A Sustainable Flow Synthesis of a Versatile Cyclopentenone Building Block

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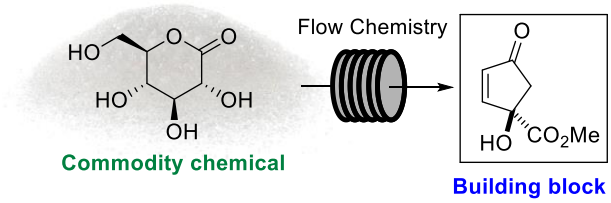
Graphical TOC:



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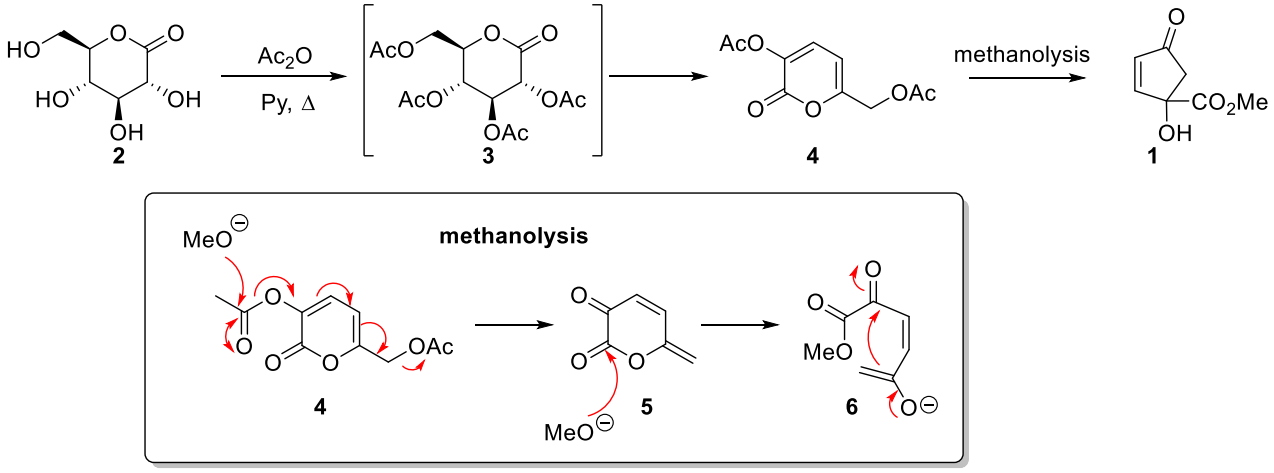
ABSTRACT: A flow based multi-step processing sequence to reliable provide the delivery of a highly functional cyclopentenone is described. The exemplification of employing solid dosing of reagents and in-line aqueous extraction has enabled an integrated workflow in a highly automated reactor set-up.

1. Introduction

Appropriately functionalized molecular building blocks are pivotal to the design and success of innovative synthesis programs being the starting point for the efficient preparation of new chemical targets. Ideally, these core units should ideally be obtained from commercial sources at low cost, however, it is not uncommon that more bespoke structures require *de novo* synthesis. As the synthetic advancement of viable building blocks typically aims to adhere to modern synthesis principles the original preparation of these building blocks should also strive to embrace the same criteria such as sustainability, atom-efficiency and eco-friendliness. In this respect modern synthesis techniques which enhance productivity and synthetic efficiency should also be embraced such as continuous flow processing technologies.[1]

In need of a robust route to the substituted cyclopentenone **1** (methyl 1-hydroxy-4-oxocyclopent-2-ene carboxylate, Scheme 1) we were challenged to devise and execute a reliable approach delivering ~100 g lots of **1** to supply an advanced synthesis program. Assessment of

the literature indicated several potential routes towards compounds similar to **1** based on multistep sequences.[2] However, a potentially flow amenable and scalable route starting from *D*-glucono-1,5-lactone (**2**, GDL, food additive E575), a cheap and readily available carbohydrate building block produced industrially by enzymatic oxidation of glucose[3] offered several opportunities for flow process intensification and additional route optimization. The overall process (Scheme 1) was anticipated to follow a peracetylation (**3**) /elimination (**4**) reaction followed by a base mediated ring opening and rearrangement of the resulting pyranone species to furnish the desired enone (**1**) in a short sequence.[4]



Scheme 1. Planned route for converting *D*-glucono-1,5-lactone (**2**) into cyclopentenone (**1**).

Despite having some attractive features, several issues restricted the direct scale-up of this chemistry. For instance, the requirement for excess pyridine (7.3 equiv.) and Ac_2O (6.2 equiv.) in the first step (**2**→**3**) strongly impacts the eco-sustainability of the process. Moreover, due to their physical properties several intermediates (i.e. **3** and **4**) cannot be easily purified by means of common extraction or crystallization techniques, making their isolation challenging to perform at scale. These issues in downstream operations along with problems in the generation of stable

holding batches inevitably lead to reduced quality control and overall process reproducibility concerns.

Other technical problems were foreseen in the sensitivity of the methanolysis step with respect to the base addition rate and reaction time. This step requires precise control of the base dosing to prevent competing transformations; an exacting operation that is difficult to achieve in a batch set-up as scale increases. In addition, the inherent instability of intermediate **4** (scale restricting in batch) under the required alkaline methanolysis conditions further impinges upon the robustness of the synthesis as it necessitates a rapid acid quench of the product which introduces further timing issues upon scale-up. Consequently, we were inclined to pursue the development of an integrated flow process that would help mitigate risks both in terms of technical operation and moreover key safety concerns. From a practical point of view, we initially proceeded by establishing key reaction parameters through a rapid batch evaluation of the process, the results of which were subsequently implemented in the final continuous flow process at larger scale. We have found such a batch investigation strategy helpful in identifying critical bottlenecks and problematic reaction operations which can subsequently be removed through judicious engineering and set-up of the final flow system. It has also allowed us to work in parallel at different stages of the process enabling full exploration of the chemistry before attempting to telescope the individual components together in a unified flow process.

