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Synthesis of Nororipavine and Noroxymorphone via N- and O-Demethylation of Iron Tricarbonyl Complex of Thebaine

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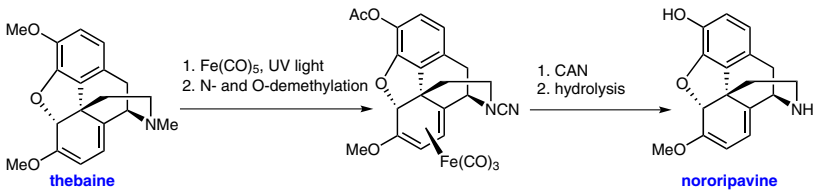

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Abstract Thebaine was converted into its iron tricarbonyl complex, which underwent successive N- and O-demethylation with BrCN and BBr_3, respectively. Decomplexation of the iron tricarbonyl moiety was accomplished with ammonium cerium(IV) nitrate (CAN) and base-catalyzed hydrolysis furnished nororipavine. When excess CAN was used the methoxydiene unit was converted into its C-14 nitrate that on hydrogenation and further hydrolysis furnished noroxymorphone. Full experimental and spectral data are provided for all key compounds.

Key words alkaloids, iron–diene complexes, nororipavine synthesis, iron decomplexation, demethylation

Opiate-derived medicinal agents that are used for treating various conditions such as pain relief, cough suppression, treatment of overdose, and alcohol addictions possess diverse chemical structures but share a few common features (Figure 1). All of them are tertiary amines, some have a free phenol functionality, **1**, **5**–**9**, **11**–**13**, and others contain the C-14 hydroxy, **4**, **6**–**9**. Apart from the well-known natural opiates, such as morphine (**1**) and codeine (**2**) that originate in poppies and are used as such, all other medicinal agents are produced by semi-synthesis. Their production requires two major operations: efficient hydroxylation at C-14 and equally efficient methods for N- and O-demethylation. These aspects are especially crucial for the production of compounds such as naloxone (**7**), naltrexone (**8**), and buprenorphine (**12**) that require the replacement of the N-methyl moiety with other alkyl groups. The most convenient starting materials for the semi-synthetic opiates are clearly thebaine (**10**) and oripavine (**11**), in which N-demethylation would be required prior to the installation of other alkyl groups at N-17.[1]

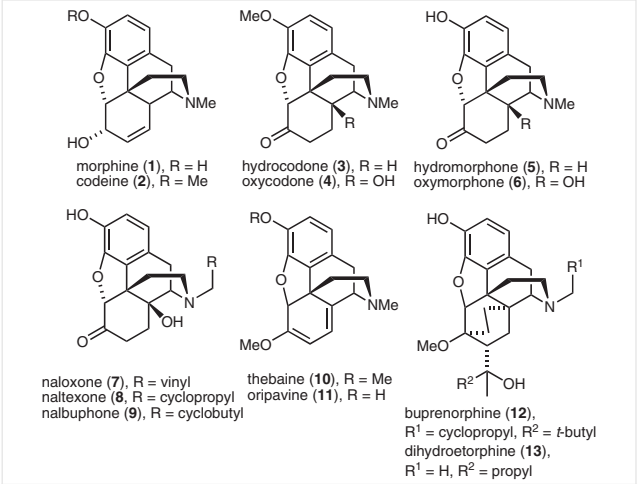
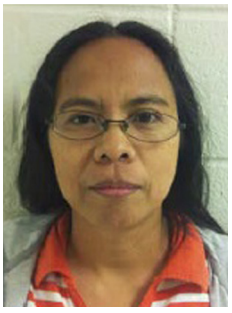


Figure 1 Morphine alkaloids and medicinal agents derived by semi-synthesis

In the past ten years, thebaine and oripavine have become the starting materials of choice in the pharmaceutical industry because of at least three reasons. The first and the most apparent to chemists is their structure and functionality; they are perfectly predetermined for the installation of the hydroxy group at C-14 (see 'Nal-drugs' **7**–**9**) or for performing the Diels–Alder reaction on the methoxydiene moiety to produce the backbone of buprenorphine (**12**) or

Biographical Sketches

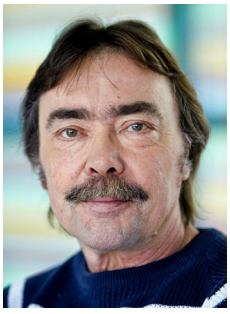
Aleš Machara was born in 1981 in Prague, Czechoslovakia. He received his Ph.D. from the Institute of Chemical Technology in 2008 under the supervision of Professor Jiri Svoboda. After a year at Gilead Sciences Research Center at the Institute of Organic Chemistry and Biochemistry in Prague (IOCB), he joined the group of Professor Tomáš Hudlický at Brock University (Canada). In 2011 Aleš moved back to Prague where he was appointed as a research fellow at IOCB. He started his independent career as a lecturer at Charles University in the beginning of 2012. His research interest focuses on the chemistry of heterocycles, natural compounds, and antiviral drugs.



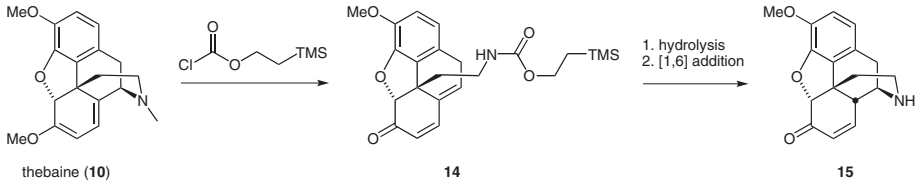
Mary Ann A. Endoma-Arias was born in 1969 in Rizal, Philippines. After completing her B.Sc. (1990) at the University of the Philippines Diliman, in Quezon City, Philippines, she started her Ph.D. studies at Virginia Tech, in Blacksburg, VA, under the supervision of Professor Tomáš Hudlický, in 1992. She moved with Professor Hudlický in 1995 to the University of Florida, in Gainesville, FL, where she completed her Ph.D. in 1997. Upon completion of her Ph.D., she returned to the University of the Philippines where she rose to the rank of Associate Professor. Her main interest during her research career in the Philippines focused on the synthesis and conjugation of compounds with medicinal properties to liposomes and hydrophilic polymers for targeted delivery. During this time she continued to work closely with the Hudlický Research Group. She has published 24 papers and 5 patents. In 2010 she joined the research group of Professor Hudlický at Brock University in St. Catharines, ON, Canada as a Senior Research Associate.

Ivana Císařova was born in 1955 in Planá, Czechoslovakia. Following her undergraduate studies at Charles University in Prague (RNDr, 1980), she completed her Ph.D. in chemistry (1988) at the Department of Inorganic Chemistry. She was a member of the structure analysis group at the Institute of Physics, Czechoslovak Academy of Science from 1980–1992. Since 1992 she has worked as senior lecturer at Department of the Inorganic Chemistry, Charles University.

D. Phillip Cox is currently Chief Scientist at Noramco, Inc. He received his Ph.D. in organic chemistry from the Flinders University of South Australia under the supervision of Dr. Bill Adcock and graduated in 1979. After post-doctoral fellowships at the University of Lausanne, Switzerland with Professor Hans Dahn, Princeton University with Professor Andrew Bocarsly, and Rutgers University with Professor Robert Moss, he joined Lonza at their Fair Lawn NJ Specialty Chemicals R&D facility. He then did a 3-year job rotation at the Lonza Visp, Switzerland R&D Headquarters and re-located back to the Lonza Conshohocken PA Fine Chemicals facility. In 1996, he moved to Noramco, the chemical manufacturing company for the Johnson & Johnson Pharma sector in the United States and has occupied positions of increasing responsibility and is now the Chief Scientist, responsible for outsourced R&D projects, Intellectual Property Management, and Business Excellence.



