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Multikilogram Synthesis of 4-D-Erythronolactone via Batch and Continuous Processing

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ABSTRACT: The conversion of a batch process to continuous (flow) operation has been investigated. The manufacture of 4,D-erythronolactone at kilogram scale was used as an example. Fully continuous processing was found to be impracticable with the available plant because of the difficulty in carrying out a multiphase isolation step continuously, so hybrid batch−continuous options were explored. It was found that very little additional laboratory or process safety work other than that required for the batch process was required to develop the hybrid process. A hybrid process was chosen because of the difficulty caused by the precipitation of solid byproduct during the isolation stage. While the project was a technical success, the performance benefits of the hybrid process over the batch were not seen as commercially significant for this system.

INTRODUCTION

The replacement of batch processing with continuous and/or batch−continuous hybrid processes has been a theme attracting significant interest for some years in the fine/specialty chemicals and pharmaceuticals industries.[1] The potential to access more efficient, safer, and less polluting processes is attractive to sectors that face a range of regulatory and commercial pressures. However, adoption has been slower than many had hoped. There are a variety of reasons for this, for example existing batch capital assets, a perception of difficulty, fear of the novel, lack of suitable resources to explore the possibilities, and concerns about the potential time to develop continuous processes. In many cases where a serious exploration has taken place (or even when a continuous process has been implemented) the business benefits are often not found to be overwhelmingly attractive versus the traditional batch options. It has recently been estimated that the pharmaceutical industry has invested $600 million in continuous processing research but has rather little to show in terms of benefits.[2]

The work reported here is part of a broader programme in the investigation of the opportunities and challenges for innovative (and often continuous) processing for high-value chemicals. The aim is to overcome at least some of the barriers to uptake through developing and making available experience and comparative studies at a credible scale.

This work set out to explore the conversion of a simple batch process to continuous operation, and to demonstrate batch and continuous processes at a small pilot scale The production rate was chosen to deliver the equivalent quantity of product to a 2−3 kg batch process. This allowed for a direct comparison of efficiency between the batch and continuous process. There were multiple objectives in doing this:

- To provide a real example for the comparison of batch and continuous processes making the same product
- To understand where and how the deployment of continuous processing brings benefits and problems
- To act as a motivating example for the design and operation of a multipurpose continuous facility [though this is not described in any detail here]
- To explore how various process development and scale-up tools [PAT, calorimetry, laboratory experimentation, knowledge capture tools] performed in the batch-to-continuous conversion and to look for gaps where new methods and tools could be useful

The synthesis of 4,D-erythronolactone was used as the working example. A batch process was adapted from the literature using normal practices in scale-up. The approach to continuous process design was broadly to convert the batch process step-by-step to continuous stages, looking to make only small changes (for example in concentration to maintain mobility), and avoiding the presence of solids where practicable. Kinetic and thermal measurements were used to support sizing and/or rating of equipment—and where practicable the ones used were those that had already been carried out for development of the batch process.

Broadly, the example is seen as equivalent to the conversion of an existing batch process based on reasonable (though not excessive) process understanding already available. The aim was not to develop an "optimal" process from first principles. This is a realistic position for many in the fine chemicals and pharmaceuticals industry, where the opportunity to obtain step change improvements in an existing process performance might be considered to address cost or regulatory concerns.

Cohen et al.[3] published a 1 L laboratory-scale batch procedure for the synthesis of the isopropylidene acetal of 4-DEL which also formed the basis for a patented procedure towards the total synthesis of Swainsonine.[4] A 20 L laboratory-scale procedure (704 g) was published by Dunigan[5] in 1991 following Cohen's procedure (Scheme 1).

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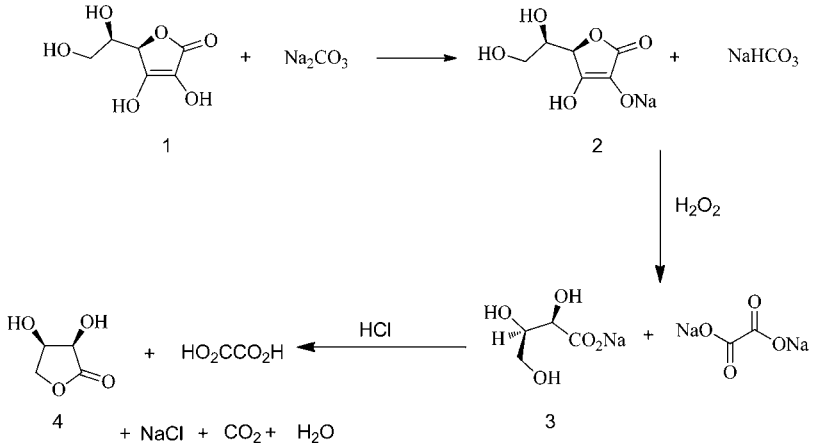
Scheme 1. Salt formation [1 to 2], oxidation [2 to 3] and cyclisation [3 to 4] reactions



This example was chosen as a suitable target as the compound is a potential building block in the synthesis of many natural product molecules and the synthetic route is a simple peroxide oxidation carried out in aqueous solution. It also demonstrated sufficiently complex process behaviours to be a challenging problem: multiple phases, the potential to form sticky solids, some slow and some fast reactions, and nonfacile separations processes. It was not intended to give an easy target but rather a more realistic representation of the large number of processes that have solids as raw materials, intermediates, or products.[6]

Approach to Continuous Process Development. Our first approach to design of the continuous process is to match closely the steps of the (existing) batch process, modifying only where necessary. This has the advantage of reducing or eliminating the need for additional process development studies beyond the batch method, which appears to reduce development time assuming, that a viable process emerges. Of course, this reduces the chance of identifying significantly different processing steps. However, there will be many existing processes where rapid evaluation to identify the potential benefits of conversion to a continuous process would be a worthwhile exercise.

The division into process steps was to some extent arbitrary. The analysis used the BRITEST[a] tools, and in particular the Process Definition Diagram to abstract the key features of the process.[7,8] Note that the PDD is independent of whether the process is operated in batch in continuous mode – it is an equipment-independent representation. Using such a representation matching of the process steps to continuous equipment can be carried out, based on the process engineers' experience of the capabilities of the relevant continuous equipment. As a result of our learning in this and other projects, some generic learning is being deployed to help in this. Some common aspects of the approach are as follows.

