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Total synthesis of gelsemoxonine*

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Abstract: The first total synthesis of gelsemoxonine has been accomplished. A divinylcyclopropane–cycloheptadiene rearrangement of the highly functionalized substrate successfully assembled the spiro-quaternary carbon center connected to the bicyclic seven-membered core structure. A one-pot isomerization reaction of the α,β-unsaturated aldehyde to the saturated ester via a trimethylsilyl cyanide–diazabicycloundecene (TMSCN–DBU) reagent combination allowed a facile and diastereoselective introduction of the latent nitrogen functionality in the unique azetidine moiety.

Keywords: alkaloid synthesis; gelsemium alkaloids; gelsemoxonine; organic synthesis; redox reactivity; total synthesis.

Gelsemium alkaloids occupy a relatively large portion within the monoterpenoid indole alkaloids [1]. These alkaloids have offered opportunities to exhibit the state-of-the-art synthetic abilities owing to their highly complex, compact, and strained structures. Recently, we have focused on the construction of the core structure of gelsedine-type alkaloids and their comprehensive total syntheses (Fig. 1). So far, these alkaloids have garnered less attention compared to the other members of gelsemium alkaloids. Synthetic studies on gelsedine-type alkaloids were disclosed only from Baldwin [2], Hamer [3], and Kende [4]. Later, Takayama reported the comprehensive semisyntheses of gelsedine (**1**), gelsenicine (**2**), and gelselegine (**3**) from koumine-type alkaloid koumidine based on the biogenetic pathway of gelsemium alkaloids. Eventually Hiemstra succeeded in synthesizing *ent*-gelsedine (*ent*-**1**) in 2000 [5], which consists of the only de novo total synthesis to date. To develop a general and flexible synthetic route to these alkaloids, we have selected gelsemoxonine (**4**) as our initial synthetic target owing to its relatively high oxidation state. Gelsemoxonine (**4**) was isolated in 1991 from the leaves of *Gelsemium elegans* [6]. As the structure of gelsemoxonine was originally misassigned, Aimi revised it in 2003 based on X-ray crystallographic analysis [7]. The corrected structure features a unique azetidine substructure bearing a tetra-substituted carbon center, which is not familiar among indole alkaloids. Combined with the quaternary center of the spiro-*N*-methoxy indolinone and the complex caged cyclic system, synthesis of **4** defies a conventional approach.

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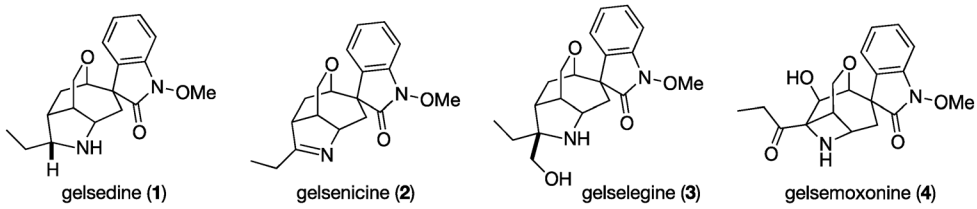
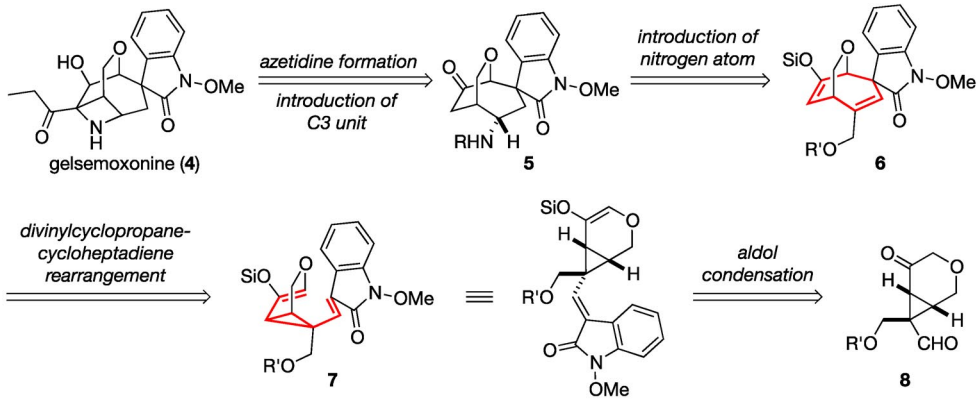


