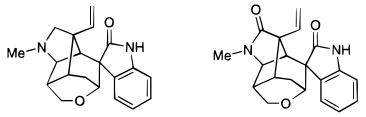
# Stereocontrolled Total Synthesis of (±)-Gelsemine

Tohru Fukuyama* and Gang Liu[1]

*Department of Chemistry, Rice University*
*Houston, Texas 77005-1892*
*Faculty of Pharmaceutical Sciences*
*University of Tokyo*
*Hongo, Bunkyo-ku, Tokyo 113, Japan*

*Received May 20, 1996*

Gelsemine (**1**) has long been known as the major alkaloid component of *Gelsemium sempervirens* (Carolina jasmine).[2] Since the structure of gelsemine was determined in 1959,[3] it has attracted numerous synthetic efforts due to its unique hexacyclic cage structure.[4] While three groups reported total syntheses of (±)-gelsemine (**1**) in 1994 via its minor congener 21-oxogelsemine (**2**), none of them have succeeded in controlling the stereochemistry of the critical spiroindolinone system.[5] Herein we report a stereocontrolled total synthesis of (±)-gelsemine (**1**), which features a stereoselective construction of the bicyclo[3.2.1] framework by means of a divinylcyclopropane−cycloheptadiene rearrangement.[6]

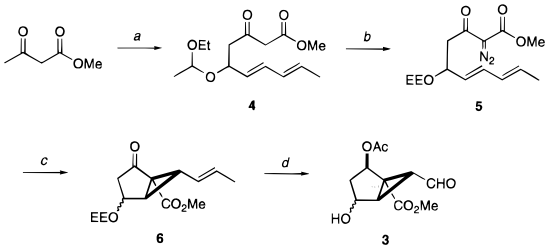



Our synthesis started with the preparation of the requisite intermediate **3** according to the protocol of Kondo.[7] Thus, addition of the dianion derived from methyl acetoacetate to sorbic aldehyde followed by immediate protection of the unstable alcohol gave ethoxyethyl ether **4** (Scheme 1). Diazo transfer reaction of the β-keto ester **4** under standard conditions furnished diazo compound **5**, which was subjected to copper-mediated cyclopropanation to give the bicyclic ketone **6**. Reduction of ketone **6** with sodium borohydride, acetylation of the resultant alcohol, hydrolysis of the ethoxyethyl ether, and subsequent ozonolysis of the olefin furnished the aldehyde **3**.

Knoevenagel condensation of aldehyde **3** and oxindole gave a 4:1 mixture of *E*- and *Z*-isomers **7** and **8** (Scheme 2). Attempted photochemical isomerization of the *E*-isomer to the desired *Z*-isomer gave a 1:1 mixture at best. In an effort to further bias the product distribution, we decided to introduce a bulky substituent to the 4-position of the oxindole. As expected,[8] condensation of 4-iodooxindole[9] with aldehyde **3** furnished (*Z*)-alkylidene indolinone **9** in 89% yield as the exclusive product. Pfitzner−Moffatt oxidation[10] of alcohol **9** followed by elimination of acetic acid furnished the unstable enone **10**.[11] When heated at 90 °C, compound **10** underwent an exceptionally smooth rearrangement to give the desired bicyclo[3.2.1] system **11a** in 98% yield as a highly crystalline solid. The stereochemistry of the spiro center was confirmed by a single-crystal X-ray analysis of the corresponding bromide **11b** obtained from the same synthetic pathway. The subsequent radical deiodination provided the key intermediate **12**.

