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Concise Syntheses of (−)-Galanthamine and (±)-Codeine via Intramolecular Alkylation of a Phenol Derivative

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The amaryllidaceae alkaloid (−)-galanthamine **1**[1] is a potent acetylcholinesterase inhibitor and has found extensive use in the early treatment of Alzheimer's disease, Figure 1.[2] This has caused a renewed interest in the synthesis of **1**, since its extraction from the bulbs of snow drops does not supply sufficient material for the clinical evaluation of early Alzheimer's patients.

The strategies used for the synthesis of **1** are predominantly phenolic oxidation,[3a−n] Heck coupling,[4a−c] and a variety of other ingenious solutions.[5a−j] While there are efficient enantioselective syntheses of **1**, this is not necessary since racemic narwedine **2** undergoes a spontaneous resolution when crystallized in the presence of 1% of (+)-galanthamine[6] [(±)-narwedine is resolved into (−)-narwedine in the presence of 1% (+)-galanthamine]. Reduction of (−)-narwedine with L-Selectride provides (−)-galanthamine (99%). Currently, commercial supplies of **1** are available from Sanochemia AG using the Fröhlich-Jordis[3i−k] route in nine steps and an overall yield of 12%. The key phenolic oxidation coupling reaction proceeds in 40−54% yield.

Since the report by Robinson in 1925 of the structures of codeine **3** and morphine **4**[7] there have been numerous total and formal syntheses of these alkaloids spanning a period of approximately 55 years from 1952 to 2007.[8a,aa,9a−c] Nevertheless, there is no practical synthetic source of these opium alkaloids other than the Rice adaptation of the Grewe strategy.[10]

The chemical feature that connects these two alkaloids is that they are both biosynthesized by *o-p* phenolic oxidation. The biosynthesis of morphine alkaloids is well understood. (*R*)-Reticuline is converted into salutaridine through an enzymatically mediated *o-p* phenolic oxidation.[11,12] Salutaridine is subsequently transformed *in vivo* into codeine **3** and demethylated to give morphine **4**. Similarly, norbelladine undergoes *o-p* coupling to give narwedine **2**, Figure 1. Attempts to mimic this chemistry in the laboratory for the practical production of these important compounds in an efficient and economical manner has not resulted in good yields of **1** or **3**, or related derivatives.

Despite the enormous amount of work devoted to the efficient synthesis of **1** and **3**, the simple *para*-alkylation of an appropriately substituted phenol such as **5** to generate the cross-conjugated 2,5-cyclohexadienone **6** has not been reported, Figure 2.[13] This strategy would avoid the phenolic oxidation reaction, and the product **6** merely requires reductive amination of the aromatic aldehyde and latent aliphatic aldehyde (acetal), either sequentially or in concert, to arrive at racemic narwedine **2**. The C9,10 atoms of **1** are derived from **5**, and similarly the C15,16 atoms of **3** as indicated. The crucial C8 and C13 quaternary atoms in **1** and **3** respectively are established by intramolecular phenol *p*-alkylation. The second synthesis of **4**

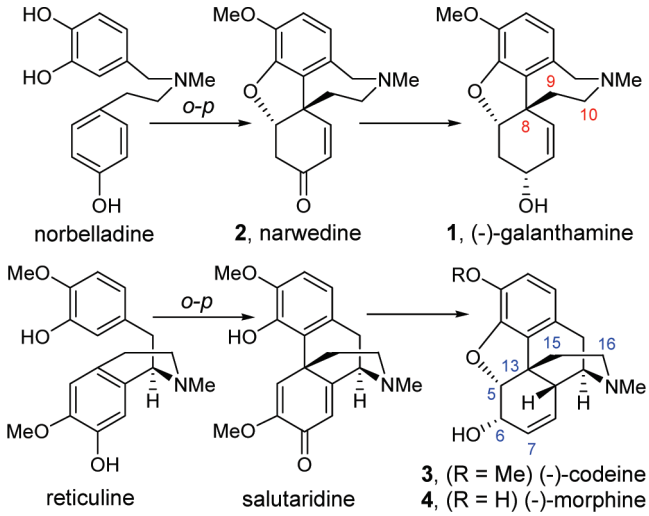


Figure 1. Biogenetic *o,p*-phenolic oxidative coupling of norbelladine and reticuline leading to **2** and salutaridine, and subsequently to **1**, **3**, and **4**.

