this solution on 0.5 g of 230-400-mesh silica gel, eluting with the same solvent. The free base had R_f 0.33 when analyzed by TLC on silica gel with the same solvent system.

Because the amounts of (±)-2 and natural 2 at our disposal were very small (on the order of 1 mg each), we were unable to make a valid ^{1}H NMR comparison in $CDCl_3$ solution. It appears that only trace amounts of adventitious acid can give rise to extensive broadening of certain peaks. However, the ^{1}H NMR spectra of C_6D_6 were quite reproducible. ^{1}H NMR spectra of the synthetic and natural alkaloids are shown in the supplementary material.

Acknowledgment. This work was supported by a research grant from the National Science Foundation (CHE-84-18437). We are indebted to Professors Y. Hirata and S. Yamamura for authentic samples of codaphniphylline and methyl homodaphniphyllate.

Registry No. (±)-2, 104115-43-7; (±)-4, 104115-44-8; (±)-5, 138489-23-3; (±)-6, 138489-24-4; 8, 62240-37-3; 8 (phthalimide derivative), 84764-41-0; (±)-9, 138489-25-5; (±)-10, 104115-45-9; (±)-11, 104115-46-0; 13, 23769-10-0; (±)-15, 138489-26-6; (±)-16, 104115-47-1; (±)-17 (isomer 1), 138489-27-7; (±)-17 (isomer 2), 138602-80-9; 19, 138489-28-8; (±)-20, 104115-48-2; (±)-21 (isomer 1), 138604-10-1; (±)-21 (isomer 2), 138489-29-9; 22 (2″-ene isomer), 138489-31-3; 22 (3″-ene isomer), 138489-30-2; 23, 3102-33-8; (±)-24 (isomer 1), 138602-81-0; (±)-24 (isomer 2), 138602-82-1; (±)-25, 138602-83-2; (±)-27, 138602-84-3; (±)-28, 138489-32-4; (±)-29, 104115-52-8; (±)-30, 138489-33-5; (±)-31, 138489-34-6; (±)-32, 138489-35-7; (±)-33, 138489-36-8; (±)-34a, 138489-37-9; (±)-34b, 138489-38-0; (±)-36, 104115-53-9; (±)-37·HCl, 138516-33-3; (±)-43, 138515-96-5; (±)-44, 138602-86-5; (±)-46, 104115-54-0; (±)-47, 138489-39-1; (±)-48, 104115-56-2; (±)-49, 138515-97-6; (±)-50, 104115-57-3; (±)-51, 104154-52-1; (±)-51·HCl, 138515-98-7; (±)-52, 104115-58-4; (±)-53, 104154-53-2; $BnO(CH_2)_3Br$, 54314-84-0; methyl (±)-2-oxocyclopentanecarboxylate, 53229-93-9; ethyl (±)-1-(methoxycarbonyl)-2-oxocyclopentanecarboxylate, 122040-88-4.

Supplementary Material Available: A poem by Suimei Kawai, *Yuzuri-ha*, in the original Japanese and an English translation, a more detailed discussion of the network analysis of methyl homodaphniphyllate, experimental procedures for compounds 4, 5, 6, 9, 17, 21, 22, 32, 33, 34, 35, 43, and 44, and ^{1}H NMR spectra of compounds 34a, 34b, 35, 43, 44, 49, 50, 51, 52, and 53 (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

Daphniphyllum Alkaloids. 11. Biomimetic Total Synthesis of Methyl Homosecodaphniphyllate. Development of the Tetracyclization Reaction[1]

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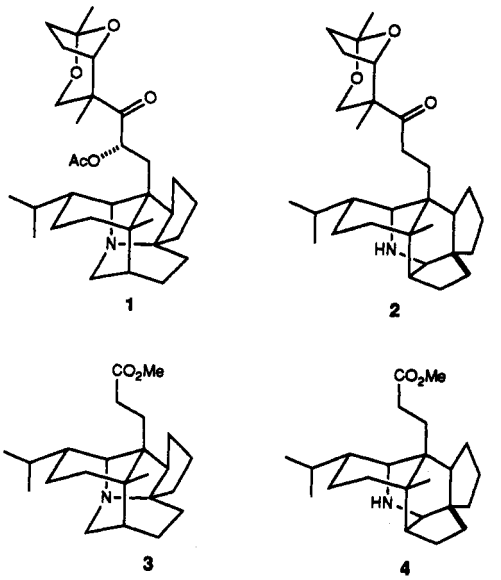
Received August 6, 1991

