

Palladium-Catalyzed *N*-Demethylation/*N*-Acylation of Some Morphine and Tropane Alkaloids

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Abstract: Hydrocodone was converted to various *N*-acyl derivatives *via* a one-pot *N*-demethylation/*N*-acylation protocol catalyzed by palladium(II). The procedure has also been successfully applied to sev-

eral *N*-methyltropane alkaloids. A plausible mechanism is suggested.

Keywords: acylation; alkaloids; demethylation; hydrocodone; palladium catalysis

Introduction

Our ongoing investigation^[1] of the chemistry of morphine alkaloids and their derivatives, such as hydrocodone (**3**) and oxycodone (**4**) (Figure 1), has led to the discovery of conditions for a one-pot sequence of oxidative *N*-demethylation and subsequent *N*-acylation reactions. Such a transformation holds immense potential for the production of morphine-derived antagonists such as naloxone (**5**), naltrexone (**6**), and other medicinally significant compounds. The semisynthesis

of these derivatives from opium-derived natural products traditionally involves standard procedures for demethylation with subsequent formation of carbamate or acyl intermediates that permit further synthetic manipulation such as the introduction of a C-14 hydroxy group. Here we report a mild, one-pot procedure for *N*-demethylation and acylation of hydrocodone, one that is also applicable to other *N*-methylated compounds.

N-Demethylation and *N*-acylation reactions of morphine-type alkaloids have been extensively studied. The standard procedures for *N*-demethylation of alkaloids, including morphine derivatives, involve the use of cyanogen bromide (the von Braun reaction),^[2] the reaction of a tertiary amine with chloroformates followed by hydrolysis,^[3] photochemical demethylation,^[4] Polonovski-type reactions,^[5,6] and other methods. The case of Pd-catalyzed oxidative demethylation with stoichiometric amounts of Pd/C appears in a single report by Chaudhuri,^[7] however, our repetition of this procedure with hydrocodone (**3**) resulted in the isolation of only *N*-formylnorhydrocodone in low yield.

Results and Discussion

Our treatment of **3** with catalytic Pd(OAc)₂ in the presence of acetic anhydride in benzene or dioxane yielded *N*-acetylnorhydrocodone (**7**), but without acetic anhydride, norhydrocodone (**8**) was obtained, Figure 2. An X-ray crystal analysis of the equatorial

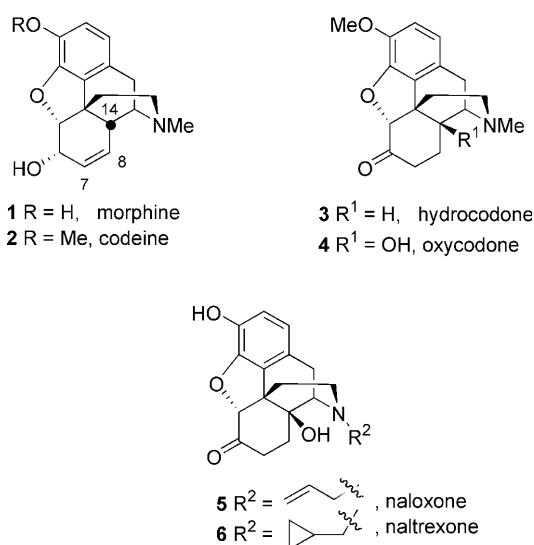


Figure 1. Morphine alkaloids and derivatives.

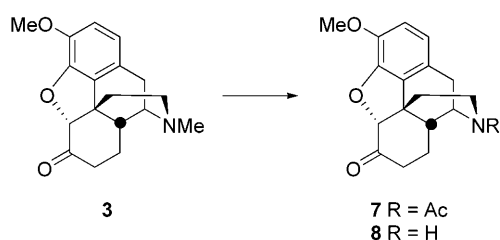


Figure 2. *N*-Acetylnorhydrocodone (**7**) and norhydrocodone (**8**).

isomer of *N*-acetylnorhydrocodone confirmed the structure of **7**.

Our initial experiments using stoichiometric amounts of palladium were conducted in benzene, but further optimization of reaction conditions resulted in excellent yields when dioxane was used as solvent with catalyst loading at 0.2 equivalents. Multiple experiments under varying conditions demonstrated that the influence of light, dissolved oxygen and moisture had no effect on the outcome of the reaction and that the use of coordinating solvents such as acetonitrile and methanol led to reduced yields. The use of PdCl₂ rather than Pd(OAc)₂ resulted in a dramatic decrease in yield, and less economical Pd(0) sources offered no further advantages. The most significant experiments are summarized in Table 1.

Under all conditions tested, the *N*-acetyl derivative **7** was produced as a mixture of equatorial and axial isomers (3:1). We explored the reactivity of a series of anhydrides and carbonates leading to the production of a range of novel *N*-acylated norhydrocodone derivatives, as shown in Table 2.

In all cases the acylated products were produced as mixtures of axial and equatorial isomers, varying in ratios from 3:2 to 7:2 in favor of the equatorial isomer. These results show that the nitrogen of the morphine skeleton does not undergo inversion, as has

also been observed with *N*-oxides^[8] or quaternary salts derived from various morphine alkaloids.^[9]

To demonstrate the generality and the practicality of this methodology, as well as compatibility of the method with other functional groups such as ketones and esters,^[10] we extended the study to *N*-methylated heterocycles such as atropine and its derivatives. The results of the demethylation/acylation sequence with tropane-type alkaloids are shown in Table 3.^[11]

Two possible mechanistic options for the demethylation/acylation process are suggested in Figure 3. Insertion of Pd(0), formed under the reaction conditions, into a molecule of acetic anhydride produces acyl-palladium species **25**, according to published precedent.^[12] Quaternization of the basic nitrogen and regeneration of a Pd(0) species is followed by release of acetate and demethylation yielding methyl acetate, option A. Alternatively, immonium ion **26** may generate the *N*-acetoxymethyl species **27**, followed by extrusion of formaldehyde to produce **28**, option B. Conducting the reaction in the absence of a palladium source yielded only starting material, while in the absence of anhydride and with stoichiometric amounts of Pd(OAc)₂, norhydrocodone (**8**)^[13] was obtained, Figure 4.