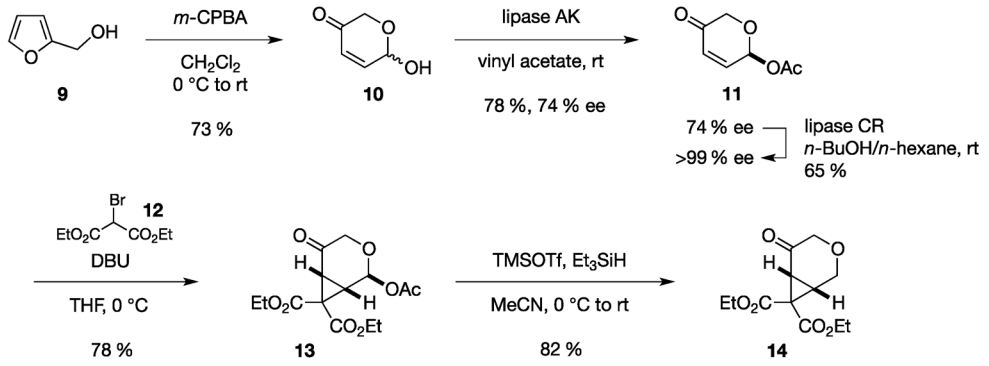
Fig. 1 Gelsedine-type alkaloids.

As shown in our retrosynthetic analysis (Scheme 1), formation of the azetidine moiety and introduction of a three-carbon unit could be performed in the late stages of the synthesis. The configurationally controlled nitrogen functionality on the carbon skeleton of **5** could be introduced via transformation of the allylic alcohol moiety in **6**. We planned to construct the oxabicyclo[3.2.2]nonane skeleton of **6** through a process involving a divinylcyclopropane–cycloheptadiene rearrangement [8]. Substrate **7**, which possesses a densely functionalized cyclopropane moiety, was envisioned to form through an aldol condensation between *N*-methoxyindolinone and aldehyde **8**.



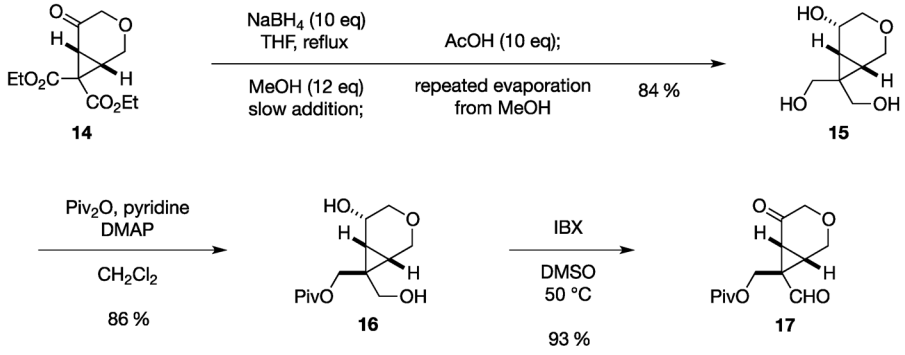
Scheme 1 Retrosynthetic analysis.

Our synthesis began with the Achmatowicz reaction [9] of furfuryl alcohol (**9**) to afford hydroxy enone **10** (Scheme 2). According to a report by Feringa [10], we employed lipase AK to enantioselectively prepare (*S*)-**11** via dynamic kinetic resolution (DKR), albeit with moderate enantiopurity (74 % ee). Thus, solvolysis of the DKR product was examined to selectively remove the undesired *R*-isomer using lipase CR from *Candida rugosa* [11]. As expected, solvolysis gave the opposite result of lipase AK and yielded the *S*-isomer with over 99 % ee on a 10-g scale. With the optically pure material in hand, **11** was treated with diethyl bromomalonate (**12**) and diazabicycloundecene (DBU). Conjugate addition of the bromomalonate anion from the less-hindered α-face of the enone and subsequent cyclization delivered cyclopropane **13** as a single isomer. With the construction of the quaternary stereocenter secured, we next focused on the removal of the acetoxy group. Despite the fact that **13** is unstable under acidic conditions, extensive examination of the reduction conditions eventually revealed that a combination of Et_3SiH and trimethylsilyl trifluoromethanesulfonate (TMSOTf) in acetonitrile efficiently converted **13** to **14**.