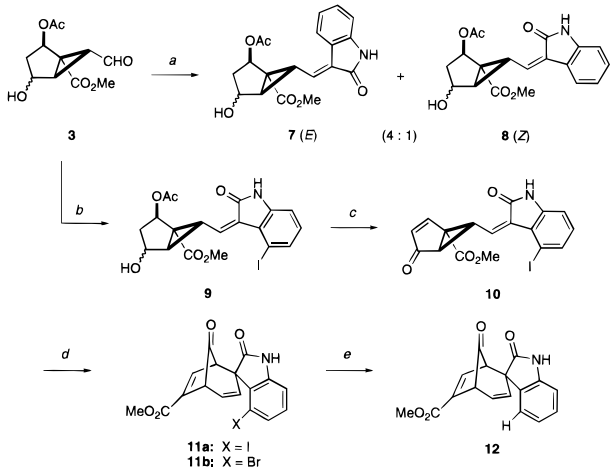
With the critical bicyclo[3.2.1] framework in hand, we then turned our attention to the construction of the remaining pyrrolidine and tetrahydropyran rings. Since the ketone and the α,β-unsaturated ester of **12** have similar reactivities toward nucleophiles, selective elongation of the ketone proved to be quite difficult. Fortunately, treatment of **12** with $(EtO)_2POCH$-

**Scheme 1**[a]




[a] Conditions: (a) NaH, THF, 0 °C, then BuLi; sorbic aldehyde, 0−23 °C; ethyl vinyl ether, $POCl_3$, $CH_2Cl_2$, 0−23 °C, 53% (two steps); (b) $TsN_3$, $Et_3N$, $CH_2Cl_2$, 0 °C, 83%; (c) catalytic $Cu(acac)_2$, $CuSO_4$, PhH, 85 °C, 3 h, 68%; (d) $NaBH_4$, MeOH, 0 °C; $Ac_2O$, pyridine, 23 °C; TsOH, $^iPrOH/H_2O$, 23 °C, 74% (three steps); $O_3$, 10% $MeOH/CH_2Cl_2$, −78 °C, then $Me_2S$, −78 to +23 °C, 89%.

**Scheme 2**[a]




[a] Conditions: (a) oxindole, catalytic piperidine, MeOH, 23 °C, 60%; (b) 4-iodooxindole, catalytic piperidine, MeOH, 23 °C, 89%; (c) DCC, DMSO, pyridinium trifluoroacetate, 23 °C; $Et_3N$, $CH_2Cl_2$, 23 °C, 91% (two steps); (d) 90 °C, toluene/$CH_3CN$ (1:1), 45 min, 98%; (e) $^nBu_3SnH$, catalytic AIBN, toluene, 95 °C, 1 h, 85%.

* To whom correspondence should be addressed at the University of Tokyo.

(1) Rice University. Present address: D-47V, AP-10, Abbott Laboratories, Abbott Park, IL 60064.

(2) For reviews of *Gelsemium* alkaloids, see: (a) Liu, Z.-J.; Lu, R.-R. In *The Alkaloids;* Manske, R. H. F., Ed.; Academic Press: New York, 1988; Vol. 33, pp 83−140. (b) Saxton, J. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. 8, pp 93−117.

(3) (a) Lovell, F. M.; Pepinsky, R.; Wilson, A. J. C. *Tetrahedron Lett.* **1959**, No. 4, 1−5. (b) Conroy, H.; Chakrabarti, J. K. *Tetrahedron Lett.* **1959**, No. 4, 6−13.

(4) (a) Fleming, I.; Moses, R. C.; Tercel, M.; Ziv, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 617−626. (b) Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283−2286. (c) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859−4862.

(5) (a) Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 765−766. (b) Newcomb, N. J.; Ya, F.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 767−768. (c) Kuzmich, D.; Wu, S. C.; Ha, D.-C.; Lee, C.-S.; Ramesh, S.; Atarashi, S.; Choi, J.-K.; Hart, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 6943−6944.

(6) For a review of this interesting rearrangement, see: Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. *Org. React.* **1992**, *41*, 1−133.

(7) Kondo, K.; Umemoto, T.; Yako, K.; Tunemoto, D. *Tetrahedron Lett.* **1978**, *19*, 3927−3930.

