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Communication

Opioid Synthesis

Direct Synthesis of Noroxymorphone from Thebaine: Unusual Ce^{IV} Oxidation of a Methoxydiene-Iron Complex to an Enone-γ-Nitrate

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Abstract: Noroxymorphone was prepared from thebaine in seven operations. The key steps involved the successive *N*- and *O*-demethylations of an iron tricarbonyl complex of thebaine followed by the unusual ceric ammonium nitrate oxidation of the methoxydiene moiety to the corresponding enone-γ-nitrate during the decomplexation of the iron tricarbonyl functionality.

Introduction

The commercial production of opiate-derived analgesic pharmaceutical agents and antagonists, such as naltrexone (**3**) and naloxone (**4**) shown in Figure 1, depends on semi-synthesis from naturally occurring morphine alkaloids. Convenient starting materials for the large-scale synthesis are the morphine congeners thebaine (**1**) and oripavine (**2**).

The conversions require efficient solutions to several issues: (a) oxidation of the diene unit to introduce C-14 hydroxyl; (b) replacement of the *N*-methyl group with other alkyl groups; and (c), in case of thebaine, *O*-demethylation of the C-3 methyl ether. Many solutions exist for all of these processes but further refinements would be welcome.

We have recently reported several diverse methods for the *N*-demethylations of morphinans and their derivatives.[1] These include the nucleophilic demethylation of quaternary salts,[2] palladium-catalyzed oxidative demethylation with intramolecular acyl transfer from C-14,[3] Burgess reagent demethylation of *N*-oxides,[4] and fungal cytochrome oxidative demethylation of several morphine alkaloids to the corresponding secondary amines.[5] A direct synthesis of naltrexone and (*R*)-methyl naltrexone became available by singlet oxygen addition to quaternary salts of oripavine.[6]

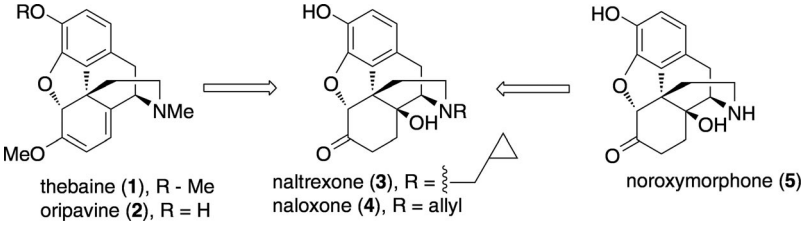

Figure 1. Various morphinans and their conversion to C-14 hydroxylated antagonists.

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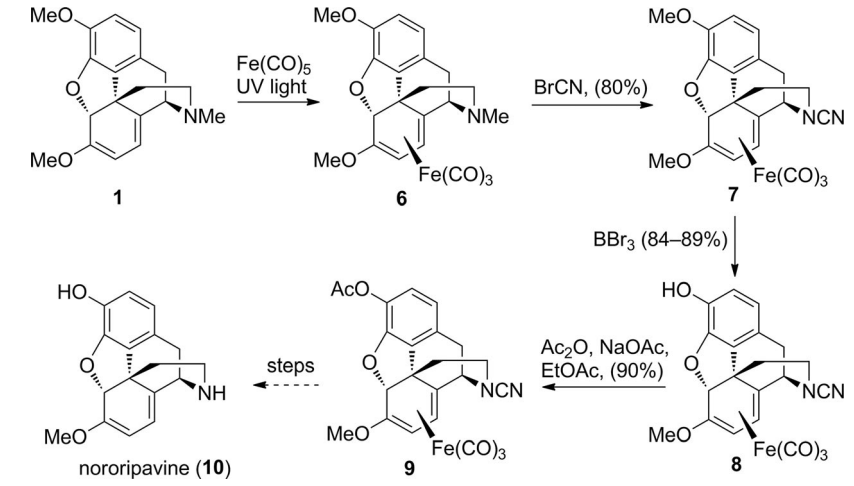
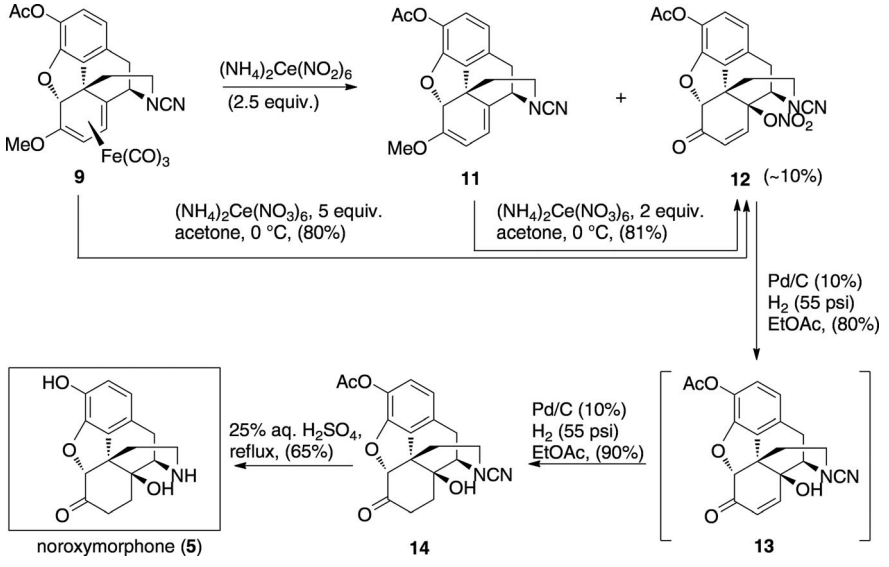
Results and Discussion

