Sustainable and Scalable Synthesis of Noroxymorphone via a Key Electrochemical N-Demethylation Step

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Noroxymorphone is a pivotal intermediate in the synthesis of important opioid antagonists such as naloxone and naltrexone. The preparation of noroxymorphone from thebaine, a naturally occurring opioate isolated from poppy extract, is a multistep sequence in which oxycodone is first generated and then N- and O-demethylated. Both demethylations are problematic from the safety and sustainability viewpoint, as they involve harmful reagents such as alkyl chloroformates or boron tribromide. Herein, we present a green, safe an efficient telescoped process for the N- and O-demethylation of oxycodone. The method is based on the anodic oxidative intramolecular cyclization of the N-methyl tertiary amine with the 14-hydroxyl group of the morphinan, followed by hydrolysis with hydrobromic acid, which releases the carbon from both heteroatoms. The electrolysis process has been transferred to a scalable flow electrolysis cell, significantly improving the reaction throughtput and increasing the space-time yield over 300-fold with respect to batch. The sustainability of the new methodology has been assessed by means of green metrics and qualitative indicators. The sustainability assessment has demonstrated that the new methodology is far superior to the conventional chloroformate process.

INTRODUCTION

Semisynthetic opioids constitute a very important class of pharmaceutical compounds. Due to their specific interactions with the opioid receptors, they are most often used either as analgesics[1] or as treatments to prevent opioid abuse or overdoses (antagonists).[2] Within the family of semisynthetic opioids, 14-hydroxy morphinans are arguably most relevant drugs.[3] Notably, oxycodone - a semisynthetic opioid produced in the largest volume - peaked at 138 tons global production volume in 2013.[4] Oxycodone is a widely used analgesic for the treatment of moderate to severe pain. It is listed in the WHO Model List of Essential Medicines as an alternative to morphine.[5] Modification of the N-methyl group of morphinan alkaloids has a significant impact on their pharmacological properties.[6,7] For example, substitution of the N-methyl group of oxymorphone (a 3-OH analog of oxycodone) by an N-allyl or an N-cyclopropylmethyl group produces naloxone and naltrexone, two potent opioid antagonists. Naloxone, for instance, is used as an emergency treatment for drug overdoses[8] and it is also included in the WHO list of essential medicines. Naltrexone, on the other hand, is used to treat opioid and alcohol dependence.[9]

14-Hydroxy morphinans are typically prepared from naturally occurring oripavine (**1a**) or thebaine (**1b**) (Fig. 1).[6,7] Over the past decades, the development of mutagenized *Papaver somniferum* variants has enabled improved yields for these two natural opiates.[10] Indeed, poppy capsules containing exclusively thebaine and oripavine in a ca. 4:1 ratio have been achieved (natural opium contains morphine as the main alkaloid).[11] Generation of oxymorphone (**2a**) and oxycodone (**2b**) from oripavine and thebaine, respectively, is well-established and involves C14-hydroxylation followed by catalytic hydrogenation (Fig. 1).[12,13] Access to opioid antagonists such as naloxone **4** and naltrexone **5** is possible both form thebaine and oripavine.[6,7,12] Classically, thebaine has been the starting material of choice due to its higher abundance and lower price. However, the thebaine route requires an additional O-demethylation step, usually carried out using excess amounts of BBr_3, a toxic and corrosive reagent.[14] To avoid this issue, the oripavine route has also been explored.[15] It involves an additional protection step, although the phenol can be conveniently acetyl-protected and then deprotected during a hydrolysis step. A greener and safe methodology for the removal of the O-methyl group from morphinan alkaloids, avoiding the use of BBr_3, would circumvent the main disadvantage of using thebaine as starting material for the preparation of naloxone and naltrexone.

Transformation of oxycodone or oxymorphone into opioid antagonists also involves a N-demethylation step, leading to the corresponding nor-opiates **3** (Fig.1). In fact, noroxymorphone (**3a**) is a key intermediate which can be readily derivatized to naloxone, naltrexone, and other opioid medicines by N-alkylation.[12] Selective removal of the N-methyl group from

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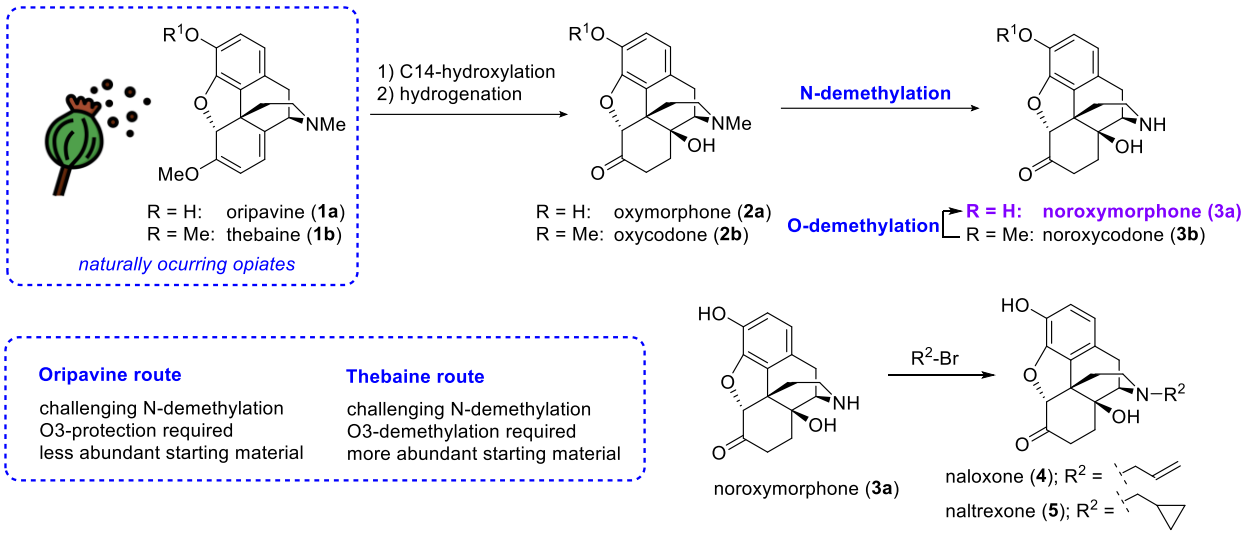


Figure 1. Overview of the synthetic routes toward the opioid antagonists naloxone (**4**) and naltrexone (**5**) from naturally occurring oripavine (**1a**) and thebaine (**1b**).

oxycodone and other opiates is considered as a difficult task.[16] Traditional methods involve the use of toxic and corrosive reagents such as cyanogen bromide (von Braun reaction)[17] or alkyl chloroformates (Fig. 2a).[18] Other methodologies comprise of excess amounts of peroxides and acylating agents (classical Polonovski reaction)[19] or anodic oxidation combined with stoichiometric amounts of TEMPO.[20] Greener approaches, including palladium-catalyzed aerobic oxidations,[21] photochemistry[22] and enzimatic,[23] have been reported during the past decade. Nevertheless, the N-demethylation of 14-hydroxy morphinans on commercial scale is still largely carried out using chloroformate chemistry.[24]

Recently, we have reported a reagent- and catalyst-free electrochemical procedure for the N-demethylation of oxycodone **2b** and other opioid compounds (Fig. 2b).[25] The electrochemical method proceeded in very good yields (89% for oxycodone). However, industrial implementation of this promising methodology was hampered by a series of disadvantages: 1) to avoid the formation of morphinan dimers, the electrolysis had to be carried out under rather diluted conditions. Yet, small amounts of dimer (up to 5%) had to be separated by column chromatography, 2) the supporting electrolyte utilized (Et_4NBF_4) could not be recovered after the electrochemical protocol. Et_4NBF_4 is of significant cost and is a harmful substance, and 3) the solvent system utilized (MeCN/MeOH 4:1) is not ideal, also due to heath concerns. Additionally, electrolysis of oxycodone followed by hydrolysis (Fig. 2b) yields noroxycodone **3b**. Thus, an O-demethylation step is still required for the preparation of the opioid antagonists naloxone and naltrexone, which feature a 3-OH group.

To turn the electrochemical procedure amenable for industrial implementation,[26] we envisaged a modified procedure based on KOAc, which played a dual role as an inexpensive supporting electrolyte and an overoxidation barrier that fully prevents formation of dimers. Furthermore, modification of the hydrolysis step with aqueous HBr enables simultaneous removal of both the N- and O-methyl groups in an efficient and

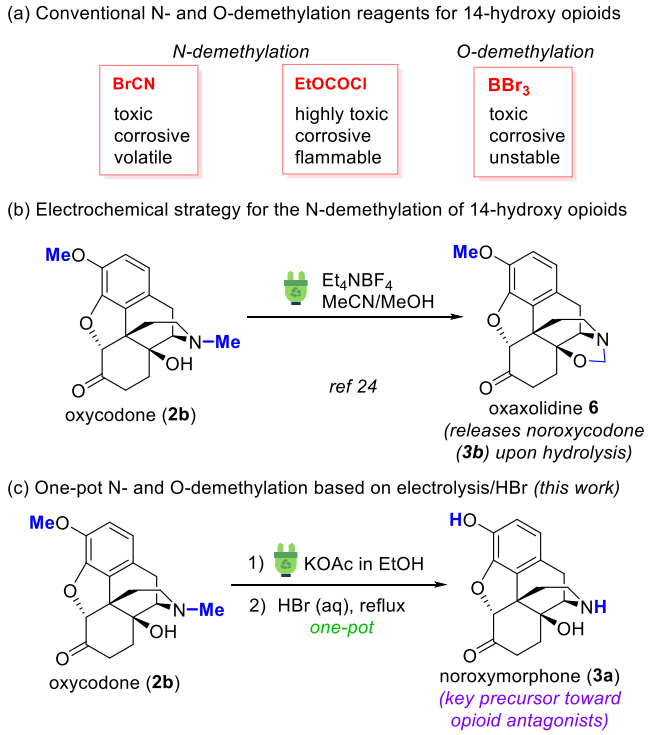


Figure 2. (a) Conventional reagents utilized for the N- and O-demethylation of 14-hydroxymorphinans, (b) reagent- and catalyst-free electrochemical strategy for the N-demethylation via oxazolidine **6** intermediate, and (c) improved telescoped procedure for the N- and O-demethylation based on anodic oxidation and hydrolysis with HBr.

sustainable telescoped protocol, avoiding the use of both chloroformates and BBr_3 in the synthetic process (Fig. 2c). Herein we present details on the optimization of the improved N-/O-demethylation procedure, transfer of the electrochemical

step to a scalable continuous flow electrolysis platform, and a detailed analysis of the green merits of the new process compared to previous protocols.