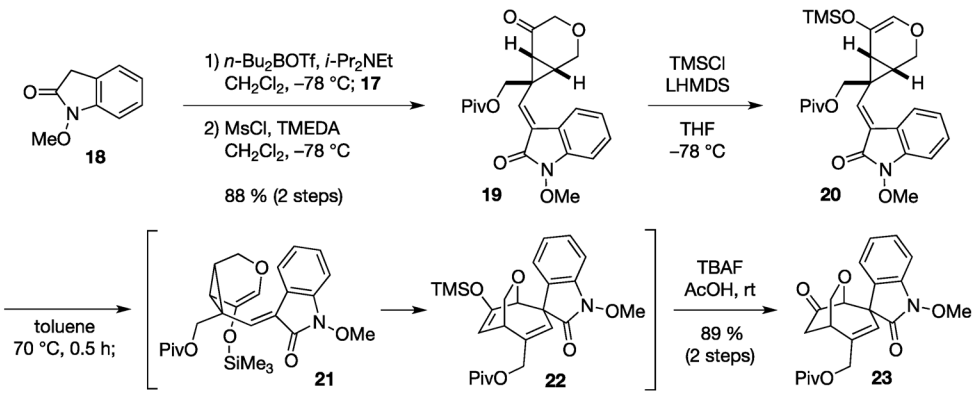
Scheme 2 Construction of cyclopropane moiety via enantiopure acetoxy enone.

Although **14** could be readily reduced by treatment with $LiAlH_4$, isolation of the resultant triol **15** proved troublesome owing to its high chelating ability and water solubility. After extensive experimentation, we found that Soai reduction [12] cleanly gave the desired triol **15**. Quenching the reaction with acetic acid and repeated evaporation–addition cycles from methanol to remove volatile trimethyl borate produced a mixture of sodium acetate and triol **15**, which could be purified by silica gel chromatography after filtration. The less-hindered primary alcohol in **15** was selectively protected as pivalate **16**, and subsequent oxidation of the resulting diol with *o*-iodoxybenzoic acid (IBX) afforded keto-aldehyde **17** in 93 % yield (Scheme 3).



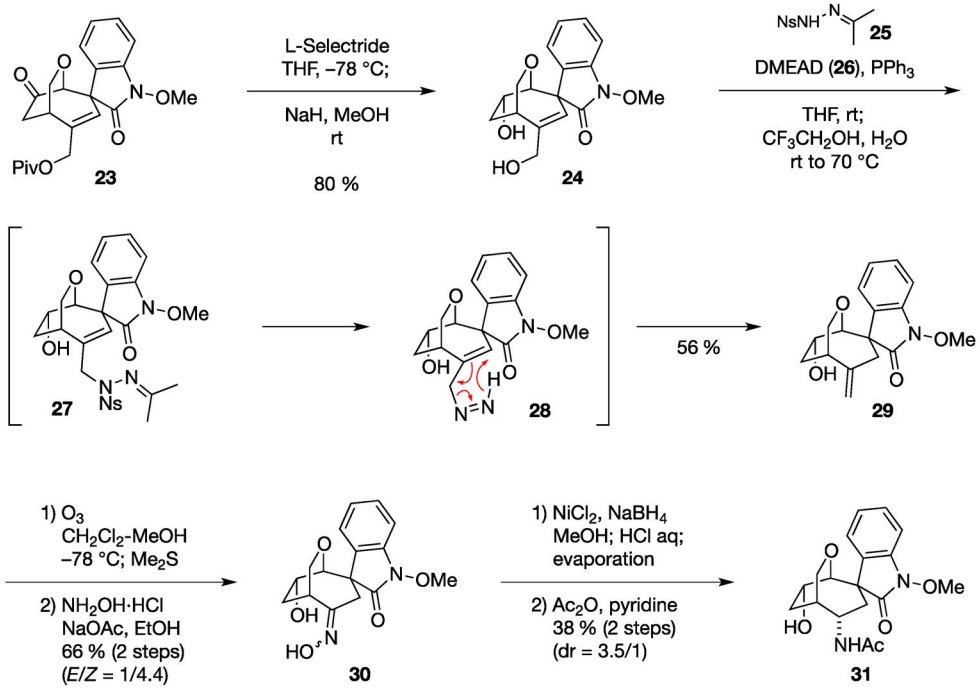
Scheme 3 Reduction of ketodiester and preparation of ketoaldehyde.

