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Access to 7β-analogs of codeine with mixed μ/δ agonist activity via 6,7-α-epoxide opening

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ABSTRACT

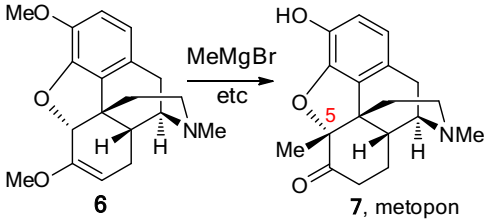
(−)-Codeine **1** was converted into previously unknown 7β-methyl-7,8-dihydrocodeine/morphine derivatives such as **13** via classical diaxial opening of α-epoxide **3**. Several analogs exhibited dual μ/δ-agonist activity.

(−)-Codeine **1** and (−)-morphine **2** have occupied a central place in analgesia for centuries, long before their structures were known.[1,2] Established side effects associated with these drugs are nausea, vomiting, constipation, sedation, respiratory depression, tolerance, and addiction.[3] However, due to inefficacy of non-opioid pathways for treatment of moderate to severe pain it is imperative to develop opioids with significantly greater therapeutic index.

In 1936, Small reported the reaction of dihydrothebaine **6** with MeMgBr to give a mixture of compounds, one of which was converted to **7**, and subsequently referred to as metopon (Scheme 1).[4] The structure of metopon was only hypothesized at that time. In 1953, Stork established the structure indirectly,[5] and in 1982 it was confirmed by Gates following its synthesis and X-ray analysis of a derivative.[6] Until the discovery of metopon, it was assumed that an increase in analgesic potency inevitably resulted in increased side effects. However, in vitro, metopon is approximately threefold *more* potent than morphine, but exhibits *less* respiratory depression and development of tolerance.[7] Due to the absence of a viable large scale synthetic route to metopon its widespread utilization never materialized.[7e,8] Presumably, the structural feature of metopon that endows it with greater therapeutic index than morphine is the methyl group on the β-face at C5. Without the C5-methyl, the compound is hydromorphone with the usual opioid side effects.

In 2009 we reported a synthesis of (±)-codeine **1** [and thereby (±)-morphine **2**] using a new strategy for this class of natural products that involved *para*-phenolic alkylation to form a key cross-conjugated 2,5-cyclohexadienone.[9] An intermediate in the subsequent reaction sequence, the 6,7-alkene **5**,[10] was converted into the 6,7-α-epoxide **3** via bromohydrin **4**, circumventing the usual stereochemical correction of the *sec*-hydroxyl group at the 6-position (Scheme 2).[11] The 6,7-α-epoxide **3** provides access to unknown 7β-substituted derivatives through diaxial opening with nucleophiles at C7. Additionally, manipulation of the resultant hydroxyl group at C6 and the bromine at C1 provides three handles for the application of structure–activity studies and optimization of pharmacological properties.

Since the total synthesis of the key intermediate 6,7-α-epoxide **3** is racemic, it was decided to explore the conversion of naturally occurring, enantio-enriched (−)-codeine into **5** (suggested by J.W.C.). This would allow the generation of enantio-enriched analogs. Furthermore, the envisioned route would obviate the need to use the racemic synthesis we reported in 2009, thereby reducing the number of steps to the epoxide from 13 to 4.



Scheme 1.

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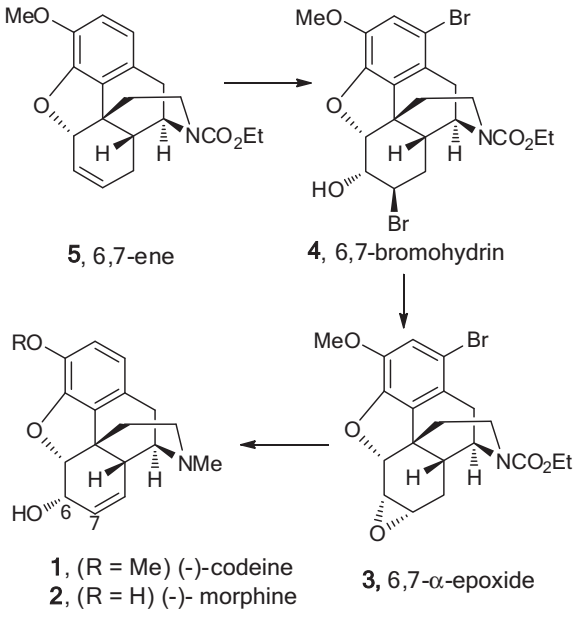
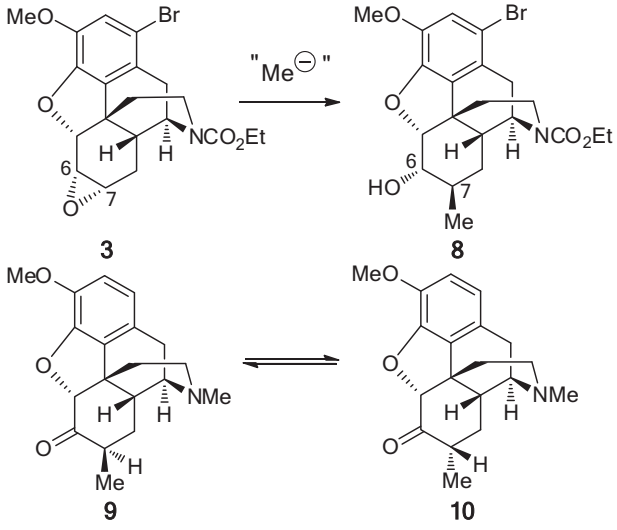