- Maintaining reactants and byproduct in solution with appropriate concentration to avoid precipitation for continuous process.
- The use of predissolved solid feeds rather than solids addition. This avoids the use of difficult and expensive continuous solids feeding and the use of slurries as feeds. Of course, this would require (either on the manufacturing site or at a supplier's site) the dissolution operation. However, this is usually a relatively simple operation and one that probably does not need a high-cost process vessel (such as a batch reactor).
- Transfer/motion of slurries from step to step is avoided where possible; where the solids cannot be used fully dissolved, it is preferable to use them in something like a stirred tank, where the design of the reactor can prevent solids passing forward to the next unit where other operations are occurring.
- Taking account of the reaction time through the provision of a suitable residence time for the reaction (e.g. under the same conditions of temperature and composition, a true batch reaction with a completion time of 20 min would require a continuous reaction residence time in plug flow of 20 min). In making this assessment it is important to consider whether the batch and continuous systems provide equivalent conditions. For example a continuous stirred tank reactor has its contents mostly at the exit concentration while a batch reactor will necessarily spend some time with at least reactant at a high (initial) concentration. In general, a detailed kinetic model would only be attempted if oversizing of the continuous reactor would lead to reduced performance or high cost, and this can often readily be assessed using batch experimentation and prior knowledge, without the need for detailed modelling.
- While a key feature of developing a batch process is to ensure volume efficiency in order to maximise the yield per run in a given plant, this can be relaxed in a continuous plant, especially where reactions are inherently fast.
- Process steps with two (and, even worse, more) phases are to be avoided where practicable. In a continuous system it is a significant challenge to maintain/control the desired phase ratio except in some relatively simple cases where one phase is used to exhaustion or is held stationary. Where possible, it is useful to suppress at least one of the phases. In the example that follows, control of gas formation was required to reduce problems with flow in the continuous system.

BATCH PROCESS DEVELOPMENT

First, work was carried out to establish and operate the batch process at a 60 L scale (this being the size of the available processing vessels). Initial laboratory familiarisation trials were carried out, and the literature procedure was found to proceed as expected with some minor modifications (discussed below)

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to ensure safe and effective handling at scale both in batch and continuous processes.

The procedure published by Cohen and co-workers[3] was found to produce a significant level of carbon dioxide evolution during both the pH adjustment and oxidation stages. This was due to the single charge of sodium carbonate giving a large excess throughout the reactions. During mixing of this material into the D-isoascorbic acid, local excesses of acid caused formation of carbon dioxide gas, resulting in frothing of the reaction mixture.

In order to achieve better control of the oxidation reaction in a large-scale process we ensured that the mixture was maintained at optimum suitable pH for the reaction to occur by simultaneous dosing of sodium carbonate as a solution during the peroxide addition. Hydrogen peroxide, 30% solution, has a pH of 3−3.5 and is known to undergo rapid decomposition above pH 10. Additionally, it was seen that the reaction stalled at pH below 5.0. We chose to maintain pH 8.5−9.5 since this gave a clean and rapid reaction with no gas evolution observed. This pH was maintained by concurrent addition of a 20% solution of sodium carbonate during the hydrogen peroxide addition. By maintaining sufficient sodium carbonate addition to facilitate the reaction we aimed to minimise peroxide decomposition. Thus, a lower peroxide excess would be required, minimising handling, operator exposure, and cost of reagents.

The procedure from the literature also required destruction of excess hydrogen peroxide using either activated carbon or manganese dioxide. During our initial development work, we chose simply to raise the pH to such a level using dilute aqueous sodium hydroxide to destroy any excess peroxide in a clean and controlled manner. Hydrogen peroxide is known to decompose under basic conditions, particularly at high ionic strength and temperatures greater than 30 °C.[9]

In order to minimise any accumulation of peroxide during the reaction we chose to start the oxidation reaction at 40 °C (±3). The development experiments were observed to proceed well with no significant exotherm or gas evolution observed.

During development work, when residual peroxide was detected at the end of the reaction using peroxide test strips, addition of a dilute sodium hydroxide solution to pH > 10 was found to give a negative test. Even without the addition of hydroxide, it was also found that stirring the reaction mixture at 40 °C for >1 h) was found to decompose any excess reagent since the pH was already above neutral. At pilot scale, the stir-out was used as a default, with the provision for raising pH if residual peroxide remained. The latter was not required in practice.

Once no peroxide could been detected, acidification to form the desired lactone was carried out using 6 M hydrochloric acid to pH 1. It is reported in the patented procedure[4] that a deterioration in product quality at low pH is observed. However, in our hands it was found that pH 1−1.5 was essential in obtaining good yield and product quality and in particular to ensure the correct product was formed, avoiding the precipitation of a sticky intermediate product obtained at pH 2−4 during concentration.

Isolation of the product from the solution was initially carried out by the procedure used in the early-stage development based on the method of Cohen et al.[3] where the aqueous solution was concentrated to dryness under reduced pressure (<0.6 mbar). The resultant semisolid was reslurried repeatedly with ethyl acetate to separate the desired erythronolactone from sodium chloride and oxalic acid byproduct. Concentration of the combined ethyl acetate fractions to low volume then afforded crystalline 4-D-erythronolactone. Evidently, this process is unsuitable for larger-scale production (at least without highly specialised equipment), and the process had to be modified for batch operation.

Standard processing equipment such as agitated filter dryers, although considered, were not found to be appropriate for this process for a number of reasons. First, the crude product and byproduct mixture had a tendency to form a sticky solid which was not readily transferrable. Second, during our development work it was found that the product had extremely high miscibility with water, close to that of the oxalic acid byproduct, and thus, it was chosen to investigate the possibility of scaling up the hot reslurry procedure for large-scale processing.

We determined that complete removal of water was unecessary for separation of the product from the byproduct, and we were able to concentrate the acidic solution to 10−15% of the original volume at 10−20 mbar, thus affording a stirrable slurry. The slurry was hot extracted with ethyl acetate four times to isolate the product in solution, which could then be crystallised and filtered. This gave a process that was viable to operate at the 60 L scale.[b]

Process Studies. The process was evaluated and confirmed using a Mettler Toledo RC1e at a scale of around 100 mL. The enthalpy of the oxidation reaction was measured to be significant at 760 kJ/mol, leading to a potential adiabatic temperature rise of 110 K. The oxidation reaction as seen in the RC1 proved to be rapid and addition rate controlled. (Figures 1 and 2)

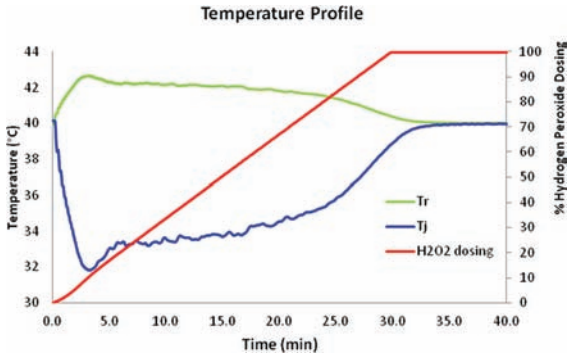

Figure 1. Results from RC1 calorimetry showing jacket and reactor temperatures as a function of time during and after addition of hydrogen peroxide.

