Sustainable synthesis of enantiopure fluorolactam derivatives by a selective direct fluorination - amidase strategy

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SUPPORTING INFORMATION 2

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SI-2.1 General

The following formulae were used for calculating Atom Economy (AE), Reaction Mass Efficiency (RME) and Mass Intensity (MI) [D. J. C. Constable, A. D. Curzons, V. L. Cunningham Green Chem., 2002, 4, 521-527.]

\[
AE = \frac{\text{Molecular Weight of Product}}{\text{Total Molecular Weight of Reactants}} \times 100
\]

\[
RME = \frac{\text{Mass of Isolated Product}}{\text{Total Mass of Reactants}} \times 100
\]

\[
MI = \frac{\text{Total Mass in a Process or Process Step}}{\text{Mass of Product}}
\]

For the calculation of cumulative metrics over several synthetic steps, the following formulae were used:

\[
A + B \rightarrow C \quad C + D \rightarrow E
\]

\[
MW = \text{molecular weight of compound; } m = \text{weight of component.}
\]

\[
AE(E) = \frac{MW(E)}{MW(A) + MW(B) + MW(D)} \times 100 = \frac{MW(E)}{AE(C) + MW(D)} \times 100
\]

\[
RME(E) = \frac{m(E)}{m(D) + m(C)} \times 100 = \frac{m(E)}{RME(C) + m(D)} \times 100
\]

\[
MI(E) = \frac{m(C) \times MI(C) + \text{Total Mass of Other Chemicals in the Step}}{\text{Mass of Product}}
\]

The specific MI for Reaction, Solvents and Workup were calculated using the MI formula using only the corresponding data (total mass of reaction components, solvents and work-up components).
SI-2.2 Literature synthesis methods

Reported procedures for the synthesis of diethyl fluoromalonate do not always contain all the required information, therefore, some realistic assumptions were used where appropriate and are italicised in the calculations given below. Drying agents, when used, were not included in the calculations.


Experimental procedure: To a solution of sodium (7.0 g, 0.3 mol) in ethanol (200 mL) and diethyl malonate 3a (992 g, 6.2 mol) there was added acrylonitrile (168.5 g, 3.2 mol) at such a rate to maintain the temperature below 35 °C. The product was distilled under vacuum (104-110 °C, 0.8 mbar) to yield diethyl 2-(2-cyanoethyl)-malonate 3b (421 g (average of 3 experiments), 61 %) as a colourless oil.
Materials used for metrics calculations: Sodium (7.0g, 0.3 mol), ethanol (200 mL, 158 g), diethyl malonate (945 mL, 992 g, 6.2 mol), acrylonitrile (208 mL, 168.5 g, 3.2 mol), diethyl 2-(2-cyanoethyl)-malonate (421 g, 1.97 mol).

\[
AE(3b) = \frac{213.23}{160.17 + 53.06} \times 100 = 100
\]

\[
RME(3b) = \frac{421}{992 + 168.5} \times 100 = 36.3
\]

\[
MI(3b) = \frac{7 + 158 + 992 + 168.5}{421} = 3.1
\]

\[
MI(3b \text{ reaction}) = \frac{7 + 158 + 992 + 168.5}{421} = 3.1
\]

\[
MI(3b \text{ solvents}) = \frac{158}{421} = 0.4
\]

\[
MI(3b \text{ work – up}) = \frac{0}{421} = 0
\]


Experimental procedure: A solution of diethyl 2-(2-cyanoethyl)-malonate 3b (380 g) in ethanol (1.3 L) was reduced using Raney Nickel (7-10 g) and hydrogen (1000 psi = 69 bar) at 80 °C. The solution was evaporated (assuming a filtration to remove catalyst) and the residue poured into Skelly B (1 L, assume hexanes) with stirring. The product was filtered and air dried to give ethyl 2-oxopiperidine-3-carboxylate 3c (278.5 g, average of 3 runs, 90 % yield) as a solid.