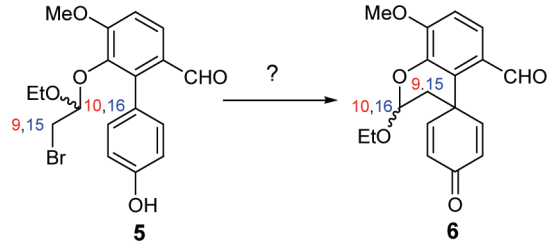


Figure 2. Key intramolecular phenol alkylation.

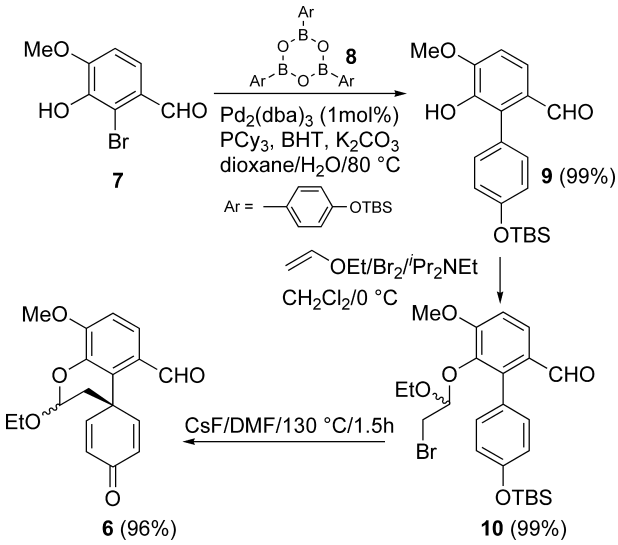
by Ginsburg and Elad established this bond by alkylation of an octahydrophenanthrene derivative.[8b]

Commercially available **7** was coupled to the boronic acid tris anhydride **8** using Suzuki reaction conditions to give **9** (99%), Scheme 1. Treatment of **9** with ethylvinylether/Br_2/*N*,*N*-diisopropylethylamine/CH_2Cl_2 at 0 °C resulted in the ether **10** (99%). Exposure of **10** to CsF (3 equiv) in *N*,*N*-dimethylformamide at 130 °C resulted in a clean transformation into **6** (96%, structure by X-ray), thus confirming the viability of the strategy suggested in Figure 2. The route from **7** to **6** *via* **9** and **10** proceeds in three steps with an overall yield of 94%. It should be noted that racemic **6** is a single compound since the stereochemical relationship between epimers at the C16 lactol is that they are mirror images (axial symmetry of the dienone).

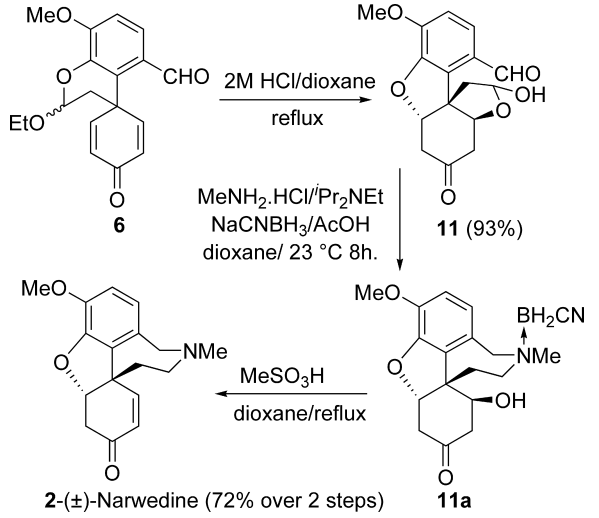
Acid catalyzed hydrolysis of **6** using 2 M HCl in dioxane heated at reflux resulted in **11** (93%, 88% from **7**, structure by X-ray), Scheme 2. Reductive amination of **11** with $MeNH_2 \cdot HCl$ (1.2 equiv)/$^iPr_2NEt$/$NaCNBH_3$ (1.5 equiv)/AcOH (5 equiv) at 23 °C gave **11a**,

† Author for inquires concerning the X-ray data.

