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SYNTHESIS STUDIES DIRECTED TOWARD GELSEMINE. A NEW SYNTHESIS OF HIGHLY FUNCTIONALIZED *CIS*-HYDROISOQUINOLINES

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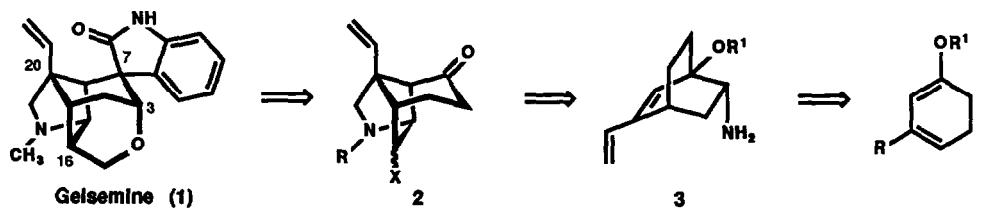
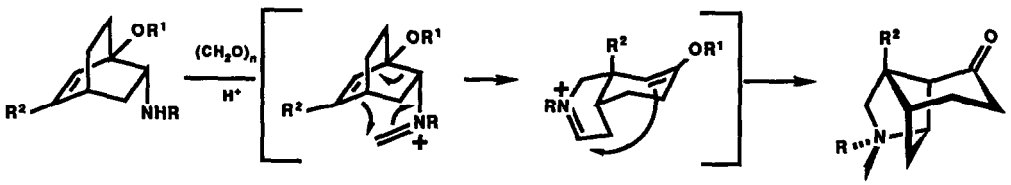
Abstract: *Cis-Hydroisoquinolines can be prepared in good yields by treatment of readily available endo-1-(cyanomethyl)-6-hydroxybicyclo[2.2.2]oct-5-en-1-yl amines with KH as summarized in Scheme 3*

Gelsemine (**1**), the major alkaloid of *gelsemium sempervirens* (Carolina or yellow jasmine) was first isolated in the 1870's[2] yet not fully characterized until 1959 [2,3] *Gelsemium sempervirens* has a long medicinal history[4] and *in vivo* physiological studies reveal that gelsemine has strong CNS stimulant as well as antihypertensive activity.[2,4] The unusual and compact hexacyclic skeleton of gelsemine presents a formidable synthesis challenge. Although some progress has been recorded,[5] gelsemine has not yielded thus far to total synthesis. We report here a new method for preparing highly functionalized *cis*-hydroisoquinolines which was developed during the early phase of our gelsemine total synthesis program In the accompanying communication we describe elaboration of one of these intermediates to assemble five of the six rings of gelsemine.

Scheme 1



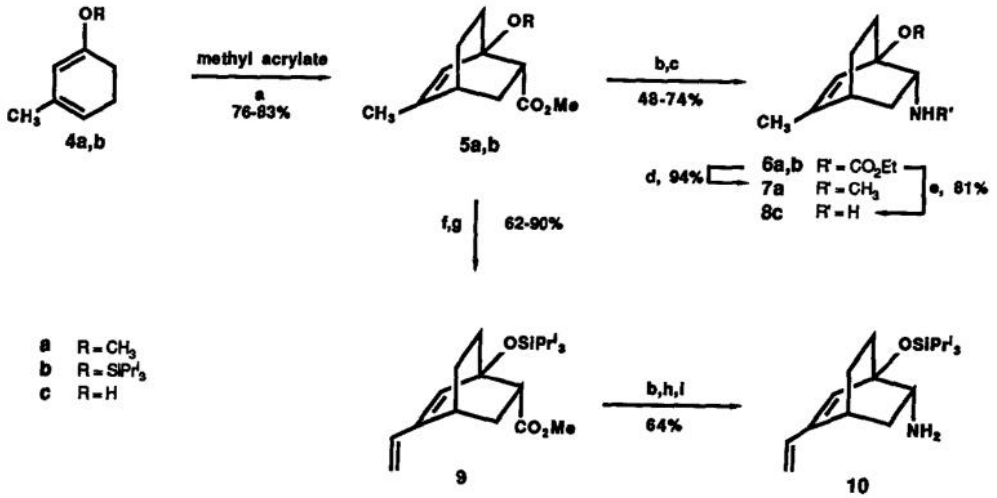
Our basic approach to gelsemine is outlined in Scheme 1 and features construction of the azatricyclo[4 4 0.0^{2,8}]decane substructure of gelsemine from a readily available bicyclo[2 2 2]octenyl amine precursor (i.e. **3** → **2**). We envisaged initially that the cationic aza-Cope rearrangement-Mannich cyclization reaction[6] outlined in equation 1 might accomplish this critical reorganization.