2. Results and Discussion

Preliminary batch feasibility studies

Initially, we aimed at improving process efficiency and product quality through modelling and optimisation of each single step in the synthesis, taking into consideration green chemistry

principles[5] where appropriate. While developing an efficient synthesis of the *2H*-pyran-2-one derivative **4** we specifically focused on avoiding or minimising the use of organic bases such as pyridine. We thus commenced our efforts through a preliminary kinetic study of the acetylation of *D*-glucono-1,5-lactone (**2**) which revealed that the formation of the fully acetylated gluconolactone derivative **3** is a rapid process which is quickly followed by regioselective elimination of the acetyl group at the 4-position to generate the corresponding enone **7**. A second elimination step then follows at a much slower rate to yield pyranone **4** in nearly complete conversion after 1 hour (Figure 1). We therefore envisaged that a progressive temperature gradient would enable us to access either intermediate **7** or pyranone **4** selectively also minimizing eventual side products and energy consumption.

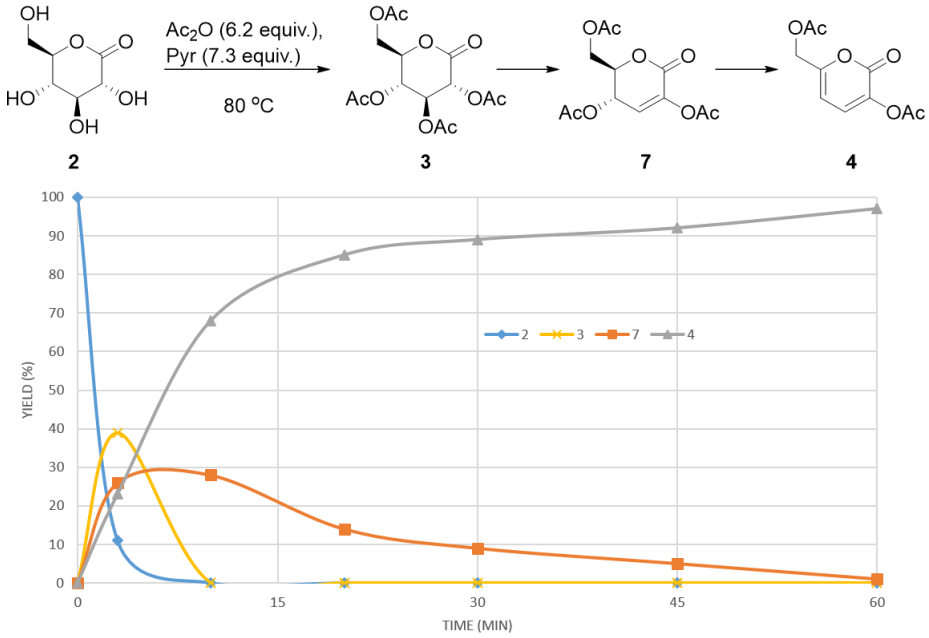


Figure 1. Kinetic evaluation of the acetylation/elimination step. The yields were determined by ^{1}H-NMR analysis using 18-crown-6 as the internal standard.

These findings were then expanded upon to evaluate the effectiveness of acid catalysis conditions to trigger the successive elimination reactions (**3**→**4**). This study was expatiated using an automated microwave platform[6] to explore and extend the available chemical space. This facilitated a range of different Lewis and Brønsted acids to be tested covering several scenarios in terms of temperature, reaction time and acid catalyst amount (Supporting Information Section 2.1). In summary, we found that using forcing conditions the desired product **4** could be formed in both appreciable recovery (54-69%) and reasonably short reaction times (190 °C for 20 min in the presence of 4.2 equiv. of Ac_2O and 0.07 equivalents of $ZnCl_2$), however this typically also generated polymeric impurities (including charred insoluble material), leading to complex mixtures difficult to both handle and purify. Partial purification could be effected by treatment with activated charcoal but at the expense of yield and this also necessitated extensive extraction of the acetic acid with hexane or diethyl ether (12-16 volumes) prior to the treatment (Supporting Information Section 2.2). It was eventually shown that the selective formation of the fully acetylated intermediate **3** could be realised using Ac_2O (4.2-4.5 equiv.) as the reagent and solvent in the presence of a catalytic amount of $ZnCl_2$ (0.07 equiv. 5 min, 100 °C) or more conveniently silica-supported H_2SO_4 (5 wt%).[7] Using the latter method we were able to quantitatively produce **3** at moderate temperature (100 °C) and within a short reaction time (3 min) enabling the generation of a stable holding batch of the peracetate **3** enabling subsequent investigations on the crude material.

In tandem with the above study and confident that the presence of a basic species was a key requirement to promote the subsequent elimination reactions (**3**→**4**), we performed a series of tests using substoichiometric amounts of different bases (Supporting Information Section 2.3). Of particular interest was a finding that heating a crude solution of tetra-acetate **3** at 80 °C for 10

min in the presence of a catalytic amount of Et_3N (0.25 equiv.) resulted in selective formation of the mono-deacetylated intermediate **7** (96% conversion, 93% isolated yield from column chromatography). In contrast, full conversion of **3** into the *2H*-pyran-2-one **4** was observed only in a few cases when using molar excess of base in combination with prolonged reaction times and yielding low mass return rendering this approach less desirable. In addition, the attempted treatment of **3** with a variety of inorganic bases (e.g. Bu_4NOH, K_2CO_3, NaOH, KF or combinations thereof to generate *in situ* hydroxide - i.e. DBU/H_2O) in a proposed one pot process only led to the progressive deacylation of the parent peracetate compound **3** without the formation of either compound **7** or **4**. Unexpectedly, it was found that the primary elimination product **7** reacted very differently in the presence of a strong inorganic base generating preferentially the desired species **4**. Consequently, this observation coupled with the feasibility of being able to selectively and efficiently generate compound **7** rapidly and at scale prompted us to investigate a revised synthetic strategy.

