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SYNTHESIS OF NOROXYMORPHONE BY N-DEMETHYLATION/ INTRAMOLECULAR ACYLATION OF OXYMORPHONE CATALYZED BY IRON(II) CHLORIDE

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Abstract – Oxymorphone was converted to its 3,14-diacetate and subjected to Fe(II)/*t*-BuOOH-catalyzed N-demethylation that occurred with concomitant acyl migration from the C-14 hydroxyl to the N-17 nitrogen. The resulting diacetyl compound was hydrolyzed in dilute sulfuric acid to noroxymorphone in good yield.

Dedicated to Professor Lutz F. Tietze on the occasion of his 75th birthday and in recognition of his contributions to the art of organic synthesis.

The semisynthesis of several opiate-derived pharmaceutical agents requires N-demethylation of either naturally occurring morphine alkaloids or the C-14 hydroxy derivatives such as oxycodone or oxymorphone. Some of the useful analgesics and/or antagonist agents are shown in Figure 1.

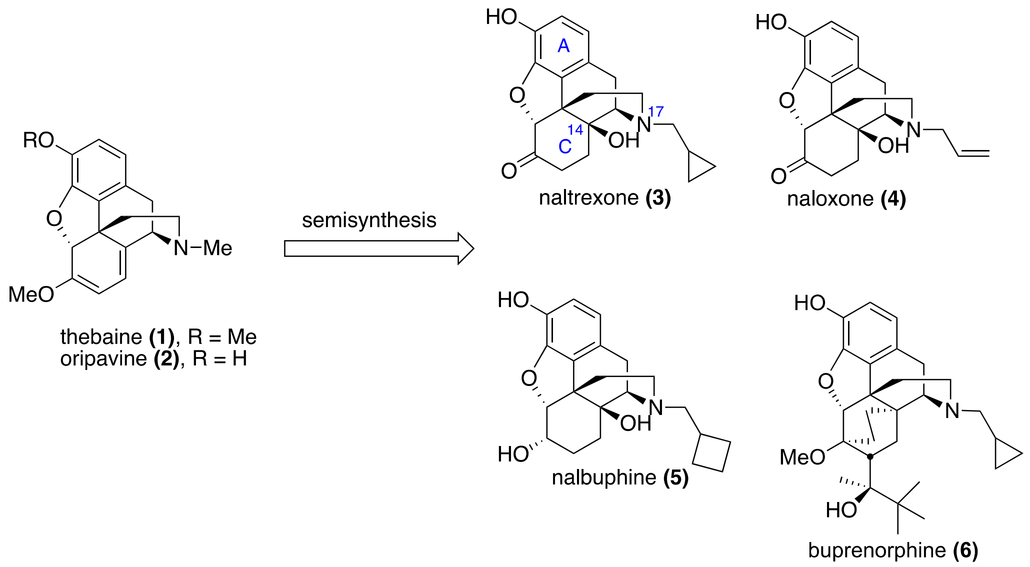
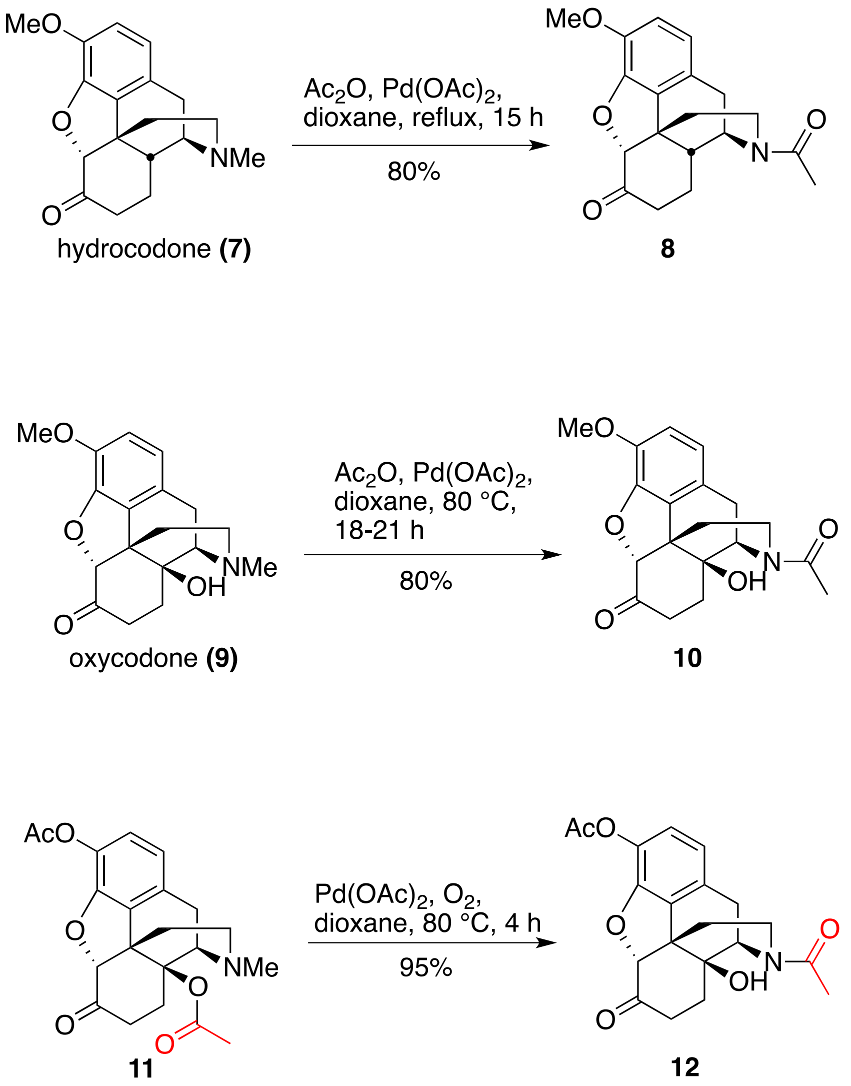


