

Total Synthesis of Gelsenicine via a Catalyzed Cycloisomerization Strategy

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S Supporting Information

ABSTRACT: The first total synthesis of (\pm)-gelsenicine is reported. The synthetic route is highly efficient (13 steps), featuring (1) a pivotal metal-catalyzed isomerization/rearrangement process that forges the central core of the molecule and (2) two facile C–N bond-forming steps that establish the flanking heterocycles.

The Gelsemium alkaloids have a storied history in natural products chemistry.¹ Belonging to the family Gelsemiaceae, the flowering plants that produce these alkaloids all possess a toxicity that has been recognized for hundreds of years. They have also been used in traditional Asian medicine for the treatment of numerous ailments,² and both their toxicity and medicinal properties are attributed to the high concentration of alkaloids within these plants. Specific alkaloids have been shown to have promising therapeutic effects, including antipsoriasis, antitumor, and analgesic characteristics, among others.³ With over 100 structurally distinct alkaloids in this family, comprehensive biological profiling remains lacking, markedly constrained by synthetic accessibility. This dilemma is reflective of the structural complexity of these molecules; their compact, dense architectures with relatively few functional groups as synthetic handles render their intricate challenges for construction. Of the general gelsemium alkaloid structure types, synthetic approaches toward gelsemine-type (specifically gelsemine itself, Figure 1A) are the most prevalent.⁴ Gelsedine-

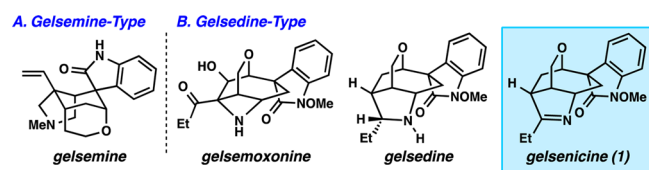


Figure 1. Representative Gelsemium alkaloids.

type alkaloids (Figure 1B) have received relatively lesser attention, with just a small number of elegant semisyntheses⁵ and total syntheses⁶ having been disclosed. Recent synthetic approaches to gelsedine by Fukuyama^{6c} and Carreira^{6d,e} exemplify the innovation these compounds continue to inspire. Although remarkable accomplishments have been documented in these syntheses, more efficient strategies featuring significantly shorter step counts may define a clear pathway to connect this family of molecules to biology and medicine. Herein, we report our approach toward these alkaloids, culminating in a notably quick total synthesis of gelsenicine (1, 13 steps LL). The overall

route hinges upon the efficient formation of the alkaloid core, exploiting a strategic isomerization sequence to establish the bicyclic architecture decorated with the requisite functionality for rapid molecule completion.

Our generalized retrosynthesis for gelsenicine is illustrated in Figure 2. We envisioned that the natural product could arise from

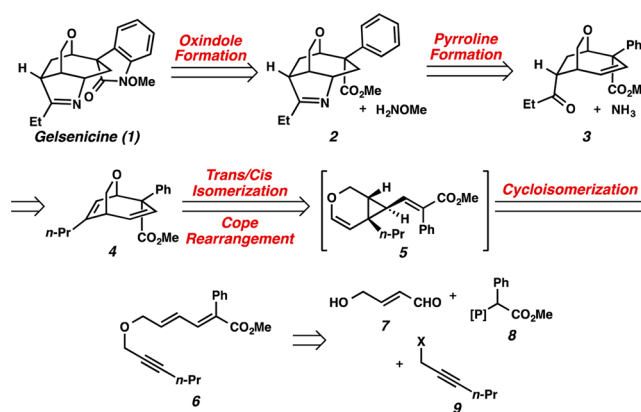


Figure 2. Gelsenicine: proposed retrosynthesis.

precursor 3 by two heterocyclization processes. The oxindole could be considered to arise from a variety of possible acylation and C_{aryl}–N bond-forming strategies. The pyrroline, meanwhile, can be established via the merging of a ketone, an alkene, and an amine. This precursor (3), a much more manageable target, could be ideally generated from structure 4. Bridged bicycle 4 was a pivotal intermediate, as we anticipated it would arise from a rearrangement process involving metal-catalyzed cycloisomerization and a strain-release Cope rearrangement, leading back to a greatly simplified dienyne compound (6). The tandem process was originally reported on unfunctionalized diene arylalkyne substrates using Pt catalysis by Chung and co-workers.⁷ Encouraged by our previous efforts in catalytic cycloisomerization chemistry⁸ and inspired by the creative use of π -acid mediated alkyne activation in complex molecule synthesis,⁹ we were curious if this tandem process could be applied in this specific setting. Compound 6 would be synthesized from components 7, 8, and 9 via etherification and olefination. In this overarching approach, major questions would need to be addressed. First, there was the aforementioned notion of exploiting the rearrangement process as the key step with the