Results and Discussion

Introduction of Potassium Acetate as Labile Supporting Electrolyte

Electrochemical oxidation of the N-methyl tertiary amine of oxycodone (**2b**) generates an iminium cation[25] (similar to the Shono oxidation[27]) that is rapidly trapped by the C14-hydroxyl group, thus forming oxazolidine **6**. Our previous investigations[25] demonstrated that dimers such as **7** are the main side products observed during the electrolysis (Fig. 3). Cyclic voltammetry analysis of oxycodone **2b** revealed that oxidation of the electron-rich aromatic ring occurs at an anode potential approximately 0.5 V higher than the oxidation of the tertiary amine [$E_{p/2}$ (N-ME) = +1.10 V vs SCE vs $E_{p/2}$ (Ar) = +1.66 V vs SCE]. Electrolysis under galvanostatic conditions provided high selectivity (> 94%) toward amine oxidation, with variable amounts (1-5%) of opioid dimers formed.[25] However, dimeric structures had to be removed from the reaction product by column chromatography, which is detrimental to the reaction sustainability and an undesired workup procedure for industrial applications. Although electrolysis under potentiostatic conditions may alleviate this issue, constant potential operation requires a 3-electrode setup and is difficult to scale-up. To alleviate this issue, we utilize potassium acetate (KOAc) as additive in the reaction. KOAc can act as a good supporting electrolyte material, it is safe and inexpensive, and it degrades by anodic oxidation to CO_2 and ethane at $E_{p/2}$ ($^-$OAc) = +1.47 V vs SCE.[28] The presence of KOAc in the reaction solution was therefore expected to prevent overoxidation of the reaction product and thus undesired dimer formation (Fig. 3).

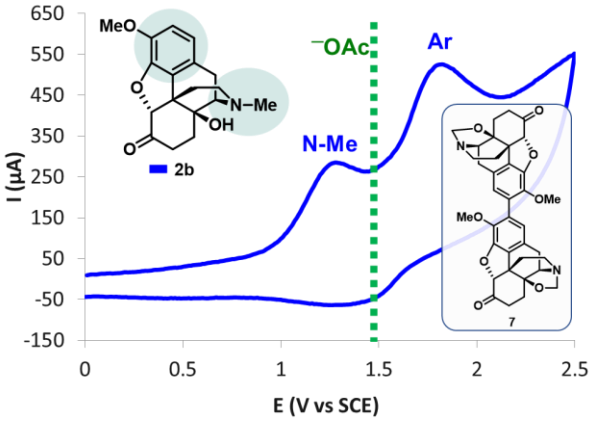
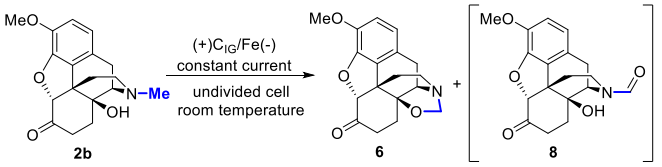


Figure 3. Cyclic voltammogram of oxycodone (**2b**), overlap of the oxidation potential of the acetate anion (+1.47 V vs SCE) and structure of the dimer **7** formed at higher electrode potentials.

Synthesis-scale experiments where then carried out to evaluate this new anodic oxidation strategy (Table 1). All reaction were carried out in undivided 5 mL IKA ElectraSyn 2.0 cells under constant current conditions. Standard stainless steel electrodes from IKA were used as cathode material in all cases. Impervious graphite, machined to the exact dimensions of an ElectraSyn 2.0 electrode, was used as anode material (see ESI for details). Impervious graphite is a graphite-based material filled with a phenolic resin, which avoids permeation of the reaction mixture into the pores. This material typically features improved yields, as the reaction mixture cannot penetrate the electrode, compared to normal graphite. Moreover, its leak-proof properties make it ideal for translation of the process to a flow cell (vide infra).[29]

Initial experiments were carried out using a 20% excess of charge (2.4 F/mol) and 5 mA of current (3.3 mA/cm^2). An initial solvent screening (Table 1, entries 1-3) revealed that a combination of KOAc as supporting electrolyte and ethanol as solvent provides excellent selectivity (entry 3). Importantly, no traces of dimer formation could be observed by HPLC analysis. Nearly quantitative HPLC yield (97% conversion and complete selectivity, entry 4) could be achieved by simply passing a larger excess of charge (3 F/mol) through the reaction.

Table 1. Optimization of the conditions for the electrolysis of oxycodone **2b**.[a]



Entry	Solvent	2b (mM)	KOAc (mM)	I (mA)	Q (F/mol)	Conv [%][b]	Select [%][b,c]
1	MeCN/MeOH 4:1	50	100	5	2.4	93	94
2	MeOH	50	100	5	2.4	88	75
3	EtOH	50	100	5	2.4	80	99
4	EtOH	50	100	5	3	97	99
5	EtOH	50	100	10	3	75	80
6	EtOH	100	50	5	3	95	99(9)
7	EtOH	100	100	5	3	98	99
8	EtOH	200	100	5	3	86	99(14)
9	EtOH	200	200	5	3	95	99(6)
10	EtOH	200	100	5	4	99	99(21)

[a] IKA ElectraSyn 2.0, 5 mL vial, 3 mL solvent, 1.5 cm^2 electrode area. [b] Determined by HPLC-UV (205 nm) peak area percent. [c] Selectivity refers to the HPLC area percent (205 nm) of compounds **6** and **8** combined with respect to all other peaks except the starting material. Amount of **8** indicated in parenthesis. C_{IG}: impervious graphite. Fe: stainless steel.

Although the current density could not be increased successfully (entry 5), the reaction concentration could be gradually incremented from 0.05 M to 0.2 M (entries 6-10). The amount of KOAc could be kept at half the concentration compared to substrate. When 0.5 equiv of KOAc were utilized, decreased current efficiencies were typically observed (entry 6 vs 7, entry 8 vs 9), although this could be readily solved by further increasing the amount of charge (entry 10). Notably, variable amounts of the N-formyl derivative **8** were also

observed at increased reaction concentrations (amount noted in parenthesis in the selectivity column). Formation of **8** could be ascribed to overoxidation of oxazolidine **6**, forming a cyclic iminium cation which is trapped by a nucleophile or water. Gratifyingly, the presence of **8** did not cause any problems to the overall reaction outcome, as both the oxazolidine **6** and the N-formyl compound **8** are readily hydrolyzed to the target nor-derivative **3** (vide infra). It should be noted that the quality of EtOH utilize did not impact the reaction outcome. Thus, technical grade (96%) EtOH could be used for the transformation without issues.

Notably, the high conversion and selectivity with which the electrolysis took place applying the reaction conditions shown in entry 7 (Table 1) enabled a simple extraction as workup to remove the potassium salts from the product. In a 0.3 mmol experiment, 90 mg (98% yield, 96% purity by HPLC) of oxazolidine **6** were obtained.

Scalable Electrolysis in a Flow Cell – Single-Pass Processing and Electrolyte Recirculation

The scale up of electroorganic synthesis is based on the utilization of flow electrolysis cells.[30] Scaling up batch electrochemical reactions is problematic due to mass transfer limitations and a decrease of the electrode surface area to reactor volume ratio as the vessel size increases.[31] These issues are alleviated in flow cells, featuring small interelectrode distances (< 1mm), high mass transfer efficiency, low cell resistance, and a very high electrode area-to-volume ratio which remains constant during scale up.[32]

To ensure smooth scale up of our electrochemical procedure, the electrolysis was transferred to a laboratory scale flow cell. The cell, which has been described elsewhere,[33] consisted of two parallel plate electrodes (impervious graphite as the anode material and stainless steel as the cathode) separated by a polymer membrane containing a flow channel (see Figure S1). The flow channel provided an electrode surface contact area of 6.4 cm^2, an interelectrode gap of 0.1 mm and a reactor volume of 63 µL. A single-pass electrolysis approach was initially evaluated (Fig. 4). Single-pass electrolysis aims at high conversion of the starting material after the reaction solution has been pumped once through the cell. This type of flow approach is very attractive, as a genuinely continuous synthesis is achieved, permitting the integration of the electrochemical reaction with other synthetic or workup steps. Thus, a solution of oxycodone **2b** (50 mM) in EtOH containing 50 mM KOAc was pumped through the cell using a peristaltic pump (Figure S2). To optimize the flow electrolysis conditions, the pump flow rate and the current setting of the power supply were varied. Aliquots of the crude reaction mixture were collected form the reactor output under steady state conditions for each of the settings and analyzed by HPLC (Fig. 4). Gratifyingly, quantitative HPLC yield was obtained at flow rater up to 87 µL/min by applying sufficient current to pass 3 F/mol.