A biomimetic total synthesis of (±)-methyl homosecodaphniphyllate has been developed. The synthesis starts with a triply convergent, tandem Michael addition–enolate alkylation, wherein amide 9, enoate 7, and alkyl iodide 5 are assembled in essentially quantitative yield to obtain compounds 13, 14, and 15. The major isomer 13 is converted in three steps into a 1:1 mixture of diols 18a and 18b. These diols are subjected to a two-step process involving Swern oxidation and treatment of the resulting dialdehyde sequentially with ammonia and acetic acid; pentacyclic unsaturated amine 23 is obtained in 82% yield. Three additional functional group steps are used to convert 23 into racemic methyl homosecodaphniphyllate ((±)-4). The synthesis requires nine steps and proceeds in 48% overall yield from 5, 7, and 9. The tetracyclization process was shown to proceed via dialdehyde 26, tricyclic aza diene 27, and tetracyclic imine 28. An interesting and potentially useful variant of the tetracyclization procedure employs methylamine or benzylamine instead of ammonia. In this modification, the final reaction product is pentacyclic amine 29, in which the isopropenyl double bond has also been reduced. It is suggested that this reduction occurs by intramolecular hydride transfer at the stage of cationic intermediate 33.

Daphniphylline (1) and secodaphyniphylline (2) represent two of the three basic classes of C-30 *Daphniphyllum* alkaloids. They are accompanied in nature by their C-22 counterparts, methyl homodaphniphyllate (3) and methyl homosecodaphniphyllate (4). Of these two basic skeletal types, daphniphylline is more common than secodaphniphylline. For example, 1000 kg of *D. macropodum* leaves yielded 100 g of 1 and only 1.1 g of 2.[3] Largely for this reason, we selected methyl homodaphniphyllate (3) as the first target of our synthetic investigations.

Concurrent with the final stages of the synthesis described in the foregoing paper, we began to think about the problem of *Daphniphyllum* alkaloid synthesis in a different way.[4] Examination of the skeleton of seco-



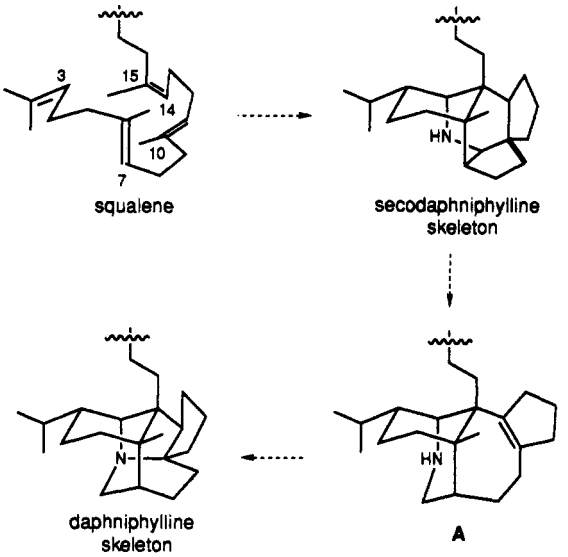
1 2 3 4

daphniphylline reveals that the unbroken squalene molecule may be traced through the pentacyclic domain. To

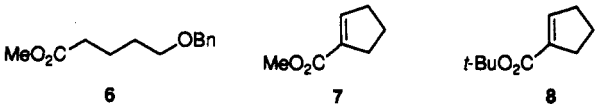
(1) For part 10, see: (a) Heathcock, C. H.; Davidsen, S. K.; Mills, S. G.; Sanner, M. A. *J. Org. Chem.*, preceding paper in this issue.
(2) (a) Present address: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285. (b) Present address: Department of Chemistry, Yale University, New Haven, CT 06511.
(3) Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron* **1972**, *28*, 1477.
(4) For a preliminary communication, see: Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734.

0022-3263/92/1957-2544$03.00/0

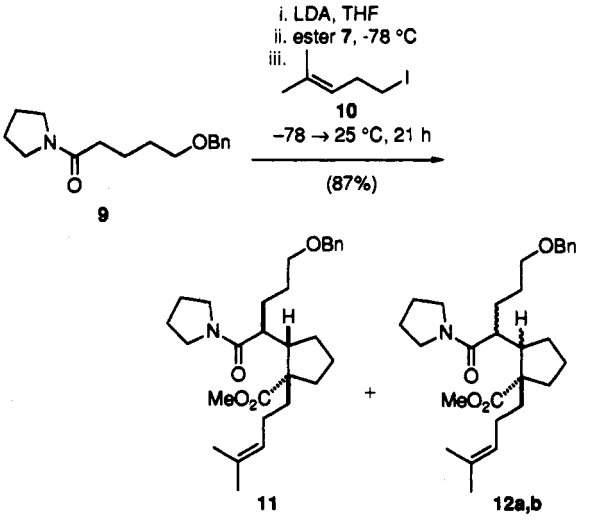
convert squalene into secodaphniphylline, it is necessary to form four C–C bonds: C-10 to C-14; C-6 to C-15; C-3 to the C-15 methyl group; C-7 to the C-10 methyl group. In addition, the nitrogen is inserted between the C-10 and C-15 methyl groups. For daphniphylline, however, the nitrogen seems to have been inserted between C-10 and its methyl group. Thus, it is likely that secodaphniphylline precedes daphniphylline biosynthetically. A plausible biosynthetic link between the two skeletons is the unsaturated amine **A**.



