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One-Pot Conversion of Thebaine to Hydrocodone and Synthesis of Neopinone Ketal

Robert J. Carroll,[†] Hannes Leisch,[†] Lena Rochon,[†] Tomas Hudlicky,*[,†] and D. Phillip Cox[‡]

Department of Chemistry and Centre for Biotechnology, Brock University, 500 Glenridge Avenue, St. Catharines, ON, Canada, L2S 3A1, and Noramco Inc., 503 Carr Road, Suite 200, Wilmington, Delaware 19809

thudlicky@brocku.ca

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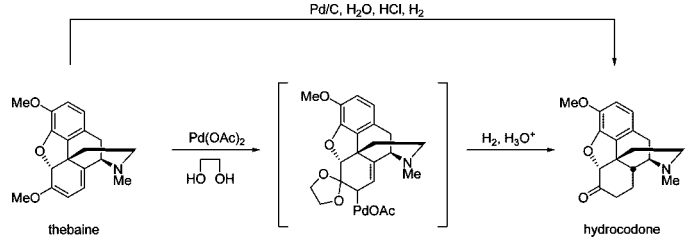

The ethylene glycol ketal of neopinone was prepared in a one-pot procedure by the reaction of thebaine with ethylene glyocol in the presence of *p*-toluenesulfonic acid. The ketal is also an intermediate in the conversion of thebaine to hydrocodone with ethylene glycol and $Pd(OAc)_2$, followed by hydrogenation. Additionally, a one-pot procedure for the conversion of thebaine to hydrocodone was achieved by employing palladium catalysis in aqueous medium. Palladium serves a dual purpose in this transformation, first for the activation of the dienol ether of thebaine and second as a hydrogenation catalyst. This procedure was found to be comparable to the two-step protocol which employs diimide reduction of thebaine followed by acid-catalyzed hydrolysis of the resulting 8,14-dihydrothebaine to hydrocodone. Experimental and spectral data are provided for all compounds.

Introduction

The supply of morphine and morphine-derived products in medicine depends on the isolation of major constituents of the opium poppy such as morphine (**1**), codeine (**2**), and thebaine (**3**) (Figure 1).[1] These alkaloids can be converted by semisynthesis to other medicinally useful agents such as hydrocodone (**4**), oxycodone (**5**), naltrexone (**6**), and naloxone (**7**). Morphine is employed in anesthesia and pain control, and in the U.S. alone, approximately 35 tons of morphine sulfate are supplied for this purpose. The worldwide consumption is estimated at 400 tons/annum.[2] The world market for oxycodone and hydrocodone is estimated at more than 80 tons/annum, and the consumption of associated antagonists in the U.S. is about 1 ton/annum, all derived from morphine, codeine, or thebaine, whose U.S. production quota is 126 metric tons.[3] Consumption of morphine-derived antagonists is expected to grow with the recent approvals of naltrexone (Vivitrex) for treatment of alcoholism, buprenorphine for the treatment of addiction, and methylnaltrexone for treatment of constipation,[4] induced by the use of opiate-derived analgesics.

Thebaine, usually a minor constituent of opium latex, is isolated as a major component from genetically engineered hybrids introduced by the company Tasmanian Alkaloids.[5] Thebaine, an ideal precursor to most C-14 hydroxylated derivatives, is easily transformed to 14-hydroxycodeinone by treatment with formic acid and hydrogen peroxide, according to the procedure first used by Freund and Speyer in 1916,[6] by Seki in 1960,[7] and further refined in more recent applications.[8]

[†] Brock University.
[‡] Noramco Inc.

(1) (a) Zezula, J.; Hudlicky, T. *Synlett* **2005**, 388. (b) Novak, B. H.; Hudlicky, T.; Reed, J. W.; Mulzer, J.; Trauner, D. *Curr. Org. Chem.* **2000**, *4*, 343. (c) Butora, G.; Hudlicky, T. *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Stamford, CT, 1998; Vol. 4, pp 1−51. (d) Hudlicky, T.; Butora, G.; Fearnley, S.; Gum, A.; Stabile, M. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1996; Vol. 18, p 43.

(2) Report of the International Narcotics Control Board for 2005, ISBN 92-1-148209-7 ISSN 0257−3717, Page 17.

(3) For production quotas of morphine alkaloids for the U.S., see: http://www.deadiversion.usdoj.gov/quotas/quota_history.htm.

(4) The Electronic Orange Book, http://www.fda.gov/cder/ob/default.htm, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research,Office of Pharmaceutical Science, Office of Generic Drugs.

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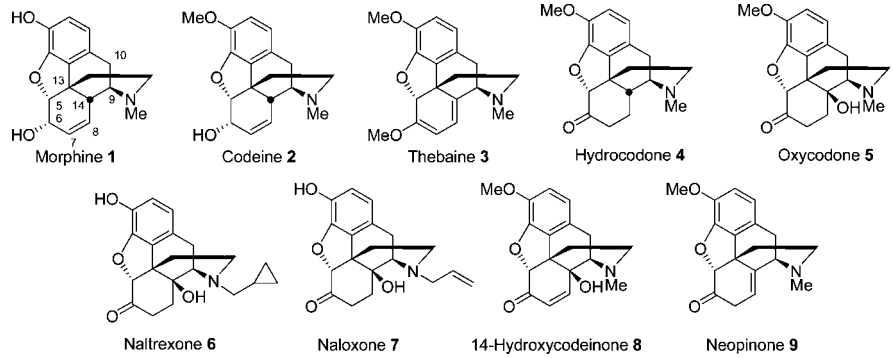

FIGURE 1. Opium constituents and their derivatives derived by semisynthesis.

