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An Integrated Continuous Flow Synthesis of a Key Oxazolidine Intermediate to Noroxymorphone from Naturally Occurring Opioids

Alejandro Mata,[a,b] David Cantillo*[a,b] and C. Oliver Kappe*[a,b]

Abstract: A telescoped procedure for the direct preparation of an advanced intermediate towards noroxymorphone from the naturally occurring alkaloids oripavine and thebaine is presented. The reaction procedure involves an intensified continuous flow hydroxylation, followed by a continuous solvent switch and hydrogenation in a packed-bed hydrogenator (H-Cube). The obtained reaction mixture, containing oxymorphone as intermediate in excellent yield and purity, can be then directly converted to the desired noroxymorphone oxazolidine intermediate via palladium catalyzed *N*-methyl oxidation.

Introduction

Naltrexone and naloxone are arguably some of the most important substances used as opioid antagonists.[1] Naloxone is on the World Health Organization's List of Essential Medicines and it is used since the 1960s as a treatment of acute opioid overdose. It is normally administered to the patient in parenteral form, although more recently intranasal formulations have also become available.[2] Naltrexone is a longer-acting opioid antagonist primarily used in the management of opioid and alcohol dependence. Naloxone and naltrexone are prepared from oxymorphone (**3**) following an *N*-demethylation and *N*-alkylation sequence (Scheme 1) via noroxymorphone (**4**). Indeed, noroxymorphone, the direct product of the *N*-demethylation of oxymorphone is the key intermediate in the synthesis of various opioid antagonists apart from naloxone and naltrexone, including nalmefene (Scheme 1).[3-5] Oxymorphone, in turn, can be prepared from the naturally occurring opioids oripavine (**1**) and thebaine (**1'**) via C-14 hydroxylation and subsequent hydrogenation pathways (Scheme 1).

Recently, our group has developed a series of strategies for the generation of noroxymorphone (**4**) from 14-hydroxymorphinone under continuous flow conditions.[6-8] The crucial reaction step towards the generation of **4** was an unprecedented aerobic *N*-methyl oxidation using palladium(0) as catalyst, which generates oxazolidine **5** as intermediate (Scheme 1). Hydrolysis of **5** readily provides **4** under mild conditions. Palladium(0) particles of high catalytic activity were generated by heating $Pd(OAc)_2$ in DMA/AcOH. With the 14- *N*-hydroxy opioids dissolved in this solution, a rapid and selective methyl oxidation to 1,3-oxazolidines ensued in the presence of O_2.[6-8] The reaction, based on the original method developed by Hudlicky et al. in 2008,[9] consumes only O_2 as stoichiometric reagent and produces H_2O as the only by-product. A hydrogenation/oxidation sequence allows employing the same palladium catalyst for the transformation directly from 14-hydroxymorphinone, consuming only hydrogen and oxygen in the process.[6]

The missing link toward a process which enables the preparation of noroxymorphone (**4**) from the naturally occurring oripavine (**1**) and thebaine (**1'**) is therefore the C14 hydroxylation reaction to 14-hydroxymorphinone. This reaction is typically performed using hydrogen peroxide and formic or acetic acid mixtures,[10] generating reactive peracids that rapidly oxidize the diene group of the opioid. This method was adapted to continuous flow conditions by scientists from Siegfried AG.[11] Unfortunately, the high amounts of water and acid present in the performic acid reaction mixture make a direct telescoped process towards noroxymorphone (**4**) virtually impossible. Isolation of the reaction intermediates (i.e., 14-hydroxymorphinone (**2**), oxymorphone (**3**)) is usually required, which inevitably reduces reaction yield and increases the amount of solvent waste generated. Due to the increasing demand of opioid antagonists based on *N*-alkylated noroxymorphones,[1,2] a suitable telescoped process for the preparation of the *N*-demethylated derivative from oripavine is highly desirable. In this context, continuous flow processing has demonstrated to be an ideal tool for the development of uninterrupted multistep reactions.[12] The integration of several sequential steps can be readily achieved via continuous quenching, liquid-liquid extraction or even filtration stages enabling genuine fully integrated processes. With this in mind, we envisaged a modular continuous flow reactor set-up which combines the (i) performic acid-mediated C14-hydroxylation, (ii) hydrogenation, and (iii) aerobic oxidation steps into a single telescoped process. We envisaged that the hydrogenation and aerobic oxidation steps, which require a non-protic polar solvent (DMA) and anhydrous conditions,[6-8] could be combined with the initial C14-hydroxylation after a sequential continuous flow liquid-liquid extraction, phase separation and solvent exchange process (Figure 1). Herein, we report on the details of the individual reaction steps and the developments of an integrated, telescoped continuous flow process.