Materials used for metrics calculations: Diethyl 2-(2-cyanoethyl)-malonate (380 g, 1.8 mol), ethanol (1300 mL, 1026 g), Raney Nickel (10 g, 0.17 mol), hydrogen (assuming use of 5 L autoclave meaning 3.5 L gas volume, treating hydrogen as an ideal gas gives 16.6 g, 8.2 mol, 2.75 equivalents) Skelly B (assume hexanes, 660 g), ethyl 2-oxopiperidine-3-carboxylate (278.5 g, 1.63 mol).
\[
AE(3c) = \frac{171.20}{213.23 + 2 \times 2.02} \times 100 = 78.8
\]
\[
RME(3c) = \frac{278.5}{380 + 20} \times 100 = 69.6
\]
\[
MI(3c) = \frac{380 + 1026 + 10 + 16.6 + 660}{278.5} = 7.5
\]
\[
MI(3c\ reaction) = \frac{380 + 1026 + 10 + 16.6}{278.5} = 5.1
\]
\[
MI(3c\ solvents) = \frac{1026 + 660}{278.5} = 6.0
\]
\[
MI(3c\ work - up) = \frac{660}{278.5} = 2.4
\]

**Cumulative metrics:**

\[
AE(3c\ cumulative) = \frac{171.20}{160.17 + 53.06 + 2 \times 2.02} \times 100 = 78.8
\]
\[
RME(3c\ cumulative) = \frac{278.5}{380 + \frac{0.363}{0.01}} \times 100 = 26.1
\]
\[
MI(3c\ cumulative) = \frac{380 \times 3.1 + 1026 + 10 + 16.6 + 660}{278.5} = 10.4
\]
\[
MI(3c\ reaction\ cumulative) = \frac{380 \times 3.1 + 1026 + 10 + 16.6}{278.5} = 8.0
\]
\[
MI(3c\ solvents\ cumulative) = \frac{380 \times 0.4 + 1026 + 660}{278.5} = 6.6
\]
\[
MI(3c\ work - up\ cumulative) = \frac{380 \times 0 + 660}{278.5} = 2.4
\]

Experimental procedure: The sodium salt of the benzensulfonimide (16.0 g, 0.05 mol) was dissolved in 10% v/v water-acetonitrile mixture (150 mL). This was cooled to -10 °C and a gaseous mixture of 10% F₂ in nitrogen (v/v) was added at a rate of 100 cc/min (25 mmol/hour). Over two hours, one equivalent of fluorine was added, the reaction was evaporated to dryness, dissolved in DCM (135 mL), filtered to remove the insoluble material (sodium fluoride) and evaporated to dryness to give N-fluorobenzenesulfonimide (13.5 g, 85 % yield) as a white solid. [US5403957]

Materials used for metrics calculations: Benzenesulfonimide sodium salt (16 g, 50 mmol), water (15 mL, 15 g), acetonitrile (135 mL, 106 g), fluorine (1.9 g, 50 mmol), DCM (135 mL, 180 g), N-fluorobenzenesulfonimide (13.5 g, 42.5 mmol).

\[ AE(\text{NFSI}) = \frac{315.33}{319.32 + 38.00} \times 100 = 88.2 \]

\[ RME(\text{NFSI}) = \frac{13.5}{16 + 1.9} \times 100 = 75.4 \]

\[ MI(\text{NFSI}) = \frac{16 + 15 + 106 + 1.9 + 180}{13.5} = 23.6 \]

\[ MI(\text{NFSI reaction}) = \frac{16 + 15 + 106 + 1.9}{13.5} = 10.3 \]

\[ MI(\text{NFSI solvents}) = \frac{15 + 106 + 180}{13.5} = 22.3 \]

\[ MI(\text{NFSI work – up}) = \frac{180}{13.5} = 13.3 \]

