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Photo-Oxidation of Cyclopentadiene using Continuous Processing: Application to the Synthesis of (1*R*,4*S*)-4-hydroxycyclopent-2-en-1-yl acetate

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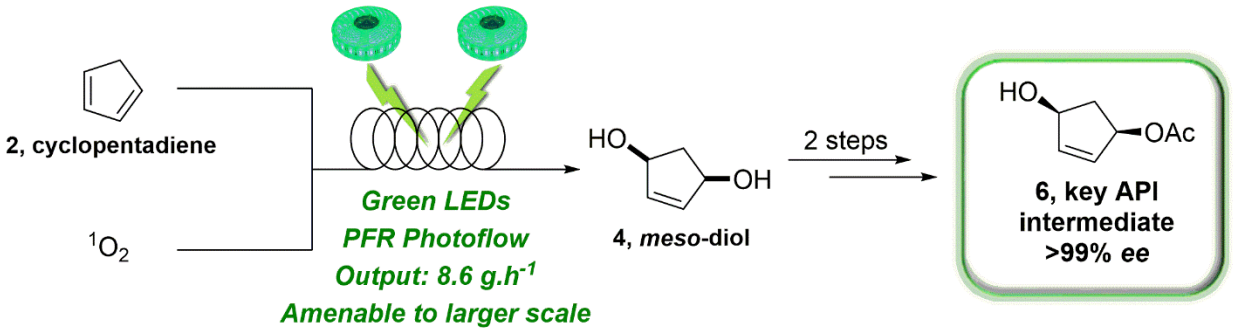
Photo-oxidation, flow chemistry, continuous process, cyclopentadiene, meso desymmetrization, Novozyme.


2, cyclopentadiene
$^1O_2$
Green LEDs
PFR Photoflow
Output: 8.6 g.h^{-1}
Amenable to larger scale
HO
OH
4, meso-diol
2 steps
HO
OAc
6, key API intermediate
>99% ee

ABSTRACT

(1*R*,4*S*)-4-Hydroxycyclopent-2-en-1-yl acetate is a chiral small building block that was requested to advance several Pfizer programs into the clinic. Pfizer and Syncom partnered to develop a photo-oxidation process of cyclopentadiene using a flow approach followed by subsequent bis-acetylation of the meso diol and final biocatalytic desymmetrization. This continuous process was demonstrated on a 6 $g.h^{-1}$ input and is amenable to larger scale. The optimization and scale-up of this sequence is described therein.

Keywords: flow, photoredox, oxidation, cyclopentadiene, Novozyme, desymmetrization

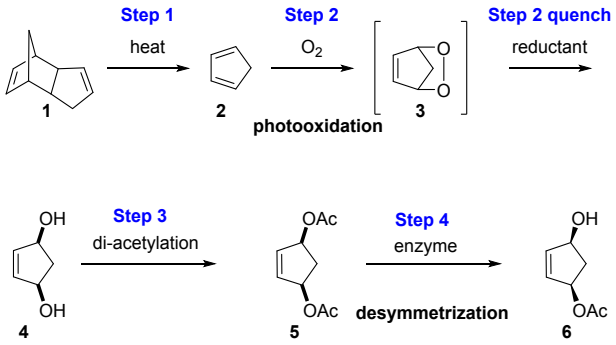
INTRODUCTION

The increased use of continuous reactors on laboratory scale has allowed "old fashioned" chemistry to flourish.[1] A prime example for this is photochemistry, which was deemed impractical for large scale application and mostly utilized in academic settings. The use of flow reactors has changed this completely, bringing this technology back into the spotlight. Flow reactors, having small irradiation pathways, allow problems associated with the low transmission of light through reaction mixtures to be overcome. As a result, photochemistry in flow has experienced an outburst of activity in the recent years.[2]

However, adoption of flow technologies also comes with challenges. Commercial continuous reactors are advertised as fit-for-purpose, which can be quite a drawback when not working in a production environment. For this reason, we custom built our flow reactors for a specific reaction or series of transformations.[3] The advantages of this approach are: 1) reactors are made of different modules which can be assembled to accommodate different processes; 2) reactors are

tailor made to the specific needs of the reaction; 3) as the modules employed are normally inexpensive, this approach is more cost efficient compared to acquiring commercial equipment.

