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Position of Coordination of the Lithium Ion Determines the Regioselectivity of Demethylations of 3,4-Dimethoxymorphinans with L-Selectride

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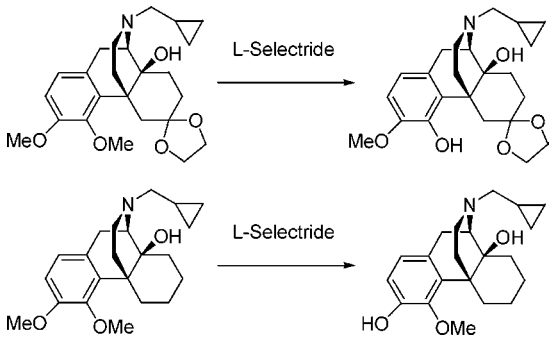
ABSTRACT



L-Selectride is an efficient agent for the 3-O-demethylation of opioids and is known to cleave the least hindered methoxyl group in a molecule. The treatment of a 3,4-dimethoxymorphinan containing a 6-ketal with L-Selectride gave selective 4-O-demethylation, rather than cleavage of the less hindered 3-methoxyl. In contrast, a 3,4-dimethoxymorphinan lacking a 6-ketal gave selective 3-O-demethylation, suggesting that the regiochemistry of L-Selectride-mediated O-demethylation can be manipulated through altering the position of coordination of the lithium ion.

The presence of a 3-phenolic group such as that present in 4,5-epoxymorphinan (morphine) (**1**) (Figure 1) has generally been considered essential for high-potency opioid analgesics.[1] The corresponding morphinan 4-phenols have been shown to possess lower potency as analgesics,[2] and this has been attributed to their lower affinity at μ-opioid receptors through a combination of the undesirable 4-phenol and 3-methoxyl groups.[3] Recent studies have refocused on morphinan 4-phenols,[4,5] on the basis of the hypothesis that the introduction

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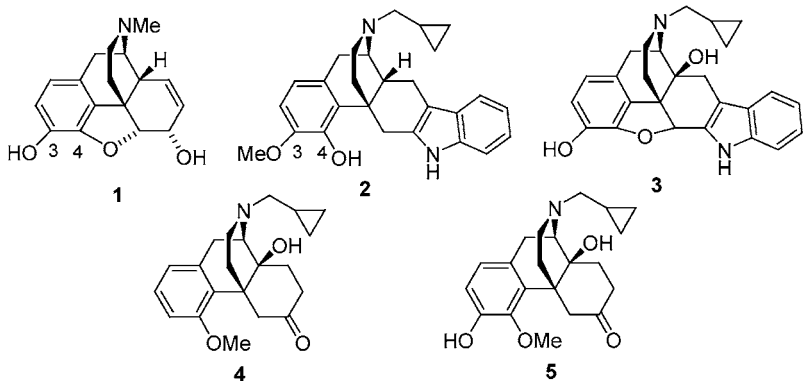

Figure 1. Structures of important 4,5-epoxymorphinans and 4-substituted morphinans.

of a 4-phenol and 3-methyl ether might prove to be an attractive approach to reduce μ-affinity in opioids to achieve greater selectivity for the other opioid receptors (κ and δ). We showed that the introduction of a 4-phenol into the indolomorphinan series of compounds led to **2** (Figure 1), a compound with low μ-affinity and vastly greater δ-selectivity than the indoloepoxymorphinan naltrindole (**3**).[5] It was found during the course of these studies that 4-phenolic morphinans appear to be quite prone to oxidation,[5] and it was considered that this property may prove to be problematic for the development of 4-phenolic indolomorphinan-based therapeutic agents.

In addition to the problems with oxidation, the pharmacology of the 4-phenolic indolomorphinans cannot be directly compared to the 4,5-oxygen-bridged compounds (indoloepoxymorphinans) due to the fact that opening the bridge changes the conformation of the opioid skeleton.[5] Thus, to further investigate this series of compounds and the effects of conformational change on pharmacological activity, it was necessary to prepare morphinan analogues that do not have a 4-phenolic group such as 3,4-dimethoxy- and 3-hydroxy-4-methoxy-substituted indolomorphinans. The preparation of 3,4-dimethoxy-substituted morphinans has been previously reported by methylating 4-phenols with trimethylphenylammonium chloride.[6] 3-Hydroxy-4-methoxy-substituted morphinans have received less attention but were prepared as analogues of cyprodime (**4**).[7] Compounds such as **5** were prepared through benzylation of the 3-phenol of a morphinan, ring opening to give the 4-phenol, and methylation of the 4-phenol, followed by debenzylation to the desired substitution.

