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Total Synthesis of (±)-Powelline and (±)-Buphanidrine

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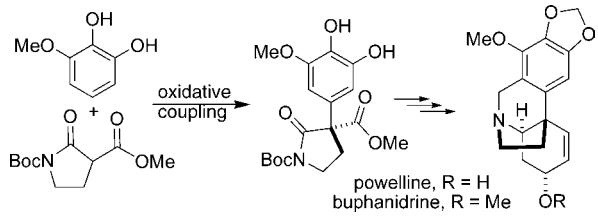
ABSTRACT



The total synthesis of (±)-powelline (13 linear steps in an overall yield of 6%) and (±)-buphanidrine (14 linear steps and a 6% overall yield) and has been achieved using a novel approach to the crinane skeleton. An organocatalytic oxidative coupling allowed direct construction of the key quaternary carbon-to-aryl bond in high yield allowing rapid access to the target alkaloids.

Plants of the Amaryllidaceae family have provided nearly 500 structurally diverse alkaloids that exhibit a broad spectrum of biological activity.[1] Several of the established skeletal structural classes contain a catechol derivative covalently bonded to an all-carbon-quaternary stereogenic center.

Powelline (**1**) and buphanidrine (**2**) have been isolated from several Amaryllidaceae species.[2] Characterized by the 5,10b-ethanophenanthridine crinane skeleton, both contain three stereogenic centers, one of which is quaternary, and differ in the substituent on the allylic alcohol. Both alkaloids have shown affinity for the serotonin transporter in [H3]-citalopram binding assays.[3] Several syntheses of crinine and other related alkaloids have been reported,[4] and similar chemistry has been applied recently in the synthesis of (±)-powelline.[5] To date, no synthesis of buphanidrine has been reported. Construction of the sterically congested arylated quaternary stereogenic center is pivotal to the synthesis of this class of alkaloid, and we believed that these two alkaloids would be ideal targets to showcase our recently reported oxidative coupling methodology for the direct formation of such motifs.[6]

Key to our synthetic plan was the direct catalyzed construction of the quaternary carbon-to-aryl bond via the

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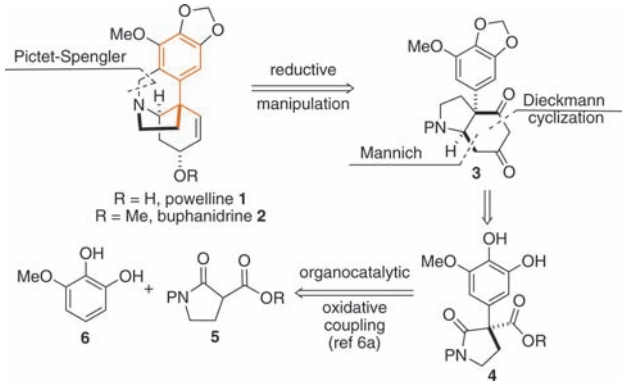
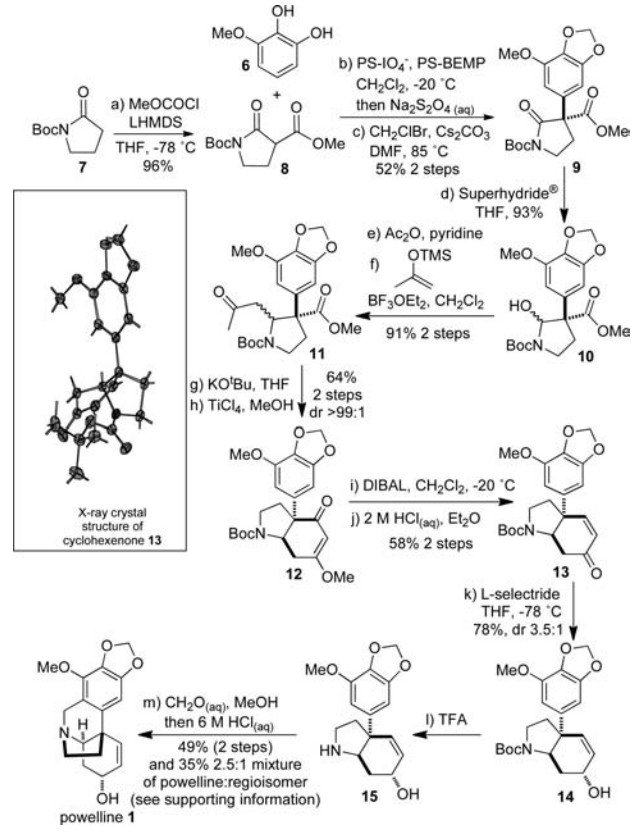
oxidative coupling of readily prepared pro-nucleophile of type **5** and commercially available 3-methoxycatechol **6** (Scheme 1). We envisaged that transformation of **4** to the key cyclohexandione late-stage intermediate **3** common to both targets would be possible via formal reductive homologation followed by Dieckmann-type cyclization. From cyclohexandione **3** reductive manipulation, deprotection and Pictet−Spengler cyclization should provide rapid access to the target alkaloids.