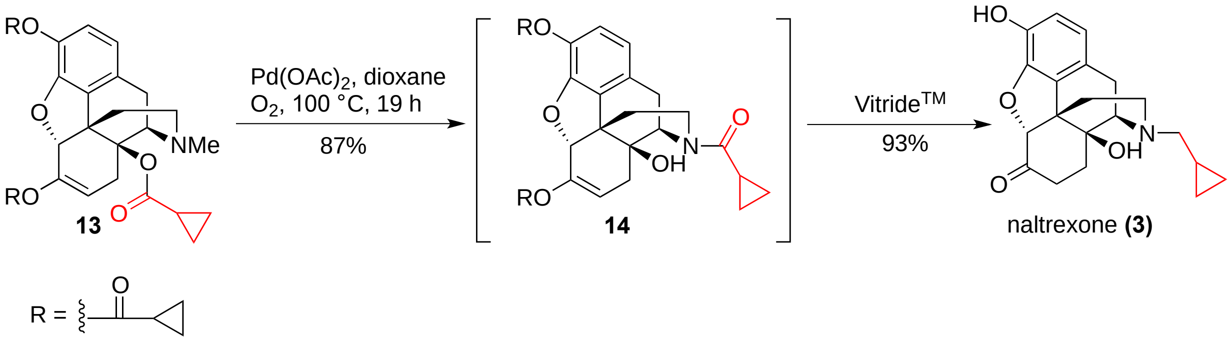
Figure 1. Semisynthesis of some opiate-derived agents

As discussed on several occasions,[1] such demethylation protocols are frequently arduous and employ harsh conditions or toxic reagents, such as cyanogen bromide[2] or various chloroformates.[3] Several years ago we reported palladium-catalyzed N-demethylation of hydrocodone that yielded, in the presence of acetic anhydride, *N*-acetyl norhydrocodone **8**, Scheme 1.[4] Under similar conditions, oxycodone **(9)** yielded the *N*-acetyl derivative **10**.[5] When this process was applied to acetyl-protected oxymorphone **11** in the absence of acetic anhydride and under oxygen atmosphere we found that the O-14 acyl group migrated to the nitrogen providing the *N*-acetyl product **12** in 95% yield.