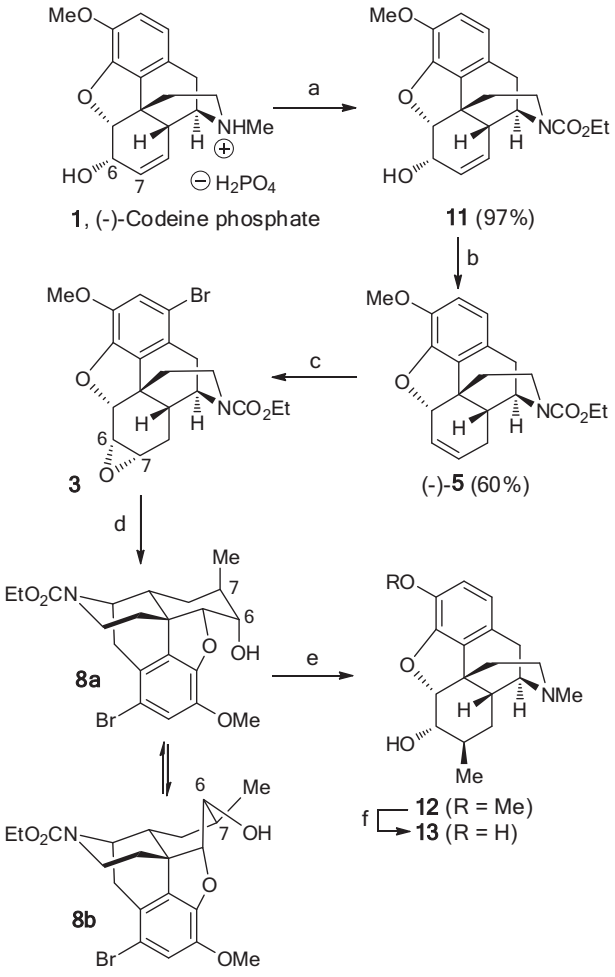
Scheme 2.



Scheme 3.

Synthetic efforts were primarily directed at representative analogs involving each of the three handles. As an entrée, the reaction of the 6,7-α-epoxide **3** with a methyl nucleophile at C7 (diaxial opening) to give **8** was pursued. It was anticipated that 7β-methyl-7,8-dihydrocodeinone **9** could readily epimerize to give the thermodynamically more stable and *biologically inactive* 7α-epimer **10**.[12a,13] Thus, a chief advantage of the α-epoxide opening strategy is that it fixes the incoming nucleophile on the more exposed β-face (Scheme 3).

(−)-Codeine **1** (as its phosphate salt) was converted into the carbamate **11** following literature procedures[14] (Scheme 4). Treatment of **11** with DEAD/PPh_3/NMM/NBSH following Myers' protocol[15] for reductive transposition of allylic alcohols, gave the 6,7-alkene **5** as a single enantiomer. Conversion of **5** into **3** proceeded as previously reported.[9] It was found that the epoxide **3** was converted into the bromohydrin **4** in a yield of 90% when treated with MeMgBr via the action of $MgBr_2$ (Schlenk equilibrium).[16] The structure was confirmed by X-ray crystallography demonstrating the



Scheme 4. Reagents and conditions: (a) $ClCO_2Et/K_2CO_3$/reflux (97%); (b) DEAD/PPh3/*o*-nitrobenzenesulfonyl hydrazine (NBSH)/N-methylmorpholine (NMM) (60%); (c) 1,3-dibromo-5,5-dimethylhydantoin, then KOH at 75 °C (50% from **5**); (d) Me_3Al/PhMe/*cat*.H_2O (80%); (e) LAH/THF/0 °C (63%); (f) BBr_3/DCM/23 °C (43%).

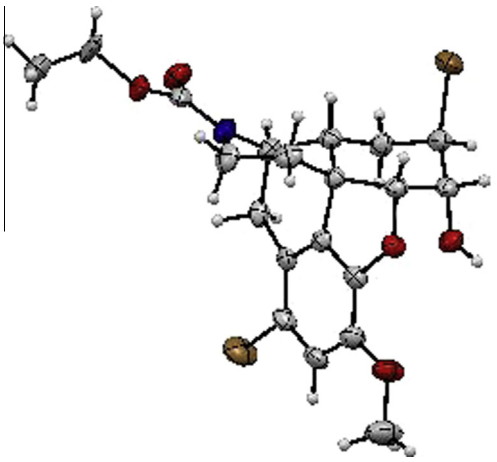


Figure 1.

diaxial relationship of the bromine and the hydroxyl groups (Fig. 1). A similar result was obtained using MeMgCl (chlorohydrin), although the reaction was slower.

Treatment of epoxide **3** with $AlMe_3$/PhMe/H_2O gave **8** with a yield of 80%. In the absence of water the yield of **8** was 40%. Longer