Tomáš Hudlický was born in 1949 in Prague, Czechoslovakia and emigrated to the USA in 1968. He received his B.S. in 1973 from Virginia Tech and earned his Ph.D. in 1977 at Rice University under the direction of Ernest Wenkert. After a year at the University of Geneva with Wolfgang Oppolzer, he joined the faculty at the Illinois Institute of Technology in 1978. He returned to Virginia Tech in 1982 and rose to the rank of professor in 1988. In 1995, he moved to the University of Florida in Gainesville. Since 2003 he has been at Brock University, where he currently holds a Canada Research Chair (Tier I) professorship in Organic Synthesis and Biocatalysis. His research is focused on chemoenzymatic synthesis of natural products, most notably Amaryllidaceae and morphine alkaloids.



Scheme 1

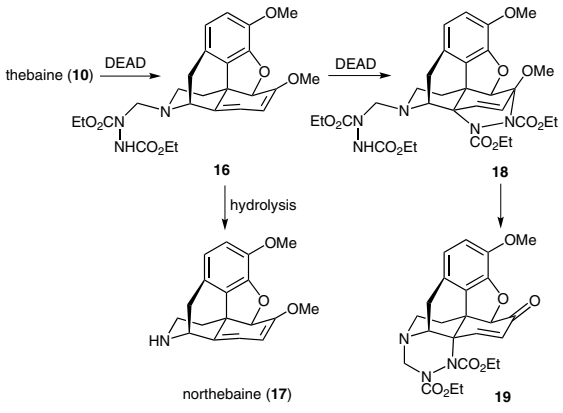
other superpotent opiates such as dihydroetorphine (**13**).[2] The second reason is the recent change in their availability; the content of both thebaine and oripavine in *Papaver somiferum* is very low,[3] but recently modified plant cultivars called 'Norman', 'Ted', or 'Eve' have become available and these produce high levels of either thebaine or oripavine with very low content of other morphine alkaloids.[4] The third reason which may be behind the preference for thebaine and oripavine is of regulatory nature; in 1981 the US government passed regulations proposing that 80% of morphine derivatives purchased by US companies has to originate in Turkey and India.[5] This legislation is circumvented by the utilization of thebaine and oripavine, which were not included in the aforementioned US regulation.

For the conversions of thebaine or oripavine into the opiate-derived agents some adjustments to the currently available methodologies need to be made. Many methods for N-demethylation of tertiary amines have been disclosed in the literature.[6] Predominantly, these methods include the use of cyanogen bromide (von Braun reaction),[7] chloroformates,[8] or dialkyl azodicarboxylates.[9] More recently reported methods used N-oxidation with subsequent elimination,[10] nucleophilic demethylation of quaternary salts,[11] oxidative demethylations catalyzed by palladium[12] or iron salts,[13] and demethylations catalyzed by fungal cytochromes.[14] These methods have been successfully applied to various morphine alkaloids, as well as to some of the semi-synthetic derivatives such as oxymorphone and thevinone derivatives, but most of these protocols are not suitable for use with the more functionally sensitive compounds such as thebaine and oripavine. In this paper we report a new protocol for O- and N-demethylation that preserves the methoxydiene moiety and is well suited for the production of nororipavine and other key compounds.

The presence of the methoxydiene moiety in thebaine and oripavine in both alkaloids allows for a variety of useful reactions, such as oxidations, reductions, additions, and cycloadditions. Unfortunately, this sensitive functionality also rules out many other reactions required for N- and O-demethylations, for example the aforementioned von Braun reaction. In general, during reactions of thebaine or oripavine with cyanogen bromide,[15] chloroformates,[16] anhydrides,[17] acyl chlorides,[18] or tosyl bromide[19] the allylic C-9 carbon–nitrogen bond is cleaved and the ethyl amino bridge is eliminated, with the concomitant assistance of the nucleophilic dienol ether. In 1969 Birch made the following statement which completely sums up the observed reactivity:[20] '*Reaction of Thebaine itself with cyanogen bromide results not only in the expected alternation of the NMe to NCN, but also in extensive rearrangement of the skeleton, which must be due to the presence of the cyclohexadiene structure, since heroin behaves normally.*'

Scheme 1 illustrates similar fragmentation caused by chloroformate.[16] Thebaine (**10**) undergoes the N-demethylation with concomitant cleavage to dienone **14**. In principle, this compound could be converted in two steps into norcodeinone **15** via 1,6 addition of the ethylamino bridge according to protocols published for similar compounds.[21] However, the utility of the methoxydiene functionality required for further transformations (C-14 hydroxylation, Diels–Alder cycloaddition) would be lost.

There are only two successful N-demethylation procedures for thebaine and oripavine reported in the literature. The first one uses diethyl azodicarboxylate (DEAD) to oxidize the N-methyl moiety to the oxidation state of formaldehyde aminal **16**, subsequent hydrolysis of which affords northebaine (**17**) in 37–55% yield (Scheme 2).[22] Surprisingly, the N-methyl moiety reacts faster than the methoxydiene which, if DEAD is used in excess, subsequently undergoes cycloaddition with the second molecule of DEAD to produce **18** and eventually, through an unprecedented rearrangement, leads to **19**.[23]



Scheme 2

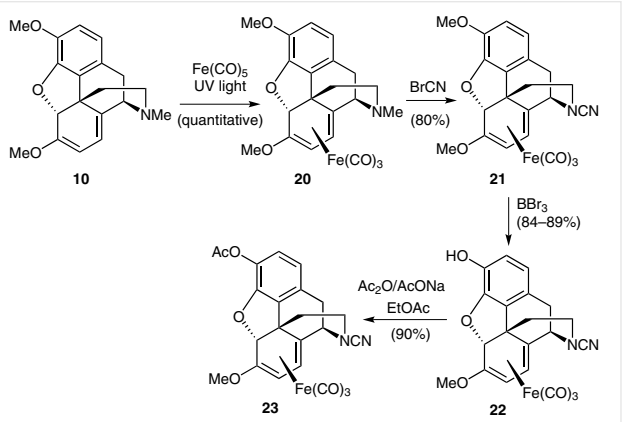
The second N-demethylation protocol for thebaine and oripavine was reported by Scammells and utilized its *N*-oxide hydrochloride salts, which were converted into northebaine and nororipavine by the action of Fe(0) in 86% and 40% yield, respectively.[24] Further optimization of this approach using zero-valent iron revealed that N-demethylation of oripavine is particularly sensitive to subtle changes in experimental conditions (including stoichiometry, temperature, the nature of 'iron' in the steel reactor, and solvents). Under the best conditions nororipavine was obtained in 76% yield along with 20% yield of recovered oripavine.[25]

In principle, oripavine could be prepared from thebaine by O-demethylation, but one must note that thebaine and oripavine have distinctly different reactivity compared to other opiates. Standard protocols using either boron tribromide[26] or thiolates[27] lead only to extensive decomposition because of the sensitivity of the methoxydiene functionality to acids,[28] bases, and certain nucleophiles.[29] To date, direct 3-O-demethylation of thebaine to produce oripavine has only been accomplished by L-Selectride, albeit in low yield (35%) and after a long reaction time (2 weeks).[30] The authors observed the formation of byproducts, notably due to the competing 6-O-demethylation. We might hypothesize that another course of reaction apart from 6-O-demethylation could be involved because there is a report on the formation of β-dihydrothebaine from thebaine by treatment with lithium aluminum hydride.[31] Sipos and coworkers disclosed an elegant synthesis that combines stepwise reaction of thebaine with DEAD (N-demethylation) followed by treating with L-Selectride (O-demethylation). This protocol gave nororipavine in an overall yield of 64%.[32]

Recently, we reported on a high yielding O-demethylation of thebaine derivatives in which the diene moiety was 'protected' either as its iron tricarbonyl complex or as a bicyclic dihydrothiopyran Diels–Alder adduct. For successful O-demethylation, such protective operations of the methoxydiene moiety in thebaine proved to be an absolute necessity. Both of the protective operations were easily reversible; iron decomplexation or the retro-cycloaddition restores the C ring with dienol ether function intact.[33] In addition, we found that the thebaine–iron complex is very stable even under extremely acidic conditions. However, after O-demethylation a phenolic iron complex was formed that proved quite sensitive to basic conditions, especially to the presence of ammonia and amines. We speculated that the tertiary amine still present in the intermediate causes the inherent instability.