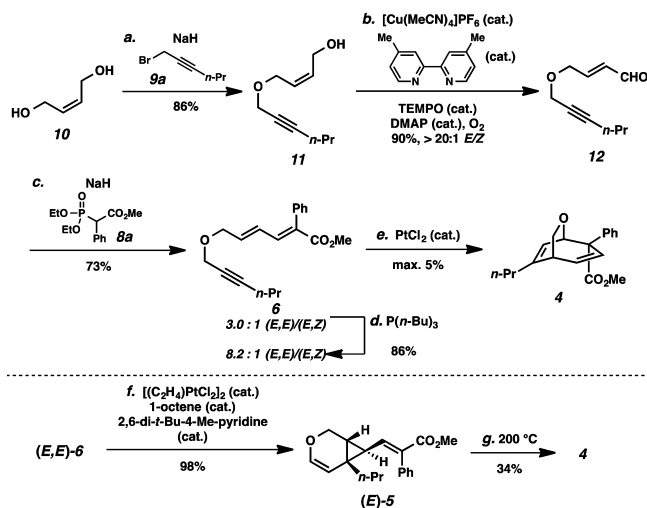
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appropriate substitutions necessary for gelsenicine. Moreover, even if the proposed key sequence was achieved, we would need to identify how this product could be efficiently advanced to our target alkaloid. Specific potential complications included the sufficient reactivity differentiation of the two alkenes in compound **4** in their respective functionalization events, and the regio- and diastereoselective installation of the C–N bond on to the disubstituted alkene of core **4** (i.e., **3** → **2**).

The synthesis of core **4** commenced with (*Z*)-but-2-ene-1,4-diol (Scheme 1). Alkylation with bromide **9a**¹⁰ followed by Cu-

Scheme 1. Initial Synthetic Approach to Bicyclic Core 4^a



^aReagents and conditions: (a) NaH, **9a**, DMF, 0 → 23 °C, 86%; (b) [Cu(MeCN)₄]PF₆ (1 mol %), 4,4'-dimethyl-2,2'-bipyridyl (1 mol %), TEMPO (1 mol %), DMAP (2 mol %), O₂ (1 atm), CH₃CN, 23 °C, 90%, >20:1 *E/Z*; (c) NaH, **8a**, THF, 0 → 23 °C, 73%; (d) P(*n*-Bu)₃, THF, 45 °C, 86% ((*E,E*)-isomer only); (e) PtCl₂ (7 mol %), PhCH₃, 70 °C, <5%; (f) [(C₂H₄)PtCl₂]₂ (3 mol %), 1-octene (10 mol %), 2,6-di-*tert*-butyl-4-methylpyridine (10 mol %), PhCH₃, 40 °C, 98%; (g) 200 °C, 34%.

catalyzed oxidation/isomerization as described by Christmann¹¹ afforded enal **12**. Horner–Wadsworth–Emmons olefination of the enal with phosphonate **8a**¹² yielded the target diene with acceptable geometrical selectivity. Notably, we could enrich the alkene geometry via a phosphine-mediated isomerization in excellent yield.¹³ With this diene in hand, we next tested the isomerization sequence. A single-step cascade was barely successful; the desired adduct (**4**) could be obtained in a maximum 5% yield. An exhaustive evaluation revealed that a two-stage process improved this overall transformation, as performing the cycloisomerization below the temperature threshold of the Cope rearrangement was desirable.¹⁴ The use of Zeise's dimer provided a soluble Pt salt at that lower temperature, while 1-octene prolonged the catalyst lifetime and the hindered base prevented alkene *E/Z* isomerization. With these conditions applied, oxabicyclo[3.1.0]heptene derivative (*E*)-**5** was formed in 98% yield. The rearrangement was best achieved neat at 200 °C, yet compound **4** was formed in only 34% yield. Although the increase in structural complexity over diene (*E,E*)-**6** that was established via this transformation was highly advantageous, the still modest yield made it difficult to proceed onward. We opted to analyze this key sequence in more detail, in hopes of devising an improved strategy.

