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Enantioselective Synthesis of (−)-Codeine and (−)-Morphine

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The nearly 2 000 years of therapeutic use of opiates has made the active principles and related substances represented by (−)-morphine **1**, (−)-codeine **2**, (−)-thebaine **3** (see Figure 1) as well

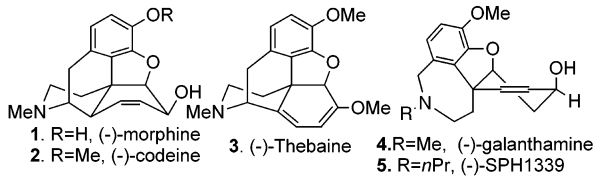


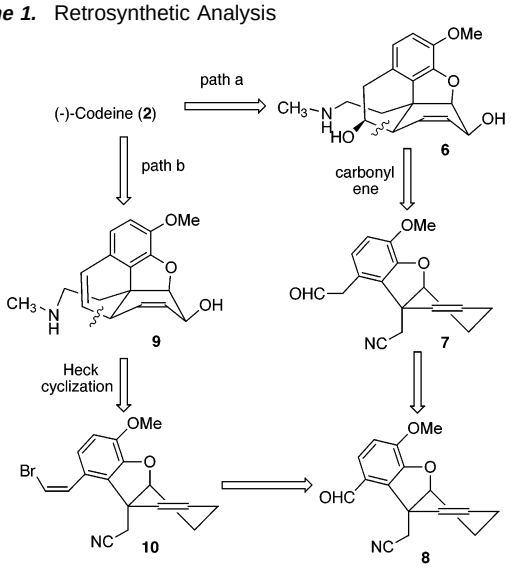
Figure 1. Opium and amaryllidaceae alkaloids.

as simpler morphinan and benzomorphan analogues quintessential targets for synthesis. Even though 2002 is the 50th anniversary of the first synthesis of morphine,[1] interest in developing improved asymmetric total synthetic routes continues[2] because of the broad ranging pharmacological properties and the growing importance of related amaryllidaceae alkaloids such as galanthamine **4** and its analogues such as (−)-SPH 1339 **5**. Despite the extensive synthetic work, only one asymmetric synthesis of galanthamine[3] and two of morphine[4] without using resolution appeared prior to our work.[5] Morphine and galanthamine share the same tricyclic core and, biosynthetically, derive from an oxidative bisphenolic coupling. Previously, we reported an efficient asymmetric total synthesis of galanthamine and its analogue **5**.[6] Herein, we report that both alkaloid families can be accessed synthetically from a common intermediate in which the final ring closure involves a novel intramolecular hydroamination.

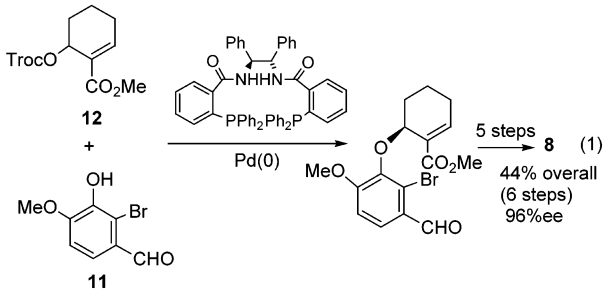
Scheme 1 outlines two strategies based upon formation of the piperidine ring as the final ring-forming event.[7] In path a, a straightforward displacement of amino alcohol **6** envisions formation of the latter via a carbonyl ene reaction of aldehyde **7** which, in turn, may derive by homologation of cyanoaldehyde **8**. Path b outlines a more intriguing, but more speculative, strategy in which the piperidine ring would arise by a hydroamination of amine **9** which, in turn, may derive from Heck vinylation of (*Z*)-vinyl bromide **10**. A simple olefination protocol should allow the latter to derive from the same aldehyde **8**. In our synthesis of galanthamine, we established a practical synthesis of this cyanoaldehyde[6] in only six steps from bromovanillin **11**[8] and the allylic ester **12**[9] which is available in two steps from glutaraldehyde and the Emmons−Wadsworth−Horner reagent (eq 1). Equation 2 outlines the initial efforts based upon path a. Homologation of the aldehyde proceeded uneventfully via rearrangement of an epoxide intermediate. All attempts to effect the intramolecular carbonyl ene reaction to form alcohol **13** failed.

