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Enantioselective Total Synthesis of (+)-Gelsemine: Determination of Its Absolute Configuration**

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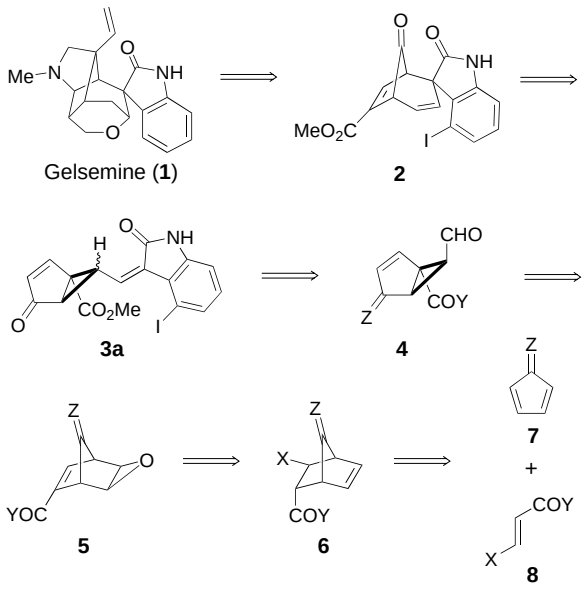
Since the structure of gelsemine (**1**) was determined in 1959, many efforts have been directed toward total synthesis of this unique hexacyclic cage-like molecule.[1] While three groups independently accomplished the total synthesis of racemic gelsemine in 1994, none of them succeeded in controlling the stereochemistry of the critical spiroindolinone system.[2] In 1996, our own approach culminated in the completely stereocontrolled total synthesis of (±)-gelsemine featuring a divinylcyclopropane rearrangement to control the stereochemistry of the spiroindolinone system.[3] Despite these intensive studies, an enantioselective total synthesis of gelsemine has not been reported to date.[4] Herein, we disclose the first enantioselective total synthesis of (+)-gelsemine.

Our retrosynthetic analysis of optically active gelsemine is illustrated in Scheme 1. According to our racemic synthesis, the stereochemistry of the spiroindolinone system could be



Scheme 1. Retrosynthesis of gelsemine.

controlled by thermal rearrangement of the key intermediate **3a**, which should be prepared easily by condensation of aldehyde **4** and 4-iodooxindole. The aldehyde **4** could in turn be derived from norbornene epoxide **5** according to the rearrangement reported by Meinwald et al.[5] It seems quite likely that **5** could be prepared from Diels–Alder adduct **6**.

Our enantioselective total synthesis of gelsemine commenced with a chiral auxiliary controlled asymmetric Diels–Alder reaction. In the presence of Et_2AlCl, the Diels–Alder reaction between dienophile **9** and 5-dimethylsilylcyclopentadiene (**10**)[6] proceeded smoothly to give adduct **11** as a single isomer (Scheme 2).[7] The relative and absolute configurations of the adduct were determined by X-ray analysis, based on the configuration of the Evans chiral auxiliary derived from L-phenylalanine.[8] The chiral auxiliary was removed by treatment with $Sm(OTf)_3$ in MeOH to afford methyl ester **12**.[9] Oxidation of the dimethylsilyl group in **12** with H_2O_2 in the presence of KF to provide alcohol **13**,[6, 10] followed by epoxidation with *t*BuOOH and $VO(acac)_2$, gave epoxide **14**.[11] After protection of the alcohol as the TES ether, dehydrochlorination by treatment with *t*BuOK furnished α,β-unsaturated ester **15**.