Use of Fenton's reagent,^[14] with iron sulfate and hydrogen peroxide under various conditions, as well as screening of metal salts used previously in oxidative demethylations proved discouraging, however, a combination of copper acetate and ammonium peroxy sulfate in aqueous acetonitrile, resulted in a 64% conversion of hydrocodone to its nor-derivative. These conditions were also successful for the demethylation of codeine to norcodeine in 22% yield.

Unlike the conditions reported by Scammells,^[5] which require the initial formation and isolation of the corresponding *N*-oxide prior to subsequent demethylation, the present process constitutes a one-pot procedure. In fact, we found that prior formation of the corresponding hydrocodone *N*-oxide and subse-

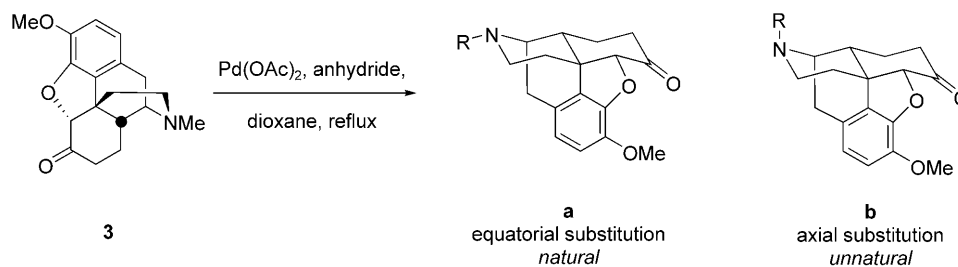
Table 1. Optimization of conditions for *N*-demethylation-acetylation of hydrocodone (**3**).

Entry	Catalyst	Conditions ^[a]	Yield ^[b] [%]
1	Pd(OAc) ₂ (1.2 equiv.)	MeCN, Ac ₂ O, 80 °C	0
2	PdCl ₂ (1.2 equiv.)	benzene, Ac ₂ O, 80 °C	50
3	Pd(OAc) ₂ (0.2 equiv.)	benzene, Ac ₂ O, 80 °C	67
4	Pd(dba) ₂ (0.5 equiv.)	benzene, Ac ₂ O, 80 °C	76
5	Pd(OAc) ₂ (0.2 equiv.)	dioxane (dry), Ac ₂ O, 80 °C	80
6	Pd(OAc) ₂ (0.2 equiv.)	dioxane (wet), Ac ₂ O, 80 °C	80
7	Pd(OAc) ₂ (0.2 equiv.)	toluene, Ac ₂ O, 80 °C	67
8	Pd(OAc) ₂ (0.2 equiv.)	MeOH, Ac ₂ O, r.t., 3 days	15
9	PdCl ₂ (0.2 equiv.)	dioxane, Ac ₂ O, 80 °C	17
10	Pd(PPh ₃) ₄ (0.2 equiv.)	dioxane, Ac ₂ O, 80 °C	76
11	Pd(dba) ₂ (0.2 equiv.)	dioxane, Ac ₂ O, 80 °C	72

^[a] Reaction time of 15 h, unless otherwise noted.

^[b] Yields refer to clean isolated material.

Table 2. Synthesis of new *N*-acylhydrocodone derivatives.



Reagent	Product	R	Time [h]	Yield ^[a] [%]	Ratio ^[b] a:b
acetic anhydride	7	Ac	15	80	3:1
cyclopropyl anhydride	9		24	76	3:1
isobutyric anhydride	10	COCH(CH ₃) ₂	24	13	13:4
<i>n</i> -propyl anhydride	11	COCH ₂ CH ₃	24	53	3:1
decanyl anhydride	12	CO(CH ₂) ₈ CH ₃	120	36	3:1
dodecanyl anhydride	13	CO(CH ₂) ₁₀ CH ₃	120	43	7:2
dimethyl dicarbonate	14	Moc	120	33	3:2
di- <i>tert</i> -butyl dicarbonate	15	Boc	120	15	3:2

^[a] Yields refer to clean isolated material.

^[b] Ratios were determined by NMR.

Table 3. *N*-Demethylation/*N*-acylation of tropane alkaloids.

Entry	Substrate	Conditions Pd(OAc) ₂ (0.2 equiv.)	Product and Yield ^[a] [%] (conversion ^[b])
1		a) Ac ₂ O neat, 80 °C, 14 h b) PhH, Ac ₂ O, 80 °C, 60 h c) MeOH, Ac ₂ O, r.t., 3 days	 a) 72% (100%) b) 48% (60 %) c) no reaction
2		Ac ₂ O neat, 80 °C, 14 h	 70% (100%)
3		Ac ₂ O neat, 80 °C, 14 h	 43% 35%
4		PhH, Ac ₂ O, 80 °C, 60 h	 85%

^[a] Yields refer to clean isolated material.

^[b] Conversion was determined by GC/MS.