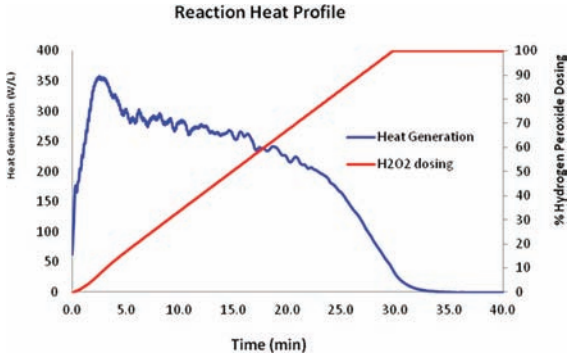

Figure 2. Heat generation vs addition of peroxide as measured in the RC1 calorimeter.

A low thermal accumulation of less than 1% was observed which indicated that the oxidation was fast and readily addition rate controlled, provided the heat generated could be removed by the cooling capacity of the reactor. The data obtained from

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the RC1 run was then taken through to process safety evaluation and both batch and continuous process and equipment design.[c]

The RC1 studies were used to estimate the predicted behaviour on a 60 L scale in the batch reactor.

Following the RC1 experiments, adiabatic calorimetry using an automatic pressure tracking adiabatic calorimeter (APTAC) was carried out. This indicated that in the event of dosing control failure there was the potential for a pressure buildup exceeding 5 bar accompanied by a rapid temperature increase of ~90 °C (see Figure 3). The resultant runaway reaction is

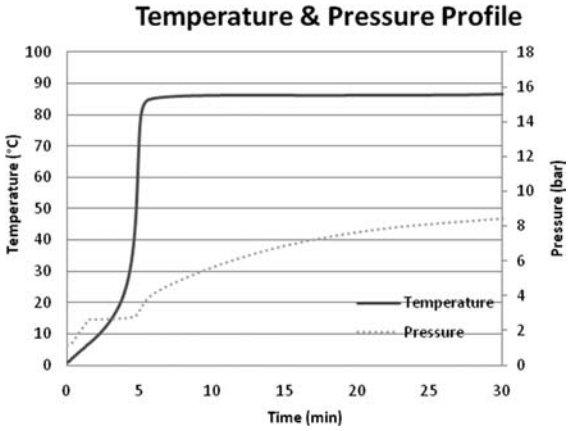

Figure 3. Study of the oxidation reaction by adiabatic calorimetry.

very rapid with a temperature increase of 140 °C/min accompanied by a pressure increase of 1.6 bar/min. This leads to the use of semibatch addition of peroxide to the system as a means of controlling the exotherm.

Stability of the isolated solid lactone product was examined by DSC and TGA (Figures 4 and 5). The product was seen to

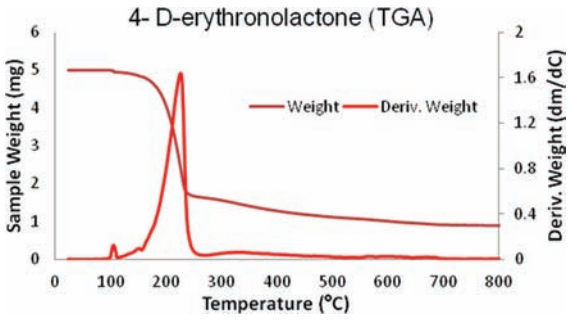

Figure 4. Thermogravimetry of 4,D-erythronolactone.

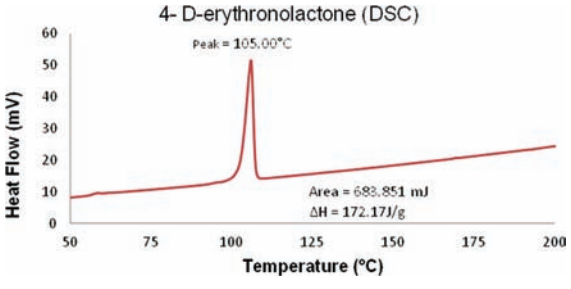

Figure 5. Differential scanning calorimetry of 4,D-erythronolactone.

decompose at approximately the reported melting point of 106 °C, but the decomposition did not indicate any serious process safety issues, only a loss of product quality if overheated.

A full HAZOP and preparation of a detailed process batch record was carried out, and the process was scaled up to 60 L batch plant.

Analytical Development. No existing procedure for in-process analysis was available, and in the published procedures[3−5] the final product was analysed by ^{1}H NMR, GC purity, and optical rotation. Initially, we chose to examine the possibility of following the oxidation reaction by HPLC and develop a procedure for inline Raman analysis simultaneously. Unfortunately, overlapping peaks meant that we were unable to use HPLC successfully for examining the crude reaction mixture even though solutions of the individual components showed good peaks (i.e. the components were visible to the detector). Raman spectroscopy again showed some overlapping components, but we were able to follow the reaction through from the initial salt formation to the oxidation through the use of BTEM curve resolution and multiple linear regression.

In situ Raman spectroscopy was used to investigate the various stages of 4-DEL synthesis in the laboratory. Figure 6 shows changes in the Raman vibrational peaks across the range ~300−1800 cm^{-1} during isoascorbic acid dissolution, neutralization (salt formation), oxidation, and acidification stages. Offline multivariate chemometric data analyses, in particular, the band-target entropy minimization (BTEM) curve resolution algorithm[10,11] and multilinear regression[12] were used to analyse the in situ Raman spectra obtained. In spite of the fact that Raman peaks are overlapping, BTEM successfully recovered the pure component Raman spectra of sodium D-isoascorbate and its oxidation product upon reaction with hydrogen peroxide. Their relative concentration profiles subsequently obtained by multilinear regression showed that the oxidation reaction between sodium D-isoascorbate and hydrogen peroxide was not as instantaneous as thermal data from the RC1 had suggested. (Figure 7) A time lag of about 7.5 min was observed between the time where sodium isoascorbate was seen to fall and the oxidation product (erythronic acid sodium salt) started to be formed significantly. The reasons behind this are not yet clear (most likely that the initial exothermic oxidation step is followed by a slower molecular rearrangement), but the results demonstrate that calorimetry analysis is not always able to give us a full understanding of the reaction progress.

The Raman spectra for the final acidification stage showed changes in vibrational peaks as the reaction progressed. However, for our chosen reaction conditions, the concentration of the final lactone product after acidification was too low to be detected by Raman spectroscopy. Nonetheless, the observed changes in the Raman spectra (i.e. decrease of the erythronic acid salt) were helpful for monitoring reaction progress as the pH of the mixture decreased with hydrochloric acid dosing.

For final product analysis we chose GC as our method using an Agilent DB-1701 column. GC analysis also proved to be the simplest quantitative method for estimating a yield from the crude product solution before isolation using a simple calibration curve.