With the desire of promoting both the secondary elimination (**7**→**4**) and rearrangement steps (**4**→**1**), we ran a series of explorative reactions addressing the potential of creating a telescoped process starting from a crude solution of enone **7** (Supporting Information section 2.4). From a preliminary screen NaOH was chosen as the preferred base and subsequently screened against different solvent systems as well as different base stoichiometries (Table 1). Despite investigating many different variations the desired compound **1** could only be isolated in low yields of 13-29%. No conversion was observed when performing the reaction in water (entry 1) or when employing biphasic solvent mixtures (entries 2-6). Further attempts using methanol as the solvent with stoichiometric or sub-stoichiometric amounts of base did not lead to significant improvements (entries 9-11). However, of note was the observation that when purified samples

of intermediate **7** were used substantially improved yields of the desired product **1** were achieved (Entries 7 & 9 Table 1). Consequently, the necessity of purifying the crude material **7** by means of an aqueous work-up at this stage was identified as a crucial process operation for the successful development of a telescoped approach.

Table 1. Selected results of conditions screened for the preparation of **1** using isolated compound **7** as starting material (0.85 M concentration of **7**). Optimization was performed using DoE using a full experimental domain interrogated through a central composite design (CCD) - JMP Statistical Software.

Entry	Solvent	*NaOH equiv.*	Temperature (^{o}c)	Time (h)	Conversion	Yield[a)]
1	H_2O	1	25	15	0%	0%
2	H_2O/THF[b)]	1	60	1	0%	0%
3	H_2O/DCM[b)]	1	60	1	0%	0%
4	H_2O/Dioxane[b)]	1	60	1	0%	0%
5	H_2O/Toluene[b)]	1	60	1	0%	0%
6	H_2O/MeOH[b)]	1	60	15 h	82%	6%
7	THF	1	25	15 h	58%(85%)[d)]	28%[c)](44%)[d)]
8	*t*-BuOH	1	25	1 h	22%	0%
9	MeOH	1	25	1 h	100%	29%(46%)[d)]
10	MeOH	0.5	25	3 h	57%	24%
11	MeOH	0.25	25	3 h	36%	13%

a) Isolated yield. b) 0.2 equivalents of TBAB were used. c) Referred to the carboxylic acid derivative. d) conversion/yield based upon the use of purified compound **7**.

In the past we have found the use of immobilised polymeric and ion exchange bases to be beneficial in promoting a series of catalysed transformations by facilitating work-up operations and thereby avoiding time consuming extractions and water washing steps. In line with this approach we evaluated the bases Amberlyst 26[8] and Ambersep 900 (both hydroxide form)[9] to

promote this transformation along with scoping a suitable working temperature window (Table 2, Entries 1-6).

Table 2. Selected conditions screened for the preparation of **1** using solid supported bases. Optimization was performed using DoE using a full experimental domain interrogated through a central composite design (CCD) - JMP Statistical Software.

Entry	Solvent	Concentration	*Base*	Temperature (ºC)	Conversion	Yield[a)]
1	MeOH	0.7 M	A-26[b)]	100	82%	40%
2	MeOH	0.7 M	A-26 [b)]	120	100%	51%
3	MeOH	0.7 M	A-26 [b)]	140	100%	43%
4	MeOH	0.7 M	A-900 [b)]	100	80%	41%
5	MeOH	0.7 M	A-900 [b)]	120	100%	53%
6	MeOH	0.7 M	A-900 [b)]	140	100%	46%
7	MeOH	0.35 M	A-900 [b)]	120	80%	44%
8	MeOH	0.18 M	A-900 [b)]	120	63%	33%
9	MeOH	0.12 M	A-900 [b)]	120	46%	31%
10	MeOH	0.12 M	A-900 [c)]	120	83%	59%
11	MeOH	0.12 M	A-900 [d)]	120	91%	63%
12	Toluene/MeOH 2:1 v/v	0.12 M	A-900 [c)]	120	62%	39%
13	Toluene/MeOH 2.5:0.5 v/v	0.12 M	A-900[c)]	120	42%	24%

a) Isolated Yield, mass difference ascribed to unidentified polymeric and baseline material. Reactions were performed under microwave irradiation for 10 minutes. b) Base/3 ratio 1:1 w/w. c) Base/3 ratio 1:2 w/w. d) Base/3 ratio 1:3 w/w.