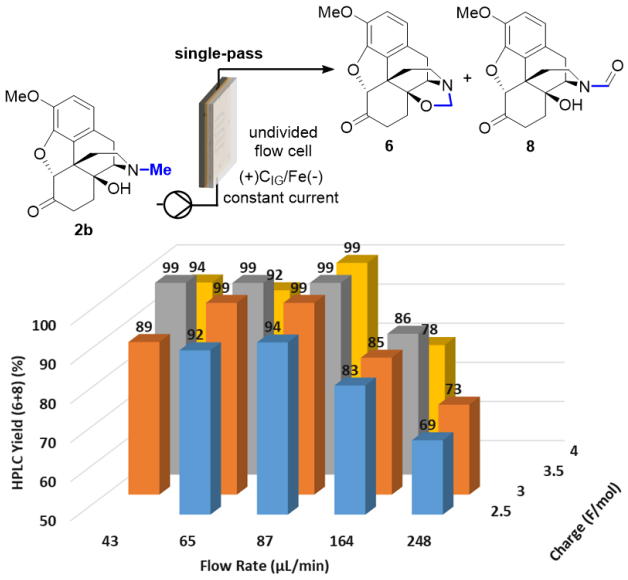
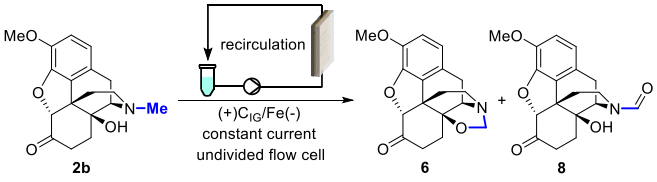


Figure 4. Schematic view of the continuous flow setup for the single-pass flow electrolysis of oxycodone **2b** and optimization of the reaction conditions.

The reaction concentration could not be increased above 50 mM using the single-pass approach, due to the low solubility of **2b** in EtOH. Mixtures containing 100 mM of **2b** resulted in slurries, which are difficult to process in flow cells. For this reason, and as intermediates **6** and **8** are well soluble in EtOH, we next looked into an electrolyte recirculation approach for the electrochemical reaction with the flow cell (Table 2). In this case, the reaction mixture was continuously pumped through

Table 2. Optimization of the electrolysis conditions of oxycodone **2b** using a flow cell in electrolyte recirculation mode.[a]



Entry	2b (mM)	KOAc (mM)	Gap (mm)	I (mA)	Q (F/mol)	Conv (%)[b]	Selec (%)[b,c]
1	50	50	0.3	16	3	88	99(-)
2	50	50	0.3	21	4	99	99(-)
3	50	50	0.1	42	3	99	99(12)
4	50	50	0.1	63	3	82	98(12)
5	100	100	0.1	42	3	90	99(7)
6	100	100	0.1	42	4	99	99(15)
7	200	100	0.1	42	4	95	99(18)

[a] The flow cell described in Fig. S1 was used. [a] Determined by HPLC-UV (205 nm) peak area percent. [c] Amount of **8** indicated in parenthesis. C_{IG}: impervious graphite. Fe: stainless steel.

the cell and returned to the reaction vessel until the desired amount of current had been passed through the solution. A filter plug was attached to the tubing of the pump input, thus only permitting the liquid phase of the reaction mixture

entering the cell. As the reaction proceeded, **2b** dissolved and the reaction mixture became homogeneous. This strategy enabled gradually increasing the concentration of **2b** to 200 mM (Table 2). An interelectrode gap of 0.3 mm was initially evaluated to ensure that no electrode bridging occurred (i.e., solid particles contacting both electrodes provoking a short-circuit). However, only a limited cell current (21 mA, entries 1 and 2) could be applied. Reducing the interelectrode gap to 0.1 mm enabled gradually increasing the cell current to 42 mA. At 63 mA ca. 2% of dimer was observed by HPLC analysis (entry 4). Therefore 42 mA were applied to all subsequent experiments. Gradual increase of the concentration of **2b** (entries 5-7) confirmed that, using an electrolyte recirculation approach, 100 mA and 200 mM concentrations can be processed with ease. Using this flow procedure, gram-scale electrolysis could be demonstrated. For this experiment, conditions in which **6** is selectively formed (Table2, entry 2) were applied, to characterize the product and obtain the isolated yield of pure material. Thus, a solution containing 4.2 mmol of oxycodone **2b** was processed using the flow cell. Workup of the reaction mixture provided 1.16 g (93% yield, 96% HPLC purity) of oxazolidine **6**.

It should be emphasized that, using a very low volume reactor (63 µL), an 8-fold increase in the process productivity compared to the batch cell could be attained. These data result in a space-time yield approximately 380-fold higher compared to the batch experiments described above.

Telescoped N-/O-Demethylation

The process to remove the O-methyl group from noroxycodone **3b** and other opiates derived from thebaine typically involves treatment with an excess amount of BBr_3.[14] L-Selectride has also been shown as an effective reagent to promote O-demethylation of morphinans.[34] Unfortunately, both compounds are harmful and their substitution by more benign reagents is highly desired. On the other hand, HBr-mediated O-demethylation of simpler aryl methyl ethers, such as anisole derivatives, is well-known.[35] Selective O-demethylation of opioid derivatives with aqueous HBr has been evaluated in the past, although only low to moderate yields (27%-34%) were obtained.[36] We anticipated that aqueous HBr should be a suitable O-demethylation reagent if the reaction time and temperature, as well as the HBr concentration, are carefully adjusted. To test this hypothesis, samples of isolated noroxycodone **3b** were treated with aqueous solutions of HBr and heated in sealed vessels (Table 3). As expected, when commercial 47 wt% aqueous HBr was directly utilized, good selectivity was only observed at relatively low conversion (entry 1). Heating the reaction mixture for longer periods to increase the conversion resulted in significant product degradation (entry 2). By gradually decreasing the HBr concentration and careful adjusting the reaction temperature and time (entries 3-7), the conversion and selectivity could be improved. Heating at 120 °C for 5 h in a 25 wt% HBr solution provided excellent conversion and selectivity to the target noroxymorphone **3a** (entry 8).

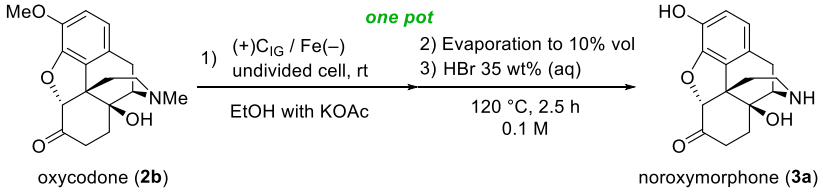
Table 3. Optimization of reaction conditions for the HBr-mediated O-demethylation of noroxycodone **3b**.[a]

3b (0.1 M) **3a**

Entry	HBr (aq) (wt%)	T (°C)	t (h)	Conv (%)[b]	Select (%)[b]
1	47	100	0.5	57	99
2	47	100	1	84	76
3	40	100	1	56	99
4	40	100	2	82	91
5	30	100	5	65	99
6	30	120	2	99	87
7	25	120	2	74	99
8	25	120	5	98	99

[a] 0.1 mmol scale, 30.1 mg **3b** in 1 mL HBr solution. [b] Determined by HPLC-UV (205 nm).

We next focused our attention into a telescoped procedure for the preparation of noroxymorphone (**3a**) from oxycodone (**2b**). Transformation of oxazolidine **6** into noroxycodone **3b** is usually carried out by hydrolysis with aqueous HCl. It was expected that treatment of **6** with HBr instead of HCl would effect both the ring-opening/N-demethylation of oxazolidine **6** and the O-demethylation simultaneously. To achieve this (Fig. 5), the crude reaction mixture from the electrochemical step was partially evaporated (10% volume remaining). Then, the



oxycodone (**2b**) noroxymorphone (**3a**)

Figure 5. One pot electrochemical N-demethylation followed by HBr-mediated O-demethylation of oxycodone (**2b**).

solution was diluted with 35 wt% aqueous HBr and heated at 120 °C for 2.5 h. Partial removal of EtOH prior to treatment with HBr was needed, as high alcohol content inhibited the reaction. Moreover, the concentration of HBr had to be increased from 25 wt% (Table 3, entry 8) to 35 wt%. This was due to the fact that the electrolysis mixture contained KOAc. Under these conditions, quantitative HPLC yield for the target compound **3a** was obtained (see Table S5 in the Supplementary Material for details on the optimization). The product **3a** could be crystallized, by adjusting the pH of the aqueous mixture with $NaHCO_3$ to pH = 9, providing an isolated yield of 74% (>99% HPLC purity). As anticipated, when electrolysis solutions containing mixtures of oxazolidine **6** and the N-formyl derivative **8** were hydrolyzed under the same conditions, both intermediates were smoothly transformed into **3a**, confirming that formation of **8** during the electrochemical step is not problematic.

Process Green Metrics and Sustainability Qualitative Indicators

Turning a conventional process electrochemical does not guarantee improved sustainability, as often large amounts of supporting electrolytes or diluted conditions are needed in electroorganic synthesis.[37] To demonstrate the superior performance of the second-generation electrochemical N-demethylation methodology presented herein, it was evaluated in detail by means of quantitative green metrics and qualitative sustainability indicators. Additionally, it was benchmarked with the conventional chloroformate protocol[24] and the first-generation electrochemical method (Table 4).[25] The assessment compares the formation of N-EtOCO-noroxycodone with chloroformate and oxazolidine **6** by electrolysis, prior to the hydrolysis step to the nor-derivative **3b**, which is analogous for each of the three procedures.

