Scale-Up of a Continuous Extraction Process for Driving an Equilibrium-Limited Reaction to Completion

Supporting Information

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Experimental Setup

Figure S1. Block diagram of experimental setup for the continuous extractor



- Pressure-equalizing addition furnel (settler) Pump 2 Pump 2 Fresh n-heptane Name Reactor (mixer) Pump 3
- *Figure S2.* Photo of the experimental setup for the continuous extractor when run on 50 g scale

Table S1. Pump settings for the continuous extractor

Reaction Scale	Pump 1 Flow Rate (mL/min)	Pump 2 Flow Rate (mL/min)	Pump 3 Flow Rate (mL/min)
5.00 g	0.14	2.5	2.36
50.0 g	1.111	10.000	8.889

Table S2. Equipment used for the continuous extractor

Pump #	Type ^a	Description	Purpose
1	Eldex Pump	Model 1LMP, reciprocating piston pump, 6000 psi capability, 0.002-2.5 mL/min	Pump extraction solvent (<i>n</i> -heptane) into reactor
2	Syrris Pump	Asia Syringe Pump with Asia Red Syringes (2.5 mL/5 mL), 290 psi capability, 0.05-10 mL/min	Pump biphasic reaction mixture into addition funnel (settler)
3	Thar Pump	Series III single-piston pump, 6000 psi capability, 0.01-10 mL/min	Recycle reactive phase (MeOH) from settler back into reactor

(a) 1/16" OD PFA tubing was used throughout the system. The 1/16" OD PFA tubing and flangless PEEK or PFA fittings were all obtained from IDEX.

Analytical Section

In-process sample for Deprotection and HPLC purity of the isolated product

Column:	Supelco Ascentis Express C18 (Catalog# 53829-U)
Column dimensions:	$4.6 \times 150 \text{ mm}$
Particle size:	2.7 μm
Column temp:	35 °C
Detection wavelength:	210 nm
Typical injection amount:	5 µL
Total mobile phase flow:	1.0 mL/min
Mobile phase A:	0.1% v/v HClO ₄ in water
Mobile phase B:	acetonitrile

Table S3. HPLC Parameters

Table S4. HPLC Solvent Gradient Profile

Time (minutes)	Mobile Phase A	Mobile Phase B
0.00	95	5
15.00	5	95
17.00	5	95
17.10	95	5
20.00	95	5









Table	S5.	HPLC	Parameters
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Column:	Supelco Ascentis Express C18 (Catalog# 53829-U)
Column dimensions:	$4.6 \times 150 \text{ mm}$
Particle size:	2.7 μm
Column temp:	35 °C
Detection wavelength:	210 nm
Typical injection amount:	5 µL
Total mobile phase flow:	1.0 mL/min
Mobile phase A:	0.1% v/v HClO ₄ in water
Mobile phase B:	acetonitrile

Table S6. HPLC Solvent Gradient Profile

Time (minutes)	Mobile Phase A	Mobile Phase B
0.00	95	5
5.00	95	5
15.00	5	95
17.00	5	95
17.10	95	5
20.00	95	5

Figure S5. Example HPLC trace of a typical in-process mixture



GC Conditions for Partition Coefficient Studies

Column:	DB-5
Column dimensions:	30 x 0.53 mm
Particle size:	1.5 μm
Injector:	200 °C, 3.6 psi, 32.4 mL/min
Typical injection amount:	1 µL
Split mode:	5:1 ratio, 24.9 mL/min
Constant flow column:	3.6 psi, 5.0 mL/min, 35 cm/s average velocity

Table S8. GC Oven Conditions

Time (minutes)	Temperature (°C)	Rate (°C/min)
0.00-4.00	40	0
4.00-12.40	40-250	25
12.40-27.40	250	0

NMR Spectra



Figure S6. Lactone Diol (4) ¹H NMR ((CD₃)₂SO, 600 MHz)



Figure S7. Lactone Diol (4) ¹³C NMR ((CD₃)₂SO, 150 MHz)