In the course of our investigations, we needed to develop a scalable route towards (1R,4S)-4-hydroxycyclopent-2-en-1-yl acetate (**6**), a known building block in the construction of prostaglandins,[4] and a key raw material for one of our API manufacture. Our previous experience with this compound shed light on the lack of multiple suppliers for this building block on scale. Therefore, we decided to develop a custom synthesis of **6**. Synthetic methods have been reported in the literature,[5] but of particular interest was the singlet-oxygen mediated oxidation of cyclopentadiene **2** as a key step,[6] followed by acetyl protection and selective deprotection (Scheme 1). The short synthetic sequence and use of inexpensive reagents made this approach attractive, although the key photochemical step to the meso diol **4** seemed to be a challenge on our way to a process-friendly procedure towards compound **6**. It was clear that this process would benefit tremendously from being performed in continuous flow, so we decided to assess the reported chemistry with this technology in mind.[7]



Scheme 1. General synthetic approach to (1*R*,4*S*)-4hydroxycyclopent-2-en-yl acetate **6**.

RESULTS AND DISCUSSION

Following the strategy described in Scheme 1, we initiated this work with the retro-Diels Alder reaction of dicyclopentadiene **1**. This well-known chemistry proceeded uneventfully via a

modification of the Moffett procedure.[8] It should be noted that cyclopentadiene **2** slowly dimerizes unless stored at -18 °C as a solution in methanol (100 mg/g). Typically, 30-50 g batches of cyclopentadiene **2** were freshly prepared and stored for less than 16 h prior to use.

With decent quantities of cyclopentadiene **2** readily available, we tackled the key step. Batch photooxidation of cyclopentadiene **2** has been reported using Rose Bengal[6a-f] and porphyrin analogues[6g] as photosensitizers in the presence of oxygen and under light. In situ generation of singlet oxygen oxidizes cyclopentadiene **2** to epidioxide intermediate **3**. This labile intermediate can be treated with various reductants[9] to afford meso diol **4**. Encouraged by these previous reports, we started to explore the adaptation of the photo-oxidation step using continuous flow processing.

The photoreactor was constructed using commercially available parts, as shown in figure 1. The setup consists of a HPLC pump connected to PFA[10] tubing (6.5 m 1/16", 9 mL) coiled around a Drechsel bottle which is used as a cooling system. This unit was fitted into a metal box containing 2 LED chips on each side (530 nm, 8 x 30 W for green and 450 nm for blue). A gas compatible back pressure regulator was placed at the end of the reactor and was set at 8 bars. It is important to maintain the system under pressure to ensure good mixing between the liquid and gas phases and to be able to introduce enough oxygen into the reactor. An inexpensive needle-valve was used to control the oxygen, which was used in excess. The oxygen is being consumed as it travels through the tubing and reacts with the substrate, which results in a "flow-gradient" in the reactor. This makes both the overall flow rate and the residence time extremely challenging to calculate. Therefore, for ease of interpretation, the flow rates reported thereafter are only taking in consideration liquid flow rates, which were used to determine corresponding estimated residence time. The flow was adjusted to ensure that some oxygen remained unconsumed after irradiation.

From a process safety perspective, it is important to note that pure oxygen was used here and that the final solution has high levels of oxygen in a flammable solvent. The safety risk is mitigated by the use of flow technology here, since the reactor volume is very small compared to a batch mode approach. Also, excess oxygen was purged by a nitrogen stream in the receiver tank. On production scale, the use of diluted oxygen and in-line degasser at the end of the reactor tube would be strongly advised.