The assessment of qualitative sustainability indicators[38] (Table 4, entries 1-7) is represented by colored flags (green, amber, red). A green flag corresponds to "preferred" conditions, while amber stands for "is acceptable-some issues" and a red flag means "undesirable" conditions. Both electrochemical methods can be performed at room temperature (entry 2). The chloroformate process takes place in chloroform under reflux ca. 60 °C, which is within the recommended energy efficient temperature window (0-70°C). Thus, a green flag can also be assigned to the conventional process. However, the fact that the solvent is heated to reflux grants a red flag (entry 3), according to the CHEM21 toolkit.[38] Notably, the workup procedure for the new electrochemical process ("Electrochemical B") is a significant advantage with respect to the original electrolysis procedure ("Electrochemical A"), which required column chromatography to remove dimer impurities (entry 4). Parameters regarding environmental and health concerns, not surprisingly, clearly favor the use of electrochemistry instead of excess amounts of toxic and environmentally unfriendly ethyl chloroformate and $CHCl_3$ as solvent (entries 5-7). In this context, the optimized electrochemical process is also superior to the original one, as the use of Et_4NBF_4, MeCN and MeOH can be avoided. Indeed, the only issue with the second generation electrochemical process is the flammability of ethanol. Yet, it should be emphasized that inexpensive technical grade ethanol could be utilized for the electrochemical transformation. Moreover, as evaporation of 90% of the solvent is carried out prior hydrolysis in the next reaction step, it could be readily recycled in a potential commercial process.

Table 4. Qualitative sustainability indicators and green metrics for the conventional ethyl chloroformate process and the two electrochemical methods.[a]

Entry		EtOCOCl[b]	Electrochemical A[c]	Electrochemical B[d]
1	Type of reaction	Stochiometric Reagent	Electricity	Electricity
2	T [°C]	60	rt	rt
3	Reflux	Yes	No	No
4	Workup	Extraction	Chromatography	Extraction
5	Solvent	$CHCl_3$	MeCN/MeOH	EtOH
6	Health Concerns	H225, H290, H302, H314, H330 (EtOCOCl) H225, H290, H302, H314, H330 ($CHCl_3$)	H225, H302, H312, H319, H332 (MeCN) H226, H301, H311, H331 (MeOH) H302, H312, H332, H315, H319, H335 (Et_4NBF_4)	H225 (EtOH)
7	Environmental implications	H-412	No	No
8	Yield (%)	60	89	98
9	Quench	50 L water / kg oxycodone	No quench needed	No quench needed
10	Atom Economy (%)	12	35	81
11	PMI (without solvent)	3.5	2.9	1.2
12	PMI	37	62	15
13	EcoScale	49	60	90

[a] Comparison of the reaction of oxycodone **2b** with ethyl chloroformate or electrolysis, resulting in the N-modified intermediates N-EtOCO-noroxycodone and oxazolidine **6**, respectively, prior to hydrolysis to the nor-derivative. [b] Process described in reference 24 (example 7). [c] Process described in reference 25. [d] Process described herein.

Quantitative green metrics recommended in the CHEM21 toolkit[38] were utilized to benchmark the three processes (Table 4, entries 8-13). Importantly, the new electrochemical method provided nearly quantitative yield (98%) of the key reaction intermediate, superior to the ethyl chloroformate process (60%) and the first-generation electrochemical protocol (89%). The atom economy (entry 10) clearly improves when moving from the conventional method to the electrochemical procedures. The new electrochemical method features an impressive 80% atom economy. Interestingly, the previous version of the electrochemical procedure was inferior to the conventional method in terms of process mass efficiency (PMI) (37 vs 62, entry 12). This is due to the high dilution (0.05 M) that was required to avoid the formation of dimers. The new electrochemical method could be carried out at much higher concentrations (0.2 M) without the need of a large molecular weight supporting electrolyte (Et_4NBF_4 was substituted by KOAc), resulting in an excellent PMI of only 15.

Additionally, the EcoScale was also calculated for each of the procedures. The EcoScale is a semi-quantitative analysis that takes into account ecological and economical parameters.[39] The maximum score is 100, and several reaction parameters (yield, use of harmful or expensive chemicals, etc.) "penalize" and subtract points from the total score. The conventional process with ethyl chloroformate has an EcoScale of only 49. Significant penalties include the moderate yield as well as several safety concerns. The EcoScale was already significantly superior for the original electrochemical protocol (60, entry 13), reaching an excellent value of 90 for the new electrochemical process.

Conclusion

In summary, we have developed an efficient procedure for the electrochemical N-demethylation/HBr-mediated O-demethylation of oxycodone **2b**. The sustainable and scalable procedure provides noroxymorphone **3a**, a pivotal intermediate for the synthesis of several opioid antagonists. The initial electrolysis step, based on a previous methodology reported by our group, significantly improves both the efficiency and sustainability of the original protocol: a combination of KOAc as supporting electrolyte and ethanol as solvent suppresses the undesired formation of dimers, improves the yield to nearly quantitative values and avoids the use of large molecular weight salts such as Et_4NBF_4. The electrochemical step could be combined with an HBr-mediated O-demethylation, by simply evaporating part of the solvent after the electrolysis before treatment with HBr. This strategy avoids isolation of the intermediate and the utilization of harmful reagents such as BBr_3 or L-selectride.

The electrochemical procedure has been transferred to a flow electrolysis cell to provide a suitable platform for process scale up. Successful electrolysis both in a single pass and with electrolyte recirculation has been attained. Notably, an 8-fold productivity compared to batch has been accomplished with a low volume cell (63 µL), providing a space-time yield 380-fold higher than the batch reactor. Transfer of the process to a flow platform ensures smooth scale up to industrial electrolyzers, thus facilitating application of the transformation on a commercial setting.[31,32,40]

The greenness of the new electrochemical method has been evaluated by means of qualitative sustainability indicators and green metrics. The data reveal significant improvements in terms of safety, efficiency and waste generation with respect to conventional processes.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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Electronic Supplementary Information

Sustainable and Scalable Synthesis of Noroxymorphone via a Key Electrochemical N-Demethylation Step

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Contents

Materials and Methods

^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument. ^{13}C NMR spectra were recorded on 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, respectively. Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 mm) at 37 °C by using mobile phases A [water/acetonitrile 90:10 (v/v) + 0.1% TFA] and B (acetonitrile + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from solution 3% B to 100% B within 10 min. All electrochemical reactions were carried out in IKA ElectraSyn 2.0 undivided cells (5 mL vials). Stainless steel electrodes were washed with MeOH and polished with 3000 grit sandpaper. Graphite electrodes were polished with a whetstone 3000 grit. Impervious graphite electrodes were cut and polished to the exact same dimension of the standard IKA ElectraSyn 2.0 electrodes form an impervious graphite plate (FC-GR347B, Graphtek LLC). KOAc was purchased from Aldrich (product number: 236497; Lot: DI20313MS) All solvents were obtained from standard commercial vendors. Technical grade EtOH was obtained from VWR (product number: 85829.360; Lot: 210114). Oxycodone **2b** was prepared according a literature procedure.[S1]

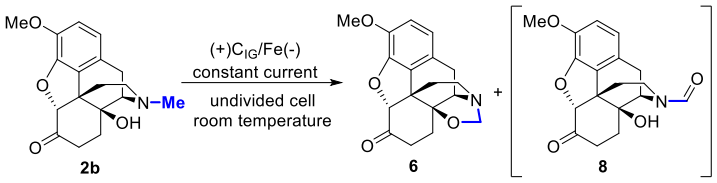
HPLC Analysis – Sample Preparation

Some of the opioid derivatives described in this work did not separate adequately in a C18 column. Thus, a derivatization procedure was applied to aliquots of the reaction mixture for analysis: 50 µL of the crude reaction mixture 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 20 min. The content of the vial was then directly analyzed by HPLC–UV/Vis with the method described above in the General Information section. Peak area integration was carried out at 205 nm.

Optimization of the electrochemical oxidation of oxycodone 2b to oxazolidine 6

The corresponding amounts of oxycodone (**2b**) and supporting electrolyte (KOAc) (Table S1) were placed in a 5 ml IKA ElectraSyn 2.0 vial. Then 3 ml of solvent were added and the mixture was stirred for 30 minutes. The cell was capped with the reaction mixture was electrolyzed under constant current and a stirring speed of 1000 rpm until the desired amount of charge had been passed. After the electrolysis, the crude reaction mixtures were analyzed by HPLC.

Table S1. Optimization of the electrolysis of oxycodone (**2b**) in batch mode.