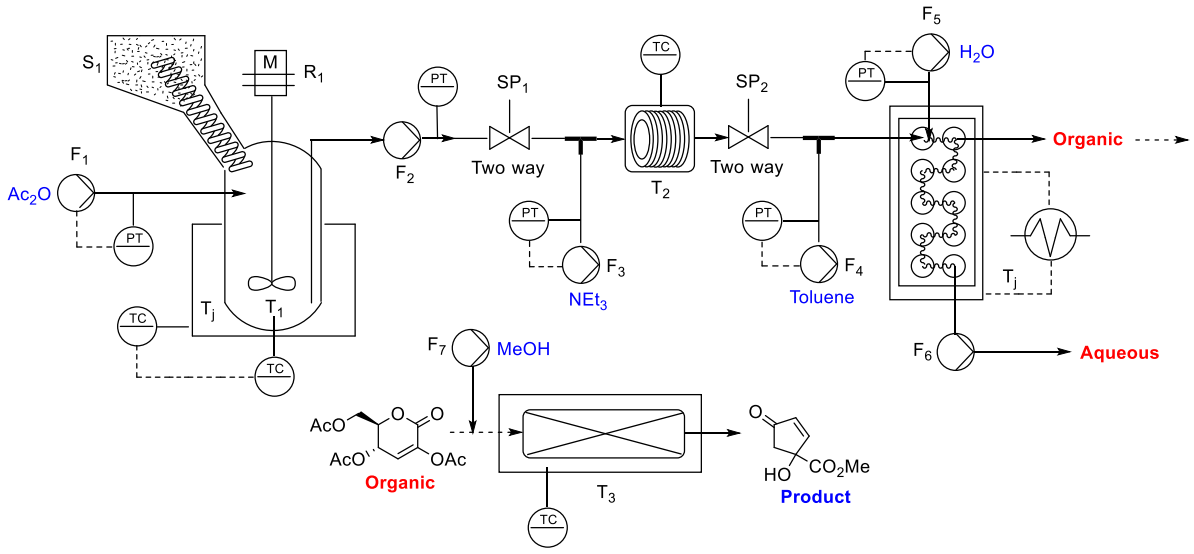
Performing the reaction in MeOH, we initially observed that elevated temperatures led to improved yields (40-60%). In particular, a reaction temperature of 120 °C in combination with Ambersep 900 resin proved fertile for further development. We therefore focused our attention on evaluating effects relating to the starting material concentration, the catalyst amount and the system solvent. The best option turned out to involve treating a 0.12 M solution of **3** in MeOH

with 1:2 w/w or 1:3 w/w Ambersep 900 at 120 °C for 10 min (Table 2, Entry 10-11). These promising results clearly indicated the feasibility of converting **2** via acetate **7** directly into **1** by means of a two-step process involving only one intermediary work-up operation.

The information gathered throughout these feasibility studies allowed us to develop a more comprehensive process understanding and as a result enabled us to define the requirements of the flow process.

Translation to a flow process

Building on our batch results we were able to translate the amassed understanding and knowledge gained into a rational design for a continuous telescoped process and by implementing a suitable suite of flow technologies (reactors/mixers/work-up units and diagnostics) aim to minimise process failure and maximise safety (Scheme 2). Upon assembly the system still required calibration and optimisation of each individual reaction step to enable smooth integration through balancing of flow rates, concentrations and event timing. Although being an integrated sequence the process can still be rationalised as 4 iterative steps; 1) peracylation, 2) elimination, 3) work-up and 4) Base mediated rearrangement.



Scheme 2: Integrated flow reactor configuration. Key: F_1-F_7 *Pump flow rates mL/min*; T_1-T_3 *Reactor hold temperatures °C*; S_1 *Solid dispensing rate g/min*; R_1 *Mixer rotation speed rpm*; SP_1-SP_2 *Sample ports*; T_j *Reactor jacket setting °C*; PT *pressure transducer with over pressure shutdown limit for associated pump*; TC *temperature controller with automatic shutdown limits*.

Reaction stage 1; peracylation

During investigation of the initial acetylation step mediated by silica supported sulfuric acid (SiO_2-H_2SO_4) we had identified critical aspects that could translate into process limitations during scale-up. These mainly refer to the reaction's runaway exothermic profile combined with the poor solubility of the starting material **2** in the reagent/solvent Ac_2O. Indeed, by adding the solid supported catalyst to a suspension of *D*-glucono-1,5-lactone (**2**) in Ac_2O, a sudden temperature rise to greater 100 °C was encountered after only a few seconds. This leads to enhanced solubility of the starting material **2** and thus further accelerates the reaction rate in a progressively uncontrollable manner. The widely adopted solution to overcome this issue at scale involves the development of a semi-batch process that allows for better control of the heat released through the slow addition of the reactive species. This concept can be further improved

towards a higher productivity by designing a set of continuous stirred tank reactors (CSTRs)[9] which minimizes unproductive periods as a result of batch changeover operations. Constant streams of starting material and reactants can thus be blended into the reaction vessel while, under ideal mass transfer regime, a solution of product is pumped out of the reactor. Whereas this approach is perfectly suited to our requirements, the insolubility of the starting material **2** in Ac_2O still restricted its immediate application. Indeed, the necessity of working with homogeneous and particle-free feedstocks represents a stringent requirement at the basis of most conventional flow processes.[11] To circumvent such issues and indeed use the insolubility of **2** in Ac_2O to our advantage we decided to exploit powder dosing equipment for the introduction of the substrate into the reactor. Among various commercially available systems, we opted for the LAMDA DOSER,[12] a versatile, simple and robust feeding tool that can be installed in either bench top platforms or more complex laboratory installations (Figure 2A). The instrument allows controlled gravimetric solid feeding based upon a hopper and rotating screw thread delivery system regulation of which is governed by an arbitrary speed setting ranging from between 1 and 999. We thus generated a calibration curve that correlates the amount of delivered material to the instrument settings for the starting material **2** (Figure 2).

