Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201400445

Conversion of Thebaine to Oripavine and Other Useful Intermediates for the Semisynthesis of Opiate-Derived Agents: Synthesis of Hydromorphone

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Received: May 3, 2014; Published online: July 30, 2014

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400445.

Abstract: Thebaine was converted to oripavine in three steps by employing two different modes of protection of the diene moiety; as an iron tricarbonyl complex and as a Diels–Alder adduct with thioformyl cyanide. The two C-ring-protected thebaine derivatives were subjected to 3-*O*-demethylation by four different protocols, providing oripavine derivatives, which yielded oripavine after deprotection. Oripavine was then converted to hydromorphone by a three-step process of ketalization, hydrogenation, and deprotection, without the isolation of intermediates.

Keywords: alkaloids; hetero-Diels–Alder cycloaddition; hydromorphone synthesis; iron-diene complexes; natural products; oripavine synthesis; protecting groups; thebaine *O*-demethylation

Introduction

Thebaine **1** and oripavine **2** are key starting materials for the commercial production of several semisynthetic opiate-derived agents,[1–5] some of which are shown in Figure 1. These compounds are medicinally important because of their high therapeutic value and low abuse potential.[6–8] Poppy plants[9,10] have been cultivated to express thebaine in high quantities in recent years for use as a starting material for the downstream production of semisynthetic opiates **5**–**11**. A scalable method for the transformation of **1** to **2** would shorten and generalize industrial preparations of semisynthetic opiate derivatives **5**, **7**–**11**.

Conditions for 3-*O*-demethylation of thebaine derivatives (intermediates used for the synthesis of **5**, **7**, **8**, **9**, **10**, **12**, and **13**) are harsh, involving long reaction times and strongly alkaline systems at high temperatures, usually between 100–240 °C.[2] To date, 3-*O*-demethylation of thebaine to produce oripavine has only been accomplished by L-Selectride, albeit in low yield and after long reaction times.[11–13] Although this represents a direct method, alternatives to the use of L-Selectride are still being sought.[11,13–17] Unfortunately, a very reliable method using sodium thiolate for 3-*O*-demethylation of thebaine failed as reported by DeGraw:

"*When the 3-O-demethylation reaction was applied to thebaine, however, none of the expected oripavine product was recovered. Thin-layer chromatography showed the disappearance of thebaine after 3 h at 110 °C, but an NMR spectrum of the product still showed strong signals for the 3- and 6-methoxy groups. Apparently, an alternate reaction course is available in the thebaine case, competitive with demethylation.*"[18]

In addition to the reactivity with thiolate, the diene of thebaine and oripavine are acid-sensitive (Lewis and Brønsted) and undergo a variety of rearrangements. The acid-catalyzed apomorphine rearrangement or vinyl ether hydrolysis during 3-*O*-demethylation was prevented by unusual protecting group chemistry.[12,25] Our method employs protection of the cyclohexadiene moiety in thebaine **1** with either iron(0) pentacarbonyl developed by Birch[19,20] or as a bicyclic dihydrothiopyran-Diels–Alder adduct.[21–24]

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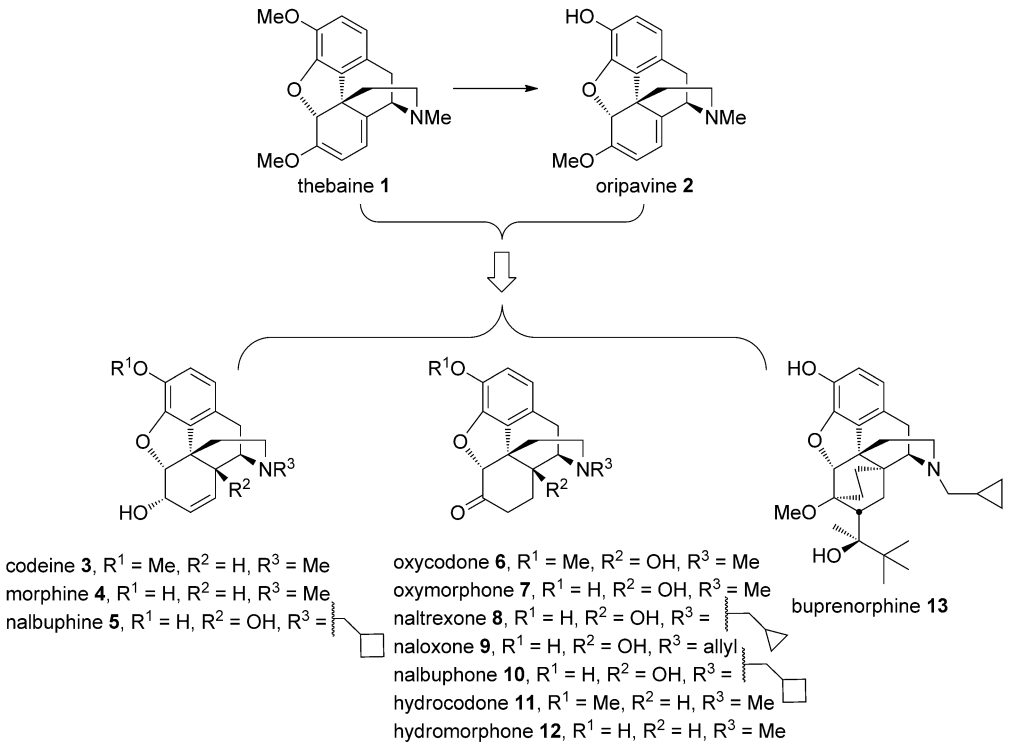


Figure 1. Examples of opiate-derived pharmaceuticals accessible from thebaine and oripavine.