In 2014 we published the conversion of thebaine to oripavine and to hydromorphone[7] via the O-demethylation of the iron carbonyl complex **6** and hydrolysis. Realizing that the best common starting material for the synthesis of the various antagonists would be either noroxymorphone (**5**) or nororipavine (**10**) we set out this time to explore the conversion of thebaine to nororipavine as shown in Scheme 1. Thebaine was converted quantitatively to the iron carbonyl complex **6**[8] whose von Braun demethylation provided the *N*-cyano derivative **7**. O-Demethylation with BBr_3 furnished cleanly phenol **8**, which was acylated to complex **9** prior to the decomplexation and hydroly-



Scheme 1.



Scheme 2.

sis. Previously we have used photolytic decomplexation of compounds similar to **9** in order to free the methoxy diene moiety but this procedure suffered from low conversions of starting material to product. When the iron carbonyl complex **9** was exposed to ceric ammonium nitrate (CAN)[9] the decomplexation occurred in good yield to produce the free diene **11**, along with small amounts (≈ 10 %) of over-oxidized product identified as the nitrate ester **12**, Scheme 2. The X-ray analysis confirmed the structure as shown in Figure 2.[10]

This surprising transformation led to a direct synthesis of noroxymorphone (**5**) that serves as a much more convenient intermediate for the production of compounds such as naltrexone and naloxone. In this paper we report the details of this unusual C-14 oxidation of the methoxy diene functionality and the preparation of noroxymorphone from thebaine.

The treatment of either diene **11** or the iron complex **9** with excess ceric ammonium nitrate produced the γ-nitrate ester **12** in excellent yields. This transformation is without precedent in the literature although it is known that ceric ammonium nitrate promotes oxidative condensation of ketones with dienes, with the occasional formation of nitrate esters in some of the products.[11] The nitrate ester was slowly hydrogenated to hydroxy enone **13**. In order to complete full hydrogenation to the saturated ketone **14** additional hydrogenation step was required, presumably because the equivalent of ammonia released during the reduction of the nitrate may act as a catalyst poison. Hydrogenation in the presence of two equivalents of acetic acid proceeded at a faster rate. However, the C-14 nitrate functionality also severely hinders the C-7/C-8 double bond in **12** and we have also encountered similar issues with the very slow rate of hydrogenation of C-14 acetoxy derivative of **12**. Finally, noroxymorphone (**5**) was obtained from **14** by hydrolysis according to the protocol published by Rice.[12]

In summary, the unusual ceric ammonium nitrate oxidation of the methoxy diene moiety in **11** or in the iron tricarbonyl complex **9** provides for a new direct route from thebaine to noroxymorphone, a compound that serves as one of the most convenient starting materials for a variety of opiate-derived

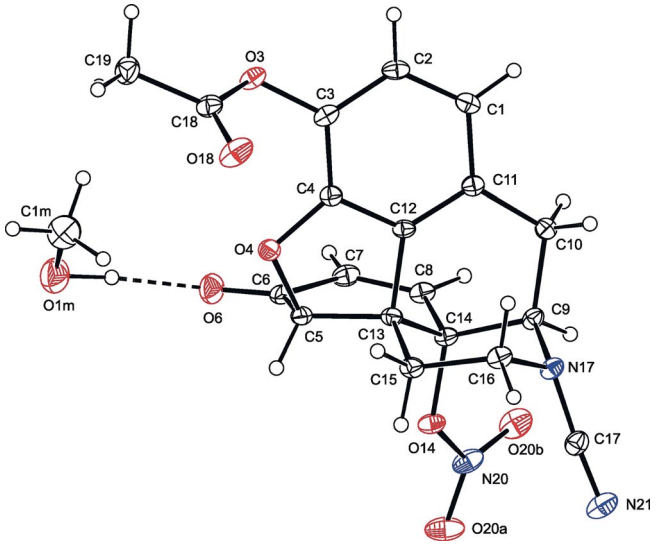


Figure 2. Structure of nitrate ester **12** obtained by X-ray crystallography as a methanol solvate.