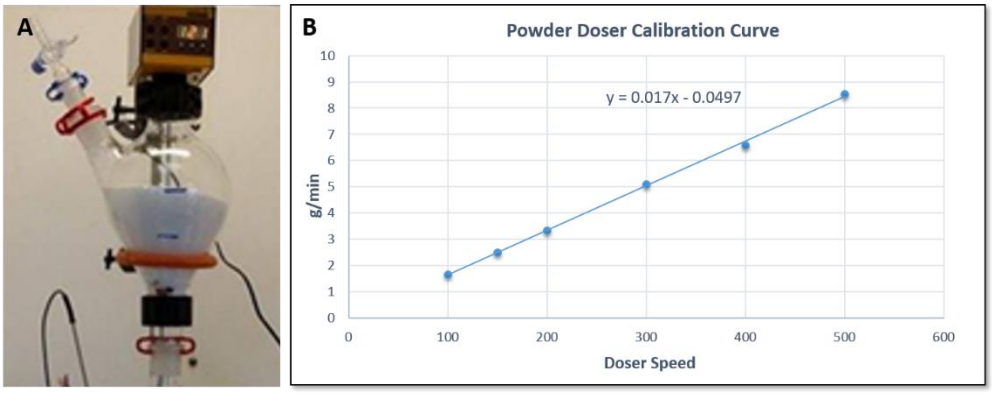


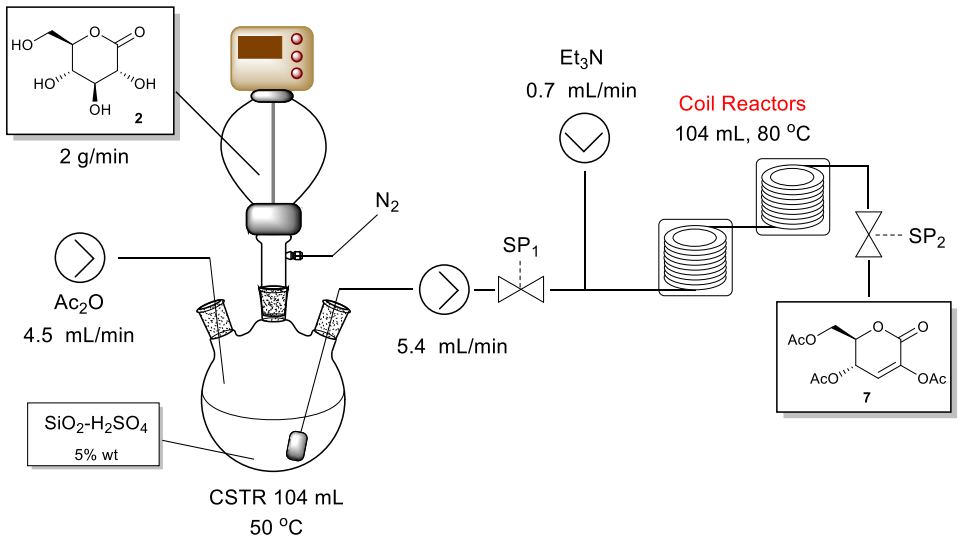
Figure 2. A) Powder doser used in a CSTR platform developed for the synthesis of compound **3**. B) Calibration curve generated weighting the amount of material delivered over a period of 10 minutes at different dosing speeds.

We incorporated the solid feed unit with a CSTR constructed using standard laboratory equipment consisting of a three-necked round-bottom flask, a stirrer hot plate and two HPLC pumps (Figure 3). Thus the *D*-glucono-1,5-lactone (**2**) was delivered by the powder dosing unit and mixed with an input stream of Ac_2O (HPLC pump 1) in the presence of the SiO_2-H_2SO_4 catalyst which was contained in the flask. The resulting reaction mixture was maintained at 50 °C. The reactor content was continuously removed from the system at a fixed flow rate (HPLC pump 2) producing a calculated average residence time of 20 min. To avoid concomitant removal of the heterogeneous catalyst or insoluble reactants, the outflow tube (to HPLC pump 2) was connected to a stainless steel sintered filter. This prototype was successfully operated uninterrupted for several hours and at steady state gave compound **3** as the sole product by ^1H NMR with a throughput of 200 g/h.

Figure 3. a) Prototype CSTR set-up for acylation of *D*-glucono-1,5-lactone (**2**) with HPLC pumps b) System coupled with the peristatic pumps of the Vapourtec E series system.

Reaction stage 2; elimination reaction

As previously reported in the batch evaluation study, reacting a crude solution of the peracetate **3** with a catalytic amount of Et_3N (25-40 mol%) at 80 °C rapidly produced the unsaturated intermediate **7** in high yield. Consequently, a telescoped flow process appending this elimination step with the above described peracylation sequence was undertaken. In order to maximize productivity, we revised the prototype reactor by installing peristaltic pumps[13] as these proved more reliable at high flow rates for pumping the viscous solutions involved (Figure 3B). A third peristatic pump was used to delivering the Et_3N base to the exiting flow stream coming from the CSTR using a simple T-piece mixer which then directed the combined outflow into two sequentially linked tubular coil reactors installed on Polar Bear plus reactor units[14] (Scheme 3).



Scheme 3. Set-up for the telescoped synthesis of compound **7**.

During the early development phase, we equipped the system with sampling ports (SP_{1-2}; Scheme 2 & 3) for analysis purposes after each reaction stage. Combined with fast analytical analysis (LC-MS, GC-MS and ^{1}H-NMR) this set-up allowed for the accelerated fine tuning of the reaction conditions and subsequent optimization of the process parameters resulting in optimal conditions when Ac_2O (3.64 equiv.) was pumped at 4.5 mL/min and the *D*-glucono-1,5-lactone (**2**) was dosed at 2 g/min. The CSTR temperature was regulated to 50 °C while the outlet pump was operated at 5.4 mL/min yielding again an average residence time of 20 minutes. The secondary stream of Et_3N was delivered at 0.7 mL/min (equating to 45 mol%) through the third peristaltic pump of a Vapourtec E-series platform[13] and the fully acetylated intermediate **3** transformed into **7** after passing through the two 52 mL coil reactors located on two Polar Bear Plus heating systems each maintained at 80 °C (Scheme 3). This process was operated continuously for more than 6 h consistently delivering high quality material with a productivity of 183 g/h and an overall isolated yield of 95%.