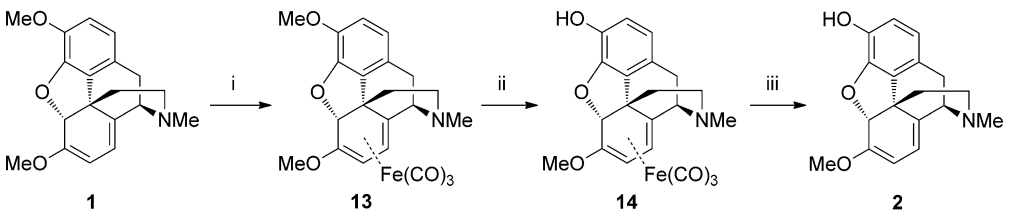
Results and Discussion

Demethylation of Thebaine Iron Complex

Thebaine and iron pentacarbonyl were irradiated with ultraviolet light providing thebaine-iron tricarbonyl complex **13** in quantitative yield. Subsequent 3-*O*-demethylation was accomplished using four different methods **A**: BBr_3,[15] **B**: $BF_3{\cdot}SMe_2$,[16] **C**: $MeSO_3H$/methionine,[17] or **D**: 9-iodo-9-BBN, producing oripavine-iron tricarbonyl **14** in 83%, 83%, 67%, and 63% yields, respectively (Scheme 1). Other demethylation procedures attempted without success include: TMSI (trimethylsilyl iodide), TMSCl and NaI, $NbCl_5$, dodecanethiolate, and refluxing concentrated HBr. The work-up of the crude oripavine-iron tricarbonyl complex proved to be very sensitive.

Complex **14** containing the free phenol was stable in acidic solutions, but substantially less stable in alkaline pH. When an aqueous solution of NH_4OH was used for work-up, immediate decomposition was observed. Use of 15% aqueous NaOH improved the stability of the demethylated complex and subsequent extraction of **14** with 10% *i*-PrOH/CH_2Cl_2 provided oripavine-iron tricarbonyl complex. The purified product is not bench stable, and must be subjected to decomplexation as soon as possible.

Removal of iron tricarbonyl group proved to be difficult as well. Different chemical methods for decomplexation of the oripavine iron complex were tested (TMANO, CAN, $CuCl_2$, $FeCl_3$) but none of them provided oripavine **2** in a reasonable yield. However, photolytic iron ligand exchange with MeCN[26] was successful. A solution of **14** in acetonitrile was irradiated by UV light at 40 °C, providing oripavine as



Scheme 1. i) UV, $Fe(CO)_5$, PhH, quantitative. ii) ***Method A:*** BBr_3, CH_2Cl_2, 0 °C to room temperature; 83%. ***Method B:*** $BF_3{\cdot}SMe_2$, CH_2Cl_2, 0 °C to room temperature; 83%. ***Method C:*** $MeSO_3H$, methionine, 50 °C, 67%. ***Method D:*** 9-I-9-BBN, CH_2Cl_2, room temperature, 70%. iii) UV, MeCN, 40 °C, 35%.

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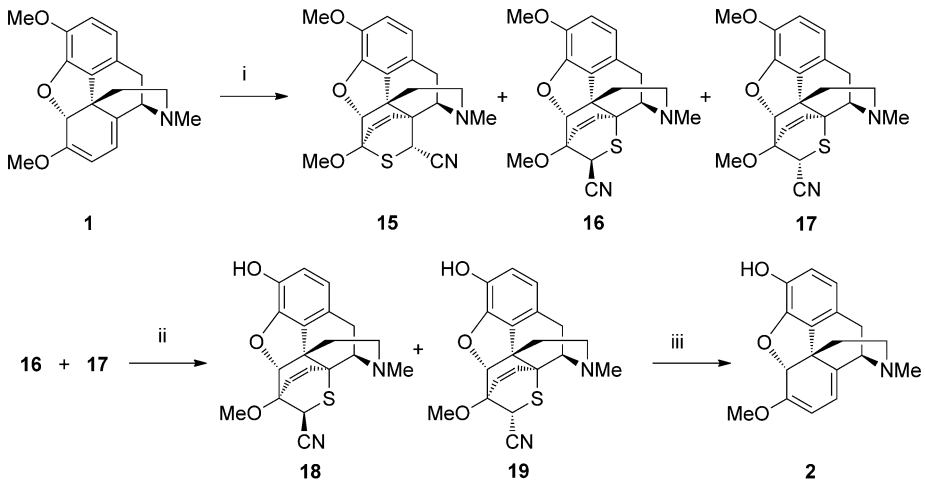

Scheme 2. i) Sodium *S*-(cyanomethyl) sulfothioate, $CaCl_2 \cdot 2H_2O$, Et_3N, 1:1 PhH:MeOH, 80% yield, product ratio **15**:**16**:**17** 1:4.2:3.2. ii) ***Method A:*** BBr_3, CH_2Cl_2, 0 °C, 85% yield. ***Method B:*** $BF_3 \cdot SMe_2$, CH_2Cl_2, 0 °C, 50% yield. ***Method C:*** $MeSO_3H$, methionine, 50 °C, 51% yield or ***Method D:*** 9-I-9-BBN, CH_2Cl_2, 72% yield. iii) ***Method E:*** 2,3-dimethylbutadiene, DMSO, 75 °C, 65% or ***Method F:*** *m*CPBA, CH_2Cl_2, room temperature, then reflux in EtOH, 78%.

a free base in 35% yield. The best conditions for the decomplexation of the iron tricarbonyl complex and minimal oripavine decomposition were achieved after 2.5 hours of irradiation.

O-Demethylation of Diels–Alder Adduct of Thioformyl Cyanide

Kirby and others report that ethyl 2-thioxoacetate acts as a reversible dienophile.[21–24,27] This observation was exploited as a methodological step in the final production of oripavine. The cycloaddition step was accomplished by slowly adding triethylamine dropwise to the off-white suspension of thebaine, $CaCl_2$, and sodium *S*-(cyanomethyl) sulfothioate in a methanolic benzene mixture (Scheme 2).

The reaction mixture became opaque yellow with the full addition of triethylamine. In the absence of calcium chloride, little product was observed by TLC, and the mixture turned dark orange, probably due to thioformyl cyanide polymerization.

The three C-ring-protected thebaine derivatives, **15**, **16**, and **17** were isolated in 80% yield after chromatography in a 1:4.2:3.2 ratio, respectively. The minor product, compound **15**, formed appropriate crystals to be analyzed by X-ray crystallography for the assignment of its absolute stereochemistry (Figure 2).