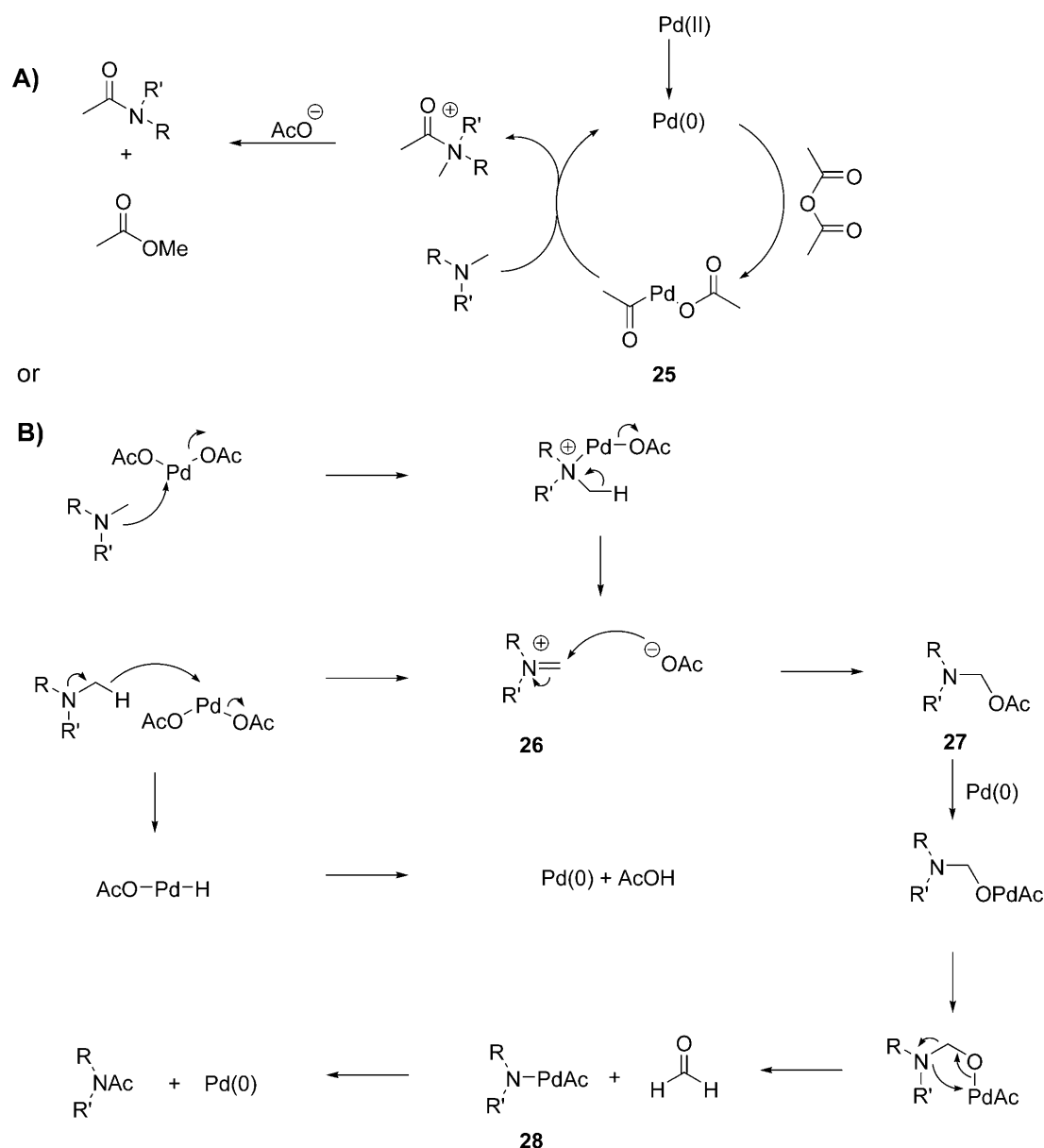


Figure 3. Speculative mechanistic options for *N*-demethylation/*N*-acylation with Pd(OAc)₂ catalysis.

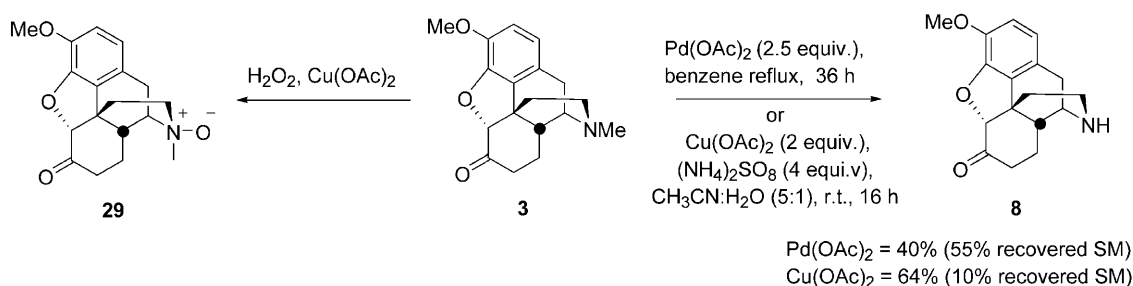


Figure 4. *N*-Demethylation of hydrocodone (**3**).

quent treatment with Cu(OAc)₂ and (NH₄)₂S₂O₈ resulted in no demethylation, suggesting that the Cu-catalyzed process follows a different mechanism.

Optimization of these conditions involved testing of various solvent mixtures, screening various copper salts (CuCl, CuI, CuCl₂·2H₂O, CuCO₃, CuSO₄·5H₂O, CuO) as well as varying the equivalents of both

Table 4. Optimization of the copper-mediated demethylation of hydrocodone (**3**).^[a]

Entry	Cu(OAc) ₂	(NH ₄) ₂ S ₂ O ₈	Norhydrocodone (8)	Hydrocodone (3)
1	0.5 equiv.	2 equiv.	20%	64%
2	1 equiv.	2 equiv.	36%	46%
3	0.5 equiv.	4 equiv.	24%	55%
4	1 equiv.	4 equiv.	36%	38%
5	2 equiv.	4 equiv.	64%	10%

^[a] All reactions were carried out at room temperature under an atmosphere of air, utilizing CH₃CN:H₂O (5:1) as solvent with 16 h reaction time.

Table 5. Variation of conditions of the copper-mediated demethylation of hydrocodone (**3**).^[a]

Entry	Variable	Norhydrocodone (8)	Hydrocodone (3)
1	oxygen atmosphere	53%	15%
2	argon atmosphere	50%	18%
3	H ₂ O ₂ (10 equiv.) as oxidant	hydrocodone <i>N</i> -oxide 29	
4	reaction temperature 50 °C	42%	32%
5	reaction temperature 60 °C	37%	51%

^[a] Reaction conditions: 2 equiv. Cu(OAc)₂, 4 equiv. (NH₄)₂S₂O₈, CH₃CN:H₂O (5:1), room temperature, 16 h.

copper acetate and ammonium peroxydisulfate, the results of which are presented in Table 4.