■ DEVELOPMENT OF A CONTINUOUS PROCESS

For the continuous process we modified conditions to maintain the entire reaction part of the process [including the ring closure] in the solution phase. This was done by ensuring that all solutions fed into the system were below saturation at room

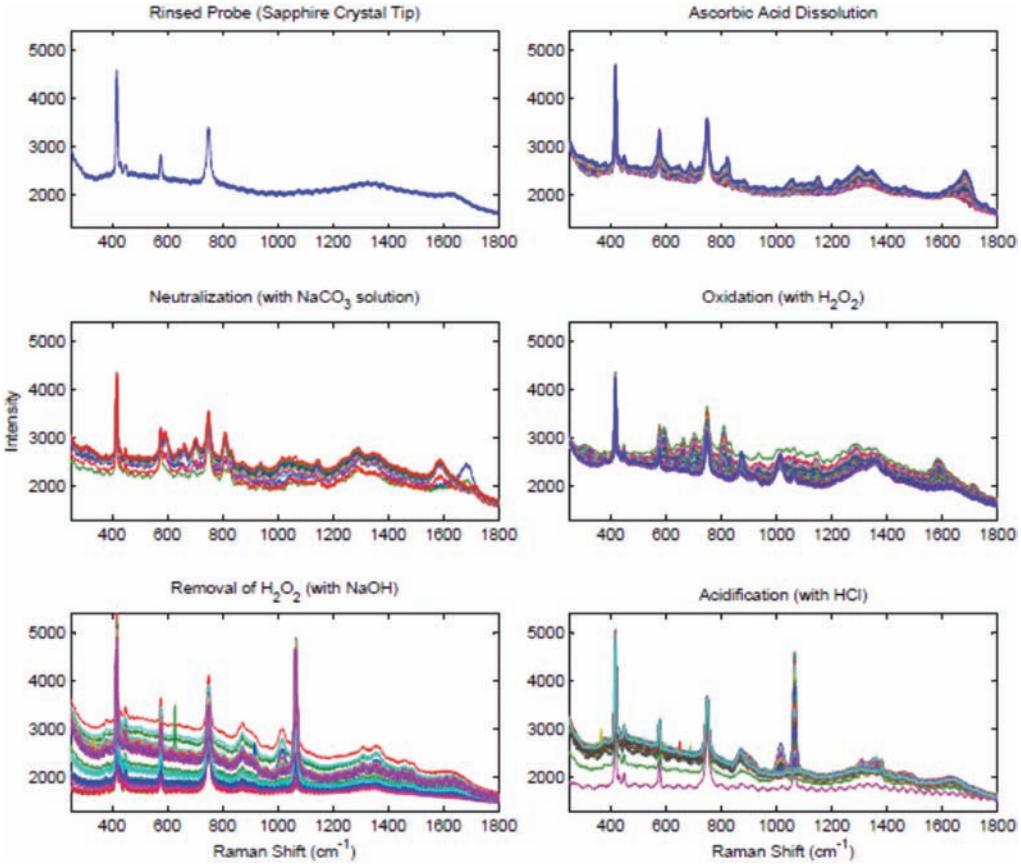

Figure 6. Raman spectra taken during lab-scale experiments.

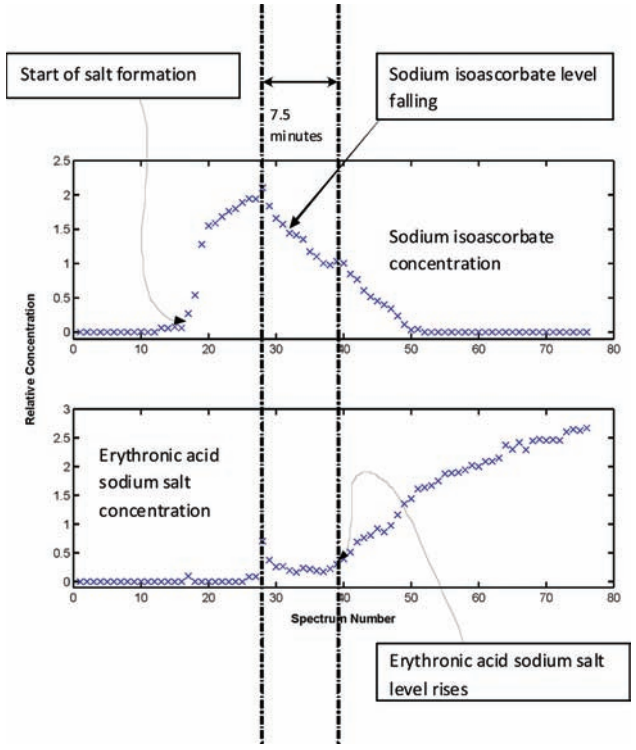

Figure 7. Multilinear regression curves from Raman measurements of the salt formation and oxidation stages.

temperature. This also avoided potential problems of precipitation in the feed system. Of course, this does not guarantee that solids will not form in the process, although in this case no further dilution was required to avoid precipitation.

The salt formation and pH adjustment reactions are essentially instantaneous with their rates controlled by mixing. There are no problems with over-reaction or change in temperature, so simple static mixers were suitable, or other devices such as a T-mixer could have been used. The intensity of mixing and residence time are not of importance in this case. However, the oxidation step was more complex, requiring both temperature and composition control. The observed lag in appearance of erythronic acid salt during the oxidation was important as it required a longer residence time for the oxidation step. Fortunately, there was no significant issue with over-reaction so a larger-than-necessary vessel could be used. For a longer residence time we considered the use of an oscillatory baffled reactor, but it was more convenient to use one of the stirred-tank 60 L reactors.

The acidification step (cyclisation) is problematic in that precipitation of solids including some product is seen to occur at less than 10 volumes of water with respect to the starting D-isoascorbic acid. This could be dealt with by dilution, but the problem is simply moved downstream to the next step. Isolation was an issue in that a solvent exchange into ethyl acetate was required, again resulting in the precipitation of sodium chloride and oxalic acid byproduct, with some product among the solids. No suitable equipment was available that could straightforwardly deliver the combination of mixing, liquid extraction, and solids suspension/separation. There are also concerns about the possibility of maintaining control of phase ratios in a three-phase (at least) system. This prompted the decision to design a hybrid process utilising a continuous front

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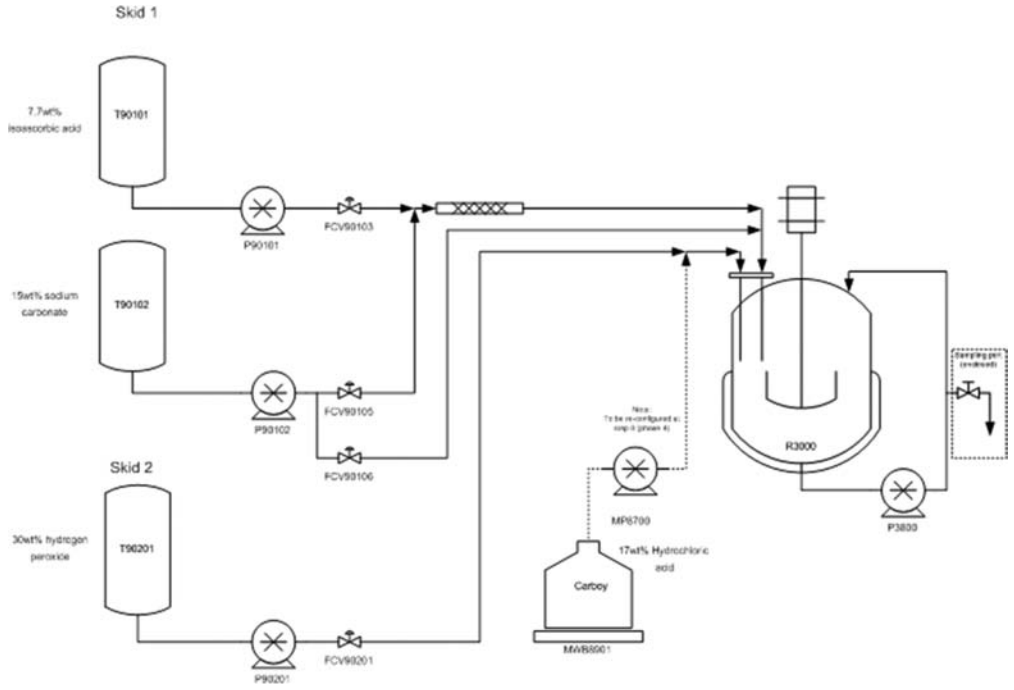