C-14 sulfides **16** and **17** were each individually subjected to the four 3-*O*-demethylation procedures, **A**, **B**, **C**, and **D**, previously described, supplying compounds **18** and **19** in 85%, 50%, 51%, and 72% yield, respectively. Boron tribromide has long been used as a demethylation reagent, and was used in our experiments as a benchmark. The work-up procedure for

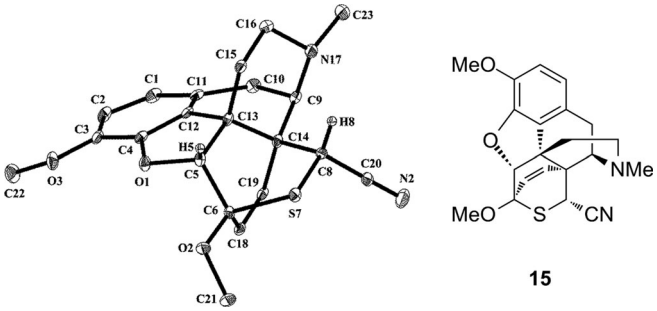

Figure 2. Labelled representation of one of the two crystallographically-independent molecules of **15** in the unit cell.

Method **A** was accomplished with relatively high yield in spite of the boron and bromide salt by-products.

Release of oripavine from the cycloadduct was accomplished by two procedures. Method **E**: thermal cycloreversion of the dihydrothiopyran provided the transient thioformyl cyanide, which was then captured by an excess of 2,3-dimethylbutadiene in a sealed tube for 8 h at 75 °C. The competitive hetero-Diels–Alder reaction led to the removal of the thioformyl cyanide and provided oripavine in 65% yield after chromatography. Alternatively, Method **F**: the sulfide adduct was oxidized with *m*CPBA to the sulfoxide, which was then released from oripavine by cycloreversion to provide a transient thioaldehyde *S*-oxide (sulfine), which was then captured *irreversibly* by ethanol, likely to form a sulfinate ester (not isolated). After evaporation of ethanol, the crude reaction mixture was purified by column chromatography to yield oripavine in 78% yield. After characterization of the individual chemical entities **15**–**19**, the sequence was repeated without separation of intermediate isomers

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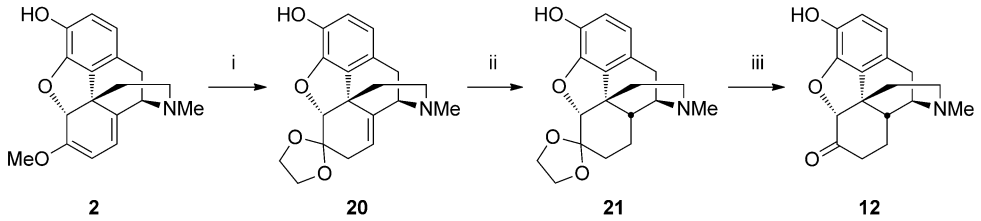

Scheme 3. i) ethylene glycol, *p*TsOH, PhH, reflux. ii) Pt/C, H_2, MeOH. iii) HCl (aq), THF, 80 °C.

utilizing Methods **A** and **E**. Thebaine **1** was transformed to oripavine **2** in three steps and one chromatographic purification in a 44% overall yield.

Synthesis of Hydromorphone from Oripavine

As there are only two patents describing the conversion of oripavine to hydromorphone, investigation of additional processes is desirable.[28] Previous attempts at selective hydrogenation of the diene system of thebaine proved to be difficult.[29] Thebaine was transformed to hydrocodone *via* a neopinone ketal, followed by hydrogenation of the C-8/C-14 olefin, and hydrolysis.[30] In analogy, we decided to explore oripavine as a possible starting material for preparation of hydromorphone by a similar sequence.

Treatment of oripavine with ethylene glycol in anhydrous benzene in the presence of at least a 2-fold molar excess of TsOH resulted in the formation of oripavine ketal **20** (Scheme 3). The use of other alcohols such as methanol did not result in any ketal formation. Other catalysts have also been tried such as TMSCl and PPTS with no success. The crude ketal was isolated by pouring the reaction mixture in saturated $NaHCO_3$ and extracting the aqueous layer further with EtOAc. The crude oripavine ketal was subjected to catalytic hydrogenation in methanol. Simple filtration of the catalyst followed by concentration of the reaction mixture afforded the crude hydromorphone ketal **21**. Deprotection of the resulting hydromorphone ketal using aqueous hydrochloric acid followed by column chromatography afforded hydromorphone **12** in 42% overall yield.

Conclusions

In conclusion, oripavine was synthesized from thebaine in three steps by 3-*O*-demethylation of substrates in which the diene system was protected either as an iron-tricarbonyl complex or as a Diels–Alder adduct of thioformyl cyanide. This synthetic sequence is an important step toward the large-scale conversion of thebaine to oripavine, and should be further investigated for process optimization. As oripavine is the most convenient source for the production of semi-synthetic opioid pharmaceuticals, its availability for commercial use is of great importance. We have demonstrated this by a short and direct conversion of oripavine to hydromorphone.

Experimental Section

General Information

All non-aqueous reactions were conducted in an inert (nitrogen or argon) atmosphere using standard Schlenk techniques for the exclusion of moisture and air. All solvents were distilled unless otherwise noted. Analytical thin-layer chromatography was performed on silica gel 60 Å 250 μm TLC plates with F-254 indicator. Flash column chromatography was performed using silica gel (230–400 mesh). Melting points are uncorrected. Optical rotations were measured in 1 dm cell at 25 °C and 589 nm, concentration in g/100 mL on a Perkin–Elmer 341 polarimeter. IR spectra were obtained on a Bruker ALPHA FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz and/or 600 MHz spectrometers. All chemical shifts are referenced to TMS or residual non-deuterated solvent. Data for proton spectra are reported as follows: chemical shift {multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m)], coupling constants [Hz], integration}. Carbon spectra were recorded with complete proton decoupling and the chemical shifts are reported in ppm (C). Mass spectra and high resolution mass spectra were performed by the analytical division at Brock University. Combustion analyses were performed by Atlantic Microlabs, Atlanta, GA.

