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Fast Attrition-Enhanced Deracemization of Naproxen by a Gradual In Situ Feed

Noorduyn, Wim L.; Kaptein, Bernard; Meekes, Hugo; Enckevort, Willem J.P. van; Kellogg, Richard M.; Vlieg, Elias

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Supporting Information

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Wim L. Noorduin, Bernard Kaptein*, Hugo Meekes, Willem J. P. van Enckevort, Richard M. Kellogg and
Elias Vlieg

Dr. B. Kaptein
DSM Pharmaceutical Products
Innovative Synthesis & Catalysis
PO Box 18, 6160 MD Geleen
The Netherlands
Fax: +31-46-4767604
E-mail: bernard.kaptein@dsm.com

W.L. Noorduin, Dr. H. Meekes, Dr. W.J.P. van Enckevort, Prof. Dr. E. Vlieg
IMM Solid State Chemistry
Radboud University Nijmegen
Heyendaalseweg 135, 6525 AJ Nijmegen
The Netherlands
Fax: +31-24-3653067
E-mail: E.Vlieg@science.ru.nl

Prof. Dr. R.M. Kellogg
Syncom BV
Kadijk 3, 9747 AT Groningen
The Netherlands
Fax: +31-50-575399
E-mail: r.m.kellogg@syncom.nl

Supporting Information

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. H₂SO₄ and the reaction mixture was stirred for overnight before it was diluted with CH₂Cl₂ (ca. 50 mL), washed with sat. NaHCO₃ aq. solution and dried over sodium sulfate. Solvent evaporation gave the title methyl ester quantitatively.

¹H NMR (400 MHz, CDCl₃): 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. H₂SO₄ and the reaction mixture was stirred for overnight before it was diluted with CH₂Cl₂ (ca. 50 mL), washed with sat. NaHCO₃ aq. solution and dried over sodium sulfate. Solvent evaporation gave the title methyl ester quantitatively.

¹H NMR (400 MHz, CDCl₃): 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 250 mL ethanol with ca. 1.2 g concentrated H₂SO₄ was converted to the title product quantitatively.

¹H NMR (300 MHz, CDCl₃): 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 H₂SO₄ was converted to the title product quantitatively.

¹H NMR (300 MHz, CDCl₃): 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. 2 mL MeOH. The chemical and enantiomeric purity was measured using chiral HPLC, ¹H-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 1 mL/min, r.t., detection λ=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 10 mL MeOH and 0.5g Na) and an oval magnetic stirring bar. The flask was agitated at 700 rpm 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. 2 mL MeOH. The chemical and enantiomeric purity was measured using chiral HPLC, ¹H-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 1 mL/min, r.t., detection λ=254 nm. Retention times (*S*)-**2** 10.2 min, (*R*)-**2** 10.8 min, (*S*)-**1** 11.5 min, (*R*)-**1** 12.8 min.