With a view toward imitating this hypothetical biosynthetic scheme in the laboratory, we turned our attention to methyl homosecodaphniphyllate as a synthetic target. The plan that surfaced is shown in retrosynthetic form in Scheme I. The key maneuver in this plan is an intramolecular Diels–Alder reaction, followed by an intramolecular ene reaction. Although thermal Diels–Alder reactions of 2-aza dienes normally require temperatures of more than 200 °C,[5] we hoped that the suggested conversion of **D** to **C** might occur under acid catalysis under much milder conditions. We thought that the required aza diene for this process might arise from a monocyclic dialdehyde (**E**) that could, in turn, arise from a three-component condensation of an enolate, an α,β-unsaturated carbonyl compound, and the known homogeranyl iodide (**5**).[6] Yamaguchi has reported the stereoselective Michael addition of ester[7] and amide enolates[8] to crotonates.[9] Furthermore, the ester enolate resulting from Michael addition was alkylated with reasonable stereoselectivity in a few cases.[10] However, when there is an alkyl substituent at the 2-position of the unsaturated ester, as in enoate **G**, the 1,4-addition of ester enolates is not favorable. Indeed, preliminary experiments with ester **6**[11] and enoates **7** or **8** were discouraging. Formation of the enolate of ester **6** with LDA in THF at −78 °C followed by addition of enoate **7** did not produce any of the desired Michael adduct. Instead, a low yield of a product tentatively identified as the 1,2-adduct was isolated. Use of HMPA as a cosolvent did not alter this result. Formation of the enolate of ester **6** with LDA in THF or THF/HMPA and addition of enoate **8** at −78 °C resulted in no reaction; warming slowly to 0 °C did not induce the desired Michael addition and starting materials were recovered. Thus, the undesired 1,2-addition was prevented using *tert*-butyl enoate **8** but 1,4-addition was still not observed. Addition of enoates **7** or **8** to the dianion[12] of the acid corresponding to ester **6** also resulted in no 1,4-adduct.



In connection with his study of the stereochemistry of the Michael reactions of the lithium enolates of amides, Yamaguchi found that the lithium enolate of *N*-propionylpyrrolidine adds smoothly to the ethyl ester corresponding to enoate **7** to give two diastereomeric products in a ratio of 1:1.[13] Since the stereoisomers result from stereorandom protonation of the ester enolate, it appears that the Michael addition itself occurs with high stereoselectivity. On the basis of this strong precedent, we prepared amide **9**. Treatment of the lithium enolate of **9** successively with ester **7** at −78 °C and then with homoprenyl iodide (**10**)[14] at room temperature gave three products in a total yield of 87%. The major isomer, obtained by silica gel chromatography in 78% yield, is assigned stereostructure **11**. The two minor isomers (**12a,b**) were obtained as a difficultly separable mixture in 9% yield. Their stereostructures are unknown.



The relative stereochemistry assigned to **11** deserves some comment. If we assume a chelated, eight-membered transition state in the Michael reaction,[15] the expected

(5) (a) Eddaif, A.; Laurent, A.; Mison, P.; Pellissier, N.; Carrupt, P.-A.; Vogel, P. *J. Org. Chem.* **1987**, *52*, 5548. (b) Cheng, Y.-S.; Ho, E.; Mariano, P. S.; Ammon, H. L. *J. Org. Chem.* **1985**, *50*, 5678. (c) Boger, D. L.; Weinreb, S. L. In *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987; pp 255–260. (d) Boger, D. L. *Tetrahedron* **1983**, *39*, 2876.

(6) (a) Corey, E. J.; Jantelat, M. *Tetrahedron Lett.* **1968**, 5787. (b) For a synthesis of iodide **5** that reports full spectral data, see: Kocienski, P.; Wadman, S.; Cooper, K. *J. Org. Chem.* **1989**, *54*, 1215. (c) The procedure we employed was adapted from a literature procedure for the preparation of a related compound: Marshall, J. A.; DeHoff, B. S. *Tetrahedron* **1987**, *43*, 4849.