Entry	Conditions	Conversion (%)[a]	Selectivity (%)[b]
1	MeCN/MeOH 4:1, 0.05 M **2b**, **0.1 M KOAc**, 5 mA, 2.4 F/mol	87	99
2	MeCN/MeOH 4:1, 0.05 M **2b**, **0.1 M KOAc**, 5 mA, **2 F/mol**	67	99
3	MeCN/MeOH 4:1, 0.05 M **2b**, **0.1 M KOAc**, 5 mA, **2.8 F/mol**	93	99
4	**MeOH,** 0.05 M **2b**, **0.1 M KOAc**, 5 mA, 2.4 F/mol	88	75
5	**EtOH,** 0.05 M **2b**, 0.1 M KOAc, 5 mA, 2.4 F/mol	80	99
6	**EtOH,** 0.05 M **2b**, 0.1 M KOAc, 5 mA, **3 F/mol**	97	99
7	EtOH, 0.05 M **2b**, 0.1 M KOAc, **10 mA**, 3 F/mol	75	80
8	EtOH, 0.05 M **2b**, **0.05 M KOAc**, 5 mA, 3 F/mol	97	99
9	EtOH, 0.05 M **2b**, KOAc 0.05 M, **10 mA**, 3 F/mol	80	94
10	**EtOH tg.,** 0.05 M **2b**, 0.05 M KOAc, **5 mA,** 3 F/mol	84	99
11	EtOH tg., 0.05 M **2b**, KOAc 0.05 M, 5 mA, **3.5 F/mol**	89	99
12	EtOH tg., 0.05 M **2b**, 0.05 M KOAc, 5 mA, **4 F/mol**	99	99
13	**EtOH, 2b 0.1 M, KOAc 0.1 M**, 5 mA, **3 F/mol**	98	99
14	EtOH, **2b 0.2 M,** KOAc 0.1 M, 5 mA, 3 F/mol	86	99(14)
15	EtOH, **2b** 0.2 M, **KOAc 0.2 M,** 5 mA, 3 F/mol	95	99(6)
16	EtOH, **2b** 0.2 M, **KOAc 0.2 M,** 5 mA, 4 F/mol	99	99(21)

[a] Determined by HPLC-UV (205 nm) peak area percent. [b] Selectivity refers to the HPLC area percent (205 nm) of compounds **6** and **8** combined with respect to all other peaks except the starting material. Amount of **8** indicated in parenthesis. C_{IG}: impervious graphite. Fe: stainless steel. tg =technical grade.

Description of the Flow Electrolysis Cell and the Flow Setup

The flow electrolysis cell used for this work followed a typical parallel plates design and has been described in detail in a previous publication.[S2] The setup consisted of 2 aluminum end plates with an attached current collector (Fig. S1). The endplates were separated from the electrodes by two Mylar films. The electrodes were aligned by additional Mylar sheets. An interelectrode gap foil (0.1 mm or 0.3 mm) incorporating a flow channel was inserted between the electrodes. The reaction channel provided a surface area of 6.4 cm². AISI 316L stainless steel plate (GoodFellow, 50x50x0.2 mm) was used as the cathode. The anode consisted of impervious graphite (FC-GR347B, Graphtek LLC, 50x50x5 mm). The cell was powered by a BK Precision 1739 power supply. The reaction mixture was pumped using a Vapourtec SF-10 peristaltic pump (Fig. S2).

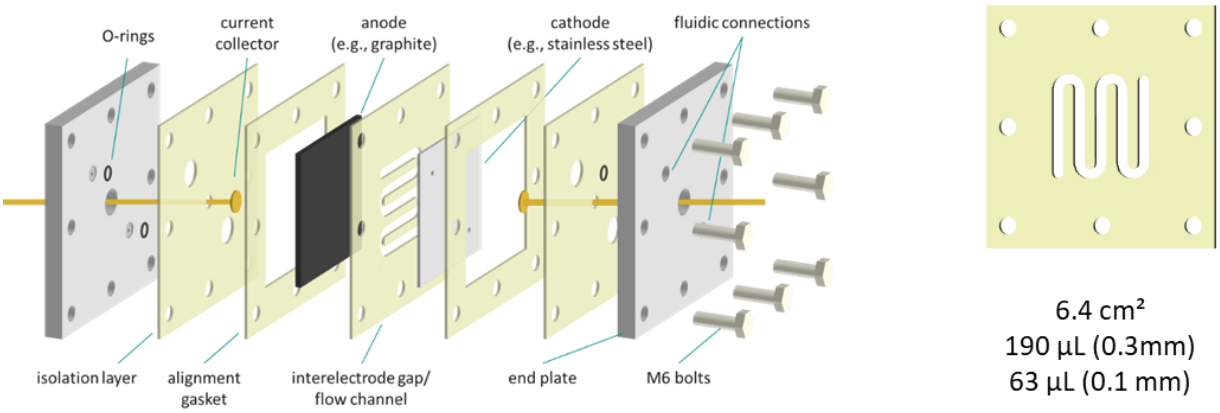


Figure S1. Exploded view of the flow electrolysis cell and the reaction channel. Images reproduced from reference S2.

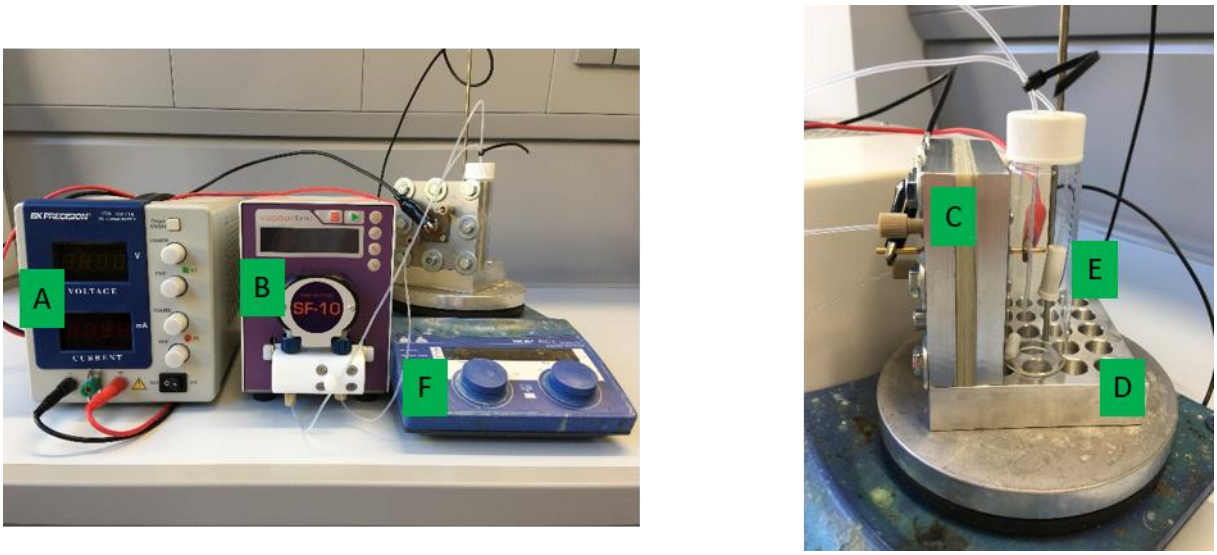
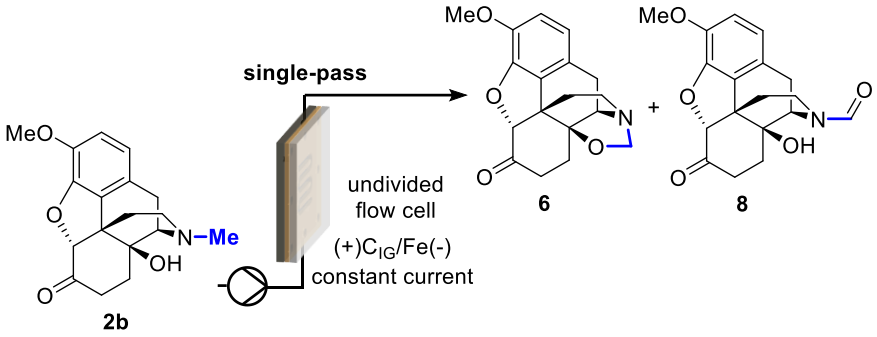


Figure S2. Photographs of the flow electrolysis setup. A: power supply; B: peristaltic pump; C: assembled flow cell; D, F: heating plate and heating block (suitable for heating the cell if needed); E: electrolyte reservoir (recirculation mode).

Optimization of the single-pass continuous flow electrolysis of oxycodone 2b

The flow electrolysis cell described in page S5 was used. A solution of **2b** (0.05 M) and KOAc (0.05 M) in ethanol was pumped through the cell. Under steady state conditions, the power supply was turned on. The current output of power supply and the pump flow rate were adjusted to meet the desired amount of charge (Table S2). After each set of conditions was inputted, 3 reactor volumes were discarded to ensure steady state conditions and then an aliquot of the crude reaction mixture was collected from the reactor output and analyzed by HPLC.

Table S2. Optimization of the single pass flow electrolysis



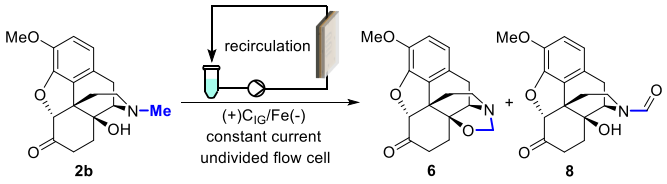
Flow rate [µL/min]	Charge [F/mol]	Current [mA]	Conversion (%)[a]	Selectivity (%)[a,b]
43	2.5	3.5	26	99 (-)
43	3.0	4.1	89	99 (10)
43	3.5	4.8	99	99 (32)
43	4.0	5.5	99	94 (50)
65	2.5	5.2	92	99 (35)
65	3.0	6.3	99	99 (25)
65	3.5	7.3	99	99 (50)
65	4.0	8.4	99	92 (46)
87	2.5	7.0	94	99 (43)
87	3.0	8.4	99	99 (36)
87	3.5	9.8	99	99 (50)
87	4.0	11.2	99	99 (50)
164	2.5	13.2	92	83 (39)
164	3.0	15.8	92	85 (55)
164	3.5	18.5	99	86 (30)
164	4.0	21.1	99	77 (99)
248	2.5	19.9	80	82 (43)
248	3.0	23.9	94	76 (63)

[a] Determined by HPLC peak area percent (205 nm). [b] Calculated as the percentage of product with respect to all other peaks except the substrate. Amount of **8** shown in parenthesis. C_{IG}: impervious graphite; Fe: steel.