Scheme 1. N-Demethylation and acetylation of morphinans

This interesting finding led eventually to a very efficient three-step synthesis of naltrexone by employing cyclopropylcarboxylate as the migrating group from O-14 to N-17, Scheme 2.[5]



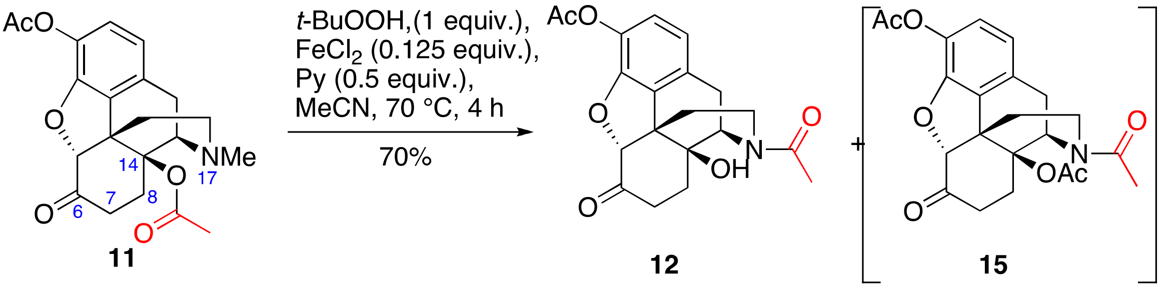
Scheme 2. A short synthesis of naltrexone by N-demethylation/intramolecular acylation

In the naltrexone the C-6 ketone was converted into acylenol ester in order to prevent the undesired installation of 7,8-double bond (leading to 14-hydroxymorphinones) that is frequently observed with compounds of type **11** when elevated temperature, prolonged reaction times, or co-catalysis with copper (II) acetate are used.

In this communication we describe further refinement of N-demethylation with concomitant acyl transfer by employing *t*-BuOOH and Fe(II) salts rather than oxygen and palladium acetate in flammable solvents.

The N-demethylation/acylation protocol described above provided *O*, *N*-diacetyl noroxymorphone **12** in excellent yield. However, the conditions employed relied on the use of a flammable solvent (dioxane) under oxygen atmosphere. The potential safety issues of such a procedure prompted us to investigate safer conditions by screening other solvents and oxidants. Therefore we turned our attention to solvents which are either inflammable or have low partial pressure and are miscible with water. The use of aqueous DMF (adapted from Wacker process conditions) provided only moderate yields (~ 50%) of amide **12**. Similar lower yields were obtained in other solvents, such as 1,2-dichloroethane. As we did not succeed in reproducing the high yields obtained in the palladium-catalyzed N-demethylation of diacetyl oxymorphone under conditions other than those requiring oxygen and dioxane we turned to screening of other catalysts.

When diacetyl oxymorphone **11** was treated with *t*-BuOOH in MeCN and in the presence of $FeCl_2$[6] the *N*-acetyl derivative **12** was obtained in 70% yield, as shown in Scheme 3.



[**15** was obtained when Ac_2O (2 equiv.) was added]

Scheme 3. N-Demethylation/acylation of intermediate *N*-oxide catalyzed by Fe(II)

The presence of pyridine is required as the migration of the acyl group from O-14 to N-17 does not proceed well unless performed under basic conditions.[7] Under some conditions (additional Ac_2O in the reaction mixture) a small amount of 3,14,17-triacetyl noroxymorphone **15** was also obtained. The reaction was studied in some detail in order to improve the conversion of **11** to **12**, as shown in Table 1. In addition, the temperature dependence of the conversion/yield was also addressed, as shown in Table 2.

Table 1. Conditions for demethylation/intramolecular acylation of diacetyl oxymorphone[8]