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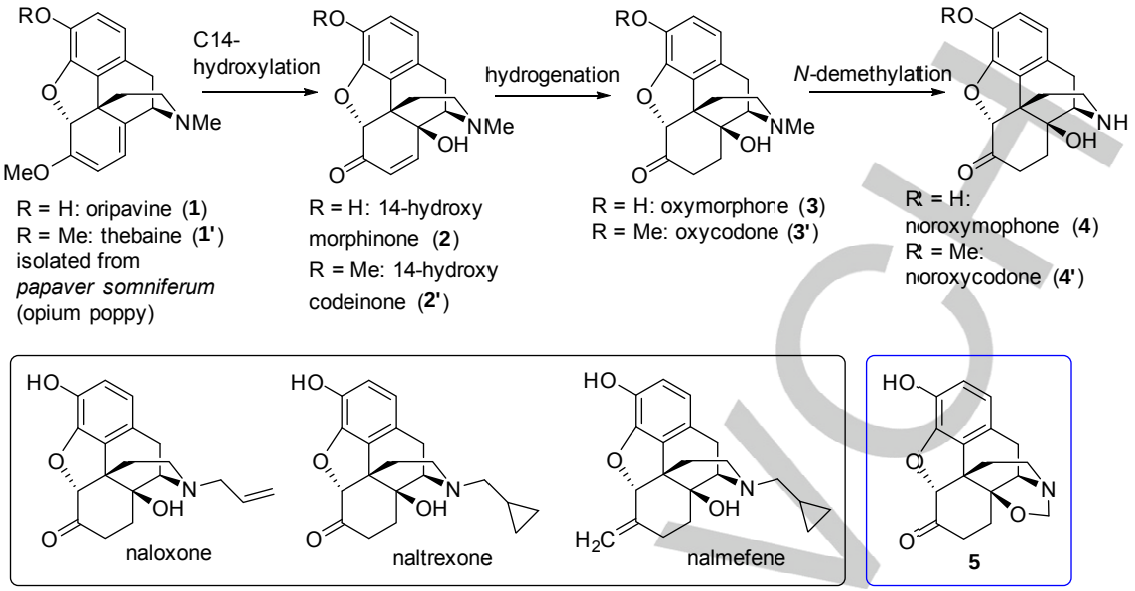


Scheme 1. Synthetic route for the preparation of semisynthetic opiates from naturally occurring oripavine **1** and thebaine **1'**.

Results and Discussion

Batch and Continuous Flow C14 Hydroxylation

The preparation of 14-hydroxymorphinone (**2**) by C14 hydroxylation of oripavine (**1**) is a well-developed process typically carried out using a combination of HCOOH and H_2O_2, which generates *in situ* performic acid as the key reactive intermediate.[10] Due to the explosive character of performic acid, which can detonate at temperatures of 80-85 °C at certain concentrations,[13] the reaction is normally carried out at room temperature or under moderate heating for several hours. The continuous process for the C14-hydroxylation of oripavine and thebaine developed by Siegfried AG was performed at temperatures of 80 °C (reaction time 15 min),[11] which is essentially the detonation limit of the reactive intermediate. Continuous flow reactors can operate within the explosive regime minimizing risks due to the small channel dimensions and the small amounts of hazardous material accumulated in the reactor, as it is generated and consumed in situ.[14-16] In this context, generation of hazardous percarboxylic acids in microreactor environments has also been described.[17] We therefore decided to explore the reaction of oripavine with H_2O_2 in HCOOH at higher temperatures. Initial batch experiments in sealed vessels using very small amounts of reagents (Table 1) revealed that the process can indeed be further intensified. At temperatures of 100 and 110 °C full conversion of the starting material was observed after 7 min and 2 min reaction time, respectively. A mixture of the desired 14-hydroxymorphinone (**2**) and small amounts of the corresponding *N*-oxide (**2b**) (5-10%) were observed in all reactions. Formation of **2b** as side product is irrelevant as its hydrogenation over Pd/C in the next step also leads to oxymorphone **3**. Excellent selectivities were observed at temperatures up to 100 °C (Table 1, entry 2). At 110 °C unsatisfactory selectivity (94%) was observed and therefore 100 °C was chosen as optimal temperature for the process.