In our evaluation, we found that the main byproduct observed was triene **13** (Figure 3), presumably arising from a 1,5-

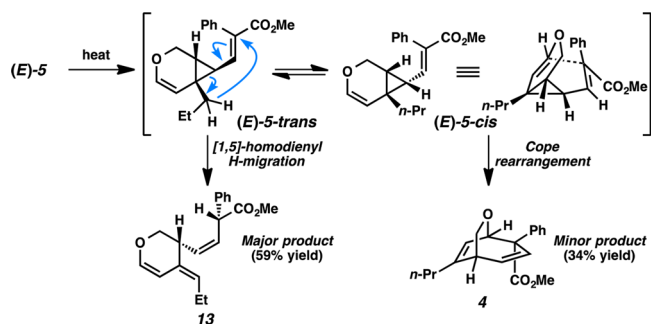


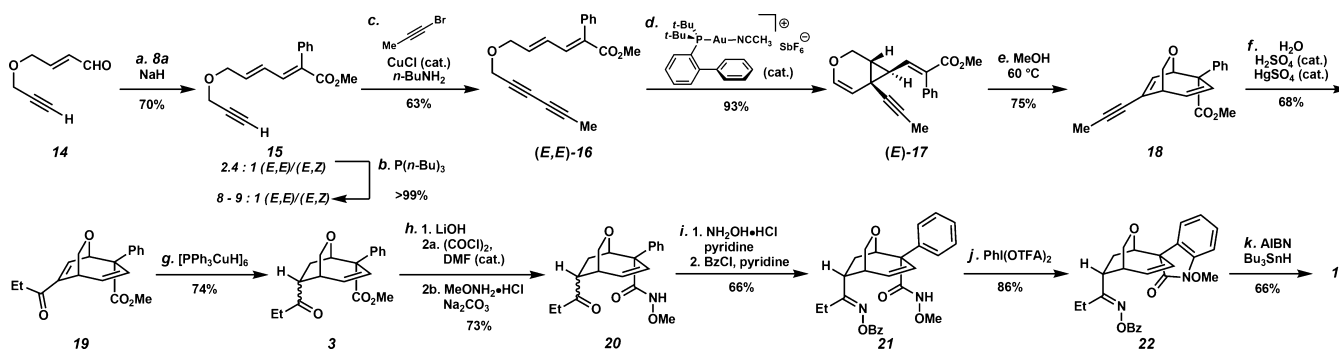
Figure 3. Cope rearrangement complication.

homodienyl hydrogen migration.^{15,16} This process likely occurs prior to the *trans*-to-*cis* isomerization necessary to initiate the Cope rearrangement.¹⁷ The presence of a propargylic hydrogen on the *n*-Pr moiety in diene (*E,E*)-**6** was thus the culprit, and we hypothesized that a different alkyne substituent that could be later transformed to an ethyl ketone (as in **3**, Figure 2) may offer a superior alternative.¹⁸

Among potential options we considered, we were hopeful diene-diyne (*E,E*)-**16** would serve our purpose (Scheme 2). The lack of available hydrogens for migration, minimal polarization contribution to the activating alkyne, and potential for downstream direct conversion to a ketone functional group all indicated promise for this strategy. This diyne precursor could be synthesized in three steps from known aldehyde **14**.¹⁹ Horner–Wadsworth–Emmons olefination and phosphine-mediated isomerization, similar to the prior route, afforded diene (*E,E*)-**15**. At this stage, a Cadiot–Chodkiewicz coupling²⁰ with *in situ*-generated 1-bromo-1-propyne²¹ yielded the diyne motif ((*E,E*)-**16**). To our delight, the cycloisomerization/Cope rearrangement sequence could be readily achieved, with no H-migration possible. In our studies of this transformation (Table 1), we found that (1) Au catalysis²² was decidedly superior to Pt catalysis in terms of yield,²³ and (2) the stepwise process gave improved diastereoselectivity over the cascade option.²⁴ This series of transformations established the core with outstanding efficiency, giving bicycle **18** in five steps from aldehyde **14**.

At this juncture, we were presumably well positioned to execute the final steps of the synthesis. An aforementioned major concern of our strategy was that the core arising from this key transformation features two rather similar alkenes that both needed to be differentially and selectively functionalized. We also had to contend with the conversion of the ester and phenyl groups to the oxindole. Gratifyingly, we were able to achieve these goals with a judicious execution of our synthetic sequence.