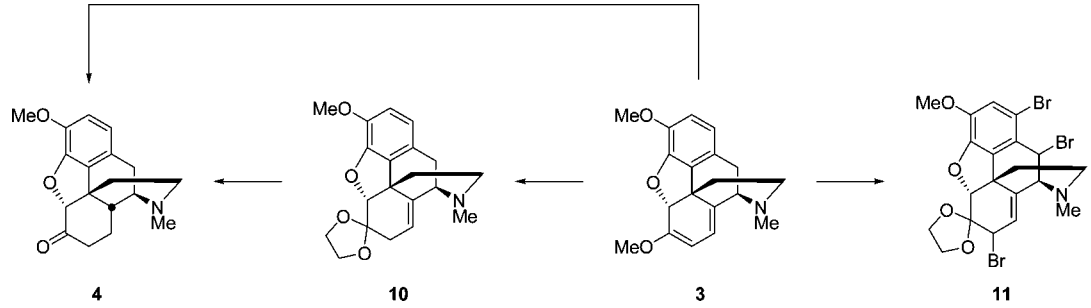

FIGURE 2. Production of hydrocodone from thebaine and synthesis of neopinone ketals.

Most C-14 hydroxylated derivatives are accessible through this or similar procedures. Recent guidelines from the International Conference on Harmonization (ICH) limit the amount of α,β-unsaturated-ketone-containing compounds in pharmaceutical preparations necessitating new routes to Active Pharmaceutical Ingredients (APIs) that avoid the production of such intermediates and/or impurities.[9] A logical alternative intermediate for C-14 hydroxylations is a β,γ-unsaturated species such as neopinone and its derivatives, which still offer the potential for functionalization of C-14 via selective transformations of the C-8/C-14 olefin. Here we report the transformation of thebaine to the neopinone ketals **10** and **11** and a one-pot conversion of thebaine to hydrocodone (Figure 2).

Results and Discussion

The conversion of thebaine to neopinone ketal **12** was demonstrated by Rapoport[10] and Dauben,[11] who used mercuric acetate to activate the dienol ether at the kinetically favored α-position, as shown in Scheme 1. Although a direct conversion of thebaine to its ketal under acid-catalyzed equilibrium conditions has not previously been reported, it is well-established that dienol ethers or α,β-unsaturated ketones can be converted to the corresponding β,γ-unsaturated ketals via kinetic protonation at the α-position and subsequent intra- or intermolecular trapping of the oxonium ion, as, for example, in the generation of ketal **14** during Heathcock's 1971 synthesis of α-bulnesene (Figure 3).[12] It is evident that protonation of **13** at the α-position to **15** is immediately followed by rapid intramolecular closure of **15** to **14** and that the isomerization of the β,γ-olefin into conjugation in **16** does not occur. The probability of the preferential formation of the deconjugated isomers such as **14** is higher when ethylene glycol (in preference to MeOH or EtOH) is used because the trapping of oxonium ion **15** is intramolecular.

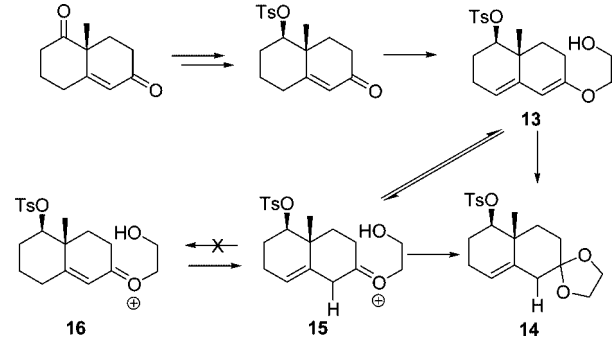

FIGURE 3. Deconjugation of α,β-enones via their ketals.

Exposure of thebaine to ethylene glycol in chloroform in the presence of TsOH led to its conversion to the corresponding ketal **10** in ~40% yield, accompanied by a minor product, phenolic in nature, but not positively identified (Scheme 2). To our knowledge, the unsaturated ethylene glycol ketal **10**, derived from neopinone, has not been previously reported. The $\Delta_{7\text{-}8}$ isomeric ketal was not detected in the reaction mixture. Encouraged by this result, we converted **10** to **17** by hydrogenation at atmospheric pressure. Acid-catalyzed hydrolysis of **17** yielded hydrocodone **4** according to a previously published

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(8) (a) Krassnig, R.; Hederer, C.; Schmidhammer, H. *Arch. Pharm.* **1996**, *329*, 325. (b) Francis, C. A.; Lin, Z.; Kaldahl, C. A.; Antczak, K. G.; Kumar, V. US 2005/0038251 A1. (c) Casner, M. L.; Dung, J. S.; Keskeny, E. M.; Luo, J.; López, D.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2000**, *65*, 4671 US 2006111383; alternative methods for C-14 hydroxylation include a photochemical approach.