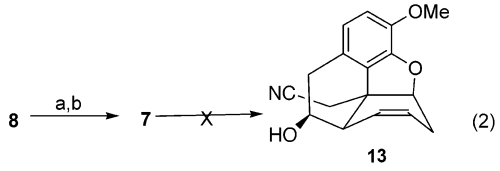
Thwarted in attempts to execute path a, we turned to path b. Olefination[10] followed by chemoselective reduction of the (*E*)-vinyl bromide[11] provided the cyclization substrate **10** (eq 3). Intra-

Scheme 1. Retrosynthetic Analysis

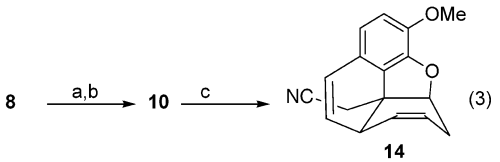


molecular Heck vinylation to the sterically congested neopentyl carbon created the tetracycle **14** in good yield under the same conditions used for the Heck reaction in the synthesis of precursor **8**.[6]





a. $(CH_3)_3S^+ \ ^-O_3SOCH_3$, NaOH, CH_2Cl_2, 81%. b. $BF_3{\bullet}OEt_2$, THF 78%.



a. CBr_4, Ph_3P, CH_2Cl_2, 91%. b. 5%$Pd(PPh_3)_4$, nBu_3SnH, $PhCH_3$, 88%. c. 15% $Pd(OAc)_2$, 15% dppp, Ag_2CO_3, $PhCH_3$, 65%. (74%brsm).

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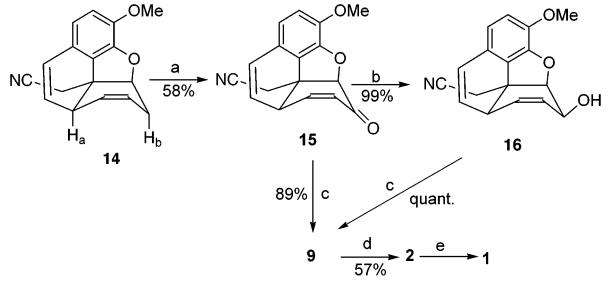
Scheme 2. End Game[a]



[a] (a) SeO_2, dioxane, sand, 75 °C, then DMP, room temperature. (b) DIBAL-H, THF/Et_2O. (c) DIBAL-H, CH_2Cl_2/Et_2O, then NH_4Br, $MeNH_2$, and then $NaBH_4$. (d) LDA/THF with tungsten bulb. (e) See ref 17.

With the skeleton of morphine in hand, attention focused on allylic functionalization (Scheme 2). On the basis of the known conformation of morphine,[12] both H_a and H_b of alkene **14** are stereoelectronically and sterically favored for allylic oxidation. Despite H_a being doubly allylic, its removal with selenium dioxide is clearly strained due to creation of the bridgehead double bond. Indeed, subjecting **14** to this reagent only involves abstraction of H_b to give the corresponding alcohol accompanied by the over-oxidation product ketone **15**. Directly adding the Dess−Martin periodinane to the reaction mixture prior to workup allowed the ketone **15** to be isolated in 58% yield. Its reduction proceeded stereoselectively with DIBAL-H in THF-ether to give the required alcohol **16** almost quantitatively. No reaction of the nitrile was observed in this solvent system. Furthermore, none of alcohol **16** was detected in the initial allylic oxidation.

Adapting a known protocol,[13] the nitrile **16** was converted to the secondary amine **9** in a one pot operation. Switching from THF to methylene chloride allowed nitrile reduction with DIBAL-H to the imine aluminum complex. Addition of ammonium bromide in dry methanol destroyed excess DIBAL-H and freed the imine. Subsequent addition of excess methylamine converted the primary imine to the more stable secondary one. The final stage involved addition of sodium borohydride, wherein amine **9** was obtained quantitatively from alcohol **16**. Performing this same protocol on ketone **15** also converted it to amine **9**, thereby saving one step.

The stage was set for the key speculative last step, an intramolecular hydroamination.[14] Simply treating **9** with LDA or *n*-butyllithium in refluxing THF led to recovered starting material up to 2 h and extensive decomposition after 8 h. With the notion that the addition might be facilitated by single electron transfer,[15] promotion of the latter by irradiation of the basic solution with an ordinary tungsten light bulb was envisioned. Indeed, subjecting the solution of amine **9** and LDA in THF to such irradiation with a 150 W tungsten light bulb led to cycloisomerization to form (−)-codeine whose spectral data are identical to those previously reported.[16] Demethylation as reported by Rice[17] with boron tribromide converts this route into a synthesis of (−)-morphine as well.

From the common intermediate **8**, which required only two steps to convert to (−)-galanthamine, (−)-codeine is now available in six steps and 15.4% overall yield. This very short asymmetric total synthesis arises because of the minimal use of protecting groups. Palladium-catalyzed reactions, asymmetric allylic alkylation (AAA) and two Heck-type reactions, create the entire carbon framework and form four of the five rings. The one pot reduction-transamination-reduction of nitriles significantly shortens the route. Most noteworthy is the effectiveness of the intramolecular hydroamination promoted by visible light − a reaction that should prove more generally useful in alkaloid synthesis. Strategically, the commonality of the amaryllidaceae and opium alkaloids from a chemical synthesis perspective has also now been established.

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Supporting Information Available: Experimental details and analytical data for all new compounds and data for synthetic codeine (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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