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SYNTHESIS STUDIES DIRECTED TOWARD GELSEMINE. PREPARATION OF AN ADVANCED PENTACYCLIC INTERMEDIATE

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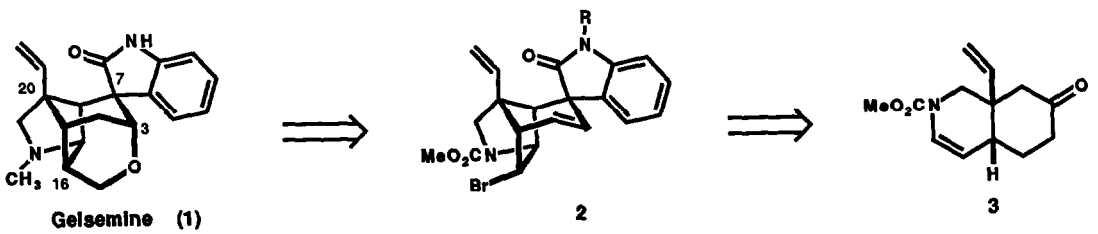
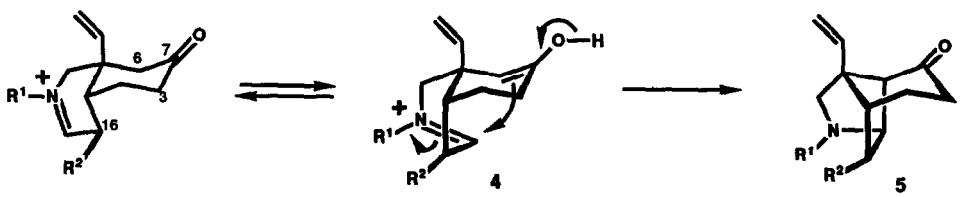
Abstract: *Pentacyclic gelsemine intermediate* **2** *was prepared from* **3** *by a six step sequence whose key steps are (a) intramolecular Mannich cyclization of an N-acyliminium ion intermediate to form the azatricyclo[4 4 0 $0^{2,8}$]decane ring system, and (b) palladium catalyzed intramolecular alkene arylation to elaborate the spirooxindole*

Gelsemine (**1**), the major alkaloid of *gelsemium sempervirens* (Carolina or yellow jasmine),[1] has attracted significant attention from synthesis chemists.[2] Although several imaginative approaches have been described,[2] no total synthesis of this complex hexacyclic oxindole alkaloid has been reported In the previous communication we outlined our basic approach toward this formidable synthesis target and reported a new efficient preparation of highly functionalized *cis*-hydroisoquinolines[3] We now report key aspects of our further investigations which have led to the preparation of pentacyclic intermediate **2** To the best of our knowledge, **2** is the most advanced gelsemine intermediate yet to be obtained by total synthesis



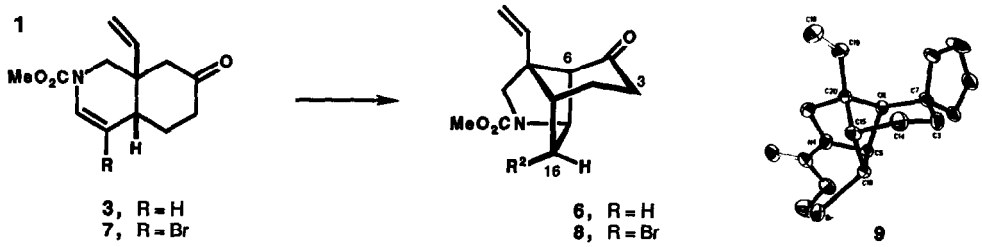
Our construction of **2** proceeds in two stages from *cis*-hydroisoquinoline **3**, the preparation of which was described in the preceding communication[3] We first construct the azatricyclo[4 4.0 $0^{2,8}$]decane substructure of gelsemine by an intramolecular Mannich cyclization (see equation 1) The strain of the tricyclo[4 4 0.$0^{2,8}$]decane ring system[4], and the anticipated kinetic barrier associated with having the tetrahydropyridinium ring of **4** adopt a high energy boat conformation in order to overlap the iminium ion and enol π-systems, suggested that this cyclization would be difficult. As a result, we examined cyclization



