DIRECT AND SIMPLE CONVERSION OF CODEINE TO THEBAINONE-A AND DIHYDROTHEBAINONE

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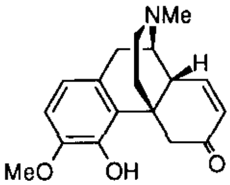
Abstract - Codeine can be rearranged directly to thebainone-A in 74% yield by treatment with BuLi. Hydrogenation of the crude material followed by crystallization as the hydrochloride salt leads to dihydrothebainone in 78% yield.

For our studies into morphinan analogs of the delta selective opioid ligand naltrindole[1,2] we required multigram quantities of thebainone-A (**1**); simple reduction gives dihydrothebainone (**2**), a key intermediate in the synthesis of the morphinans. Although **1** can be prepared from thebaine (**3**) by sodium/liquid ammonia reductive ring opening followed by acid hydrolysis,[3] the hydrolysis step is complicated and gives moderate yields due to formation of the B/C-trans isomer (**4**).[4] The recent publication by Davidson and Gregg[5] demonstrating an improved yield for this hydrolysis step (52%), prompted us to disclose our own work on the direct conversion of codeine (**5**) to **1**.



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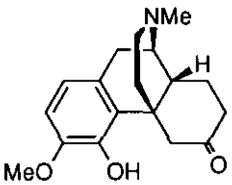

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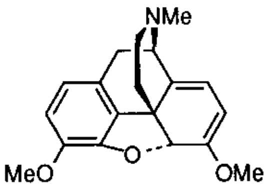

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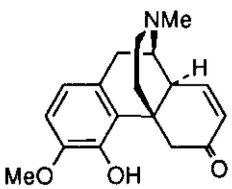

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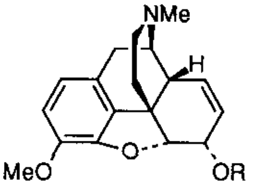
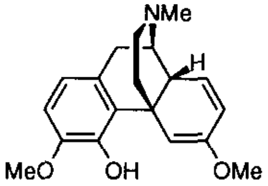
The modest yield for the hydrolysis step, coupled with the low natural abundance of **3** in opium[6] led us to consider the use of the more available opiate codeine (**5**). It has previously been shown that oxidation of the 6-hydroxyl group, followed by Zn/NH_4Cl reductive ring opening, gives good yields of **1**.[7] Obviously, the fact that **1** and **5** are at the same oxidation state raises the possibility that this transformation could be performed without the need for the oxidation/reduction sequence. Indeed, it has been shown that treatment of **5** with palladium under acidic conditions can lead directly to low yields of **1**,[8] demonstrating that a direct isomerization is possible. In addition, it is also known that codeine-6-methyl ether (**6**) can be rearranged to enol ether (**7**) by treatment with NaOEt at 100°C.[3]



5 R = H
6 R = Me



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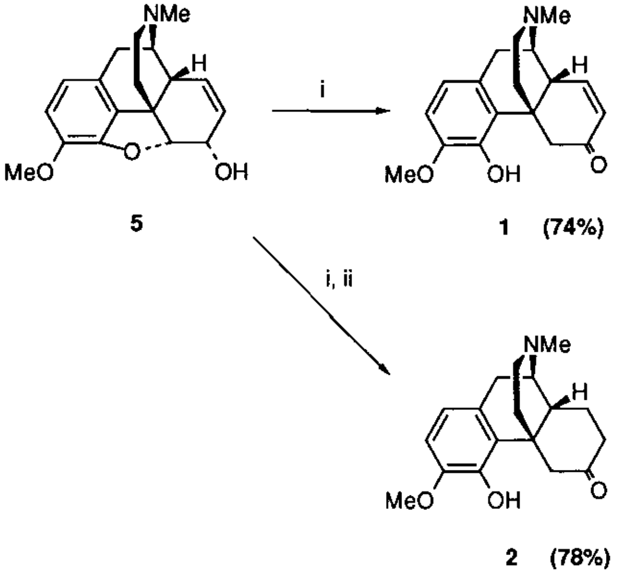
It occurred to us that the mechanism of the latter reaction probably proceeds through an E1cB type elimination through deprotonation at C-6, and that by the use of a strong lithium base, **5** may also undergo the same elimination reaction *via* dilithio species (**8**) to give **9**. Simple aqueous quenching would lead directly to **1**. Indeed, certain simple allylic alcohols have been shown to undergo reactions *via* such dilithiated intermediates when treated with BuLi, although the reaction does generally give products from addition of the butyl group to the double bond.[9]

8 **9**

In order to investigate the course of reaction with **5** we initially studied the treatment of **6** with BuLi, in order to determine if this base is capable of rendering the rearrangement without the complication of the 6-alkoxide group. It was found that the treatment of **6** with 1 equivalent of BuLi at -78°C in THF gave rise to a smooth conversion to enol ether (**7**) in 85% yield,[10] a useful alternative to the traditional harsh conditions, and this demonstrated that BuLi is indeed capable of rendering the desired rearrangement.

With this methodology in place, we turned our attention to codeine itself. As expected, it was found that the deprotonation of the 6-position did not proceed as readily as in **6** because of the presence of the adjoining 6-alkoxide group. Treatment of **5** with 2.2 equivalents of BuLi at -78°C led to unchanged starting material, however on warming to 0°C an intense red solution resulted. Quenching of the rapidly stirred solution with water[11] gave rise to almost pure thebainone-A, only a very minor quantity of butyl addition product was observed. Column chromatography yielded **1** (74%),[12] but it was found that catalytic hydrogenation of the crude product led smoothly to dihydrothebainone (**2**) which could be purified through the hydrochloride salt (78%) thus removing the need for chromatography.



(i) 2.2 eq. BuLi, -78-0°C, THF; (ii) H_2, Pd/C (10%), AcOH

This procedure represents a simple and practical method for the preparation of gram quantities of **1** and **2** from readily available codeine. Although we have invoked a dilithiated species such as proposed by Crandall and Clark,[9] the actual mechanism of this rearrangement has yet to be determined.[13] Further studies into the scope and mechanism of this rather unique reaction are currently underway.

ACKNOWLEDGEMENTS

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8. U. Weiss and N. Weiner, *J. Org. Chem.*, 1949, **14**, 194.
9. J. K. Crandall and A. C. Clark, *J. Org. Chem.*, 1972, **37**, 4236.
10. Structure confirmed by comparison to an authentic sample prepared following the procedure in reference 3, and by acidic hydrolysis to thebainone-A (87%).
11. Quenching with aqueous NH_4Cl led to lower yields of **1** and increased amounts of polar colored material.
12. Spectra identical to an authentic sample prepared following the procedure in reference 3.
13. An E2 type elimination or a mechanism involving radical species could also be invoked.

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