The ease of preparation of the iron tricarbonyl complex derived from thebaine[33,34a] prompted us to consider a general approach from thebaine to nororipavine by consecutive N- and O-demethylations. Based on previous experience, we reasoned that if the von Braun reaction is performed **prior to** O-demethylation, the intermediate N-17 cyanamide, which is not basic, should not contribute to the instability of reaction intermediates.

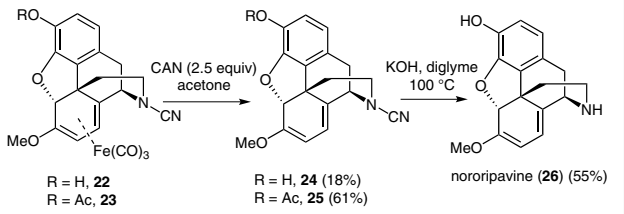
Thebaine and iron pentacarbonyl were irradiated with ultraviolet light providing the iron tricarbonyl complex **20** in quantitative conversion (Scheme 3).



Scheme 3

Subsequent N-demethylation was accomplished using cyanogen bromide[20] and we were pleased to find that the average yield of cyanamide **21** was consistently ~80%, in perfect agreement with the range reported by Birch.[34a] Complex **21** was subjected to O-demethylation with boron tribromide under previously developed conditions[33] providing smoothly phenol **22** in consistent yields of ~87%. Phenol **22** (with the N–CN moiety) is significantly more stable than the similar compound containing the *N*-methylamine,[33] but we have observed formation of small amounts of black solid (of iron origin) during its handling. We have, therefore, protected the free phenol at C-3 as its acetate in order to increase the stability and the ease of handling. Acetate **23**, a stable crystalline compound, was prepared by treatment of the phenol either with acetyl chloride/lutidine (85%) or with acetic anhydride/sodium acetate mixture in ethyl acetate (90%). Additional improvement materialized by performing the acetylation directly on the crude phenol after the O-demethylation step and this resulted in obtaining acetate **23** in overall yield higher than 90% (93% on 640 mg scale).

Initial attempts at the decomplexation of the iron complex by employing reported conditions were not satisfying. Decomplexation of **22** or **23** either with iron(III) chloride[34] or with anhydrous trimethylamine *N*-oxide (TMANO)[34a,35] in DMF at 70 °C did not furnish the desired products. Decomplexation of either the free phenol **22** or its acetate **23** was accomplished in 18% and 61% yield, respectively by a mild oxidation with 2.5 equivalents of ammonium cerium (IV) nitrate (CAN)[36] in acetone (Scheme 4).



Scheme 4

Iron decomplexations using *N*-oxides were later reinvestigated. This time the reactions were performed at room temperature instead of 70 °C. Reaction of **22** with ten equivalents of anhydrous TMANO in dry toluene proceeded smoothly with a 70% isolated yield of **24**. Reaction of **23** under the same conditions afforded acetate **25** in 46% yield. Encouraged by this finding, the decomplexation of compound **23** was performed with the significantly cheaper anhydrous *N*-methylmorpholine *N*-oxide (NMO). Treatment of **23** with seven equivalents of NMO furnished acetate **25** in 10 minutes with yields in the range of 51–56%. Replacement of toluene with acetonitrile, DMF, or ethyl acetate did not affect the yield. In all cases reaction mixture turned dark brown and became a thick slurry.

Hydrolysis of cyanamide **25** to nororipavine (**26**) turned out to be tricky. The starting material **25** completely decomposed when standard conditions for N–CN hydrolysis with KOH were applied.[37] In addition, the presence of the labile methoxydiene functionality precludes the use of acid-catalyzed hydrolysis because under such conditions the skeletal rearrangements to apomorphine[28] and thebenine occur.[38] Under the optimal conditions (10 equivalents of potassium hydroxide, diglyme, 100 °C) nororipavine (**26**) was obtained in 55% yield.

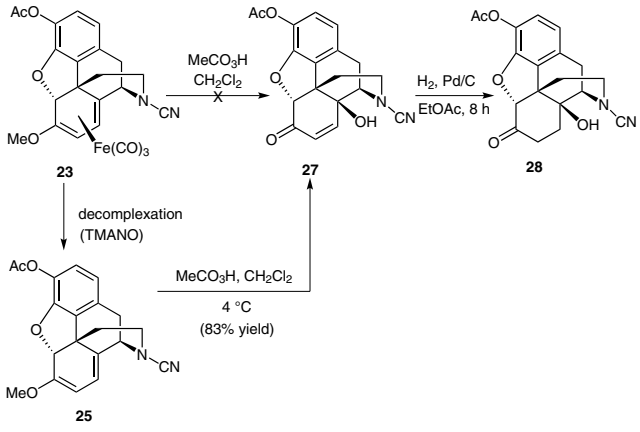
Finally, in addition to the synthesis of nororipavine from thebaine, we have investigated a practical approach to noroxymorphone. We assumed that oxidative decomplexation of the iron tricarbonyl complex **23** would proceed further to hydroxy enone **27** under conditions normally used for oxidation of thebaine ($MeCO_3H$). Surprisingly iron tricarbonyl complex **23** was not converted into enone **27** even when six equivalents of peracetic acid were used. Formation of various compounds was observed during monitoring of the reaction, but enone **27** was not detected. Small amounts of methoxydiene **25** were present indicating partial decomplexation under the conditions used. Standard oxidation of methoxydiene **25** (obtained by decomplexation of **23** with TMANO) with peracetic acid in dichloromethane did afford enone **27**, which was subsequently subjected to palladium-catalyzed hydrogenation in ethyl acetate to furnish intermediate **28** in 83% yield (Scheme 5). Additional experiments with various peroxides (magnesium monoperoxyphthalate, sodium perborate, sodium percarbonate, ammonium persulfate) also failed to provide either **25** or **27** from complex **23**.

In the course of the investigation of iron decomplexation with ammonium cerium(IV) nitrate (CAN), we have discovered that decomplexation performed with five equivalents of CAN furnished 80% yield of nitrate ester **29** (Scheme 6).[39] This unprecedented formation of a nitrate ester from the methoxydiene provided an opportunity for the preparation of noroxymorphone without relying on TMANO-mediated decomplexation, considered to be the bottle neck of nororipavine synthesis (*vide supra*).

