Natural Products

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Biomimetic Total Synthesis of (+)-Gelsemine**

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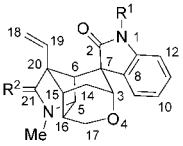
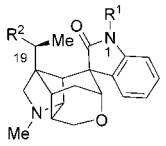
(+)-Gelsemine, a major alkaloid component of *Gelsemium sempervirens*, was first isolated in 1876.[1] Its intriguing structure was elucidated in 1959 by NMR spectroscopy[2] and X-ray crystallographic analysis.[3] To date, seven members of the gelsemium alkaloid family have been characterized (**1**–**7**).[4] These oxindole alkaloids have a hexacyclic architecture



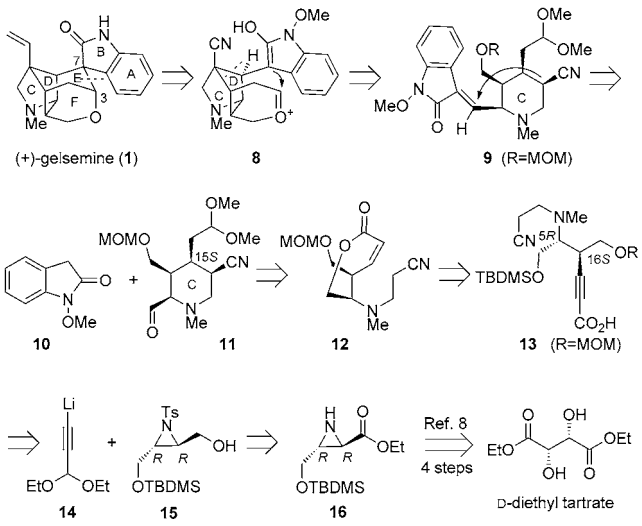
(+)-gelsemine (**1**), R^1 = H, R^2 = H, H
(+)-gelsevirine (**2**), R^1 = OMe, R^2 = H, H
(+)-21-oxogelsemine (**3**), R^1 = H, R^2 = O
(+)-21-oxogelsevirine (**4**), R^1 = OMe, R^2 = O



(+)-19-hydroxydihydrogelsemine (**5**)
R^1 = H, R^2 = OH
(+)-19-hydroxydihydrogelsevirine (**6**)
R^1 = OMe, R^2 = OH
(+)-19-acetoxydihydrogelsevirine (**7**)
R^1 = OMe, R^2 = OAc

and seven carbon stereocenters, including two quaternary stereocenters compacted into a small cage. The challenging structure of gelsemine (**1**) has been the target of extensive synthetic efforts around the world;[5] within the last two decades a number of total syntheses were reported by the research groups of Johnson, Speckamp, Fukuyama, Hart, Overman, and Danishefsky.[6] Among these total syntheses, there was only one asymmetric total synthesis accomplished by the Fukuyama group.[6g] Furthermore, none of these total syntheses has sufficiently illustrated the possible biosynthetic pathway of the gelsemine family. Herein, we report a biomimetic total synthesis of (+)-gelsemine, in which the key reaction involves an intramolecular enol–oxonium cyclization that assembles the cage structure in a highly efficient way. Besides, a new biosynthetic pathway for the late stage of the biosynthesis of gelsemine is proposed based on the achieved enol–oxonium cyclization procedure.[7]

The retrosynthetic analysis of (+)-gelsemine is shown in Scheme 1. We speculated that the cage structure of (+)-gelsemine could be assembled from an intermediate such as **8** in



Scheme 1. Retrosynthetic analysis of (+)-gelsemine. TBDMS = *tert*-butyldimethylsilyl, MOM = methoxymethyl, Ts = toluene-4-sulfonyl.