Although the conventional Knoevenagel condensation between aldehyde **17** and indolinone **18** [13] proved unsuccessful, the aldol reaction via the boron enolate [4] followed by dehydration by means of MsCl and tetramethylethylenediamine (TMEDA) [14] at –78 °C successfully afforded **19** as a single diastereomer. Subsequent treatment with lithium hexamethyldisilazide (LHMDS) in the presence of chlorotrimethylsilane (TMSCl) furnished divinylcyclopropane **20**, the substrate for the key divinylcyclopropane–cycloheptadiene rearrangement. As expected, silyl enol ether **20** rearranged smoothly upon heating at 70 °C for 30 min to furnish the desired bicyclic ketone **23** in 89 % yield from **19** after the removal of the trimethylsilyl (TMS) group. The stereochemistry of **23** was consistent with that predicted from transition state **21**. Consequently, the stereochemistry of the double bond was successfully transferred to the quaternary spirocenter (Scheme 4).



Scheme 4 Divinylcyclopropane–cycloheptadiene rearrangement realized the construction of highly functionalized oxabicyclo[3.2.2]nonane core structure.

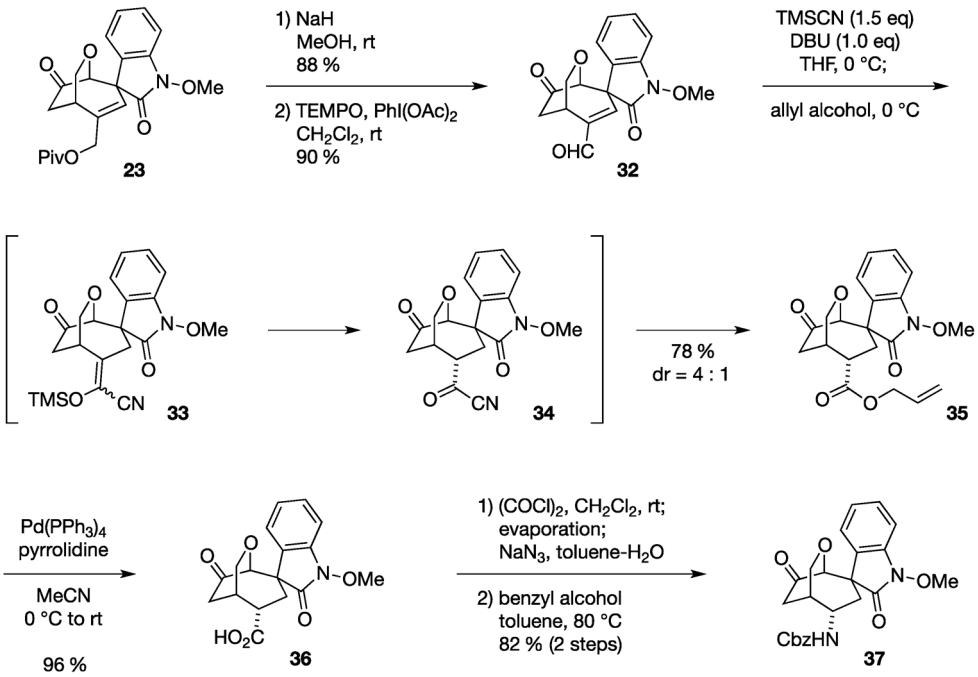
With the core seven-membered structure of gelsemoxonine constructed, the next task was to introduce a nitrogen atom to the seven-membered carbon skeleton with the desired configuration. As is often the case for densely functionalized and crowded molecules, manipulation of the C–C double bond on the bicyclic structure **23** proved extremely difficult. To introduce the nitrogen function to the bicyclo[3.2.2]skeleton, a hydrogen atom was introduced to the highly crowded neopentyl position. At first, hydride was employed as the source of this necessary hydrogen atom (Scheme 5).



Scheme 5 Strategy via diazene rearrangement to install nitrogen functionality.

