*Pure & Appl. Chem.*, Vol. 69, No. 3, pp. 501–505, 1997.
Printed in Great Britain.

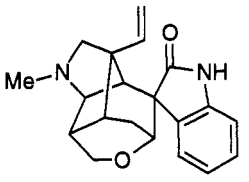

# Stereocontrolled total synthesis of (±)-gelsemine

Tohru Fukuyama[a] and Gang Liu[b]

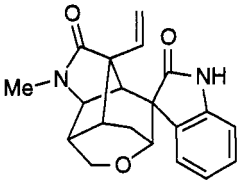
[a]*Faculty of Pharmaceutical Sciences, University of Tokyo,Bunkyo-ku, Tokyo 113, JAPAN*
[b]*Department of Chemistry, Rice University, Houston, Texas 77005-1892, U.S.A.*

*Abstract*: The stereocontrolled total synthesis of gelsemine (**1**) via 21-oxogelsemine (**2**) is reported. Our total synthesis features a stereoselective condensation of cyclopropyl carboxaldehyde **11** and 4-iodo-oxindole, a facile construction of the bicyclo[3.2.1] intermediate **20** with a complete control of the stereochemistry by means of a novel application of divinylcyclopropane-cycloheptadiene rearrangement, and an unprecedented silver ion-mediated lactam formation between carbamoyl chloride and enecarbamate.

Gelsemine (**1**) has long been known as the major alkaloid component of *Gelsemium sempervirens* (Carolina jasmine).[1] Since the structure of gelsemine was determined in 1959,[2] it has attracted numerous synthetic efforts due to its unique hexacyclic cage structure.[3] While three groups reported the total syntheses of (±)-gelsemine in 1994 via its minor congener, 21-oxogelsemine (**2**), none of them has succeeded in controlling the stereochemistry of the critical spiro-indolinone system.[4] 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.[5]



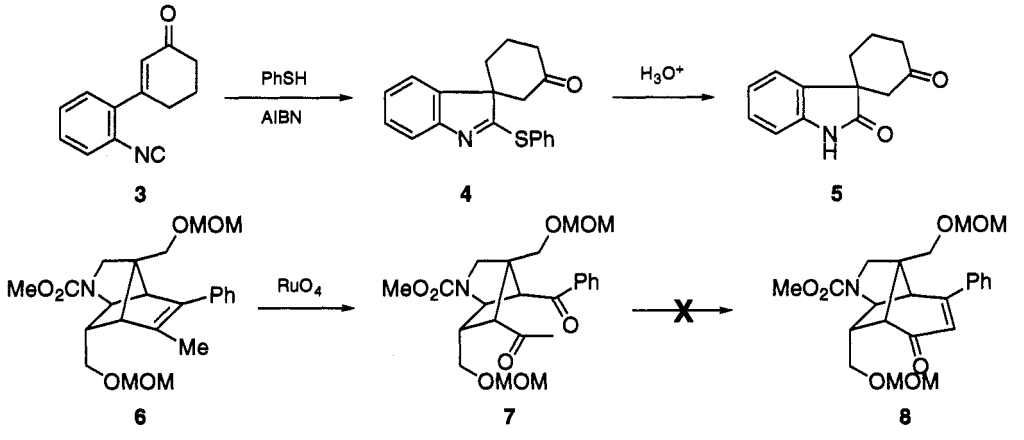

**1:** Gelsemine




**2:** 21-Oxogelsemine

We initiated our quest for the total synthesis of gelsemine because of the successful model studies shown in Scheme 1. When isonitrile **3** was subjected to the radical-forming conditions, a facile cyclization occurred to form thioimidate **4** which underwent smooth hydrolysis to give the desired spiro-indolinone system **5**. Having succeeded in constructing the spiro systme, we then turned our attention to the