a single step by acid-catalyzed enol–oxonium cyclization to form, simultaneously, the E ring, the F ring, the C7 quaternary stereocenter of spirooxindole, and the C3-stereocenter. We reasoned that the D ring could be constructed by intramolecular Michael addition of highly functionalized nitrile **9**, which can be readily prepared by intermolecular aldol addition of oxindole **10** to *cis* tetra-substituted piperidinoaldehyde **11**, followed by dehydration. The 15*S* configuration in **11** could be generated by stereoselective formation of the C ring by an intramolecular Michael addition of oxepinone **12**. Partial hydrogenation of alkynyl acid **13** could yield the *cis* double bond in **12**. The *S* configuration at C16 in **13** could be produced by regio- and stereoselective ring opening of aziridine (*R*,*R*)-**15** induced by the hydroxy group. The stereochemistry in (*R*,*R*)-**15** could be generated from the known ester (*R*,*R*)-**16**,[8] which is easily prepared from D-diethyl tartrate in a four-step procedure.

Our biomimetic total synthesis of (+)-gelsemine began by converting (*R*,*R*)-**16** into the chiral *cis* tetra-substituted piperidinoaldehyde **11** (Scheme 2). Two steps of reduction

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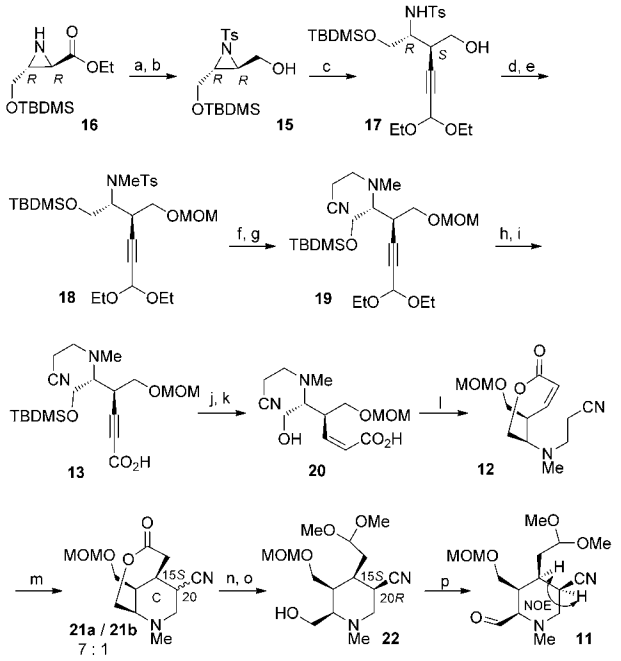


