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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Total Synthesis of (±)-Gelsemoxonine

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Supporting Information

ABSTRACT: Gelsemoxonine (**1**) is a *Gelsemium* alkaloid incorporating an unusual azetidine. Its total synthesis was achieved employing a novel ring contraction of a spirocyclopropane isoxazolidine to furnish a β-lactam intermediate. This β-lactam ring was further elaborated into the azetidine of Gelsemoxonine. In addition, the synthesis includes a highly diastereoselective reductive Heck cyclization for the installation of the oxindole ring system as well as a directed hydrosilylation of an alkyne to access the ethyl ketone of the natural product.

Plants from the genus *Gelsemium* have proven to be a rich source of structurally diverse monoterpenoid indole alkaloids.[1] The compact structures of these natural products have inspired multiple generations of chemists to develop strategies for their synthesis.[2] Of the three known *Gelsemium* species, extracts of *Gelsemium elegans benth* have found use in traditional Asian medicine for over a thousand years.[3] It is from this source that in 1991 Clardy isolated the alkaloid Gelsemoxonine (**1**) (Figure 1).[4] Revision of the originally

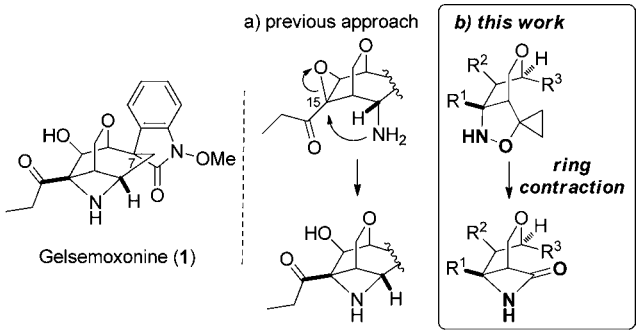


Figure 1. Gelsemoxonine (**1**) and strategies for azetidine formation.

proposed structure based on X-ray crystallographic analysis revealed that it includes an azetidine embedded within a compact polycyclic scaffold.[5] Furthermore, Gelsemoxonine harbors six contiguous, densely packed stereocenters, including a quaternary carbon at the spirocyclic junction and a fully substituted carbon within the azetidine. These features, along with its medical relevance, render it a veritable target for study. Herein, we report a total synthesis of Gelsemoxonine that utilizes a strategic ring contraction of a spirocyclopropane isoxazolidine to provide access to the azetidine (Figure 1b). An additional salient feature of the synthesis is the introduction of the congested quaternary oxindole stereocenter at C(7) by a diastereoselective reductive Heck cyclization.

In contrast to other small saturated heterocycles such as oxetanes or epoxides, azetidines have only been found in a handful of natural products to date.[6] In a prior approach to Gelsemoxonine, Fukuyama employed a biomimetic strategy for the formation of this unusual motif in which epoxide ring opening at C(15) is coupled to azetidine formation (Figure 1a).[7] Our interest in small saturated heterocycles and their utility in modifying the underlying physicochemical properties of a scaffold in drug discovery have prompted us to examine novel strategies for their synthesis.[8] The occurrence of the embedded azetidine in Gelsemoxonine provided an opportunity to examine less common methods for azetidine synthesis in more complex settings.

In our retrosynthetic analysis of the targeted natural product, we envisioned late-stage construction of the oxindole by arylation at C(7) (Figure 2). β-Lactam **2** was envisioned as a

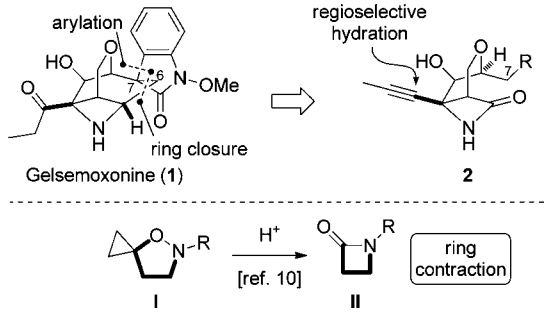


Figure 2. Retrosynthetic strategy for gelsemoxonine (**1**) and key ring contraction.

key intermediate in the route for the construction of the Gelsemoxonine tricyclic core. However, it was not clear how implementation of conventional approaches to the synthesis of β-lactams would enable an access route to **2**.[9] A synthesis plan was devised that centered on the use of an uncommon ring contraction of *N*-alkylated spirocyclopropane isoxazolidines to form the corresponding β-lactam (**I**→**II**) first reported by Brandi.[10] The successful implementation of this transform would offer access to the azetidine ring at the heart of Gelsemoxonine.