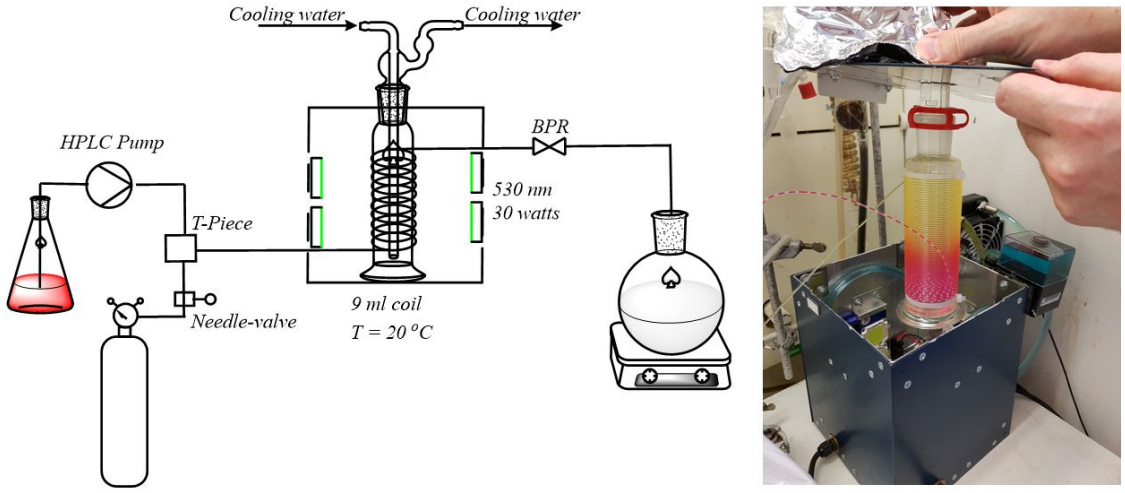
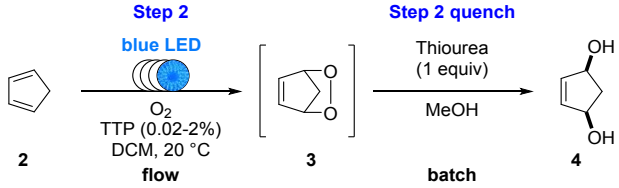


Figure 1. Schematic overview and picture of the photochemical reactor with green LED chips.

Our initial efforts focused on the use of tetraphenylporphyrin (TTP) as the photosensitizer in combination with blue LED chips. Since intermediate **3** was too unstable to subject to analysis, the mixture was quenched with a solution of thiourea in methanol to generate the diol **4**, then analyzed by GC (Table 1).

Table 1. Photooxidation reaction with TPP/blue LED system.



Entry	Feed conc. (mg/mL)	TPP (equiv)	Flowrate (mL/min)	Conversion (GC)	Isolated yield
1	10	0.02	1	100%	-
2	10	0.002	1	100%	-
3	10	0.001	1	100%	-
4	10	0.0002	1	100%	-
5	25	0.001	1	100%	-
6	50	0.001	1	100%	-
7	100	0.001	1	100%	-
8[a]	100	0.001	10	92%	10%

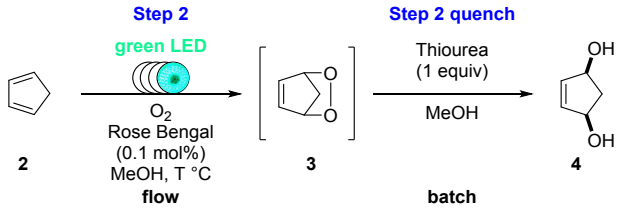
[a] Tubing diameter increased to 1/8" from 1/16" to accommodate higher flow rate.

First, we studied the amount of sensitizer needed to reach full conversion keeping all other parameters constant (Table 1, entries 1-4). In all cases, full conversion was achieved according to GC analyses. We then turned our attention to the concentration of the substrate solution in order to maximize the throughput (entries 5-7), and once again full conversion was achieved up to 100 mg/mL, at a constant 1 mL/min flowrate. We then decided to switch to large tubing diameter (from 1/16" to 1/8") to accommodate higher flow rates. A dichloromethane solution of cyclopentadiene **2** (58 g, 100 mg/mL) was flowed through the reactor at a 10 mL/min flow rate and quenched in batch mode with a solution of thiourea in methanol (entry 8). Although 92% conversion was observed by GC, only 10 g of diol **4** (10 g/h, 10% yield) was isolated after distillation. At this point, it became evident that GC data did not reflect the accurate performance of the reaction and that further work on the analytical method was required. Secondly, we believe that the heat-exchange between the cooling and the larger tubing was insufficient, which in turn led to decomposition of the cyclic peroxide intermediate **3** before thiourea mediated reduction.[11] This

prompted us to revert to 1/16" tubing diameter, and switch to a Rose Bengal/green LEDs system that was known to generate less heat.

This second approach was performed using a methanol solution of the substrate in which Rose Bengal was fully soluble. A more reliable and accurate analytical method for optimization of all parameters was also established. After quench, the crude diol solution was analyzed by ^{1}H NMR and the ratio of residual thiourea against diol **4** was used to determine *in situ* yield. Results of this study are summarized in Table 2.

