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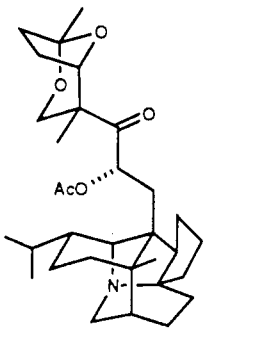
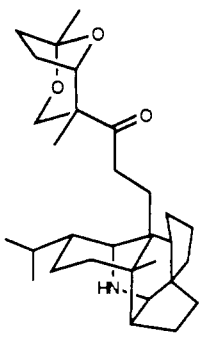
The *Daphniphyllum* alkaloids fall into two major groups—those containing 30 skeletal carbons [e.g., daphniphylline (**1**), secodaphniphylline (**2**)] and those containing 22 skeletal carbons [e.g., yuzurimine (**3**)].[2] Daphnilactone A (**4**)[3] is unique in that it



1



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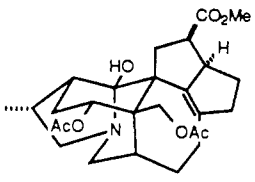

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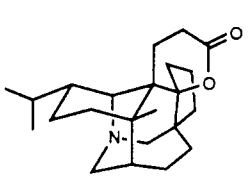

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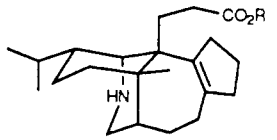
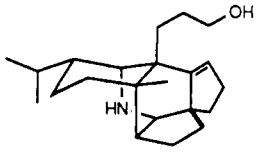
contains 23 skeletal carbons, one of which is not derived from squalene. It has been proposed that the odd carbon derives from a formaldehyde equivalent and that amino acid **5** or amino ester **6** is a key biosynthetic intermediate linking a secodaphniphylline-type precursor with alkaloid **4**.[1c,4] 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.



5: R = H
6: R = CH_3

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



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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

(1) Part 5 in a series of papers on the *Daphniphyllum* alkaloids. (a) Part 1: Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650-5561. (b) Part 2: Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 5745-5746. (c) Part 3: Ruggeri, R. B.; Heathcock, C. H. *Pure Appl. Chem.*, in press. (d) Part 4: Ruggeri, R. B.; Hansen, M. N.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734.

(2) (a) Yamamura, S.; Hirata, Y. *Alkaloids (N.Y.)* **1975**, *15*, 41-81. (b) Yamamura, S.; Hirata, Y. *Int. Rev. Sci., Org. Chem., Ser. 2* **1976**, *9*, 161-189. (c) Yamamura, S. *Alkaloids (N.Y.)* **1986**, *29*, 265-286.

