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

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Abstract

We report a strategy for implementing a scalable continuous extraction to drive an equilibrium-limited reaction to completion. Our approach is simple, requiring only standard equipment and glassware, and can be designed to meet the needs of the process (e.g. reduced cycle time or reduced solvent use) with minimal development time. We investigated the process parameters, such as the flow rate of fresh *n*-heptane (extracting solvent) into the system, at a 0.5-5 g scale and reduced the overall time and total amount of *n*-heptane needed to drive the reaction to completion. The improved conditions for the extraction were demonstrated at the 50 g scale, leading to similar yield of the desired product and total reaction time at the 5 g scale, verifying that our reactions and extraction conditions were scalable. In particular, our fit-for-purpose approach is customizable to a number of systems and can be implemented in a short period of time with a limited amount of material.

Keywords: continuous extraction, equilibrium reaction, deprotection, scale-up

Introduction

Liquid-liquid extraction is a simple, effective, and mild method for purifying reaction mixtures in organic chemistry. Mixing two immiscible liquid solvents causes the solutes to partition themselves between the two phases based on each solute's thermodynamic preference for residing in the two phases.[1] This thermodynamic partitioning can be exploited to drive mass transfer of either the desired products or the

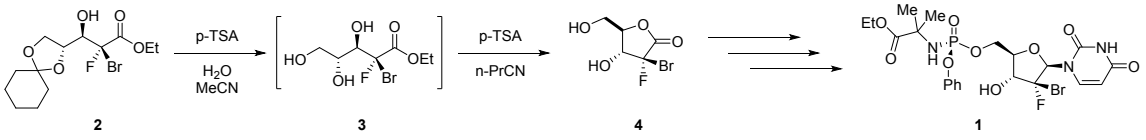
undesired impurities into the extracting phase.[2] The two liquid phases are separated and the phase containing the desired products is carried forward in the process. Extraction occurs frequently at mild temperatures, which is important when thermally or chemically unstable species are present and must be removed from the reaction mixture quickly.[3] One of the most attractive features of extractions is that they are usually readily transferrable from laboratory to manufacturing scale.[4] Furthermore, extractions may be executed in several stages in batch processes or operated as continuous flow systems, demonstrating the flexibility of extraction as a unit operation.[5] In flow, common arrangements of continuous extraction equipment include mixer-settlers, packed columns, and centrifugal extractors. Mixer-settlers are particularly useful for extractions that require only a few equilibrium stages, provide flexible and simple operation, and are readily scalable. Extraction technology is versatile and the desired unit operation is a choice of cost, convenience, and ease of scale, among other factors.

In the pharmaceutical industry, the vast majority of liquid-liquid extractions are carried out in batches, leaving continuous separation technology underdeveloped. In particular, there are situations where batch extraction is inefficient and cumbersome to scale compared to a continuous flow extraction process. For example, when a large number of batch extractions are required to purify the reaction mixture, the process incurs significant costs in labor and solvent use. In such cases, continuous flow extraction is highly appealing from a number of perspectives. For extractions that operate far from thermodynamic equilibrium, the flow rate of fresh extracting solvent can be tuned to increase the rate of mass transfer (when quickly removing an unstable material is the main objective at the expense of increased use of solvent) or to reduce the amount of

fresh solvent needed to perform the extraction (at the expense of increased operating time). Additionally, implementing a continuous process reduces the labor requirement inherent to a large number of manufacturing-scale batch extractions and can reduce the total operating time compared to a batch extraction.[6] Continuous extractions can be integrated with flow reactors and other continuous flow unit operations to intensify and streamline the overall process and potentially reduce the footprint needed to execute the process at larger scales.[4d, 4e, 7]

We recently encountered a situation in which implementing a continuous extraction provided an opportunity for process intensification. During optimization of the route to nucleoside **1** (see Figure 1), the nominal procedure for the deprotection/lactonization reaction of cyclohexylidene ester **2** to lactone diol **4** (Step 4) was identified as being difficult to scale up.

