Concise Total Synthesis of (±)-Crinine

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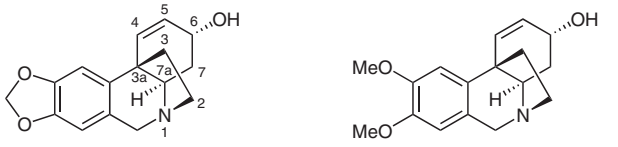
Abstract: The concise total synthesis of (±)-crinine was accomplished in 24% overall yield and eleven steps starting from an easily available allylic alcohol. The key step of the current synthesis involved the NBS-promoted semipinacol rearrangement reaction of allylic alcohols. The hydroindole skeleton with the sterically congested quaternary carbon center was established concisely by utilizing this semipinacol rearrangement followed by a combination of intramolecular aldol and aza-Michael reactions.

Key words: aldol reaction, alkaloids, aza-Michael reaction, semipinacol rearrangement, total synthesis

Crinine-type alkaloids (e.g., **1** and **2** in Figure 1) isolated from *Amaryllidaceae*,[1] which possess a wide range of biological activity,[1a,2] represent an important subclass within the large family of *Amaryllidaceae* alkaloids. Their typical structural feature is the *cis*-arylhydroindole core bearing a crucial all-carbon quaternary center, and the efficient and stereoselective establishment of this core structure is one of the central synthetic challenges in the efficient synthesis of *cis*-arylhydroindole alkaloids.



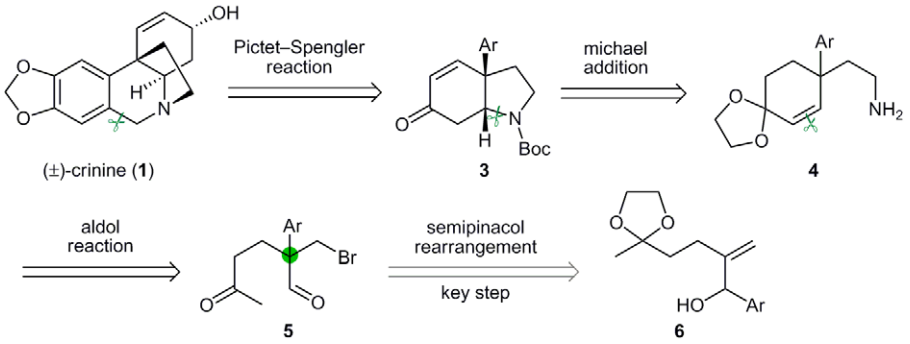
(±)-crinine (**1**) (±)-maritidine (**2**)

Figure 1 Two representative molecules of the crinine-type *Amaryllidaceae* alkaloids

In connection with our current interests on the semipinacol rearrangement of allylic alcohols and its synthetic applications,[3] recently we have further explored its potential in the total synthesis of *Amaryllidaceae* alkaloid crinine.[3e–g] Over the past four decades, several strategies for the synthesis of crinine had been developed to give access to the vital quaternary carbon center, which have included Claisen rearrangement,[4a] aza-cope rearrangement/Mannich cyclization,[4c–e] thermal *N*-vinyl-aziridine rearrangement,[4b] intramolecular [3+2] cycloaddition,[4g] intermolecular [4+2] reaction,[4i] alkylation of carbonyl derivatives,[4f] as well as intramolecular Heck reaction.[4h] Our current total synthesis, however, is distinguished by the application of NBS-promoted semipinacol rearrangement reaction of allylic alcohols. Herein we present our results concerning the concise total synthesis of (±)-crinine.

Our retrosynthetic analysis is shown in Scheme 1. The target molecule **1** could be achieved by methylenation of arylhydroindole enone **3** through Pictet–Spengler cyclization. The construction of the crucial C–N bond in **3** was envisioned by acid-mediated in situ intramolecular aza-Michael addition of primary aliphatic amine **4**. The requisite double bond in **4** could be derived from the intramolecular aldol reaction of dicarbonyl compound **5**. As one of the key steps, the sterically congested quaternary carbon center in **5** could be efficiently established by the NBS-promoted semipinacol rearrangement of allylic alcohol **6**.