Figure 8. Hybrid process configuration A: continuous salt formation, fed batch oxidation.

end of the process feeding a batch process for product recovery.[d]

A liquid–liquid extraction experiment was carried out at a temperature of 60 °C to determine the partition coefficient. With high solubility of 4DEL in water as compared to that in ethyl acetate, a partition coefficient of less than 0.1 was not surprising. Batch liquid–liquid extraction is not ideal due to the large volume of solvent and the high number of extractions required. A solvent-swap operation was carried out in an attempt to replace water with ethyl acetate and create a slurry of byproduct and 4DEL in the solvent which then can be filtered and reslurried to further extract 4DEL in the solids. This proved unsuccessful due to the strong affinity of compound to water and possibly due to the long exposure of the product to elevated temperature which created "sticky" solids on the side of the vessels. The procedure not only resulted in a very poor volume and time-efficient process but also achieved very low yield of approximately 20%.

At the low concentration chosen for the continuous process, it was found that a crude solution (post acidification) of 4-D-erythronolactone was stable for several weeks at ambient temperature and no discolouration was observed. The batch process was run with an initial charge of 7 volumes of water with regards to D-isoascorbic acid, giving a final reaction mixture of double the concentration of that obtained during the continuous. This in turn gave a higher concentration of acid in the batch process, leading to conditions under which the lactone can ring open to give erythronic acid and undergo subesquent self-esterification leading to dark-coloured polymeric material.

However, if less acid was used in giving a higher pH as reported in the patented procedure, we found that incomplete cyclisation of the erythronic acid sodium salt was obtained, also leading to the formation of sticky polymeric materials.

The continuous process allowed splitting of the process where the crude product could be stored safely while awaiting batch recovery of product. However, the concentrated (batch) solution degraded in a matter of days to afford a darker, off-white product.

Two main hybrid processes were tried at scale. In one (configuration A) the isoascorbic acid was co-fed with peroxide to a batch reactor and the process run until sufficient material had been accumulated so that acidification would fill the vessel. The process was then carried through as a batch process. This used the configuration shown in Figure 8.

The second process involved using a 60 L reactor as a continuous stirred tank reactor (configuration B). Here, after an initial build-up of oxidising material in the reactor, flow out of the vessel into another 60 L vessel was started at a rate that maintained the level in the first reactor. In this configuration the oxidation is truly continuous, and the volume of the pipe between the oxidation reactor and the acidification reactor is important to ensure that the oxidation is essentially complete. The acidification step was carried out in a static mixer en route to the second vessel—which acted as a crude product receiver/storage. Configuration B is shown in Figure 9.

■ OPERATION OF THE HYBRID PROCESSES

Configuration A. This "limited" application of continuous processing allowed us to check the start up dynamics of the system at pilot scale through use of PAT. In situ Raman instrumentation was incorporated into various points of the process line, including the hydrogen peroxide feed line and the recirculation loop of the reactor. During the preliminary testing, the Raman spectroscopic measurements were integrated with the real-time monitoring of process variables[12] (flow rates, volumes, pressures, temperatures, etc.) through in-house programming of the Siemens WinCC and Siemens PAT (SiPAT) software. Multilinear regression of the collected Raman spectra was done using script files executed on a remote computing running MATLAB R2009b that is integrated with SiPAT. The regression was performed for the oxidation phase of the 4-DEL synthesis using the BTEM pure component spectra obtained during laboratory in situ Raman experimentation, and the

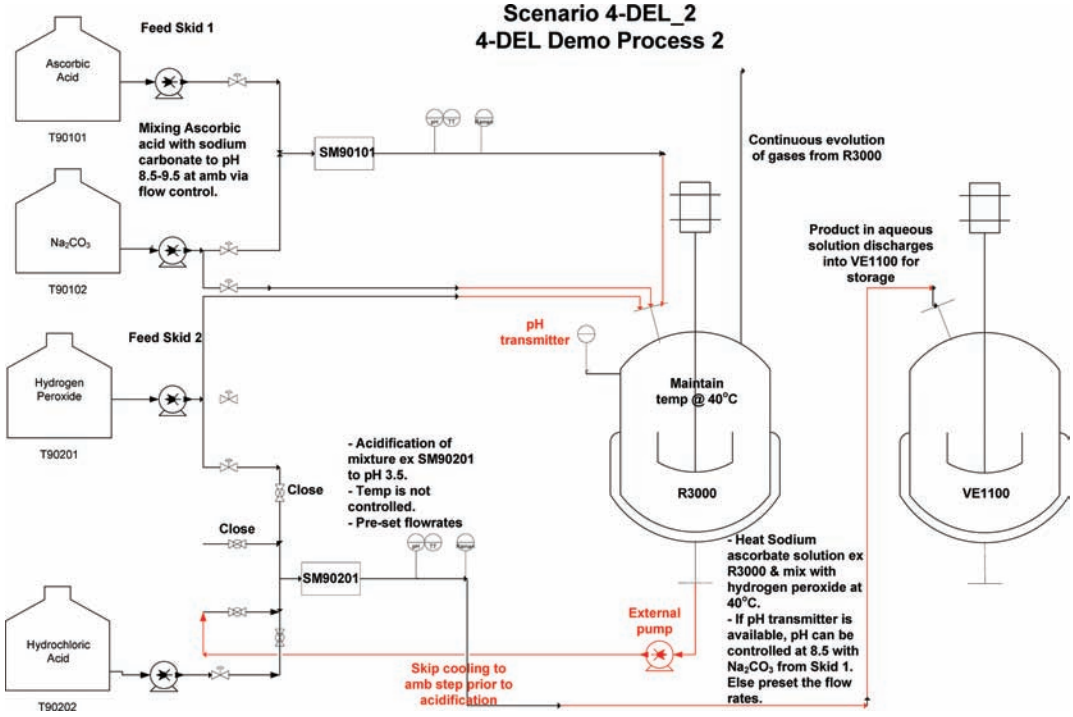

Figure 9. Configuration B: continuous oxidation and acidification.