Tricarbonyl[(6,7,8,14-η)-(5α)-6,7,8, 14-tetradehydro-4,5-epoxy-3,6-dimethoxy-17-methylmorphinan]iron(0) (13)

Thebaine iron tricarbonyl **13** was prepared by the previously published method of Birch.[19] Thebaine (2 g, 6.4 mmol) was dispersed in benzene (20 mL), the solution was degassed by bubbling with argon for 3 min and iron pentacarbonyl (5 mL, 37 mmol) was added. This mixture was irradiated in a UV reactor for 48 h at 40 °C. The reaction mixture was then concentrated under vacuum and purified by column chromatography (10:1 CH_2Cl_2:MeOH). The purified product was recrystallized from absolute ethanol as an orange solid. Spectral data were in agreement with previously published data;[19] yield: 2.84 g (95 %); $R_f = 0.81$ (10:1 CH_2Cl_2:MeOH); mp 126–127 °C (EtOH); $[\alpha]_D^{20}$: −188° ($c =$

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1.28, $CHCl_3$). IR (neat): $\nu = 2930$, 2030, 1975, 1942, 1626, 1500, 1436, 1326, 1207 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.68$ (d, $J = 8.0$ Hz, 1H), 6.59 (d, $J = 7.8$ Hz, 1H), 5.32 (d, $J = 3.5$ Hz, 1H), 4.92 (s, 1H), 4.55 (d, $J = 4.4$ Hz, 1H), 3.82 (s, 3H), 3.58 (s, 3H), 3.24 (d, $J = 17.7$ Hz, 1H), 3.00 (d, $J = 6.0$ Hz, 1H), 2.81–2.16 (m, 7H), 1.66 (d, $J = 12.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 211.9$, 143.5, 142.7, 137.9, 126.5, 120.4, 116.3, 112.9, 87.9, 77.3, 74.9, 61.9, 56.9, 56.3, 47.8, 45.4, 42.9, 35.2, 29.2; MS (EI^+): m/z (rel. %) = 451 (10), 395 (55), 311 (50), 254 (100), 239 (80), 211 (23), 83 (30), 42 (35); HR-MS (EI): $m/z = 451.07033$, calcd. for $C_{22}H_{21}FeNO_6$: 451.07179; anal. calcd. for $C_{22}H_{21}FeNO_6$: C 58.56, H 4.69; found: C 58.28, H 4.79. CCDC 988980 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Tricarbonyl[(6,7,8,14-η)-(5α)-6,7,8,14-tetradehydro-4,5-epoxy-6-methoxy-17-methylmorphinan-3-ol]-iron(0) (14)

Method A: To a solution of thebaine iron tricarbonyl **13** (200 mg, 0.44 mmol) in dry CH_2Cl_2 (20 mL) was slowly added BBr_3 (0.66 g, 2.6 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 20 min at 0 °C and then removed from the ice bath and stirred for another 15 min. This mixture was poured into cold water and its acidity was slowly adjusted to pH 6 with 15% aqueous NaOH solution. The mixture was extracted with 10:1 CH_2Cl_2:*i*-PrOH four times. The combined organic phases were concentrated under vacuum and purified by column chromatography (CH_2Cl_2:MeOH, 7:1) furnishing **13** as a dark green solid; yield: 160 mg (83%).

Method B: To a solution of thebaine iron tricarbonyl **13** (200 mg, 0.44 mmol) in dry CH_2Cl_2 (20 mL) was slowly added $BF_3{\cdot}SMe_2$ complex (0.28 mL, 2.67 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 4 h at 0 °C and then removed from the ice bath and stirred for another 1.5 h. Quench and work-up procedure were the same as for method **A**, affording **13** as a dark green solid; yield: 160 mg (83%).

Method C: To a solution of thebaine iron tricarbonyl **13** (183 mg, 0.41 mmol) in dry $MeSO_3H$ (3.0 mL, 48.8 mmol) was slowly added methionine (213 mg, 1.42 mmol). The orange solution was then heated to 50 °C and left to stir for 28 h. The reaction was monitored by HPLC. The reaction was quenched and the product isolated in the same fashion as for methods **A** and **B**, affording **13** as a dark green solid; yield: 120 mg (67%).

Method D: To a solution of thebaine iron tricarbonyl **13** (90 mg, 0.2 mmol) in dry CH_2Cl_2 (5 mL) was slowly added 9-I-9-BBN (1 M in hexanes; 0.4 mL, 0.4 mmol) at room temperature. After two hours, the reaction was quenched and the product isolated in the same fashion as previously described to give **13** as a dark green solid; yield: 61 mg (70%); $R_f = 0.52$ (10:1 CH_2Cl_2:MeOH); IR (neat): $\nu = 2915$, 2036, 1948, 1613, 1444, 1207, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.67$ (s, 1H), 6.54 (s, 1H), 5.31 (s, 1H), 4.91 (s, 1H), 4.54 (s, 1H), 3.58 (s, 3H), 3.20 (s, 1H), 3.02 (s, 1H), 2.83–2.15 (m, 7H), 1.66 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 211.9$, 142.4, 139.3, 137.8, 124.9, 120.4, 116.7, 116.5, 87.6, 76.6, 76.4, 75.2, 61.9, 55.7, 45.1, 41.6, 34.4, 29.0; MS (EI^+): m/z (rel. %) = 437 (70), 381 (70), 353 (100), 325 (23), 297 (40), 281 (22); HR-MS (EI): $m/z = 437.05614$, calcd. for $C_{21}H_{19}FeNO_6$: 437.05484.

Sodium *S*-(Cyanomethyl)-sulfothioate (*Bunte Salt*)

A mixture of $Na_2S_2O_3{\cdot}5H_2O$ (9.97 g, 63 mmol), chloroacetonitrile (5 g, 66 mmol), in water (20 mL) and EtOH (20 mL) was heated at 80 °C for 1 hour, then left stirring at room temperature overnight. The mixture was cooled to 0 °C and then filtered, and rinsed with ethanol. The product was recrystallized from hot ethanol and dried under vacuum to afford white crystals; yield: 7.06 g (64%); mp 90–92 °C (EtOH); IR (neat): $\nu = 3623$, 3448, 2966, 2260, 1637, 1209, 1034 cm^{-1}.

(4*R*,4a*S*,7*R*,7a*R*,12b*R*,15*R*)-7,9-Dimethoxy-3-methyl-1,2,3,4,7,7a-hexahydro-7,4a-(epithiomethano)-4,12-methanobenzofuro[3,2-*e*]isoquinoline-15-carbonitrile (15)

(4*R*,4a*S*,7*S*,7a*R*,12b*S*,14*S*)-7,9-Dimethoxy-3-methyl-1,2,3,4,7,7a-hexahydro-4a,7-(epithiomethano)-4,12-methanobenzofuro[3,2-*e*]isoquinoline-14-carbonitrile (16)

(4*R*,4a*S*,7*S*,7a*R*,12b*S*,14*R*)-7,9-Dimethoxy-3-methyl-1,2,3,4,7,7a-hexahydro-4a,7-(epithiomethano)-4,12-methanobenzofuro[3,2-*e*]isoquinoline-14-carbonitrile (17)

Thebaine (930 mg, 3 mmol), calcium chloride dihydrate (620 mg, 4.2 mmol), and sodium *S*-(cyanomethyl)-sulfothioate (735 mg, 4.2 mmol) were dispersed in benzene (7 mL) and MeOH (7 mL) and stirred vigorously. Triethylamine (420 mg, 4.2 mmol) was added dropwise. After stirring at room temperature for 8 h, the reaction was diluted with EtOAc (20 mL), and then centrifuged for 20 min at 7000 rpm. The supernatant was concentrated under vacuum and the crude residue was purified by column chromatography (2:1 hexane:EtOAc) to provide **15** (yield: 110 mg), **16** (yield: 450 mg), and **17** (yield: 350 mg); total yield: 910 mg (80%). Each isomer was then recrystallized from methanol.