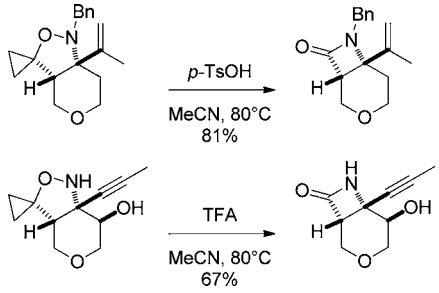
The initial reports on the intriguing ring contraction reaction to β-lactams was limited to a handful of simple substrates. Thus, we first conducted prospecting experiments to establish the operational parameters of the transformation, its generality, and potential use in the context of the target alkaloid. As shown in

Received: April 17, 2013
Published: May 21, 2013

   dx.doi.org/10.1021/ja403823n | J. Am. Chem. Soc. 2013, 135, 8500−8503

Scheme 1, we observed ring contraction to the corresponding β-lactam product for two relevant model substrates in excellent

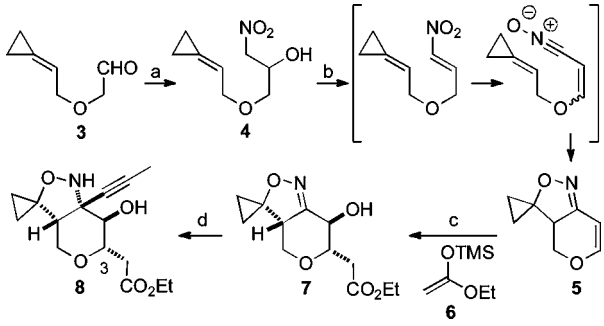
Scheme 1. Model Studies for the Ring Contraction



yield. It is noteworthy that nitrogen protecting groups were not required for the transformation. The success of the model systems compelled us to examine the ring contraction toward the synthesis of Gelsemoxonine. However, as discussed below, we ultimately opted for a more complex pyran substrate than those suggested by the model systems in Scheme 1.

The synthesis route commenced with the construction of a suitably substituted precursor for the key ring contraction as depicted in Scheme 2. A key difference to the model systems

Scheme 2. Synthesis of Isoxazolidine 8[a]

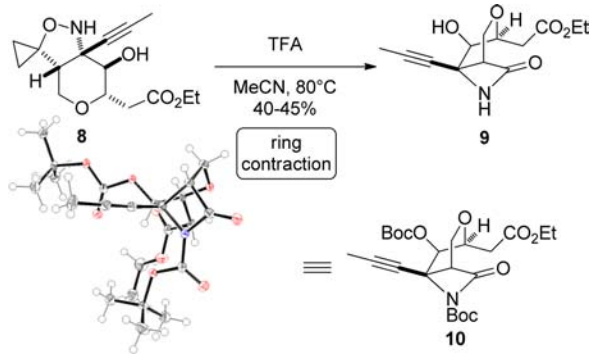


[a]Reagents and conditions: (a) $MeNO_2$, LDA, 30 min; then **3**, THF, −78 °C to rt, 2 h, 70%. (b) Boc_2O, DMAP, toluene, rt, 12 h, 79%. (c) DMDO, CH_2Cl_2/ acetone (1:1), 0 °C, 2 h; then **6**, $InBr_3$ (5 mol %), CH_2Cl_2, −60 °C to rt, 2 h, 56%. (d) 1-Bromo-1-propene, nBuLi, 1.5 h; then anhydrous $CeCl_3$, 30 min; then **7**, $BF_3{\cdot}OEt_2$, THF, −78 °C, 2 h, 78%.