Stage 3; Work-up of the elimination reaction

The necessity of removing the excess acetic acid in order to progress the material in the subsequent base mediated transformations had been convincingly identified in the preliminary batch investigations. Therefore having succeeded with an exceptional throughput of **7** achieved via a small footprint synthesis platform, we acknowledged that a conventional downstream isolation process would represent a bottleneck in terms of time, manpower and facility requirements. Indeed, the optimized batch work-up procedure demanded the use of a non-ideal solvent, toluene, for compatibility reasons with the subsequent synthesis step (a solvent exchange was deemed non ideal). The use of toluene, in combination with the large amount of acetic acid

present, required several aqueous washes to ensure complete removal of acetic acid from the organic phase. For instance, in a process planning evaluation for a 4 h process batch of **7** we determined that the delivered 1.5 L of crude reaction solution needed diluting with a minimum of 3.5 L of toluene and required three extraction cycles with 1.35 L of H_2O. This operation emerged laborious and time consuming and, overall, inadequate when seen in comparison to resources and facilities required for the synthesis process. Consequently, we elected to exploit a continuous work-up technique that would expedite this process as well as minimize the amounts of aqueous waste produced through improved extraction efficiency. We focused our efforts on developing a counter current extraction[15] method using a commercially available AM technology ACR device.[16] This specific reactor set-up comprises of ten interconnected chambers built into a PTFE block arranged in a cascade-like fashion. Each stage (chamber) has a separate side inlet and is connected to an adjacent chamber by twin flow channels. The mixing is realized through shaking freely moving agitators placed inside the chambers that therefore behave as mini CSTRs. As depicted in Figure 4A, our configuration consisted of a 4-pump system. The crude solution of **7** (via pump 1) was combined with a stream of toluene (pump 2) and directed to the second from bottom chamber of the ACR reactor. A third pump was used to introduce water into the system from the second from the top chamber. The light toluene phase passes (vertically up) through the system and was thus collected from the highest outlet (eluted by the internal system pressure) while the heavier aqueous phase (traversing vertically down) was pumped out from the lowest chamber (pump 4). For evaluation purposes, we targeted an average residence time of about 1 min for each extraction stage/cell and thus pumped the crude organic mixture with a combined flow rate of 9 mL/min while water was introduced at 6 mL/min. We optimized the performance of the outflow pump based upon these parameters (8 mL/min – pump 4) to give an idealized

extraction. To enhance the mixing and extraction efficiency the process was further calibrated evaluating different mixing elements and different oscillation frequencies. Accordingly, we initially operated this set-up using 8 springs at 8 Hz (Figure 4B).

