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A Zincke aldehyde approach to gelsemine

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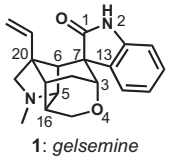
ABSTRACT

We have developed a Zincke-aldehyde-based approach to the complex alkaloid gelsemine. It features a key thermal pericyclic cascade that converts a Zincke aldehyde bearing a pendant alkene into a hydroisoindolone product that shares many structural features with the target molecule. Our efforts to convert these intermediates to gelsemine are also discussed.

Introduction

Gelsemine (**1**), the flagship member of the oxindole alkaloids from plants of the genus *Gelsemium*, has inspired a great deal of activity in chemical synthesis. Completed syntheses have been reported from the groups of Johnson, Speckamp, Hart, Fukuyama, Overman, Danishefsky, and Qin.[1,2] Clever strategies toward gelsemine have been published by the groups of Fleming, Stork, Penkett, Pearson, Aubé, and Simpkins.[3] Gelsemine's interesting topology presents several challenges in assembling the carbon skeleton. Woven throughout the caged, tetracyclic core are two different heteroatoms (N22, O4), seven contiguous stereocenters, two of which are quaternary (C7, C20), and one of which is part of a spiro-fused oxindole moiety (C7). As described by many of those who have worked on gelsemine, its compact and congested nature often leads to undesired reactivity and difficulty in manipulation of sterically hindered functional groups.



1: *gelsemine*

Our research group has used Zincke aldehydes (**5**, Scheme 1), readily available donor–acceptor dienes, for the synthesis of heterocycles and alkaloids, and in cascade reactions to generate complex polycyclic structures.[4] Of particular relevance to the work described herein, we have found that Zincke aldehydes undergo a pericyclic cascade rearrangement to α,β,γ,δ-unsaturated amides (**6** → **7**);[5] furthermore, when the Zincke aldehyde bears a pendant alkene, an intramolecular Diels–Alder reaction ensues (**11** → **12**).[6] In this Letter, we disclose our strategy for a concise synthesis of gelsemine featuring exactly this type pericyclic cascade reaction of a complex Zincke aldehyde.

Synthesis plan

We noticed a structural relationship between compounds of type **12** and the *cis*-fused octahydroisoindole ring system of gelsemine. That connection led to the synthesis strategy shown in Scheme 2. Complex Zincke aldehyde **13** would generate **15** via the type of pericyclic cascade reaction shown in Scheme 1. This key intermediate bears appropriate functionality in the appropriate positions for elaboration to the target. For example, simple redox manipulations would be expected to generate enol ether/iminium ion **16**, Mannich cyclization of which would forge the critical C5–C16 bond.[7] It is even conceivable that a one-pot process could convert **15** into **17** (see below). Finally, the C3–C7 alkene in **17** presents many options for formation of the pyran and the spiro-fused oxindole.

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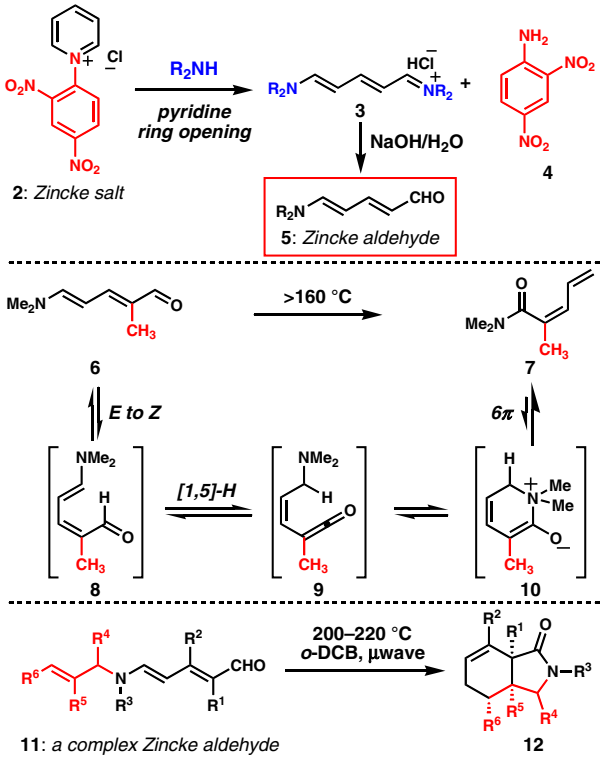
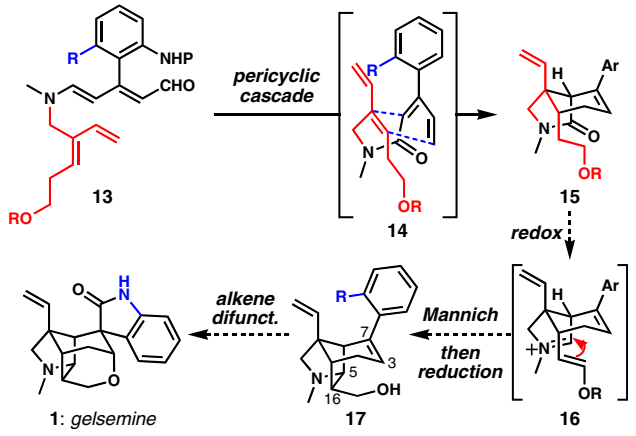


Scheme 1. Synthesis of Zincke aldehydes, and the generation of complex hydroisoindolones of type **12** from rearrangement of Zincke aldehydes derived from unsaturated amines.



