Table I. Vibrational Frequency of the Normal Mode Converting 1 → 2

method/basis	ν^a (cm^{-1})	E_{tot} (hartree)
RHF/3-21G	137i	-269.702 33
RHF/4-31G	136i	-270.801 10
RHF/6-31G	154i	-271.084 21
RHF/6-311G	182i	-271.128 54
RHF/4-31G*	70	-270.932 31
RHF/6-31G*	53	-271.200 61
RHF/6-311G*	116	-271.245 66
RHF/6-31G**	69	-271.218 71
MP2/6-31G*	291	-272.134 07

[a] This is the lowest vibrational frequency in Hartree-Fock but the second lowest in MP2.

sets used are 3-21G, 4-31G, 6-31G, 6-311G, 4-31G*, 6-31G*, 6-311G*, and 6-31G**.[6] For each basis, the nonclassical structure was determined by automatic energy minimization in C_s symmetry. This was followed by analytic force constant calculations at the optimized geometry. The lowest vibrational frequency and the total energy of the optimized geometry obtained with each basis set are listed in Table I. All frequencies listed correspond to the same symmetry-breaking vibrational mode which moves the system toward a classical structure. For unpolarized basis sets, the nonclassical structure has one imaginary frequency and therefore corresponds to a saddle point, not a minimum. With the addition of one set of d functions to the carbon basis the nonclassical structure becomes a minimum with no imaginary vibrational frequencies. The lowest frequency corresponds to the same symmetry-breaking vibrational mode which has the imaginary frequency in the unpolarized basis set calculations. Improvements of the basis set beyond the 6-31G* level, expansion of the sp basis, and addition of p functions to the H basis make the lowest frequency larger, i.e., the potential well steeper. Further expansion of the basis set will not qualitatively change this result. Therefore, the nonclassical structure is a minimum in the Hartree-Fock potential energy surface of the 2-norbornyl cation.

Second-order Moller-Plesset perturbation theory (MP2)[6] vibrational frequencies were calculated by numerical differentiation of analytical gradients with the 6-31G* basis at the MP2/6-31G* optimized structure of the nonclassical 2-norbornyl cation. The lowest vibrational mode, with a frequency of 255 cm^{-1}, corresponds to the second lowest SCF vibrational mode. The vibrational mode that moves the system toward a classical structure is the second lowest mode at 291 cm^{-1}. Thus electron correlation makes the nonclassical well considerably steeper, increasing the vibrational frequency by 238 cm^{-1}.

Our previous calculations[7] showed (1) there is no potential minimum in the 6-31G* SCF potential energy surface corresponding to a classical structure of the 2-norbornyl cation (**2**) (the classical structure found in 4-21G and 4-31G SCF calculations is an artifact of inadequate basis set); (2) the edge-protonated structure (**3**) corresponds to a saddle point; and (3) electronic correlation favors a nonclassical structure over classical structures determined by small basis set calculations. The last result is supported by an independent calculation.[8] These results, taken together with our current result, force the conclusion that the 2-norbornyl cation is nonclassical in the gas phase.

In a recent paper, Dewar, Healy, and Ruiz[9] criticized previous theoretical work on the 2-norbornyl cation for not having calculated force constants with the basis sets used in optimizing the geometry. They concluded that there is "no reason to believe that the symmetrical structure is not in fact the transition state for interconversion of two unsymmetrical π complexes." Their conclusion ignores the first two of our previous findings listed above. Since neither the classical structure nor the edge-protonated structure correspond to potential minima, it is difficult to imagine what the symmetric structure could be a transition state for. Nevertheless, our present result directly answers their criticism. Force constant calculations using extended basis sets show unequivocally that the symmetric structure is a minimum.

The data in Table I suggest that the 6-31G* basis can give reliable structures for carbocations. This is supported by our calculations in progress on $C_3H_7^+$ and $C_4H_7^+$.

Calculations presented above were done on IBM 3090 Model 200 computers at the IBM Data Systems Division's Kingston Numerically Intensive Computing Center and the IBM Dallas National Engineering and Scientific Support Center. The force constant calculation with the 6-31G* basis required only 5 h of processor time and 9 h of elapsed time. These calculations demonstrate the capabilities of ab initio computational chemistry, the new GAUSSIAN 86 program, and modern supercomputers.

Acknowledgment. We thank Y. Singh, Director of the IBM Kingston NIC Center, for providing the computing resource and P. Sonnenberg of the same organization for facilitating our calculations. Thanks also go to D. Gerson of the IBM Dallas National Engineering and Scientific Support Center for making available computing resource and facilitating our calculations.

Registry No. 2-Norbornyl cation, 24321-81-1.

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(8) Raghavachari, K.; Haddon, R. C.; Schleyer, P. v. R.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1983**, *105*, 5915.
(9) Dewar, M. J. S.; Healy, E. F.; Ruiz, J. M. *J. Chem. Soc., Chem. Commun.* **1987**, 943.