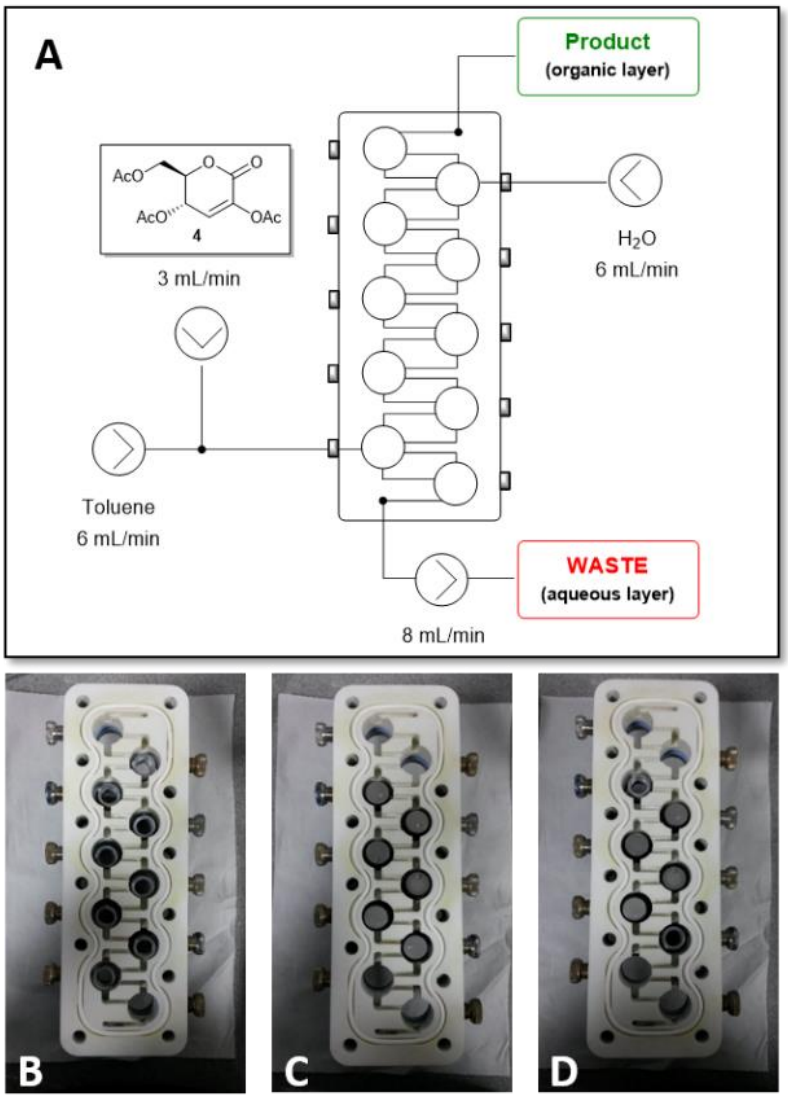


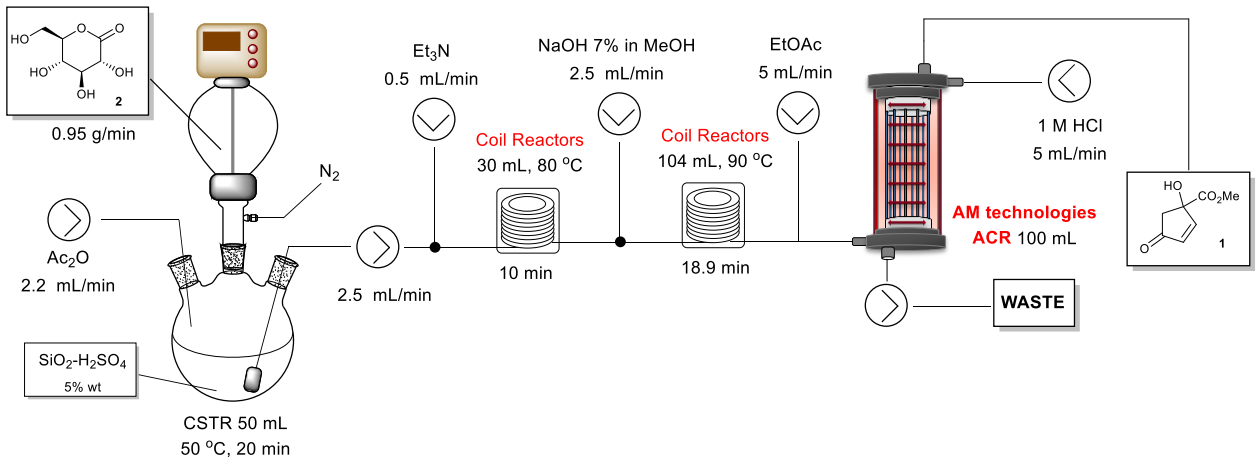
Figure 4. A) Continuous counter current extraction set-up. B-D) Examples of different mixing element combinations tested.

The initial set-up led to excellent phase separation albeit delivering a poor extraction efficiency which we inferred was due to inadequate mixing. With the aim of improving the mixing capability we thus equipped the ACR module with six cylindrical heavy inserts (Figure 4C). Despite also reducing the shaking frequency to 6 Hz as well as decreasing the number of mixing element (8→6), an emulsion was continuously generated. The best results in terms of both phase separation and extraction efficiency were obtained using solid cylinder inserts for the middle 4 cells and open springs for the two peripheral chambers (Figure 4D). This set up was operated at 6 Hz frequency yielding high quality material suitable for the subsequent step. The isolated yield (85.3 g/h) was determined to be 90% based upon a theoretical throughput of 94.8 g/h. Extensive analysis of the waste aqueous fraction indicated only minor traces of the product (1.4-2.2 %) further supporting the high extraction efficiency of the process. Of particular note was that the yield was in range with results obtained through batch extraction using various solvents and wash sequences (83-91%). Of additional processing value was the determination that these toluene extracts of intermediate **7** showed excellent stability even over prolonged storage times (> 2 week) with no evidence of decomposition or hydrolysis as determined by GC-MS, LC-MS and ^{1}H NMR. This allowed us to use this as a staging point allowing convenient collection of material into secondary processing batches for later transformation.

Stage 4; Base mediated rearrangement

Encouraged by these results we next aimed at linking all the individual stages into a telescoped process generating the desired target **1** in a fully continuous fashion (Scheme 4). To this end, we decided to attempt the base-mediated rearrangement of pyranone **7** into cyclopentenone **1** prior to the final in-line countercurrent extraction. This rearrangement was realized by combining the

crude stream of pyranone **4** with a solution of sodium hydroxide in methanol (7% w/w) before passing this mixture into two consecutive 54 mL heated coil reactors (Polar Bear plus) both maintained at elevated temperature (90 °C, 18.9 min residence time). At the outlet the reaction mixture was diluted with EtOAc before being directed into the countercurrent extraction module as described above in which water was replaced by aqueous hydrochloric acid (1 M) in order to neutralize and eliminate alkaline species (NEt_3, NaOH/NaOMe). After collecting and evaporating the resulting product stream the desired cyclopentenone product **1** was obtained in 71% yield. However, the purity of the material obtained was modest (~79%) and despite repeated attempts through modification of the various reaction parameters this could not be improved. After purification (short plug chromatography or distillation) an isolated yield of product **1** in only 48-50% was realized. Although enabling a single integrated process to be exemplified the productivity and efficiency of the process did not meet our specific project requirements.



Scheme 4. Fully continuous telescoped synthesis of cyclopentenone **1**.

Indeed, this somewhat disappointing outcome mirrored our preliminary findings from the batch experimentation which had indicated lower yields in the final methanolysis step when crude **7** and homogeneous conditions were employed (Supporting Information Section 2.4). We therefore reverted to our original plan (Scheme 2) where the scheduled extraction of compound **7** with toluene had worked well and evaluated a heterogeneously promoted methanolysis step using the knowledge gained from the batch evaluation.

To test the flow compatibility of using Ambersep 900 to mediate the desired rearrangement a stock solution of purified compound **7** was prepared (0.12 M MeOH). The solution was pumped at a flow rate of 0.15 mL/min using the Vapourtec E-series flow system so that it passed through a heated glass column (i.d. 15 mm, length 100 mm; 85 °C) containing 8 g of Ambersep 900 resin (hydroxide form). Although discoloration of the resin was observed as the substrate passed through the heated column[17] the desired cyclopentenone product **1** was consistently isolated in good yield (74-78%) and high purity after simple evaporation of the solvent. Due to the simplicity of this flow approach we were further encouraged to investigate its scalability and thus decided to process a larger batch of **7** (13 g in 150 mL MeOH; 0.73 M) through a three-column set-up (3 × 100 mm length, 10 mm i.d.; containing 3 × 5 g of resin) heated at 85 °C (Figure 5).

