Total Synthesis of *dl*-21-Oxogelsemine

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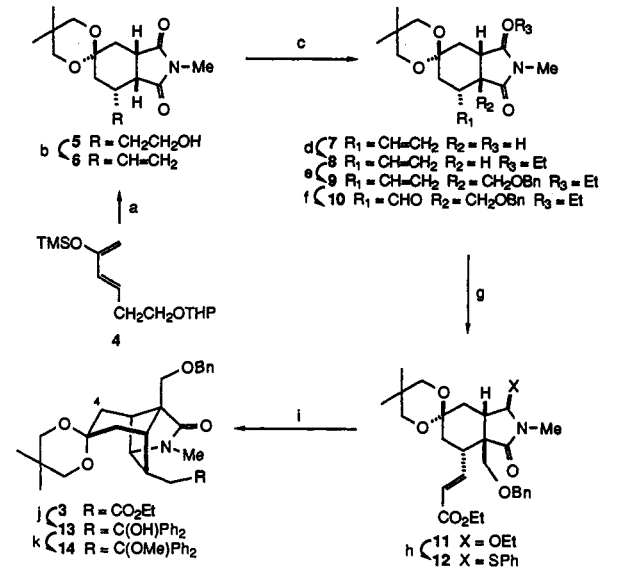
Received May 16, 1994

Gelsemine (**1**), the major alkaloid of *Gelsemium sempervirens* (Carolina jasmine), has been the target of numerous synthetic studies.[1,2] Although the cage substructure of gelsemine has been prepared by a number of research groups,[3-6] only recently have two syntheses of gelsemine been described.[7] Both of these syntheses proceed through 21-oxogelsemine (**2**), a bis-lactam reported to be a minor constituent of *G. sempervirens*.[8,9] We have also recently completed a synthesis of racemic **2**, and our route is described herein.

Our plan revolved around preparation of the tricyclic gelsemine substructure **3**, followed by sequential introduction of the oxindole at C-4, construction of the tetrahydropyran substructure, and conversion of the C-20 substituent into a vinyl group. We have already described a synthesis of a structure related to tricyclic lactam **3**, but several operational changes that were critical to completion of the synthesis of **2** have been developed during the interim, and these are described in Scheme 1.[10] A Diels–Alder reaction between *N*-methylmaleimide and diene **4** (toluene, 110 °C), followed by treatment of the crude cycloadduct with 2,2-dimethyl-1,3-propanediol and catalytic amounts of *p*-toluenesulfonic acid, gave perhydroisoindole **5** in 43% yield. Formal dehydration of **5** following the Grieco protocol gave **6** in 79% yield, and reduction of the imide with sodium borohydride gave carbinol lactam **7** in 80% yield.[11] Early in our studies, acidic ethanol was used to convert **7** to **8**, but this process proved to be capricious due to problems associated with ketal hydrolysis. It was eventually found that treating **8** with sodium hydride and ethyl iodide accomplished the same transformation in 98% yield without complications. Alkylation of the lithium enolate of **8** with benzyl chloromethyl ether proceeded smoothly to give **9** in 95% yield. Although we were able to convert **9** to aldehyde **10** under Johnson–Lemieux conditions, this reaction also proved capricious, as epimerization of the aldehyde was frequently a problem.[12] Ozonolysis of **9** followed by a reductive workup with dimethyl sulfide, however, reproducibly gave crystalline **10** (mp 117–119 °C) in 64–67% yields. Wittig olefination of **10** gave **11** and ethoxy–thiophenoxy exchange afforded **12** in 65% overall yield. Finally, free-radical cyclization gave the gelsemine substructure **3** (mp 109–110 °C) in 61% yield.

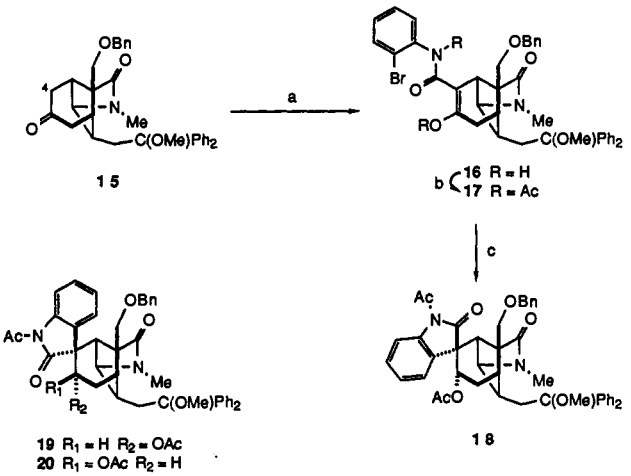
The next task was introduction of the oxindole substructure at C-4. This was to be accomplished by free-radical cyclization of appropriate derivatives of vinylogous carbamic acid **16**, whose preparation is described in Schemes 1 and 2.[13] Treatment of **3** with phenylmagnesium bromide, alkylation of the resulting tertiary alcohol **13** (mp 186–188 °C) with iodomethane, and

Scheme 1[a]



[a] (a) *N*-Methylmaleimide, toluene, Δ; 2,2-dimethyl-1,3-propanediol, *p*-TsOH. (b) *o*-$NO_2PhSeCN$, *n*-Bu_3P; H_2O_2. (c) $NaBH_4$, MeOH. (d) NaH, EtI, THF. (e) LDA, $BnOCH_2Cl$. (f) O_3, MeOH; Me_2S. (g) $(Ph)_3P{=}CHCO_2Et$, CH_2Cl_2. (h) PhSH, *p*-TsOH, CH_2Cl_2. (i) *n*-Bu_3SnH, AIBN, PhH, Δ. (j) PhMgBr, THF. (k) NaH, MeI, DMF.