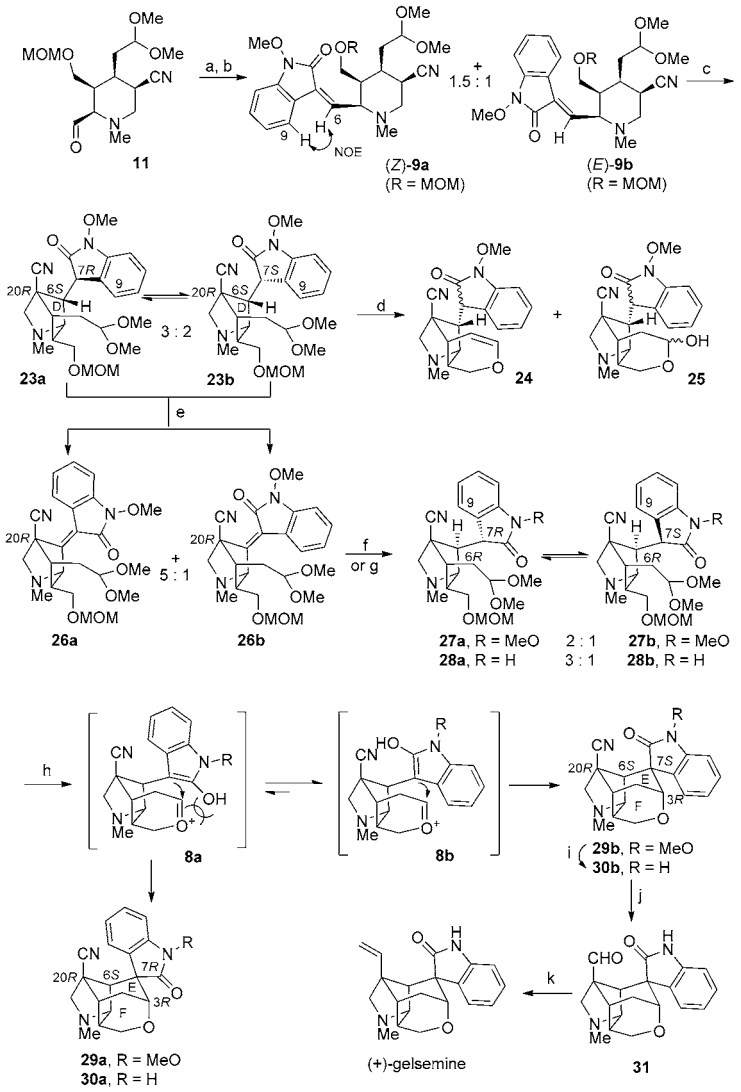
Scheme 2. Preparation of the chiral *cis* tetra-substituted piperidine ring. Reagents and conditions: a) $LiAlH_4$, EtOH, 0 °C→25 °C, 3 h, 85 %; b) TsCl, Et_3N, CH_2Cl_2, 0 °C→25 °C, 3 h, 90 %; c) (3,3-diethoxyprop-1-yn-1-yl)lithium **14**, THF, 0 °C→25 °C, 5 h, 95 %; d) MeI, K_2CO_3, DMF, 25 °C, 98 %; e) MOMCl, NaH, THF, 0 °C, 2 h, 95 %; f) Mg, MeOH, ultrasound, 0 °C, 3 h, 90 %; g) acrylonitrile, MeOH, reflux, 10 h, 95 %; h) TFA, CH_2Cl_2, −10 °C, 3 h, 85 %; i) $NaClO_2$, NaH_2PO_3, *t*BuOH/H_2O 1:1, 25 °C, 3 h, 94 %; j) Lindlar cat, H_2, EtOH, 25 °C, 10 h, 95 %; k) HF, pyridine, 0 °C→25 °C, 10 h, 90 %; l) DCC, DMAP, CH_2Cl_2, 25 °C, 10 h, 85 %; m) LiHMDS, THF, −78 °C, 10 min, 66 %; n) DIBAL-H, CH_2Cl_2, −78 °C, 30 min, 60 %; o) $HC(OMe)_3$, *p*-TsOH, MeOH, 0 °C→25 °C, 2 h, 80 %; p) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, 1 h, 92 %. TFA = trifluoroacetic acid, DCC = dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, HMDS = 1,1,1,3,3,3-hexamethyldisilazanide, DIBAL-H = diisobutylaluminum hydride, DMSO = dimethylsulfoxide.