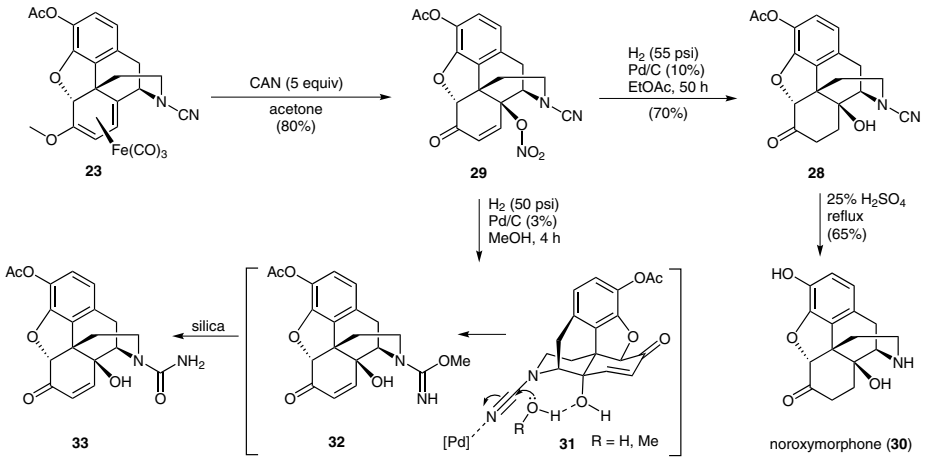
The mechanism for the formation of the nitrate ester may be postulated as shown in Scheme 7 and previously reported in the preliminary communication.[39]

Hydrogenation of nitrate ester **29** in ethyl acetate, somewhat sluggish because of the steric hindrance at C-14, provided hydroxy ketone **28**, whose acid-catalyzed hydrolysis furnished the desired noroxymorphone **30** in good yield.[39]

Hydrogenation under milder conditions (3% wt. Pd/C, paste; 60% moisture) in methanol afforded a very polar compound **33,** identified by X-ray crystallographic analysis



Scheme 5

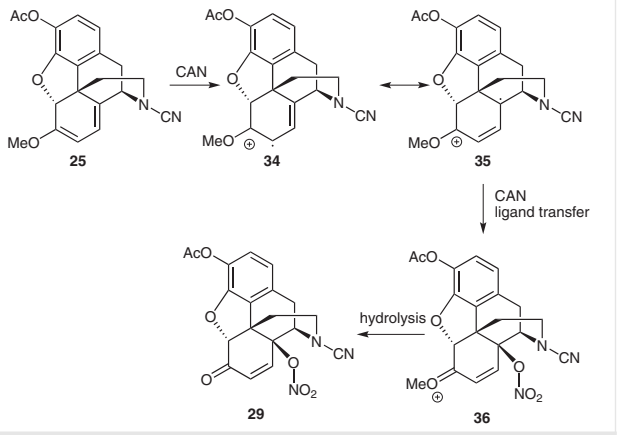


Scheme 6

(Figure 2), as a product of nitrate reduction but with the intact enone and, surprisingly, with the cyanamide moiety hydrolyzed to a urea, as suggested in Scheme 6. We speculate that this unprecedented mild hydration is facilitated by the neighboring C-14 hydroxy functionality since hydrolysis of cyanamides to ureas usually requires harsh conditions. The role of palladium catalyst in this particular reaction is unclear, but its coordination to the cyano moiety may increase the partial positive charge at its carbon. Hydrogen bonding of either methanol or water with the C-14 hydroxy group would then allow for the intramolecular hydration under the mild conditions observed.

To understand whether the slow rate of hydrogenation of the enone in nitrate ester **29** is due to steric hindrance or other factors we prepared the C-14 acetate derivative **37** (Scheme 8). Thebaine was subjected to oxidation, O-demethylation, and acetylation to **39**, whose von Braun N-demethylation furnished the desired enone **37** in modest yield. Subjecting acetate **37** to hydrogenation under the same conditions as those used for the saturation of **27** and **29** did not give the saturated ketone **40**. The hydrogenation of hydroxy enone in **27** proceeds in 8 hours whereas the hydrogenation of the enone in the nitrate ester **29** requires 50 hours and the hydrogenation of C-14 acetate to saturated ketone **40** does not take place at all. The slow rate of hydrogenation of the enone containing a functionalized C-14 hydroxy (as in **29** and **37**) may indeed be due to steric hindrance. The fact that **29** is eventually (after 50 h) converted into saturated ketone **28** seems to indicate that the nitrate moiety sterically hinders hydrogenation of the double bond and must be reduced first to hydroxy enone **27**, in which the saturation proceeds normally to **28**. This assumption was confirmed by isolation of **27** from the reaction mixture in hydrogenation of nitrate ester **29**. It is not clear why the hydrogenolysis of the nitrate N–O bond is so slow as it seems sterically quite accessible.

In summary, we have demonstrated that consecutive N- and O-demethylation of thebaine–iron carbonyl complex followed by iron decomplexation and cyanamide hydrolysis allows for a practical preparation of nororipavine. Furthermore, we also found that diene iron tricarbonyl complexes are air and bench stable if C-3 phenol is protected and N-17



Scheme 7

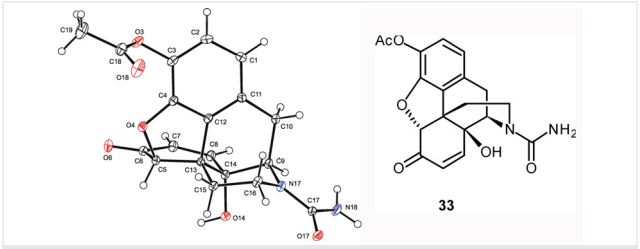
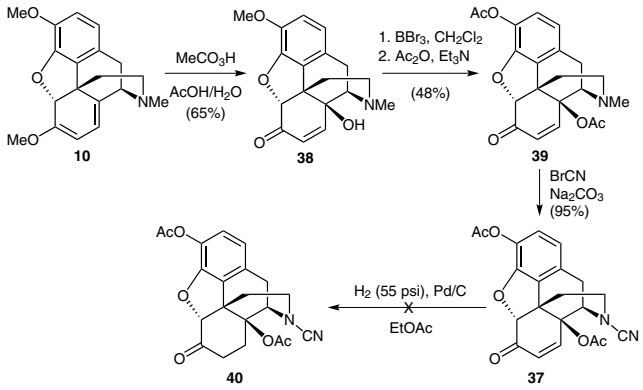


Figure 2 View on the molecular structure of **33**, the displacement ellipsoids are drawn on 30% probability level



Scheme 8

carries an electron-withdrawing group (N–CN). Norororipavine serves as a convenient starting material for the synthesis of a number of pharmaceutical opiate-derived agents, including naltrexone, nalbuphine, and buprenorphine. The exceptionally mild hydrolysis of the cyanamide to an urea, observed under palladium catalysis during hydrogenation in methanol is interesting and could perhaps be exploited for further improvements. Finally, an expeditious synthesis of noroxymorphone was accomplished through a new method of C-14 hydroxylation. In the course of the decomplexation of the iron tricarbonyl complex of thebaine by ammonium cerium(IV) nitrate, an unexpected formation of the nitrate ester at C-14 of the methoxydiene functionality occurred. This result was recently reported in a preliminary communication.[39]

All solvents were used as obtained unless otherwise stated. Thebaine was purchased from Tasmania Alkaloids and from MD Pharm. Pd/C was purchased either from Sigma or from Johnson Matthey. All other reagents were obtained from commercial sources. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 MHz (^{1}H at 300 MHz, ^{13}C at 75 MHz) or Bruker 600 MHz as solutions. Melting points were determined using a Leica Galen melting point apparatus. Mass spectra (HRMS) measurements were recorded on LTQ Orbitrap XL and the mass ion was determined by electrospray ionization. Infrared spectra were recorded on Perkin-Elmer FT-IR or Bruker Alpha-P FT-IR spectrophotometer as $CHCl_3$ solutions. Fluka 60 silica gel was used for column chromatography. TLC was performed on silica gel 60 F_{254}-coated aluminum sheets (Merck). DMA = *N*,*N*-dimethylacetamide.