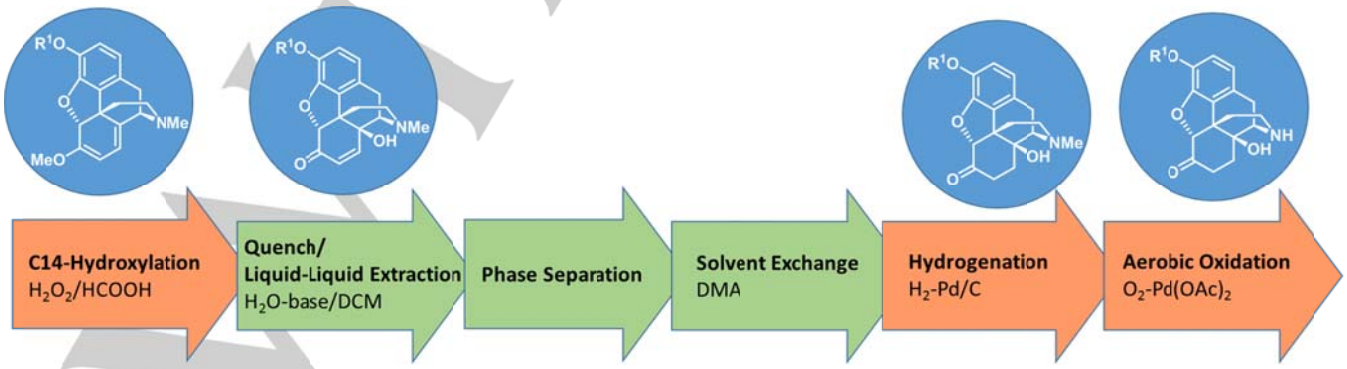
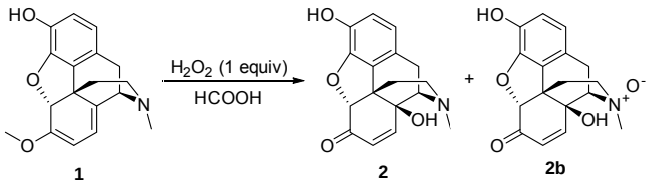


Figure 1. Proposed concept for the continuous telescoped synthesis of noroxymorphone from oripavine.



Scheme 2. C14-hydroxylation of oripavine **1** with H_2O_2 in HCOOH.

Table 1. Batch intensification of the C14-hydroxylation of oripavine (**1**).[a]

	Temp (°C)	Time (min)	Conv (%)[b]	**2**:**2b**	Select (%)[b,c]
1	80	15	99	9:1	99
2	100	7	99	9:1	98
3	110	2	99	9:1	94

[a] Conditions: sealed vessel, 0.5 mmol substrate in 0.5 mL HCOOH, 1 equiv H_2O_2 (30% aqueous solution). [b] Determined by HPLC peak area integration (215 nm) after derivatization with Ac_2O (see Experimental Section). [c] Relative amount of **2**+**2b** with respect to other side products.

With the optimal conditions in hand we translated the C14 hydroxylation process to continuous flow conditions (Figure 2). The flow setup consisted of two feeds containing the substrate (**1**) in HCOOH (Feed A) and H_2O_2 (Feed B), respectively. The pumping system (Uniqsis binary pumping module) was fed with HCOOH (A) and water (B), and the substrate and H_2O_2 were introduced via sample loops. The liquid streams were mixed using a T-mixer (0.5 mm id) before entering a residence time unit (PFA tubing, 3 mL, 0.8 mm id) at 100 °C. The system was pressurized using an adjustable back-pressure regulator (Vapourtec) at 4 bar.

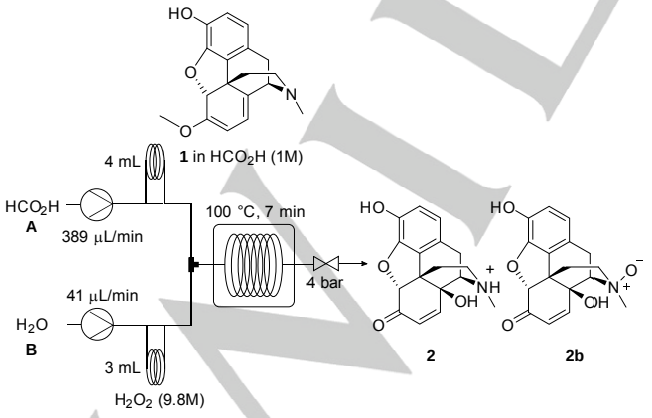


Figure 2. Schematic view of the continuous flow setup for the C14 hydroxylation of oripavine (**1**).