Our synthesis commenced with the preparation of allylic alcohol **6** from the commercially available ethyl acetoacetate (**7**). As shown in Scheme 2, the alkylation of the eno-



Scheme 1 Retrosynthetic analysis of (±)-crinine; Ar = 3,4-methylenedioxyphenyl

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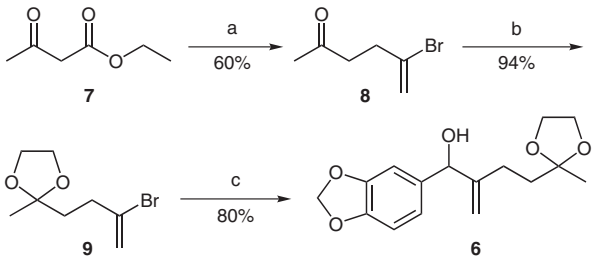
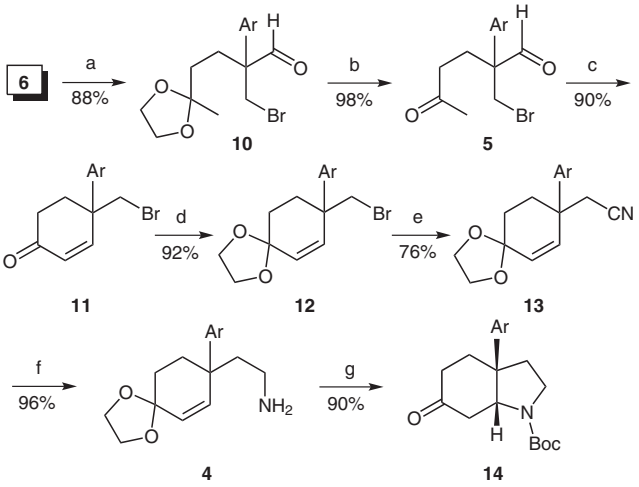
late of **7** with 2,3-dibromopropene and the hydrolysis of the ester followed by the in situ decarboxylation furnished 5-bromo-5-hexen-2-one (**8**).[5] Sequentially, the carbonyl group of **8** was protected with ethylene glycol in the presence of PTSA to give the vinyl bromide **9**. The desired allylic alcohol **6** was readily afforded by lithium–bromide exchange of **9** followed by the addition of piperonal.



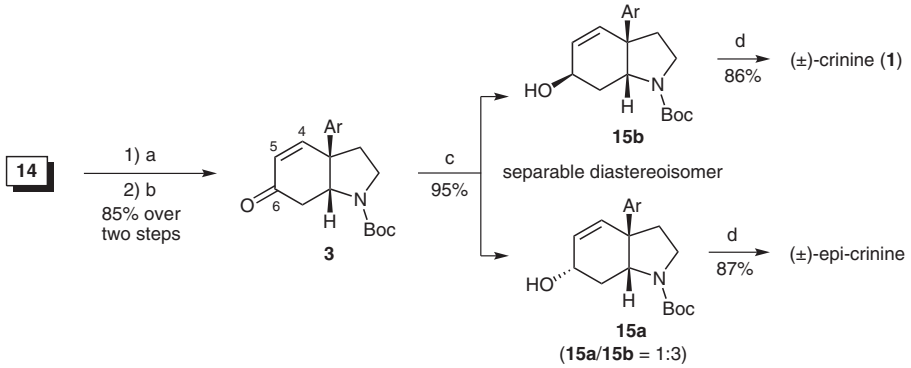
Scheme 2 Preparation of allylic alcohol **6**. *Reagents and conditions*: (a) (i) NaOEt, EtOH, 20 min; (ii) 2,3-dibromopropene, 30 min; (iii) 50% NaOH, reflux, 1 h, then concd HCl, reflux, 2 h; (b) ethylene glycol, PTSA, benzene, reflux, 12 h; (c) (i) *n*-BuLi, THF, –78 °C; (ii) Ar-CHO, THF, –78 °C.