Table 2. Photooxidation reaction with Rose Bengal/green LED system.



Entry	Feed conc. (mg/mL)	T (°C)	Flowrate (mL/min)	Conversion (^{1}H NMR)
1	100	20	3	25%[a]
2	100	0	3	25%[a]
3	100	20	5	12%[a]
4	100	20	3	N/A[b]
5	100	20	3	33%[c]
6	100	20	3	25%[d]
7	100	20	3	traces[e]
8	50	20	3	50%[c]
9	**33**	**20**	**3**	**64%[c]**
10	25	20	3	66%[c]
11	10	20	3	66%[c]
12	33	20	1	40%[c]

13	33	20	5	55%[c]
14	33	20	6	40%[c,f]
15	33	20	9	33%[c,f]

Note: reactor set-up: 1/16" tubing diameter with 9 mL coil volume unless stated otherwise. [a]quench method: receiver tank contained a solution of thiourea (1 equiv) in MeOH at 20 °C and ^{1}H NMR analysis was conducted at the end of the run. [b]quench method: in-line thiourea quench attempt resulted in clogging the BPR. [c]quench method: receiver tank contained a solution of thiourea (1 equiv) in MeOH at 20 °C and ^{1}H NMR analysis was conducted after stirring overnight. [d]quench method: receiver tank contained a solution of thiourea (1 equiv) in MeOH at -40 °C and ^{1}H NMR was conducted after stirring overnight at 20 °C. [e]quench method: receiver tank contained a solution of $NaBH_4$ (0.25 equiv) in MeOH at 20 °C and ^{1}H NMR was conducted at the end of the run. [f]reactor set-up was changed to 1/8" tubing diameter with a 32 mL coil volume.

We started by feeding a solution of Rose Bengal (0.1 mol%) and **2** (100 mg/mL) through the custom-made photoreactor at a 3 mL/min flowrate at 20 °C. The output solution was quenched directly into a 20 °C solution of thiourea (1 equiv) in MeOH. Analysis of the thiourea/diol **4** ratio by ^{1}H NMR at the end of the run suggested a 25% *in situ* yield (Table 2, entry 1). It is known that the epidioxide intermediate **3** is unstable at temperatures higher than -30 °C.[4b] Yet, no difference in conversion was observed at 0 °C (entry 2), which may be explained by the short residence time (3 minutes). Increasing the flowrate to 5 mL/min was detrimental to the formation of **4** (entry 3, 12% *in situ* yield), likely due to a shorter residence time. At this flow rate, oxygen bubbles are still visible towards the end of the coil. In contrast, at 3 mL/min, oxygen bubbles decreased after approximately 2/3 of the reactor coil length, suggesting that the conversion is complete (Figure 2).

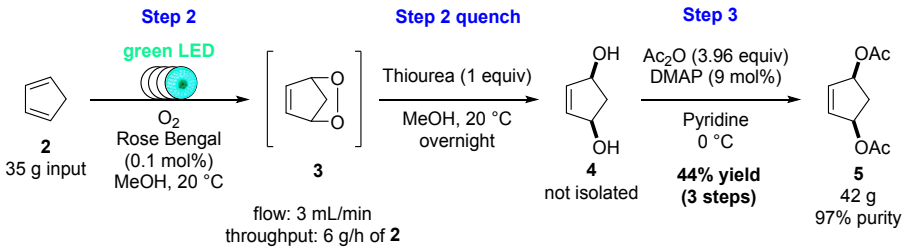
Figure 2. Oxygen consumption seen over the length of the coil at a 3 mL/min flow rate.

Next, we turned our attention to the quench method. Adding thiourea (1 equiv) to the feed solution to implement in-line quenching proved extremely challenging due to precipitation of elemental sulfur that clogged the BPR after only 5 minutes (entry 4). For this reason, the quench had to be performed in batch mode and we ensured that no degradation over time was observed in the collection vessel. We also quickly realized that stirring the quench solution overnight prior to the ^{1}H NMR analysis slightly increased the yield (33%, entry 5) compared to immediate analysis (25%, entry 1). Quenching at -40 °C did not improve the *in situ* yield (entry 6) while serious degradation was observed when using sodium borohydride as the reductant (entry 7).