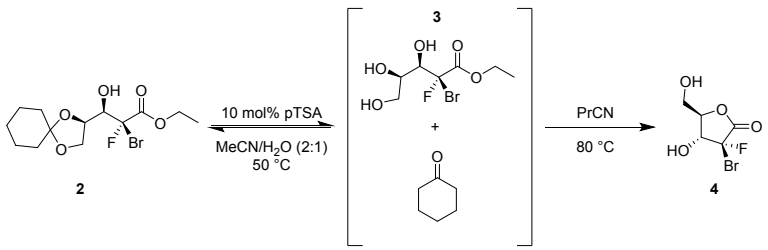
Figure 1. Synthesis of nucleoside **1**.[a]



Although appearing to be quite simple, the initial deprotection step in the reaction proved challenging due to the deprotected ethyl ester triol (**3**) and cyclohexanone being in equilibrium with the cyclohexylidene ester starting material (**2**, Figure 2).

Figure 2. Equilibrium between the deprotected ethyl ester triol (**3**) and cyclohexylidene ester (**2**) starting material.

[a] The syntheses of compounds **1** and **2** will be disclosed in a future publication.



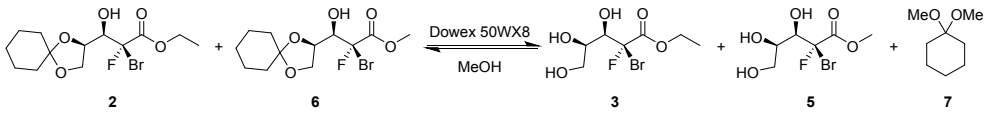
In order to drive the equilibrium towards desired deprotected ethyl ester triol (**3**), the nominal procedure required distillation with an extensive amount of solvent to drive off cyclohexanone. While this approach was effective on decagram scale, the distillations proved to be difficult to perform and the results were thus expected to be challenging to reproduce on kilogram scale. In addition, it was noted during the optimization of the nominal procedure that most of the water used in the reaction must be removed prior to lactonization to prevent hydrolysis of the deprotected ethyl ester triol (**3**) to the corresponding acid. This acid would cyclize during the lactonization to an undesired six-membered lactone that did not reject well in the crystallization. Removing the water required azeotroping with butyronitrile several times, which would also be problematic at kilogram scale. With multi-kilogram deliveries of nucleoside **1** planned to begin in six weeks, the project team began exploring alternative methods to make the process more amenable to running on kilogram scale.

Results and Discussion

The investigation into alternative processes began with attempting to find the best conditions for the deprotection, since that part of the reaction was the most problematic to scale. After exploring several different conditions for the deprotection, an approach using an acidic resin (Dowex 50WX8) appeared most promising (see Figure 3). Unfortunately, the reaction appeared to stall at ~50% conversion despite screening

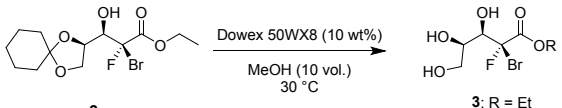
various solvents, temperatures, resins, and loadings. Since the initial equilibrium conversion could not be further improved, efforts were made to find ways other than distillation to increase the conversion after reaching an initial equilibrium.

Figure 3. Deprotection using Dowex 50WX8 resin.



One such approach, inspired by the protocol used by Evans et. al.,[8] was to filter off the acidic resin used for the deprotection, extract the MeOH solution with *n*-heptane three times, and then re-subject the MeOH solution to the resin. After performing five cycles of filtering, extracting, and then adding the resin back to the solution, the reaction reached 100% conversion to a mixture of the ethyl ester triol (**3**) and methyl ester triol (**5**, see Table 1, Entry 1). The reaction was therefore scaled-up from 100 mg to 5 g, which required 14 cycles (42 total extractions) to reach 99% conversion (see Table 1, Entry 2). The significant increase in the number of extractions needed when increasing the scale of the reaction was alarming in the sense that the reaction would be run on kilogram quantities of material and the cause of this dramatic increase was unclear.

Table 1. Extracting with *n*-heptane to push the reaction to complete conversion.



Entry	Scale	Inital Conversion	Extractions	Final Conversion
1	100 mg	49% (22.5 h)	15	100%
2	5.00 g	47% (17.5 h)	42	99%

To further explore this issue, an investigation into the partition coefficients of cyclohexanone dimethyl ketal (**7**, generated instead of cyclohexanone when MeOH is the solvent for the reaction) into other organic solvents was conducted. As shown in Table 2,

the partition coefficient of cyclohexanone dimethyl ketal only slightly favors extraction from MeOH in all solvent systems explored (the small number of systems explored is due to only *n*-hexane, *n*-heptane, and cyclohexane being immiscible with MeOH).[9] These partition coefficient values help to explain why so many extractions are needed to drive the reaction to completion, as each extraction only removes small amounts of cyclohexanone dimethyl ketal. This discovery led to consideration of a continuous extraction approach, as it would allow for constant removal of cyclohexanone dimethyl ketal.