**Scheme 1.**



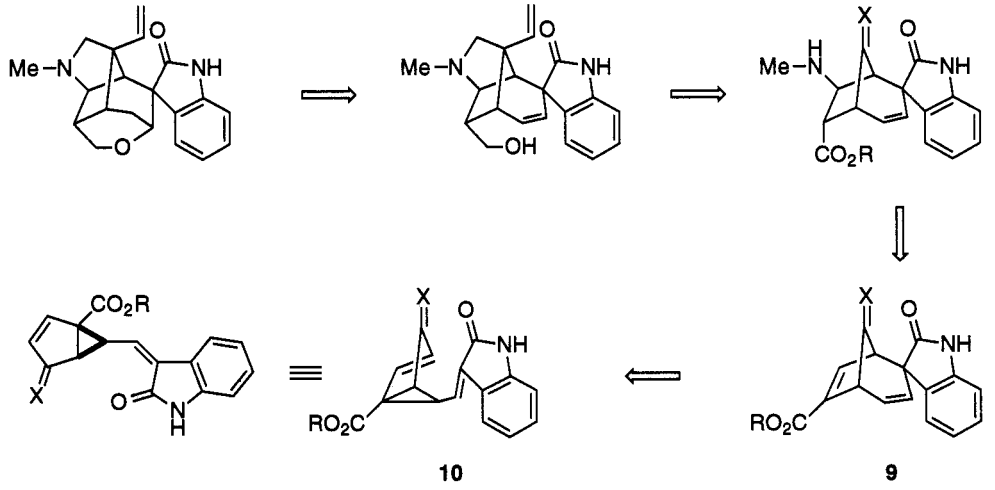

**3** **4** **5**

**6** **7** **8**

preparation of the tricyclic system **8** from the diketone **7**. Unfortunately, every attmept to perform the aldol cyclization was unsuccessful.

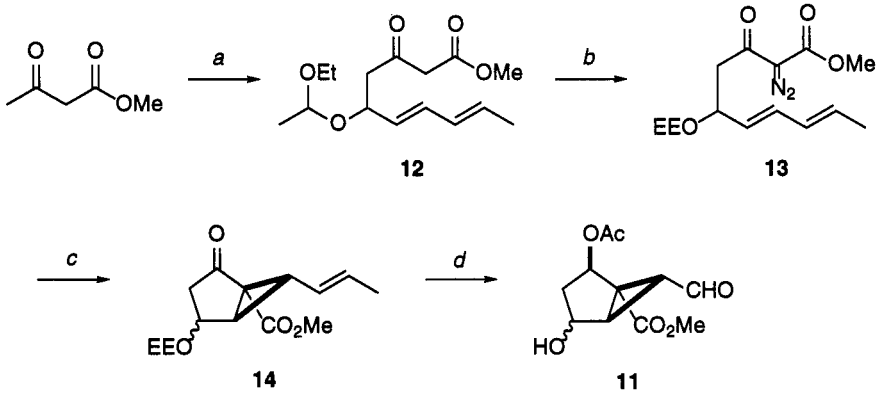
During the course of the initial model studies, it occurred to us that the key bicyclic indolinone **9** might be constructed by means of the divinylcyclopropane rearrangement of **10**. On the basis of this risky, yet fascinating idea, we formulated the retrosynthetic analysis of gelsemine as illustrated in Scheme 2.

**Scheme 2.**




Our total synthesis started with the preparation of the requisite intermediate **11** according to the protocol of Kondo.[6] Thus, addition of the dianion derived from methyl acetoacetate to sorbic aldehyde followed by immediate protection of the unstable alcohol gave ethoxyethyl ether **12** (Scheme 3). Diazo transfer reaction of the β-keto ester **12** under standard conditions furnished diazo compound **13**, which was subjected to copper-mediated cyclopropanation to give the bicyclic ketone **14**. Reduction of ketone **14** with sodium borohydride, acetylation of the resultant alcohol, hydrolysis of the ethoxyethyl ether, and subsequent ozonolysis of the olefin furnished the aldehyde **11**.