Substrate concentration was also studied, and illustrated that in situ yield increased as concentration decreased (entries 8-11). Optimum concentration was determined to be 33 mg/mL to balance both *in situ* yield (64%) and material throughput (entry 9). The effect of changing the flow rate at that concentration was also investigated. When the flow rate was decreased, and thus a longer reaction time was maintained, significantly lower conversion was observed (40%, entry 12). A possible explanation for this would be degradation of the epidioxide intermediate **3**. When

the reaction time was decreased by increasing the flowrate to 5 mL/min, the conversion decreased as well (entry 13), suggesting an optimal flowrate of 3 mL/min. Finally, increasing the tubing diameter size to 1/8" at higher flowrate was attempted to improve material throughput (entries 13 and 14). While *in situ* yields were somewhat lower in both instances, these two runs demonstrated that this chemistry should be amenable to large scale production with some further optimization.

With optimized conditions identified for this flow photooxidation, a scale-up run was performed on 35 g of cyclopentadiene **2**. The total irradiation time was 6 hours, giving a throughput of 6 g of cyclopentadiene per hour, which correlates to a production of 8.6 g of diol **4** per hour. Since the resulting diol **4** was found to be highly water soluble, extractive workup and isolation were challenging. Therefore, the diacetylation step was telescoped, using reported reaction conditions.[12] Diacetate **5** was obtained in 44% yield (42 g) over three steps (Scheme 2). This result is noteworthy, as reported batch experiments were only performed on small scale and needed long irradiation times (16 hours).[5b] In addition, the use of the flow process reduced the solvent consumption by half and minimized formation of by-products, allowing a simple aqueous work-up to remove most impurities and obtain diacetate **5** in >97% purity.

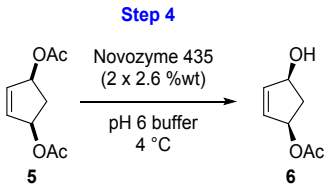


Scheme 2. Scale-up synthesis of diacetate **5** from diene **2**.

The final step of the sequence was the desymmetrization towards monoacetate **6** using Novozyme 435, based on a literature precedent as a starting point.[5a] And while the reaction performed quite well under the reported conditions with 98.9% selectivity, some over-hydrolysis

generating **4** as an impurity was detected (Table 3, entry 1). For this reason, an optimization of relevant parameters (pH, temperature, reaction time and concentration) was undertaken, with the aim to achieve a robust and scalable desymmetrization process.

Table 3. Optimization of the biocatalyzed desymmetrization of diacetate **5**.

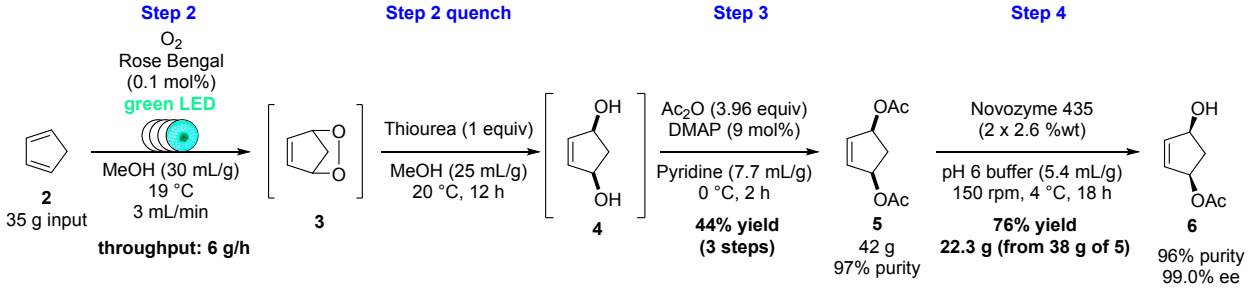


Entry	Substrate 5 conc.	T (h)	T (°C)	pH	6 by GC (area%)	6 ee% (GC)	4 by GC (area%)
1	0.2 M	18	25	8.5	86%	98.9%	10%
2	0.2 M	5	25	8.5	99%	97.2%	ND
3	0.2 M	5	15	8.5	98%	97.3%	ND
4	0.2 M	5	4	8.5	97%	97.3%	ND
5	0.2 M	4	25	6	99%	99.4%	ND
6	0.2 M	4	25	7	98%	98.7%	ND
7	0.2 M	4	25	9.2[a]	99%	98.2%	ND
8	0.2 M	5	15	6	99%	98.9%	ND
9	0.2 M	5	4	6	99%	99.1%	ND
10	0.5 M	27	4	6	99%	98.9%	ND
11	**1.0 M**	**27**	**4**	**6**	**99%**	**98.9%**	**ND**

Conditions: scale: 1mmol of substrate. Buffer (K_2HPO_4/KH_2PO_4; 0.1 M), [a]Buffer ($Na_2CO_3/NaHCO_3$; 0.1 M); ND: not detected.