Table 2. Partition coefficient of cyclohexanone dimethyl ketal (**7**) in various solvent systems.

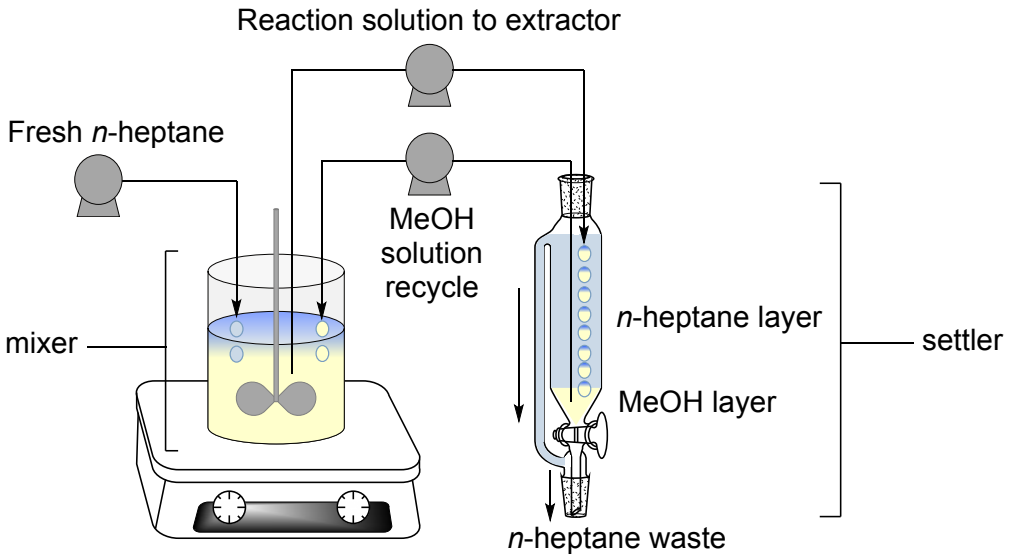
$$partition\ coefficient = \frac{[analyte\ in\ solvent\ A]}{[analyte\ in\ solvent\ B]}$$

Solvent A	Solvent B	Analyte	Partition Coefficient	Ratio Solvent A:Solvent B for Phase Cut
n-hexane	MeOH	cyclohexanone dimethyl ketal	1.24	2:3 (slow phase cut)
n-heptane	MeOH	cyclohexanone dimethyl ketal	1.36	1:1 (fast phase cut)
cyclohexane	MeOH	cyclohexanone dimethyl ketal	1.51	2:1 (slow phase cut)

A continuous extractor was constructed from simple and readily available lab equipment, as shown in Figure 4, to obtain proof of concept. A pump was used to dose *n*-heptane into the reaction vial, which contained the cyclohexylidene ester starting material (**2**), resin, and MeOH at 30 °C (the mixer). A second pump removed solution from the reaction vial and into a pressure-equalizing addition funnel (the settler). This addition funnel was pre-filled with enough *n*-heptane to reach the sidearm. As the reaction solution was pumped into the addition funnel, *n*-heptane would flow down the sidearm and collect in a waste flask. Finally, a third pump transferred MeOH solution from the bottom of the addition funnel and back into the reaction flask. Therefore, as fresh *n*-heptane was being pumped into the reaction vial, the biphasic mixture in the vial

was being pumped out into the addition funnel where the MeOH droplets (containing compounds **2**, **3**, **5**, and **6**) would flow through the *n*-heptane layer (thus continuing the extraction of cyclohexanone dimethyl ketal that started in the mixer) and settle to the bottom before being pumped back into the reaction vial.