With the allylic alcohol **6** in hand, we then focused on our synthetic efforts towards the construction of the *cis*-arylhydroindole core. According to our proposed synthetic strategy depicted in Scheme 1, allylic alcohol **6** was subjected to the NBS-promoted semipinacol rearrangement protocol, which was recently developed in our group, to stereoselectively deliver the 2-quaternary-1,3-diheteroatom units; the desired 2-quaternary-3-bromoaldehyde **10** was smoothly obtained in 88% yield (Scheme 3). Hydrolysis of the ketal moiety followed by proline-mediated intramolecular aldol reaction furnished the enone **11**. Then the carbonyl of the resulting enone **11** was protected with ethylene glycol to afford the bromide **12**. In order to introduce the amino group, one-carbon homologation by cyanation of the related bromide was conducted;[6] the corresponding cyanide **13** was then reduced with $LiAlH_4$, giving the primary aliphatic amine **4**. Accompanied by the deprotection of the ketal in **4**, the in situ aza-Michael reaction under acidic conditions proceeded smoothly in one pot, yielding the expected *cis*-arylhydroindole **14** after Boc-protection of the resulting secondary amine (Scheme 3).



Scheme 3 Construction of the arylhydroindole skeleton **14**. *Reagents and conditions*: (a) *N*-bromosuccinimide (NBS), acetone, r.t.,10 min; (b) 10% HCl, THF, 12 h; (c) proline, PPTS, MeCN, 40 °C, 12 h; (d) ethylene glycol, PPTS, benzene, reflux, 5 h; (e) NaCN, 18-crown-6, 4 Å MS, DMSO, 80 °C, 2 d; (f) $LiAlH_4$, Et_2O, 0 °C to r.t., 1 h; (g) (i) 10% HCl, THF, reflux, 2 h; (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, r.t., 2 h.

After the expeditious establishment of the *cis*-arylhydroindole skeleton, the installation of the C4=C5 double bond and the total synthesis of (±)-crinine (**1**) were then investigated. As shown in Scheme 4, the regioselective dehydrogenation at C4–C5 of the ketone **14** was readily achieved by LDA-mediated enolization of the carbonyl group and the sequential TMSCl silylation followed by direct $Pd(OAc)_2$-mediated oxidation of the crude resulting silyl enol ethers,[7] furnishing the key intermediate enone **3** in 85% yield over two steps. The subsequent reduction of enone **3** by the bulky reductive reagent L-selectride afforded two separable diastereoisomers **15a** and **15b** (**15a**:**15b** = 1:3) in 95% yield, in which the relative configuration of major isomer **15b** was confirmed by comparison of further cyclization product **1** with the literature.[4g] After removal of the Boc-protecting groups of **15b** and **15a** with TFA, the Pictet–Spengler reaction was conducted in one pot, to readily give the desired (±)-crinine (**1**) and (±)-*epi*-crinine, respectively, in good yields.



Scheme 4 Accomplished total synthesis of (±)-crinine (**1**) and its epimer. *Reagents and conditions*: (a) LDA, TMSCl, THF, –78 °C; (b) $Pd(OAc)_2$, MeCN, r.t., 12 h; (c) L-Selectride, THF, –78 °C, 15 min; (d) TFA, $ClCH_2CH_2Cl$, r.t., 5 h; then 37% aq HCHO, 6*N* HCl, MeOH, 5 h.

In conclusion, an expeditious and concise total synthesis of (±)-crinine (**1**) was accomplished in eleven steps and 24% overall yield starting from the easily available allylic alcohol **6**. The key step in our present total synthesis consists of the NBS-promoted semipinacol rearrangement reaction of allylic alcohols, wherein the construction of the hydroindole nucleus with the crucial quaternary carbon center was achieved by our semipinacol rearrangement protocol followed by the combination of intramolecular aldol and aza-Michael reactions. The current synthesis should demonstrate its value in the synthesis of related alkaloids with the unique quaternary carbon units.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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