Alteration of the conditions (Table 5) including the atmosphere under which the reaction was conducted, the oxidant, as well as the reaction temperature did not lead to significant improvements in the yield of norhydrocodone (**8**).

Conclusions

Our methodology is applicable to the synthesis of a wide range of acyl derivatives of hydrocodone and of some tropane compounds under mild and catalytic conditions. In addition, a convenient procedure for *N*-demethylation of hydrocodone was also discovered. These mild conditions have been applied on a gram scale with the operational simplicity of a one-pot procedure.

Experimental Section

General Experimental Details

Dioxane and benzene were distilled from sodium and benzophenone. Dichloromethane (DCM) and acetonitrile were

distilled from calcium hydride. Methanol and ethanol were distilled from magnesium turnings and iodine under nitrogen, either directly into the reaction vessel, or stored over activated 3 Å molecular sieves. Liquid reagents were distilled prior to use; commercial solids were used without further purification. Reactions were run under a positive pressure of argon. NMR analyses were performed in CDCl₃; chemical shifts are quoted in ppm relative to TMS (as referenced to residual CHCl₃, δ_H=7.26 or CDCl₃, δ_C=77.0) with coupling constants quoted in Hz. Infrared analyses of liquid compounds were recorded as a thin film on NaCl plates and of solid compounds as KBr discs. Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. Mass spectra were recorded on Kratos/MSI Concept 1S mass spectrometer at Brock University.

General Procedure for *N*-Demethylation/Acylation Reaction

To the tertiary amine (0.1 mmol, 1.0 equiv.) dissolved in an appropriate anhydride (1 mL) and dioxane (1 mL) was added Pd(OAc)₂ (0.01 mmol, 0.1 equiv.). The mixture was heated at 80 °C for 18 h, cooled to room temperature and filtered through a plug of silica with DCM:MeOH:NH₄OH, 80:20:1 as eluent. The volatiles were removed under vacuum, and the residue was suspended in saturated aqueous NaHCO₃. The aqueous phase was extracted with DCM three times, and the organic extracts were combined and washed with 1 M aqueous HCl and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and the volatiles were removed under reduced pressure to yield the crude product, which was subjected to flash column chromatography (DCM:MeOH, gradient) to give the pure acylated compound.

General Procedure for Pd(OAc)₂-Mediated Demethylation

To the tertiary amine (0.1 mmol, 1.0 equiv.) dissolved in benzene (1 mL) was added Pd(OAc)₂ (0.25 mmol, 2.5 equiv.). The mixture was heated at reflux for 36 h, cooled to room temperature, and filtered through a plug of silica with DCM:MeOH:NH₄OH, 80:20:1 as eluent. Following the removal of volatiles under reduced pressure, the residue was suspended in aqueous NaHCO₃, then extracted with CHCl₃. The organic layer was dried over magnesium sulfate and filtered, then the volatiles removed under vacuum. Flash column chromatography (silica gel; CHCl₃:MeOH:NH₄OH, 96:4:1) of the crude material affords analytically pure demethylated product.

General Procedure for Cu(OAc)₂-Mediated Demethylation

To the tertiary amine (0.1 mmol, 1.0 equiv.) dissolved in CH₃CN:H₂O; 5:1 (1 mL), was added Cu(OAc)₂ (0.2 mmol, 2.0 equiv.) and (NH₄)₂S₂O₈ (0.4 mmol, 4.0 equiv.). The mixture was stirred at room temperature for 12 h, then, the reaction was quenched with aqueous 10% Na₂S₂O₃. The organic solvent was removed under reduced pressure, the residue was basified to pH 9 with concentrated aqueous NH₄OH, then extracted three times with DCM. After combining the organic layers, drying over anhydrous magnesium

sulfate, and filtration, the volatiles were removed under vacuum. Flash column chromatography (silica gel; CHCl₃:MeOH:NH₄OH, 96:4:1) of the crude material afforded analytically pure demethylated product.

All analytical data for compounds **8**,^[15] **14**,^[16] **17**,^[17] **19**,^[18] **21**,^[19] and **22**^[20] are in agreement with those reported in the literature.

N-Acetylnorhydrocodone (7)

The title compound was isolated following the general procedure for *N*-demethylation acylation reaction as a mixture of two isomers in a ratio of 3:1; yield: 80%; mp 99–100 °C (DCM); *R*_f 0.3 (DCM:MeOH, 96:4); FT-IR (film): ν_{\max} = 2929, 1727, 1628, 1505, 1436, 1325, 1274, 1241, 1121, 1061, 1026 cm⁻¹.

Major isomer: ¹H NMR (CDCl₃, 600 MHz): δ = 6.77 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 5.25–5.28 (m, 1H), 4.69 (s, 1H), 3.94 (s, 3H), 3.67 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.09 (dt, *J* = 13.2, 4.0 Hz, 1H), 2.91 (dd, *J* = 18.6, 6.1 Hz, 1H), 2.67 (d, *J* = 18.5 Hz, 1H), 2.32–2.51 (m, 3H), 2.14 (s, 3H), 1.91–2.02 (m, 3H), 1.20–1.32 (m, 1H); ¹³C NMR (CDCl₃, 150 MHz): δ = 206.8, 169.0, 145.6, 143.2, 126.0, 124.9, 120.4, 115.1, 91.0, 56.8, 47.6, 47.3, 41.2, 40.5, 39.9, 35.5, 28.4, 25.3, 22.1.