Scheme 1. Synthesis of Key Cyclohexadienone **6**



Scheme 2. Synthesis of (±)-Narwedine **2**



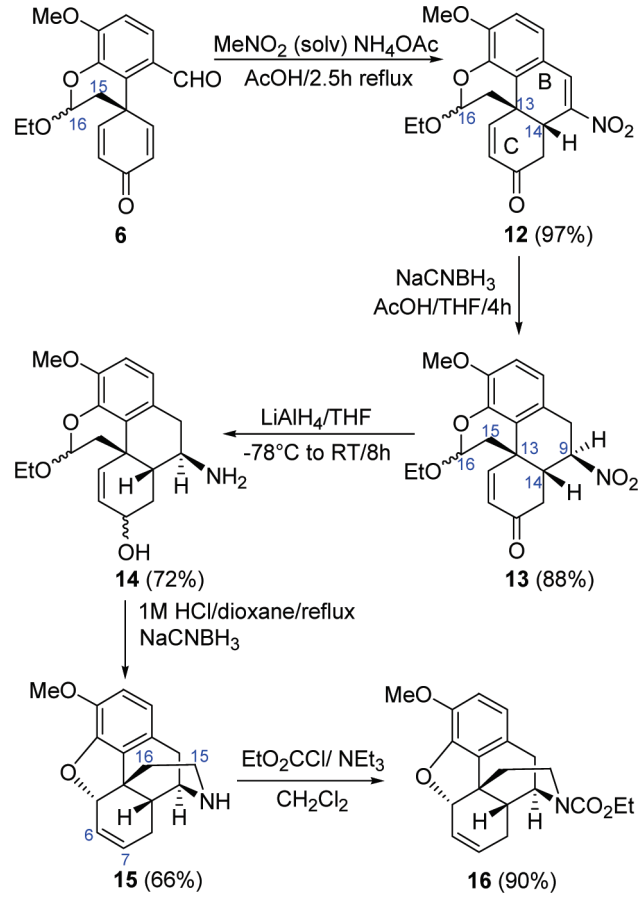
which was converted into (±)-narwedine **2** (72% from **11**) by treatment with 1 M $MeSO_3H$/aqueous dioxane at 80 °C.

Since (±)-narwedine **2** has been converted into (−)-galanthamine **1** by spontaneous resolution followed by L-Selectride reduction in virtually quantitative yield,[6] this completes the synthesis of **1** in eight steps with an overall yield of 63% which is approximately five times the yield of the current commercial process.[3i−k]

Using the same cross-conjugated 2,5-cyclohexadienone **6**, it was treated with nitromethane under standard Henry-aldol reaction conditions resulting in **12** (97%, crude) as a mixture (1:1) of epimers at C-16, Scheme 3. These epimers were characterized by X-ray crystallography. Most importantly, we only observe the correct *cis*-stereochemical relationship between the newly formed B-ring and the C-ring (C-13, 14) in **12**.

Treatment of **12** with sodium cyanoborohydride gave **13** (88%, structure by X-ray). The stereochemistry at C9 is the result of axial protonation of the intermediate nitronate anion. Further reduction of **13** with lithium aluminum hydride gave **14** (72%). Exposure of **14** to reductive amination reaction conditions resulted in compound **15** (66%) which was characterized as the known carbamate derivative **16** from Taber's synthesis of morphine.[8x]