Scheme 2[a]



[a] (a) NaH/KH, *o*-BrC_6H_4NCO, THF, Δ. (b) Ac_2O, Et_3N, DMAP, DMF. (c) *n*-Bu_3SnH, *hν*, PhH.

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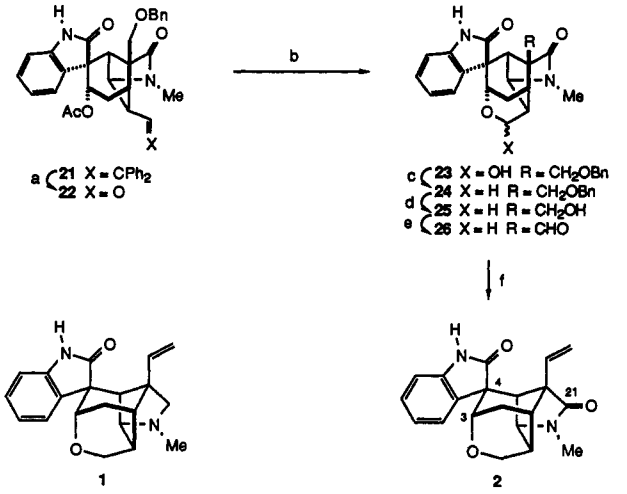
Scheme 3[a]



[a] (a) O_3, CH_2Cl_2–MeOH; Me_2S. (b) 6 N aqueous HCl, DME, 48 °C, 18 h. (c) TFA, Et_3SiH, CH_2Cl_2. (d) BBr_3, CH_2Cl_2. (e) Dess–Martin oxidation. (f) Cp_2TiMe_2, THF, Δ.

deblocking of ketal **14** (mp 74–79 °C) using *p*-toluenesulfonic acid in acetone, gave ketone **15** (mp 165–167 °C) in 81% overall yield. Acylation of ketone **15** using sodium hydride, catalytic amounts of potassium hydride, and *o*-bromophenyl isocyanate gave **16** (mp 173–180 °C) in 81% yield.[14] Free-radical cyclizations of several derivatives of **16** were examined, and it was eventually determined that **17**, prepared in 98% yield from **16**, provided the most useful results in terms of stereochemistry. Thus, treatment of **17** with tri-*n*-butyltin hydride under photochemical conditions gave oxindole **18** (mp 133–135 °C) in 40% yield, along with 15% of **19** and 10% of 20.[15]

The synthesis of 21-oxogelsemine was completed as shown in Scheme 3. Treatment of **18** with *p*-toluenesulfonic acid in dichloromethane followed by the addition of methanol to the reaction mixture gave olefin **21** (mp 211–212 °C) in 90% yield. Ozonolysis of the double bond gave **22** (mp 231–233 °C) in 65% yield, along with 15% of an epoxide derived from **21**.[16] Treatment of **22** with hydrochloric acid in aqueous DME at 48 °C for 18 h accomplished acetate hydrolysis and isomerization of the aldehyde to afford a mixture of diastereomeric hemiacetals **23** in 64% yield. Reduction of this mixture with triethylsilane–trifluoroacetic acid gave **24** (81%, mp 189–190 °C), and removal of the benzyl protecting group with BBr_3 afforded alcohol **25** (90%, mp 303–309 °C), whose structure was confirmed by X-ray crystallographic analysis.[17-19] Oxidation of **25** using the Dess–Martin periodinane gave aldehyde **26** (mp 278–280 °C) in 71% yield.[20] Finally, methylenation of **26** using bis(cyclopentadienyl)-dimethyltitanium afforded 21-oxogelsemine (**2**) in 75% yield (mp 155–159 °C).[21,22]

In summary, a total synthesis of 21-oxogelsemine has been accomplished in 23 steps from diene **4**.[23] The synthesis features two free-radical cyclization reactions and a protocol for construction of the tetrahydropyran after installation of the oxindole substructure.

Acknowledgment. We thank the National Institutes of Health for supporting this research.

Supplementary Material Available: ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra of synthetic **2** and ^1H-NMR (300 MHz) spectrum of natural **2** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(22) Synthetic **2** gave ^1H and ^{13}C NMR spectra identical to those reported for the natural product (see ref 9) and was identical (TLC, ^1H NMR) to an authentic sample kindly provided by Professor G. Cordell.

(23) The preparation of **4** requires four steps from commercially available 3-buten-1-ol (see reference 10).