for the ring contraction reaction is that the targeted pyran incorporates a substituent at C(3), as shown for **8**. To this end, aldehyde **3**[11] was subjected to a Henry reaction with lithiated nitromethane, furnishing secondary alcohol **4** in 70% yield. This intermediate was then treated with Boc_2O in the presence of DMAP delivering isoxazoline **5** via a sequence consisting of alcohol activation, elimination, dehydrative formation of a nitrile oxide, and intramolecular dipolar cycloaddition.[12] Epoxidation of the enol ether **5** using DMDO[13] produced an unstable epoxide intermediate, which was immediately subjected to nucleophilic opening by ketene silyl acetal **6** under Lewis acid catalysis to furnish alcohol **7** in 56% yield. Although the epoxidation proceeded to give a 2:1 mixture of epoxide diastereomers in favor of the desired epoxide isomer, careful tuning of the reaction conditions allowed for differential opening of only the major epoxide isomer, with the minor diastereomer remaining unreactive. With isoxazoline **7** in hand, introduction of an alkyne as a surrogate for the ethylketone was subsequently addressed. Accordingly, addition of 1-propynyllithium to **7** in the presence of anhydrous $CeCl_3$ and $BF_3{\cdot}OEt_2$ furnished diastereomerically pure oxazolidine **8** in 78% yield.[14] Interestingly, the free secondary alcohol in **7** proved essential for the addition to proceed. We speculate that the hydroxyl group is involved as a directing group for the incoming organometal species.

With a short route to spirocyclopropane isoxazolidine **8** secured, the key ring contraction to the projected β-lactam could now be addressed, as shown in Scheme 3. We were

Scheme 3. Ring Contraction of Isoxazolidine 8

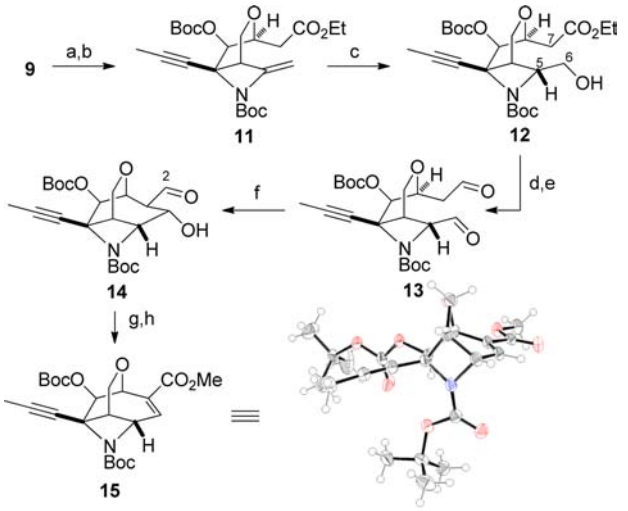


curious to know whether the densely functionalized intermediate **8** would undergo the desired reaction. To our delight, when **8** was treated with TFA at 80 °C, the system underwent ring contraction to yield the highly substituted β-lactam **9** in 40−45% after complete consumption of **8**.[15] The structure of **9** was unambiguously confirmed by X-ray crystallographic analysis of its carbonate derivative **10**. The rearrangement of **8** to **9** along with the model systems is noteworthy, as it underscores the generality of the transformation and the compatibility with a number of functional groups, including alcohol, alkyne, ether, and ester.

The next hurdle in the synthetic effort was the methenylation of β-lactam **9** (Scheme 4). To this end, amide **9** was first protected using Boc_2O to furnish the corresponding imide in 85% yield. Exposure of this substrate to Petasis' olefination conditions[16] led to clean conversion to strained enecarbamate **11**, obtained in 77% yield. The stereocenter at C(5) was then installed by a hydroboration reaction. In this transformation we observed that the strained olefin in **11** reacts exclusively from the *exo*-face. Thus, following oxidative workup ($NaBO_3$) primary alcohol **12** is obtained in 92% yield as a single diastereomer as determined by NMR spectroscopy. With the full carbon backbone of the Gelsemoxonine core in place, closure of the seven-membered carbocycle was pursued. A variety of conditions were examined to displace derivatives of the primary alcohol at C(6) by the ester derived enolate, without success. Finally, we decided to explore an aldol condensation approach to achieve the requisite ring closure. To this end, dialdehyde **13** was prepared by DIBAL reduction of **12** followed by oxidation of the intermediate diol under Swern conditions. When **13** was treated with 20 mol % of proline, aldol product **14** was isolated as a single diastereomer in 82% yield. Notably, no elimination of the secondary alcohol was observed under these conditions. A sequence consisting of Pinnick oxidation/esterification in the presence of a free secondary alcohol delivered the corresponding methyl ester in 91% yield. Finally, elimination of the alcohol using TFAA