15: yield: 110 mg (12%); $R_f = 0.73$ (1:1 hexane:EtOAc); mp 184–185 °C (MeOH); $[\alpha]_D^{20}$: −319.1° ($c = 1.0$, $CHCl_3$); IR (neat): $\nu = 2915$, 2841, 2797, 2232, 1442, 1050, 869, 817, 795, 592 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.66$ (d, $J = 8.2$ Hz, 1H), 6.59 (d, $J = 8.2$ Hz, 1H), 6.39 (dd, $J = 9.1$, 1.3 Hz, 1H), 5.66 (d, $J = 9.1$ Hz, 1H), 5.38 (s, 1H), 4.92 (s, 1H), 3.80 (s, 3H), 3.62 (s, 3H), 3.54 (d, $J = 6.6$ Hz, 1H), 3.31 (d, $J = 18.6$ Hz, 1H), 2.55 (dd, $J = 18.6$, 6.6 Hz, 2H), 2.46–2.38 (m, 4H), 2.01–1.93 (m, 1H), 1.90 (dd, $J = 13.6$, 2.9 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 146.8$, 142.2, 133.2, 131.5, 130.9, 126.9, 119.6, 119.1, 113.7, 92.3, 89.9, 59.1, 56.4, 53.9, 47.6, 45.0, 43.5, 36.1, 33.8, 22.8; MS (EI^+): m/z (rel. %) = 382 (93), 311 (50), 325 (23), 296 (25), 267 (22), 255 (35), 230 (55), 58 (100); HR-MS (ESI): $m/z = 382.1351$, calcd. for $C_{21}H_{22}N_2O_3S$: 382.1351; anal. calcd. for $C_{21}H_{22}N_2O_3S$: C 65.95, H 5.80; found: C 66.01, H 5.79. CCDC 988979 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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16: Yield: 450 mg (50%); $R_f = 0.58$ (1:1 hexane:EtOAc); mp 145–150 °C (MeOH); $[\alpha]_D^{20}$: −218.2° ($c = 1.0$, $CHCl_3$); IR (neat): $\nu = 2935$, 2836, 2792, 2234, 1499, 1279, 1107, 1021, 906, 793 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.65$ (d, $J =$ 8.1 Hz, 1H), 6.56 (d, $J = 8.1$ Hz, 1H), 5.91 (q, $J = 9.1$ Hz, 2H), 5.00 (s, 1H), 3.83 (s, 3H), 3.77 (s, 1H), 3.67 (s, 3H), 3.39 (d, $J = 6.6$ Hz, 1H), 3.27 (dd, $J = 18.3$, 10.6 Hz, 1H), 2.93 (td, $J = 12.7$, 5.5 Hz, 1H), 2.68 (dd, $J = 12.2$, 5.3 Hz, 1H), 2.53–2.44 (m, 2H), 2.40 (s, 3H), 1.89 (dd, $J = 13.1$, 2.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 147.0$, 142.5, 138.0, 133.2, 126.6, 124.6, 119.9, 117.4, 114.6, 91.4, 79.9, 60.0, 56.9, 53.9, 52.9, 50.5, 45.8, 43.4, 35.2, 32.7, 23.2; MS (EI^+): m/z (rel. %) = 382 (7), 311 (95), 297 (50), 255 (22); HR-MS (ESI): $m/z = 382.1351$, calcd. for $C_{21}H_{22}N_2O_3S$: 382.1351; anal. calcd, for $C_{21}H_{22}N_2O_3S$: C 65.95, H 5.80; found: C 65.99, H 5.81.

17: Yield: 350 mg (38%); $R_f = 0.50$ (1:1 hexane:EtOAc); mp 164–165 °C (MeOH); $[\alpha]_D^{20}$: +5.9° ($c = 1.0$, $CHCl_3$); IR (neat): $\nu = 2948$, 2802, 2235, 1500, 1284, 1108, 1019, 894, 760 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.66$ (d, $J =$ 8.2 Hz, 1H), 6.58 (d, $J = 8.2$ Hz, 1H), 6.00 (d, $J = 8.8$ Hz, 1H), 5.95 (d, $J = 9.0$ Hz, 1H), 4.52 (s, 1H), 4.08 (s, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.47 (d, $J = 6.5$ Hz, 1H), 3.26 (d, $J =$ 18.5 Hz, 1H), 2.71 (td, $J = 12.6$, 5.5 Hz, 1H), 2.61 (dd, $J =$ 12.2, 5.3 Hz, 1H), 2.54 (dd, $J = 18.5$, 6.6 Hz, 1H), 2.47–2.40 (m, 1H), 2.39 (s, 3H), 1.81 (dd, $J = 12.8$, 2.7 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 146.5$, 142.5, 136.4, 133.1, 126.4, 126.4, 120.2, 117.8, 114.1, 90.8, 80.2, 77.3, 77.0, 76.8, 60.0, 56.6, 53.1, 52.5, 50.7, 45.6, 43.3, 35.7, 32.9, 23.2; MS (EI^+): m/z (rel. %) = 382 (7), 311 (95), 296 (50), 255 (22); HR-MS (ESI): $m/z = 382.1351$, calcd. for $C_{21}H_{22}N_2O_3S$; 382.1351; anal. calcd. for $C_{21}H_{22}N_2O_3S$: C 65.95, H 5.80; found: C 66.68, H 5.83.