(7) Yamaguchi, M.; Tsukamoto, M.; Tanaka, S.; Hirao, I. *Tetrahedron Lett.* **1984**, *25*, 5661.

(8) Yamaguchi, M.; Hasebe, K.; Tanaka, S.; Minami, T. *Tetrahedron Lett.* **1986**, *27*, 959.

(9) For a review on the stereochemistry of Michael additions of preformed lithium enolates, see: Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1990**, *20*, 87.

(10) Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Tetrahedron Lett.* **1985**, *26*, 1723.

(11) Hoye, T. R.; Kurth, M. J.; Vincent, L. *Tetrahedron Lett.* **1981**, *22*, 815.

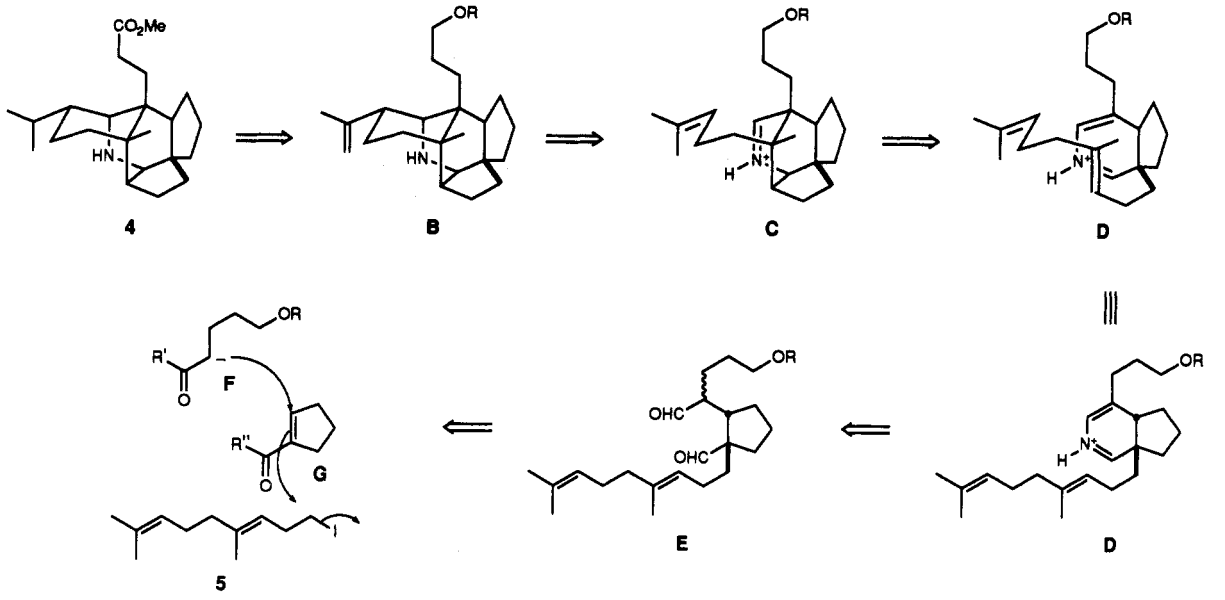
(12) Mulzer, J.; LaSalle, P.; Chucholowski, A.; Blaschek, U.; Bruntrup, G. *Tetrahedron* **1984**, *40*, 2211.

(13) Yamaguchi, M. *Yuki Gosei Kagaka* **1986**, *44*, 405. We thank Dr. Ichiro Mori for bringing this article to our attention and for translating it into English.

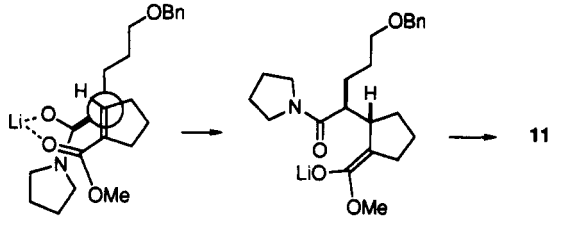
(14) McCormick, J. P.; Barton, D. C. *J. Org. Chem.* **1980**, *45*, 2566.

(15) Oare, D. A.; Henderson, M. N.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132.