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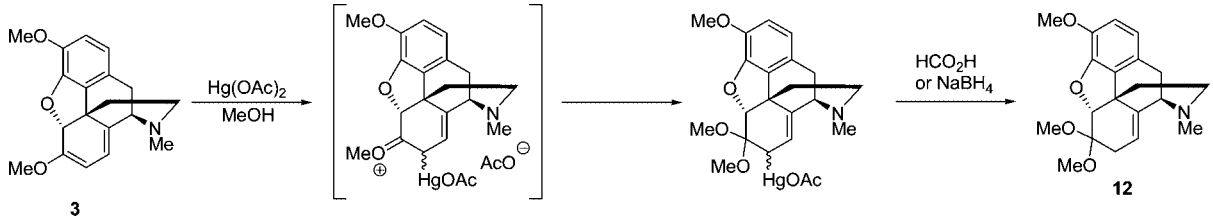
(12) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.

SCHEME 1. Mercuric Acetate Mediated Formation of Neopinone Ketal 12 from Thebaine (3)



SCHEME 2. Formation of Neopinone Ketal 10 and Its Conversion to Hydrocodone (4)

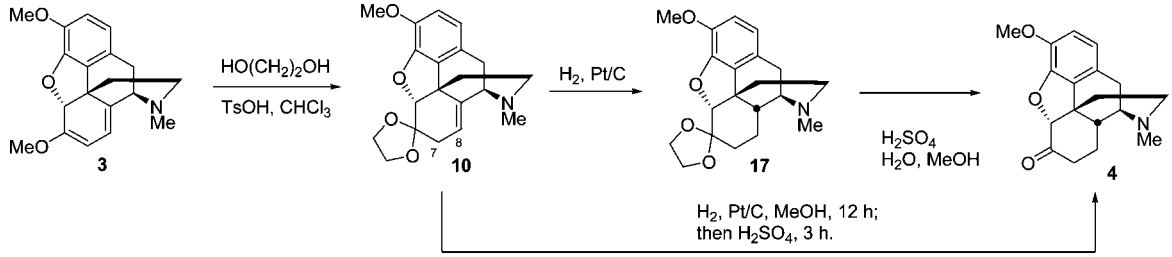


TABLE 1. Reaction Conditions for the Formation of Neopinone Ketal 10

entry	conditions[a]	thebaine consumption (%)	yield of **10** (%)[b]
1	3.3 equiv of $TsOH·H_2O$, 10 equiv of glycol, $CHCl_3$	100	38 (isolated)
2	3.3 equiv of $TsOH·H_2O$, 10 equiv of glycol, $CHCl_3$, 4Å MS	65	17
3	3.3 equiv of polyphosphoric acid, 10 equiv of glycol, $CHCl_3$	100	N/A
4	3.3 equiv of oxalic acid·$2H_2O$, 10 equiv of glycol, $CHCl_3$	100	N/A
5	3.3 equiv of acetic acid (glacial), 10 equiv of glycol, $CHCl_3$	100	N/A
6	3.3 equiv of $TsOH·H_2O$, 10 equiv of glycol, EtOAc	100	16
7	3.3 equiv of $TsOH·H_2O$, 10 equiv of glycol, EtOAc, 4Å MS	100	20
8	3.3 equiv of $TsOH·H_2O$, 10 equiv of glycol, EtOAc, 4Å MS, 0.16 M	100	21
9	3.3 equiv of $TsOH·H_2O$, 10 equiv of glycol, EtOAc, 4Å MS, 5 h, 0.04 M	59	6
10	3.3 equiv of $TsOH·H_2O$, 10 equiv of glycol, EtOAc, 4Å MS, 0.04 M	100	8
11	3.3 equiv of $TsOH·H_2O$, 10 equiv of glycol, PhMe, 40 °C	100	10
12	3.3 equiv of $TsOH·H_2O$, 10 equiv of glycol, PhMe, 60 °C	100	12
13	3.3 equiv of $TsOH·H_2O$, 10 equiv of glycol, PhMe, 110 °C	100	multiple products
14	3.3 equiv of $TsOH·H_2O$, 10 equiv of glycol, 1,2-dichlorobenzene	100	8
15	5 equiv of $TsOH·H_2O$, 10 equiv of glycol, $CHCl_3$	100	36
16	10 equiv of $TsOH·H_2O$, 10 equiv of glycol, $CHCl_3$	100	17

[a] All reactions were carried out at reflux of the stated solvent for 45 min unless otherwise noted. [b] Based on ^1H NMR of crude product after workup.

procedure.[13] Subsequently, we have demonstrated that **10** can be directly converted to **4** by means of a one-pot hydrogenation and hydrolysis procedure.

The incompatibility of thebaine with strong protic acids is well-documented,[14] and we have observed competing acid-induced pathways during the synthesis of **10**, hence the modest yield of the ketal, despite focused attempts at optimization of conditions for this reaction, as summarized in Table 1.

We therefore examined alternative conditions for the conversion of the enol ether of thebaine to its ketal in order to generate **10**. The use of bromine as a "pseudoproton" in the presence of ethylene glycol led to the perbrominated ketal **11** (proposed structure, tentatively assigned by NMR and low resolution mass spectrometry), which is potentially convertible to hydrocodone by hydrogenation and hydrolysis (Scheme 3). Because of the rather low yield (27%) of this material, we have not further converted **11** to hydrocodone and pursued instead investigations of other conditions, namely, palladium-catalyzed reactions of the dienol ether moiety in thebaine.