Tricarbonyl[(6,7,8,14-η)-(5α)-6,7,8,14-tetradehydro-4,5-epoxy-3,6-dimethoxy-17-methylmorphinan]iron(0) (20)

Thebaine iron tricarbonyl was prepared by the previously published method of Birch.[34a] Thebaine (2 g, 6.4 mmol) was dispersed in benzene (20 mL), the solution was degassed by bubbling with argon for 3 min and $Fe(CO)_5$ (5 mL, 37 mmol) was added. This mixture was irradiated in a UV reactor for 48 h at 40 °C. The mixture was then concentrated under vacuum and purified by column chromatography (CH_2Cl_2/MeOH 10:1). Recrystallization (abs EtOH) afforded **20** (2.84 g, 95%) as an orange solid; mp 126–127 °C (EtOH); R_f = 0.81 (CH_2Cl_2/MeOH 10:1). Spectral data were in agreement with previously published data.[33]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.68 (d, *J* = 8.0 Hz, 1 H), 6.59 (d, *J* = 7.8 Hz, 1 H), 5.32 (d, *J* = 3.5 Hz, 1 H), 4.92 (s, 1 H), 4.55 (d, *J* = 4.4 Hz, 1 H), 3.82 (s, 3 H), 3.58 (s, 3 H), 3.24 (d, *J* = 17.7 Hz, 1 H), 3.00 (d, *J* = 6.0 Hz, 1 H), 2.81–2.16 (m, 7 H), 1.66 (d, *J* = 12.4 Hz, 2 H).

Tricarbonyl[(6,7,8,14-η)-(5α)-6,7,8,14-tetradehydro-4,5-epoxy-3,6-dimethoxy-17-cyanomorphinan]iron(0) (21)

To a stirred suspension of thebaine complex **20** (2.5 g, 5.54 mmol) in dry $CHCl_3$ (50 mL) and powdered K_2CO_3 (1.2 g, 8.68 mmol) was added a solution of 3 M BrCN (2.27 mL, 6.81 mmol) dropwise over 10 min under an argon atmosphere. The mixture was heated to reflux for 2 h. The volatiles were removed by vacuum distillation and the solid residue was chromatographed (silica gel, CH_2Cl_2/MeOH 9:1) to afford **21** (2.3 g, 89%) as an orange solid, whose spectral and physicochemical properties matched those given in the literature; mp 174 °C (CH_2Cl_2/hexanes) [Lit.[20] 174 °C (EtOH)]; $[\alpha]_D^{20}$ –157.4 (*c* 0.62, $CHCl_3$).

IR (film, $CHCl_3$): 3010, 2961, 2208, 2046, 1972, 1628, 1503, 1440, 1213 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.71 (d, *J* = 8.2 Hz, 1 H), 6.62 (d, *J* = 8.2 Hz, 1 H), 5.36 (m, 1 H), 4.91 (s, 1 H), 4.57 (m, 1 H), 3.82 (s, 3 H), 3.66 (d, *J* = 6.8 Hz, 1 H), 3.58 (s, 3 H), 3.31 (m, 2 H), 3.23 (dd, *J* = 18.4, 7.0 Hz, 1 H), 3.16 (m, 1 H), 2.39 (td, *J* = 12.6, 6.5 Hz, 1 H), 1.73 (d, *J* = 13.0 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 211.8, 145.0, 144.5, 137.4, 125.1, 122.2, 118.3, 117.8, 114.9, 88.8, 79.2, 75.7, 72.5, 61.1, 58.4, 57.6, 49.0, 43.6, 37.1, 35.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}FeN_2O_6$: 463.0587; found: 463.0589.

Tricarbonyl[(6,7,8,14-η)-(5α)-6,7,8,14-tetradehydro-4,5-epoxy-3-hydroxy-6-methoxy-17-cyanomorphinan]iron(0) (22)

To a solution of **21** (0.22 g, 0.476 mmol) in ice-cold CH_2Cl_2 (20 mL) was added dropwise 1 M BBr_3 in heptane (2.85 mL, 2.85 mmol) under an argon atmosphere. The flask containing the mixture was removed from the ice bath and the mixture was stirred for 30 min at r.t. Then the mixture was cooled down in an ice bath and the reaction was quenched by the addition of water (5 mL). The pH was set to neutral by careful addition of aq NaOH, the aqueous layer was separated and it was extracted with CH_2Cl_2 (3 ×). The combined organic layers were

washed with water and brine and dried ($MgSO_4$). The drying agent was then removed and filtrate was evaporated. Column chromatography (hexane/EtOAc 1:1) of the residue afforded **22** (0.18 g, 84%) as a yellowish solid; mp 122–125 °C (MeOH); $[\alpha]_D^{20}$ –146.5 (*c* 0.35, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 8.2 Hz, 1 H), 6.58 (d, *J* = 8.2 Hz, 1 H), 5.37 (d, *J* = 5.0 Hz, 1 H), 4.93 (s, 1 H), 4.69 (s, 1 H), 4.57 (d, *J* = 5.0 Hz, 1 H), 3.67 (d, *J* = 6.1 Hz, 1 H), 3.61 (s, 3 H), 3.42–3.29 (m, 2 H), 3.20 (m, 2 H), 2.51–2.26 (m, 1 H), 1.76 (d, *J* = 13.2 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 210.4, 142.4, 139.0, 136.2, 123.5, 121.5, 117.4, 117.0, 116.0, 88.1, 77.9, 74.4, 71.4, 59.8, 57.2, 48.0, 42.4, 36.0, 34.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}FeN_2O_6$: 449.0430; found: 449.0432.

Tricarbonyl[(6,7,8,14-η)-(5α)-6,7,8,14-tetradehydro-4,5-epoxy-3-acetoxy-6-methoxy-17-cyanomorphinan]iron(0) (23)

To an ice-cold solution of **21** (0.64 g, 1.38 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise 1 M BBr_3 in heptane (8.3 mL, 8.31 mmol) under an argon atmosphere. The mixture was stirred at r.t. for 40 min and then was again cooled down and was quenched by the addition of water (10 mL). The aqueous layer was separated, the pH was adjusted to neutral and then the layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with water and brine, and evaporated to give a thick oil that was dissolved in EtOAc (20 mL). To the solution was added Ac_2O (0.55 g, 5.35 mmol) and solid AcONa (0.26 g, 3.21 mmol). The mixture was stirred overnight and then it was quenched with water (10 mL). The aqueous layer was separated and extracted with EtOAc (3 ×). The combined organic layers were washed with water and brine, and dried ($MgSO_4$). Column chromatography (hexane/EtOAc 1:1) afforded **23** (0.63 g, 93%) as a yellowish solid; mp 137–139 °C (MeOH); $[\alpha]_D^{20}$ –123.7 (*c* 0.74, $CHCl_3$).

IR (film, $CHCl_3$): 2932, 2212, 2054, 1985, 1762, 1443, 1198 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.84 (d, *J* = 8.1 Hz, 1 H), 6.66 (d, *J* = 8.2 Hz, 1 H), 5.36 (m, 1 H), 4.92 (d, *J* = 1.7 Hz, 1 H), 4.57 (d, *J* = 5.0 Hz, 1 H), 3.67 (d, *J* = 5.7 Hz, 1 H), 3.57 (s, 3 H), 3.40–3.26 (m, 2 H), 3.22 (d, *J* = 9.3 Hz, 2 H), 2.52–2.31 (m, 1 H), 2.27 (s, 3 H), 1.79 (d, *J* = 15.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.4, 168.4, 146.8, 137.1, 132.7, 129.6, 123.1, 121.0, 117.0, 116.2, 88.4, 77.8, 74.4, 70.9, 59.62, 57.3, 47.7, 42.3, 36.1, 34.1, 20.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{19}FeN_2O_7$: 491.0542; found: 491.0536.