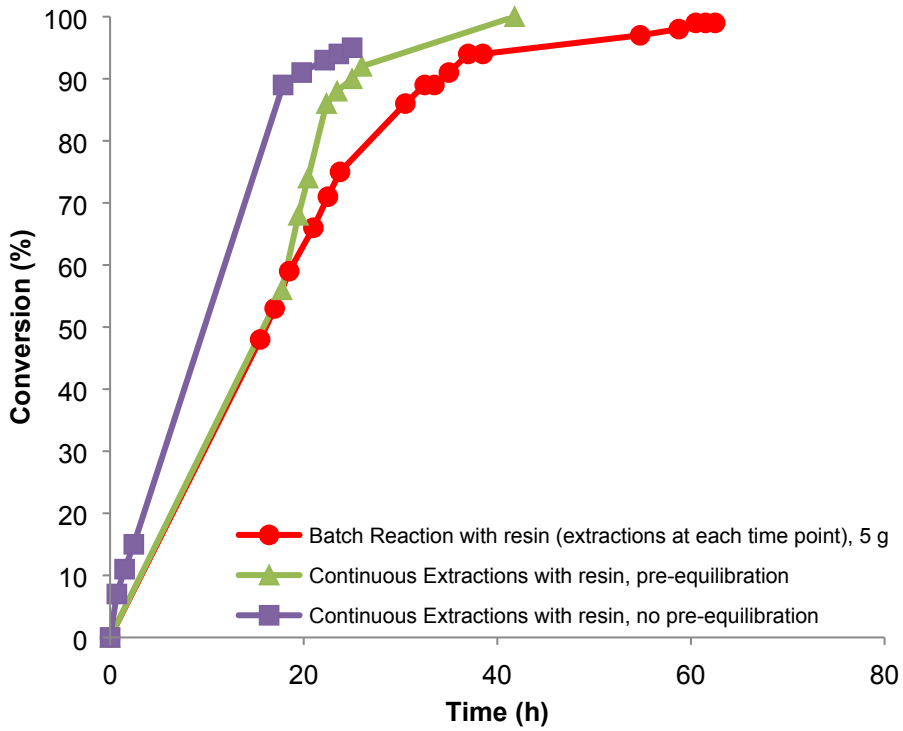
Figure 4. Continuous extractor design.



With a suitable design for the continuous extractor in hand, initial experiments were run to test feasibility. Two experiments were performed at 500 mg scale to evaluate the most efficient way to use the continuous extractor. In one experiment, a pre-equilibration period was utilized, where the continuous extractor was turned off for the first 18 h, to allow the reaction to reach its initial equilibrium conversion. In a second experiment, the continuous extractor was turned on from the beginning of the reaction. As shown in Figure 5, both reactions proceeded noticeably faster than the 5 g batch reaction. The difference in reaction time between these two reactions was most likely due to using a longer than necessary pre-equilibration time, as the reaction likely stalled

long before the continuous extractor was started. In light of these promising results, it was hypothesized that the reaction could be even faster if a soluble acid was used in place of the acidic resin. Once the MeOH phase exits the mixer, it is not exposed to the acidic resin and the deprotection reaction stops. Therefore, any time the MeOH solution resides in the tubing or the addition funnel, no reaction occurs, which unnecessarily increases the time required to reach complete conversion. This change would potentially reduce reaction time, which would in turn lower the amount of *n*-heptane used to reach 100% conversion.

Figure 5. Reaction conversion: batch conditions vs. continuous extractor.



To test this hypothesis, the reaction was set up as before (no pre-equilibration period was used since it did not seem to positively affect the rate of the reaction with the

acidic resin), using p-TSA as the acid instead of the acidic resin. As shown in Figure 6, the reaction reached 100% conversion in less than a day and was significantly faster than the corresponding reaction with the acidic resin. With these results in hand, the reaction was scaled up to 5 g (see Table 3, Entry 1 for results). In this reaction, the reactor initially contained 25 mL (5 volumes) *n*-heptane, assuming that this would allow for quicker removal of the cyclohexanone dimethyl ketal (**7**) from the reaction solution. While the potency adjusted yield (PAY) of the lactone diol (**4**) was as expected (63%, see **Experimental Section** for procedure to synthesize lactone diol **4** following completion of the deprotection reaction), the final amount of *n*-heptane used (175 volumes) was excessive for a commercial process. The process was thus improved to reduce the amount of *n*-heptane being used.

Figure 6. Reaction conversion: acidic resin vs. p-TSA with the continuous extractor.

