column, eluent n-hexane/2-propanol 98/2 v/v%, flow 1mL/min, r.t., detection $\lambda$=254 nm. Retention times (S)-1 11.5 min, (R)-1 12.8 min.

Transesterification mediated deracemization of methyl (RS)-2-(6-methoxynaphthalen-2-yl)propanoate 1
Under Schlenck conditions, to a standard 25 mL roundbottom flask were added 8.7 g glass beads, 0.6120 g (RS)-2, 0.050 g (S)-1 and 6.502 g of a 13.8 wt% solution NaOMe in MeOH (from a stock containing 10mL MeOH and 0.5g Na) and an oval magnetic stirring bar. The flask was agitated at 700rpm and watches were synchronized. For sampling, 0.3 mL of the slurry was taken using a syringe, filtered on a P4 glass filter and washed with ca. 2mL MeOH. The chemical and enantiomeric purity was measured using chiral HPLC, $^1$H-NMR and XRPD. HPLC analysis was performed on Chiralcel-OJ (250x4.6 mm ID) column, eluent n-hexane/2-propanol 98/2 v/v%, flow 1mL/min, r.t., detection $\lambda$=254 nm. Retention times (S)-2 10.2 min, (R)-2 10.8 min, (S)-1 11.5 min, (R)-1 12.8 min.