Table 1. Flow rates used in configuration A, together with masses used over a 2 h run

stage	species	% w/w solution	flow rate (kg/h)	flow rate (g/s)		flow rate (mol/s)	mol equiv	total mass (kg)
salt formation (phases 1 and 3)	D-isoascorbic acid	7.7	9.60	2.67	0.21	0.0012	1.0	19.20
	water				2.46	0.1367		
	sodium carbonate	15	3.30	0.92	0.13	0.0013	1.17	6.6
	water				0.77	0.0434		
oxidation (phases 2 and 3)	hydrogen peroxide	30	1.05	0.29	0.09	0.0026	2.2	2.09
	water				0.20	0.0113		
	sodium carbonate	15	6.38	1.77	0.27	0.0025	2.2	12.76
	water				1.51	0.0837		
acidification *batch phase 4	HCl	18	4.17	1.16	0.21	0.0057	4.9	8.34

relative concentration of the sodium isoascorbate salt was data logged in real-time into the WinCC SCADA database.

During operation there were four operating phases:

- Phase 1: Salt formation/pH adjustment of D-isoascorbic acid with sodium carbonate. This reaction was carried out continuously in a static mixer, with the pH of the product solution measured by an inline pH probe and the flow of carbonate adjusted to control it. Sodium ascorbate was fed into R3000 until 20 L had accumulated.
- Phase 2: The generation and flow of sodium ascorbate was stopped. Dosing into R3000 of hydrogen peroxide (30% aqueous solution) and sodium carbonate was started from a second feed skid. The reaction temperature of 40 °C was maintained in R3000 by temperature control using a heat/cool loop on the jacket. Reaction monitoring using a 1/4-in. in situ Raman probe was used to observe disappearance of the sodium salt and formation of the straight-chain erythronic acid salt.
- Phase 3: Once the Raman indicated completion of the oxidation in R3000, the flow of ascorbate was restarted, and simultaneous addition with the peroxide and carbonate was continued. This was the period of "steady state" continuous operation, accumulating product in R3000.
- Phase 4: Once the reactor had reached the desired level, all additions were stopped and hydrochloric acid could be dosed into R3000 to perform the ring closure.

The flow rates and stoichiometric ratios of each component are shown in Table 1.

As a result of the real-time monitoring, it was possible to observe the oxidation (stages 2 and 3).

Figure 10 indicates that in situ Raman monitoring follows closely the conversion of the sodium isoascorbate to form erythronic acid by hydrogen peroxide oxidation. The sodium isoascorbate and erythronic acid relative concentrations level off around ~71 min, which indicates reaction completion. The subsequent nonzero baseline for the sodium isoascorbate concentration is due to a baseline drift, as this was the very first time multivariate calculation was attempted in conjunction with in situ Raman monitoring through the Siemens SIPAT platform. Work is currently being undertaken to correct this baseline issue in future runs. The observation made during the

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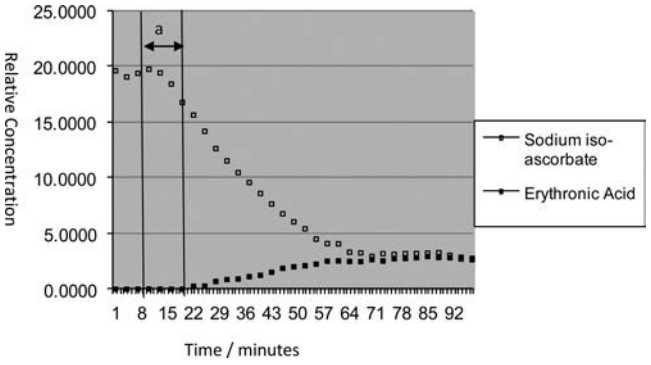

Figure 10. Stage 2 of configuration A: the start of oxidation in the stirred tank monitored using in situ Raman.

early development work where a small time lag prior to completion of the oxidation reaction (i.e. appearance of the product) during peroxide addition was confirmed during our monitoring of the process at large scale.

Configuration B. This mode of operation has a much larger proportion of the process running continuously, with continuous oxidation in a continuously operated stirred tank, and the process being buffered only after the acid dosing. The following description refers to numbering of equipment as shown in Figure 9.

Phase 1: Salt Formation at Static Mixer [SM90101]. D-Isoascorbic acid and sodium carbonate were mixed and reacted at the static mixer as for phase 1 of configuration A. Once this was established, material could be routed to R3000

Phase 2: Oxidation in Reactor R3000. R3000 was initially filled with 10 L of water, the minimum stir volume. The content was heated to and maintained at 40 °C. Hydrogen peroxide from skid 2, intermediate product from SM90101, and sodium carbonate were all pumped into R3000. Since there was no pH transmitter on R3000 at the time, the pH of the product in R3000 was tested manually with pH paper to ensure that it was between 8.5 and 9.5 before further processing. QUANTOFIX peroxide test sticks indicated the completion of oxidation. Only when the intermediate product from R3000 was on specification, was it pumped (11.7 L/h) into SM90201 in skid 2 for ring-closure step.

Phase 3: Ring Closure at SM90201. The discharge from R3000 was mixed and reacted with hydrochloric acid at SM90201. A pH/temperature transmitter (PHT90201) was used to monitor the pH of the flow out from SM90201. The desired pH was 3.5–4.5. When found to be on specification, the product mixture was routed to VE1100 for storage. The stream-out from static mixer was set up to be diverted to a waste carboy before its pH reached the desired steady-state range. The pH was found to have achieved the desired range within 5 min of the flow commencing and remained stable throughout the run.

This process consists of three chemical transformations involving liquid-phase reaction with the possibility of gas evolution. One interesting example of the differences between batch and continuous processing was in the salt formation step. This has the possibility to form carbon dioxide, particularly if any excess of acid encounters the carbonate. In the batch processing of the same chemicals, this was not an issue since the CO_2 evolved had ample time to leave the system or be reabsorbed into the liquid, giving a stable, reproducible pH.

In the continuous system, the gas formation was hoped to be less as a result of better mixing. However, on startup we noted flow that oscillated between a surge with high (CO_2) gas content followed by a slower volume flow with little or no gas. The oscillations were accompanied by oscillations in pH. The oscillations were traced back to the release of gas on reaction, which then only reabsorbed slowly. This in turn led to a higher pressure drop downstream (from the two-phase flow), increasing the back pressure at the mixer. At a slightly higher pressure, CO_2 gas was not released (remaining in solution) long enough for complete mixing (at the final pH, CO_2 was dissolved in the liquid phase). With the resultant single-phase flow, the pressure drop reduced, and thus the reactor pressure dropped, allowing evolution of CO_2 to resume.