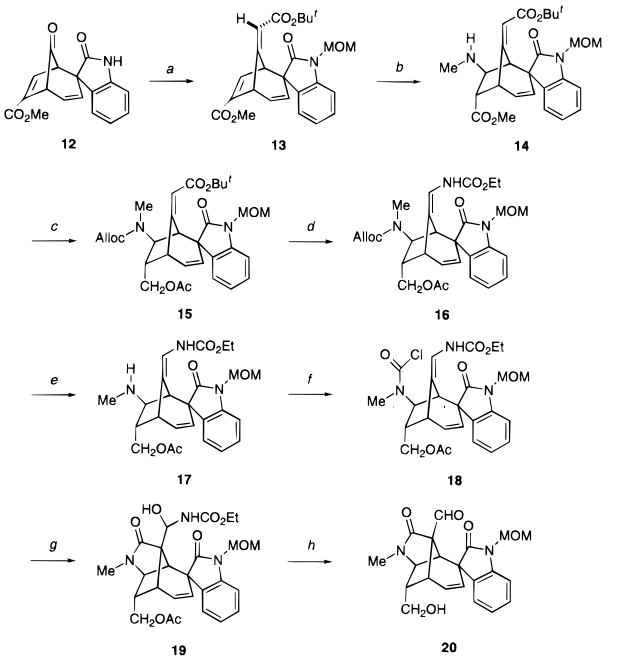
(8) According to the PM3 calculation, the iodinated *Z*-isomer is more stable than the *E*-isomer by 9.4 kcal/mol (MOPAC Version 94.1 in CAChe, Version 3.6, CAChe Scientific, 1994).

(9) 4-Iodooxindole was prepared from commercially available 2-methyl-3-nitroaniline in 39% yield via a five-step sequence [(1) $H_2SO_4$, $NaNO_2$, then KI, 0−90 °C; (2) NBS, BPO, $CCl_4$, 70 °C; (3) NaCN, DMSO, $H_2O$, 23 °C; (4) 6 M $H_2SO_4$, 110 °C; (5) 20% aqueous $TiCl_3$, $AcOH-H_2O$ (3:1), 23 °C].

(10) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661−5670.

(11) Compound **10** gradually rearranged to **11a** when stored at room temperature.

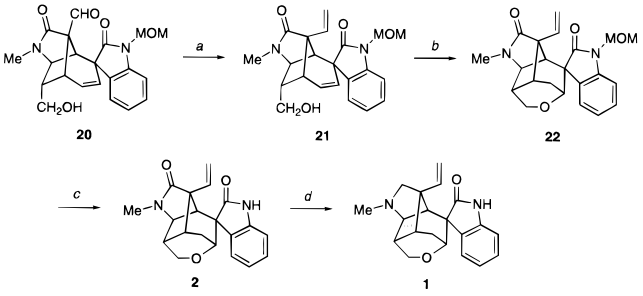
**Scheme 3**[a]



[a] Conditions: (a) $(EtO)_2P(O)CH_2CO_2{}^tBu$, BuLi, THF, 65 °C, then MOMCl, $^t$BuOK, 23 °C, 70%; (b) $MeNH_2$, MeOH, 23 °C, 100%; (c) $ClCO_2CH_2CH{=}CH_2$, pyridine, DMAP, $CH_2Cl_2$, 0 °C; $LiBH_4$, catalytic $LiBEt_3H$, THF, 23 °C; $Ac_2O$, pyridine, 73% (three steps); (d) $HCO_2H$, 23 °C, 79%; $ClCO_2Et$, $Et_3N$, THF, 0 °C; $^nBu_4NN_3$; toluene, catalytic $Et_3N$, reflux, then EtOH, 23 °C, 76% (three steps); (e) $Pd(PPh_3)_4$, $PPh_3$, pyrrolidine, $CH_2Cl_2$, 23 °C; (f) $COCl_2$, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 95% from **16**; (g) AgOTf, $Ag_2CO_3$, $CH_2Cl_2$, 45 °C, 15 min, 52%; (h) 3 N HCl, THF, 23 °C, 18 h.