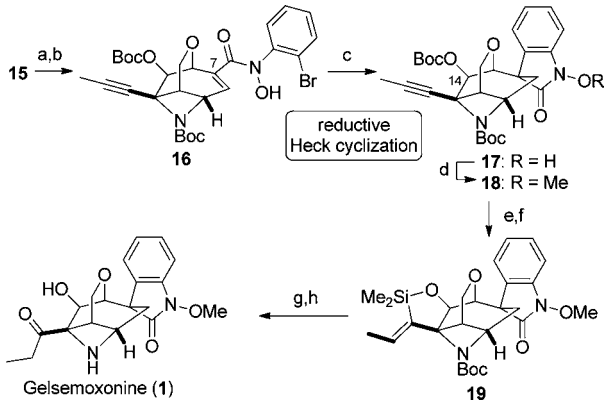
dx.doi.org/10.1021/ja403823n | J. Am. Chem. Soc. 2013, 135, 8500−8503

Scheme 4. C(6)−C(7) Ring Closure[a]



[a]Reagents and conditions: (a) Boc_2O, NEt_3, DMAP, CH_2Cl_2, rt, 30 min, 85%. (b) Cp_2TiMe_2, pyridine, toluene, 70 °C, 8 h, 77% (85% brsm). (c) 9-BBN dimer, THF, rt, 45 min; then $NaBO_3{\cdot}4H_2O$, THF/H_2O (1:1), rt, 1 h, 92%. (d) DIBAL-H, THF/CH_2Cl_2 (2:1), −78 °C, 75 min, 81%. (e) $(COCl)_2$, DMSO, 15 min; then diol substrate, 45 min; then NEt_3, CH_2Cl_2, −78 °C to rt, 1 h, 73%. (f) DL-proline (20 mol %), DMSO, rt, 12 h, 82%. (g) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*BuOH/H_2O (4:1), rt, 20 min; then $TMSCH_2N_2$, CH_2Cl_2/MeOH (9:1), rt, 10 min, 91%. (h) TFAA, DBU, THF, rt, 30 min, 94%.

Scheme 5. Completion of the Synthesis[a]



[a]Reagents and conditions: (a) Me_3SnOH, 1,2-dichloroethane, 80 °C, 24 h. (b) $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt, 1 h; then *N*-(2-bromophenyl)hydroxylamine, $NaHCO_3$, Et_2O/CH_2Cl_2 (3:1), 0 °C, 45 min, 58% (85% brsm, 2 steps). (c) $PdCl_2(MeCN)_2$ (10 mol %), 1,2,2,6,6-pentymethylpiperidine, HCOOH, DMF, 60 °C, 1.5 h, 72%. (d) NaH, MeI, DMF, 0 °C to rt, 45 min, 92%. (e) K_2CO_3, MeOH, 50 °C, 30 min, 87%. (f) $(Me_2SiH)_2NH$, 50 °C, 2.5 h; then $\{[RuCl_2(C_6H_6)]_2\}$ (20 mol %), CH_2Cl_2, rt, 17 h, 58%. (g) KHF_2, Ac_2O, H_2O_2, DMF, rt, 12 h, 65%. (h) 3 M HCl, EtOAc, 0 °C, 10 min, 97%.

furnished unsaturated ester **15** in 94% yield. In addition to full 2D NMR spectroscopic characterization, the structure of **15** was unambiguously confirmed by X-ray crystallographic analysis.

