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Total Synthesis of Gelsemoxonine

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Supporting Information

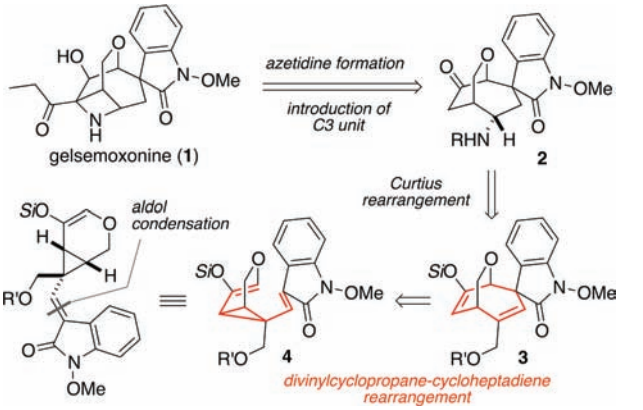
ABSTRACT: The first total synthesis of gelsemoxonine (**1**) has been accomplished. Divinylcyclopropane−cycloheptadiene rearrangement of the highly functionalized substrate was successfully applied to assemble the spiro-quaternary carbon center connected to the bicyclic seven-membered core structure. A one-pot isomerization reaction of the α,β-unsaturated aldehyde to the saturated ester via the TMSCN−DBU reagent combination allowed a facile diastereoselective introduction of the latent nitrogen functionality of the unique azetidine moiety.

Among the vast array of monoterpenoid indole alkaloids, gelsemium alkaloids constitute a relatively large family. These alkaloids have provided a benchmark for state-of-the-art synthetic strategies due to their highly complex, compact, and strained structures. Gelsemine, the most well-known member of this family, has long been a challenging target, and a variety of its total syntheses have been reported to date.[1] A relatively new member of these attractive gelsemium alkaloids, gelsemoxonine (**1**), was isolated in 1991 from the leaves of *Gelsemium elegans*.[2] The structure of gelsemoxonine was originally misassigned, but was later revised by Aimi in 2003 on the basis of an X-ray crystallographical analysis.[3] The corrected structure features the unique azetidine substructure bearing a tetra-substituted carbon center, which is atypical among indole alkaloids. Combined with the quaternary center of the spiro-*N*-methoxy indolinone and the intricate cyclic system, **1** posed a formidable challenge to synthetic chemistry. Inspired by the unique and complex structure, along with the intriguing cytotoxic potency of the closely related natural products,[4] we embarked on a synthetic study of **1**.

As shown in our retrosynthetic analysis (Scheme 1), formation of the azetidine moiety and introduction of a three-carbon unit would be performed in the late stages of the synthesis. The requisite amine moiety on the carbon skeleton of **2** is to be introduced via a process involving a Curtius rearrangement from **3**. We planned the construction of the oxabicyclo[3.2.2]nonane skeleton of **3** through a process involving the divinylcyclopropane−cycloheptadiene rearrangement.[5] Substrate **4**, bearing a densely functionalized cyclopropane moiety, was envisioned to form through an aldol condensation.

Our synthesis began with the *m*-CPBA-mediated Achmatowicz reaction[6] of furfuryl alcohol (**5**) to afford the hydroxy enone **6** (Scheme 2). According to the report by Feringa,[7] we employed lipase AK for the enantioselective preparation of (*S*)-**7** via dynamic kinetic resolution (DKR), albeit with rather unsatisfactory enantiopurity (74% ee). Solvolysis of the DKR product was thus examined for the selective removal of the undesired *R*-isomer using a lipase that exhibited a selectivity opposite that of

Scheme 1. Retrosynthetic Analysis



lipase AK. To our delight, the enantiopurity of the *S*-isomer improved through the use of lipase CR from *Candida rugosa*.[8] **7** was reproducibly obtained with greater than 99% ee on a 10-g scale. With the optically pure material in hand, **7** was treated with diethyl bromomalonate (**8**) and DBU. Conjugate addition of the bromomalonate anion from the less hindered α-face of the enone, followed by cyclization, delivered cyclopropane **9** as a single isomer. Chiral HPLC analysis of the product indicated no signs of base-induced racemization. Therefore, stereochemical control of the cyclopropane moiety was successfully achieved. With the construction of the quaternary stereocenter secured, we next turned our attention to the removal of the acetoxy group. Despite the fact that **9** was found to be unstable under acidic conditions, extensive examination of the reaction conditions eventually led to finding that the combination of Et_3SiH and TMSOTf in acetonitrile effected the efficient reduction of **9** to **10**. Notably, the use of acetonitrile was indispensable to suppress the decomposition of **9**.

