130 °C for 16 h. The refluxed samples were designated CAH5-RX or CAP10-RX, where X is the reflux time in hours.

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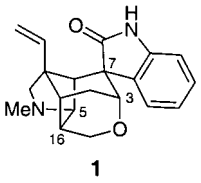
Total Synthesis of (±)-Gelsemine**

Andrew Madin, Christopher J. O'Donnell, Taeboem Oh, David W. Old, Larry E. Overman,* and Matthew J. Sharp

Gelsemine (**1**), the major alkaloid component of *Gelsemium sempervirens* (Carolina or yellow jasmine), was isolated in the 1870s.[1, 2] After eighty years of extensive, and largely inconclusive degradative studies, the structure was solved in 1959 by both NMR and X-ray spectroscopic methods.[3] The densely functionalized hexacyclic skeleton of gelsemine stimulated intensive synthetic efforts throughout the world, which resulted in four total syntheses of (±)-gelsemine.[4] In 1988 we described the preparation of an advanced pentacyclic intermediate,[5] which, although incorporating all the carbon atoms of gelsemine,[5c] did not ultimately prove to be a viable precursor to this hexacyclic alkaloid. Herein we report the total synthesis of (±)-gelsemine by a sequence whose key strategic steps are a sequential anionic aza-Cope rearrangement and Mannich cyclization, an intramolecular Heck reaction, and a complex base-promoted molecular reorganization to generate the hexacyclic ring system.



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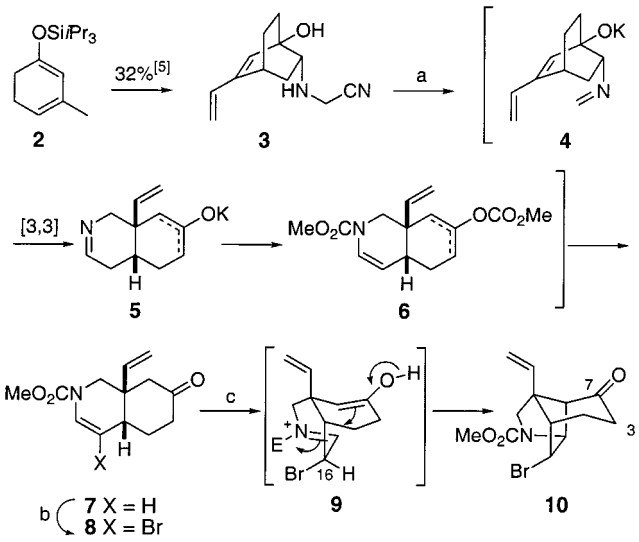
The azatricyclodecane ring system of gelsemine was assembled using a slight modification of the route we reported earlier (Scheme 1).[5] The sequence began with 1-triisopropylsiloxy-3-methyl-1,3-cyclohexadiene (**2**),[6] which was converted into the bicyclo[2.2.2]octene **3** in eight steps (32 % overall yield).[5] Exposure of **3** to potassium hydride and



Scheme 1. Reaction conditions: a) KH, [18]crown-6, THF, rt; $ClCO_2Me$, DTBMP, −78 °C → rt; KOH, MeOH, H_2O, rt, 81 %; b) Br_2, 1,2,2,6,6-pentamethylpiperidine, CH_2Cl_2, −78 °C; c) TFA, reflux, 67 % over 2 steps. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

[18]crown-6 at room temperature promoted the anionic aza-Cope rearrangement of the derived formaldimine alkoxide **4**.[7] Quenching the resulting product **5** with excess methyl chloroformate, followed by selective cleavage of the carbonate functional group of **6** produced *cis*-hexahydroisoquinolinone **7** in 81 % yield. The enecarbamate functional group of **7** was selectively brominated and the resulting product **8** was heated at reflux in trifluoroacetic acid (TFA) to provide the azatricyclodecanone **10** as a single diastereomer in 67 % yield. In this Mannich cyclization, the tetrahydropyridine ring of **8** needs to adopt a high-energy boat conformation **9** in order for the iminium ion and the enol π system to overlap. Preferential cyclization of the thermodynamically favored C16 epimer **9** of the *N*-acyliminium intermediate, delivers tricyclic product, **10** with the bromine substituent on the *exo* face. By using this extensively optimized sequence, **10** could be prepared from commercially available 3-methylanisole in 12 steps and 16 % overall yield.