(1)

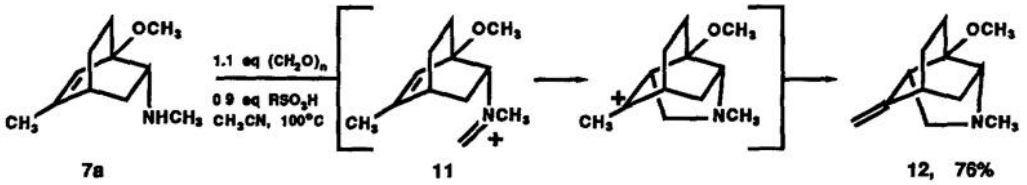
Our investigations began with the stereoselective synthesis of several *endo*-bicyclo[2 2.2]oct-5-en-1-yl amines by the straightforward Diels-Alder cycloaddition[7]-Curtius rearrangement approach summarized in Scheme 2 [8] Most notable in this sequence is the high stereoselectivity (*endo exo* = 8-10:1) of the $AlCl_3$ catalyzed Diels-Alder reaction of 1-alkoxy-1,3-cyclohexadienes **4a**[9] and **4b**[10] with methyl acrylate. The terminal vinyl substituent, destined for the angular C-20 position of gelsemine, was readily introduced by SeO_2 oxidation of **5b** followed by Wittig methylenation of the resulting enal to provide **9**.

Scheme 2



[a] $AlCl_3$, CH_2Cl_2, -78°C [b] KOH, EtOH-H_2O, 90°C [c] $(ClCO)_2$, CH_2Cl_2, 0°C, NaN_3, acetone-H_2O 0°C, EtOH, 80°C [d] AlH_3, THF, 23°C [e] Bu_4NF, THF, 23°C; KOH, MeOH-H_2O, 70°C [f] SeO_2, dioxane, 100°C [g] $Ph_3P{=}CH_2$, THF, -78-->0°C. [h] $(ClCO)_2$, CH_2Cl_2, 0°C, NaN_3, acetone-H_2O, toluene, reflux [i] KOH, dioxane-H_2O, 23°C

Initially, in a model series, we explored rearrangement of the formaldiminium ion derived from **7a**. To our disappointment, **11** did not undergo [3,3]-sigmatropic rearrangement but underwent simple Mannich cyclization at the proximal terminus of the alkene double bond to afford ultimately the 10-methylene-4-azatricyclo[4 3.1.$0^{3,7}$]decane **12**[8] (see equation 2). As a result of the high electrophilicity of the iminium ion grouping, bond formation may be far advanced with respect to bond cleavage in iminium ion [3,3]-sigmatropic rearrangements[11] Thus, the greater strain of the twistane tricyclodecane skeleton **14** relative to **13** provides a rationalization for the failure of **11** to undergo the desired aza-Cope rearrangement[12]



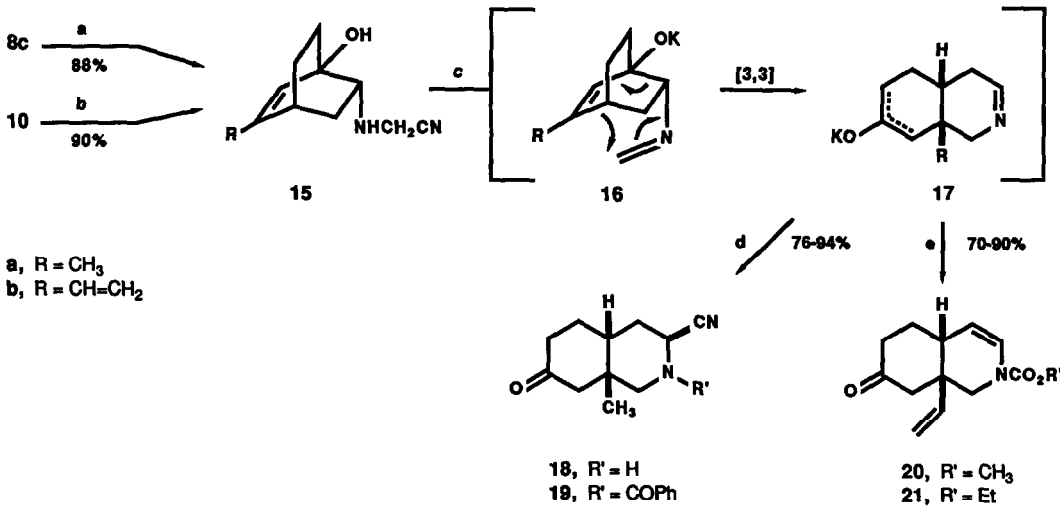
(2)