Minor isomer: ¹H NMR (CDCl₃, 600 MHz): δ = 6.77 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 4.70 (s, 1H), 4.56 (dt, *J* = 14.2, 3.1 Hz, 1H), 4.27–4.31 (m, 1H), 3.94 (s, 3H), 3.67 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.09 (dt, *J* = 13.2, 4.0 Hz, 1H), 2.97 (dd, *J* = 18.2, 5.8 Hz, 1H), 2.76 (d, *J* = 18.1 Hz, 1H), 2.53–2.61 (m, 1H), 2.32–2.51 (m, 2H), 2.14 (s, 3H), 1.91–2.02 (m, 2H), 1.20–1.32 (m, 1H); ¹³C NMR (CDCl₃, 150 MHz): δ = 206.7, 168.7, 145.6, 143.6, 126.0, 123.9, 120.3, 115.3, 91.0, 56.8, 53.8, 47.2, 42.1, 39.7, 35.4, 34.7, 29.2, 25.5, 21.9; MS (EI): *m/z* (%) = 327 (24), 241 (23), 117 (10), 87 (68), 86 (21), 85 (72), 84 (31), 83 (100), 57 (12), 49 (13), 48 (12), 47 (28), 43 (23), 41 (10); HR-MS: *m/z* = 327.1483, calcd. for C₁₉H₂₁NO₄: 327.1470, anal. calcd.: C 69.71, H 6.47; found: C 69.38, H 6.47.

N-Cyclopropylcarbonylnorhydrocodone (9)

The title compound was isolated following the general procedure for *N*-demethylation acylation reaction as a mixture of two isomers in a ratio of 3:1; yield: 76%; *R*_f 0.28 (DCM:MeOH, 96:4); FT-IR (film): ν_{\max} = 3448, 3007, 2929, 1728, 1631, 1505, 1438, 1327, 1275, 1115, 960, 753 cm⁻¹.

Major isomer: ¹H NMR (CDCl₃, 600 MHz): δ = 6.76 (d, *J* = 8.2 Hz, 1H), 6.64–6.70 (m, 1H), 5.22–5.26 (m, 1H), 4.69 (s, 1H), 4.09 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.92 (s, 3H), 3.12 (dt, *J* = 13.2, 3.7 Hz, 1H), 2.89 (dd, *J* = 18.3, 6.2 Hz, 1H), 2.65 (d, *J* = 18.5 Hz, 1H), 2.31–2.63 (m, 5H), 2.04 (dt, *J* = 12.5, 5.1 Hz, 1H), 1.89–2.00 (m, 1H), 1.70–1.78 (m, 1H), 1.18–1.36 (m, 1H), 0.96–1.09 (m, 1H), 0.74–0.92 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz): δ = 207.1, 172.0, 145.6, 143.3, 126.2, 125.1, 120.4, 115.1, 91.1, 67.1, 56.7, 48.3, 47.4, 42.1, 39.9, 36.2, 29.7, 28.4, 11.5, 8.8, 7.6.

Minor isomer: ¹H NMR (CDCl₃, 600 MHz): δ = 6.76 (d, *J* = 8.2 Hz, 1H), 6.64–6.70 (m, 1H), 4.73–4.77 (m, 1H), 4.70 (s, 1H), 4.50 (dd, *J* = 13.9, 3.6 Hz, 1H), 3.92 (s, 3H), 2.99 (dd, *J* = 18.0, 5.7 Hz, 1H), 2.80 (d, *J* = 18.1 Hz, 1H), 2.31–2.63 (m, 5H), 2.04 (dt, *J* = 12.5, 5.1 Hz, 1H), 1.89–2.00 (m, 1H), 1.81–1.83 (m, 1H), 1.57–1.65 (m, 1H), 1.18–1.36 (m,

1H), 0.96–1.09 (m, 1H), 0.74–0.92 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz): δ = 206.9, 171.9, 145.5, 143.1, 126.2, 125.1, 120.2, 114.9, 91.0, 67.1, 56.7, 48.3, 47.4, 41.2, 39.7, 35.7, 29.4, 25.3, 11.5, 7.5, 7.3; MS (EI): *m/z* (%) = 354 (17), 353 (66), 301 (28), 300 (11), 242 (30), 241 (57), 240 (14), 213 (11), 199 (11), 185 (19), 164 (30), 141 (10), 129 (16), 128 (12), 127 (10), 115 (15), 114 (11), 113 (61), 112 (82), 111 (28), 109 (11), 99 (11), 98 (73), 97 (11), 88 (23), 87 (19), 86 (48), 85 (89), 84 (80), 83 (100), 82 (18), 72 (13), 71 (21), 70 (25), 69 (81), 68 (14), 60 (12), 59 (18), 58 (22), 57 (37), 56 (13), 55 (31), 49 (21), 48 (13), 47 (36), 45 (22), 44 (28), 43 (40), 42 (32), 41 (77); H-RMS (EI): *m/z* = 353.1612, calcd. for C₂₁H₂₃NO₄: 353.1627.

N-Isobutyrylnorhydrocodone (10)

The title compound was isolated following the general procedure for *N*-demethylation acylation reaction as a mixture of two isomers in a ratio of 13:4; yield: 13%; *R*_f 0.32 (DCM:MeOH, 96:4); FT-IR (film): ν_{\max} = 3444, 2970, 2933, 1728, 1643, 1634, 1505, 1435, 1327, 1276, 1260, 1177, 1156, 1032, 958, 754 cm⁻¹.

Major isomer: ¹H NMR (CDCl₃, 300 MHz): δ = 6.77 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 8.6 Hz, 1H), 5.26–5.33 (m, 1H), 4.68 (s, 1H), 3.94 (s, 3H), 3.74–3.84 (m, 1H), 2.73–3.12 (m, 3H), 2.62 (d, *J* = 18.5 Hz, 1H), 2.28–2.51 (m, 3H), 1.87–2.06 (m, 3H), 1.20–1.30 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 75.5 MHz): δ = 206.9, 175.4, 145.6, 143.2, 126.2, 125.1, 120.4, 115.1, 91.0, 56.8, 47.6, 47.4, 41.4, 39.9, 39.4, 35.9, 30.5, 28.5, 25.4, 19.6, 19.1 ppm; MS (EI): *m/z* (%) = 355 (34.5), 242 (12.5), 241 (33.7), 115 (98.6), 100 (12.5), 88 (12.7), 87 (16.0), 86 (65.9), 84 (100.0), 72 (23.7), 55 (10.7), 49 (19.5), 47 (23.7), 43 (52.9), 41 (15.1); HR-MS (EI): *m/z* = 355.1777, calcd. for C₂₁H₂₅NO₄: 355.1784.