Entry	Substrate	Reaction Conditions (As shown in Scheme 3 unless otherwise noted. *t*-BuOOH is used as 70% solution in H_2O)	% Yield of **12** (unless otherwise stated)
1	**Diacetyl oxymorphone**	**MeCN, 85 °C, 4 h**	**70%**
2	Diacetyl oxymorphone	MeCN, Ac_2O, 85 °C, 4 h	Mixture of **12** and **15** (75%, ratio of **12** to **15** was 3:1)
3	Diacetyl oxymorphone	DCE, 85 °C, 1.5 h	60%
4	Diacetyl oxymorphone	MeCN, 85 °C, *t*-BuOOH in nonane as oxidant, 1.5 h	62%
5	Diacetyl oxymorphone	MeCN, 85 °C (200 mg scale), 4 h	65%
6	Diacetyl oxymorphone	MeCN, 85 °C, O_2 (1 atm) instead of *t*-BuOOH as oxidant, 2 h	20%
7	Diacetyl oxymorphone	MeCN, 85 °C, *t*-BuOO*t*-Bu (2.5 eq) instead of *t*-BuOOH as oxidant, 3 h	41%
8	Diacetyl oxymorphone	MeCN, 85 °C, *t*-BuOO*t*-Bu (5.0 eq) instead of *t*-BuOOH as oxidant, 3 h	52%
9	Diacetyl oxymorphone	MeCN, 85 °C, $FeCl_2$ (0.25 eq) *t*-BuOO*t*-Bu (2.5 eq) instead of *t*-BuOOH as oxidant, 3 h	58%
10	Diacetyl oxymorphone	MeCN, 85 °C, *t*BuOO*t*-Bu (2.5 eq) instead of *t*-BuOOH as oxidant, Ac_2O, 3 h	55%
11	Diacetyl oxymorphone	MeCN, 85 °C, *t*-BuOOH in nonane as oxidant, Ac_2O, 3 h	65%
12	**Diacetyl oxymorphone**	**MeCN, 70 °C, 4 h**	**70%**
13	Diacetyl oxymorphone	MeCN, 100 °C, 1 h	55%
14	Diacetyl oxymorphone	DMF, 100 °C, 2 h	25%
15	Diacetyl oxymorphone	DMA, 100 °C, 2 h	10%
16	oxymorphone	MeCN, 85 °C, 2 h	decomposition
17	oxymorphone	MeCN, Ac_2O (2 equiv.), 85 °C, 2 h	Mixture of **12** and **15** (40%, ratio of **12** to **15** was 4:1)

Table 2. Temperature dependence of N-demethylation reaction

Conditions: MeCN, $FeCl_2$ (0.16 eq), t-BuOOH (1.0 eq, 70% aqueous solution), pyridine (1.5 eq)Bath Temperature	Time of reaction	% yield of **12**
100 °C	1 h	56%
85 °C	1 h	68%
80 °C	**2 h**	**71%**
80 °C	1 h	70%
75 °C	2 h	63%
75 °C	1 h	63%
70 °C	2 h	62%
60 °C	2 h	61%
50 °C	2 h	46%
40 °C	2 h	33%

We were delighted to find that the O-14 acetyl group also migrated under the iron-catalyzed conditions, suggesting that the reaction sequence proceeds by a mechanism similar to the one we proposed for the palladium-catalyzed process, as shown in Figure 2. The preliminary optimization of the reaction provided the *N*-acetyl compound **12** in reproducible 70% yields. We proposed the sequence **17** to **20** to explain the intramolecular acyl migration, driven eventually by the greater thermodynamic stability of the amide over the ester. The same migration of acyl group from the *O*- to the *N*- was also observed for 14-acyloxy-*N*-cyanonorcodeine.[7] It was observed to occur in basic media and the process was proposed to be occurring through cyclic intermediates. The reverse process, namely the migration of the acyl group from *N*- to *O*- proceeds under acid catalysis. In the current case the nitrogen-stabilized radical **21** undergoes further one–electron oxidation to the iminium species **18**, intersecting the previously suggested mechanistic events at that stage.