13, Steric Energy = 30 4 kcal/mol (MM-2)

14, Steric Energy = 32.6 kcal/mol (MM-2)

One way to relieve constraints imposed by the rigid bicyclo[2.2.2]octenyl skeleton would be to alter the electronic nature of the rearranging system in such a way to advance bond cleavage relative to bond formation The important studies of Evans and Goddard[13] on the origin of base acceleration[14] in the oxy-Cope rearrangement[1] suggested that the base-catalyzed hydroxy-aza-Cope rearrangement[15] (see Scheme 3, **16** → **17**) would have a "looser" transition state than the rearrangement of the corresponding alkoxy iminium ion. The desired anionic [3,3]-sigmatropic rearrangement was successfully accomplished by treatment of hydroxy cyanomethylamine **15**[8] with excess KH at room temperature[14,16] In the case of **15a**, quenching this rearrangement after 2 5 h with an excess of HCN provided the crystalline (mp 128-129°C) *cis*-hydroisoquinoline **18**[8] in yields that ranged from 76-94% The structural assignment for this product was unambiguously established by single-crystal x-ray diffraction analysis of benzamide derivative **19**[17] Alternatively, imine enolate **17b** was acylated at both heteroatoms by quenching with an excess of methyl or ethyl chloroformate, followed by selective cleavage of the resulting encarbonate functionality to afford the bicyclic keto encarbamates **20**[8] and **21**[8] in excellent yield.

Scheme 3



[a] $(CH_2O)_n$, HCl-KCN, THF,23°C [b] $ClCH_2CN$, 2 mol% Bu_4NI, IPr_2NEt, THF, 67°C , Bu_4NF, THF, 0°C
[c] excess KH, THF, 23°C [d] HCN-KCN, H_2O [e] $ClCO_2R'$, py, -78-->23°C , KOH, MeOH-H_2O,23°C

The preparation of functionalized *cis*-hydroisoquinolines from readily accessible *endo*-6-hydroxybicyclo[2.2 2]oct-5-en-1-yl amines constitutes a new and useful synthesis of this widely occurring ring system.[18] The ability to occasion aza-Cope rearrangements in electron excessive (imine-alkoxide) as well as electron deficient (iminium ion-hydroxyl) systems considerably broadens the scope of the aza-Cope synthesis strategem. The conversion of **20** to an advanced gelsemine intermediate is described in the following communication

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 assistance of Professor R.J Doedens with the x-ray study and the technical assistance of M. Roof.

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1. NIH Postdoctoral Fellow (GM 08155), 1981-1983.

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7 For an earlier, less stereoselective preparation of **5a**, see Alfaro, I; Ashton, W.; McManus, L D.; Newstead, R.C., Rabone, K.L.; Rogers, N.A.J; Kernick, W. *Tetrahedron* **1970**, *26*, 201. The *endo* and *exo* isomers are misassigned in this paper, see Jacobsen, E.J *Ph.D Thesis*, University of California, **1983**

8. 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.

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11. In the mechanistic limit, this rearrangement could even occur by a stepwise Mannich cyclization-Grob fragmentation sequence

12. Formaldiminium ions derived from analogs of **11** with vinylic H or COOMe substituents instead of CH_3 also undergo Mannich cyclization rather than [3,3]-sigmatropic rearrangement.

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17. The final unweighted and weighted R values were 0.062 and 0.072 Details will be published with a subsequent full acount of this study

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