agents. We can speculate on the possible mechanism of this transformation as shown in Figure 3. Ceric ammonium nitrate is an efficient one-electron oxidant and has been shown to generate α-ketoalkyl radicals from trimethylsilyl enol ethers and to oxidize silyl dienol ethers to α-carbonylallyl radicals.[13] The cerium(IV)-mediated oxidation is believed to proceed by a radical mechanism involving successive one-electron transfers. In the proposed mechanism CAN reacts with the methoxydiene moiety of **11** to generate radical cation **15**. Subsequently, this species undergoes transfer of a nitrate radical from the second molecule of CAN to yield intermediate **17**. The fact that ceric ammonium nitrate has been shown to efficiently nitrate radicals by ligand transfer mechanism would support this proposal.[14] The observed regioselectivity may be rationalized by considering that the reaction of nitrate with the tertiary radical at C-14 position leads eventually to a conjugated enone, formed by hydrolysis in **17**.

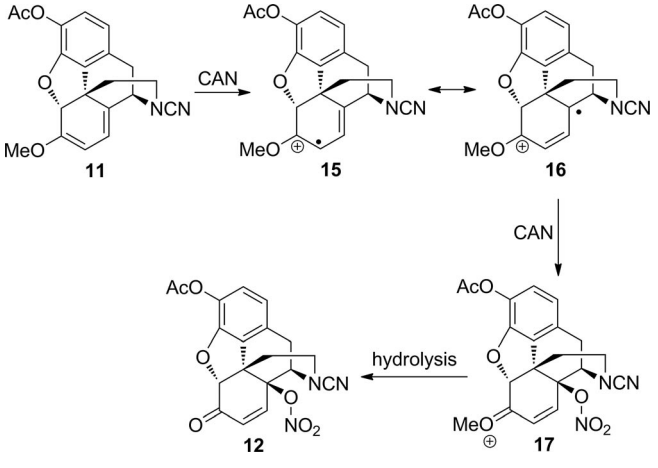


Figure 3. Suggested mechanism for the cerium(IV)-promoted oxidation of methoxydiene in thebaine-type compounds.

Conclusions

The protocol for large-scale conversion of the methoxydiene unit to the corresponding γ-hydroxyenone is well established through the use of common oxidation conditions, for example: H_2O_2 and HCO_2H,[15] *m*-CPBA,[16] and singlet oxygen.[6] The CAN process offers an interesting alternative to the C-14 hydroxylation of thebaine or oripavine. We will report on the optimization of this unusual process as well as on its general applications to the cerium-mediated oxidations of dienes in due course.

Supporting Information (see footnote on the first page of this article): Experimental procedures and ^1H and ^{13}C NMR spectra are provided for key compounds.

Acknowledgments

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Keywords: Medicinal chemistry · Opioids · Alkaloids · Iron complexes · Oxidation

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[10] Crystal data for compound **12**: $C_{19}H_{15}N_3O_7 \cdot CH_4O$, M_r = 429.38; Monoclinic, *P* 2_1 (No 4), *a* = 8.5114(3) Å, *b* = 10.6058(4) Å, *c* = 10.8789(4) Å, β = 104.755(1), *V* = 949.66(6) Å^3, *Z* = 2, D_x = 1.502 Mg m^{-3}, colorless prism of dimensions 0.73 × 0.51 × 0.49 mm, multi-scan absorption correction (μ = 0.12 mm^{-1}) T_{min} = 0.919, T_{max} = 0.945; a total of 7547 measured reflections (θ_{max} = 27.5°), from which 3782 were unique (R_{int} = 0.017) and 3553 observed according to the $I > 2\sigma(I)$ criterion. The refine-

ment converged (Δ/σ_{max} = 0.001) to R = 0.032 for observed reflections and $wR(F^2)$ = 0.085, GOF = 1.06 for 282 parameters and all 3782 reflections. The final difference Fourier map displayed no peaks of chemical significance ($\Delta\varrho_{max}$ = 0.18, $\Delta\varrho_{min}$ = –0.21 e Å^{-3}). For the assignment of absolute configuration the known chirality on C-5, C-9 and C-13 carbons was used. The displacement ellipsoids are drawn on 30 % probability level. There is a hydrogen bond between MeOH and the C-6 carbonyl oxygen [O–O distance 2.807(2) Å, angle at H 172.00°]. CCDC 1446875 (for **12**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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