(1)

of *N*-acyliminium ion intermediates (equation 1, R^1=COOR), since an *N*-acyl group would help mitigate[5] retro-Mannich fragmentation of the tricyclic Mannich product Simple heating of **3** in refluxing formic acid for 4-6 h cleanly occasioned the desired transformation and provided a single tricyclic product **6**[6] in 65% yield

Scheme 1



3, R = H
7, R = Br

6, R = H
8, R = Br

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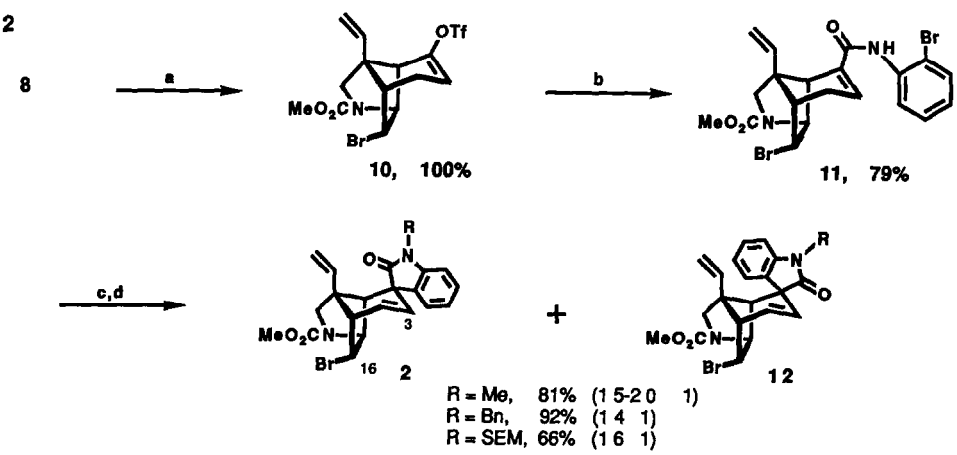
In order to introduce functionality at carbon 16, which would allow eventual elaboration of the hydropyran ring of gelsemine, **3** was treated at 23°C with 1 equiv of Br_2 in the presence of 1,2,2,6,-pentamethylpiperidine to give the ß-bromo encarbamate intermediate **7** in 88% yield[6] Immediate cyclization (CF_3COOH, reflux, 8-10 h) of this somewhat unstable bromide afforded the tricyclic product **8**[6] in 85% yield The structure of this key intermediate was confirmed by x-ray analysis of the crystalline, mp 114.5-116°C, ethylene ketal derivative **9**. A view of the molecular structure of **9** is shown in Scheme 1 To the limits of detection by high field NMR, cyclization of the encarbamates **3** and **7** occurred **regioselectively** at carbon 6 to provide only the azatricyclic products **6** and **8**[7] The x-ray structure of **9**, moreover, establishes that a ß-substituent on the starting encarbamate ends up on the *exo* face of the tricylic product, consistent with preferential cyclization of the *thermodynamic*[8] *N*-acyliminium ion intermediate **4** (R^2=Br).