**Scheme 3.**[a]

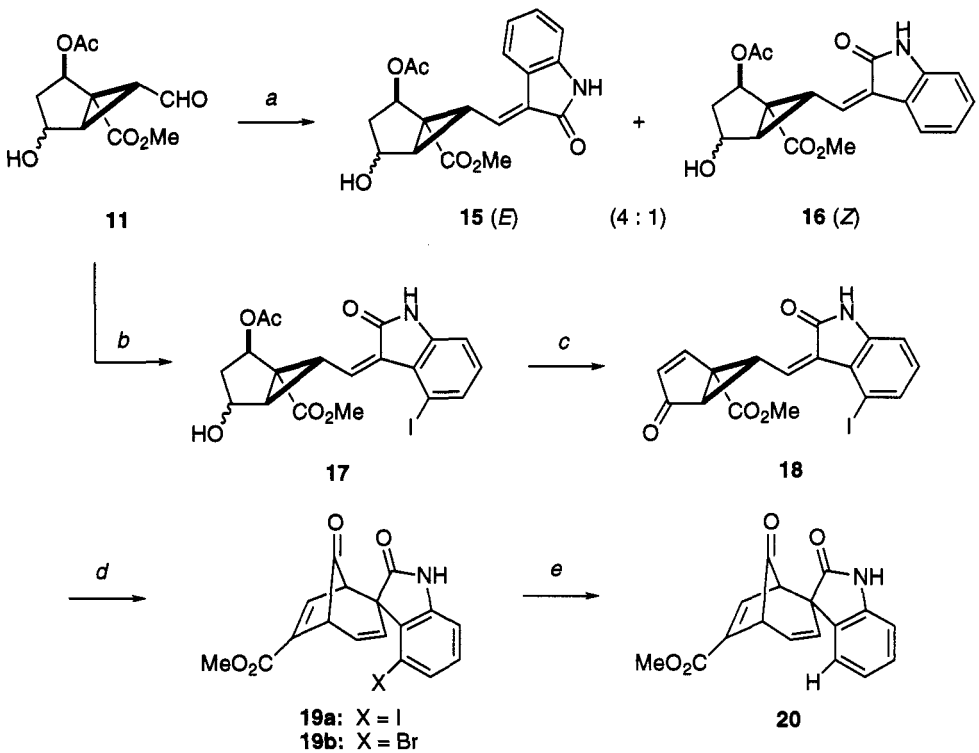



[a] (a) NaH, THF, 0 °C, then BuLi; sorbic aldehyde, 0 to 23 °C; ethyl vinyl ether, $POCl_3$, $CH_2Cl_2$, 0 to 23 °C, 53% (2 steps); (b) $TsN_3$, $Et_3N$, $CH_2Cl_2$, 0 °C, 83%; (c) cat. $Cu(acac)_2$, $CuSO_4$, PhH, 85 °C, 3 h, 68%; (d) $NaBH_4$, MeOH, 0 °C; $Ac_2O$, pyridine, 23 °C; TsOH, *i*-PrOH/$H_2O$, 23 °C, 74% (3 steps); $O_3$, 10% MeOH/$CH_2Cl_2$, –78 °C, then $Me_2S$, –78 to 23 °C, 89%.

Knoevenagel condensation of aldehyde **11** and oxindole gave a 4:1 mixture of *E*- and *Z*-isomers, **15** and **16** (Scheme 4). 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,[7] condensation of 4-iodooxindole[8] with aldehyde **11** furnished *Z*-alkylidene indolinone **17** in 89% yield as the exclusive product. Pfitzner-Moffatt oxidation[9] of alcohol **17** followed by elimination of acetic acid furnished the unstable enone **18**.[10] When heated at 90 °C, compound **18** underwent an exceptionally smooth rearrangement to give the desired

bicyclo[3.2.1] system (**19a**) 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 **19b** obtained from the same synthetic pathway. The subsequent radical deiodination provided the key intermediate **20**.