N-*n*-Propanoylnorhydrocodone (11)

The title compound was isolated following the general procedure for *N*-demethylation acylation reaction as a mixture of two isomers in a ratio of 3:1; yield: 53%; *R*_f 0.32 (DCM:MeOH, 96:4); FT-IR (film): ν_{\max} = 3436, 2918, 2849, 1727, 1634, 1505, 1437, 1276, 1118, 1031, 971 cm⁻¹.

Major isomer: ¹H NMR (CDCl₃, 600 MHz): δ = 6.68 (d, *J* = 8.2 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 5.17–5.22 (m, 1H), 4.60 (s, 1H), 3.85 (s, 3H), 3.62 (dd, *J* = 13.4, 5.0 Hz, 1H), 2.96 (dt, *J* = 13.0, 3.8 Hz, 1H), 2.83 (dd, *J* = 18.6, 6.0 Hz, 1H), 2.56 (d, *J* = 8.5 Hz, 1H), 2.20–2.47 (m, 6H), 1.81–1.93 (m, 3H), 1.10 (t, *J* = 7.7 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz): δ = 206.9, 172.3, 145.6, 143.3, 126.2, 125.2, 120.5, 115.2, 91.1, 56.8, 47.9, 47.3, 41.4, 40.1, 39.5, 35.9, 28.5, 27.2, 25.4, 9.7; MS (EI): *m/z* (%) = 341 (33.1), 242 (12.2), 241 (30.6), 188 (11.1), 185 (11.0), 167 (10.8), 149 (28.3), 129 (13.2), 113 (10.0), 102 (11.2), 101 (100.0), 72 (17.6), 71 (13.6), 70 (13.5), 57 (85.0), 56 (10.7), 55 (19.3), 43 (18.2), 41 (13.8); HR-MS (EI): *m/z* = 341.1628, calcd. for C₂₀H₂₃NO₄: 341.1627.

N-*n*-Decanoylnorhydrocodone (12)

The title compound was isolated following the general procedure for *N*-demethylation acylation reaction as a mixture of two isomers in a ratio of 3:1; yield: 36%; *R*_f 0.35

(DCM:MeOH, 96:4); FT-IR (film): ν_{\max} = 3435, 2926, 2850, 1726, 1626, 1505, 1436, 1155, 1030, 892, 753 cm^{-1} .

Major isomer: $^1\text{H NMR}$ (CDCl_3 , 600 MHz): δ = 6.68 (d, J = 8.2 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 5.18–5.21 (m, 1H), 4.60 (s, 1H), 3.84 (s, 3H), 3.62 (dd, J = 13.5, 4.6 Hz, 1H), 3.38 (m, 1H), 2.96 (dt, J = 13.1, 3.8 Hz, 1H), 2.83 (dd, J = 18.6, 6.1 Hz, 1H), 2.55 (d, J = 18.4 Hz, 1H), 2.34–2.40 (m, 1H), 2.20–2.33 (m, 3H), 1.81–1.93 (m, 2H), 1.59–1.65 (m, 2H), 1.49–1.58 (m, 2H), 1.13–1.33 (m, 12H), 0.81 (t, J = 6.8 Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 150 MHz): δ = 207.3, 171.9, 145.6, 143.4, 126.2, 124.9, 120.7, 115.1, 91.3, 56.7, 47.4, 41.3, 39.9, 39.7, 35.7, 34.0, 33.8, 31.9, 31.7, 29.5, 29.4, 28.4, 25.6, 25.4, 25.0, 22.7, 14.1; MS (EI): m/z (%) = 439 (1.0), 224 (41.8), 172 (10.1), 143 (36.3), 100 (15.8), 99 (56.6), 98 (36.9), 83 (18.2), 82 (11.2), 70 (21.3), 67 (10.4), 61 (52.2), 57 (19.3), 56 (100.0), 55 (43.2), 44 (14.1), 43 (46.5), 41 (42.7); HR-MS (EI): m/z = 439.2719, calcd. for $\text{C}_{27}\text{H}_{37}\text{NO}_4$: 439.2723.

***N*-n-Dodecanoylnorhydrocodone (13)**

The title compound was isolated as a mixture of two isomers in a ratio of 7:2; yield: 42%; R_f 0.35 (DCM:MeOH, 96:4); FT-IR (film): ν_{\max} = 3334, 2926, 2852, 1729, 1627, 1575, 1505, 1438, 1275, 1031, 965 cm^{-1} .

Major isomer: $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ = 6.77 (d, J = 8.2 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 5.24–5.32 (m, 1H), 4.69 (s, 1H), 3.93 (s, 3H), 3.66–3.76 (m, 1H), 3.42–3.58 (m, 1H), 2.98–3.11 (m, 1H), 2.91 (dd, J = 18.6, 6.1 Hz, 1H), 2.63 (d, J = 18.5 Hz, 1H), 2.23–2.52 (m, 3H), 1.87–2.04 (m, 4H), 1.54–1.79 (m, 4H), 1.20–1.47 (m, 15H), 1.01–1.20 (m, 3H), 0.89 (t, J = 6.5 Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 75.5 MHz): δ = 207.2, 171.8, 145.9, 143.3, 126.2, 125.2, 120.5, 115.2, 91.1, 56.8, 49.4, 47.6, 47.4, 41.4, 39.8, 35.9, 35.7, 34.2, 34.0, 32.1, 32.0, 29.7, 29.6, 29.5, 25.8, 25.4, 25.0, 22.8, 14.3; MS (EI): m/z (%) = 467 (2.5), 224 (21.4), 143 (17.6), 100 (10.0), 99 (27.0), 98 (17.4), 61 (23.2), 56 (100.0), 55 (19.9), 43 (20.5), 41 (19.1); HR-MS (EI): m/z = 467.3037, calcd. for $\text{C}_{29}\text{H}_{41}\text{NO}_4$: 467.3036.