The flow rates for the liquid feeds were set to 389 µL/min and 41 µL/min for Feed A and B, respectively, to obtain the desired reagent stoichiometry (1 equiv) and residence time within the reactor (7 min). Without further optimization 4 mmol of oripavine (**1'**) were processed using the continuous flow setup. HPLC monitoring of the crude reaction mixture collected from the output revealed excellent conversion (99%) and selectivity (99%) for the desired products (the HPLC chromatogram of the crude reaction mixture is shown in Figure S1 of the Supporting Information). The **2**:**2b** ratio was 95:5 in the continuous flow run. Due to the high selectivity achieved, the product (containing 5% N-oxide, which results in the same product after hydrogenation in the next step) could be isolated after simple evaporation of the solvent under reduced pressure as the formate salt (94% isolated yield, 97% purity by ^{1}H NMR).

Using the same continuous flow setup and conditions thebaine (**1'**) could be also successfully C14-hydroxylated to the corresponding 14-hydroxycodeinone (**2'**) (cf. Scheme 1). As for oripavine (**1**), excellent conversion and selectivities were achieved, and a 93% isolated yield for the desired 14-hydroxy derivative **2'** was obtained (purity 98% by ^{1}H NMR).

C14 Hydroxylation/Hydrogenation Sequence

Hydrogenation of the 7,8-olefine group of 14-hydroxymorphinone (**2**) is the common route for the preparation of oxymorphone (**3**) in batch.[10a,c] The reaction has been extensively described in batch as well as under continuous flow conditions using Pd/C as catalyst.[6-8,10] Our group has described in previous reports the hydrogenation of 14-hydroxymorphinone **2** using polar non-protic solvents such as DMA.[6-8] Protic solvent mixtures like iPrOH/HCOOH are commonly used as well in batch procedures.

The third step in the route towards noroxymorphone, i.e., the aerobic oxidation of oxymorphone to oxazolidine **5**, has been shown in our previous work to be sensitive to protic solvents (DMA being the solvent of choice).[6-8] A solvent switch from the HCOOH/H_2O mixture from the C14-hydroxylation to DMA is therefore needed enabling a telescoped process from **1** to **5** (or **1'** to **5'**). To decide whether this solvent swap is more beneficial to be performed prior or after the hydrogenation, we performed some preliminary batch experiments to evaluate the performance of the hydrogenation in DMA and HCOOH/H_2O (with the second solution being the crude reaction mixture obtained from the previous step). Thus, 1 mmol 14-hydroxymorphinone **2** and 1 mol% Pd/C 10% were placed in a round bottom flask and DMA or HCOOH were added. The reaction mixtures were stirred under H_2 atmosphere (1 bar) and monitored by HPLC. Surprisingly, the reduction of the alkene was much faster in DMA as solvent. Full conversion to oxymorphone **3** was achieved after 1 h reaction, while in HCOOH ca. 3 h were required.

Continuous flow hydrogenation experiments were carried out using a commercially available hydrogenator (H Cube, ThalesNano) equipped with a packed bed reactor containing 10% Pd/C. To evaluate the potential process integration with the previous step starting solutions were prepared using the crude

reaction mixture obtained from the C14-hydroxylation flow setup (see above). The samples were diluted with DMA to a 0.2 M concentration and directly subjected to continuous hydrogenation with the H Cube. Due to the short residence times obtained within the packed bed reactor (< 1 min) the reaction temperature and hydrogen pressure were gradually increased to obtain full conversion to the desired oxymorphone (**3**) (Table 2). Thus, using 20 bar and room temperature as initial set of conditions only 20% conversion was achieved (entry 1). At 60 °C and 60 bar (entry 5) H_2 pressure more than 95% was obtained maintaining excellent selectivity towards the desired product **3**. Under intensified conditions a 91% isolated yield of oxymorphone (with respect to the initial oripavine) was obtained after simply evaporating the solvent under reduced pressure (purity 90% by 1H NMR).

Table 2. Continuous flow hydrogenation of 14-hydroxymorphinone **2** to oxymorphone **3** in an H-Cube reactor (Thalesnano).[a]

	Temp (°C)	Pressure (bar)	Conv (%)[b]	Select (%)[b]
1	rt	20	35	99
2	50	20	40	99
3	50	30	50	99
4	50	60	90	99
5	60	60	95	99

[a] Conditions: 0.2 M substrate in DMA/HCOOH, 0.3 mL/min. [b] Determined by HPLC peak area integration (215 nm) after derivatization with Ac_2O (see Experimental Section).