Optimization of the electrolysis of oxycodone 2b in flow with electrolyte recirculation

A solution of **2b** and KOAc in EtOH was prepared in a volumetric flask. The reaction mixture was pumped through the empty cell and the cell output line was placed into the same volumetric flask to recirculate the reaction mixture. Once the cell had been filled with liquid (no air bubbled visible at the output line), the power supply was turned on under constant current mode. When the desired amount of charge had been passed (Table S3), the input line of the cell was removed from the reaction mixture, allowing air to enter the cell and emptying all the solution into the reservoir. The reaction progress was monitored by collecting aliquots of the crude mixture from the solution reservoir during the electrolysis.

Table S3. Optimization of the electrolysis of **2b** in flow recirculation mode.



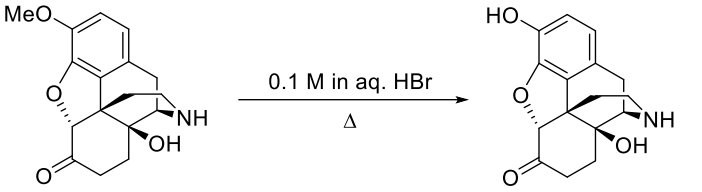
Conditions	Conv (%)[b]	Select (%)[c]
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, 5 mL/min, 16 mA, 2 F/mol	71	99 (-)
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, 5 mL/min, 16 mA, **3 F/mol**	89	99 (-)
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, 5 mL/min, 16 mA, **4 F/mol**	94	99 (-)
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, **10 mL/min,** 16 mA, **2 F/mol**	74	99 (-)
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, 10 mL/min, 16 mA, **3 F/mol**	88	99 (9)
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, **5 mL/min, 21 mA, 2 F/mol**	68	99 (-)
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, 5 mL/min, 21 mA, **3 F/mol**	89	99 (10)
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, 5 mL/min, 21 mA, **4 F/mol**	95	99 (13)
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, **10 mL/min,** 21 mA, **2 F/mol**	85	99 (-)
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, 10 mL/min, 21 mA, **3 F/mol**	99	99 (-)
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, 10 mL/min, 25 mA, **2 F/mol**	60	99 (8)
EtOH, KOAc 0.05 M, **2b** 0.05 M, Gap 0.3 mm, 10 mL/min, 25 mA, **3 F/mol**	83	99 (-)
EtOH, **KOAc 0.1 M, 2b 0.1 M,** Gap 0.3 mm, 10 mL/min, **42 mA, 2 F/mol**	80	99 (-)
EtOH, KOAc 0.1 M, 2b 0.1 M, Gap 0.3 mm, 10 mL/min, 42 mA, **3 F/mol**	90	99 (7)
EtOH, KOAc 0.1 M, 2b 0.1 M, Gap 0.3 mm, 10 mL/min, 42 mA, **4 F/mol**	99	99 (15)
EtOH, KOAc 0.1 M, **2b 0.2 M,** Gap 0.3 mm, 10 mL/min, 42 mA, **2 F/mol**	72	99 (5)
EtOH, KOAc 0.1 M, 2b 0.2 M, Gap 0.3 mm, 10 mL/min, 42 mA, **3 F/mol**	87	99 (18)
EtOH, KOAc 0.1 M, 2b 0.2 M, Gap 0.3 mm, 10 mL/min, 42 mA, **4 F/mol**	93	99 (43)
EtOH, **KOAc 0.05 M, 2b 0.05 M, Gap 0.1 mm,** 10 mL/min, 42 mA, **2 F/mol**	82	99 (-)
EtOH, KOAc 0.05 M, 2b 0.05 M, Gap 0.1 mm, 10 mL/min, 42 mA, **3 F/mol**	99	99 (12)
EtOH, KOAc 0.05 M, 2b 0.05 M, Gap 0.1 mm, 10 mL/min, **63 mA, 2 F/mol**	62	99 (10)
EtOH, KOAc 0.05 M, 2b 0.05 M, Gap 0.1 mm, 10 mL/min, 63 mA, **3 F/mol**	82	98 (12)
EtOH tg., KOAc 0.05 M, 2b 0.05 M, Gap 0.1 mm, 10 mL/min, 63 mA, **3 F/mol**	80	99 (20)
EtOH tg., KOAc 0.05 M, 2b 0.05 M, Gap 0.1 mm, 10 mL/min, 63 mA, **4 F/mol**	99	99 (21)

[a] Determined by HPLC peak area percent (205 nm). [b] Calculated as the percentage of product with respect to all other peaks except the substrate. Amount of **8** shown in parenthesis. C$_{IG}$: impervious graphite; Fe: steel.

Optimization of the HBr-mediated O-Demethylation of Noroxycodone (3b)

In an HPLC vial were placed a stir bar, 15 mg (0.05 mmol) of noroxycodone (**3b**) and 0.5 mL of an aqueous solution of HBr in water. The vial was sealed and heated in an aluminum heating block for the desired amount of time. Upon cooling, the crude reaction mixture was analyzed by HPLC (Table S4).

Table S4. Optimization of the HBr-mediated O-demethylation of noroxycodone (**3b**)



noroxycodone (**3b**) noroxymorphone (**3a**)

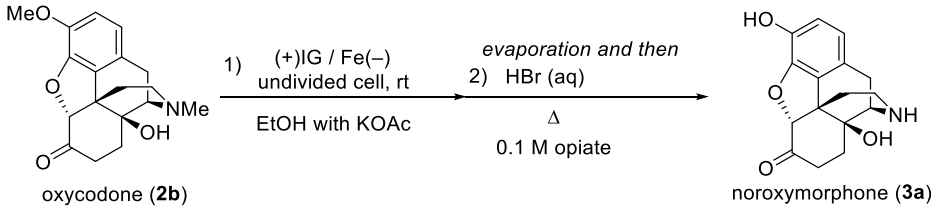
Conditions	Conversion (%)[a]	Selectivity (%)[b]
47 wt% HBr, 100 °C, 15 min,	37	99
40 wt% HBr, 100 °C, 15 min	16	99
33 wt% HBr in AcOH, 100 °C, 15 min	-	-
33 wt% HBr in AcOH, 100 °C, **30 min**	72	40
30 wt% HBr, 100 °C, 15 min	3	99
20 wt% HBr, 100 °C, 15 min	-	-
10 wt% HBr, 100 °C, 15 min	-	-
47 wt% HBr, **120 °C**, 15 min	83	79
47 wt% HBr, **80 °C**, 15 min	7	99
47 wt% HBr, **60 °C**, 15 min	-	-
47 wt% HBr, **100 °C**, **60 min**	84	76
47 wt% HBr, 100 °C, **30 min**	57	99
47 wt% HBr, 100 °C, 30 min, **0.5 M NOC**	77	78
47 wt% HBr, **80 °C**, **4 h**	79	85
47 wt% HBr, **70 °C**, **8 h**	36	99
30 wt% HBr, 100 °C, **2.5 h**	41	99
30 wt% HBr, 100 °C, **5 h**	64	99
30 wt% HBr, 100 °C, **7.5 h**	82	99
40 wt% HBr, 100 °C, **60 min**	56	99
30 wt% HBr, 120 °C, **2 h**	98	88
25 wt% HBr, 120 °C, 2 h	73	99
25 wt% HBr, 120 °C, **5 h**	98	99
25 wt% HBr, **140 °C, 1 h**	94	96
20 wt% HBr, 140 °C, 1 h	57	99
20 wt% HBr, **160 °C, 30 min**	78	99

[a] Determined by HPLC peak area percent (205 nm). [b] Percent of product with respect to all peaks except the substrate (HPLC peak area percent, 205 nm).

Optimization of the One-Pot Electrochemical N-Demethylation/HBr-Mediated O-Demethylation of Oxycodone (2b) to Noroxymorphone (3a)

A stock solution of oxycodone **2b** and KOAc in ethanol was electrolyzed following the optimal conditions described above (Table S1, entry 12). Then, an aliquot of the crude electrolysis mixture containing 0.05 mmol of **6** was placed in a HPLC vial. The solvent was partially evaporated (volume left indicated in Table S5) and the residue diluted with 0.5 mL of an aqueous solution of HBr. The vial was sealed and the reaction mixture heated in an aluminum heating block. Experiments under reflux conditions were carried out in a 5 mL flask instead of a HPLC vial.

Table S5. Optimization of the One-Pot N-/O-Demethylation of **2b** into **3a**.



oxycodone (**2b**) noroxymorphone (**3a**)

Entry	Conditions	Conversion (%)[a]	Selectivity (%)[b]
1	25 wt% HBr, 120 °C, 5 h, 0% EtOH	75	99
2	**35 wt% HBr,** 120 °C, 5 h, 0% EtOH	99	88
3	35 wt% HBr, 120 °C, **2.5h,** 0% EtOH	99	99
4	**30 wt% HBr,** 120 °C, 2.5 h, 0% EtOH	84	99
5	**35 wt% HBr,** 120 °C, 2.5h, **10% EtOH**	93	99
6	35 wt% HBr, 120 °C, 2.5h, **20% EtOH**	76	99
7	35 wt% HBr, 120 °C, 2.5h, **30% EtOH**	23	99
8	35 wt% HBr, 120 °C, 2.5h, **40% EtOH**	17	99
9	35 wt% HBr, 120 °C, 2.5h, **50% EtOH**	9	99
10	35 wt% HBr, 120 °C, 2.5h, **60% EtOH**	4	99
11	35 wt% HBr, 120 °C, 2.5h, **70% EtOH**	4	99
12	35 wt% HBr, 120 °C, 2.5h, **80% EtOH**	15	99
13	35 wt% HBr, 120 °C, 2.5h, **90% EtOH**	9	99
14	35 wt% HBr, 120 °C, 2.5h, **100% EtOH**	-	-
15	35 wt% HBr, reflux, **5 h, 0% EtOH**	82	99
16	35 wt% HBr, reflux, **7.5 h,** 0% EtOH	94	99
17	35 wt% HBr, reflux, **8.5 h,** 0% EtOH	99	99
18	35 wt% HBr, reflux, **8.5 h,** 0% EtOH	99	99
19	25 wt% **HBr,** reflux, **3 h,** 0% EtOH	42	99
20	25 wt% HBr, reflux, **7 h,** 0% EtOH	80	99
21	25 wt% HBr, reflux, **10 h,** 0% EtOH	92	99
22	25 wt% HBr, reflux, **13 h,** 0% EtOH	99	99

[a] Determined by HPLC peak area percent (205 nm). [b] Percent of product with respect to all peaks except the substrate (HPLC peak area percent, 205 nm). % EtOH refers to the amount of solvent left after the electrolysis step.