With the tricyclic core scaffold of Gelsemoxonine in hand, we focused on the introduction of the spiro-fused oxindole at C(7) (Scheme 5). The stereoselective construction of the quaternary oxindole stereocenter has proven to be a major challenge in many syntheses of *Gelsemium* alkaloids.[2] The system investigated herein proved resistant to a number of intermolecular arylation attempts with various derivatives of **15**. Hence, we turned our attention to the intramolecular addition of aryl nucleophiles to the *α,β*-unsaturated carbonyl. Thereby, an intramolecular reductive Heck reaction would offer an attractive approach to achieve such a transformation. Although the Heck reaction has been commonly used for the construction of quaternary stereocenters, including oxindole ring systems,[17] the envisioned reductive variant of this transformation posed a few challenges when applied to projected substrate **16**. Given that a putative arylpalladium intermediate would need to add regiospecifically to the congested C(7) carbon, the stereochemical outcome could not be predicted on steric grounds.[18] Additionally, the reductive quenching of the resulting alkylpalladium species could be complicated by a variety of undesired competing side reactions. This includes reopening of the oxindole ring, *β*-hydride elimination, side reactions involving the adjacent azetidine ring, and potential cleavage of the N−O bond in **16**. In order to test the strategy, hydroxamic acid **16** was prepared following hydrolysis of ester **15** using Me_3SnOH.[19] The resulting carboxylic acid was then converted into the acid chloride and coupled to *N*-(2-bromophenyl)hydroxylamine.[20] Gratifyingly, upon exposure of aryl bromide **16** to reductive Heck conditions,[21] employing formic acid as the reductant, the formation of oxindole **17** was observed in 72% yield and as a single diastereoisomer.[22] The *N*-hydroxyl in **17** was methylated to deliver *N*-methoxy oxindole **18** in 92% yield.

With the introduction of the oxindole secured, installation of the ethyl ketone remained as the final task in the synthesis route. To this end, a protocol involving hydroxyl directed hydrosilylation of the triple bond was employed.[23] Following this strategy, the C(14) Boc carbonate could be selectively cleaved using K_2CO_3 in MeOH in 87% yield. The resulting secondary alcohol was subjected to hydrosilylation conditions employing $\{[RuCl_2(C_6H_6)]_2\}$ as a catalyst to furnish vinylsilane **19** in 58% yield as an inconsequential mixture of double bond isomers.[24] Oxidation of this mixture under Tamao−Fleming conditions[25] delivered ethyl ketone product in 65% yield. Final removal of the *N*-Boc carbamate using 3 M HCl delivered the natural product Gelsemoxonine (**1**) in 97% yield. The characterization data of the synthetic material matched the reported data for natural Gelsemoxonine[5] in all respects.

In summary, we have achieved the total synthesis of Gelsemoxonine (**1**) in a sequence of 21 linear steps starting from aldehyde **3**. The synthesis relies on the ring contraction of a spirocyclopropane isoxazolidine to deliver a *β*-lactam intermediate, which was further used to build up the azetidine ring of Gelsemoxonine. Additional salient features of the synthesis include a diastereoselective reductive Heck cyclization for the construction of the oxindole ring and directed hydrosilylation of a triple bond to generate the ethyl ketone. Over the course of the synthesis, we have established the use of the ring contraction reaction of spirocyclopropane isoxazolidine to give a *β*-lactam in a complex setting. This little-studied, mechanistically intriguing reaction is sure to find additional tactical applications in the synthesis of complex structures incorporating azetidines.

dx.doi.org/10.1021/ja403823n | *J. Am. Chem. Soc.* 2013, 135, 8500−8503

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

■ ACKNOWLEDGMENTS

We dedicate this manuscript to Prof. Dr. Scott E. Denmark in honor of his 60th birthday. We are grateful to Dr. B. Schweizer and M. Solar for X-ray crystallographic analysis and to Dr. M.-O. Ebert, R. Arnold, R. Frankenstein, and P. Zumbrunnen for NMR measurements. S.D. acknowledges the Stipendienfonds Schweizerische Chemische Industrie (SSCI).

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