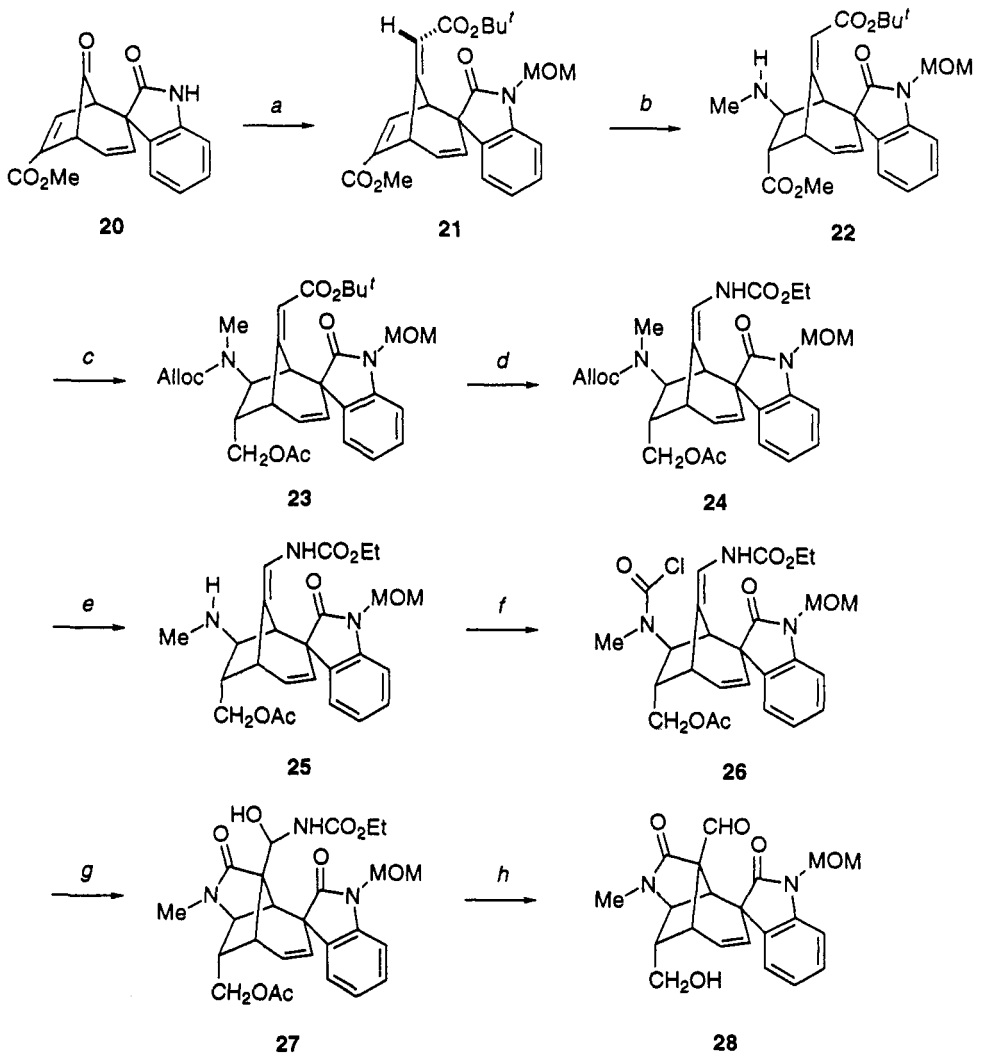
**Scheme 4.**[a]




[a] (a) oxindole, cat. piperidine, MeOH, 23 °C, 60% ; (b) 4-iodooxindole, cat. piperidine, MeOH, 23 °C, 89%; (c) DCC, DMSO, pyridinium trifluoroacetate, 23 °C; $Et_3N$, $CH_2Cl_2$, 23 °C, 91% (2 steps); (d) 90 °C, toluene/$CH_3CN$(1:1), 45 min, 98%; (e) *n*-$Bu_3SnH$, cat. AIBN, toluene, 95 °C, 1 h, 85%.

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 **20** have similar reactivities towards nucleophiles, the selective elongation of the ketone proved to be quite difficult. Fortunately, treatment of **20** with $(EtO)_2POCH(Li)CO_2{}^tBu$ followed by one-pot protection of the indolinone nitrogen afforded a single isomer of *t*-butyl ester **21** (Scheme 5). As a result of the fact that the *endo*-side of **21** was completely blocked by the benzene ring, the Michael addition of methylamine to the α,β-unsaturated ester occurred exclusively from the less hindered, *exo*-side to give the *trans*-amino ester **22** in a quantitative yield. Protection of the amine as an allyl carbamate, selective reduction of methyl ester,[11] and acetylation of the resultant alcohol yielded acetate **23**. In order to increase the electron density of the exocyclic olefin, the *t*-butyl ester of **23** was converted to the ethyl urethane **24** by means of the conventional Curtius rearrangement. Deprotection of the Alloc group[12] of **24** followed by treatment of the resultant amine **25** with phosgene gave the chromatographically separable carbamoyl chloride **26**. Upon treatment with silver triflate and silver carbonate in anhydrous dichloromethane at 45 °C, **26** underwent a hitherto unprecedented cyclization to give the stable lactam **27** in 52% yield, along with an 18% yield of the recyclable methylamine **25**. The unusual stability of the aminal urethane **27** 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 **28**.