Experimental procedure: 2,6-Lutidine (31.7 g, 296 mmol) was added dropwise over 30 min to a suspension of ethyl 2-oxopiperidine-3-carboxylate 3c (101.2 g, 591 mmol), ((S)-BINAP)Pd(H$_2$O)$_2$(OTf)$_2$ [A. Fuji, E. Hagiwara and M. Sodeoka, J. Am. Chem. Soc., 1999, 121, 5450-5458] (3.14 g, 2.96 mmol) and N-fluorobenzenesulfonimide (242 g, 768 mmol) in EtOH (500 mL) at 0 °C in an ice bath. The temperature was maintained at approximately 10 °C during addition and allowed to warm up to room temperature overnight as the ice melted. The reaction was filtered and the solid was washed with EtOH (estimated 200 mL) then DCM (200 mL). The liquors were evaporated and re-dissolved in DCM (3500 mL), the organics were washed with saturated NH$_4$Cl solution (300 mL) and the aqueous phase was extracted with DCM (2 x 200 mL). The combined organics were evaporated and re-dissolved in DCM (300 mL), filtered through celite and washed with DCM (200 mL). The organic solution was allowed to stand overnight, a fine precipitate formed and the mixture was filtered through celite and washed with DCM (estimated 200 mL). The organic fraction was loaded onto silica (1500 g, estimated volume: 2.4 L) and was purified on the companion XL eluting with 0-100% ethyl acetate in cyclohexane gradient (estimated 10 column volumes = 12 L each). Appropriate fractions were identified by LC-MS, combined and the solvent evaporated to give ethyl 3-fluoro-2-oxopiperidine-3-carboxylate 2a (92.2 g, 82 %, 44 % ee after vacuum drying) as a yellow solid. High purity (99 % ee) product was obtained by preparative scale chiral chromatography. [F. L. Atkinson, M. D. Barker, C. Douault, N. S. Garton, J. Liddle, V. K. Patel, A. G. S. Preston, D. M. Wilson, US20130040984].

Materials used for metrics calculations: 2,6-Lutidine (31.7 g, 296 mmol), ethyl 2-oxopiperidine-3-carboxylate (101.2 g, 591 mmol), ((S)-BINAP)Pd(H$_2$O)$_2$(OTf)$_2$ (3.14 g, 2.96 mmol), N-fluorobenzenesulfonimide (242 g, 768 mmol), EtOH (700 mL, 552 g), DCM (4800 mL, 6384 g), saturated aq. NH$_4$Cl solution (300 mL, 318 g), silica (1500 g assume 2.4 L volume, 1 g =1.6 mL), ethyl acetate (assume 5 column volumes: 12 L, 10.7 kg),
cyclohexane (assume 5 column volumes: 12 L, 9.35 kg), ethyl 3-fluoro-2-oxopiperidine-3-carboxylate (92.2 g, 44% ee after vacuum drying).

\[
AE(2 \text{ 44%ee}) = \frac{189.19}{171.20 + 315.33} \times 100 = 38.9
\]

\[
RME(2 \text{ 44%ee}) = \frac{92.2}{101.2 + 242} \times 100 = 26.9
\]

\[
MI(2 \text{ 44%ee}) = \frac{32 + 101 + 3 + 242 + 552 + 6384 + 318 + 1500 + 10700 + 9350}{92.2} = 316.5
\]

\[
MI(2 \text{ reaction 44%ee}) = \frac{32 + 101 + 3 + 242 + 395}{92.2} = 8.4
\]

\[
MI(2 \text{ solvents 44%ee}) = \frac{552 + 6384 + 318 + 10700 + 9350}{92.2} = 296.1
\]

\[
MI(2 \text{ work – up 44%ee}) = \frac{158 + 6384 + 318 + 1500 + 10700 + 9350}{92.2} = 308.1
\]

Ethyl 3-fluoro-2-oxopiperidine-3-carboxylate 2a cumulative metrics:

\[
AE(2 \text{ 44%ee cumulative}) = \frac{MW(2)}{MW(3c) + MW(NFSI)} \times \frac{AE(3c \text{ cumulative}) + AE(NFSI)}{100} \times 100
\]

\[
AE(2 \text{ 44%ee cumulative}) = \frac{189.19}{171.20 + 315.33} \times \frac{0.788 + 0.882}{0.882} = 32.9
\]

\[
RME(2 \text{ 44%ee cumulative}) = \frac{m(2)}{m(3c) + m(NFSI)} \times \frac{RME(3c \text{ cumulative}) + RME(NFSI)}{100} \times 100
\]

\[
RME(2 \text{ 44%ee cumulative}) = \frac{92.2}{101.2 + 242} \times \frac{0.261 + 0.754}{0.754} = 13.0
\]