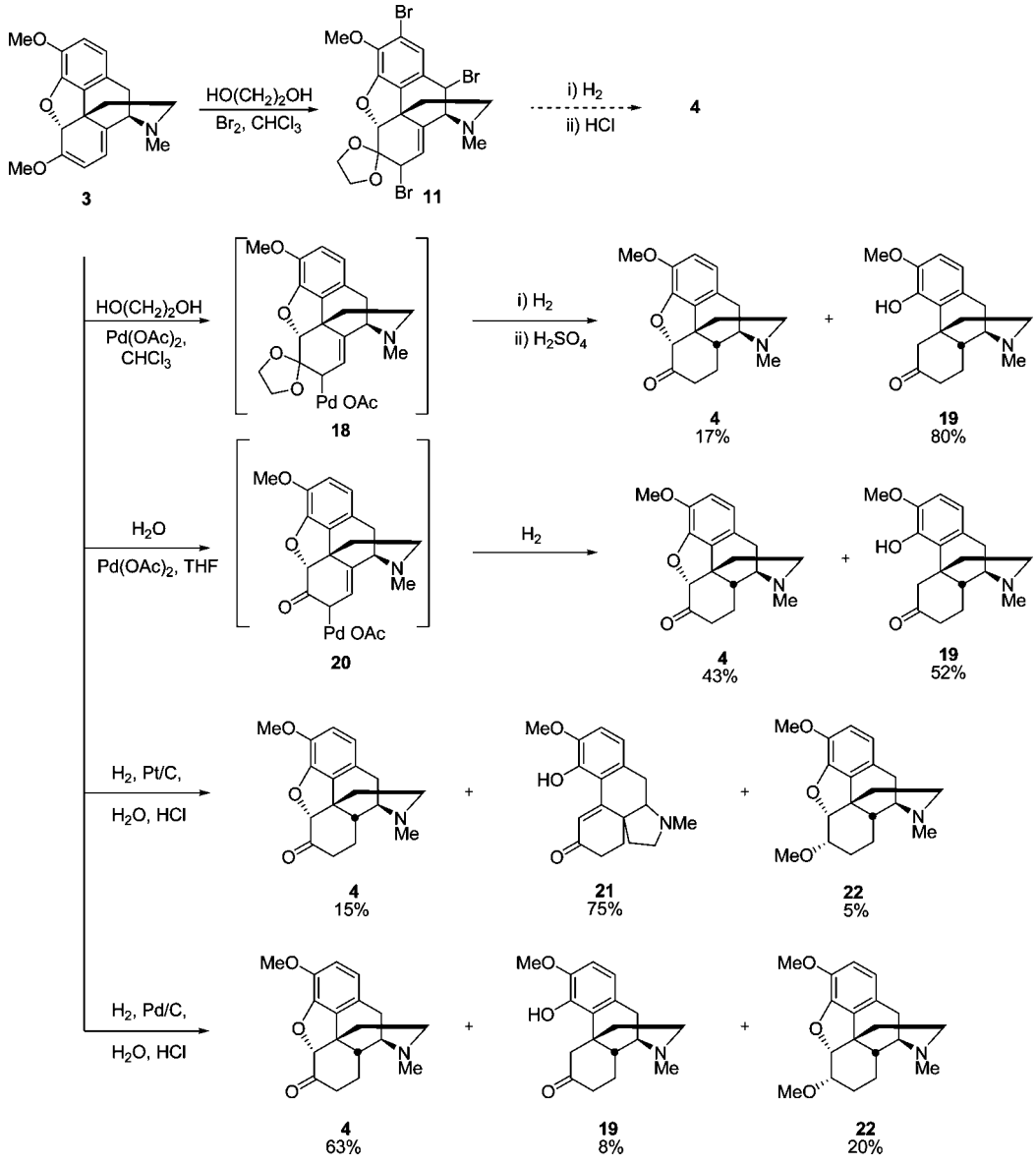
When $Pd(OAc)_2$, in the presence of ethylene glycol, was used with the dual purpose of acting initially as a proton surrogate and later as a hydrogenation catalyst, hydrocodone was obtained in a one-pot sequence from thebaine in 17% yield at the expense of the formation of dihydrothebainone (**19**)[15] (Scheme 3). Addition of $Pd(OAc)_2$ to a solution of thebaine in ethylene glycol and chloroform resulted in the formation of a deep-red-colored reaction mixture. After 2 h, the mixture was hydrogenated at 1 atm for 4 h and finally aqueous H_2SO_4 in MeOH was introduced for the final hydrolysis to **4**. We assumed the intermediacy of **18** as the species present immediately before hydrogenation and reasoned that the ketalization step could be avoided altogether if an intermediate of type **20** could be generated from thebaine in aqueous media under palladium catalysis. Indeed, treatment of thebaine in aqueous THF with $Pd(OAc)_2$ led rapidly to the formation of the presumed intermediate **20** (dark red in color), which was immediately treated with hydrogen at atmospheric pressure to yield hydrocodone **4** in 43% yield, with the attendant diminishment of dihydrothebainone **19**.

(13) Trauner, D.; Bats, J. W.; Werner, A.; Mulzer, J. *J. Org. Chem.* **1998**, *63*, 5908.

(14) For examples, see: (a) Conroy, H. *J. Am. Chem. Soc.* **1955**, *77*, 5960. (b) Batterham, T. J.; Bell, K. H.; Weiss, U. *Aust. J. Chem.* **1966**, *19*, 321, and references cited therein.

(15) Moos, W. H.; Gless, R. D.; Rapoport, H. J. *J. Org. Chem.* **1983**, *48*, 227.