17-Cyanonororipavine (24)

Method A: To an ice-cold solution of **22** (0.24 g, 0.536 mmol) in acetone (5 mL) was added solid CAN (0.88 g, 1.61 mmol) portionwise. Within a few minutes the mixture turned from a black suspension into a pale yellow solution. After 30 min the mixture was quenched with water (10 mL) and the product was extracted with CH_2Cl_2 (10 mL). The aqueous layer was set to pH 9 by the addition of sat. aq $NaHCO_3$ and then it was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated to dryness. Column chromatography (hexane/EtOAc 1:1 to EtOAc) afforded **24** (0.03 g, 18%) as a white solid; mp 290–293 °C (MeOH).

Method B: To a solution of **22** (0.065 g, 0.145 mmol) in freshly distilled toluene (3 mL) was added TMANO (0.11 g, 1.45 mmol). The reaction was stirred for 30 min under argon atmosphere and then was evaporated to dryness. Column chromatography (hexane/EtOAc 1:1) of the residue afforded **24** (0.04 g, 70%) as a white solid; $[\alpha]_D^{20}$ –157.5 (*c* 0.49, $CHCl_3$).

IR (film, $CHCl_3$): 3568, 2937, 2209, 1607, 1508, 1455, 1379, 1020 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.71 (d, *J* = 8.1 Hz, 1 H), 6.60 (d, *J* = 8.1 Hz, 1 H), 5.66 (d, *J* = 6.5 Hz, 1 H), 5.31 (s, 1 H), 5.13 (s, 1 H), 5.09 (d, *J* = 6.5 Hz, 1 H), 4.27 (d, *J* = 6.9 Hz, 1 H), 3.65 (s, 3 H), 3.52 (td, *J* = 13.2, 3.5 Hz, 1 H), 3.33 (dd, *J* = 13.5, 5.2 Hz, 1 H), 3.29 (d, *J* = 18.2 Hz, 1 H), 3.14 (dd, *J* = 18.5, 7.0 Hz, 1 H), 2.31 (td, *J* = 12.8, 5.4 Hz, 1 H), 1.83 (dd, *J* = 12.8, 2.3 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 152.9, 143.2, 138.9, 131.4, 128.0, 125.1, 120.2, 117.6, 116.9, 113.4, 95.9, 88.9, 59.0, 55.3, 45.8, 43.3, 36.7, 36.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.1239; found: 309.1235.

3-Acetyl-17-cyanonororipavine (25)

Method A: To an ice-cold solution of **23** (0.16 g, 0.326 mmol) in acetone (10 mL) was added solid CAN (0.45 g, 0.816 mmol) portionwise. Within a few minutes the mixture turned from a black suspension into a pale yellow solution. After 30 min was the mixture quenched with water (10 mL) and product was extracted with CH_2Cl_2 (10 mL). The aqueous layer was set to pH 9 by the addition of sat. aq $NaHCO_3$ and then it was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated to dryness. Column chromatography (hexane/EtOAc 1:1 to EtOAc) afforded **25** (0.07 g, 61%) as a white solid; mp 196–199 °C (MeOH).

Method B: To a solution of **23** (0.27 g, 0.551 mmol) in freshly distilled toluene (10 mL) was added NMO (0.45 g, 3.85 mmol). The reaction was stirred for 30 min under an argon atmosphere and then was evaporated to dryness. Column chromatography (hexane/EtOAc 1:1) of the residue afforded **25** (0.10 g, 51%) as a white solid; R_f = 0.43 (hexane/EtOAc 1:1); $[\alpha]_D^{20}$ –126.3 (*c* 0.61, $CHCl_3$).

IR (film, $CHCl_3$): 2027, 2936, 2209, 1762, 1607, 1445, 1371, 1242, 1201, 1020 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.81 (d, *J* = 8.2 Hz, 1 H), 6.65 (d, *J* = 8.2 Hz, 1 H), 5.66 (d, *J* = 6.5 Hz, 1 H), 5.29 (s, 1 H), 5.05 (d, *J* = 6.5 Hz, 1 H), 4.27 (d, *J* = 6.9 Hz, 1 H), 3.61 (s, 3 H), 3.47 (td, *J* = 13.2, 3.4 Hz, 1 H), 3.30 (d, *J* = 18.4 Hz, 2 H), 3.15 (dd, *J* = 18.6, 7.0 Hz, 1 H), 2.28 (s, 3 H), 2.25 (m, 1 H), 1.90–1.70 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.6, 153.1, 148.0, 132.7, 132.7, 131.0, 127.4, 122.8, 119.6, 117.4, 113.8, 95.7, 89.1, 58.7, 55.3, 45.3, 43.1, 36.6, 36.6, 20.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}N_2O_4$: 351.1339; found: 351.1340.

Variation of Decomplexation Protocol

Attempts to improve yields of **25** by using various additives were only partially successful. With EDTA disodium salt (1 equiv) in MeCN similar yields (~56%) were obtained, but reactions were less vigorous and had a pale yellow color compared to reactions without EDTA salt. Also workups (hydrolysis and extractions) were easier. Reactions with EDTA acid as another additive in dry MeCN or in dry DMF furnished even lower yields of **25**. At this time we speculated that lower yields could be caused by presence of formed Fe(II)/Fe(III) salts which are too acidic for the methoxydiene moiety (causing Lewis acid mediated decomposition). To address problems that might be caused by iron salt(s), we decided to use DMA as a solvent because DMA is known for its good metal complexation properties. The reaction performed in DMA had a yield of 56% (standard yield) and the appearance of the mixture was acceptable. A similar reaction [NMO (7 equiv), DMA] but

with tartaric acid (3 equiv) which can also chelate iron species gave a 70% yield. When tartaric acid (4 equiv) in DMA was used, the reaction afforded a comparable yield (65%). Although the application of tartaric acid did not improve the yield significantly, it needs to be stressed that tartaric acid prevents the formation of a suspension (likely of iron origin) during workup and immensely simplifies it.

Nororipavine (26)

A glass, thick-wall tube was charged with **24** (0.040 g, 0.114 mmol), KOH (0.064 g, 1.14 mmol), and diglyme (2 mL), purged with argon, and sealed. The mixture was stirred at 100 °C for 16 h. Then the mixture was mixed with water (5 mL), the pH was adjusted to 9 with aqueous HCl and the product was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with water and brine, and evaporated to dryness. Column chromatography (CH_2Cl_2/MeOH/NH_4OH 90:10:2.5) afforded **26** (0.018 g, 55%) as a white powder; mp >320 °C (MeOH); $[\alpha]_D^{20}$ –267.0 (*c* 0.22, DMSO).

IR (KBr): 3306, 2911, 2582, 1601, 1455, 1258, 1231, 1029, 808 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 9.08 (bs, 1 H), 6.49 (d, *J* = 8.0 Hz, 1 H), 6.43 (d, *J* = 8.0 Hz, 1 H), 5.42 (d, *J* = 6.4 Hz, 1 H), 5.16 (s, 1 H), 5.10 (d, *J* = 6.4 Hz, 1 H), 3.75 (dd, *J* = 5.2, 1.9 Hz, 1 H), 3.31 (bs, 1 H), 3.04–2.81 (m, 3 H), 2.70 (dd, *J* = 13.3, 4.3 Hz, 1 H), 1.96 (td, *J* = 12.5, 5.0 Hz, 1 H), 1.64–1.46 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 151.8, 143.3, 139.2, 135.2, 133.4, 126.4, 118.9, 116.0, 108.7, 96.2, 87.9, 54.6, 52.9, 46.5, 40.2, 37.9, 37.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}NO_3$: 284.1281; found: 284.1281.