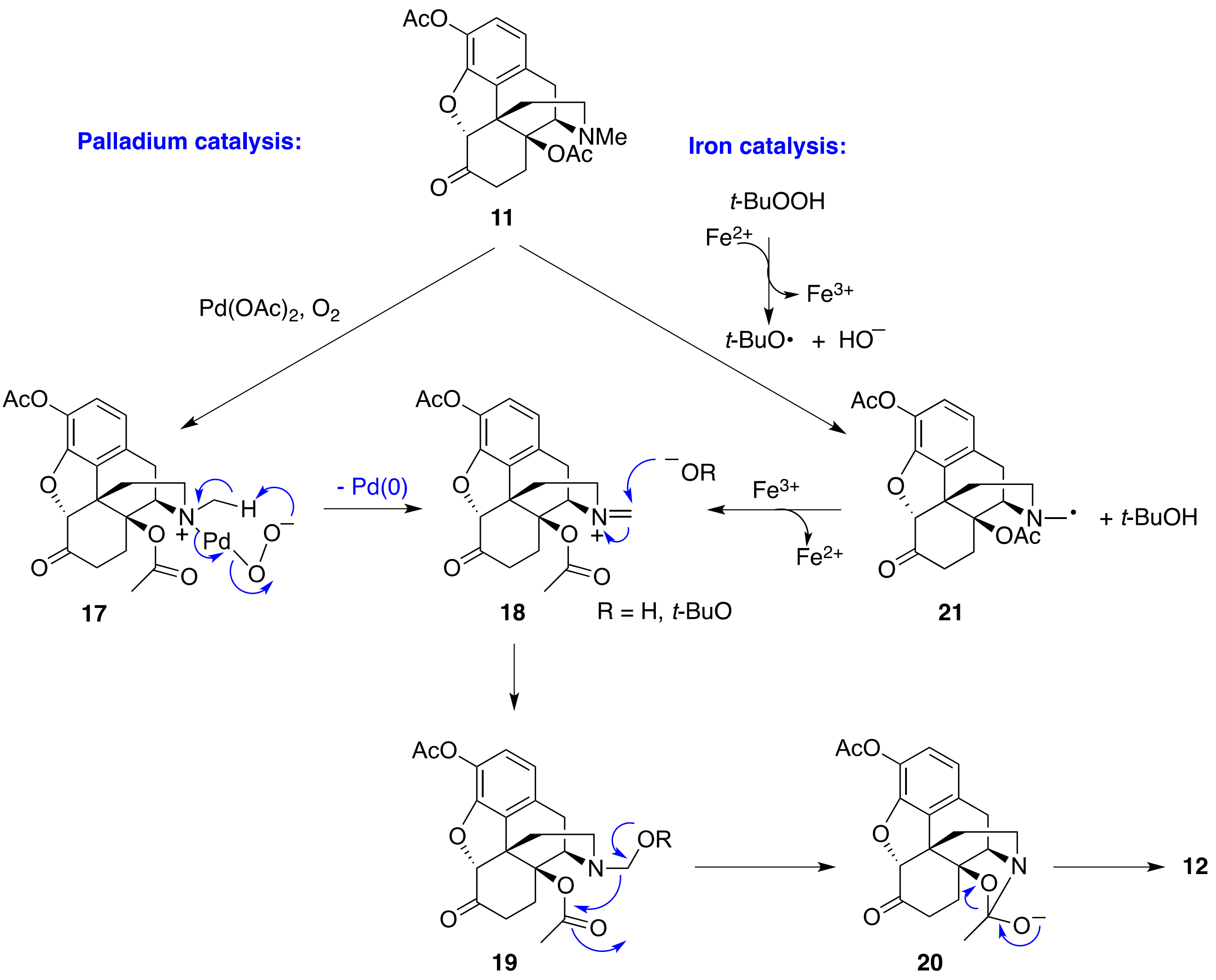
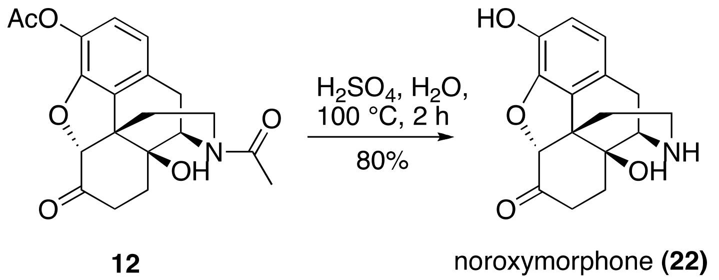


Figure 2. Suggested mechanism for the acyl migration from O-14 to N-17 under palladium or iron catalysis

Diacetyl noroxymorphone **12** and similar compounds are converted by hydrolysis to noroxymorphone by literature methods,[9] Scheme 4.[10]



Scheme 4. Hydrolysis of diacetyl noroxymorphone to noroxymorphone

We have briefly investigated the N-demethylation/acylation sequence also on **11** protected as the C-6 ketal in order to minimize potential side products that would be derived by Baeyer-Villiger oxidation of the C-6 carbonyl moiety. However, the use of the ketal in the iron-catalyzed process led to diminished yields and was not further investigated. Future improvements in the conversion of oxymorphone to noroxymorphone may focus on the acyl transfer of less robust acyl groups such as various singly, multiply, or polyfluorinated acetates or propionates that would be more easily hydrolyzed to the desired product.

In conclusion, we have demonstrated that the N-demethylation/intramolecular acyl transfer form C-14 to N-17 is also accomplished in good yields by an iron-catalyzed process rather than by catalysis with palladium salts and oxygen. Additional optimization of yields and detailed study of various acyl groups suitable for the acyl migration from C-14 to N-17 will be reported in due course.