A regioselective Hg-catalyzed alkyne hydration²⁵ afforded enone **19**. With the alkenes now electronically distinct, conjugate reduction with Stryker's reagent²⁶ worked efficiently to afford ketone **3** in good yield. While the reduction favored the desired stereogenicity (~4:1), we found that this orientation was thermodynamically preferred at approximately these levels and thus carried the mixture onward. From this point, we required two heterocyclizations with requisite C–N bond formations. For the pyrroline, we envisioned a 5-*exo* reductive cyclization using the iminyl radical chemistry of Zard²⁷ would install the C–N bond on the disubstituted alkene with regio- and stereocontrol, based on the ketone spatial positioning. Meanwhile, a number of

Scheme 2. Total Synthesis of (±)-Gelsegincine^a

^aReagents and conditions: (a) **8a**, NaH, THF, 23 °C, 70%; (b) P(*n*-Bu)₃, THF, 55 °C, >99%; (c) 1-bromo-1-propyne, CuCl (40 mol %), NH₂OH·H₂O (60 mol %), *n*-BuNH₂/H₂O, 0 °C, 63% ((*E,E*)-isomer only); (d) LAu(CH₃CN)SbF₆ (2 mol %), CH₂Cl₂, 23 °C, 93%; (e) CH₃OH, 60 °C, 75% (+ 23% diastereomer); (f) HgSO₄ (2 mol %), cat. H₂SO₄, THF/H₂O (7:3), 50 °C, 68%; (g) [PPh₃CuH]₆ (0.3 equiv), PhCH₃, 23 °C, 74% (4:1 dr); (h) 1) LiOH, H₂O/1,4-dioxane, 90 °C; 2) (COCl)₂, cat. DMF, CH₂Cl₂, 0 → 23 °C; 3) MeONH₂·HCl, Na₂CO₃, H₂O/C₆H₆, 0 → 23 °C, 73% over 3 steps (5:1 dr); (i) 1) NH₂OH·HCl, pyridine, 0 → 23 °C; 2) BzCl, pyridine, THF, 0 → 23 °C, 66% over 2 steps (single diastereomer); (j) PhI(OTFA)₂, CHCl₃, 0 °C, 86%; (k) Bu₃SnH, AIBN, PhCH₃/cyclohexane, 120 °C, 66%.

Table 1. Cycloisomerization/Cope Rearrangement of (*E,E*)-16

Process	Catalytic Conditions	Yield (%)	18 dr
Pt cascade	cat. [(C ₂ H ₅)PtCl ₂]/β-pinene MgSO ₄ , CH ₂ Cl ₂ , 60 °C, 24 h	64	2.6 : 1
Au cascade	cat. LAu(CH ₃ CN)SbF ₆ CH ₂ Cl ₂ , 23 °C, 18 h → 60 °C, 8 h	83	1.9 : 1
Au stepwise	cat. LAu(CH ₃ CN)SbF ₆ CH ₂ Cl ₂ , 23 °C, 18 h, purify; MeOH, 60 °C, 8 h	91	3.2 : 1

methods were deliberated for installation of the oxindole moiety, chief among them selective hydroxamate oxidation²⁸ and C–H functionalization.²⁹ From compound **3**, the ester functional group was converted to an *N*-methoxyamide using straightforward amidation chemistry. Oxime formation with hydroxylamine followed by benzylation proceeded uneventfully.³⁰ Oxindole closure was achieved first, employing PhI(OCOCF₃)₂ in CHCl₃.²⁸ Finally, radical ring closure on this penultimate species under carefully controlled conditions using Bu₃SnH and AIBN^{27a} was successful, completing gelsegincine (**1**). Overall, this route represents the first total synthesis of this alkaloid and is among the shortest total syntheses of any gelsemium alkaloid to date.

In summary, we have completed the total synthesis of gelsegincine in 13 steps (LL) from known aldehyde **14**. A pivotal cycloisomerization/rearrangement sequence reconstructs a relatively simple substrate into the complex central core of the alkaloid. This step definitively leverages the capacity of alkynophilic-catalyzed cyclization chemistry in a total synthetic context. Furthermore, this protecting group-free synthetic effort is among the shortest total syntheses of a gelsemium alkaloid to date, and it will ideally set the stage for synthetic access and biological studies for multiple alkaloids within the gelsemium

family. Further investigations in these areas will be reported in due course.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12263.

Experimental details, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(19) This aldehyde is synthesized in two steps from (*Z*)-but-2-ene-1,4-diol and propargyl bromide in 70% yield following the procedure described by Lu. See the [Supporting Information](#) and ref 10.

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