5 α -4,5-Epoxy-3-methoxy-6-oxomorphinan-17-carboxylic Acid Methyl Ester (14)

To hydrocodone bitartrate (100 mg, 0.22 mmol) suspended in benzene (1 mL) and dimethyl dicarbonate (1 mL) was added Pd(OAc)₂ (2 mg, 0.01 mmol). The mixture was heated at 80 °C for 18 h, then cooled to room temperature and filtered through a plug of Celite. The solvent was evaporated, and the residue was taken up in CHCl_3 . The organic layer was washed with 1 N aqueous HCl, then dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated. The residue was purified by flash column chromatography (CHCl_3 :MeOH, 100:0 to 90:10) to give compound **14** as mixture of two isomers in a ratio of 3:2 as a colorless oil; yield: 25 mg (33%); R_f 0.55 (DCM:MeOH, 92:8); FT-IR (film): ν_{\max} = 3019, 2955, 2934, 2842, 2806, 1744, 1637, 1610, 1506, 1441, 1325, 1263, 1164, 1040 cm^{-1} .

Both isomers: $^1\text{H NMR}$ (CDCl_3 , 600 MHz): δ = 6.75 (d, J = 8.2 Hz, 2H), 6.63–6.68 (m, 2H), 4.77–4.81 (m, 1H), 4.67–4.70 (m, 2H), 4.60–4.64 (m, 1H), 4.10 (dd, J = 13.5, 5.0 Hz, 1H), 3.93–3.98 (m, 1H), 3.92 (s, 6H), 3.80–3.88 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 2.83–2.91 (m, 2H), 2.75–2.82 (m, 2H), 2.68–2.74 (m, 2H), 2.42–2.48 (m, 4H), 2.34–2.41 (m, 2H), 1.82–2.00 (m, 4H), 1.18–1.28 (m, 2H); $^{13}\text{C NMR}$

(CDCl_3 , 150 MHz): δ = 207.2, 155.9, 155.5, 145.5, 143.1, 126.1, 124.9, 124.7, 120.4, 120.3, 114.9, 114.8, 91.2, 56.7, 52.9, 52.8, 50.9, 50.6, 47.24, 47.17, 41.5, 41.4, 40.7, 39.9, 39.8, 38.01, 37.97, 35.0, 34.8, 28.9, 28.5, 25.4, 25.3; HR-MS (EI): m/z = 343.1421, calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5$: 343.1420; anal. calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_5 \cdot 1/6\text{H}_2\text{O}$: C 69.07%, H 6.51%; found: C 69.07%, H 6.41%.

5 α -4,5-Epoxy-3-methoxy-6-oxomorphinan-17-carboxylic Acid *tert*-Butyl Ester (15)

To hydrocodone bitartrate (100 mg, 0.22 mmol) suspended in benzene (1 mL) and di-*tert*-butyl dicarbonate (1 mL) was added Pd(OAc)₂ (2 mg, 0.01 mmol). The mixture was heated at 80 °C for 18 h, then cooled to room temperature and filtered through a plug of Celite. The solvent was evaporated, and the residue was taken up in CHCl_3 . The organic layer was washed with 1 N aqueous HCl, dried over anhydrous magnesium sulfate, filtered, then the solvent was evaporated. The residue was purified by flash column chromatography (CHCl_3 :MeOH, 100:0 to 90:10) to give compound **15** as mixture of two isomers in a ratio of 3:2 as a colorless oil; yield: 19 mg (15%); R_f 0.60 (DCM : MeOH, 92:8); FTIR (film) ν_{\max} : 3366, 2975, 2932, 1728, 1683, 1505, 1366, 1259, 1165, 1126 cm^{-1} .

Major isomer: $^1\text{H NMR}$ (CDCl_3 , 600 MHz): δ = 6.74 (d, J = 8.1 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 4.67 (s, 1H), 4.48 (br s, 1H), 3.91 (s, 3H), 2.73–2.89 (m, 2H), 2.69 (d, J = 17.8 Hz, 1H), 2.32–2.48 (m, 3H), 1.78–1.99 (m, 3H), 1.47–1.54 (m, 10H), 1.13–1.16 (m, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 150 MHz): δ = 207.3, 156.3, 154.8, 145.5, 143.1, 126.2, 120.3, 114.8, 114.8, 91.2, 80.0, 56.7, 51.2, 49.9, 41.4, 39.9, 38.3, 35.1, 28.6, 25.4, 24.3; HR-MS (EI): m/z = 385.1879, calcd. for $\text{C}_{22}\text{H}_{27}\text{NO}_5$: 385.1892.

***N*-Formylnorhydrocodone**

To hydrocodone (50 mg, 0.17 mmol) dissolved in MeOH (1 mL), Pd/C (10%) (89 mg, 0.08 mmol) was added at 0 °C. The mixture was stirred open to air at room temperature for three days, then filtered through a plug of Celite. The solvent was evaporated, and the residue was purified by flash column chromatography (CHCl_3 :MeOH: NH_4OH , 100:0:0 to 85:15:1) to give a colorless oil consisting of a 4:3 mixture of two isomers of the title compound; yield: 10 mg (17%); R_f 0.53 (DCM:MeOH, 92:8); FT-IR (film): ν_{\max} = 3007, 2932, 1728, 1660, 1609, 1505, 1438, 1276, 1108 cm^{-1} .