The densely substituted cyclopropane moiety in **4** was constructed from **10** by way of the triol **11**. While **10** could be readily reduced by treatment with $LiAlH_4$, isolation of the resultant triol **11** proved troublesome due to its high chelating ability and water solubility. After extensive experimentation, we were pleased to find that the reduction could be achieved by $NaBH_4$ in refluxing THF with a slow addition of methanol.[9] Quenching of the reaction with acetic acid and repeated evaporation−addition cycles from methanol to remove trimethyl borate gave the mixture of sodium acetate and the triol **11**, which could be purified by silica gel chromatography after filtration. With access to the desired

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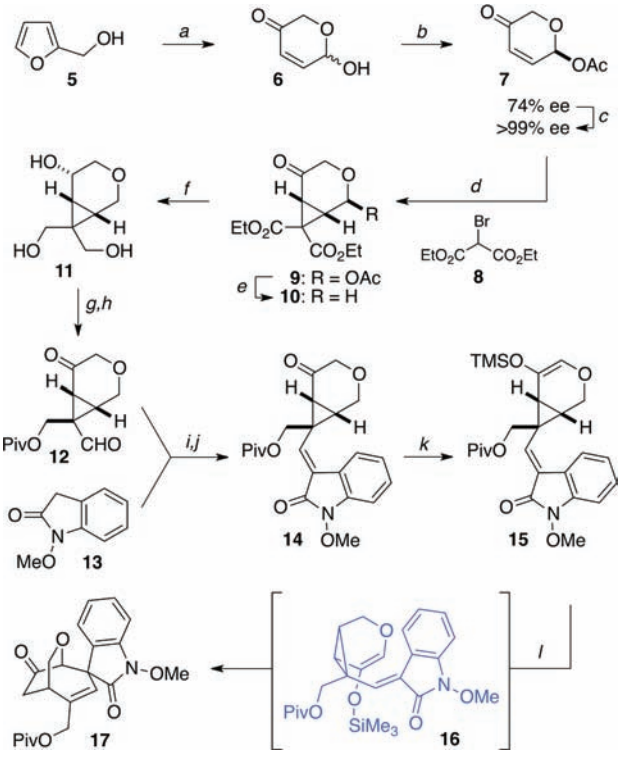
Scheme 2. Divinylcyclopropane−Cycloheptadiene Rearrangement[a]



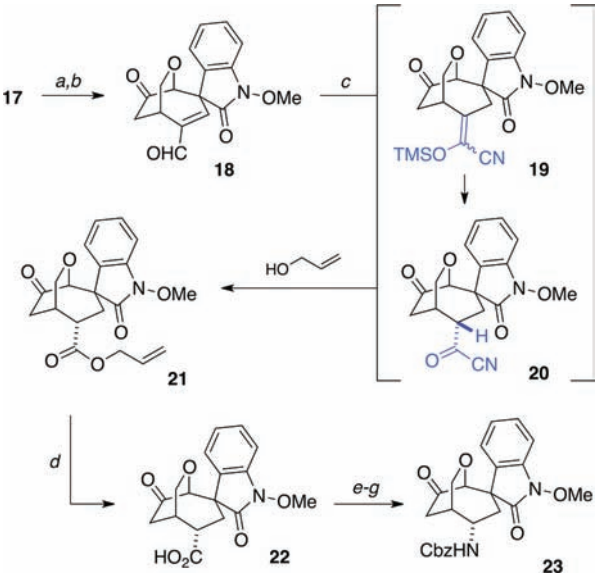
[a] Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 73%; (b) lipase AK, vinyl acetate, rt, 78%, 74% ee; (c) lipase CR, *n*-BuOH/*n*-hexane, rt, 65%, >99% ee; (d) **8**, DBU, THF, 0 °C, 78%; (e) TMSOTf, Et_3SiH, MeCN, 0 °C to rt, 82%; (f) $NaBH_4$ (10 equiv), MeOH (12 equiv, slow addition), THF, reflux; AcOH, 0 °C, 84%; (g) Piv_2O, pyridine, DMAP, CH_2Cl_2, reflux, 86%; (h) IBX, DMSO, 50 °C, 93%; (i) **13**, *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C; (j) MsCl, TMEDA, CH_2Cl_2, −78 °C, 88% (2 steps); (k) TMSCl, THF; LHMDS, −78 °C; (l) toluene, 70 °C, 30 min; TBAF, AcOH, rt, 89% (2 steps).