The aim of the continuous flow setup for the liquid-liquid extraction/phase separation/solvent exchange was to develop a continuous procedure which enabled the integration of the initial C14 hydroxylation step with both the subsequent hydrogenation and aerobic oxidation. Thus, the solution containing 14-hydroxymorphinone in $HCOOH/H_2O$ was quenched with a suitable base (aq. NH_4OH) releasing the opioid in its basic form, which was then extracted into an organic solvent (DCM) (Figure 3). Continuous separation of the organic and aqueous phases could be readily achieved by a gravity-based separator.[18] Such gravitational separation techniques are state-of-the-art and have been used in many continuous flow setups,[19] including continuous end-to-end manufacturing examples.[20] The (low boiling) organic solvent was then mixed with DMA using a T-mixer and the mixture heated in a residence time unit (PFA, 1.6 mm id, 14 mL). Rapid vaporization of the volatile DCM could be visually observed inside of the tubing. The gas liquid separation was performed in a vessel which was kept at 80 °C to avoid condensation of the DCM on the walls. Optimal flow rates for the liquid streams are shown in Figure 3. The DCM/aqueous mixture ratio was 8:1 and the DCM/DMA proportion 10:1 using these conditions. The remaining liquid contained 14-hydroxymorphinone (**2**) in DMA and was suitable to be pumped further to the next synthetic step. Thus, **2** in DMA, obtained using this solvent switch module, was directly pumped into the continuous flow hydrogenator using the optimal conditions (Table 2, entry 5). Notably, excellent conversion and selectivity was obtained for the desired oxymorphone (**3**). Evaporation of the solvent under reduced pressure yielded the crystalline product (86% yield over three steps, purity 90% by 1H NMR).

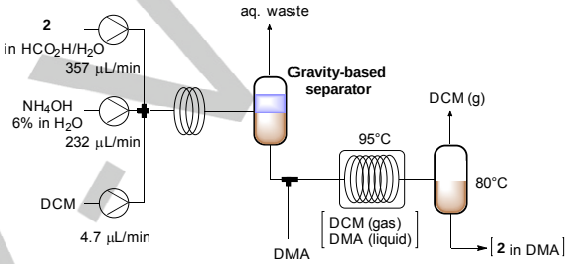


Figure 3. Schematic view of the continuous flow setup for the liquid-liquid extraction, phase separation and DCM-DMA solvent exchange.

C14 Hydroxylation/Hydrogenation/Aerobic Oxidation

The aerobic *N*-methyl oxidation of oxymorphone using palladium(0) as catalyst in continuous flow mode has been extensively studied in our group.[6-8] The optimal reaction conditions for this transformation consist of generating palladium(0) particles of high catalytic activity by heating $Pd(OAc)_2$ in DMA/AcOH. The colloidal Pd(0) is then mixed with the 14-hydroxy opioids giving 1,3-oxazolidines **5** after a rapid and selective *N*-methyl oxidation with O_2.[6-8] As this transformation had been thoroughly investigated and optimized in batch and flow conditions, we did not attempt to further modify the conditions for the aerobic oxidation in this work, which focuses in the integration of the 3-step telescoped process.

Thus, a 0.2 M solution of oxymorphone (**3**) in DMA was prepared after a sequential continuous flow C14 hydroxylation, quench, liquid-liquid-extraction, phase separation, solvent switch and hydrogenation (Figure 4) following the procedures described in detail above on a 3 mmol scale. The solution was mixed with a freshly prepared colloidal suspension of Pd(0) from $Pd(OAc)_2$ and DMA/AcOH. Heating of the reaction mixture under O_2 atmosphere was carried out in batch and monitored by HPLC. Gratifyingly, the desired 1,3-oxazolidine **5** rapidly formed attaining 85% HPLC yield after 2 h. This result is in strong contrasts to the rather poor results for aerobic oxidations that have been obtained without applying the liquid-liquid extraction and solvent switch to the reaction mixture (see above). The telescoped process