Scheme 2

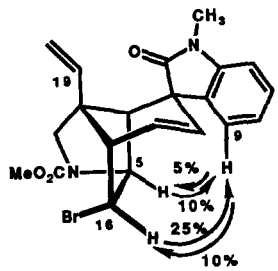


R = Me, 81% (1 5-2 0 1)
R = Bn, 92% (1 4 1)
R = SEM, 66% (1 6 1)

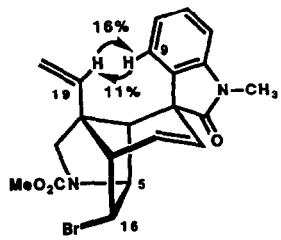
[a] LDA, $PhNTf_2$, THF, -78--> 0°C [b] 1 mol % $Pd(PPh_3)_4$, 2-bromoaniline, CO, 1 atm, DMF, 80°C
[c] NaH, RX, THF, 23°C [d] 10-20 mol % $Pd(PPh_3)_4$, CH_3CN-Et_3N, 82°C

The next stage of our gelsemine synthesis involves the elaboration of the spirooxindole at the carbonyl carbon of **8** in such a way that the adjacent carbon **3** is left functionalized for ultimate closure of the oxacyclic ring of gelsemine. Our initial model studies in this area[9] demonstrated that intramolecular palladium-catalyzed alkene arylation (Heck reaction)[10] would be useful for accomplishing this aim. The cyclization substrate, acrylamide **11**, was best prepared utilizing additional, recently reported,[11] palladium chemistry. Thus, conversion[12] of **8** to enol triflate **10**[6] followed by carbonylation, in the presence of 2-bromoaniline, provided **11**[6] in good yield. The success of this carbonylation reaction demonstrates that enol triflates undergo oxidative addition to Pd(O) more rapidly than aryl bromides[13] However, the amine must be primary, since similar reaction of *N*-benzyl-2-bromoaniline proceeded in low yield only. Cyclization of **11** proceeded under standard Heck conditions[9,10] to provide the stereoisomeric pentacyclic products **2**[6] and **12**[6] in excellent yield (see Scheme 2). That the major isomer **2** has the desired configuration at the spiro center was readily established by the ^{1}H NMR NOE experiments summarized in Figure 1

Figure 1



2



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Pentacyclic intermediate **2** is, to the best of our knowledge, the most advanced gelsemine intermediate yet synthesized. It contains sufficient functionality at carbons 3 and 16 to suggest that it may prove to be a viable precursor of the target alkaloid. Of equal significance, the total synthesis endeavors recorded in this and the previous[3] communication have served as a stimulus for the development of several new transformations of potential general utility in synthesis Specifically demonstrated in the present communication are the viability of Mannich cyclizations that proceed *via* boat tetrahydropyridinium cations[14] and the power of palladium catalyzed intramolecular insertions to establish quaternary carbons on highly congested[15] structural templates

Acknowledgment Our efforts in this area are supported by P H S Grant HL-25854 NMR, mass spectra, and x-ray experiments utilized instruments which were purchased with the assistance of N S F Shared Instrumentation Grants We particularly wish to acknowledge the the technical assistance of M Roof and thank Professor Clark Still for providing us with Macromodel

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5. See, e.g , Speckamp, W.N. *Rec Trav Chim.* **1981**, *100*, 345
6. New compounds showed ^{1}H NMR, ^{13}C NMR, IR, and mass spectra in accord with their assigned structures. Elemental composition was established by combustion or high resolution mass spectral analysis.
7. That cyclization occurs only *via* the $\Delta^{6,7}$ enol is not surprising in light of the considerably lower strain of the tricyclo[4.4 0.0^{2,8}]decane ring system relative to the tricyclo[5.3.0.0^{4,9}]decane ring system $\Delta\Delta H_f$ = 7 3 kcal/mol (Schleyer force-field);[4] $\Delta\Delta E$ = 5.0 kcal/mol (MM-2 force-field using Still's Macromodel program
8. Protonation of the encarbamate from the less hindered convex face would provide the C-16 epimer of **4** This epimer would experience serious steric interactions between R^2 and the carbocyclic ring in the intramolecular Mannich transition state.
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14. To the best of our knowledge this represents an extension of the scope of the intramolecular Mannich reaction
15. For example, the palladacyclohexane intermediate, that would be the expected[10] precursor of **2**, would have an axial palladium substituent at carbon 3.

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