\[
MI(2 \text{ 44%ee cumulative})
\]
\[
\begin{align*}
92.2 &= \frac{32 + 101 \times MI(3c) + 3 + 242 \times MI(NFSI) + 552 + 6384 + 318 + 1500 + 10700 + 9350}{92.2} \\
&= 386.1 \\
&= \frac{32 + 101 \times 8 + 3 + 242 \times 10.3 + 395}{92.2} = 40.5 \\
MI(\text{2 44\%ee cumulative reaction}) &= \frac{552 + 6384 + 318 + 10700 + 9350 + 101 \times 6 + 242 \times 22.3}{92.2} = 361.2 \\
&= \frac{101 \times 2.4 + 242 \times 13.3 + 158 + 6384 + 318 + 1500 + 10700 + 9350}{92.2} = 345.7
\end{align*}
\]


\[
\begin{align*}
\text{crude 2} &\quad \xrightarrow{\text{Chiral HPLC}} \quad \text{pure 2} \\
\text{44% ee} &= 72\% \text{ (S)} + 28\% \text{ (R)} \\
\text{72\% yield, 99\% ee} &+ \quad \text{28\% yield, 99\% ee}
\end{align*}
\]

**Experimental procedure:** Ethyl-3-fluoro-2-oxo-3-piperidinecarboxylate 2 (25 g, *assume it contributes 20 mL to total volume*) was dissolved in ethanol (450 mL) with gentle heating and sonication. The solution was then filtered through a Pall Acrodisc 37 mm syringe filter with a glass fibre membrane. The filtered solution was adjusted to a total volume of 500 mL with ethanol (*assume 30 mL*) to give a solution with nominal concentration of 50 mg/mL. The preparative HPLC details were as follows:

- **Column:** Chiralpak AD, 330 x 50 mm, 20 pm
- **Mobile Phase:** A: Heptane B: Ethanol
- **Gradient Profile:** 15% B Isocratic
- **Run Time:** 20 min
- **Flow Rate:** 473 mL/min
- **Column Temperature:** 20 °C.
- **Wavelength:** 220 nm
Materials used for metrics calculations: Ethyl 3-fluoro-2-oxopiperidine-3-carboxylate (25 g, 44 % ee), ethanol (assume 480 mL, 379 g for dissolution + 1419 mL, 1120 g for chromatography), heptane (8041 mL, 5500 g), ethyl 3-(S)-fluoro-2-oxopiperidine-3-carboxylate (assume 100 % recovery, 18 g, 99 % ee).

\[
AE(2 \text{ Chiral HPLC}) = \frac{189.19}{189.19} \times 100 = 100
\]

\[
RME(2 \text{ Chiral HPLC}) = \frac{18.0}{25.0} \times 100 = 72.0
\]

\[
MI(2 \text{ Chiral HPLC}) = \frac{25 + 1499 + 5500}{18.0} = 390.2
\]

\[
MI(2 \text{ Chiral HPLC reaction}) = \frac{25.0}{18.0} = 1.4
\]

\[
MI(2 \text{ Chiral HPLC solvents}) = \frac{1499 + 5500}{18.0} = 388.8
\]

\[
MI(2 \text{ Chiral HPLC work-up}) = \frac{1499 + 5500}{18.0} = 388.8
\]

Ethyl 3-fluoro-2-oxopiperidine-3-carboxylate 2 cumulative metrics:

\[
AE(2 \text{ cumulative}) = \frac{189.19}{0.329} \times 100 = 32.9
\]

\[
RME(2 \text{ cumulative}) = \frac{18.0}{0.130} \times 100 = 9.4
\]

\[
MI(2 \text{ cumulative}) = \frac{25 \times 386.1 + 1499 + 5500}{18.0} = 925.1
\]

\[
MI(2 \text{ cumulative reaction}) = \frac{25 \times 40.5}{18.0} = 56.3
\]

\[
MI(2 \text{ cumulative solvents}) = \frac{25 \times 361.2 + 1499 + 5500}{18.0} = 890.5
\]
\[
MI(2 \text{ work-up}) = \frac{25 \times 345.7 + 1499 + 5500}{18.0} = 868.9
\]
SI-2.3 Direct fluorination and enzymatic resolution approach

Dimethyl 2-(2-cyanoethyl)-2-fluoromalonate $4b$

$$\begin{align*}
\text{MW: 132.12} & \quad \text{MW($F_2$): 38.00} \\
\text{4} & \quad \text{4b, 60 \%}
\end{align*}$$

Experimental procedure: as described in SI-1.9.