(4*R*,4a*S*,7*S*,7a*R*,12b*S*,14*S*)-9-Hydroxy-7-methoxy-3-methyl-1,2,3,4,7,7a-hexahydro-4a,7-(epithiomethano)-4,12-methanobenzofuro[3,2-*e*]isoquinoline-14-carbonitrile (18)
(4*R*,4a*S*,7*S*,7a*R*,12b*S*,14*R*)-9-Hydroxy-7-methoxy-3-methyl-1,2,3,4,7,7a-hexahydro-4a,7-(epithiomethano)-4,12-methanobenzofuro[3,2-*e*]isoquinoline-14-carbonitrile (19)

Method A: To a solution of **16** or **17** (200 mg, 0.52 mmol) in dry CH_2Cl_2 (10 mL) was slowly added BBr_3 (0.780 g, 3.12 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 20 min at 0 °C and then removed from the ice bath and stirred for another 15 min. This mixture was poured into cold water and its acidity was slowly adjusted to pH 8 with 15% aqueous NaOH solution. The mixture was then extracted with CH_2Cl_2 (3 × 70 mL). The combined organic phases were concentrated under vacuum and purified by column chromatography (1:1 hexane:EtOAc) affording **18** or **19**; yield: 162 mg (85%).

Method B: To a solution of **16** (150 mg, 0.4 mmol) in dry CH_2Cl_2 (15 mL) was slowly added $BF_3{\cdot}SMe_2$ complex (0.25 mL, 2.36 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 4 h at 0 °C and then 2 h at room temperature. The mixture was then decanted into ice-water (20 mL) and its acidity was slowly adjusted to pH 8 with 15% aqueous NaOH solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and then washed with brine and dried over Na_2SO_4, concentrated under vacuum, then purified by column chromatography (1:1 hexane:EtOAc) to afford **18**; yield: 74 mg (50%).

Method C: To a solution of **16** (170 mg, 0.395 mmol) in dry $MeSO_3H$ (1.15 mL, 11.8 mmol) was slowly added methionine (90 mg, 0.594 mmol). The orange solution was then heated to 50 °C and left to stir for 8 h. The reaction was monitored by HPLC. The reaction mixture was then decanted into ice-water (20 mL) and its acidity was slowly adjusted to pH 8 with 15% aqueous NaOH solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and then washed with brine and dried over Na_2SO_4, concentrated under vacuum and the product was purified by column chromatography (1:1 hexane:EtOAc) to furnish **18**; yield: 73 mg (51%).

Method D: To a solution of **16** or **17** (110 mg, 0.287 mmol) in dry CH_2Cl_2 (5 mL) was slowly added 9-I-9-BBN (1 M in hexanes; 0.86 mL, 0.863 mmol) at room temperature. After four hours, the reaction mixture was then decanted into ice-water (20 mL) and its acidity was slowly adjusted to pH 8 with 15% aqueous NaOH solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and then washed with brine and dried over Na_2SO_4, concentrated under vacuum, then purified by column chromatography (1:1 hexane:EtOAc) to afford **18** or **19**; yield: 80 mg (72%).

18: yield: 162 mg (85%); $R_f = 0.35$ (1:1 hexane:EtOAc); mp 145 °C (MeOH); $[\alpha]_D^{20}$: −199.2° ($c = 0.25$, MeOH); IR (neat): $\nu = 3189$, 2936, 2803, 2235, 2069, 1455, 1154, 1102, 1028, 943, 905, 757 cm^{-1}; ^1H NMR (600 MHz, MeOD): $\delta =$ 6.53 (d, $J = 8.1$ Hz, 1H), 6.48 (d, $J = 8.1$ Hz, 1H), 6.02–5.95 (m, 2H), 4.83 (s, 1H), 4.15 (s, 1H), 3.62 (s, 3H), 3.42 (d, $J =$ 6.6 Hz, 1H), 3.26 (d, $J = 18.5$ Hz, 1H), 2.87 (td, $J = 12.7$, 5.5 Hz, 1H), 2.64 (dd, $J = 12.2$, 5.2 Hz, 1H), 2.56 (dd, $J =$ 18.5, 6.7 Hz, 1H), 2.46 (td, $J = 12.3$, 3.7 Hz, 1H), 2.37 (s, 3H), 1.81 (dd, $J = 13.0$, 2.8 Hz, 1H); ^{13}C NMR (151 MHz, MeOD): $\delta = 146.9$, 140.2, 139.5, 134.1, 126.8, 124.4, 121.2, 118.9, 118.5, 92.7, 81.2, 61.2, 54.0, 53.7, 51.6, 49.9, 46.9, 43.5, 35.4, 33.7, 24.0; MS (EI^+): m/z (rel. %) = 368 (10), 297 (40), 241 (15), 184 (40); HR-MS (ESI): $m/z = 368.1194$, calcd. for $C_{20}H_{20}N_2O_3S$: 368.1195.

19: Yield: 80 mg (76%); $R_f = 0.41$ (1:1 hexane:EtOAc); mp 170–174 °C (MeOH); $[\alpha]_D^{20}$: −4.64° ($c = 0.5$, MeOH); IR (neat): $\nu = 3509$, 3358, 2926, 2803, 2241, 1638, 1497, 1112, 1030, 891, 761 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): $\delta =$ 6.49 (d, $J = 8.0$ Hz, 1H), 6.43 (d, $J = 8.0$ Hz, 1H), 6.03 (d, $J =$ 8.9 Hz, 1H), 5.74 (d, $J = 8.7$ Hz, 1H), 4.94 (s, 1H), 4.73 (s, 1H), 3.51 (s, 3H), 3.43 (d, $J = 6.4$ Hz, 1H), 3.10 (d, $J =$ 18.4 Hz, 1H), 2.65 (td, $J = 12.7$, 5.4 Hz, 1H), 2.57–2.45 (m, 8H), 2.27 (s, 3H), 2.26–2.20 (m, 1H), 1.63 (dd, $J = 12.9$, 2.6 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6): $\delta = 145.2$, 138.9, 136.5, 132.9, 126.8, 124.8, 119.9, 118.7, 117.1, 87.1, 79.9, 59.2, 52.5, 51.4, 50.1, 45.2, 42.8, 33.6, 32.2, 22.5; MS (EI^+): m/z (rel. %) = 362 (10), 297 (20), 78 (90), 63 (100); HR-MS (ESI): $m/z = 368.1195$, calcd. for $C_{20}H_{20}N_2O_3S$: 368.1195.