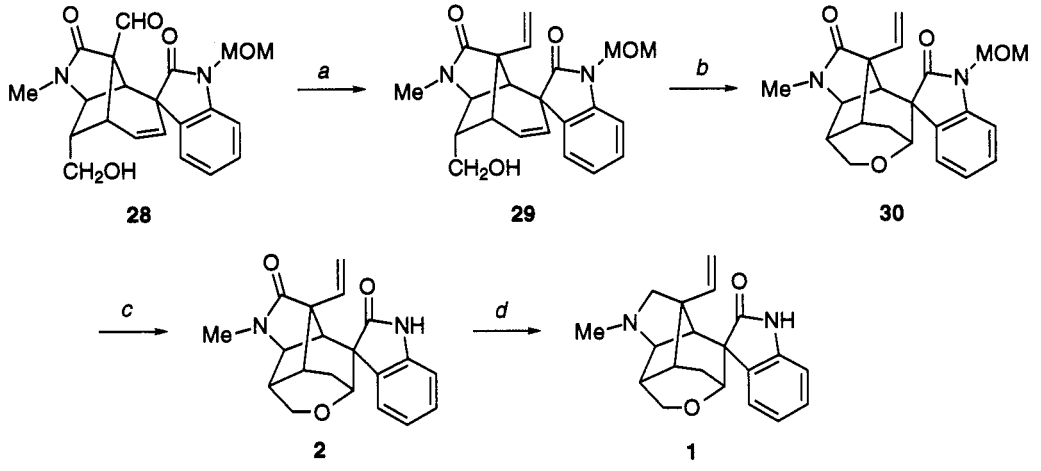
**Scheme 5.**[a]




[a] (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; $LiBH_4$, cat. $LiBEt_3H$, THF, 23 °C; $Ac_2O$, pyridine, 73% (3 steps); (d) $HCO_2H$, 23 °C, 79%; $ClCO_2Et$, $Et_3N$, THF, 0 °C; *n*-$Bu_4NN_3$; toluene, cat. $Et_3N$, reflux, then EtOH, 23 °C, 76% (3 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 **24**; (g) AgOTf, $Ag_2CO_3$, $CH_2Cl_2$, 45 °C, 15 min, 52%; (h) 3N HCl, THF, 23 °C, 18 h.

The methylenation of the sterically hindered aldehyde **28** was best effected by treatment with Tebbe reagent,[13] giving the vinyl compound **29** in 65% yield from **19** (Scheme 6). In order to construct the remaining tetrahydropyran ring, intramolecular oxymercuration of **29** was performed according to the Speckamp procedure.[5b] Reduction of the resultant organomercurial compound with alkaline sodium borohydride in a two-phase system[14] 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.[15]

**Scheme 6.**[a]




[a] (a) Tebbe reagent, THF, 40 to 0 °C, 3 h, 65% from **27** ; (b) $Hg(OTf)_2$·$PhNMe_2$, $MeNO_2$, 23 °C, 1 h, then satd NaCl; $NaBH_4$, 10 % aq NaOH, $BnEt_3NCl$, $CH_2Cl_2$ , 23 °C, 63% (2 steps); (c) TMSCl, NaI, 0 °C; MeOH, $Et_3N$, 55 °C, 88% (2 steps); (d) DIBALH, toluene, 0 to 23 °C, 82%.

**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 (CA28119) and the Robert A. Welch Foundation is gratefully acknowledged.

## References and Footnotes

(1) 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.

(2) (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.

(3) (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.

(4) (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.

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

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

(7) 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).

(8) 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) 6M $H_2SO_4$, 110 °C; (5) 20% aq $TiCl_3$, AcOH-$H_2O$ (3:1), 23 °C].

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

(10) Compound **18** gradually rearranged to **19a** when stored at room temperature.

(11) Brown, H. C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604-1606.

(12) Deziel, R. *Tetrahedron Lett.* **1987**, *28*, 4371-4372.

(13) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Soc. Chem.* **1978**, *100*, 3611-3613.

(14) 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 the fact that high concentration of the substrate (0.4 M) is essential for the reductive demercuration.

(15) 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.