The next stage of the synthesis involved construction of the spirooxindole at C7 of **10** in such a way that C3 was substituted with a group containing an oxygen functionality that could be employed to form the pyran ring of gelsemine. This objective was accomplished by initially oxidizing the

[*] Prof. L. E. Overman, A. Madin, C. J. O'Donnell, T. Oh, D. W. Old, M. J. Sharp
Department of Chemistry, University of California
516 Rowland Hall, Irvine, CA 92697-2025 (USA)
Fax: (+1) 949-824-3866
E-mail: leoverma@uci.edu

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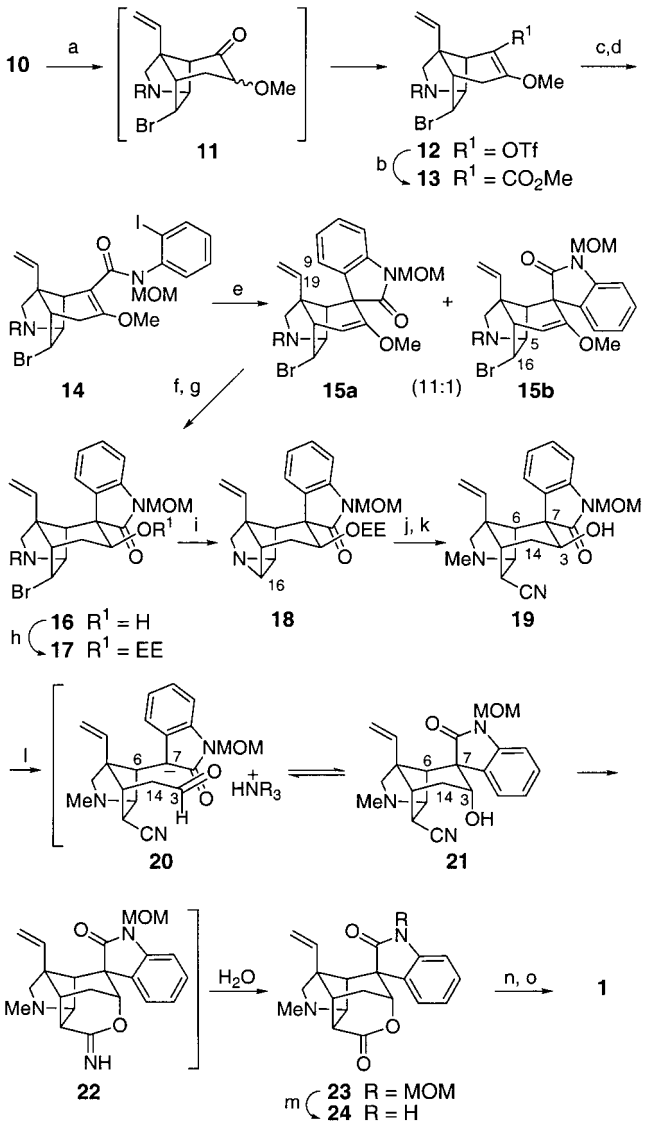
enoxytriethylsilane derivative of **10** with iodosobenzene and $BF_3 \cdot Et_2O$ in the presence of methanol to generate the corresponding α-methoxy ketone **11** as a mixture of stereoisomers (Scheme 2).[8] Treatment of this crude intermediate with potassium hexamethyldisilazane, followed by quenching with Comins' reagent[9] provided enol triflate **12** in 61% overall yield from **10**. Palladium-catalyzed carbonylation of **12** in the presence of methanol gave methyl ester **13** in high yield.