and tosylation of **16** provided alcohol (*R*,*R*)-**15** in moderate yield. The attack by **14** on **15** occurred from the top face of the aziridine ring to afford **17** as a single stereomer in 95 % yield. The excellent regio- and stereoselectivity is probably due to coordination of the lithium reagent **14** with the hydroxy group and efficient blockage of the bottom face of the aziridine ring by the bulky OTBDMS group in **15**.[9] Two steps of methylation with MeI and protection of the hydroxy group in **17** provided compound **18** in excellent yield. After removal of the tosyl group in **18** with Mg dust using ultrasound,[10] the resulting amine reacted with acrylonitrile in MeOH at reflux to give **19** in excellent yield. Treatment of **19** with TFA at −10 °C, and subsequent oxidation of the resulting aldehyde group with sodium chlorite yielded acid **13** in 85 % yield in two steps. Partial hydrogenation of the alkynyl group with Lindlar catalyst and removal of the TBDMS group with HF/pyridine in **13** provided *cis* olefin **20** in excellent yield. To prepare the piperidine ring with an *S* configuration at C15 as in the (+)-gelsemine structure, an oxepinone ring was first generated by condensation of the acid group with the hydroxy group in **20** to give **12** in 85 % yield. Intramolecular Michael addition at low temperature yielded two inseparable diastereomers (15*S*,20*R*)-**21a** and (15*S*,20*S*)-**21b** in 66 % yield in a 7:1 ratio. The mixture of diastereomers **21a** and **21b** became separable after the lactone group in **21** was reduced to an aldehyde with DIBAL-H at low temperature, and the resulting aldehyde group was protected with a dimethoxy group, affording the major isomer (15*S*,20*R*)-**22** in 48 % yield in two steps. Oxidation of the hydroxy group in **22** provided the *cis* tetra-substituted piperidinoaldehyde **11** in 92 % yield. The *cis* relationship was confirmed by a strong NOE observed between the two protons at carbon atoms C15 and C20.

After having synthesized the *cis* tetra-substituted piperidinoaldehyde **11** with the required stereochemistry, we began to prepare compound **9**, which is the precursor for forming the D ring through a Michael addition (Scheme 3). Condensation of **11** with *N*-methoxyoxindole **10** in the presence of LDA at −78 °C, followed by dehydration of the resulting hydroxy group with $SOCl_2$/pyridine provided two separable geometric isomers (*Z*)-**9a** and (*E*)-**9b** in a 1.5:1 ratio. The *Z* conformation of the double bond in **9a** was confirmed by a strong NOE observed between the olefin proton at C6 and the aromatic proton at C9. As expected, the mixture of **9a** and **9b** easily underwent Michael addition in the presence of LDA in THF at −78 °C to yield two inseparable diastereomers **23a** and **23b** epimerized at C7 in 75 % yield. The Michael addition of **9** not only formed the D ring, but also created the correct C20 quaternary carbon center with an *R* configuration. However, the addition led to an *S* configuration at C6 rather than the desired *R* configuration. The *S* configuration at C6 prevented that the oxindole moiety gained access to the oxonium cation that was formed in situ when the MOM group and the two methoxy groups in **23** were removed under acidic conditions. Indeed, initial attempts to form the E and F ring by enol–oxonium cyclization generated both olefin **24** and pyranol **25** when the mixture of **23a** and **23b** was treated with either TFA at room temperature or TsOH in $CHCl_3$ at reflux.

To invert the C6 *S* configuration in **23** to an *R* configuration and thereby allow construction of the E and F rings by enol–oxonium cyclization, a double bond between C6 and C7 was generated to yield two separable geometric isomers **26a** and **26b** in 72 % yield in a 5:1 ratio by using a standard protocol of olefination with PhSeCl/LDA/$NaIO_4$ (Scheme 3). Hydrogenation of the double bond in **26** with Lindlar catalyst at 1 atm of hydrogen pressure in MeOH within three hours resulted in two inseparable diastereomers **27a** and **27b** in 90 % yield in a 2:1 ratio. The hydrogenation proceeded such that the nucleophilic attack occurred from the less hindered bottom face of the double bond, thereby yielding **27a** and **27b** with C6 exclusively in the *R* configuration. In contrast, hydrogenation of **26** with the more active catalyst Pd/C under the same conditions yielded two inseparable *N*-demethoxy products **28a** and **28b** in a 3:1 ratio in quantitative yield.