SCHEME 3. Preparation of Hydrocodone 4 from Thebaine 3



Literature reports and patents from the 1920s[16] and 1930s[17] revealed that thebaine was previously converted to hydrocodone by hydrogenation over platinum and palladium in acidic medium. In one report,[16b] "...thebaine is treated in the presence of a catalyser, especially palladium, platinum, or their salts in comparatively large amounts and preferably in the form of 'black'..." to furnish hydrocodone in unspecified yield for the conversion. A later publication in 1935 from Goto and Shishido[17] reported the hydrogenation of thebaine to hydrocodone, dihydrothebainone **19** and, metathebainone **21**[18] in acidic medium, with the yield of hydrocodone estimated from the data provided being about 30%. We examined the hydrogenation of thebaine under palladium catalysis in detail in order to provide for optimum conditions, as shown in Table 2, and the process was reduced to a one-pot procedure for the conversion of thebaine to hydrocodone. Treatment of thebaine in 10−20% aqueous HCl under 1 atm of hydrogen in the presence of 5% w/w Pd/C (10%) provided hydrocodone **4** in 63% yield, along with dihydrothebainone **19** (20%) and tetrahydrothebaine **22** (8%) (Scheme 3). Tetrahydrothebaine **22** was first isolated by Schopf in 1927,[19] and considerable amounts were detected in previous hydrogenation studies of thebaine using homogeneous hydrogen catalysts in our own laboratory.[20] The formation of *meta*-thebainone **21** was observed in significant amounts when platinum on charcoal was used as catalyst (Table 2).

Conclusions

The one-pot synthesis of hydrocodone in 63% yield from thebaine compares favorably with previously reported protocols. Grew and Robertson[21] reported 88% yield for the two-step

(16) (a) Knoll & Co DE 441613. (b) Knoll & Co GB 225,824.
(17) Goto, K.; Shishido, H. *Bull. Chem. Soc. Jpn.* **1935**, *10*, 597.
(18) (a) Cahn, R. S. *J. Chem. Soc.* **1933**, 1038. (b) Bentley, K. W.; Dyke, S. F.; Marshall, A. R. *Tetrahedron* **1965**, *21*, 2553.
(19) (a) Schopf, C. *Ann.* **1927**, *452*, 232. (b) Janssen, R. H. A. M.; Wijkens, P.; Kruk, C.; Biessels, H. W. A.; Menichini, F.; Theuns, H. G. *Phytochemistry* **1990**, *29*, 3331.
(20) Leisch, H.; Carroll, R. J.; Hudlicky, T.; Cox, D. P. *Tetrahedron Lett.* **2007**, *48*, 3979.
(21) Grew, E. L.; Robertson, A. A. US 3812132.

TABLE 2. Hydrogenation of Thebaine 4 in Aqueous Acidic Solution

entry	conditions[a]	hydrocodone (**4**)	dihydrothebainone (**19**)	*meta*-thebainone (**21**)	tetrahydro-thebaine (**22**)
1	Pd/C (10%), H_2 (1 atm), 20% aqueous HCl, 18 h	63%	8%	0%	20%
2	Pd/C (10%), H_2 (2 atm), 20% aqueous HCl, 18 h	62%	8%	0%	25%
3	PdO, H_2 (1 atm), 20% aqueous HCl, 18 h	58%	14%	0%	19%
4	$PtCl_2$, H_2 (1 atm), 20% aqueous HCl, 18 h	13%	4%	0%	13%
5	Pt/C (5%), H_2 (1 atm), 20% aqueous HCl, 18 h	40%	6%	14%	30%
6	Pd/C (10%), H_2 (1 atm), 20% aqueous HCOOH, 18 h	0%	73%	0%	18%
7	Pt/C (1%), vanadium doped, 20% aqueous HCl, H_2 (1 atm), 18 h	15%	0%	75%	5%

[a] All reactions were carried out with 5 wt % of catalyst loading.

conversion of thebaine to hydrocodone via diimide reduction followed by hydrolysis. In our hands, the repetition of this procedure yielded hydrocodone in ~65%. Our lower yield may be rationalized by the difference in the scale of this experiment. The patented process was performed on 62 g of technical thebaine (99%), while our repetition was done on a 100 mg scale. The major advantage of our method is the fact that the one-pot protocol is performed in aqueous medium (as opposed to morpholine, ethanolamine, or a mixture of 2-methoxyethanol and ethanolamine).

The ethylene glycol derived ketal of neopinone was prepared in modest yield (~40%), due to the known instability of thebaine to protic acids. The corresponding neopinone ketal derived from methanol was prepared by Rapoport in 85% yield by treating thebaine with $Hg(OAc)_2$ in MeOH, followed by reduction with borohydride or formic acid.[10] Clearly, further improvements in the preparation of neopinone ketal **10** would be required for this material to be used for either hydrocodone synthesis via hydrogenation and hydrolysis or the preparation of C-14 hydroxylated analogues. The hydrolysis of 8,14-dihydroneopinone ketal **17** was reported by Mulzer in 95%.[13] Our repetition of this procedure provided hydrocodone in ~75% yield when Mulzer's conditions (3 N HCl(aq) at 90 °C) were used. The same transformation was achieved in 77% yield by treating the ketal intermediate with aqueous H_2SO_4 in methanol at room temperature.