As shown in Table 3, decreasing the temperature did not have a huge impact on the outcome of the reaction (entries 2, 3 and 4). In contrast, a change in pH (entries 5-7) led to dramatically different reaction profiles. At pH 6, optical purity achieved 99.4%, and most importantly over-hydrolysis was shut down under these conditions (entry 5).

As pH 6.0 seemed to eliminate over-hydrolysis, the reaction was performed at this pH at 15 °C and 4 °C (entries 8 and 9). Performing the hydrolysis at 4 °C and pH 6.0 afforded monoacetate **6** in the highest selectivity and yield. To further improve the scalability of this process, the concentration of the substrate was increased using optimized conditions (entries 10 and 11). In both cases only traces of starting material were observed after 27 hours. The product was obtained with very good selectivity in both cases (98.9% *ee*) and therefore the substrate could be utilized at a remarkable 1 M concentration. The reaction was scaled up seamlessly allowing the conversion of 38 g of diacetate **5**. Compound **6** was isolated in 76% yield (22.3 g) and 99.0% *ee*. The final product **6** could be recrystallized to increase enantiomeric excess to 99.8%, although this final re-work was not fully optimized.



Scheme 3. Full optimized sequence from cyclopentadiene **2** to key building block **6**.

In conclusion, we have developed a straightforward process to produce (1*R*,4*S*)-4-hydroxycyclopent-2-en-1-yl acetate in multigram scale. One of the key improvements of this route relies in the use of flow chemistry during the photochemical step. This technology clearly enhanced the overall reaction profile, output of material (up to 8.6 g of **4** per hour) while reducing by half solvent consumption compared to batch. The flow reactor was constructed from inexpensive and widely available components, and is clearly capable of supporting larger scale production. Increasing the coil length by only 5x with additional lamp power would lead to an

output of at least 1 Kg/day of diol **4**. The enzymatic desymmetrization step was also further optimized, revealing that pH plays a crucial role during this transformation. Indeed, lowering the pH to 6 led to full conversion with undetectable amount of over-hydrolyzed product and with >99% enantiomeric purity. We expect this process would be easily adapted for large-scale synthesis and could supply the synthetic chemistry community with this particularly useful building block.

EXPERIMENTAL SECTION

Cyclopenta-1,3-diene (2). In a distillation setup, dicyclopentadiene (DCPD) (approximately 150 mL, 1.84 mol) was loaded into a 250 mL 3-neck flask (equipped with thermometer) and was heated to reflux temperature (167 °C) (heater set: 210 °C). When the collection flask (placed in an ice batch) was filled until half (~ 4 hours), distillation was stopped, and the colorless oil analyzed by 1H-NMR. The collected clear oil (35 g, 0.53 mol) was diluted with methanol (530 mL) to provide a 1M solution. The solution was stored at -18 °C overnight. 1H NMR (300 MHz, $CDCl_3$) δ 6.63 – 6.53 (m, 2H), 6.52 – 6.43 (m, 2H), 2.99 (s, 2H).

Photo-flow reactor setup: 6.5 m PFA (Perfluoroalkoxy) tube (1/16" OD) with the correspondent fittings was coiled around a Drechsel bottle used as cooling system to make the 9 ml reactor and placed in the middle of the closed irradiation system. The used light source is green LED (525 nm). The income of the coil was connected to a T-piece, one side of the T-piece was connected to the HPLC pump and the other side to the O_2 cylinder with a needle valve. At the outcome of the coil a Zaiput back pressure regulator (BPR) was connected to maintain the system under 8 bar pressure. A thermometer was attached to the coil, in order to study the increase of the temperature during the reaction (see set up in Figure SX of the supporting information).

Process Safety note: since O_2 is used in excess and expected in the effluent, a N_2 sweep was used in the receiver head space.