3-Acetyl-17-cyano-14-hydroxynormorphinone (27)

To an ice-cold solution of **25** (0.06 g, 0.17 mmol) in dry CH_2Cl_2 (3 mL) was added solution of 39% peracetic acid in AcOH (0.04 g, 0.21 mmol). The mixture was stirred for 2 h and then the solvent was evaporated. Column chromatography (EtOAc) afforded **27** (0.05 g, 83%) as a white solid; mp >320 °C (MeOH); $[\alpha]_D^{20}$ –91.7 (*c* 0.22, DMSO).

IR (film, $CHCl_3$): 3451, 2214, 1765, 1689, 1445, 1193 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$ with drop of DMSO-d_6): δ = 6.85 (d, *J* = 8.2 Hz), 6.76 (d, *J* = 10.1 Hz), 6.73 (d, *J* = 8.2 Hz), 6.33 (s, 1 H, OH), 6.07 (d, *J* = 10.1 Hz), 4.78 (s), 3.80 (d, *J* = 5.0 Hz), 3.30 (m), 3.26 (m), 3.14 (td, *J* = 13.1, 3.9 Hz), 3.01 (dd, *J* = 18.8, 5.6 Hz), 2.77 (td, *J* = 12.7, 5.6 Hz), 2.27 (s, 3 H), 1.64 (dd, *J* = 12.7, 3.4 Hz).

^{13}C NMR (150 MHz, $CDCl_3$ with drop of DMSO-d_6): δ = 192.9, 167.8, 147.7, 147.6, 132.8, 132.5, 130.0, 129.2, 123.4, 120.0, 118.5, 87.3, 67.0, 61.1, 46.6, 43.1, 31.4, 26.5, 20.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{16}N_2NaO_5$: 375.0951; found: 375.0952.

3-Acetyl-17-cyanonoroxymorphone (28)

Method A: To a solution of **27** (0.10 g, 0.284 mmol) in EtOAc (7 mL) was added 10% Pd/C (0.01 g). The flask containing the mixture was evacuated/refilled with H_2 gas (3 ×). The mixture was then shaked in a Parr shaker under 55 psi of H_2 gas for 8 h. The catalyst was removed by filtration through a syringe filter. The filtrate was concentrated using a rotary evaporation to afford a crude residue. Column chromatography (EtOAc) gave **28** (0.08 g, 83%).

Method B: To a solution of **29** (0.10 g, 0.251 mmol) in EtOAc (7 mL) was added 10% Pd/C (0.01 g). The flask containing the mixture was evacuated/refilled with H_2 gas (3 ×). The mixture was then shaked in a Parr shaker under 55 psi of H_2 gas for 50 h. The catalyst was removed by filtration through a syringe filter. The filtrate was concentrated using rotary evaporation to afford a crude residue. Column chromatography (EtOAc) gave **28** (0.062 g, 70%) as a white solid; mp 188–191 °C (EtOAc); $[\alpha]_D^{20}$ –191.0 (*c* 0.74, $CHCl_3$).

IR (film, $CHCl_3$): 3570, 2937, 2215, 1764, 1731, 1622, 1496, 1371, 1157 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 8.2 Hz, 1 H), 6.77 (d, *J* = 8.2 Hz, 1 H), 4.71 (s, 1 H), 3.88 (bs, 1 H), 3.70 (d, *J* = 5.3 Hz, 1 H), 3.34–3.23 (m, 2 H), 3.17–2.97 (m, 3 H), 2.67 (td, *J* = 12.9, 5.6 Hz, 1 H), 2.33 (s, 3 H), 2.31 (t, *J* = 3.1 Hz, 1 H), 1.99–1.89 (m, 1 H), 1.68–1.58 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 206.2, 168.4, 148.0, 133.2, 128.3, 123.9, 119.9, 118.4, 90.2, 70.4, 62.9, 60.4, 49.6, 42.9, 35.4, 31.3, 31.1, 27.8, 20.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_2O_5$: 355.1289; found: 355.1289.

3-Acetyl-17-cyano-14-(nitrooxy)normorphinone (29)

To an ice cold solution of **23** (0.23 g, 0.469 mmol) in acetone (10 mL) was added solid CAN (1.29 g, 2.34 mmol) portionwise. Within a few minutes the mixture turned from a black suspension into a pale yellow solution. After 30 min the mixture was quenched with water (30 mL) and the product was extracted with CH_2Cl_2 (10 mL). The aqueous layer was set to pH 9 by the addition of sat. $NaHCO_3$ and then extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated to dryness. Column chromatography (EtOAc) afforded **29** (0.15 g, 80%) as a yellowish white solid; mp 166–169 °C (MeOH); R_f = 0.36 (hexane/EtOAc 1:1); $[\alpha]_D^{20}$ –75.9 (*c* 0.32, $CHCl_3$).

IR (film, $CHCl_3$): 3015, 2217, 1765, 1697, 1653, 1447, 1288, 1158, 1042, 842 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 8.2 Hz, 1 H), 6.89 (d, *J* = 10.1 Hz, 1 H), 6.78 (d, *J* = 8.2 Hz, 1 H), 6.40 (d, *J* = 10.2 Hz, 1 H), 4.81 (s, 1 H), 4.68–4.58 (m, 1 H), 3.46 (d, *J* = 18.9 Hz, 1 H), 3.40 (dd, *J* = 13.5, 5.4 Hz, 1 H), 3.27 (td, *J* = 13.1, 4.0 Hz, 1 H), 3.16 (dd, *J* = 19.3, 5.9 Hz, 1 H), 2.70–2.51 (m, 1 H), 2.28 (s, 3 H), 1.85 (dd, *J* = 13.4, 3.5 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 190.2, 167.9, 147.6, 139.6, 137.7, 133.3, 128.2, 128.1, 124.8, 120.4, 116.4, 86.6, 81.7, 56.7, 46.9, 42.5, 31.6, 27.0, 20.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{15}N_3NaO_7$: 420.0802; found: 420.0802.

Noroxymorphone (30)

Cyanonoroxymorphone **28** (0.15 g, 0.423 mmol) in 25% H_2SO_4 (8 mL) was refluxed for 5 h. The mixture was placed in an ice bath and the pH was adjusted to 9 by the addition of aq NH_4. The product was extracted with $CHCl_3$/*i*-PrOH (5:1, 4 ×). The combined organic layers were dried ($MgSO_4$), filtered through cotton wool, evaporated, and the residue was recrystallized (MeOH) to give **30** (0.80 g, 65%) as a white solid; mp 285–290 °C.

^1H NMR (600 MHz, DMSO-d_6): δ = 6.57 (d, *J* = 8.0 Hz, 1 H), 6.53 (d, *J* = 8.0 Hz, 1 H), 4.69 (s, 1 H), 2.99 (d, *J* = 5.8 Hz, 1 H), 2.97–2.79 (m, 3 H), 2.63 (dd, *J* = 12.6, 4.0 Hz, 1 H), 2.37 (td, *J* = 12.6, 3.2 Hz, 1 H), 2.30 (td, *J* = 12.2, 4.6 Hz, 1 H), 2.14–1.99 (m, 1 H), 1.82–1.65 (m, 1 H), 1.42 (td, *J* = 13.8, 3.2 Hz, 1 H), 1.17 (dd, *J* = 12.4, 3.2 Hz, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 209.2, 143.9, 139.8, 129.9, 124.3, 119.4, 117.7 90.0, 70.1, 57.3, 50.8, 37.9 36.3 31.8 29.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}NO_4$: 288.1230; found: 288.1230.