Materials used for metrics calculations: Dimethyl malonate (26.4 g), Cu(NO$_3$)$_2$.2.5H$_2$O (4.65 g), acetonitrile (210 mL, 165 g), fluorine (8.36 g), K$_3$PO$_4$ (84.9 g), acrylonitrile (12.7 g), dimethyl 2-(2-cyanoethyl)-fluoromalonate (24.45 g).

$$\begin{align*}
AE(4b) &= \frac{203.17}{132.12 + 38.00 + 53.06} \times 100 = 91.0 \\
RME(4b) &= \frac{24.45}{26.4 + 8.36 + 12.7} \times 100 = 51.1 \\
MI(4b) &= \frac{26.4 + 4.65 + 165 + 8.36 + 84.9 + 12.7}{24.45} = 12.3 \\
MI(4b \text{ reaction}) &= \frac{26.4 + 4.65 + 8.36 + 42.45 + 12.7 + 118}{24.45} = 8.7 \\
MI(4b \text{ solvents}) &= \frac{165}{24.45} = 6.7
\end{align*}$$
\[ MI(4b \text{ work} - \text{ up}) = \frac{47 + 42.45}{24.45} = 3.6 \]

Dimethyl 2-(3-aminopropyl)-2-fluoromalonate, hydrochloride salt 4c

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{F} & \quad \text{CN} \\
\text{MW: 203.17} & \quad \text{2 mol % Pd/C} \\
\text{MW(H}_2\text{): 2.02} & \quad \text{16 h, RT, MeOH} \\
\text{MW(HCl): 36.45} & \\
\text{MW: 243.66} & \\
\end{align*}
\]

Experimental procedure: as described in SI-1.10.

Materials used for metrics calculations: 10 % Pd/C (2.62 g), 37 % HCl (4.85 mL, 5.82 g, 2.15 g HCl and 3.67 g water), dimethyl 2-(2-cyanoethyl)-2-fluoromalonate (10.0 g), hydrogen (1.0 g, assuming 3 L gas volume (autoclave + storage tank) at 4 bar and 20 °C), methanol (103.3 mL, 81.7 g), acetone (30 mL, 23.7 g), dimethyl 2-(3-aminopropyl)-2-fluoromalonate, hydrochloride salt (10.43 g).

\[
\begin{align*}
AE(4c) &= \frac{243.66}{203.17 + 2 \times 2.02 + 36.45} \times 100 = 100 \\
RME(4c) &= \frac{10.43}{10.0 + 2 + 2.15} \times 100 = 73.7 \\
MI(4c) &= \frac{2.62 + 5.82 + 10.0 + 1 + 81.7 + 23.7}{10.43} = 12.0 \\
MI(4c \text{ reaction}) &= \frac{2.62 + 5.82 + 10 + 1 + 34.3}{10.43} = 5.2 \\
MI(4c \text{ solvents}) &= \frac{81.7 + 23.7}{10.43} = 10.1 \\
MI(4c \text{ work} - \text{ up}) &= \frac{47.5 + 23.7}{10.43} = 6.8 \\
\end{align*}
\]

Cumulative metrics for 2 steps (50 % yield):

\[
\begin{align*}
AE(4c \text{ cumulative}) &= \frac{243.66}{203.17 + 2 \times 2.02 + 36.45} \times 100 = 92.3 \\
\end{align*}
\]
\[ RME(4\text{c cumulative}) = \frac{10.43}{\frac{10.0}{0.511} + 2 + 2.15} \times 100 = 44.5 \]

\[ MI(4\text{c cumulative}) = \frac{2.62 + 5.82 + 10.0 \times 12.3 + 1 + 81.7 + 23.7}{10.43} = 22.8 \]

\[ MI(4\text{c reaction cumulative}) = \frac{2.62 + 5.82 + 10 \times 8.7 + 1 + 34.3}{10.43} = 12.5 \]

\[ MI(4\text{c solvents cumulative}) = \frac{81.7 + 23.7 + 10 \times 6.7}{10.43} = 16.5 \]

\[ MI(4\text{c work-up cumulative}) = \frac{47.5 + 23.7 + 10 \times 3.6}{10.43} = 10.3 \]

(S)-Methyl 3-fluoro-2-oxopiperidine-3-carboxylate 2b

\[
\begin{array}{c}
\text{MW: 243.66} \\
\text{2x} \\
\text{4c} \\
\text{NH}_3^+\text{Cl}^- \\
\text{pH 7.3 buffer} \\
\text{CAL-B 10,000} \\
\text{20 °C, 8 h} \\
\text{2b} \\
\text{5b} \\
\text{MW: 175.16} \\
\end{array}
\]

Experimental procedure: as described in SI-1.11.