We investigated further the configuration of a static mixer in the skid. The initial configuration of the plant involved the acidic and basic streams meeting each other without good mixing; they started to react and evolve CO_2 gas travelling through tubing before entering the static mixer from the bottom and then vertically up. This configuration resulted in the long alterna tion pathway of liquid and gas phase and as such, large fluctuation in pH during the process. To overcome this problem, the piping was reconfigured such that the two streams met just before the static mixer and entered it horizontally. As a result of the reconfiguration, pH was observed to be stabilised, in parallel with the ceaseing of alternating gas–liquid flow. A smooth flow with small bubbles within the continuous liquid phase was finally obtained. This illustrates one of the challenges in flow systems—maintaining control in multiphase flows.

The scale-up of 4-DEL process was based on the data obtained from lab development and large-scale batch experiments. It was found that 6.8 L/h D-isoascorbic acid (7.7 wt %) and 3.6 L/h sodium carbonate (15 wt %) after a scale-up factor of 150 would be able to form salt at a pH of 8.5–9.5 in the static mixer. However, when these process parameters were used in the flow-controlled continuous process, the resultant pH hovered around 7, which was lower than the specification. This was because the lab-scale batch reactor allowed carbon dioxide to escape, while in the continuous system it was retained. Some detailed modelling showed that the retention of the carbon dioxide was sufficient to explain the difference in pH. The issue was resolved by increasing the sodium carbonate flow rate (3.0 L/h) relative to that of D- isoascorbic acid (4.8 L/h).

Overall, we managed to operate this hybrid batch–continuous process with three consecutive chemical transformations successfully. Continuous steady state could be achieved within minutes for phases running continuously, and the overall process steady state could be maintained for about an hour until the reactants were fully used up. The 4-DEL product mixture obtained was of equal or better quality to that of the batch product and was suitable for commercial sale.

■ DISCUSSION OF PROCESS PERFORMANCE AND CONCLUSIONS

Although it was a new technology for the team, and the first serious deployment of our multipurpose continuous processing equipment, the overall activity of development and design of the continuous process went well. The additional effort beyond that required for batch operation was in this case very small because the reactions generally moved towards completion and were not sensitive to mixing, residence time, etc. in any important way.[e] The oxidation reactions at all scales during batch development were found to reach completion rapidly and cleanly with no side reactions observed. No detailed kinetic studies were required, and had they been carried out, it is by no

means certain that they would have identified and allowed avoidance of the one operational problem—pulsing flow due to gas evolution.

Of the three configurations used (batch, configuration A, and configuration B) there was not a great difference in overall process performance. There was not a significant time advantage for the continuous process since setup required a full 8 h day which was the same as was required for the batch process, and the crude product solution was considerably more dilute. The batch process required a total of 21 h of processing time to obtain the crude product mixture as an aqueous solution, and the hybrid process (configuration B) required 15 h to produce the same amount of crude product. However, once steady state had been achieved, the process could readily have been run for as long as desired, thus allowing for much larger quantities of material to be produced without startup and shut-down.

If the subsequent processing of the crude product was in the receiving batch vessel (as was the case), the plant would have been occupied much longer in completing the batch, and the overall productivity benefit would have been minor. However, if the continuous process was designed to collect in a separate storage tank from which the batch product isolation ran decoupled rather into a batch reactor, the (approximately) 25% reduction of processing time might have been valuable if the process were to be run commercially.

One benefit of the hybrid process was that we were not as hampered by reactor size constraints. Our batch process was limited by a minimum stir volume at the start which led us to have too great a volume before cyclisation, thus requiring concentration step. The hybrid process was not dependent on reactor size although ultimately a more dilute solution was obtained.

Overall, it is unlikely that the configuration A or B hybrid processes did not bring a benefit that would allow significant commercial advantage. This reinforces our view that real care and forethought is needed to be able to extract value from continuous processing. However, had we been able to carry the isolation step continuously the benefits would have been substantial. The most clumsy and time-consuming part of this process is the product extraction into ethyl acetate. A liquid−liquid extraction experiment was carried out at 60 °C to determine the partition coefficient of 4-DEL between water and ethyl acetate . Solubility studies carried out in the laboratory had already demonstrated the solubility of 4DEL in water to be considerably higher than in ethyl acetate, so a partition coefficient of less than 0.1 was not surprising. Given this, it was clear that batch extraction would always be a lengthy and solvent-intensive process.

In principle continuous countercurrent extraction would be ideal for this—requiring less solvent and much less processing time. If that could be achieved then a much smaller, cheaper and efficient design could have been the result. Normally such extraction is straightforward. However, as mentioned, the situation is complicated by the presence of potentially sticky solids and no simple means could be identified.[f]

BATCH EXPERIMENTAL

General. Calorimetry was carried out using a Mettler Toledo RC1e with heat flux reactor AP01-0.5-RTC, glass pitch-blade turbine with baffle, RD10 control box, and iControl RC1e software.

Adiabatic calorimetry was performed using an automatic pressure tracking adiabatic calorimeter (APTAC).

Analysis by gas chromatography was carried out using an Agilent Technologies 7890A GC system with 7693 autosampler and a DB-1701 column. Temperature ramp: 150 to 260 °C, 10 °C/min; run time: 14 min; post run: 45 °C (3 min); injection volume: 1 μL; split mode, split ratio: 50:1; heater: 250 °C; pressure: 20 psi. Sample: 2 mg/mL in MeOH (HPLC grade).

Raman spectroscopy was carried out using a Kaiser RamanRXN3 process spectrometer with Invictus 785 nm near-infrared laser excitation with an average at source power of 350 mW. Three fibre-optic optical probe heads were used in order to accommodate immersion optics of different physical dimensions. A laser exposure of 3 s with five acquisitions was employed for a single Raman measurement in this study. A 1/2 in. OD probe was used for the laboratory-scale experiments and three 1/4 in. OD probes connected into various parts of the process flow for the hybrid process.

RC1 Experiment. The 500 mL AP01-0.5-RTC, reactor was charged with a 7.7% w/w aqueous solution of D-isoascorbic acid (16.76 g, 95 mmol in 200.8 g water) and the pH adjusted to 9.0 using a 17% w/w solution of sodium carbonate added over 15 min. The reaction mixture was stirred for 1 h while the instrument was calibrated. The contents of the RC1 were heated to 40 °C, and 30% hydrogen peroxide solution (23.75 g, 0.0.22 mol) was dosed to the reactor over 30 min with concurrent addition of a 17% w/w sodium carbonate solution, maintaining a temperature of 40 °C using contents control on the RC1. Following a 1 h calibration time, the mixture was cooled to 15−25 °C and discharged to a bottle (total weight 431.8 g). Test for peroxide using Quantofix test strips was negative following the stir-out.