Scheme 2. Reaction conditions: a) KHMDS, Et_3SiCl, THF, $-78\,^\circ C$; $(PhIO)_n$, $BF_3 \cdot OEt_2$, MeOH, CH_2Cl_2, $-78 \rightarrow 0\,^\circ C$; KHMDS, Comins' reagent, THF, $-78\,^\circ C$, 61%; b) CO (3.5 bar), $[PdCl_2(dppf)_2] \cdot CH_2Cl_2$, MeOH, $(nBu)_3N$, DMF, $80\,^\circ C$, 94%; c) 2-iodoaniline, Me_3Al, CH_2Cl_2, $0\,^\circ C \rightarrow$rt, 91%; d) NaH, MOMCl, THF, 86%; e) $[Pd_2(dba)_3] \cdot CHCl_3$, Ag_3PO_4, Et_3N, THF, reflux, 61–78%; f) conc. HCl, MeOH, rt, 98%; g) $(iBu)_3Al$, PhMe, $-78\,^\circ C \rightarrow$rt, 71%; h) ethyl vinyl ether, pyridinium *p*-toluenesulfonate, CH_2Cl_2, rt, 85%; i) NaCN, Me_2SO, $150\,^\circ C$, 99%; j) MeOTf, DTBMP, CH_2Cl_2, $0\,^\circ C$; NaCN, Me_2SO, $90\,^\circ C$, 85%; k) *p*-toluenesulfonic acid $\cdot H_2O$, CH_2Cl_2, MeOH, rt, 99%; l) DBU, PhMe, reflux, 80%; m) conc. HCl, $(MeOCH_2)_2$, $55\,^\circ C$; $(iPr)_2NEt$, MeOH, $55\,^\circ C$, 90%; n) $(iBu)_2AlH$, $PhCH_3$, $0\,^\circ C \rightarrow$rt; o) Et_3SiH, TFA, CH_2Cl_2, reflux, 65% over 2 steps. HMDS = hexamethyldisilazane, Comins reagent = 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, Tf = trifluoromethylsulfonyl, dppf = 1,1′-bis(diphenylphosphano)ferrocene, MOM = methoxymethyl, dba = dibenzylideneacetone, EE = 1-ethoxyethyl, for compounds **11** → **17**, R = CO_2Me.

This intermediate was condensed with the dimethylaluminum amide of iodoaniline[10] and the resulting secondary amide was treated sequentially with sodium hydride and chloromethyl methyl ether to yield **14**.

The stage was set for the pivotal intramolecular Heck reaction, which we approached with some trepidation since it would require the insertion of a tetrasubstituted double bond of a vinylogous carbamate.[11] Fortunately, the Heck cyclization was efficient under cationic Heck conditions and gave an 11:1 mixture of spirooxindole stereoisomers. The major product **15a**, isolated in 61–78% yield, was shown to have the opposite configuration of the spirooxindole as that found in gelsemine.[12, 13]

To complete the synthesis of gelsemine we needed to epimerize the oxindole and fashion the remaining oxacyclic ring.[14] To this end, pentacycle **15a** was hydrolyzed and the resulting ketone was reduced with triisobutylaluminum to provide equatorial alcohol **16** (71% yield) as the major product (dr = 5.6:1).[15] Protection of this alcohol to form **17**, followed by reaction with excess sodium cyanide in dimethyl sulfoxide at $150\,^\circ C$ delivered aziridine **18** in high yield.[16] Methylation of **18** with methyl trifluoromethanesulfonate, followed by regioselective opening of the resulting aziridinium salt at C16 with sodium cyanide and removal of the 1-ethoxyethyl protecting group provided **19** in 85% overall yield. Finally, heating **19** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene brought about the desired molecular rearrangement to form hexacyclic lactone **23** in 80% yield after acidic workup. This complex reorganization likely occurs by a retro aldol cleavage of the C3–C7 bond which generates an intermediate such as **20**. After rotation about the C6–C7 and C3–C14 σ bonds, aldol closure affords the intermediate **21** in which both the oxindole and C3 alcohol have been epimerized. Addition of the resulting axial alcohol to the proximal nitrile to generate hexacyclic imidate **22**, followed by hydrolysis yielded **23**.