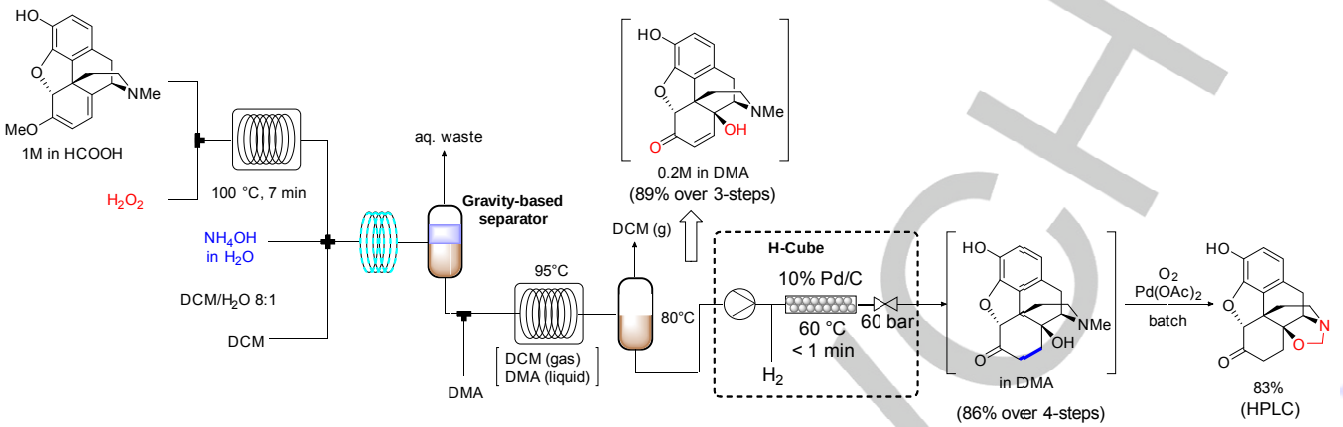


Figure 4. Telescoped continuous process for the generation of 1,3-oxazolidine **5** from oripavine **1**.

developed herein could therefore be seen as a method to integrate reaction steps where reagents or solvents present problems of compatibility.

The same process, applied to thebaine (**1'**), yielded a solution of 14-hydroxycodone (**3'**) in DMA that could also be oxidized in the presence of Pd(0) under an O_2 atmosphere to the corresponding 1,3-oxazolidine **5'**.

Conclusions

We have developed a telescoped continuous flow process which enables the generation of 1,3-oxazolidines **5** and **5'**, precursors to noroxymorphinone (**4**), a key intermediate in the synthesis of several opioid antagonists. Integration of the 3-step synthetic route (i.e., C14-hydroxylation/hydrogenation/aerobic oxidation) has been enabled via a continuous flow acid quench with aqueous NH_4OH followed by a sequential liquid-liquid extraction/phase separation/solvent switch protocol. Thus, the C14-hydroxylation reaction mixture, consisting of the corresponding 14-hydroxy-opioid **2** in HCOOH/H_2O is transformed into a DMA solution of the intermediate, suitable for the hydrogenation/aerobic oxidation steps. The telescoped process has been applied to the naturally occurring oripavine (**1**) and thebaine (**1'**) alkaloids to generate oxazolidines (**5**) and (**5'**) in clean, high yielding processes.

Experimental Section

General: ^{1}H NMR spectra were recorded with a Bruker 300 MHz spectrometer. ^{13}C NMR spectra were recorded with the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. Analytical HPLC–UV/Vis (Shimadzu LC20) analysis was carried out with a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 µm) at 37 °C by using mobile phases A [water/acetonitrile, 90:10 (v/v) + 0.1 % TFA] and B (MeCN + 0.1 % TFA) at a flow rate of 1.5 mL/min (the following gradient was applied: linear increase from 3 % B to 100 % B in 17 min). MW heated reaction were performed in a single-mode Biotage Initiator+ instrument.

HPLC Samples Preparation - Ac_2O derivatization: The crude reaction mixture (50 µL) and Ac_2O (200 µL) were added to a HPLC vial containing a saturated aqueous solution (1 mL) of $NaHCO_3$. The vial was capped, the septum perforated with a needle, and the mixture stirred vigorously at room temperature for 10 min. The content of the vial was then directly analyzed by HPLC–UV/Vis with the method described above in the General section.

C14 Hydroxylation of Oripavine (1) in Batch: Oripavine (150 mg) and formic acid (0.5 mL) were placed in a microwave vial and stirred until the substrate was fully dissolved. Then, 51 µL of H_2O_2 (30% in water, 1 equiv) were added under stirring. The vial was capped and heated at the desired temperature (Table 1) in a dedicated microwave reactor. After the desired reaction time was completed the vial was cooled to 50 °C with compressed air. Method 2 was used for HPLC analysis.