Materials used for metrics calculations: 0.06 M Na$_2$HPO$_4$: 0.06 M KH$_2$PO$_4$ buffer (assume overall 246 mL, assume d = 1.0 g/mL, 246 g), 4c (10.0 g), 05 M NaOH solution (assume 1 equivalent NaOH, 82 mL, 83.6 g solution), Fermase immobilised CAL-B 10,000 (7.2 g), water (30 mL, 30 g), 20 % formic acid (assume d = 1.04 g/mL, 30 mL, 31.2 g), acetone (10 mL, 7.9 g), (S)-methyl 3-fluoro-2-oxopiperidine-3-carboxylate 2b (3.15 g).

\[ AE(6a) = \frac{175.16}{2 \times 243.66} \times 100 = 35.9 \]

\[ RME(6a) = \frac{3.15}{10.0} \times 100 = 31.5 \]

\[ MI(6a) = \frac{246 + 10 + 83.6 + 7.2 + 30 + 31.2 + 7.9}{3.15} = 132.0 \]

\[ MI(6a \text{ reaction}) = \frac{246 + 10 + 83.6 + 7.2}{3.15} = 110.1 \]

\[ MI(6a \text{ solvents}) = \frac{246 + 83.6 + 30 + 31.2 + 7.9}{3.15} = 126.6 \]
\[ MI(6a \text{ work-up}) = \frac{30 + 31.2 + 7.9}{3.15} = 21.9 \]

Cumulative metrics for 3 steps (22 % overall yield):

\[ AE(6a \text{ cumulative}) = \frac{175.16}{2 \times 0.923} \times 100 = 33.2 \]

\[ RME(6a \text{ cumulative}) = \frac{3.15}{10.0} \times 100 = 14.0 \]

\[ MI(6a \text{ cumulative}) = \frac{246 + 10 \times 22.8 + 83.6 + 7.2 + 30 + 31.2 + 7.9}{3.15} = 201.2 \]

\[ MI(6a \text{ reaction cumulative}) = \frac{246 + 10 \times 12.5 + 83.6 + 7.2}{3.15} = 146.6 \]

\[ MI(6a \text{ solvents cumulative}) = \frac{246 + 83.6 + 30 + 31.2 + 7.9 + 10 \times 16.5}{3.15} = 179.0 \]

\[ MI(6a \text{ work-up cumulative}) = \frac{30 + 31.2 + 7.9 + 10 \times 10.3}{3.15} = 54.7 \]

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<th>Chiral chromatography (2)</th>
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<td>Yield</td>
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<td>90 %</td>
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<tr>
<td>Health and Safety</td>
<td>H330, H350, H411, H410</td>
<td>H370</td>
<td>First pass OK</td>
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<td>MI: Total</td>
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<td>12.1</td>
<td>132.0</td>
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<tr>
<td>MI: Reaction</td>
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<td>5.3</td>
<td>110.1</td>
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<tr>
<td>MI: Workup</td>
<td>3.6</td>
<td>6.8</td>
<td>21.9</td>
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<tr>
<td>Catalysts used</td>
<td>Cu(NO₃)₂.2.5H₂O</td>
<td>Pd/C 10%</td>
<td>Fermase CAL-B 10,000</td>
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<tr>
<td>Catalysts recovered</td>
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<td>No catalysts recovered</td>
<td>All catalysts recovered</td>
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<tr>
<td>Reactor</td>
<td>Batch</td>
<td>Batch</td>
<td>Batch</td>
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<tr>
<td>Elements</td>
<td>P, Cu</td>
<td>Pd</td>
<td></td>
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<tr>
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<td>Work-up</td>
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<td>Ion exchange</td>
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<table>
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<tr>
<th>Enantioselective fluorination (literature procedure)</th>
<th>Chemo-enzymatic route (this work)</th>
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<tbody>
<tr>
<td>Yield</td>
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<td>32 % (99 % ee)</td>
<td>22 % (99 % ee)</td>
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<td>RME</td>
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<td>AE</td>
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<tr>
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<td>56.3</td>
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