3-Acetyl-14-hydroxynormorphinone-17-carboxamide (33)

To a solution of **29** (0.02 g, 0.05 mmol) in MeOH (5 mL) was added 3% Pd/C (0.004 g). The flask containing the mixture was evacuated/refilled with H_2 gas (3 ×). The mixture was then shaked in a Parr shaker under 50 psi of H_2 gas for 4 h. The catalyst was removed by filtration through a syringe filter. The filtrate was concentrated using rotary evaporation to afford a crude residue. Column chromatography (EtOAc/MeOH 7:1) gave **33** (0.016 g, 85%) as a white solid; mp 175–178 °C (MeOH); $[\alpha]_D^{20}$ –95.5 (*c* 1.0, CH_2Cl_2/MeOH 5:1).

IR (film, $CHCl_3$): 3512, 3008, 2978, 2929, 1705, 1585, 1366, 1178, 1061 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 6.97 (d, *J* = 10.2 Hz, 1 H), 6.87 (d, *J* = 8.1 Hz, 1 H), 6.76 (d, *J* = 8.1 Hz, 2 H), 6.11 (d, *J* = 10.2 Hz, 1 H), 4.77 (s, 1 H), 4.66 (m, 1 H), 3.87 (m, 1 H), 3.02 (m, 1 H), 2.89 (m, 1 H), 2.61 (td, *J* = 12.5, 5.4 Hz, 1 H), 1.66 (m, 1 H), 1.31 (m, 1 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 194.0, 168.6, 160.5, 149.4, 147.3, 132.4, 130.9, 130.7, 122.9, 119.8, 87.3, 70.1, 67.2, 54.9, 37.6, 31.6, 27.0, 18.9.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_6$: 371.1238; found: 371.1239.

14-Hydroxycodeinone (38)

To an ice-cold solution of thebaine (**10**, 0.40 g, 1.28 mmol) in a mixture of AcOH (2 mL) and water (2 mL) was added solution of 39% peracetic acid in AcOH (0.30 g, 1.54 mmol). The mixture was stirred for 2 h and then was adjusted to pH 8 with aqueous ammonia. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water and brine, and evaporated to dryness. Column chromatography (CH_2Cl_2/MeOH 10:1) afforded **38** (0.26 g, 65%) as a white solid; mp 284–286 °C (MeOH).

IR (film, $CHCl_3$): 3354, 2946, 1685, 1507, 1450, 1281, 1115, 1048 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.69 (d, *J* = 8.2 Hz, 1 H), 6.61 (m, 2 H), 6.18 (d, *J* = 10.1 Hz, 1 H), 4.70 (s, 1 H), 3.84 (s, 3 H), 3.23 (d, *J* = 18.7 Hz, 1 H), 3.03 (d, *J* = 5.9 Hz, 1 H), 2.55 (m, 2 H), 2.44 (s, 3 H), 2.38 (m, 1 H), 2.29 (dd, *J* = 11.4, 3.5 Hz, 1 H), 1.69 (dd, *J* = 12.5, 2.5 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 194.3, 147.4, 142.7, 134.7, 130.5, 124.9, 119.6, 115.1, 87.1, 67.8, 64.2, 56.9, 46.7, 45.2, 42.6, 29.5, 22.4.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{20}NO_4$: 314.1387; found: 314.1387.

3,14-Diacetoxy-7,8-didehydro-4,5-epoxy-17-methylmorphinan-6-one (39)

To an ice-cold solution of **38** (0.24 g, 0.77 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise neat BBr_3 (1.53 g, 6.13 mmol) under an argon atmosphere. The mixture was stirred at r.t. overnight and then was cooled down and was quenched with water (10 mL). The aqueous layer was separated, the pH was adjusted to neutral with aqueous ammonia, and then the layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with water and brine, and evaporated to a thick oil that was dissolved in EtOAc (20 mL). To the solution was added Ac_2O (1.0 g, 9.80 mmol) and Et_3N (1.0 g, 9.8 mmol). The mixture was allowed to stir overnight and then was quenched with water (10 mL). The aqueous layer was separated and extracted with EtOAc (3 ×). The combined organic layers were washed with water and brine, and dried ($MgSO_4$). Column chromatography (CH_2Cl_2/MeOH 10:1) afforded **39** (0.14 g, 48%) as a white solid; mp 247–250 °C; $[\alpha]_D^{20}$ –64.3 (*c* 1.0, $CHCl_3$).

IR (film, $CHCl_3$): 2936, 1762, 1733, 1688, 1448, 1370, 1227, 1156, 1042 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 10.1 Hz, 1 H), 6.83 (d, *J* = 8.2 Hz, 1 H), 6.68 (d, *J* = 8.2 Hz, 1 H), 6.16 (d, *J* = 10.1 Hz, 1 H), 4.78 (s, 1 H), 4.10 (d, *J* = 5.3 Hz, 1 H), 3.32 (d, *J* = 18.9 Hz, 1 H), 2.60–2.43 (m, 3 H), 2.39 (s, 3 H), 2.35–2.30 (m, 1 H), 2.27 (s, 3 H), 2.09 (s, 3 H), 1.74 (dd, *J* = 12.0, 2.9 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 192.5, 170.0, 168.2, 147.5, 146.4, 134.1, 132.2, 131.3, 130.7, 123.0, 119.6, 87.8, 58.1, 46.9, 45.2, 42.8, 29.0, 22.8, 21.6, 20.7.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}NO_6$: 384.1441; found: 384.1441.

3,14-Diacetoxy-17-cyano-7,8-didehydro-4,5-epoxynormorphinan-6-one (37)

To a stirred suspension of **39** (0.17 g, 0.443 mmol) in dry 1,2-dichloroethane (4 mL) and powdered Na_2CO_3 (0.28 g, 2.66 mmol) was added solid BrCN (0.28 g, 2.66 mmol) under an argon atmosphere. The mixture was stirred at 65 °C overnight. The volatiles were evaporated, the residue was dissolved in MeOH (5 mL), volatiles were again evaporated, and the final oily residue was chromatographed (silica gel, EtOAc/hexane 2:1) to afford **37** (0.16 g, 95%) as a white solid; mp 255–259 °C (MeOH); $[\alpha]_D^{20}$ –25.4 (*c* 1.0, $CHCl_3$).

IR (film, $CHCl_3$): 2964, 2214, 1766, 1745, 1692, 1446, 1370, 1196, 1044 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.98–6.83 (m, 2 H), 6.75 (d, *J* = 8.2 Hz, 1 H), 6.26 (d, *J* = 10.1 Hz, 1 H), 4.83 (s, 1 H), 4.53 (d, *J* = 5.4 Hz, 1 H), 3.38–3.30 (m, 2 H), 3.28–3.19 (m, 1 H), 3.11 (dd, *J* = 19.3, 6.2 Hz, 1 H), 2.56 (td, *J* = 12.9, 5.7 Hz, 1 H), 2.29 (s, 3 H), 2.22 (s, 3 H), 1.83 (dd, *J* = 13.3, 3.1 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 191.2, 170.2, 168.0, 147.8, 141.6, 135.7, 133.0, 128.7, 124.3, 120.1, 117.4, 87.4, 75.1, 57.6, 46.7, 42.8, 31.3, 27.1, 21.4, 20.6.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{21}H_{18}N_2O_6$: 417.1057; found: 417.1056.

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Supporting Information

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