triol **11** assured, the less hindered primary alcohol was selectively protected as the pivalate. Subsequent oxidation of the resulting diol with IBX afforded the keto-aldehyde **12** in 93% yield.

Since the conventional Knoevenagel condensation between the aldehyde **12** and indolinone **13**[10] proved unsuccessful, a two-step aldol condensation by means of boron enolate[11] was chosen instead. Gratifyingly, the aldol reaction followed by dehydration, mediated by MsCl and TMEDA[12] at −78 °C, successfully afforded **14** as a single diastereomer. Subsequent treatment with LHMDS in the presence of TMSCl furnished the divinylcyclopropane **15**, the substrate for the key divinylcyclopropane−cycloheptadiene rearrangement. In accordance with our retrosynthetic analysis, the silyl enol ether **15** rearranged smoothly, upon heating at 70 °C for 30 min. Removal of the TMS group with TBAF in the presence of acetic acid furnished the desired bicyclic ketone **17** in 89% yield from **14**. The stereochemistry of **17** was consistent with that predicted from the stereochemistry of the transition state **16**, thereby affording the bicyclic structure with the correct stereochemistry of the quaternary spirocenter.

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

Scheme 3. Pivotal, Stereoselective Introduction of a Nitrogen Atom[a]



[a] Reagents and conditions: (a) NaH, MeOH, 0 °C to rt, 88%; (b) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 90%; (c) TMSCN, DBU, THF, 0 °C; allyl alcohol, 0 °C, 78% (**21**:*epi*-**21** = 4:1); (d) $Pd(PPh_3)_4$, pyrrolidine, MeCN, 0 °C to rt, 96%; (e) $(COCl)_2$, CH_2Cl_2, rt; (f) NaN_3, toluene·H_2O, 0 °C; (g) benzyl alcohol, toluene, 80 °C, 82% (3 steps).

molecules, manipulation of the carbon−carbon double bond on the bicyclic structure **17** proved extremely difficult. After extensive studies, we shifted our focus on the redox isomerization of the unsaturated aldehyde **18** (Scheme 3).[13] Thus, solvolysis of **17** followed by TEMPO oxidation provided the α,β-unsaturated aldehyde **18**. Upon treatment of **18** with TMSCN and DBU, the α,β-unsaturated nitrile **19** arose from the DBU-mediated isomerization of the incipient cyanohydrin trimethylsilyl ether.[14] Interestingly, ensuing treatment of the reaction mixture with allyl alcohol resulted in the selective protonation of the silyl enol ether **19** to afford the acyl cyanide **20**, which was further transformed to the corresponding allyl ester **21** (78%) in one pot[15] as a 4:1 diastereomeric mixture with the thermodynamically more stable *epi*-**21**.[16] The ester **21** thus prepared could be transformed to the Cbz-protected amine **23** in a three-step sequence involving deallylation, Curtius rearrangement of the resulting carboxylic acid **22**, and treatment with benzyl alcohol. Stereoselective introduction of the nitrogen atom on the bicyclic skeleton was thus achieved.