Experimental Section

(5α)-Cyclic-1,2-ethanediyl acetal-8,14-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-one (10). Thebaine (0.5 g, 1.6 mmol) was dissolved in $CHCl_3$ (0.9 mL), and freshly distilled ethylene glycol (1.0 g, 16.1 mmol) was added. To this biphasic mixture was added $TsOH \cdot H_2O$ (1.0 g, 5.3 mmol) under vigorous stirring. The reaction mixture was heated to reflux for 45 min, cooled to 0 °C, and the pH was adjusted to 11 with saturated aq K_2CO_3. The solution was extracted three times with $CHCl_3$ (5 mL), and the organic layers were combined. Drying over anhydrous Na_2SO_4, filtration, and evaporation of the solvent provided a dark yellow residue, which was purified by flash column chromatography ($CHCl_3$/MeOH/NH_4OH, 98:2:1) to provide the title compound as a pale yellow oil in 38% yield: R_f 0.55 (DCM/MeOH/NH_4OH, 96:4:1); FTIR (film) ν_{max} 3407, 3031, 2924, 2903, 2833, 2791, 1634, 1603, 1504, 1448, 1325, 1277, 1258, 1165, 1050, 1035, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.74 (d, J = 8.2 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 5.56 (d, J = 5.6 Hz, 1H), 4.70 (s, 1H), 4.28 (q, J = 6.2 Hz, 1H), 3.93 (q, J = 6.8 Hz, 1H), 3.86−3.90 (m, 4H), 3.81 (q, J = 6.2 Hz, 1H), 3.64 (d, J = 3.64 Hz, 1H), 3.26 (d, J = 18.1 Hz, 1H), 2.67−2.78 (m, 2H), 2.61 (dd, J = 12.6, 4.6 Hz, 1H), 2.50 (d, J = 1.1 Hz, 1H), 2.47 (s, 3H), 2.14 (dd, J = 16.2, 6.4 Hz, 1H), 2.06 (td, J = 12.5, 5.0 Hz, 1H), 1.85 (dd, J = 12.3, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 145.6, 142.1, 138.4, 131.8, 127.2, 119.4, 113.8, 113.2, 108.1, 93.1, 66.7, 65.4, 61.2, 56.8, 45.9, 45.8, 42.2, 36.2, 32.7, 26.8; MS (EI) m/z (%) 342 (23.1), 341 (100.0), 326 (10.0), 269 (10.6), 268 (21.24), 255 (17.5), 254 (52.4), 240 (10.0), 226 (14.5), 212 (11.1), 85 (22.2), 83 (34.4), 42 (18.4); HRMS (EI) calcd for $C_{20}H_{23}NO_4$ 341.1627; found 341.1621.

(5α)-Cyclic-1,2-ethanediyl acetal-4,5-epoxy-3-methoxy-17-methylmorphinan-6-one (17). A solution of **10** (100 mg, 0.3 mmol) in $CHCl_3$ (1 mL) was treated with Pt/C (10%) under H_2 (1 atm) for 16 h. Filtration through a plug of silica and elution with $CHCl_3$/MeOH/NH_4OH, 92:8:1 gave the title compound in quantitative yield. Data (^1H and ^{13}C NMR spectra) for **17** matched closely to those published in the literature:[13] R_f 0.55 (DCM/MeOH/NH_4OH, 96:4:1); FTIR (film) ν_{max} 2941, 2926, 2889, 1636, 1611, 1502, 1441, 1325, 1275, 1258, 1190, 1155, 1060, 922 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.67 (d, J = 8.2 Hz, 1H), 6.55 (d, J = 8.2 Hz, 1H), 4.42 (s, 1H), 4.12 (q, J = 6.5 Hz, 1H), 3.97 (q, J = 5.0 Hz, 1H), 3.78−3.85 (m, 5H), 3.72 (q, J = 6.3 Hz, 1H), 3.01−3.05 (m, 1H), 2.93 (d, J = 18.3 Hz, 1H), 2.44 (dd, J = 12.1, 4.3 Hz, 1H), 2.33 (s, 3H), 2.27 (dd, J = 18.2, 5.4 Hz, 1H), 2.09−2.17 (m, 2H), 1.79 (dt, J = 12.3, 4.9 Hz, 1H), 1.56−1.66 (m, 2H), 1.41−1.50 (m, 2H), 1.08 (td, J = 12.7, 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 146.6, 142.1, 129.2, 126.5, 118.6, 113.4, 108.6, 94.4, 66.4, 64.9, 59.5, 56.5, 47.1, 43.6, 42.9, 42.6, 36.5, 33.4, 22.3, 20.1; MS (EI) m/z (%) 344 (23.3), 343 (100.0), 342 (13.4), 329 (14.4), 256 (11.4), 244 (17.2), 198 (11.1), 99 (86.9), 59 (16.5), 55 (12.0); HRMS (EI) calcd for $C_{20}H_{25}NO_4$ 343.1784; found 343.1777.

Hydrocodone 4 (from 17). A solution of compound **17** (80 mg, 0.23 mmol) in 25% (v/v) solution of H_2SO_4/MeOH (0.5 mL) was was stirred for 3 h. The pH of the solution was adjusted to 11 with saturated aq K_2CO_3 and extracted with $CHCl_3$ (5 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered, concentrated, and then the crude material was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 98:2:1) to yield 54 mg of hydrocodone in 77% yield. All analytical data generated for hydrocodone synthesized in this manner are identical with those of an authentic sample.