As both 3,4-dimethoxy- and 3-hydroxy-4-methoxy-substituted analogues are potentially of interest, it was considered that a direct, selective method of cleaving the 3-methyl ether in the presence of a 4-methyl ether would offer significant advantages in terms of less synthetic steps. Although the 3-ether appears to be less hindered, as the 4-ether is ortho to a tertiary carbon atom, the selective removal of the 3-methyl ether has not been previously reported. In fact, treatment under the standard thiolate demethylation conditions has been reported to give selective 4-O-demethylation.[8] This result remains to be satisfactorily explained, as thiolate would be expected to react with the least hindered methoxyl group. L-Selectride has previously been shown to efficiently 3-O-demethylate a range of opioids to give the corresponding 3-phenols,[9] and it is known that the selectivity of this bulky reagent is dominated by steric factors.[10] We considered that a similar reaction on 3,4-dimethoxymorphinans (such as **8**) would lead to lithium coordination to both the 3- and 4-oxygens and yield selective 3-O-demethylation due to the greater steric hindrance of the 4-methyl ether by the ortho tertiary carbon atom.

Naltrexone was converted to its 3-methyl ether, followed by ring opening using methods previously reported by ourselves to give **6**.[5] Methylation of the 4-phenol of **6** with trimethylphenylammonium chloride under standard conditions[6] gave only water-soluble material (Scheme 1). Mass spectral analysis of the material indicated that formation of quaternary nitrogen salts was a major competing reaction, and in our hands, it dominated over the desired 4-O-methylation. We thus turned to trimethylsilyldiazomethane ($TMS-CHN_2$), which methylates 3-phenolic opioids,[11] and found that it cleanly methylated the 4-phenol to give **7** (Scheme 1) in 89% yield. The use of $TMS-CHN_2$ to methylate 4-phenols of opioids is therefore an attractive

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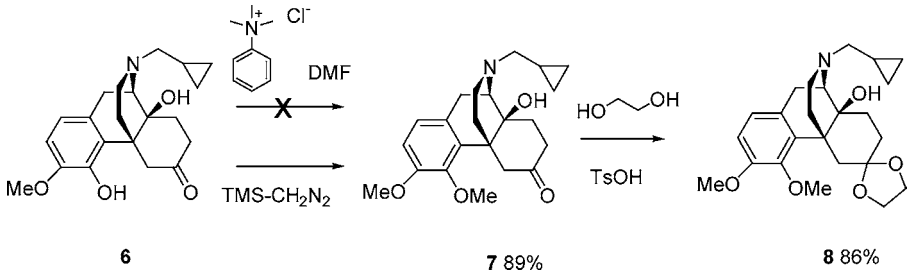
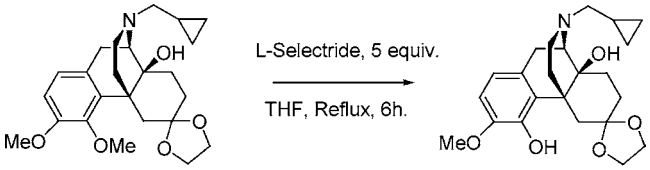
Scheme 1. Formation of the Protected 3,4-Dimethoxymorphinan **8**



alternative to the use of quaternary salts for the laboratory preparation of 4-methyl ethers. The 6-ketone of **7** was subsequently protected as the ethylene ketal to give the desired compound (**8**).

Treatment of **8** with L-Selectride at reflux for 6 h gave rise to a single product by TLC in 91% yield. The product was shown to give a positive blue result to Gibbs' Reagent,[12] indicating a phenol with no para substituent (Scheme 2). A

Scheme 2. 4-O-Demethylation of the 3,4-Dimethoxymorphinan **8**



phenol was confirmed by NMR, as only one methoxyl signal was observed at 3.85 ppm, and acidic hydrolysis of **9** confirmed 4-O-demethylation, as the ketone product was identical to **6**. Thus, selective 4-O-demethylation had occurred to give **9**, which is consistent with the results of Rapoport, who obtained selective 4-O-demethylation with a similar compound on treatment with thiolate,[8] but different from our expectations due to the tertiary carbon atom ortho to the 4-methoxyl group.