Scheme 1. Synthetic Plan for the Total Synthesis of Powelline and Buphanidrine



In order to heighten the acidity of the pro-nucleophile **5**, an electron-withdrawing protecting group (P = EWG) for the pyrrolidinone was desirable. *N*-Boc was chosen for ease of selective removal at a later stage in the synthesis. Initially, the methyl ester pro-nucleophile **8** was synthesized and reacted with 3-methoxycatechol **6** in the presence of 10 mol % of PS-BEMP and superstoichiometric polymer-supported periodate ($PS\text{-}IO_4^-$).[7] The crude catechol intermediate was not purified but reacted directly with bromochloromethane under standard conditions to give the desired methylenedioxy product **9** in 52% yield over the two steps (Scheme 2).[8]

Scheme 2. Total Synthesis of (±)-Powelline



With the protected oxidative coupling product in hand, we continued the planned synthesis of the key cyclohexandione intermediate of type **3**. A three-carbon homologation of the lactam was required to give the keto-ester **11** substrate ready for the Dieckmann-type cyclization. A chemoselective reduction of the ketonic γ-lactam carbonyl with Superhydride gave aminol **10**. A subsequent acetylation then allowed us to conduct an *N*-acyliminium ion homologation using (isopropenyloxy)trimethylsilane as a nucleophilic trap and $BF_3{\cdot}OEt_2$ as the mediator. The diastereoselectivity in the formation of **11** was dependent upon the reaction solvent and ranged from 3:1 in dichloromethane to 7:1 in acetone. The Dieckmann-type cyclization, mediated by 2.1 equiv of potassium *tert*-butoxide, proceeded smoothly to give the diketone as a single diastereoisomer. Interestingly, none of the other bases screened gave conversion to the desired 5,6-

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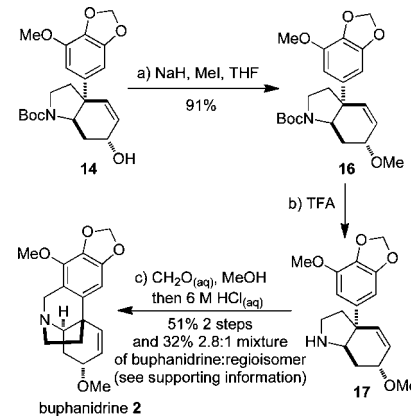
bicycle. Furthermore, the yield and diastereoselectivity of the cyclization step were found to be independent of the diastereomeric ratio of the keto-ester starting material **11**. This is consistent with a rapid and reversible base-catalyzed epimerization process, presumably via retro-Michael/Michael addition, occurring faster than the Dieckmann-type cyclization step to give the cis-fused 5,6-bicyclic diketone. The diketone product (of type **3**) was difficult to handle and so was transformed without purification into methyl enol ether **12**.[9] The DIBAL reduction/acid hydrolysis of alkyl enol ether systems to their enone products is well precedented.[10] However, in THF and toluene the predominant product was that resulting from a competing reaction sequence of 1,4-reduction, elimination of methanol, and a further 1,4-reduction to give a saturated ketone (see the Supporting Information for details). Switching the reaction solvent to dichloromethane significantly reduced the amount of 1,4-reduction product obtained and gave the desired cyclohexenone **13** in 58% yield over two steps. The cis stereochemistry of **13** was unambiguously proven by single-crystal X-ray diffraction (Scheme 2, inset).

In order to convert intermediate **13** into the target alkaloids, a diastereoselective reduction of the cyclohexenone carbonyl was required. Under standard Luche reduction conditions, the desired diastereomer **14** was produced as the *minor* component of a separable 5.5:1 mixture. Mesylation and inversion of the allylic alcohol has been shown to be an effective but lengthy strategy for synthesis of the desired allylic alcohol in related alkaloids.[11] However, when this approach was adopted on our system, loss of the stereochemical integrity of the allylic alcohol was observed. Pleasingly, a screen of reducing agents for **13** showed that L-Selectride efficiently generated the desired diastereomer **14** as the major isomer (3.5:1 dr). NOE studies on both allylic alcohol diastereomers allowed assignment of relative stereochemical configurations. Facile deprotection of the Boc group was accomplished in neat TFA, and the free base of amine **15** was used directly in the final Pictet−Spengler cyclization without purification. Formation of the final ring was readily achieved through reaction with formaldehyde in 6 M HCl at room temperature in 10 min, completing the 13-step total synthesis of (±)-powelline. Gratifyingly, the two possible regioisomers in the Pictet−Spengler reaction were formed with an ∼7:1 ratio in favor of the desired product.[12] The spectroscopic data (^{1}H NMR, ^{13}C NMR) and high-resolution mass spectrometric data of synthetic powelline were consistent with the published data.[13]

For the total synthesis of buphanidrine, allylic alcohol **14** was *O*-methylated under standard conditions and the same deprotection Pictet−Spengler sequence was followed (Scheme 3). Again, the Pictet−Spengler step was found to be regioselective, forming the desired isomer in a ∼10:1 ratio. (±)-Buphanidrine was synthesized in 14 linear steps and a 6% overall yield. The spectroscopic data (^{1}H NMR, ^{13}C NMR) and high-resolution mass spectrometric data of synthetic buphanidrine were in excellent agreement with the published data.[14]

Scheme 3. Total Synthesis of (±)-Buphanidrine



In summary, the total synthesis of (±)-powelline (13 linear steps in an overall yield of 6%) and (±)-buphanidrine (14 linear steps and a 6% overall yield) has been achieved. In a novel approach to the crinane skeleton, an organocatalytic oxidative coupling allowed direct construction of the key quaternary carbon-to-aryl bond in high yield, allowing rapid access to the target alkaloids. Efforts toward an enantioselective total synthesis are ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral data for compounds **8**−**17**, **1**, and **2**, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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