With **27a** and **27b** in hand, we carried out the planned one-pot, multi-step enol–oxonium cyclyzation reaction cascade to efficiently assemble both the E and F rings, and simultaneously establish the C3- and C7-stereocenters. When the mixture of **27a** and **27b** was treated with stoichiometric TsOH in CH_3Cl at reflux for four hours, two separable



Scheme 3. Synthesis of (+)-gelsemine. Reagents and conditions: a) **10**, LDA, THF, −78 °C, 12 h, 75%; b) $SOCl_2$, pyridine, 0 °C, 5 min, 90%; c) LDA, THF, −78 °C, 30 min, 75%; d) condition a: TfOH, $CHCl_3$, RT. 24 h or condition b: *p*-TsOH, $CHCl_3$, reflux, 10 h. e) LDA, PhSeCl, THF, −78 °C, 30 min; then $NaIO_4$, $NaHCO_3$, MeOH/THF/H_2O 5:1:1, 25 °C, 10 h, 70% in 2 steps; f) Lindlar cat., H_2, MeOH, 25 °C, 3 h, 90% (gave **27a** and **27b**); g) 5% Pd/C, H_2, MeOH, 25 °C, 10 h, 98% (gave **28a** and **28b**); h) *p*-TsOH, $CHCl_3$, reflux, 4 h, 73%, **29a**/**29b** 1:10 ratio; i) 5% Pd/C H_2, MeOH, 25 °C, 10 h, 98%; j) DIBAL-H, Tol, −78 °C, 10 h, 72%; k) Tebbe reagent, THF, pyridine, reflux, 10 h, 60%. LDA = lithium diisopropylamide, Tf = trifluoromethanesulfonyl.

diastereomers **29a** and **29b** were obtained in 73% yield in a 1:10 ratio. Apparently, the reaction proceeded via two transition states **8a** and **8b**. The natural major isomer **29b** with the desired 7*S* configuration was produced from the favored transition state **8b**, in which an electronic repulsion between the oxonium cation and the hydroxy group of the enol functionality is avoided. In contrast, the disfavored transition state **8a**, in which both electron repulsion and a steric effect are present, led to the unnatural minor isomer **29a** with the inverse 7*R* configuration. Interestingly, when the same reaction conditions were applied to **28a** and **28b**, a complex mixture resulted, rather than the corresponding cyclization products **30a** and **30b**. These results indicate that, in the absence of a methoxy substituent on the oxindole nitrogen atom, an enol functionality does not efficiently form during the reaction.[11]

After having successfully synthesized **29b**, which possesses all the ring systems and correct stereochemistry of the carbon stereocenters of the target (+)-gelsemine, we turned our effort to the final task of converting the nitrile substituent at C20 in **29b** to an ethylene substituent (Scheme 3). After removal of the methoxy group in **29b** by hydrogenation with 5% Pd/C, the nitrile group in **30b** was reduced to an aldehyde group to provide **31** in 71% yield in two steps. Initial efforts with olefination of **31** using the Wittig reagent $Ph_3P{=}CH_2$ failed under various conditions, because the aldehyde group in **31** was severely hindered. Fortunately, olefination of **31** with Tebbe reagent yielded (+)-gelsemine in 60% yield.[12] The synthetic (+)-gelsemine showed ^1H and ^{13}C NMR spectra that were identical to those of a previous report[6f] and the commercially available (+)-natural gelsemine.[13]

In summary, the biomimetic total synthesis of (+)-gelsemine from (*R*,*R*)-aziridine **16** has been accomplished in 25 steps with approximately 1% overall yield. A multi-step, one-pot enol–oxonium cyclization cascade is used in a highly efficient way to construct, simultaneously, the E ring, F ring, C3-stereocenter, and C7 quaternary stereocenter. The current synthesis using the enol–oxonium cyclization reaction as a key step to make the cage structure has demonstrated a possible biosynthetic pathway. We also demonstrated that without a methoxy substitutent on the oxindole nitrogen atom, the enol–oxonium cyclization does not work (failure of converting compound **28** to compound **30**). This result is meaningful for elucidating the function of the methoxy group in the proposed biosynthetic procedure, and to partially explain why most members of the gelsemine family have a methoxy substitutent on the oxindole nitrogen atom.

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