For the construction of the azetidine moiety, an epoxide functionality with the proper stereochemistry must be introduced to the bicyclic structure. This should require a prior introduction of a 1-propanoyl group at the α-position of the ketone in **23**. Since introduction of a three-carbon unit to **23** met with failure, we opted to employ a stepwise approach. Fortunately, introduction of a one-carbon unit using Bredereck's reagent[17] (**24**) proceeded smoothly to give **25**, in spite of the presence of the nearby carbamate (Scheme 4). The vinylogous amide **25** was then treated with Vilsmeier's reagent to give the β-chloro unsaturated aldehyde **26**.[18] Dechlorination was subsequently achieved by treatment with $Pd(PPh_3)_4$ and Et_3SiH[19] to furnish the aldehyde **27**. Addition of EtMgBr followed by IBX oxidation afforded the ethyl ketone **28** and provided the complete carbon framework of gelsemoxonine (**1**). To our delight,

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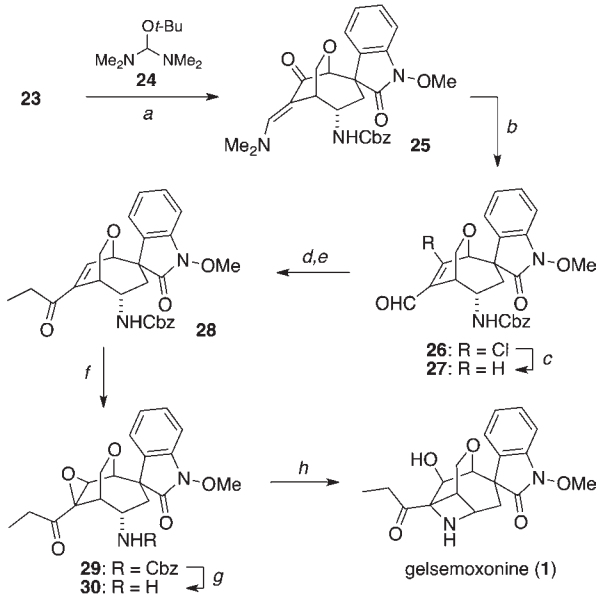
Scheme 4. End Game of the Total Synthesis of Gelsemoxonine[a]



[a] Reagents and conditions: (a) Bredereck's reagent (**24**), toluene, 70 °C, 97%; (b) $(COCl)_2$, DMF, 70 °C, 80%; (c) $Pd(PPh_3)_4$, Et_3SiH, Et_3N, DMF, 80 °C, quant.; (d) EtMgBr, THF, −78 °C; (e) IBX, DMSO, 50 °C, 65% (2 steps); (f) TBHP, Triton B, THF, −20 °C, 95%; (g) TMSI, CH_2Cl_2, 0 °C; (h) EtOH, reflux, 79% (2 steps).

introduction of the desired epoxide moiety to the α,β-unsaturated ketone **28** was accomplished upon exposure to TBHP and Triton B at −20 °C. The nucleophile was delivered from the opposite face to the bulky indolinone and selectively provided the desired diastereomer **29**. Since the *N*−*O* bond of the *N*-methoxyindolinone moiety in **29** did not survive the hydrogenolysis conditions, deprotection of the Cbz group was effected by trimethylsilyl iodide[20] to give the penultimate intermediate **30**. Despite extensive efforts, all attempts to accomplish the requisite opening of the epoxide by changing protic and Lewis acids as well as bases in a variety of solvents failed. It was, therefore, entirely surprising to find that the ring-opening reaction proceeded when **30** was simply heated in boiling ethanol,[21] giving almost exclusively the desired gelsemoxonine (**1**) on over 300-mg scale. Spectral data of the synthetic gelsemoxonine were identical to those of the natural product in all respects.

In summary, the work described above constitutes the first total synthesis of gelsemoxonine, featuring a divinylcyclopropane−cycloheptadiene rearrangement for the construction of a challenging quaternary center of the spiro indolinone (**15**→**17**) and a redox isomerization via the TMSCN−DBU combination (**18**→**21**) as two key transformations.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, copies of spectral data, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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