C14 Hydroxylation in Flow: The flow set-up depicted in Figure 2 was used. Flow rates for Feeds A and B were set to 389 µL/min and 41 µL/min, respectively. The GC-oven temperature was set to 100 °C. A 1 M solution of the substrate (3 mmol) (oripavine **1** or thebaine **1'**) in HCOOH was introduced in the Feed A sample loop. 30% H_2O_2 in water was introduced in Feed B loop. When the system was stable reagent samples were simultaneously injected into the liquid streams. The reaction mixture collected from the reactor output was immediately analyzed by HPLC and/or evaporated under reduced pressure to obtain the corresponding 14-hydroxy-opioid as the formate salt.

Hydrogenation in Batch: 1 ml of the crude reaction mixture obtained from the C14 hydroxylation flow reactor (see above) was diluted with DMA to obtain a 0.1 M solution. 1 mol% of 10% Pd/C was added. The reaction mixture was stirred at room temperature under H_2 atmosphere. The reaction was stopped after HPLC analysis showed >95% conversion (1 hour). Method 1 was used for HPLC analysis.

Hydrogenation in Flow: The starting solution was prepared by diluting the crude reaction mixture from the C14 hydroxylation flow reactor (see above) with DMA to a concentration of 0.2 M. The hydrogen level of the H-Cube was set to "full H2" mode; the reactor containing a Pd/C cartridge was preheated at 60 °C, the pressure to 60 bar, and the flow rate to 0.1 mL/min. When the reactor was stable the reaction mixture was processed. The mixture collected from the output was evaporated under reduced pressure yielding oxymorphone (91%, purity 90% by ^{1}H NMR).

Aerobic *N*-Methyl Oxidation: $Pd(OAc)_2$ (2.3 mg, 5% mol) and AcOH (23 µL, 3 equiv.) were dissolved in DMA (1 mL). The mixture was heated for 15 min at 120 °C. A deep-black solution of colloidal Pd^0 was obtained. The mixture was cooled down to 110 °C. 1 mL of the solution obtained from the hydrogenation module (see Figure 4) was added. The solution was stirred at 110 °C under O_2 atmosphere and monitored by HPLC.

End-to-End Generation of Oxazolidine 5 from Oripavine. A solution containing oripavine 1 in HCOOH (1 M, 3 mmol) was loaded in the feed A sample loop of the C14-hydroxilation setup depicted in Figure 2. 30% H_2O_2 in water was introduced in Feed B loop. Flow rates for feeds A and B were set to 389 µL/min and 41 µL/min, respectively. The GC-oven temperature was set to 100 °C. When the system was stable reagent samples were simultaneously injected into the liquid streams. The reaction mixture collected from the reactor output was then directly used in the liquid-liquid extraction, phase separation and DCM-DMA solvent exchange flow setup depicted in Figure 3, using the flow rates stated in the schematic diagram. The resulting solution obtained, containing **2** in DMA was then processed in the H Cube hydrogenation reactor. The hydrogen level of the H-Cube was set to "full H2" mode; the reactor containing a Pd/C cartridge was preheated at 60 °C, the pressure to 60 bar, and the flow rate to 0.1 mL/min. When the reactor was stable the reaction mixture was processed. The mixture collected from the H Cube output was mixed with a suspension of colloidal Pd(0) freshly prepared from heating $Pd(OAc)_2$ (2.3 mg, 5% mol) and AcOH (23 µL, 3 equiv) in in DMA (1 mL). The mixture was stirred in batch at 110 °C under O_2 atmosphere and monitored by HPLC (83% HPLC yield).

14-Hydroxy-morphinone (2): ^{1}H NMR (300 MHz, D_2O) δ = 6.78 (d, *J* = 10.2 Hz, 1H), 6.55 (s, 2H), 5.95 (d, *J* = 10.2 Hz, 1H), 4.79 (s, *J* = 7.4 Hz, 1H), 3.74 (d, *J* = 5.9 Hz, 1H), 3.30 (d, *J* = 20.1 Hz, 1H), 3.11 (dd, *J* = 12.8, 4.3 Hz, 1H), 2.93 – 2.81 (m, 2H), 2.78 (s, 3H), 2.73 (d, *J* = 2.8 Hz, 1H), 2.67 (dd, *J* = 13.0, 3.8 Hz, 1H), 2.53 (td, *J* = 13.3, 4.7 Hz, 1H), 1.66 (dd, *J* = 13.6, 2.9 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): *δ* = 196.6, 147.1, 142.4, 138.5, 132.9, 128.3, 121.7, 121.0, 118.6, 85.6, 67.3, 64.9, 47.1, 45.4, 40.6, 26.0, 22.8 ppm.