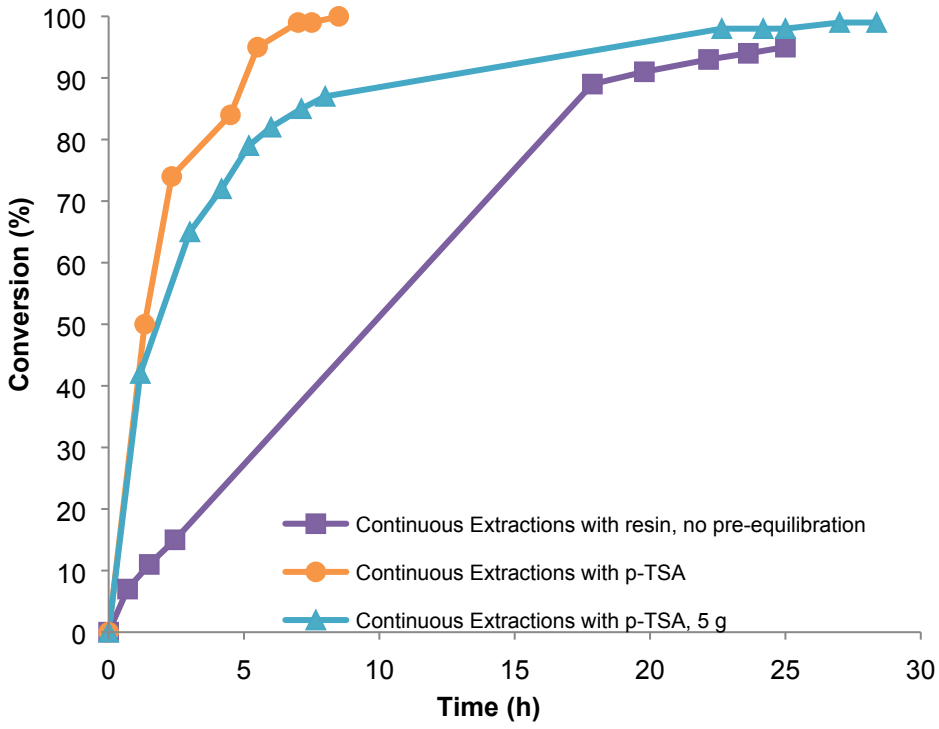
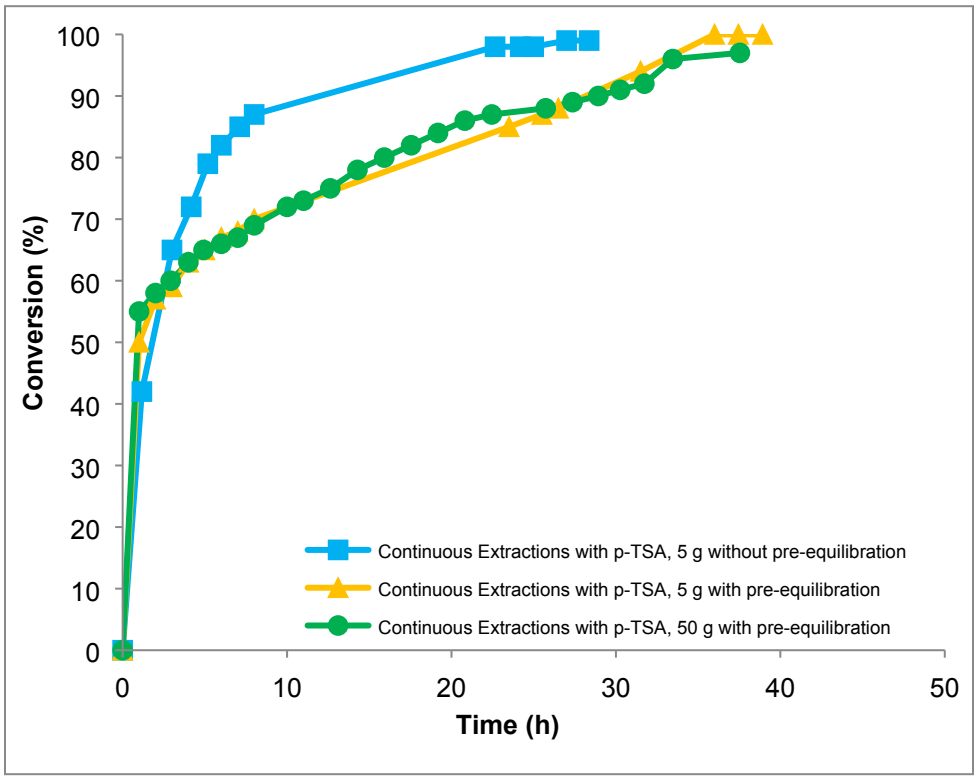


Table 3. Summary of results from scale-up/improvement of the continuous extractor system.