After extensive optimization of the acid-catalyzed rearrangement of **15**, we found that the critical rearrangement

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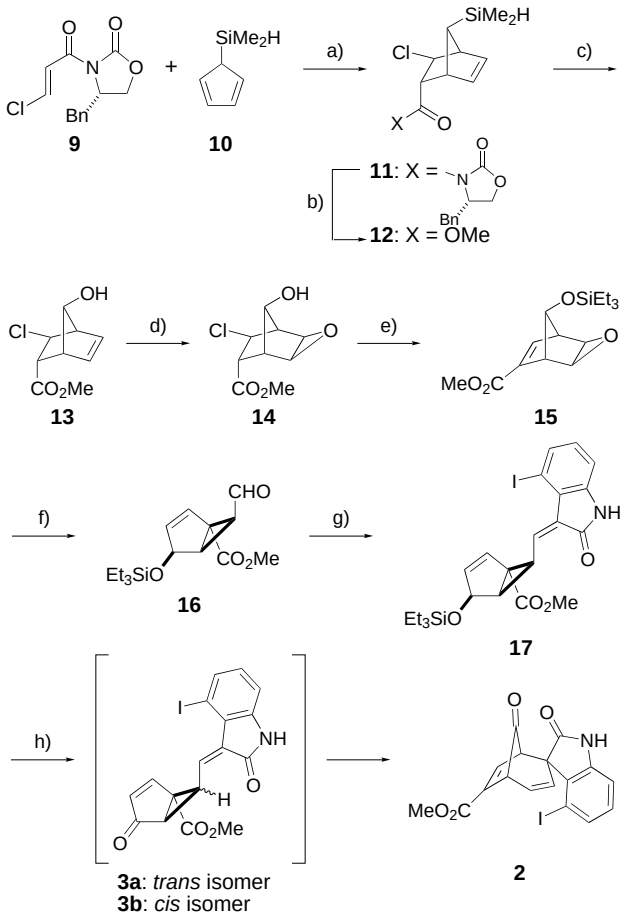
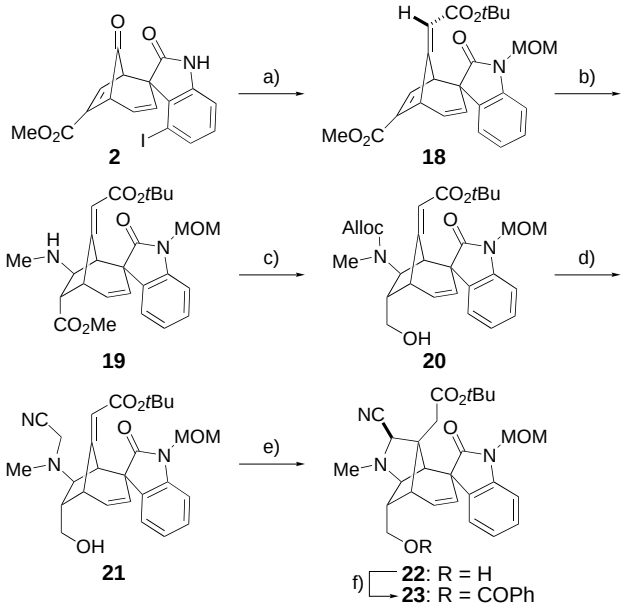


Scheme 2. Synthesis of the bicyclo[3.2.1] system. a) Et_2AlCl, CH_2Cl_2, $-78\,^{\circ}C$, 88%; b) cat. $Sm(OTf)_3$, MeOH, 99%; c) 30% H_2O_2, KF, $KHCO_3$, THF/MeOH, 53%; d) $VO(acac)_2$, *t*BuOOH, benzene, 100%; e) TESOTf, 2,6-lutidine, CH_2Cl_2, 97%; *t*BuOK, benzene, 98%; f) MAD, toluene, $-20\,^{\circ}C$; g) 4-iodooxindole, cat. piperidine, MeOH, 60% (2 steps); h) TBAF, THF, 87%; CrO_3, H_2SO_4, acetone; toluene/MeCN, 90 °C, 83% (2 steps). Bn = Benzyl, Tf = trifluoromethanesulfonyl, acac = acetylacetonate, TES = triethylsilyl, MAD = methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide), TBAF = tetrabutylammonium fluoride.