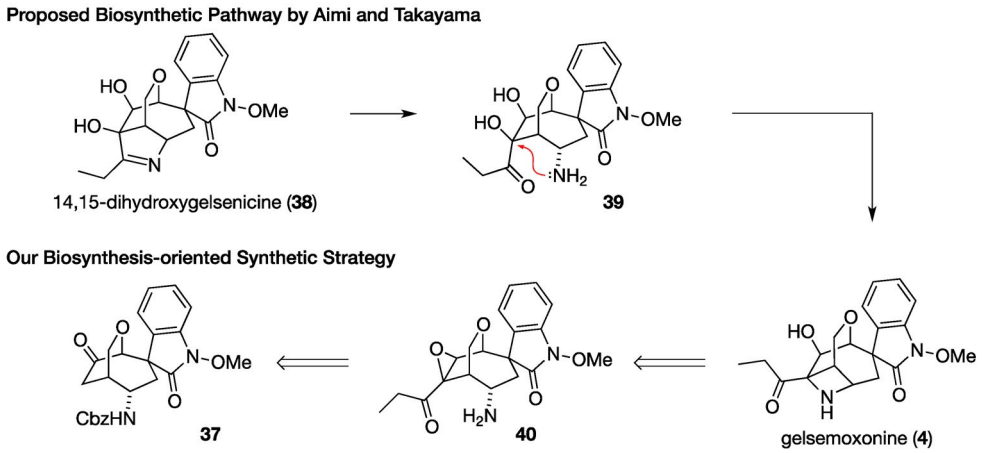
Reduction of **23** and subsequent removal of the pivaloyl group gave allylic alcohol **24**, which was subjected to the Mitsunobu reaction with *N*-isopropylidene-*N*′-2-nitrobenzensulfonyl hydrazine [15] (IPNBSH, **25**) mediated by di-2-methoxyethyl azodicarboxylate [16] (DMEAD, **26**). Hydrolysis of **27** mediated the removal of the isopropylidene moiety, and subsequent elimination of sulfinate ion generated diazene intermediate **28** in situ. Diazene rearrangement from **28** successfully delivered the desired hydride to the crowded position, yielding methylidene **29** in moderate yield. Ozonolysis of **29** gave the ketone, which was transformed to the corresponding oxime **30**. After extensive examination, we successfully reduced oxime **30** by nickel boride generated in situ. After acetylation about 3.5:1 diastereomeric mixture of acetamide **31** was produced. Although this process introduced a nitrogen functionality onto the bicyclic structure, this result was unsatisfactory from the viewpoints of scalability and step economy.

Next, we focused on the redox isomerization of the unsaturated aldehyde (Scheme 6) [17]. Methanolysis of **23** followed by 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) oxidation provided α,β-unsaturated aldehyde **32**. Upon treatment of **32** with trimethylsilyl cyanide (TMSCN) and DBU, α,β-unsaturated nitrile **33** arose from the DBU-mediated isomerization of the incipient cyanohydrin trimethylsilyl ether [18]. Interestingly, treatment of the reaction mixture with allyl alcohol resulted in selective protonation of silyl enol ether **33** to afford acyl cyanide **34**, which was further transformed into the corresponding allyl ester **35** in one pot [19] as a 4:1 diastereomeric mixture with the thermodynamically more stable *epi*-**35**. **35** was ultimately isolated in 78 % yield. Treatment with other reagents such as H_2O, MeOH, *t*-BuOH, or NH_3 aq. resulted in a low diastereoselectivity, probably due to the unselective protonation of **33** or epimerization of intermediate acyl cyanide **34**. Ester **35** could be transformed to Cbz-protected amine **37** in a three-step sequence involving deallylation, Curtius rearrangement of resulting carboxylic acid **36**, and treatment with benzyl alcohol. Hence, the nitrogen atom was stereoselectively introduced on the bicyclic skeleton.



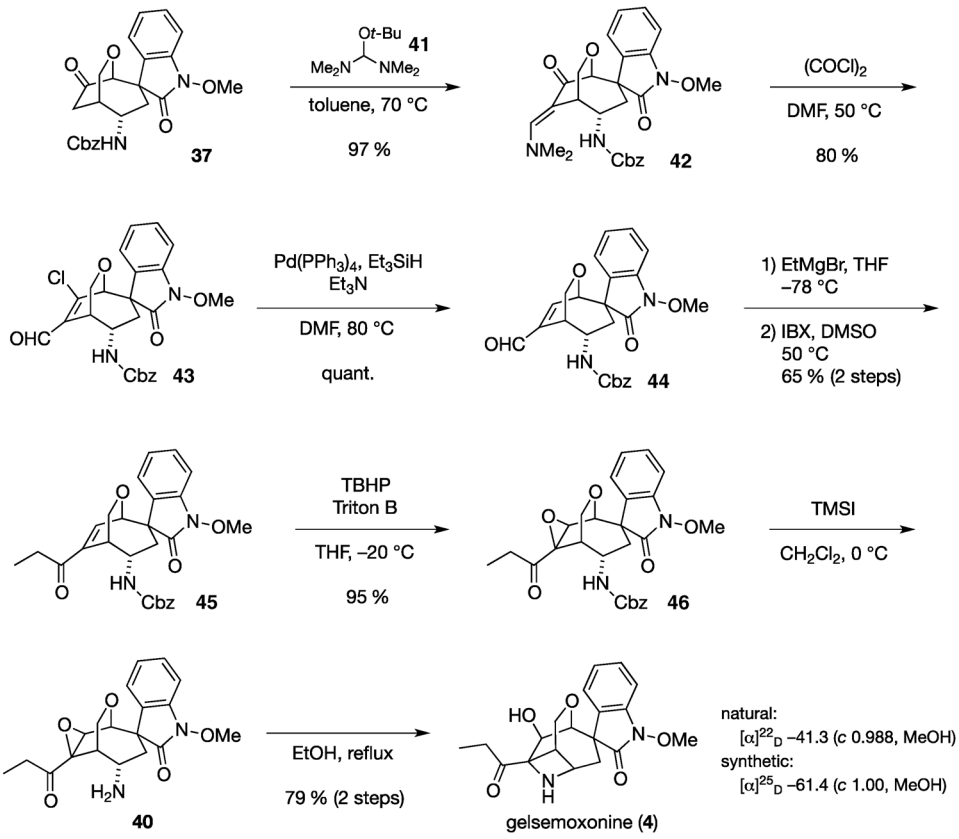
Scheme 6 Pivotal, stereoselective introduction of a nitrogen atom.