Oripavine (2)

From iron tricarbonyl complex 13: Compound **13** (60 mg, 0.137 mmol) was dispersed in acetonitrile (5 mL), the solu-

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tion was degassed by bubbling with argon for 3 min and then UV irradiated for 2.5 h at 40 °C. The reaction mixture was then concentrated under vacuum and purified by column chromatography (6:1 CH_2Cl_2:MeOH) affording 18 mg (30%) of recovered starting material and oripavine (**2**); yield: 14 mg (35%); $R_f = 0.25$ (4:1 $CHCl_3$:MeOH); $[\alpha]_D^{20}$: −215.2° ($c = 3.5$, $CHCl_3$), lit.[31] $[\alpha]_D^{20}$: −216.9° ($c = 3.44$, $CHCl_3$); mp 200–201 °C (MeOH), lit.[31] mp 201–203 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.65$ (d, $J =$ 8.1 Hz, 1H), 6.55 (d, $J = 8.1$ Hz, 1H), 5.57 (d, $J = 6.4$ Hz, 1H), 5.30 (s, 1H), 5.07 (d, $J = 6.4$ Hz, 1H), 3.82–3.50 (m, 4H), 3.31 (d, $J = 18.0$ Hz, 1H), 2.87 (t, $J = 11.2$ Hz, 1H), 2.79–2.58 (m, 2H), 2.47 (s, 3H), 2.23 (td, $J = 12.7$, 5.2 Hz, 1H), 1.74 (d, $J = 12.2$ Hz, 1H). The NMR spectra matched previously published data.[31]

From Diels–Alder adducts 15, 16, and 17: Method E: To a solution of **18** (400 mg, 1.09 mmol) in DMSO (1.5 mL) was added 2,6-di-*tert*-butyl-4-methylphenol (BHT) (21 mg, 0.109 mmol), and 2,3-dimethylbutadiene (2.5 mL, 22.1 mmol), which was then charged to a sealed tube under an argon atmosphere. The reaction mixture was stirred vigorously for 24 h at 75 °C. The 2,3-dimethylbutadiene was removed under vacuum, and then the residue was dissolved in $CHCl_3$. The organic solution was washed with water to remove DMSO. Chloroform was then evaporated and the product purified by column chromatography (9:1 CH_2Cl_2:MeOH) to afford oripavine (**2**); yield: 210 mg (65%).

Method F: To a solution of **19** (66 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was added *m*CPBA (77%; 40 mg, 0.18 mmol) and the solution was stirred overnight at room temperature under an argon atmosphere. Dichloromethane was evaporated under vacuum, and the solid was then dissolved in 20 mL of ethanol and then heated at reflux for 2.5 h. The reaction mixture was then concentrated under vacuum and the crude residue was purified by column chromatography (4:1 $CHCl_3$:MeOH) to yield oripavine.

Direct Conversion of Thebaine to Oripavine

Thebaine (250 mg, 0.8 mmol), $CaCl_2 \cdot 2H_2O$ (146 mg, 1.0 mmol), sodium cyanosulfothioate (175 mg, 1.0 mmol), were dispersed in benzene (4.5 mL) and methanol (5.5 mL). A large stir bar is necessary to prevent seizing. The mixture was stirred for 5 min, then triethylamine (0.14 mL, 1.0 mmol) was added dropwise over 90 min at room temperature. Slow addition of base is necessary to prevent thioformyl cyanide polymerization. The off-white solution/suspension began to turn yellowish with more base added. The reaction was stirred at 400 rpm for 18 h with no special exclusion of moisture or atmosphere. The reaction mixture was diluted with 15 mL of EtOAc, then filtered through a plug of sand and diatomaceous earth. The organic solvents were then removed under vacuum, and the orange solid residue as a mixture of isomers, was carried on to the next step without further purification.

The mixture of isomeric adducts was dissolved in anhydrous CH_2Cl_2 (40 mL) under an argon atmosphere, then the reaction vessel was cooled by immersion in an ice bath. BBr_3 (0.77 mL, 8.0 mmol) was then added in a single portion. The transparent orange solution immediately turned an opaque brown. The reaction was allowed to progress for 20 min at 0 °C. The reaction was then quenched by the addition of ice-cold water (1 mL), then slowly, an ice-cold 10% NaOH solution (10 mL) was added. The slightly basic biphasic solution was then filtered through a short plug of sand and silica to remove boron and bromide by-products. The reaction vessel was washed forward with $CHCl_3$:*i*-PrOH 9:1 (2 × 15 mL). The orange transparent filtrate was then added to a separatory funnel and 5 mL of brine were added. The organic phase was collected, dried over $MgSO_4$, and then concentrated under vacuum, to provide a mixture of 3-*O*-demethylated isomers; yield: 213 mg (72% for 2 steps).

The mixture of dihydrothiopyran adducts (200 mg, 0.54 mmol) of oripavine was dissolved in *i*-PrOH (2 mL), and DMSO (0.25 mL), and then transferred to a sealed tube. 2,3-Dimethylbutadiene (1.8 mL, 16.2 mmol) was added under argon, then the tube was sealed and heated to 80 °C for 20 h. Completion of the reaction was confirmed by TLC and HPLC-MS, as oripavine appeared as the major product. The contents of the sealed tube were transferred to a round-bottom flask, and then concentrated under vacuum. The crude mixture was then purified by flash column chromatography (4:1 $CHCl_3$:MeOH) to provide oripavine **2**; yield: 105 mg (65%, 44% overall yield for three steps).

(4*R*,7a*R*,12b*S*)-3-Methyl-1,2,3,4,6,7a-hexahydrospiro[4,12-methanobenzofuro[3,2-*e*]isoquinoline-7,2′-[1,3]dioxolan]-9-ol (20)