ACKNOWLEDGEMENTS

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8. *General Procedure for N-Demethylation of Diacetyl Oxymorphone:*
   To a stirred mixture of 3,14-diacetyl oxymorphone **11** (1.0 eq), and $FeCl_2$ (0.125 eq) in MeCN (1 mL) was added *t*-BuOOH (70% in water) (1.0 eq) followed by pyridine (0.5 eq). The mixture was degassed and heated to 85 °C for 1.5 h. The reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (3 mL) and then washed with 0.1 M HCl (2 x 1 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *via* rotary evaporation to afford a crude residue that was chromatographed on silica gel using EtOAc/MeOH (9:1) as eluent to afford the desired product as a white solid. NMR analysis showed two amide rotamers. 3,17-Diacetyl noroxymorphone: mp >233 °C (EtOAc/hexanes) lit.[5] mp > 235 °C (EtOH); Major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, *J*=8.2 Hz, 1H), 6.72 (d, *J*=8.2 Hz, 1H), 5.07 (d, *J*=5.9 Hz, 1H), 4.73 (s, 1H), 4.35 (s, 1H), 3.66 (dd, *J*=14.0, 4.8 Hz, 1H), 3.15-3.04 (m, 3H), 2.88 (m, 1H), 2.63 (m, 1H), 2.33 (s, 3H), 2.30 (m, 1H), 2.16 (s, 3H), 2.02 (m, 1H), 1.70 (ddd, *J*=14.0, 14.0, 3.4 Hz, 1H), 1.58 (dd, *J*=12.6, 3.0 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 207.3, 171.2, 168.5, 147.9, 132.9, 129.5, 129.2, 123.6, 119.9, 90.2, 70.7, 53.3, 50.4, 39.9, 35.7, 31.8, 31.7, 28.9, 22.1, 20.8; Minor rotamer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, *J*=8.2 Hz, 1H), 6.72 (d, *J*=8.2 Hz, 1H), 5.10 (d, *J*=5.9 Hz, 1H), 4.73 (s, 1H), 4.48 (dd, *J*=14.3, 4.9 Hz, 1H), 4.35 (s, 1H), 4.11 (d, *J*=5.6 Hz, 1H), 3.71 (m, 1H), 3.20 (dd, *J*=18.6, 5.9 Hz, 1H), 3.11 (m, 1H), 3.01 (d, *J*=18.4 Hz, 1H), 2.55 (m, 1H), 2.38 (m, 1H), 2.25 (s, 3H), 1.97 (m, 1H), 1.71-1.66 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 206.9, 170.9, 168.4, 147.9, 133.1, 129.3, 128.7, 123.7, 119.8, 90.1, 70.8, 59.7, 50.4, 39.9, 34.4, 32.4, 31.1, 28.8, 22.3, 20.8.
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10. *Hydrolysis of diacetyl noroxymorphone to noroxymorphone*: A solution of diacetyl noroxymorphone **12** (50 mg, 0.13 mmol) in 25% aq. H_2SO_4 (2 mL) was heated to 100 °C for 2 h. The reaction mixture was cooled to 0 °C and basified to pH 9 using concentrated ammonium hydroxide solution. The brown precipitate that formed was collected by centrifugation. It was washed by suspending in water followed by centrifugation (twice). The precipitate was dried by evaporation of the azeotropic mixture with benzene and drying in vacuo to afford noroxymorphone as a light brown solid (31 mg, 80%). Noroxymorphone: mp > 300 °C (water) lit[11] mp > 300 °C; ^{1}H NMR (300 MHz, D_2O, hydrochloride salt) δ 6.75-6.82 (m, 2H), 3.87 (m, 1H), 3.20-3.32 (m, 3H), 2.99 (td, *J*=14.8 Hz, 5.0 Hz, 1H), 2.85 (td, *J*=13.2 Hz, 4.3 Hz, 1H), 2.63 (td, *J*=13.4 Hz, 4.6 Hz, 1H), 2.28 (m, 1H), 2.02 (m, 1H), 1.74 (m, 1H), 1.65 (dd, *J*=14.5 Hz, 4.5 Hz).The hydrochloride salt was prepared by dissolving noroxymorphone (5 mg, 0.017 mmol) in 3 M HCl (3 drops). The excess hydrochloric acid and water

were removed by evaporation of the azeotropic mixture with benzene and drying in vacuo to afford the hydrochloride salt (5.3 mg, 95%) as a white solid.

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