Hydrocodone 4 (One-Pot Procedure from 10). A solution of **10** (45 mg, 0.13 mmol) in MeOH (90 μL) was treated with Pt/C (10%) (1 mg) under H_2 (1 atm) for 12 h. A 25% (v/v) solution of H_2SO_4/MeOH (0.5 mL) was added to the reaction solution, which was stirred for 3 h. The pH of the solution was adjusted to 11 with saturated aq K_2CO_3 and extracted with $CHCl_3$ (5 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered, concentrated, and then the crude material was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 98:2:1) to yield hydrocodone in 75% yield. All analytical data generated for hydrocodone synthesized in this manner are identical with those of an authentic sample.

Hydrocodone 4 (One-Pot Procedure from Thebaine). To thebaine **3** (100 mg, 0.32 mmol) dissolved in THF (1 mL) and H_2O

(22) The use of thebaine and other morphinans was carried out in accordance with Health Canada guidelines and procedures [licence # 2006/7531].

(1 mL) was added $Pd(OAc)_2$ (72 mg, 0.32 mmol). After 2 h at room temperature, the orange-red reaction solution contained no thebaine as evidenced by TLC. Hydrogen was introduced to the reaction vessel by use of a balloon, and the mixture was stirred for 4 h. Removal of the balloon and filtration of the suspension through a plug of silica ($CHCl_3$/MeOH/NH_4OH, 92:8:1) gave the crude products **4** and **19** in a ratio of 3:4. Purification of the crude material was achieved by column chromatography ($CHCl_3$/MeOH/NH_4OH, 98:2:1) to yield **4** in 43% and **19** in 52% yield. All analytical data generated for hydrocodone synthesized in this manner are identical with those of an authentic sample of hydrocodone. Data (^1H and ^{13}C NMR spectra) for **19** are identical to those published in the literature.[15]

4-Hydroxy-3-methoxy-17-methylmorphinan-6-one (Dihydrothebainone 19): R_f 0.35 (DCM/MeOH/NH_4OH, 96:4:1); FTIR (film) ν_{max} 3401, 2935, 2839, 2243, 1710, 1604, 1583, 1483, 1439, 1277, 1228, 1062, 922 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.68 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 4.25 (dd, J = 13.3, 2.5 Hz, 1H), 3.82 (s, 3H), 3.13−3.16 (m, 1H), 2.98 (d, J = 18.5 Hz, 1H), 2.76 (dd, J = 18.5, 6.0 Hz, 1H), 2.60−2.64 (m, 1H), 2.46 (s, 3H), 2.41−2.45 (m, 1H), 2.31 (dt, J = 12.8, 3.2 Hz, 1H), 2.23−2.28 (m, 2H), 2.12 (td, J = 12.0, 4.1 Hz, 1H), 2.05 (s, 1H), 1.84−1.93 (m, 3H), 1.68 (qd, J = 13.2, 5.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 210.7, 145.1, 144.8, 129.7, 122.6, 118.5, 109.0, 57.0, 56.1, 50.4, 46.4, 44.3, 42.1, 41.0, 40.9, 38.0, 27.0, 23.8; MS (EI) m/z (%) 302 (11.6), 301 (56.2), 300 (18.0), 242 (10.3), 164 (53.3), 88 (11.2), 86 (64.3), 84 (100.0), 60 (19.3), 59 (16.7), 49 (19.7), 47 (23.5), 45 (24.7), 44 (13.3), 43 (34.7), 42 (17.8); HRMS (EI) calcd for $C_{18}H_{23}NO_3$ 301.1678; found 301.1671.

(5α)-1,7,10-Tribromocyclic-1,2-ethanediyl acetal-8,14-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-one (11). Thebaine (50 mg, 0.16 mmol) was dissolved in THF (1 mL), and freshly distilled ethylene glycol (100 mg, 1.61 mmol) was added. Bromine (103 mg, 0.64 mmol) was added in a single portion, and the reaction mixture was stirred for 10 h. A saturated aqueous solution of Na_2SO_3 was added to remove excess bromine. The reaction was cooled to 0 °C, and the pH was adjusted to 11 with saturated aq K_2CO_3. The reaction solution was extracted five times with $CHCl_3$ (5 mL), and the organic extracts were combined and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent gave a crude mixture that was further purified by flash column chromatography ($CHCl_3$/MeOH, 200:1) to provide the title compound in 27% yield: R_f 0.60 (DCM/MeOH/NH_4OH, 96:4:1); FTIR (film) ν_{max} 2391, 2937, 2891, 1654, 1632, 1611, 1487, 1435, 1287, 1203, 1160, 1125, 1089, 1051, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.92 (s, 1H), 5.88 (d, J = 6.4 Hz, 1H), 5.25 (s, 1H), 4.61 (d, J = 6.4 Hz, 1H), 3.94−3.99 (m, 1H), 3.88 (s, 3H), 3.81−3.87 (m, 1H), 3.61−3.64 (m, 1H), 3.11 (d, J = 18.6 Hz, 1H), 3.04 (s, 3H), 2.70−2.79 (m, 1H), 2.56−2.68 (m, 2H), 2.50 (s, 3H), 2.37−2.43 (m, 1H), 1.76 (dd, J = 12.8, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 145.2, 143.1, 132.3, 126.5, 117.0, 116.3, 112.0, 98.4, 92.0, 77.2, 64.4, 62.0, 60.1, 57.0, 49.5, 46.4, 45.3, 41.9, 35.1, 30.3; MS (EI) m/z (%) 531 ($M^+ - CH_2CH_2O$), 451, 435, 420, 407, 301, 217 (15.7), 216 (80.7), 188 (53.7), 187 (100), 171 (22.3), 145 (13.4), 118 (10.9), 117 (22.0), 90 (13), 86 (19.7), 84 (24.4), 78 (15.6), 71 (10.5), 57 (11.7), 55 (13.7), 47 (12.2), 44 (28.1), 43 (40.7), 42 (12.3), 41 (32.9).