Total Synthesis of (±)-Vallesamidine

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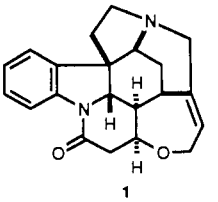
A great amount of research has been devoted to the synthesis of 2,3,3-trialkylindoline alkaloids.[1] Most synthetic approaches to these alkaloids have utilized one of two strategies. The first common strategy, exemplified in Woodward's landmark synthesis of strychnine (**1**),[2] uses a 2,3-disubstituted indole, which is further



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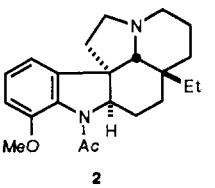

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alkylated at C-3. The second general approach to the 2,3,3-trialkylindoline skeleton employs the Fischer indole synthesis[3] for

(1) (a) Cordell, G. A.; Saxton, J. E. *Alkaloids (N.Y.)* **1981**, *20*, 1-295. (b) Cordell, G. A. *Alkaloids (N.Y.)* **1979**, *17*, 199-384. (c) Smith, G. F. *Alkaloids (N.Y.)* **1960**, *8*, 591-671.
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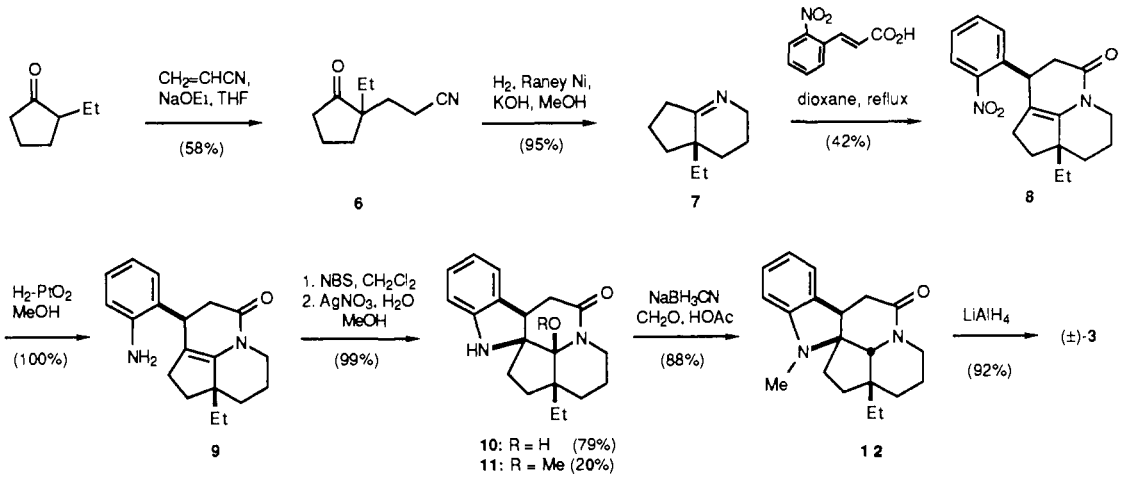
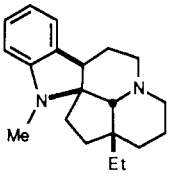
Scheme I



penultimate elaboration of the indoline moiety onto a preformed scaffold; this strategy is epitomized by Stork's synthesis of aspidospermine (**2**).[4,5]

Less success has been achieved with 2,2,3-trialkylindoline alkaloids such as vallesamidine (**3**),[6] mainly because neither of the



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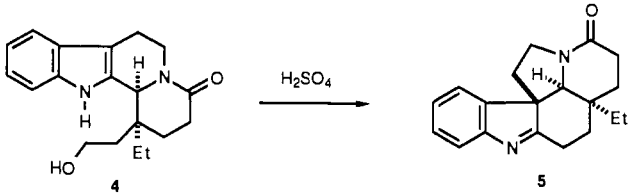
two foregoing tactics is applicable. The Fischer reaction is not usable for a trivial reason (e.g., the process starts with a ketone and must, of necessity, deliver an indole or 2,3,3-trialkyl-3*H*-indole). Alkylation at C-2 of a 2,3-disubstituted indole is not generally useful because of the propensity of the resulting cation to rearrange to the more stable 2,3,3-trialkylindoleninium ion. An example is seen in the acid-mediated conversion of **4** into **5**.[5a] In this Communication, we report a new approach to the problem, wherein the five-membered heterocycle is formed by ring closure of a pendant aniline group onto a tricyclic enamide.