Cyclopent-4-ene-1,3-diol (4). The flow system was washed with methanol at 3 mL/min for 10 min, the O_2 cylinder was opened and the system is setup for a ratio O_2/solvent 3/2 under 8 bar pressure (Zaiput BPR was used). Thiourea (40.3 g, 1 equiv, 0.53 mol) was dissolved in methanol (1 L) in a 3 L flask equipped with a stirrer, placed in an ice-bath and covered with aluminum foil. Cyclopenta-1,3-diene **2** (1 M solution in MeOH, 35 g, 0.53 mol) was diluted with methanol (530 mL) in an Erlenmeyer. Rose Bengal (539 mg, 0.1 mol%, 0.53 mmol) was added to the solution and the Erlenmeyer was placed in an ice-bath. The cooling system of the photoreactor and the light was switched on. The temperature was constant at 19 °C during the run. The solution of starting material (1.06 L) was pumped through the photoreactor (9 mL coil) at 3 ml/min (reaction time, Rt = 3 min) and the outcome collected in the quenching flask at 20 °C. The solution was stirred overnight, then the solvent was concentrated to 150 mL and filtered through diatomaceous earth. The filtrate was concentrated to give 87 g of crude material used as is in the next step (160 % crude yield). ^{1}H NMR (300 MHz, d^6-DMSO) δ 5.78 (s, 2H), 4.81 (d, J = 6.1 Hz, 2H), 4.40 (dt, J = 7.3, 6.0 Hz, 2H), 2.61 – 2.49 (m, 1H), 1.24 (dt, J = 12.9, 5.9 Hz, 1H). Selected signals of the desired product from the crude ^{1}H NMR.

Cyclopent-4-ene-1,3-diyldiacetate (5). Cyclopent-4-ene-1,3-diol (52.2 g, 1 equiv, 0.52 mol) was dissolved in pyridine (400 mL) at 0 °C under inert atmosphere. *N*,*N*-4-Dimethylaminopyridine (5.7 g, 0.09 equiv, 46.9 mmol) was added and acetic anhydride (195 mL, 3.96 equiv, 2.06 mol) was added dropwise over two hours, keeping the temperature below 7 °C. Upon completion, the mixture was poured into 750 mL ice water with caution and extracted with Et_2O (3 × 250 mL).

The organic phases were combined and washed with 1M HCl (3 × 250 ml), $NaHCO_3$ (5% aq.) (2 × 250 ml) and brine (1 × 250 ml). The organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under vacuum to give the desired diacetate **5** (42.1 g, 44 % yield over three steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (s, 2H), 5.53-5.56 (m, 2H), 2.87 (dt, *J* = 15.0, 7.6 Hz, 1H), 2.06 (s, 6H), 1.74 (dt, *J* = 15.0, 3.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (2C), 134.5 (2C), 76.5 (2C), 37.0, 21.0 (2C).

(1*R*,4*S*)-4-hydroxycyclopent-2-en-1-ylacetate (6). To a 4 °C suspension of cyclopent-4-ene-1,3-diyl diacetate **5** (38.0 g, 1 equiv, 206.5 mmol) in potassium phosphate buffer (pH 6, 206.5 mL) was charged Novozyme 435 (987.2 mg) and the mixture was stirred at 150 rpm. The reaction was monitored following this sampling procedure: a 200 µL sample was extracted with DCM (2 × 500 µL), dried over Na_2SO_4, filtered and analyzed by gas chromatography (GC). After six hours, a second charge of Novozyme 435 (987.2 mg) was added and stirring was pursued overnight. The reaction was then filtered, extracted with DCM (4 × 200 mL) and the combined organic layers were washed with water (1 × 200 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under vacuum. The crude product was isolated as a yellow liquid, 22.3 g (76% yield, 96% purity, 99.0% ee).

An analytical sample was obtained as a pale brown solid by unoptimized crystallization in diethyl ether / pentane (2:1 v/v) at -20 °C, increasing ee to 99.8%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (ddd, *J* = 5.6, 2.1, 1.2 Hz, 1H), 5.98 (ddd, *J* = 5.6, 2.1, 1.1 Hz, 1H), 5.55 – 5.43 (m, 1H), 4.71 (s, 1H), 2.80 (dt, *J* = 14.7, 7.4 Hz, 1H), 2.04 (s, 3H), 1.65 (dt, *J* = 14.6, 3.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 138.5, 132.3, 77. 1, 74.5, 40.4, 21.2.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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