Lactone **23** was readily converted into gelsemine by initially removing the methoxymethyl protecting group to provide **24**. Reduction of this intermediate with diisobutylaluminum hydride generated a mixture of lactols, which upon further reduction with triethylsilane and trifluoroacetic acid produced (±)-gelsemine (**1**) in 59% overall yield from **23**.[17]

The total synthesis of (±)-gelsemine (**1**) reported herein was accomplished in 1.2% overall yield by way of 26 isolated intermediates. Key steps include a sequential base-promoted aza-Cope rearrangement and Mannich cyclization, an unprecedented intramolecular Heck insertion of a tetrasubstituted vinylogous carbamate and a complex base-promoted skeletal rearrangement.

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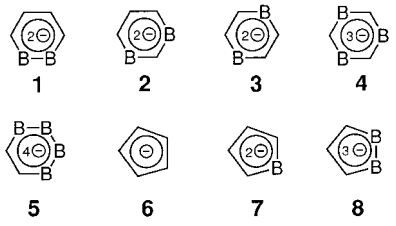
[16] It has not been determined whether this unusual reaction occurs by a double displacement sequence, an S_N1 process, or by other possible mechanisms.
[17] Synthetic (±)-gelsemine (**1**) was identical to a natural sample by TLC, ^{1}H NMR, ^{13}C NMR, IR, and HR-MS analysis.

A Five-Membered Ring with Three Negative Charges and Solvent-Free Lithium Counterions**

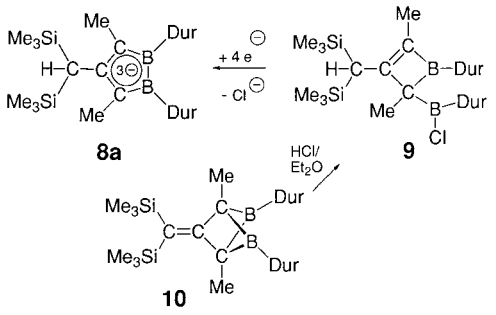
David Scheschkewitz, Matthias Menzel, Matthias Hofmann, Paul von Ragué Schleyer, Gertraud Geiseler, Werner Massa, Klaus Harms, and Armin Berndt*

Dianionic boron heterocycles like **1**–**3** and **7** are well characterized,[1] whereas triply and quadruply negatively charged systems such as **4** and **5** have only been known as



ligands in transition metal triple decker complexes.[2] The derivative of **8** described here is the first five-membered ring with three formal negative charges.[3] Its η^5-bound lithium counterions exhibit remarkably short distances to the ring and are free from "external" π and n ligands.

The orange-red trilithium compound **8a**·Li_3·$2Et_2O$ (Dur = 2,3,5,6-tetramethylphenyl) with *one* solvent-free lithium cation is the only product (besides LiCl) from the reaction of chloroborylboretene **9** with lithium metal in Et_2O. A similar reductive ring expansion in which a B–B bond was



formed during the synthesis of a four-membered ring was reported recently.[4] We isolated **8a**·Li_3·Et_2O with *two* solvent-free lithium counterions by crystallization from boiling toluene. Compound **9** is accessible from diborabicyclopentane **10**[5] and ethereal HCl. Its constitution was secured by

[*] Prof. Dr. A. Berndt, Dr. D. Scheschkewitz, Dr. M. Menzel, G. Geiseler, Prof. Dr. W. Massa, Dr. K. Harms
Fachbereich Chemie der Universität
D-35032 Marburg (Germany)
Fax: (+49) 6421-28-89-17
E-mail: berndt@ps1515.chemie.uni-marburg.de
Dr. M. Hofmann, Prof. Dr. P. von R. Schleyer
Computer Chemistry Annex, Department of Chemistry
University of Georgia, Athens, GA 30602-2525 (USA)

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