The next mission was to construct the azetidine moiety. According to the proposed biosynthesis of gelsemoxonine from 14,15-dihydroxygelsenicine (**38**), nucleophilic substitution with the amino group of **39** should affect the synthesis of the azetidine moiety bearing a tetra-substituted center (Scheme 7) [7]. Although this proposal appeared reasonable, intermediate **39** was unsuited for the synthesis of gelsemoxonine because the facile formation of the five-membered imine would preclude the expected substitution reaction. Therefore, we envisioned amino epoxide **40** as the key intermediate to circumvent the undesired formation of the cyclic imine as well as to activate the tetrasubstituted carbon center.



Scheme 7 Comparison of the biosynthetic proposal with our strategy for the construction of azetidine core structure.

Initially, we envisioned the introduction of a 1-propanoyl group at the α-position of the ketone in **37**. Since the introduction of three-carbon unit to **37** was unsuccessful, we opted to employ a stepwise approach. Fortunately, Bredereck's reagent [20] (**41**) smoothly introduced one-carbon unit to give **42** despite the presence of a nearby carbamate (Scheme 8). Vinylogous amide **42** was then treated with Vilsmeier's reagent to give β-chloro unsaturated aldehyde **43** [21]. Dechlorination was subsequently achieved by treatment with $Pd(PPh_3)_4$ and Et_3SiH [22] to give aldehyde **44**. Treatment with EtMgBr followed by IBX oxidation afforded ethyl ketone **45** and completed the formation of the carbon framework of gelsemoxonine (**4**). Exposure to *tert*-butyl hydroperoxide (TBHP) and Triton B at –20 °C introduced the desired epoxide moiety to α,β-unsaturated ketone **45**. The nucleophile was delivered from the opposite face to the bulky indolinone to selectively provide the desired diastereomer **46**. Because the N–O bond of the *N*-methoxyindolinone moiety in **46** did not survive the hydrogenolysis conditions, deprotection of the Cbz group was effected by TMS iodide [23] to give penultimate amino epoxide intermediate **40**. Despite extensive efforts, all attempts to accomplish the requisite opening of the epoxide were unsuccessful by employing the protic and Lewis acids or bases in a variety of solvents. Thus, it was indeed our great surprise to find that the ring-opening reaction proceeded by simply heating **40** in boiling ethanol [24], which almost exclusively yielded desired gelsemoxonine (**4**) on a larger than 300-mg scale. This dramatic change in reactivity could be attributed to the hydrogen-bonding network of ethanol, which activated both protonation of the epoxide and deprotonation of the primary amine [25]. Spectral data of the synthetic gelsemoxonine were identical to those of the natural product [7] in all respects.



Scheme 8 End game of the total synthesis of gelsemoxonine.

In summary, the work herein constitutes the first total synthesis of gelsemoxonine [26]. The synthesis featured a divinylcyclopropane–cycloheptadiene rearrangement to construct the challenging quaternary center of the spiro indolinone (**20** → **23**) and a redox isomerization via the TMSCN–DBU combination (**32** → **35**) to introduce the latent nitrogen functionality as two key transformations.

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