Hydrocodone 4 via Pd/C Hydrogenation of Thebaine 3. Thebaine (100 mg, 0.32 mmol) was dissolved in 20% HCl (500 μL), and Pd/C (10 wt %, 5 mg) was added. The reaction mixture was stirred under H_2 (1 atm) at room temperature for 12 h, then it was made alkaline with NH_4OH and extracted three times with DCM (2 mL). The organic layers were combined, dried over sodium sulfate, and filtered. Evaporation of the solvent gave a mixture of compounds, which were purified by flash column chromatography ($CHCl_3$/MeOH/NH_4OH, 98:2:1) to give hydrocodone **4** (63%), dihydrothebainone **19** (20%), and tetrahydrothebaine **22** (8%). Data for **22** (^{13}C NMR spectra) are identical to those published in the literature.[19]

(5α,6α)-4,5-Epoxy-3,6-dimethoxy-17-methylmorphinan (Tetrahydrothebaine 22): R_f 0.50 (DCM/MeOH/NH_4OH, 96:4:1); FTIR (film) ν_{max} 3429, 2933, 2835, 1635, 1609, 1504, 1440, 1337, 1277, 1258, 1152, 1105, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.71 (d, J = 8.2 Hz, 1H), 6.58 (d, J = 8.2 Hz, 1H), 4.68 (d, J = 5.0 Hz, 1H), 3.85 (s, 3H), 3.50−3.54 (m, 2H), 3.46 (s, 3H), 3.09−3.12 (m, 1H), 2.98 (d, J = 18.5 Hz, 1H), 2.51−2.57 (m, 1H), 2.39−2.45 (m, 4H), 2.21−2.32 (m, 2H), 1.89 (dt, J = 12.5, 4.9 Hz, 1H), 1.72 (dd, J = 11.3, 1.1 Hz, 1H), 1.37−1.54 (m, 3H); ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 147.1, 141.8, 129.9, 126.4, 118.4, 113.5, 89.3, 76.9, 59.9, 58.2, 56.5, 46.9, 42.9, 42.3, 39.9, 37.1, 24.3, 20.1, 19.4; MS (EI) m/z (%) 316 (18.3), 315 (87.3), 300 (42.5), 178 (15.0), 86 (68.8), 85 (75.8), 84 (97.1), 83 (100), 70 (18.3), 49 (30.5), 47 (53.5), 42 (19.9); HRMS (EI) calcd for $C_{19}H_{25}NO_3$ 315.1834; found 315.1831.

4-Hydroxy-3-methoxy-17-methyl-14,15-cyclo-13,15-seco-morphin-5(13)-en-6-on (*meta*-Thebainone 21). Thebaine (100 mg, 0.32 mmol) was dissolved in an aq solution of 20% HCl (0.5 mL) and Pt/C (1 wt %), and doped vanadium (16 mg) was added. The reaction mixture was stirred under 1 atm of H_2 at rt for 12 h, after which time the reaction mixture was basified with NH_4OH and extracted three times with DCM (2 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. Evaporation of the solvent gave a mixture of compounds, which was purified by flash column chromatography (DCM/MeOH, 200:1 to 200:4) to give 14 mg (15%) of hydrocodone **4**, 5 mg (5%) of tetrahydrothebaine **22**, and 72 mg (75%, 90% purity) of *meta*-thebainone **21**: R_f 0.50 (DCM/MeOH/NH_4OH, 96:4:1); IR (film) ν_{max} 3306, 2927, 2851, 2782, 1727, 1650, 1601, 1479, 1441, 1349, 1266, 1183, 1092, 1002 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.83 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.50 (s, 1H), 3.90 (s, 3H), 2.94−2.99 (m, 1H), 2.69−2.82 (m, 2H), 2.57 (dd, J = 14.9, 3.6 Hz, 1H), 2.50−2.55 (m, 1H), 2.33 (s, 3H), 2.22−2.29 (m, 2H), 2.05−2.15 (m, 2H), 2.00 (ddd, J = 13.3, 5.4, 2.1 Hz, 1H), 1.51−1.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 199.6, 158.4, 145.5, 131.4, 126.2, 120.4, 118.7, 113.9, 111.7, 73.1, 56.2, 55.3, 46.6, 40.4, 35.0, 33.9, 33.8, 30.6; MS (EI) m/z (%) 299 (7.8), 149 (16.2), 88 (10.7), 86 (62.8), 84 (100), 57 (11.1), 49 (17.4), 47 (21.1), 43 (10.8); HRMS (EI) calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1518.

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Supporting Information Available: ^1H NMR spectra of compounds **3**, **4**, **10**, **11**, **17**, **19**, **21**, and **22**, and ^{13}C NMR spectra of compounds **10**, **11**, **17**, **19**, **21**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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