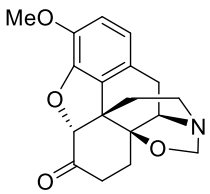
Experimental procedures and compound characterization

Electrochemical oxazolidination of oxycodone (2b) in batch

In 5 ml undivided IKA ElectraSyn vial were added 0.6 mmol of oxycodone (**2b**) and 3 ml of a 0.1 M solution of KOAc in EtOH. The cell head was equipped with a stainless steel cathode and an impervious graphite anode. The reaction mixture was stirred at 1000 rpm for a few minutes and then electrolyzed under a constant current of 5 mA until a charge of 3 F/mol had been passed. Then, the reaction mixture was evaporated under reduced pressure, and the residue extracted with aqueous $NaHCO_3$/DCM. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure, yielding 184 mg (96%) of oxazolidine **6** as a yellow solid.

Electrochemical oxazolidination of oxycodone (2b) in in flow

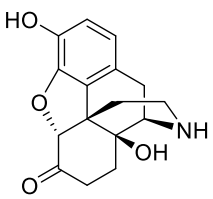
A solution of 1.261 g (4 mmol) of oxycodone and 399 mg (4 mmol) of KOAc in 80 mL of technical grade EtOH was pumped through the flow cell depicted in Fig. S2 with a flow rate of 10 mL/min. Then the cell was completely filled with liquid, a constant current of 42 mA was applied until 4 F/mol of charge had been passed. Then, the input tubing was removed from the reaction mixture, allowing air to empty the cell into the reaction mixture vessel. The crude reaction mixture was then evaporated under reduced pressure and the residue extracted with aqueous $NaHCO_3$/DCM. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to obtain 1.163 g (93 %) (96% HPLC purity) of oxazolidine (**6**) as yellow solid.



6

5aR,6R,8aS,8a1S,11aR)-2-Methoxy-5,5a,9,10-tetrahydro-7H-6,8a1-ethano-furo [2',3',4',5':4,5]phenanthro[9,8a-d]oxazol-11(11aH)-one (6). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 – 6.74 (d, 1H), 6.71 – 6,68 (d, 1H), 4.71 – 4.66 (m, 3H), 3.89 (s, 3H), 3.36 -3.17 (m, 3H), 2.87 – 2.77 (m, 3H), 2.41 – 2.36 (m, 2H), 1.99 – 1.95 (dt, 1H), 1.70 – 1.51 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 144.8, 143.0, 129.2, 123.3, 120.1, 115.3, 91.1, 86.6, 64.2, 56.9, 52.7, 44.5, 37.2, 34.2, 30.6, 26.9; These data is in agreement with previous literature.[S3]

One-Pot Electrochemical N-Demethylation/HBr-Mediated O-Demethylation of Oxycodone (2b) to Noroxymorphone (3a)



3a

A solution of 0.05 mmol oxycodone **2b** and KOAc in ethanol was electrolyzed in batch following the optimal conditions described above. Then, the reaction mixture was evaporated to 10% of the initial volume. The remaining mixture was treated with 0.5 mL of 35% aqueous HBr and heated at 120 °C for 2.5 h. Then, the solvent was evaporated under reduced pressure and the residue extracted with aqueous $NaHCO_3$/chloroform. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to obtain noroxymorphone (**3a**) as yellowish solid.10.6 mg (74 %) (99% HPLC purity); Mp = 272 °C (lit.[S4] 280 °C) ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.56 – 6.54 (dd, 2H), 4.71 (s, 1H), 3.45 (bp, 3H) 3.05 – 2.90 (m, 4H), 2.66 (m, 1H), 2.35 (m, 2H), 2.09 – 2.05 (m, 1H), 1.77 – 1.73 (m, 1H), 1.46 – 1.38 (td, 1H), 1.21 – 1.18 (d, 1H),^{13}C NMR (75 MHz, DMSO-d_6) δ 209.1, 143.9, 139.9, 129.8 124.0, 119.5, 117.7, 89.9, 70.0, 57.3, 50.7, 37.7, 36.2, 31.7, 31.4, 29.6; These data is in agreement with previous literature.[S4]

Supplementary References

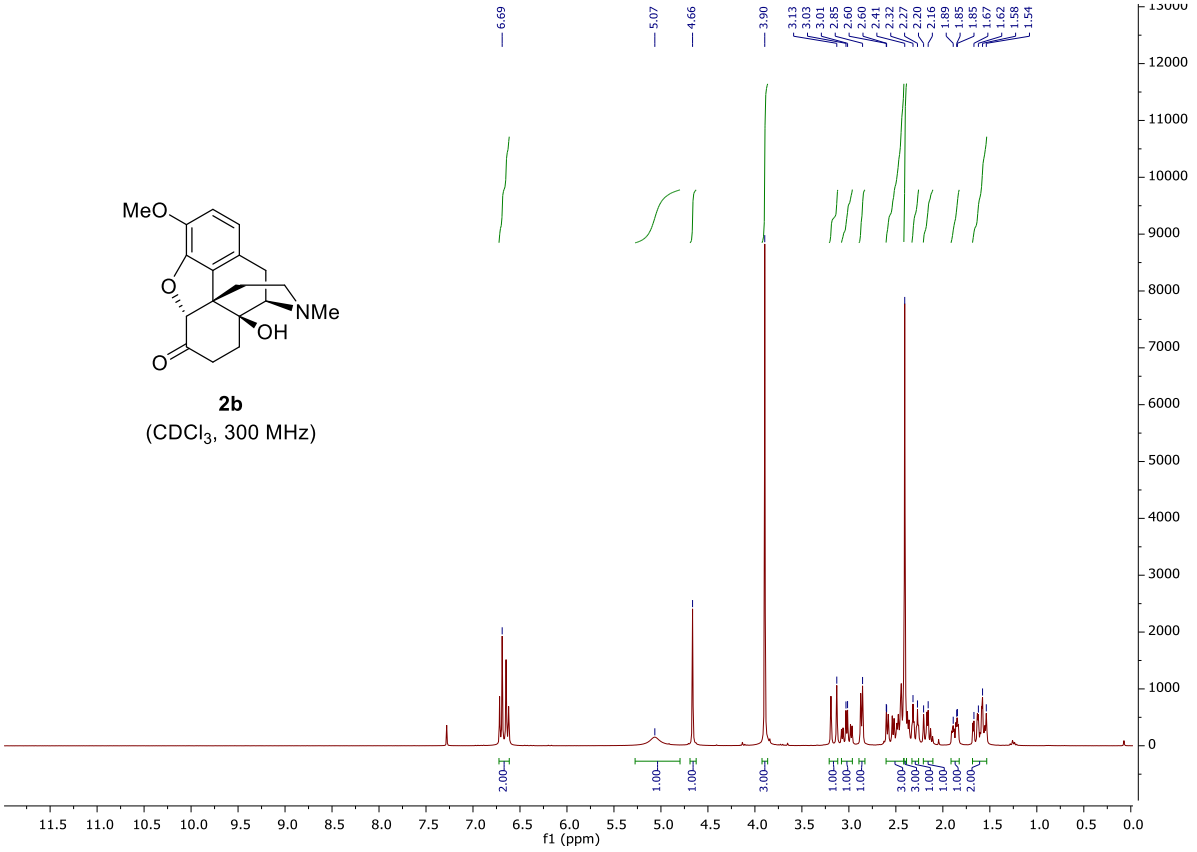
[S1] A. Mata, D. Cantillo, C. O. Kappe, *Eur. J. Org. Chem.* **2017**, *24*, 6505-6510.