4 **5**

The synthesis (Scheme I) begins with 2-ethylcyclopentanone,[7] which is cyanoethylated to give **6** (58% based on unrecovered ketone).[8,9] Reduction of **6** is accomplished by stirring the compound under 56 psi of hydrogen with a slurry of unactivated Raney nickel powder in methanolic KOH; bicyclic imine **7** is produced in 95% yield. Although intramolecular reductive amination of keto nitriles is well precedented,[10] the conversion of such a compound to an imine is uncommon.

Treatment of imine **7** with 1.25 equiv each of *o*-nitrocinnamic acid and ammonium *o*-nitrocinnamate in refluxing dioxane for 90 h gives the crystalline dihydropyridone **8** in 42% yield. The stereoselectivity of this process is approximately 95%; the relative configuration of the major isomer is assigned on the basis of an X-ray structure of the crystalline analogue produced in the reaction of **7** with cinnamic acid.[11,12]

Reduction of the nitro group in **8** is accomplished quantitatively by hydrogenation over Adams' catalyst. The resulting amine, **9**, is treated sequentially with *N*-bromosuccinimide in methylene chloride and silver nitrate in aqueous methanol to give a mixture of crystalline hydroxy amide **10** (79%) and methoxy amide **11** (20%). The structure and configuration of **10** were established by single-crystal X-ray analysis. Ether **11** is converted quantitatively into alcohol **10** by treatment with aqueous acetic acid at room temperature for several hours.[13] The mechanism of the transformation of **9** into **10** and **11** is still under scrutiny. The process involves the formation of an isolable, but unstable bromide, which appears to have a structure related to that proposed for **10**. However, there are several isomeric pentacyclic bromo lactams that can be envisioned, and the evidence currently in hand does not permit an unambiguous structure assignment.

Reaction of hydroxy lactam **10** (or a 4:1 mixture of **10** and **11**) with excess sodium cyanoborohydride in aqueous acetic acid at 50 °C for 2 h, followed by addition of formalin and further reaction at room temperature overnight, gives rise to lactam **12** in 88% yield. Further reduction of **12** (lithium aluminum hydride

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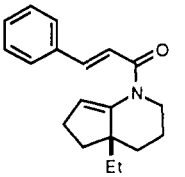
(8) The cyanoethylation reaction is carried out with 91.7 g (0.82 mol) of 2-ethylcyclopentanone, 21.7 g (0.41 mol) of acrylonitrile, and 55.8 g (0.82 mol) of sodium ethoxide in THF at room temperature. The product consists of 39.8 g of keto nitrile **6**, 23.1 g of 2,5-bis(cyanoethyl)-2-ethylcyclopentanone, and 44.5 g of recovered 2-ethylcyclopentanone.
(9) All new compounds reported in this Communication have been fully characterized by elemental, ^{1}H NMR, and ^{13}C NMR analysis. The ^{1}H NMR spectra of the synthetic alkaloid and two important intermediates are included in the Supplementary Material.
(10) Belleau, B. *Can. J. Chem.* **1957**, *35*, 651–662.
(11) This process, developed as a prototype for the conversion of **7** to **8**, proceeds in 70% yield in decahydronaphthalene at 135 °C to give a 6:1 diastereomeric mixture of products; details will be reported in the full paper.
(12) The mechanism of this process appears to involve initial Michael addition of the enamine tautomer of **7** to the cinnamic acid or cinnamate ion followed by lactam formation. An alternative path, wherein these two bond-forming steps are reversed, has been ruled out in a prototype series by the demonstration that the enamine cinnamamide **i** is not converted into the analogue of **8** under similar reaction conditions.



i

(13) The ^{1}H NMR spectra of **10** and **11** are surprisingly different, leaving open the possibility that **11** may, in fact, be a diastereomer of **10**. This point is still under investigation; further details will be reported in the full paper.

in refluxing THF) provides (±)-vallesamidine (**3**) in 92% yield. The structure of the synthetic material was confirmed by comparison with an authentic sample of the natural product kindly supplied by Professor Carl Djerassi of Stanford University.

In summary, we have devised an attractive strategy for creation of the 2,2,3-trialkylindoline skeleton and demonstrated it in a seven-step total synthesis of (±)-vallesamidine. In its current state of development, the synthesis proceeds in 19% overall yield from 2-ethylcyclopentanone. To date, we have prepared 0.360 g of **3** by this method.

Acknowledgment. This research was supported by a grant from the National Science Foundation (Grant CHE-8418427) and a National Institutes of Health Postdoctoral Fellowship to D.A.D. (Grant GM11754).