To a stirred suspension of oripavine (100 mg, 0.34 mmol) in benzene (1.5 mL) and ethylene glycol (1 mL) was added *para*-toluenesulfonic acid monohydrate (150 mg, 0.80 mmol). The mixture was heated to reflux for 30 min, then cooled to room temperature. The reaction mixture was then added to a stirred mixture of ethyl acetate (10 mL) and a saturated solution of $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum to obtain a yellow residue, which was used without further purification. A small sample was purified *via* column chromatography on silica gel (6:1 CH_2Cl_2:MeOH) for determination of spectral properties and was obtained as a white hygroscopic solid. $R_f = 0.20$ (6:1 CH_2Cl_2:MeOH); mp 135–136 °C (CH_2Cl_2:heptane); $[\alpha]_D^{20}$: +8.30 ($c = 1.0$, MeOH); IR (neat): $\nu = 3401$, 2928, 1679, 1634, 1455, 1262, 1030 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 6.70$ (d, $J = 8.1$ Hz, 1H), 6.58 (d, $J = 8.1$ Hz, 1H), 5.58 (d, $J = 5.4$ Hz, 1H), 4.71 (s, 1H), 4.24 (q, $J = 5.7$ Hz, 1H), 3.92–3.87 (m, 1H), 3.85–3.83 (m, 1H), 3.71 (d, $J = 6.6$ Hz, 1H), 3.29 (d, $J = 18.3$ Hz, 1H), 2.85–2.77 (m, 2H), 2.72–2.66 (m, 1H), 2.52 (s, 3H), 2.52–2.36 (m, 1H), 2.18–2.05 (m, 2H), 1.84 (d, $J = 12.3$ Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 144.2$, 138.1, 131.1, 129.1, 128.3, 125.7, 119.9, 116.9, 108.1, 92.9, 66.9, 65.5, 61.4, 45.9, 45.7, 41.7, 35.3, 32.8, 29.7, 22.7; MS (EI$^+$): m/z (rel. %) = 200 (18), 199 (100), 77 (10), 74 (16), 59 (25), 57 (20), 55 (10); HR-MS (ESI): $m/z = 327.1511$, calcd. for $C_{19}H_{21}NO_4$: 327.1471.

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(4*R*,4a*R*,7a*R*,12b*S*)-3-Methyl-1,2,3,4,4a,5,6,7a-octahydrospiro[4,12-methanobenzofuro[3,2-*e*]isoquinoline-7,2′-[1,3]dioxolan]-9-ol (21)

To a stirred solution of crude oripavine ketal **20** in MeOH (3 mL) was added 5% Pt on C (10 mg). The flask containing the reaction mixture was evacuated/refilled with H_2 gas three times. The reaction mixture was then stirred under an atmosphere of H_2 gas for 48 h. The catalyst was removed by filtration through diatomaceous earth. The filtrate was concentrated using rotary evaporation to afford a crude residue of hydromophone ketal which was carried on directly to the next step. A small sample was converted to its *p*-TsOH salt for determination of spectral properties and was isolated as a beige solid. $R_f = 0.22$ (6:1 CH_2Cl_2:MeOH); mp 220 °C (dec.; CH_2Cl_2:heptane); $[\alpha]_D^{20}$: −65.60 ($c = 0.7$, MeOH); IR (neat): $\nu = 3430$, 2928, 1641, 1499, 1462, 1187, 1124, 1035 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): $\delta = 7.73$ (d, $J = 7.8$ Hz, 1H), 7.26 (d, $J = 7.8$ Hz, 1H), 6.71 (d, $J = 8.1$ Hz, 1H), 6.64 (d, $J = 8.1$ Hz, 1H), 4.54 (s, 1H), 4.18 (q, $J = 5.1$ Hz, 1H), 4.03 (q, $J = 6.6$ Hz, 1H), 3.86 (q, $J = 6.6$ Hz, 1H), 3.81–3.77 (m, 2H), 3.36–3.26 (m, 2H), 3.21–3.15 (m, 2H), 2.90 (s, 3H), 2.90–2.75 (m, 3H), 2.45 (s, 3H), 2.18–2.08 (m, 1H), 1.85–1.81 (m, 1H), 1.64–1.59 (m, 3H), 1.31–1.21 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 153.3$, 145.4, 142.0, 139.6, 128.4, 126.9, 125.6, 121.1, 118.8, 117.5, 107.9, 92.8, 66.1, 64.5, 61.6, 42.2, 40.3, 34.0, 32.2, 21.3, 19.9; MS (EI^+): *m*/*z* (rel. %) = 220 (17), 206 (12), 205 (78), 199 (30), 91 (46), 74 (55), 59 (100), 57 (61), 55 (58); HR-MS (ESI): *m*/*z* = 329.1640, calcd, for $C_{19}H_{23}NO_4$ [M−*p*TsOH]: 329.1627.

(4*R*,4a*R*,7a*R*,12b*S*)-9-Hydroxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (12)

To a stirred solution of crude hydromorphone ketal **21** in THF (5 mL) was added 3 N HCl (2.5 mL). The mixture was heated to 80 °C for 4 h and then allowed to reach room temperature. The mixture was concentrated under vacuum to remove THF. A saturated solution of $NaHCO_3$ was added to adjust the pH to 8 and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification by column chromatography (6:1 CH_2Cl_2:MeOH) yielded hydromorphone as a white solid; yield: 41 mg (43% yield, over 3 steps); $R_f = 0.22$ (6:1 CH_2Cl_2:MeOH); mp > 230 °C (dec.; CH_2Cl_2:heptane), lit.[32] mp 257 °C (dec); $[\alpha]_D^{20}$: −188.0 ($c = 0.5$, dioxane), lit.[33] $[\alpha]_D^{25}$: −194 ($c = 0.98$, dioxane); ^1H NMR (300 MHz, CD_3OD): $\delta =$ 6.70 (d, $J = 14.1$ Hz, 8.4 Hz, 2H), 4.61 (s, 1H), 3.56 (s, 1H), 3.14 (d, $J = 19.2$ Hz, 1H), 2.95–2.89 (m, 1H), 2.76–2.72 (m, 4H), 2.60–2.52 (m, 1H), 2.35–2.32 (m, 1H), 2.00–1.87 (m, 1H), 1.80 (dd, $J = 13.2$ Hz, 2.7 Hz, 1H), 1.68 (dd, $J =$ 13.2 Hz, 2.7 Hz, 1H), 1.45–1.40 (m, 1H), 1.13–1.05 (m, 1H), 0.92–0.89 (m, 1H). The physical and spectral properties of **12** matched with those given in the literature.[34]

Acknowledgements

The authors are grateful to the following agencies for financial support of this work: Noramco, Inc., Natural Sciences and Engineering Research Council of Canada (NSERC) (Idea to Innovation and Discovery Grants), Canada Research Chair Program, Canada Foundation for Innovation (CFI), TDC Research, Inc., TDC Research Foundation, the Ontario Partnership for Innovation and Commercialization (OPIC), and The Advanced Biomanufacturing Centre (Brock University). We also thank Tim Jones and Razvan Simionescu for their help with MS and NMR structure assignment.

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