Both isomers: $^1\text{H NMR}$ (CDCl_3 , 600 MHz): δ = 8.23 (s, 1H), 8.06 (s, 1H), 6.78 (d, J = 8.3 Hz, 2H), 6.67–6.72 (m, 2H), 5.01–5.05 (m, 1H), 4.71 (s, 1H), 4.70 (s, 1H), 4.35 (dd, J = 14.1, 5.1 Hz, 1H), 4.07–4.10 (m, 1H), 3.94 (s, 6H), 3.87–3.99 (m, 2H), 3.45–3.50 (m, 1H), 3.10–3.17 (m, 1H), 2.91–3.04 (m, 2H), 2.77 (d, J = 18.1 Hz, 1H), 2.71 (d, J = 19.3 Hz, 1H), 2.63 (td, J = 13.1, 4.3 Hz, 1H), 2.45–2.52 (m, 3H), 2.33–2.44 (m, 4H), 1.90–2.02 (m, 6H), 1.22–1.35 (m, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 150 MHz): δ = 206.5, 206.4, 160.7, 160.5, 145.7, 143.5, 143.4, 126.0, 125.9, 124.5, 123.9, 120.5, 120.3, 115.4, 115.2, 91.1, 56.80, 56.77, 54.3, 48.1, 48.0, 46.8, 42.6, 41.3, 40.7, 39.7, 39.6, 35.5, 34.5, 34.3, 29.8, 28.2, 25.2, 25.1; HR-MS (EI): m/z = 313.1308, calcd. for $\text{C}_{18}\text{H}_{19}\text{NO}_4$: 313.1314.

8-Acetyl-8-azabicyclo[3.2.1]octan-3-yl 2-Phenylacrylate (**24**)

To atropine (100 mg, 0.35 mmol) dissolved in benzene (1 mL) and acetic anhydride (1 mL) was added Pd(OAc)₂ (16 mg, 0.07 mmol). The mixture was heated at 80 °C for 16 h, then cooled to room temperature and filtered through a plug of Celite. The solvent was evaporated and the residue was taken up in CHCl₃. The organic layer was washed with 1N aqueous HCl, dried over anhydrous magnesium sulfate, and filtered. After evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography (CHCl₃:MeOH, 100:0 to 90:10) to give compound **24** as a colorless solid; yield: 85 mg (82%); *R*_f 0.45 (DCM:MeOH, 96:4); mp 104–107 °C (DCM/hexanes); FT-IR (film): ν_{\max} = 2953, 2922, 1714, 1635, 1495, 1445, 1424, 1327, 1196, 1167, 1076, 1034 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 7.29–7.42 (m, 5H), 6.37 (s, 1H), 5.89 (s, 1H), 5.25 (t, *J* = 4.8 Hz, 1H), 4.59–4.68 (m, 1H), 4.04–4.13 (m, 1H), 2.22 (dt, *J* = 15.3, 4.3 Hz, 1H), 2.05 (s, 3H), 1.78–2.15 (m, 7H); ¹³C NMR (CDCl₃, 75.5 MHz): δ = 166.1, 165.8, 141.8, 136.7, 123.3, 128.2, 128.1, 127.0, 68.3, 54.2, 50.1, 37.3, 35.6, 28.6, 26.9, 21.5; MS (EI): *m/z* (%) = 299 (18), 257 (16), 168 (15), 152 (28), 151 (32), 136 (18), 126 (10), 111 (14), 110 (100), 109 (38), 108 (17), 103 (38), 97 (10), 86 (27), 84 (44), 83 (15), 82 (19), 81 (25), 80 (29), 77 (22), 71 (11), 69 (33), 68 (35), 67 (28), 57 (19), 55 (18), 47 (10), 43 (68), 41 (26); HR-MS (EI): *m/z* = 299.1518, calcd. for C₁₈H₂₁NO₃: 299.1521; anal. calcd. for C₁₈H₂₁NO₃·1/3H₂O: C 70.80%, H 7.15%; found: C 70.84%, H 7.18%.

5 α -7,8-Dihydro-4,5-epoxy-3-methoxy-17-methyl-6-oxomorphinan 17-Oxide (Hydrocodone *N*-Oxide) (**29**)

To hydrocodone (100 mg, 0.33 mmol) dissolved in CH₃CN:H₂O; 5:1 (2 mL), was added Cu(OAc)₂ (131 mg, 0.66 mmol, 2.0 equiv.) and 30% aqueous H₂O₂ (0.34 mL, 3.35 mmol). The mixture was stirred at room temperature for 16 h, then the reaction was quenched with aqueous 10% Na₂S₂O₃. The organic solvent was removed under reduced pressure; the residue was basified to pH 9 with concentrated aqueous NH₄OH, then extracted three times with DCM. After combining the organic layers, drying over anhydrous magnesium sulfate, and filtration, the volatiles were removed under vacuum. Flash column chromatography (silica gel; CHCl₃:MeOH:NH₄OH, 96:4:1) of the crude material afforded hydrocodone *N*-oxide as a colorless solid; yield: 70 mg (67%); mp 199–200 °C (DCM); *R*_f 0.22 (DCM:MeOH:NH₄OH, 92:8:1); ¹H NMR (CDCl₃, 600 MHz): δ = 6.77 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 4.77 (s, 1H), 4.23 (td, *J* = 13.2, 3.5 Hz, 1H), 3.90 (s, 3H), 3.56–3.60 (m, 1H), 3.35 (s, 3H), 3.11–3.17 (m, 2H), 3.02 (dt, *J* = 12.2, 3.5 Hz, 1H), 2.87–2.98 (m, 2H), 2.52 (dt, *J* = 13.8, 4.6 Hz, 1H), 2.42–2.48 (m, 2H), 1.84–1.90 (m, 1H), 1.71–1.77 (m, 1H), 1.15 (dq, *J* = 13.3, 3.2 Hz, 1H); ¹³C NMR (CDCl₃, 150 MHz): δ = 206.8, 145.6, 143.8, 126.1, 121.3, 120.3, 115.5, 90.8, 75.6, 60.7, 58.8, 56.8, 45.2, 39.9, 33.4, 30.8, 25.5, 25.1 ppm; MS (EI): *m/z* (%) = 315 (1), 299 (8), 88 (10), 86 (64), 84 (100), 59 (10), 49 (17), 47 (21); HR-MS (EI): *m/z* = 299.1520 (M⁺–16), calcd. for C₁₈H₂₁NO₃: 299.1521.

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