$(Li)CO_2{}^tBu$ followed by one-pot protection of the indolinone nitrogen afforded a single isomer of *tert*-butyl ester **13** (Scheme 3). As a result of the fact that the *endo*-side of **13** was completely blocked by the benzene ring, the Michael addition of methylamine to the $\alpha,\beta$-unsaturated ester occurred exclusively from the less hindered, *exo*-side to give the *trans*-amino ester **14** in a quantitative yield. Protection of the amine as an allyl carbamate, selective reduction of the methyl ester,[12] and acetylation of the resultant alcohol yielded acetate **15**. In order to increase the electron density of the exocyclic olefin, the *tert*-butyl ester of **15** was converted to the ethyl urethane **16** by means of the conventional Curtius rearrangement. Deprotection of the Alloc group[13] of **16** followed by treatment of the resultant amine **17** with phosgene gave the chromatographically separable carbamoyl chloride **18**. Upon treatment with silver triflate and silver carbonate in anhydrous dichloromethane at 45 °C, **18** underwent a hitherto unprecedented cyclization to give the stable lactam **19** in 52% yield, along with an 18% yield of the recyclable methylamine **17**. The unusual stability of the aminal urethane **19** may be attributed to the strong intramolecular hydrogen bondings. Acidic treatment of the aminal urethane caused concomitant hydrolysis of the acetate to give hydroxy aldehyde **20**.

**Scheme 4**[a]



[a] Conditions: (a) Tebbe reagent, THF, −40−0 °C, 3 h, 65% from **19**; (b) $Hg(OTf)_2{\cdot}PhNMe_2$, $MeNO_2$, 23 °C, 1 h, then saturated NaCl; $NaBH_4$, 10% aqueous NaOH, $BnEt_3NCl$, $CH_2Cl_2$, 23 °C, 63% (two steps); (c) TMSCl, NaI, 0 °C; MeOH, $Et_3N$, 55 °C, 88% (two steps); (d) DIBALH, toluene, 0−23 °C, 82%.

The methylenation of the sterically hindered aldehyde **20** was best effected by treatment with Tebbe reagent,[14] giving the vinyl compound **21** in 65% yield from **19** (Scheme 4). In order to construct the remaining tetrahydropyran ring, intramolecular oxymercuration of **21** was performed according to the Speckamp procedure.[5b] Reduction of the resultant organomercurial compound with alkaline sodium borohydride in a two-phase system[15] afforded *N*-MOM-21-oxogelsemine (**22**). Treatment of compound **22** with $Me_3SiI$ gave *N*-(hydroxymethyl)-21-oxogelsemine, which, upon heating with triethylamine in methanol, furnished 21-oxogelsemine (**2**). (±)-21-Oxogelsemine (**2**) was converted to (±)-gelsemine (**1**) in 82% yield by selective reduction of the lactam with diisobutylaluminum hydride in toluene. Both synthetic 21-oxogelsemine (**2**) and gelsemine (**1**) are identical to natural samples by comparison of TLC, $^1H$, $^{13}C$ NMR, and HRMS.[16]

**Acknowledgment.** We are grateful to Jeffery Eveland of Rice University for performing the X-ray crystallographic analysis. Financial assistance from the National Institutes of Health (Grant CA28119) and the Robert A. Welch Foundation is gratefully acknowledged.

**Supporting Information Available:** Listing of spectral data (10 pages). See any current masthead page for ordering information and Internet access instructions.

JA961701S

(12) Brown, H. C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604−1606.
(13) Deziel, R. *Tetrahedron Lett.* **1987**, *28*, 4371−4372.
(14) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Soc. Chem.* **1978**, *100*, 3611−3613.
(15) Benhamou, M. C.; Etemad-Moghadam, G.; Speziale, V.; Lattes, A. *Synthesis* **1979**, 891−893. We thank Professor W. Nico Speckamp of the University of Amsterdam for informing us that a high concentration of the substrate (0.4 M) is essential for the reductive demercuration.
(16) We are indebted to Professor Geoffrey A. Cordell of the University of Illinois at Chicago for the authentic samples of both 21-oxogelsemine and gelsemine.