Entry	Scale	PAY Lactone Diol (4)	HPLC Purity/Potency	Volumes *n*-Heptane Used
1	5 g	63%	98.9 peak area% purity	175
2	5 g	69.3%	98.8 wt/wt% potent	60.5
3	50 g	63.8%	97.9 wt/wt% potent	51.4

The reaction was modified, such that a 3 h pre-equilibration period was incorporated (continuous extractor turned off), but the *n*-heptane pump was used to dose 5 volumes of *n*-heptane over the course of the pre-equilibration period. After the equilibration period was over, the pumps to and from the extractor were turned on while maintaining the same flow rate of fresh *n*-heptane over the remainder of the extraction. These conditions led to a similar PAY of lactone diol **4** (69.3%); however, significantly less *n*-heptane (60.5 volumes) was used (Table 3, Entry 2). The reaction did take longer to reach full conversion (Figure 7), but since the reaction mixture appeared to be stable over time and cycle time was not considered the driving cost factor for the scale-up, it was deemed less of a concern than the *n*-heptane consumption. Finally, the reaction was scaled up to 50 g, using the same conditions, which led to similar PAY for lactone diol **4** (Table 3, Entry 3). Gratifyingly, being able to use higher flow rates on larger scale led to a similar overall reaction time (see Figure 7) as on the 5 g scale and even less *n*-heptane being used (51.4 volumes).

Figure 7. Plot comparing conversion of various scale-up conditions for the continuous extractor.



Conclusion

We have developed a simple, fit-for-purpose scalable continuous flow extraction to drive an equilibrium-limited reaction to completion, addressing an important project challenge. We demonstrated proof-of-concept at lab scale with soluble and heterogeneous acid catalysts and demonstrated ways to reduce the total amount of solvent used over the course of the extraction. The established extraction protocol was successfully demonstrated at 50 g scale. The approach described here is flexible and suitable for a number of processes, but is especially appropriate for situations where starting material and development time are limited, and the reaction must be driven to completion. This method is customizable to fit the appropriate balance between cycle time and solvent

usage and cost. The fact that this continuous extractor can be set up using readily available glassware and equipment ensures that this approach can be readily adapted to other processes that would benefit from continuous extraction.

Experimental Section

General Methods. All commercially available materials and solvents were used directly without further purification. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded with a Bruker spectrometer. See Supporting Information for HPLC and GC conditions used during experiments.

Representative Experimental Procedure for Deprotection/Lactonization Reaction (4). A 2 L 4-neck round bottom flask equipped with a thermocouple and an overhead stirrer was charged with cyclohexylidene ester starting material (**2,** 50.0 g, 1.00 equiv), *p*-toluenesulfonic acid monohydrate (2.59 g, 0.100 equiv), and MeOH (500 mL, 10 volumes) and set up with a continuous extractor as shown in Figure 4 (see Supporting Information for pump settings and types). A 25 mL pressure-equalizing addition funnel was used as the settler in Figure 4 to separate the MeOH and *n*-heptane phases. It was filled with 25 mL of *n*-heptane (enough to reach the sidearm) so that when solution was pumped into it, the *n*-heptane overflow dripped through the sidearm and into a waste flask. The solution was heated to 30 °C and stirred with the fresh *n*-heptane pump turned on (See Supporting Information for pump flow rate) and the reaction solution to extractor and MeOH solution recycle pumps turned off. After 3 h, the reaction solution to extractor and MeOH solution recycle pumps were turned on (see Supporting Information for pump flow rates). The reaction was stirred at 30 °C with the continuous extractor