14-Hydroxy-codeinone (2'): ^{1}H NMR (300 MHz, D_2O) δ = 6.75 (d, *J* = 10.2 Hz, 1H), 6.61 (q, *J* = 8.4 Hz, 2H), 5.95 (d, *J* = 10.2 Hz, 1H), 4.77 (s, 1H), 3.71 (d, *J* = 5.8 Hz, 1H), 3.53 (s, 3H), 3.29 (d, *J* = 20.2 Hz, 1H), 3.08 (dd, *J* = 12.8, 4.3 Hz, 1H), 2.85 (dd, *J* = 20.3, 6.1 Hz, 1H), 2.74 (s, 3H), 2.85 (td, *J* = 12.9, 3.7 Hz, 1H), 2.50 (td, *J* = 13.3, 4.7 Hz, 1H), 1.64 (dd, *J* = 13.5, 2.8 Hz, 1H). ^{13}C NMR (75 MHz D_2O): *δ* = 196.1, 147.0, 143.1, 142.4, 132.9, 128.1, 122.6, 121.0, 115.4, 85.7, 67.2, 64.9, 56.3, 47.0, 45.3, 40.6, 26.0, 22.7 ppm.

Oxymorphone (3): ^{1}H NMR (300 MHz, D_2O) δ = 6.70 – 6.57 (m, 2H), 4.85 (s, 1H), 3.58 (d, *J* = 5.8 Hz, 1H), 3.28 (d, *J* = 20.0 Hz, 1H), 3.13 – 3.03 (m, 1H), 2.99 (d, *J* = 6.1 Hz, 1H), 2.91 (s, *J* = 8.6 Hz, 3H), 2.84 (d, *J* = 5.2 Hz, 1H), 2.80 – 2.73 (m, 6H), 2.58 (dtd, *J* = 29.9, 13.1, 4.1 Hz, 2H), 2.14 (dt, *J* = 14.8, 2.9 Hz, 1H), 1.54 (m, 2H).). ^{13}C NMR (75 MHz, D_2O): *δ* = 211.7, 143.1, 138.7, 127.1, 121.8, 121.0, 118.6, 89.1, 70.6, 66.2, 48.6, 46.9, 40.7, 34.4, 30.5, 26.9, 23.0 ppm.

Oxycodone (3'): ^{1}H NMR (300 MHz, D_2O) δ = 6.83 – 6.64 (m, 2H), 4.84 (s, 1H), 3.71 – 3.64 (m, 3H), 3.60 – 3.54 (m, 1H), 3.28 (d, *J* = 20.1 Hz, 1H), 3.11 – 3.04 (m, 1H), 2.96 (dd, *J* = 20.2, 6.1 Hz, 1H), 2.84 (dd, *J* = 14.9, 5.2 Hz, 1H), 2.76 (s, 3H), 2.66 – 2.43 (m, 2H), 2.11 (dt, *J* = 14.9, 3.0 Hz, 1H), 1.98 (d, *J* = 19.7 Hz, 1H), 1.87 (m, 1H), 1.53 (m, 2H). ^{13}C NMR (75 MHz, D_2O): *δ* = 211.3, 143.9, 142.6, 126.8, 122.6, 121.0, 114.0, 89.3, 70.5, 66.2, 56.5, 48.5, 46.7, 40.7, 34.3, 30.4, 26.9, 22.9 ppm.

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Keywords: continuous flow • telescoped synthesis • opioid antagonists • microreactors • demethylation

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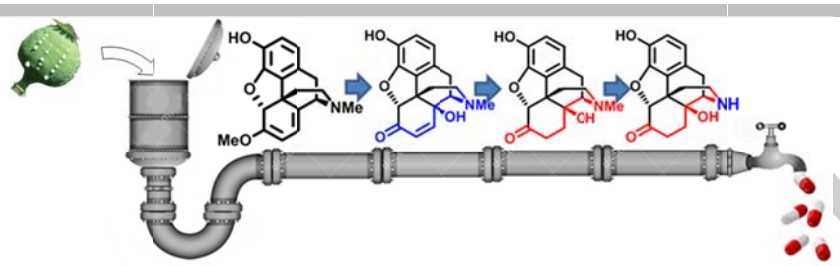

From poppy towards API: A telescoped continuous flow procedure for the preparation of an advanced intermediate for the synthesis of various opioid antagonists from oripavine and thebaine is presented.

Opioids

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