Supplementary Material Available: The actual 500-MHz ^{1}H NMR spectra of dihydropyridone **8**, hydroxy lactam **10**, and (±)-**3** (3 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Daphnilactone A: A Novel Fragmentation Reaction[1]

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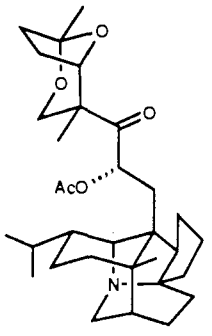
The *Daphniphyllum* alkaloids fall into two major groups—those containing 30 skeletal carbons [e.g., daphniphylline (**1**), secodaphniphylline (**2**)] and those containing 22 skeletal carbons [e.g., yuzurimine (**3**)].[2] Daphnilactone A (**4**)[3] is unique in that it



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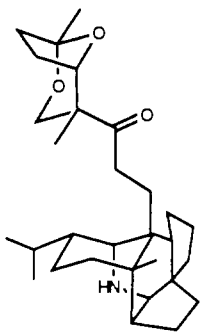

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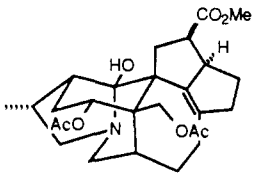

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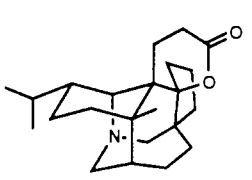

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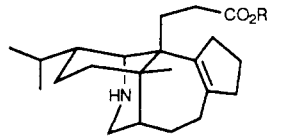
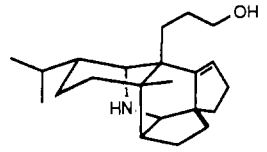
contains 23 skeletal carbons, one of which is not derived from squalene. It has been proposed that the odd carbon derives from a formaldehyde equivalent and that amino acid **5** or amino ester **6** is a key biosynthetic intermediate linking a secodaphniphyl-



5: R = H
6: R = CH_3

line-type precursor with alkaloid **4**.[1c,4] In this Communication, we report the synthesis of hexacyclic amino ether **11**, using the recently described tetracyclization process,[1d] a novel fragmentation reaction that converts the secodaphniphylline skeleton into the conjectural biosynthetic intermediate **5**, and a demonstration of the proposed Mannich conversion of **5** into (±)-daphnilactone A.

As shown in Scheme I, keto ester **8** was prepared from methyl 2-ethoxycyclopentenecarboxylate (**7**) in three steps (81% overall yield) as previously described for a related substance.[1b] Intramolecular Reformatsky cyclization of **8** provides lactone ether **9** in 90% yield.[5] Reduction of **9** affords diol **10**, which is oxidized by the Swern protocol to obtain a fragile dialdehyde. Treatment of this dialdehyde sequentially with ammonia and acetic acid provides the hexacyclic amino ether **11** in 47% yield, based on diol **10**. The yield is not as good as in the previously reported example of this tetracyclization process,[1d] probably because of the tertiary ether function, which is allylic in the intermediate azadiene. Catalytic hydrogenation of **11** quantitatively furnishes the saturated amino ether. Treatment of the latter substance with excess diisobutylaluminum hydride in refluxing toluene for 36 h causes smooth fragmentation, giving unsaturated amino alcohol **12** (60%), accompanied by a small amount of amino alcohol **13** (14%).[6] Jones oxidation of **12** delivers **5**, the hypothetical biogenic



13

precursor of daphnilactone A. This amino acid reacts with aqueous formalin at pH 7 to give (±)-daphnilactone A (**4**), identical by ^{1}H NMR spectroscopy with an authentic sample provided by Professor S. Yamamura. The overall yield for the two-step conversion of **12** to **4** is currently 50%, due to the sensitivity of **12** to oxidative conditions. Amino ester **6** is prepared from **5** by methanolic acid.

The fragmentation reaction that produces unsaturated amino alcohol **12** is interesting because the pseudosymmetry of the substrate permits two different fragmentation modes (a or b, Scheme II). Molecular models suggest that fragmentation mode b might be favored because the pertinent bond is more nearly antiperiplanar with the leaving group bond. However, molecular mechanics calculations show that the product of this cleavage, immonium ion **14**, is much more strained than that arising from fragmentation mode a (immonium ion **15**).[7] The high regioselectivity of the ring-cleavage reaction may be a manifestation of this strain energy in the transition state leading to **14**. On the

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(3) (a) Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron* **1972**, *28*, 1477-1484. (b) Sasaki, K.; Hirata, Y. *Tetrahedron Lett.* **1972**, 1275-1278. (c) Sasaki, K.; Hirata, Y. *J. Chem. Soc., Perkin Trans. II* **1972**, 1411-1415.

(4) Yamamura, S.; Terada, Y. *Chem. Lett.* **1976**, 1381-1382.

(5) The indicated stereostructure for **9** is based on single-crystal X-ray analysis of the crystalline analogue in which the homogeranyl group is replaced by methyl. Details will be reported in the full paper.

(6) The structure of this byproduct was established by oxidation, esterification, and hydrogenation to give (±)-methyl homosecodaphniphyllate.[1d]

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