running until <1 PA% total of the cyclohexylidene ester starting material (**2**) and the methyl ester cyclohexylidene starting material (**6**) were observed via HPLC analysis. The continuous extractor setup then was flushed with MeOH. The MeOH flush from the pumps and tubing, the solution remaining in the addition funnel, and the solution in the 2 L 4-neck round bottom flask were combined and transferred to a separatory funnel. The layers were separated and the MeOH layer (bottom layer) was washed twice with 250 mL (5 volumes) *n*-heptane. The MeOH solution was then partially concentrated under reduced pressure at 35 °C. To the partially concentrated MeOH solution, 250 mL (5 volumes) *n*-PrCN was added and then the solution was concentrated to an oil under reduced pressure at 35 °C. Butyronitrile (250 mL, 5 volumes) was added to the oil and the solution again was concentrated to an oil under reduced pressure at 35 °C. Butyronitrile (50 mL, 10 volumes) was then added to the oil a final time. The *n*-PrCN solution was heated to 80 °C while sparging with N_2 until <5 PA% total of the ethyl ester triol (**3**) and the methyl ester triol (**5**) remained via HPLC analysis. The solution was cooled to room temperature overnight. After cooling, the solution was partially concentrated under reduced pressure at 35 °C to 80.17 g. The solution was then passed through a 100 g (200 wt % relative to cyclohexylidene starting material **2**) silica plug, eluting with *n*-PrCN and collecting ~250 mL fractions. The fractions containing lactone diol **4** (as determined by HPLC analysis) were collected and partially concentrated under reduced pressure at 35 °C to 172.33 g. Chlorobenzene (250 mL, 5 volumes) was added to the *n*-PrCN solution, which was then partially concentrated under reduced pressure at 35 °C to 138.2 g. Chlorobenzene (250 mL, 5 volumes) was added again and the solution was partially concentrated under reduced pressure at 35 °C to 234.96 g, at which point a

brown oil was observed crashing out of solution. The mixture was seeded with crystalline lactone diol **4** (270 mg) from a previous reaction and then partially concentrated under reduced pressure at 35 °C until a brownish orange solid was observed crashing out of solution. The slurry was then stirred at room temperature as 150 mL (3 volumes) of dichloromethane was added slowly, causing more solid to crash out of solution. The resulting slurry was stirred at room temperature for 2 h and then cooled to 0 °C and stirred for an additional 45 min. The slurry was then filtered while still cold and the solids were washed twice with 50 mL (1 volume) of dichloromethane. The off-white solids were collected and dried in a vacuum oven at 50 °C for 26 h to yield 20.31 g (63.8% potency adjusted yield, 97.9 wt/wt% potent via HPLC analysis) of lactone diol **4** as an off-white solid. The solid contained 1.1 mol% p-TSA but was not purified further, as it was determined that p-TSA had no impact on downstream chemistry. ^{1}H NMR ($(CD_3)_2SO$, 600 MHz) δ_H 6.92 (s, 1H), 4.56 (dd, J = 11.3, 5.0 Hz, 1H), 4.44 (tdd, J = 5.3, 3.9, 1.5 Hz, 1H), 3.78 (dd, J = 12.7, 3.9 Hz, 1H), 3.68 (dd, J = 12.7, 5.4 Hz, 1H). ^{13}C NMR ($(CD_3)_2SO$, 150 MHz) δ_C 166.45, 166.28, 96.38, 94.62, 85.43, 73.52, 73.42, 58.97.

Partition Coefficient Studies. The partition coefficient studies were carried out by adding approximately 100 mg of 1,1-dimethoxycyclohexane (**7**) to a vial followed by MeOH and either *n*-hexane, *n*-heptane, or cyclohexane. The vials were then shaken vigorously and the layers were allowed to settle. The vials were allowed to sit over the weekend at room temperature and then an aliquot from each layer was analyzed via GC to determine the concentration of the 1,1-dimethoxycyclohexane in each solvent.

Supporting Information

The Supporting Information contains experimental setup diagrams and pictures, pump types and settings used, and detailed analytical data including methods and spectra.

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Author Contributions

†Both authors contributed equally to this work

Notes

The authors declare no competing financial interest. This study was sponsored by AbbVie Inc. AbbVie contributed to the design, study conduct, financial support and interpretation of data, writing, reviewing, and approving the publication. Michael Tudesco, Eric Moschetta and Eric Voight are employees of AbbVie Inc.

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