A portion of the reaction solution (177.56 g) was charged to the RC1 and acidified to pH 1 using 25% w/w hydrochloric acid solution (38.83 g, 1.065 mol in total required). The resultant solution was discharged from the RC1 and transferred to a 500 mL, three-necked flask equipped for distillation under reduced pressure. The mixture was concentrated at 15−20 mbar to a volume of approximately 50 mL to a thick slurry. Ethyl acetate (40 mL) was charged to the flask and the mixture heated with overhead stirring at 60 °C for 30 min. The agitation was then stopped and the suspension allowed to settle. The supernatant ethyl acetate phase was decanted from the lower slurry layer. This slurry−decant procedure was repeated a further four times with each extraction analysed by GC to detect the presence of product. The fifth extraction showed absence of product.

The combined ethyl acetate extracts were concentrated at 10−20 mbar to a volume of 100 mL and the concentrate cooled to 15−25 °C. The desired product crystallised upon cooling and was isolated by vacuum filtration followed by drying in a vacuum oven at 40 °C to constant weight to afford 3.6 g of 4-D-erythronolactone. This yield equated to a 79% yield from 16.76 g of D-isoascorbic acid.

GC purity 98.571%, $[\alpha]^{25.6}_{D}$ (c = 1.13) −75.81 (lit = −73.2) ^{1}H NMR (400 MHz, D_2O) δ 4.66 (d, J = 4.0 Hz, 1H), 4.54 (dd, J = 3.2, 4.8 Hz 1H), 4.4 (dd, J = 3.2, 10.8, 1H), 4.33 (d, J = 10.8, 1H), spectrum identical to commercial sample)

Sixty-Liter Batch Reaction. A 60 L Hastelloy C22 batch reactor was set up with a double dip-pipe configuration for simultaneous charging of two solutions, in-line Raman probe and in-line pH probe. D- isoascorbic acid (D-IAA) (3 kg, 17.0 mol) was charged to the reactor via the charge-port and dissolved in water (12 L) at ambient temperature. Sodium carbonate (20% w/w aqueous solution) was added to adjust the pH to 8.5−9.5 via a diaphragm pump, maintaining the temperature between

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20 to 30 °C (7.55 kg, 18.0 mol sodium carbonate solution required to achieve pH 9.1). The resultant solution was warmed to a contents temperature of 40 °C, and hydrogen peroxide solution (4.4 kg, 40.9 mol, 2.4 eq of 30% aq solution) was charged via peristaltic pump over 2−3 h, maintaining the reactor contents temperature at 40−45 °C, adjusting the pH as required to 8.5−9.5 with sodium carbonate solution via the configured double dip-pipe (total quantity of 20% sodium carbonate required was 17.1 kg, 40.8 mol). The Raman probe confirmed the absence of starting material at this point and the presence of the erythronic acid intermediate. The reaction mixture was sampled to test for the presence of peroxide and showed a positive test.

The reaction mixture was stirred at 40 °C for a further 60 min, then cooled to 20−30 °C and resampled for the peroxide test which was negative.

The solution was concentrated by distillation under reduced pressure to a volume of 20 L (reactor jacket set point 70 °C, 100−150 mbar). Hydrochloric acid (25% w/w aqueous solution) was charged to the reactor via controlled dosing using a peristaltic pump to a pH of 1.2 (10.8 kg, 74 mol required).

The reaction mixture was sampled for ^{1}H NMR and GC analysis and was found to contain the desired product. The solution was further concentrated to approximately 15 L to afford a slurry of sodium chloride and oxalic acid byproduct.

Ethyl acetate (18.0 L, 16.0 kg) was charged to the slurry and heated to 60 °C with stirring for 1 h. The hot upper organic layer was transferred using nitrogen pressure via a dip-pipe to a paired reactor. This extraction was repeated a further three times (total of four extractions). The ethyl acetate extracts (~75 L) were concentrated to approximately 20 L under reduced pressure, and the product was allowed to crystallise. The solid was isolated in a filter dryer to obtain 2.27 kg of 4-D-erythronolactone.

GC purity 98.37%%, $[\alpha]^{24.5}_{D}$ c = 1.25 −76.23 (lit = −73.2°), ^{1}H NMR spectrum identical to reference sample

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Notes

The authors declare no competing financial interest.

ADDITIONAL NOTES

[a]BRITEST is a not-for-profit company working in partnership with key players in the pharmaceutical industry towards whole process understanding.

[b]We would like to highlight that the compound discussed in this paper is sold commercially but no large-scale (plant) route currently exists, most probably due to the isolation issues we encountered. Further work is underway (including continuous extraction) in our team to improve this.

[c]From the results of our process safety evaluation, we chose to carry out the reaction using contents temperature control at 40 °C in order to avoid any thermal accumulation leading to an uncontrolled reaction.

[d]Analysis did suggest some options that might be beneficial but for which there was no precedent in the literature. One example is the use of a continuous distillation where the precipitated solids are maintained mobile by the liquid flow in the column, for example in a falling liquid film inside a vertical heat exchanger tube. These were taken forward as independent investigations but were seen as speculative and not consistent with the time scale of the main project.

[e]The ionic reactions are clearly ionic, and therefore very fast. We also know from the literature and GC analysis that there are no impurities from these steps. A totally clean reaction has been observed at all scales of batch and there is no indication in the literature to suggest otherwise.

[f]Karr columns and similar devices were not investigated since we believed it unlikely to be of use in this system due to the solids being rather dense and sticky by nature.

REFERENCES

(1) Schaber, S. D.; Gerogiorgis, D. I.; Ramachandran, R.; Evans, J. M. B.; Barton, P. I.; Trout., B. L. *Ind. Eng. Chem. Res.* **2011**, *50*, 10083.

(2) Rutter, A. . *Continuous Processing - How Do We Make It Succeed in the Pharmaceutical Industry?* Royal Society of Chemistry Symposium: Continuous Flow Technology, Geneva, Switzerland, 15−16 June, 2011.

(3) Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. *Org. Synth.* **1985**, *63*, 127.

(4) Tropper, F., Shah, R. N. Sharma, P. U.S. Patent 6,051,711, 2000.

(5) Dunigan, J.; Weigel, L. O. *J. Org. Chem.* **1991**, *56*, 6225.

(6) Atherton J. H., Double, J. M., Gourlay, B. *Proceedings of the 7th World Congress of Chemical Engineering*; IChemE: 2005.

(7) Wall, K, Sharratt, P. N., Sadr-Kazemi, N Borland, J. N. Plant-Independent Process Representation. *European Symposium on Computer Aided Process Engineering-10*; Pierucci, S., Ed.; Computer Aided Chemical Engineering 8; Elsevier Science BV: Amsterdam, 2000.

(8) Wall, K; Sharratt, P. N.; Sadr-Kazemi, N; Borland, J. N. *Org. Process Res. Dev.* **2001**, *5*, 434.

(9) Duke, F. R.; Haas, T. W. *J. Phys. Chem.* **1961**, *65*, 204.

(10) Chew, W.; Widjaja, E.; Garland, M. *Organometallics* **2002**, *21*, 1982.

(11) Widjaja, E.; et al. *Anal. Chem.* **2003**, *75*, 4499.

(12) Kee, B. H.; Sim, W.-S.; Chew, W. *Anal. Chim. Acta* **2006**, *571*, 113.