could be best carried out by treatment with MAD[12] in toluene at $-20\,^{\circ}C$, giving **16** in 65–78% isolated yield. Gratifyingly, the formation of the cyclopropane ring occurred exclusively at the α-position of the methyl ester.[13] A stereoselective installation of the oxindole moiety according to the procedure developed in our racemic synthesis afforded the desired *Z*-alkylidene indolinone **17** as the exclusive isomer.[14] After removal of the TES group, the resultant alcohol was subjected to Jones' oxidation to give a mixture of **3a**, **3b**, and **2**. Even at room temperature, the initial product, *cis* isomer **3b**, underwent *cis*–*trans* isomerization to afford *trans* isomer **3a**, or divinylcyclopropane–cycloheptadiene rearrangement to provide bicyclo[3.2.1] system **2**. The formation of *trans* isomer **3a** was of no consequence since it was the key intermediate of our racemic synthesis of gelsemine. Thus, by heating at 90 °C, the mixture of three compounds furnished bicyclo[3.2.1] system **2** in 83% yield.

Having established the bicyclo[3.2.1] core of gelsemine in enantiomerically pure form, we next focused our attention on the improved construction of the pyrrolidine ring. Our initial attempts to construct the ring by means of radical reactions failed, due presumably to the ring strain. After intensive investigations, we found that an intramolecular Michael addition was a viable solution.

Following the procedure established in our racemic synthesis, alcohol **20** was prepared from **2** (Scheme 3).[3] Elongation of the ketone by Horner–Emmons reaction, one-pot protection of the indolinone nitrogen, and the subsequent



Scheme 3. Construction of the pyrrolidine ring. a) $(EtO)_2POCH_2CO_2tBu$, *n*BuLi, THF, 65 °C; MOMCl, *t*BuOK, 72%; nBu_3SnH, AIBN, benzene, reflux, 75%; b) $MeNH_2$, MeOH, 100%; c) AllocCl, pyridine, cat. DMAP, CH_2Cl_2, 94%; $LiBH_4$, cat. $LiBEt_3H$, THF, 94%; d) $[Pd(PPh_3)_4]$, pyrrolidine, THF; ICH_2CN, iPr_2NEt, MeCN, 60 °C, 78% (2 steps); e) KHMDS, THF, -78 to 0 °C, 62%; f) PhCOCl, pyridine, cat. DMAP, CH_2Cl_2, 92%. MOM = methoxymethyl, AIBN = 2,2′-azobisisobutyronitrile, Alloc = allyloxycarbonyl, DMAP = 4-dimethylaminopyridine, KHMDS = potassium hexamethyldisilazide.

radical deiodination provided **18**. Michael addition of methylamine to the strained α,β-unsaturated ester took place from the less hindered *exo* side to give *trans*-aminoester **19** as a single isomer. After protection of the amine as an allyl carbamate, the methyl ester, which was prone to epimerization, was reduced with $LiBH_4$ in the presence of a catalytic amount of $LiBEt_3H$ to furnish alcohol **20**.[15]

At this stage, a cyanomethyl group was installed on the amine to perform the critical intramolecular Michael addition. Thus, removal of the Alloc group, followed by cyanomethylation by treatment with iodoacetonitrile, gave aminonitrile **21** in 78% overall yield over two steps. Upon deprotonation with KHMDS, **21** smoothly underwent the intramolecular Michael addition, giving pyrrolidine **22** in 62% yield as the sole isomer.