(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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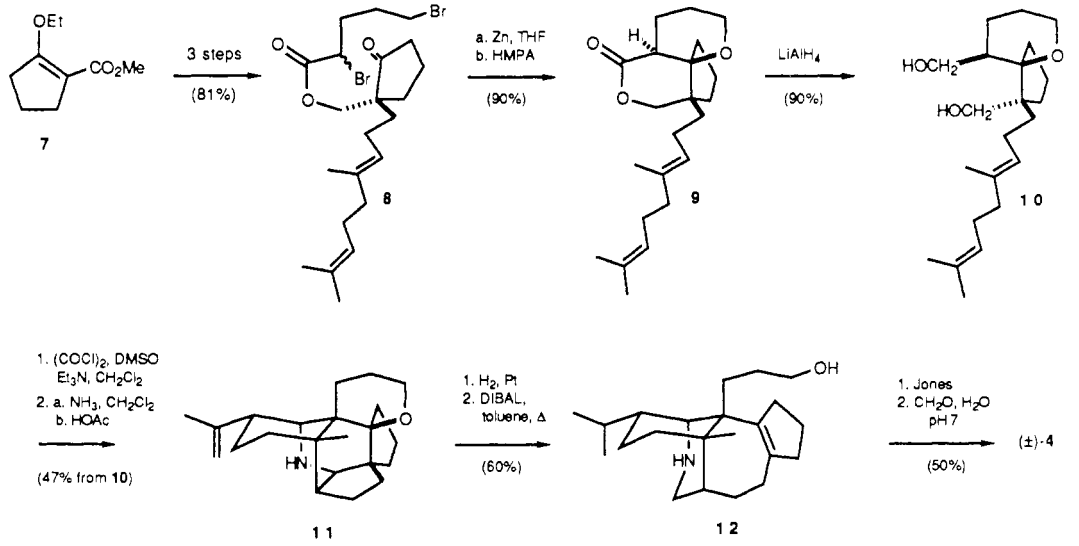
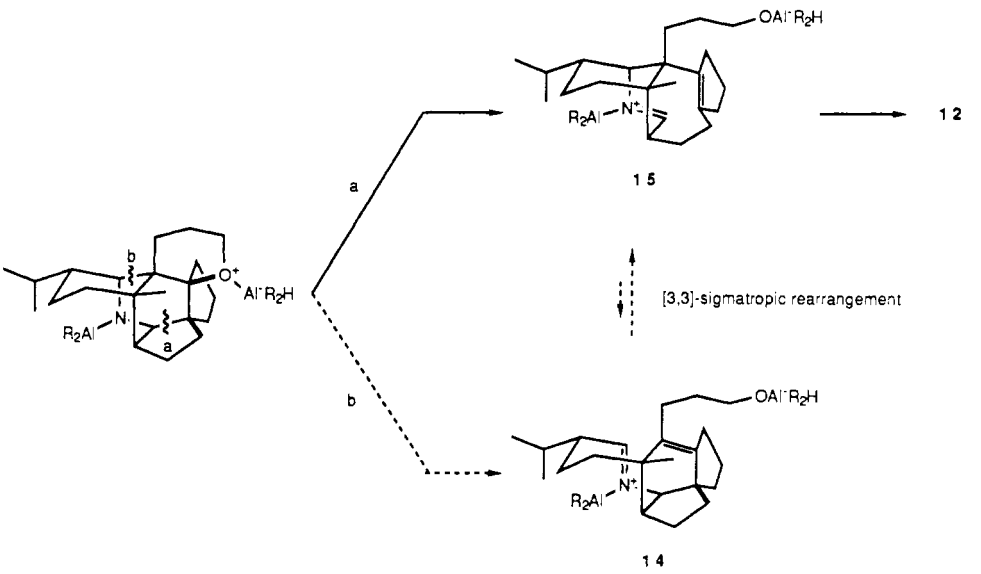
Scheme I



Scheme II



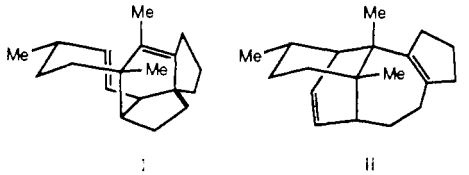
other hand, the observed product might result from fragmentation to **14** followed by Cope rearrangement to **15**.

The total synthesis of (±)-daphnilactone A reported here is brief (11 steps from methyl 2-ethoxycyclopentenecarboxylate, 9% overall yield) and represents the first total synthesis of this structurally unique *Daphniphyllum* alkaloid. More importantly, the synthesis provides easy access to unsaturated amino ester **6**, analogues of which are attractive candidates for conversion into more complex *Daphniphyllum* alkaloids, such as yuzurimine (**3**). Further progress in this direction will be reported in due course.

Acknowledgment. This work was supported by a grant from the National Science Foundation (Grant CHE-8418437) and by fellowships granted to R.B.R. by Smith, Kline, and French Research Laboratories (administered by the ACS Division of Organic Chemistry) and Pfizer, Inc. We thank Professor S. Yamamura for a sample of natural daphnilactone A.

Supplementary Material Available: Physical properties, ^{1}H NMR spectral data, ^{13}C NMR spectral data, and analytical data for compounds **4**, **6**, and **9**-**12** and copies of the ^{1}H NMR spectra of synthetic and natural daphnilactone A (4 pages). Ordering information is given on any current masthead page.

(7) Calculations were performed with the Allinger MM2 force field using Still's MACROMODEL program on hydrocarbon analogues of **14** and **15**, further simplified by replacement of the isopropyl and hydroxypropyl side chains by methyl groups (i and ii). Hydrocarbon i is more strained than hydrocarbon ii by more than 20 kcal/mol.



i ii

Reversible Alkoxide β-Hydrogen Elimination in a Homoleptic Rhenium Alkoxide Complex. Synthesis of $Re_3(\mu\text{-O-}i\text{-Pr})_3(O\text{-}i\text{-Pr})_6$

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Alkoxide β-hydrogen elimination and the reverse reaction, insertion of a ketone into a metal hydride bond, are known pro-

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