Scheme 3. Formation of the Codeine Skeleton

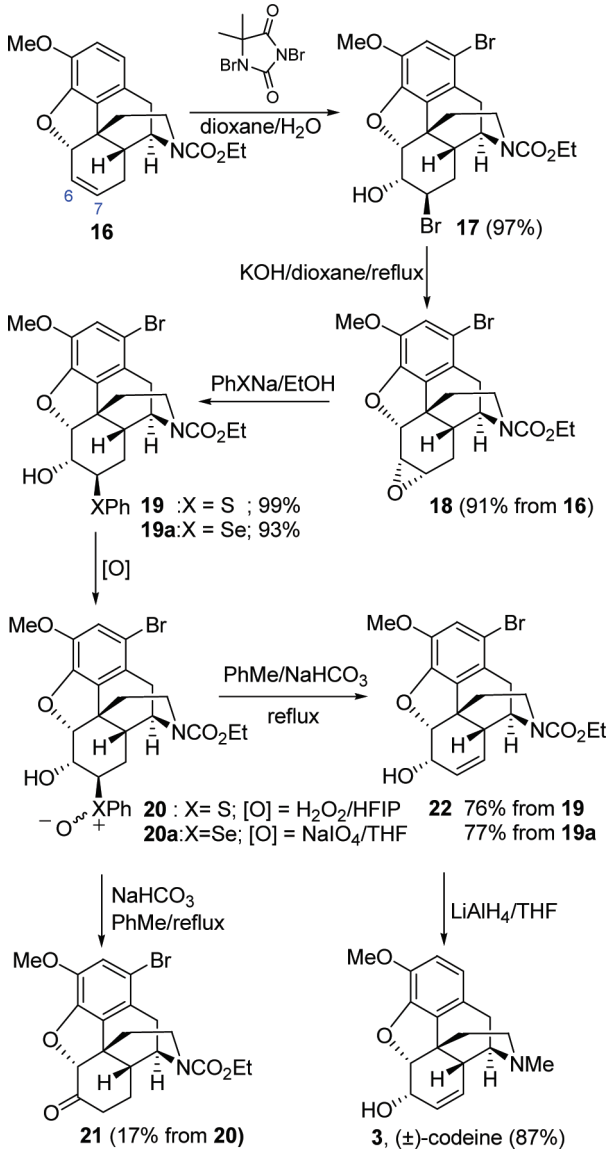


The last phase of the synthesis involves the conversion of **16** into codeine **3**. All the prior literature dealing with this topic involves proceeding *via* codeinone followed by reduction to **3**. The reason for this is that epoxidation of the 6,7-double bond in **16**, and similar substrates, proceeds from the least hindered face to give the β-epoxide, which eventually requires stereochemical inversion at C-6. It seems remarkable that given the vast literature in the codeine-morphine area, there are no reports of the addition of hypohalous acids to the 6,7-double bond. We have found that treatment of **16** with 5,5-dimethyl-1,3-dibromohydantoin gave **17** (concomitant bromination at C2), which on exposure to KOH/dioxane/reflux resulted in the α-epoxide **18** (93%). The 6,7-double bond in **16** forms a β-bromonium ion which upon diaxial opening with water results in the 6,7-diaxial bromohydrin **17**.

Treatment of **18** with PhSNa/EtOH gave **19** (99%), and it was oxidized to a mixture of diastereomeric sulfoxides **20**. Heating the mixture at 110 °C gave **21** (17%) from the minor diastereomer and **22** (76%) from the major diastereomer. The same transformation with the selenium analogue gave **22** (72% over three steps) as the only product. Reduction of **22** with $LiAlH_4$/THF at 25 °C gave codeine **3** (87%).[8a]

The synthesis of (±)-codeine **3** is summarized by the following data. Starting from commercially available 2-bromoisovanillin it takes seven steps to the codeine skeleton **15** in 38% yield. A further six steps converts **15** into **3**. Thus codeine is obtained *via* 13 reaction pots in an overall yield of 20%. We are examining the enantiose-

Scheme 4. Synthesis of (±)-Codeine **3**



lective nitroaldol Henry reaction of **6** (the C16 stereogenic center is subsequently removed) to provide an enantioselective synthesis of **3**.

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Supporting Information Available: Complete experimental details and compound characterization. This information is available free of charge via the Internet at http://pubs.acs.org.

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