To understand the course of the demethylation reaction, compound **8** was studied using molecular modeling. Model building, followed by molecular dynamics and energy minimization via both force field and quantum mechanical methods, yielded structures in qualitative agreement with an X-ray crystal structure of **8** (see Supporting Information for full details of computational methods and results and for the X-ray structure of **8**). Solvent accessibilities, a measure of steric hindrance, indicated that the 3-OCH_3 was indeed more accessible than the 4-OCH_3. Bond lengths and angles, a measure of bond strain, were not much different between the methoxyls. As L-Selectride O-demethylation occurs through the formation of a lithium complex with the ether demethylated and an ortho ether,[10] similar calculations were performed on an intermediate (**10**) (Figure 2) with a lithium ion complexed between the 3- and 4-oxygens. As with the uncomplexed species (**8**), the 4-OMe was less accessible than the 3-OMe.

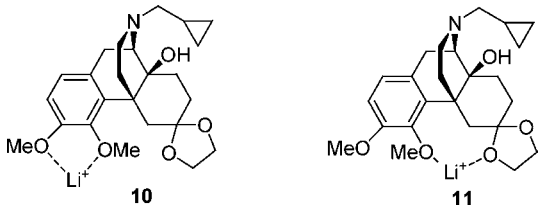


Figure 2. Possible lithium complexes of **8**.

The modeling results are consistent with our original hypothesis that 3-O-demethylation should be preferred on steric grounds and led us to reconsider the proposed mechanism of coordination of the lithium ion to both the 3- and 4-oxygen atoms. We considered that coordination of the lithium may be occurring at the 6-ketal oxygens and 4-OCH_3 as shown in structure **11** (Figure 2). Modeling studies (See Supporting Information) showed that such a complex is favored energetically over the corresponding 3,4-complex, and such a compound would be expected to demethylate only at the activated 4-ether.

A 3,4-dimethoxymorphinan (**15**) was prepared lacking oxygen functions at C-6 as shown in Scheme 3. Naltrexone-3-methyl (**12**)[5] ether was treated under Wolff−Kishner conditions[13] to give **13**, followed by catalytic reduction of the double bond to give the 6-unsubstituted 4-phenol **14**, and methylation with TMS−CHN_2 gave the desired product **15**. Treatment of **15** with L-Selectride led to a slow reaction in THF, and the reaction did not proceed until the solvent was changed to refluxing toluene to finally result in 3-O-demethylation to give **16** (Scheme 3); the balance of material being polar decomposition products. The slower reaction in this case suggests that the lithium ion does not coordinate well between the 3- and 4-methoxyl groups and explains why only product resulting from coordination of the 4-methoxyl and the 6-ketal was observed in the O-demethylation reaction of **8**. These results also offer an explanation for the

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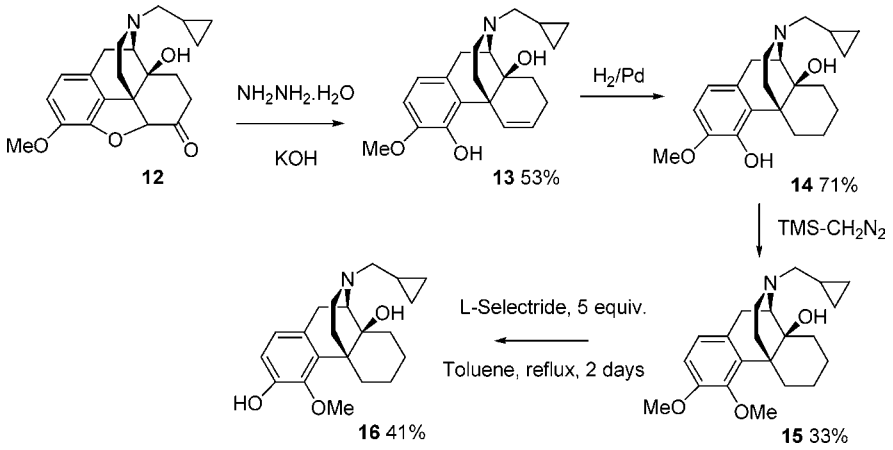
Scheme 3. Formation and O-Demethylation Reaction of 6-Unsubstituted **15**



unexpected 4-O-demethylation previously reported with thiolate,[8] as the substrate in that case possessed a ketone at the 6-position that could chelate to the sodium ion along with the 4-methoxyl oxygen atom.

These studies clearly indicate that the regioselectivity of the reaction can be modified through removing the ketal substituent and suggest that the regiochemistry of L-Selectride-mediated O-demethylation is often governed by sterics but that the regiochemistry can be modified through the introduction of additional substituents that cause different coordination positions of the lithium ion.

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Supporting Information Available: ^{1}H NMR spectra of compounds **7**−**9** and **13**−**16**, synthetic experimental methods, molecular modeling data showing the differences between the two methoxyl groups of **8** and complexes **10** and **11**, and an X-ray crystallographic structure and crystallographic information file of **8** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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