After protection of the alcohol as its benzoate **23**, the *tert*-butoxycarbonylmethyl group was converted into the vinyl side chain as shown in Scheme 4. Firstly, the *tert*-butyl ester was deprotected with formic acid without affecting the *N*-MOM group to give the carboxylic acid, which was subsequently reduced to alcohol **24** via a mixed anhydride. The

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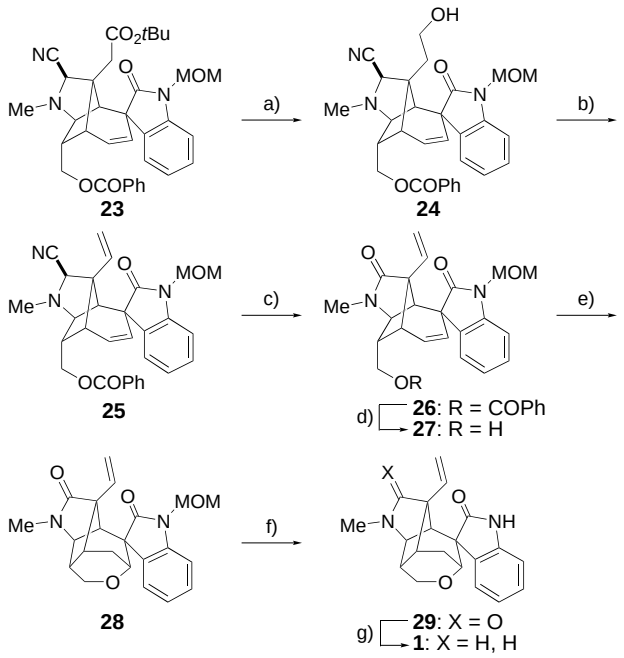

Scheme 4. Completion of the total synthesis of (+)-gelsemine (**1**). a) HCO_2H, 96%; $ClCO_2Et$, NEt_3, THF, then $NaBH_4$, H_2O, 80%; b) *o*-$NO_2C_6H_4SeCN$, PBu_3, THF; MCPBA, then NEt_3, 97%; c) MCPBA, THF/H_2O, then NEt_3, 83%; d) K_2CO_3, MeOH, 96%; e) $Hg(OTf)_2 \cdot PhNMe_2$, $MeNO_2$, then aq NaCl, 97%; $NaBH_4$, NaOH, $BnNEt_3Cl$, CH_2Cl_2/H_2O, 63%; f) TMSCl, NaI, MeCN; NEt_3, MeOH, 63%; g) DIBAL, toluene, 90%. MCPBA = 3-chloroperoxybenzoic acid, TMS = trimethylsilyl, DIBAL = diisobutylaluminum hydride.

resultant alcohol **24** was converted into vinyl compound **25** in 97% yield according to Grieco's procedure.[16]

Before construction of the remaining tetrahydropyran ring, it became necessary to transform the aminonitrile into the lactam.[17] During the course of this investigation, we have developed a facile and direct method for conversion of aminonitriles to lactams, which appears to be generally applicable. Thus, oxidation of **25** with MCPBA, followed by treatment with NEt_3, afforded **26** in 83% yield.[18] Methanolysis of **26** provided the alcohol **27**, which was converted into gelsemine following the same procedure used for our racemic synthesis.[3] The regioselective intramolecular oxymercuration of **27**, followed by reductive demercuration, gave **28**. After removal of the *N*-MOM group, which gave 21-oxogelsemine (**29**), (+)-gelsemine (**1**) was obtained by selective reduction of the *N*-methyllactam with DIBAL. The identity of synthetic gelsemine with the natural product was established by direct comparison of spectral and physical properties including optical rotation ($[\alpha]_D^{25} = +16$ ($c = 0.04$ in $CHCl_3$); ref. [19]: $[\alpha]_D = +15.9$ ($CHCl_3$)).

In conclusion, the first enantioselective total synthesis of (+)-gelsemine was accomplished, featuring a facile construction of the bicyclo[3.2.1] core of gelsemine by means of the two rearrangement reactions and the efficient formation of the pyrrolidine ring by an intramolecular Michael addition. Moreover, the absolute configuration of gelsemine, which was deduced on the basis of the biogenetic studies, was confirmed for the first time by the total synthesis.

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