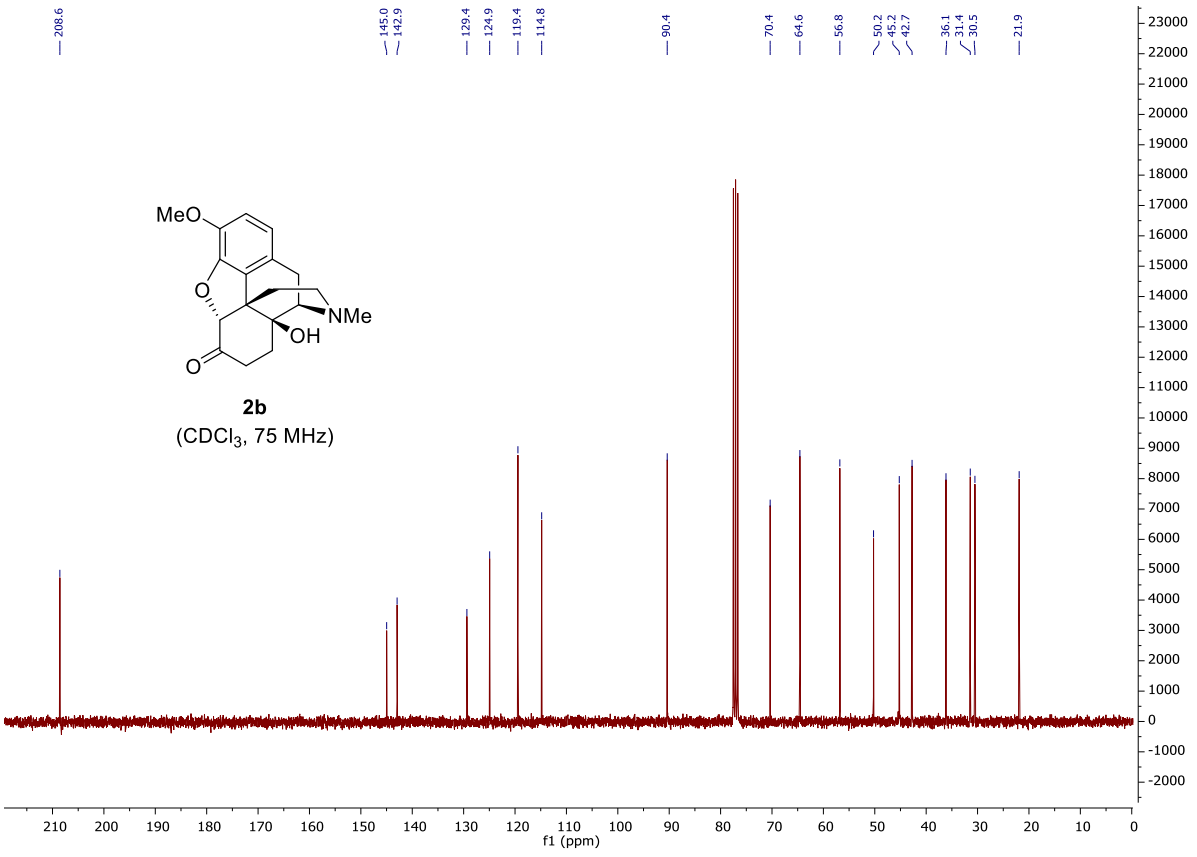
[S2] W. Jud, C. O. Kappe, D. Cantillo, *Chemistry–Methods*, **2021**, 1, 36-41.

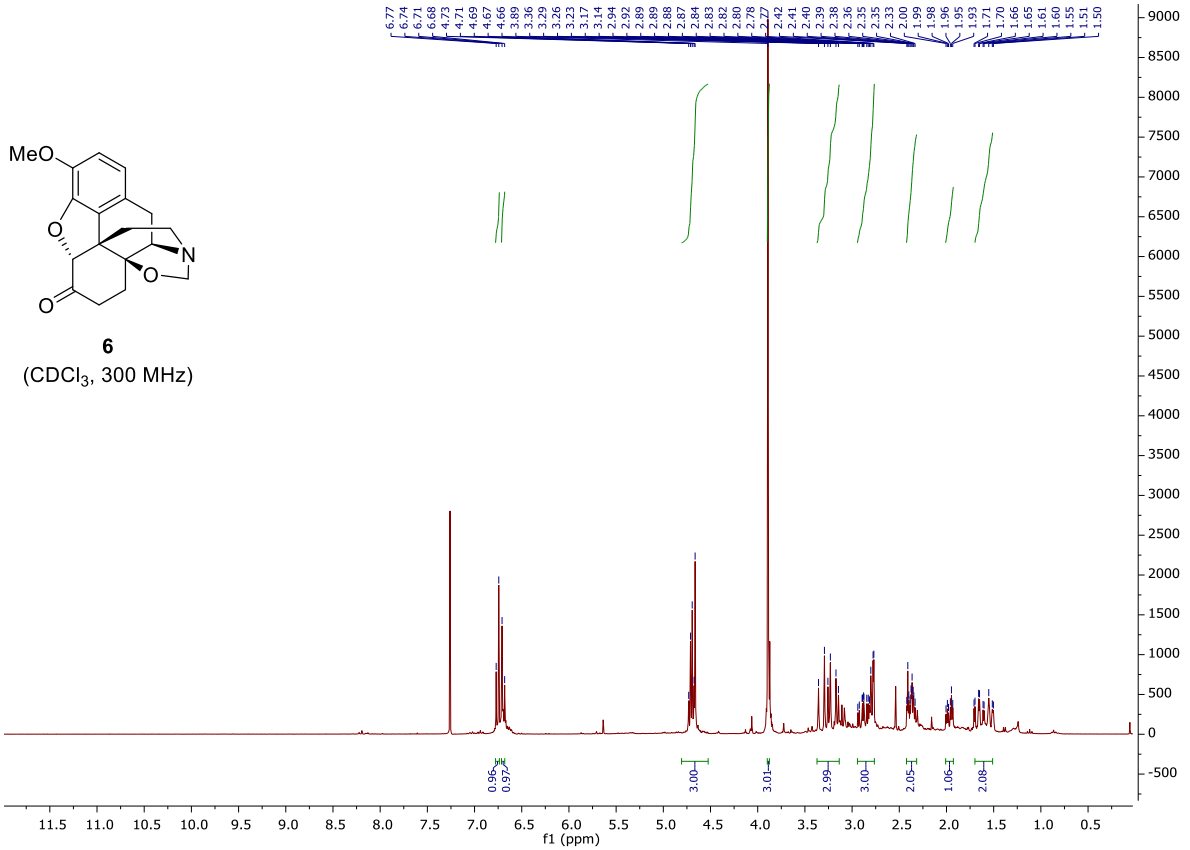
[S3] G. Glotz, C. O. Kappe, D. Cantillo, *Org. Lett.* **2020**, 22, 6891-6896

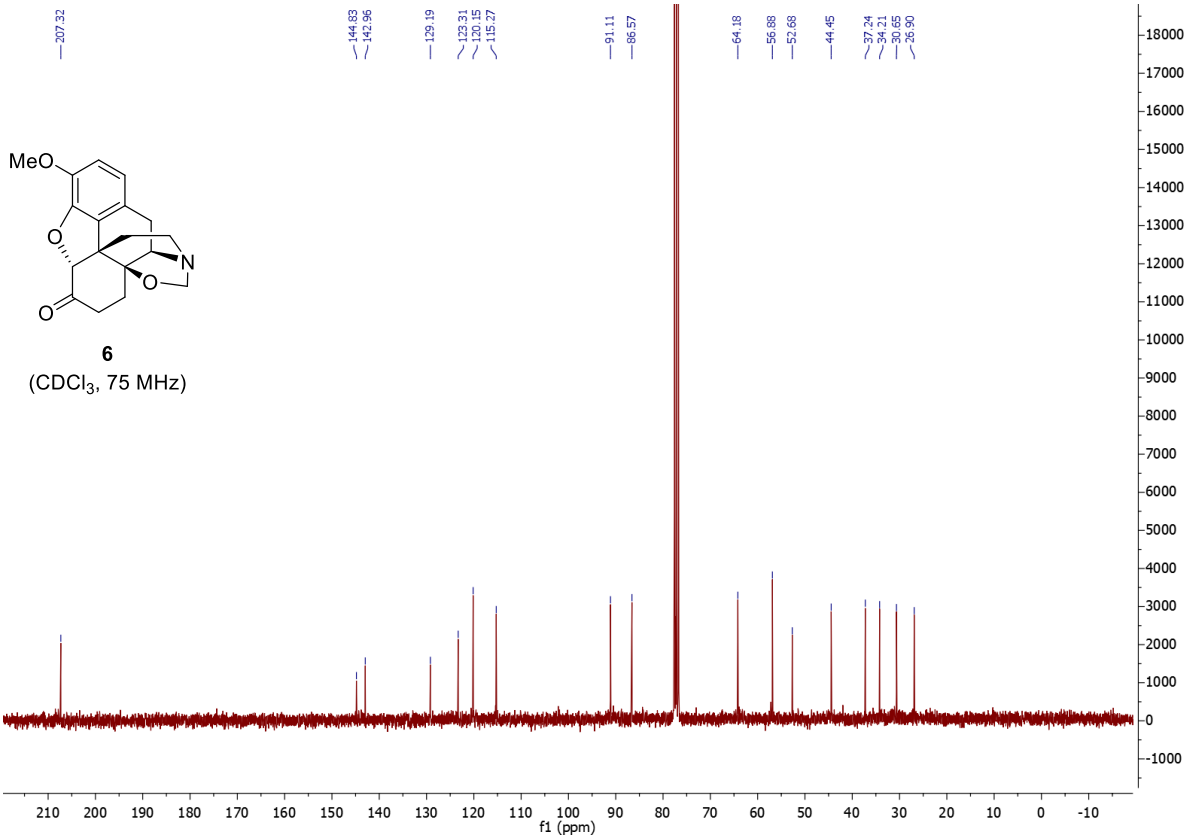
[S4] I. Köteles, K. Mazák, G. Tóth, et al., *Molecules*, **2020**, 25, 4009

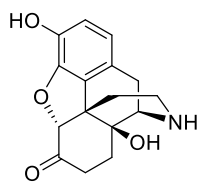
Copies of NMR Spectra



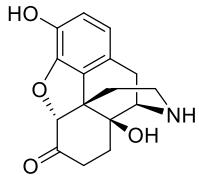



MeO
O
O
N
O
6
(CDCl3, 300 MHz)
f1 (ppm)


MeO
O
O
N
O
6
(CDCl3, 75 MHz)
f1 (ppm)



3a
(DMSO-d_6, 300 MHz)



3a
(DMSO-d_6, 75 MHz)