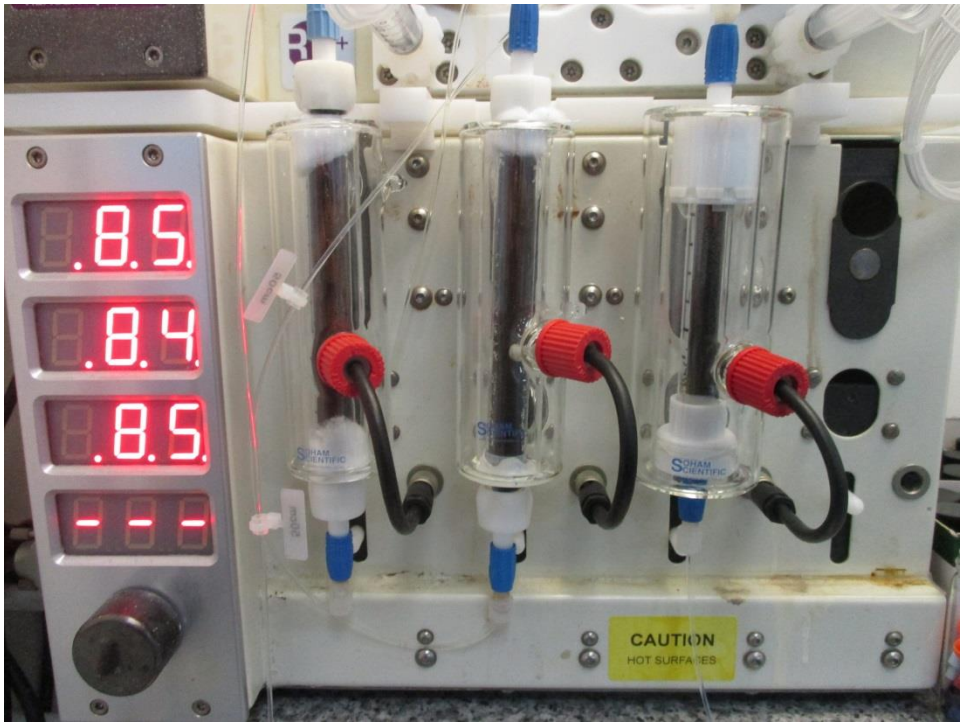


Figure 5. Ambersep 900 promoted rearrangement of compound **7** to final product **1**.

After a total processing time of 4.2 h (flow rate 0.6 mL/min) the desired product **1** was obtained following evaporation of the volatiles in an isolated yield of 87% and a purity of 78% as established using ^{1}H-NMR and 18-crown-6 as internal standard. This translates to a purified yield of 63% (isolation by distillation) and equates to a throughput of ~ 3 g/h for this 15 g packed bed. Importantly, this result also indicates that the resin retains its activity over prolonged periods of time despite the initial discolouration.

Finally, having proven the feasibility of conducting the heterogeneously promoted flow rearrangement on purified samples of intermediate **7** we endeavored to repeat the same sequence using material freshly isolated from the in-line work up of **7** as shown in Figure 4. The toluene extract from the reactor was thus diluted with 1 part MeOH to 3 parts of the toluene extract to create a solution of 0.56 M concentration (3:1 toluene:MeOH). This solution was then used as a

feedstock for the column reactor assembly described above (using 3 × 7.5 g resin filled columns). An input flow rate of 1 mL/min was employed resulting in complete conversion of **7** and an isolated yield of enone **1** in 71% following evaporation of the mixed solvents and a final vacuum distillation purification (130 °C, 0.5 mbar) of the crude product. Continuous operation of the reactor unit for 30 h generated 112 g of purified material. Indeed, as we had previously determined that the toluene extract of **7** represented a suitable and stable storage point we found it convenient to process material through the column reactor on demand as required. As demonstrated this heterogeneous approach is straightforward to operate and could through greater numbering up and parallel operation of the resin-filled columns allow increased throughput in converting triacetate **7** to the desired enone **1**.

3. Conclusion

In conclusion, we have successfully developed a fully continuous process allowing for the synthesis of a diversely functionalized cyclopentenone building block (**1**) in addition to a more convenient interrupted process allowing the final stage to be run using a heterogeneous catalyst. In the course of this endeavor we streamlined the original small scale multi-step route removing bottlenecks like the use of excess pyridine, the need for time-consuming manual purification between steps as well as eliminating concerns of potential run-away reactions. Further highlights of our approach are the use of continuous powder dosing equipment, an efficient in-line countercurrent extraction process for intermediate purification as well as the minimization of hazardous waste being produced as part of this campaign.

Supporting Information

Description and images of flow equipment used as well as experimental procedures, spectroscopic characterization and copies of NMR spectra for compounds **1**, **3**, **4** and **7**.

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Author Contributions

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6 A Biotage Initiator Microwave reactor was used (http://www.biotage.com/product-page/biotage-initiator).

7 Silica supported sulfuric acid was prepared from Merck silica gel 60 (0.040-0.063 mm) CAS 7631-86-9 (50 g) and chlorosulfuric acid (25 mL) – following the procedure by

Giri, S. K.; Kartha, K. P. R. *RSC Advances*, **2015**, *5*, 11687-11696. The sample was dried and conditioned by heating at 50 °C under high vacuum overnight before use.

8 A-26: Amberlyst® 26 hydroxide form (Sigma-Aldrich, Catalogue number 542571, 1.89 mmol/g determined by acid-base titration)

9 A-900: Ambersep® 900 hydroxide form OH form, strongly basic resin (Sigma-Aldrich, Catalogue number 06476, 2.8 mol/g determined by acid-base titration).

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12 For solid dosing a Lambda powder doser was used (http://www.lambda-instruments.com/?pages=powder_dosing_description).

13 A Vapourtec E-series flow system was used (www.vapourtec.com/products/e-series-flow-chemistry-system-overview/).

14 A Polar Bear plus system was used (http://www.cambridgereactor-design.com/polarbearplus/).

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16 A Coflore ACR lab flow reactor was employed (http://www.amtechuk.com/lab-scale-acr/).

17 CHN elemental analysis of A900 resin freshly washed and dried and prior to use C:74.20, H:8.00, N:3.47; and after processing of the carbohydrate species C:66.80, H:7.70, N:3.22 indicating the presence of additional oxygen containing functionality presumably through retention of sugar residues.