Scheme 2. Zincke aldehyde strategy for the synthesis of gelsemine.

Results and discussion

We prepared dienyl amine **23** via sulfolene chemistry related to the work of Nomoto and Takayama (Scheme 3).[8] 3-Bromomethylsulfolene was prepared by bromination of 3-methylsulfolene **18**, the commercially available adduct of isoprene and SO_2. Dehydrobromination led to a dienyl sulfone (not shown), which was not purified. Alkylation of the anion derived from this sulfone was not particularly reliable, but always generated some quantities of **21**, to which the addition of methylamine produced disubstituted sulfolene **22** in high yield. Nearly quantitative conversion to diene **23** was achieved by chelotropic extrusion under microwave irradiation. Although the alkylation step to produce **21** was capricious, we do find that the overall strategy is attractive for the stereoselective generation of highly functionalized trisubstituted alkenes such as **23**.

Secondary amine **23** was used to open the Zincke pyridinium salt derived from 4-phenylpyridine. The resulting Zincke aldehyde was formed in 85% based on the consumption of **24**; the unfortunate need for 2 equiv of complex amine in the ring-opening process was mitigated by the efficient recovery of the second equivalent. Zincke aldehyde **25** was heated to effect the key pericyclic cascade reaction, which smoothly delivered *cis*-fused bicyclic lactam **26** as a single diastereomer in 82% yield. Only traces of the hydroisoquinolone isomer derived from cycloaddition to the monosubstituted alkene were observed. As productive as this reaction is, we were interested in the idea of starting from a Zincke aldehyde bearing the diene still masked as sulfolene. Ring-opening of Zincke salt **24** with secondary amine **22** provided **28** in good yield, although recovery of excess **22** was hindered by its solubility in water. Upon thermolysis, this complex Zincke aldehyde also converted to bicyclic lactam **26** in reasonable yield, as determined by NMR spectroscopy. Although the sequence proceeding via **23** is preferred for preparative purposes, we found the pericyclic cascade reaction of **28** fascinating because it incorporates one of each of the four classes of pericyclic reactions: (1) chelotropic extrusion of SO_2; (2) [1,5]-sigmatropic shift of a hydrogen atom; (3) a 6-π electrocyclic ring-opening reaction; and (4) an intramolecular Diels–Alder cycloaddition reaction (see Schemes 1 and 2 for steps in detail).

Because of the straightforward nature of the synthesis, and in spite of the liabilities already described, we could obtain gram quantities of bicyclic lactam **26** for further elaborations toward gelsemine. The next projected stage of the synthesis was the formation of the C5–C16 bond via Mannich type cyclizations, the likes of which were used in several previous gelsemine syntheses.[1b,c,f] Our hope was to engage the proximal lactam carbonyl and pendant silyl ether of compounds of general type **15** in a redox cascade terminating in a Mannich reaction, as shown in Scheme 4.[9] Lactam activation could trigger intramolecular hydride transfer to the highly electrophilic halomethylene iminium ion in **29**;[10] expulsion of the leaving group would regenerate an iminium ion. The oxocarbenium ion that results from hydride transfer would then suffer deprotonation to make the enoxysilane in **16**, which would be poised for C5–C16 bond formation. A more stepwise route would involve generation of the enoxysilane **30**, after which lactam reduction might lead to subsequent Mannich cyclization. Unfortunately, all attempts to engage the lactam carbonyl in intermediates of type **15**, of the corresponding TIPS enol ether of type **30**, or of closely related structures were unsuccessful. We were not able to activate these lactams with any of a broad range of electrophilic reagents; the only identifiable products obtained under forcing conditions were derived from conjugation of the C3–C7 alkene with the lactam. We were equally unable to observe any clean and productive reactivity under conditions designed to reduce the lactam carbonyl. We do not understand the origins of the unusual lack of reactivity of these lactams.

With a plan to defer C5–C16 bond formation to a later point in the synthesis, we focused on the pyran and spiro-oxindole motifs. Although most of our strategies for oxindole formation relied on the inclusion of a functional group on the *ortho* position of the phenyl substituent in compounds related to **26**, we knew of at least one possibility by which modern methods for arene C–H activation might permit the productive use of the naked phenyl group (Scheme 5). Yu's conditions for oxindole formation from *O*-methyl hydroxamic acids[11] appeared to be a perfect solution to convert a late-stage intermediate of type **32** directly into gelseverine (**33**), an alkaloid one oxidation state higher than gelsemine. Presuming that the hydroxamic acid or a precursor functional group might be introduced in the same operation as the C3–O4 bond, we put