Scheme I



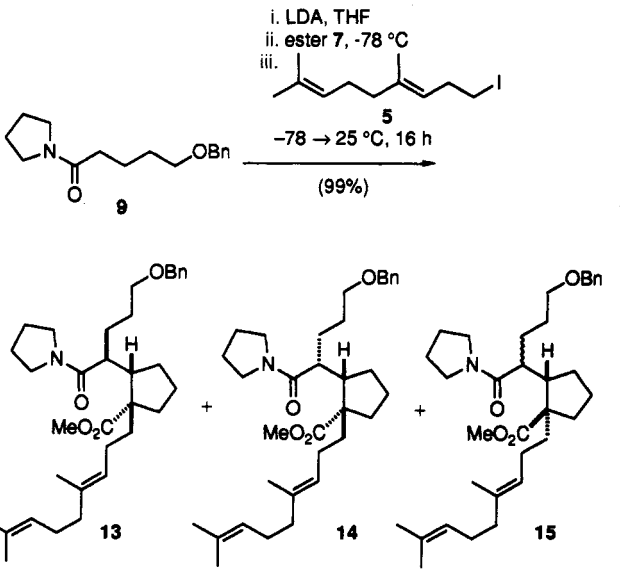
relative stereochemistry of the two stereocenters in the intermediate ester enolate is as in the following structure. In addition, this is the relative stereochemistry assigned by Yamaguchi for the products obtained in his study (vide supra). In the alkylation step, it is expected that the halide will approach the enolate trans to the bulky side chain, leading therefore to **11**. The eventual production of methyl homosecodaphniphyllate by this approach validates the assignment of the relative stereochemistry of the two cyclopentyl stereocenters.



The foregoing tandem Michael addition–alkylation was repeated using homogeranyl iodide as the alkylating reagent to obtain three diastereomeric adducts in a total yield of 99% (Scheme II). The major isomer **13** was isolated by silica gel chromatography in 87% yield. The two minor isomers, **14** and **15**, were isolated as a 2:1 mixture in a combined yield of 12%.[16]

The stereochemistry of amide **13** was assigned in the same manner as amide **11**. Amide **14** was also shown to have the homogeranyl unit cis to the hydrogen by conversion of amides **13** and **14** to the same mixture of cis lactones; the ring stereochemistry of amide **15** was demonstrated by conversion to a trans lactone (vide infra). For amide **15** the stereochemistry at the (benzyloxy)propyl side chain has not been assigned. The fourth diastereomer expected in the Michael addition–alkylation was not isolated or detected in the reaction mixture. The tandem

Scheme II



Michael addition–alkylation process allows assembly of amide **13**, which contains all of the carbons necessary for the skeleton of methyl homosecodaphniphyllate, in one step from relatively simple starting materials.

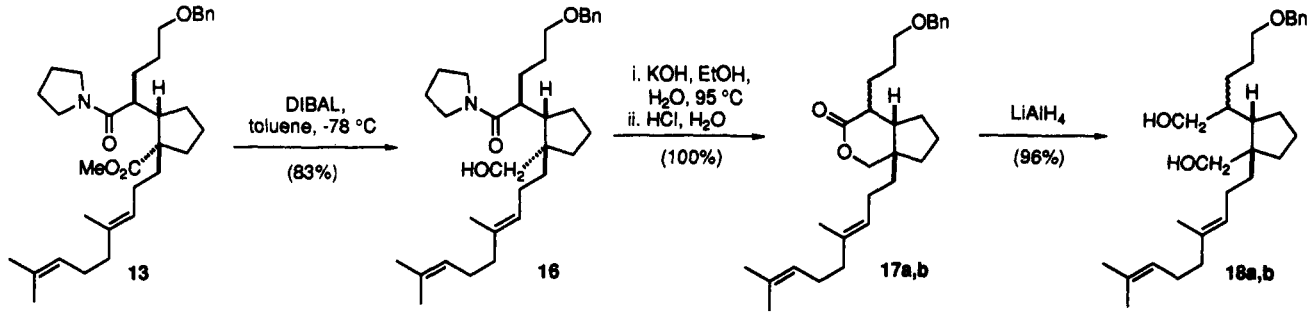
The next synthetic chore was transformation of the ester and amide groups of **13** into aldehyde groups. The initial plan required hydrolysis to the diacid, which would be reduced to a diol, which would, in turn, be oxidized to give the required dialdehyde; however, hydrolysis of amide **13** to the diacid could not be achieved under a variety of basic conditions.[17] A good deal of experimentation with the model ester–amide **11**[18] led to a three-stage protocol summarized in Scheme III. Thus, treatment of **13** with excess DIBAL gave hydroxy amide **16**, which was treated with 5 M KOH at 95 °C for 2 h. Acidification of the saponification mixture provided lactone **17** as a 1:1 mixture of

(16) If undistilled homogeranyl iodide was used in the reaction, a significant amount (up to 20% yield) of an impurity was produced. This material is quite similar to amides **13–15**; it appears to have the same number of protons and carbons as indicated by NMR spectroscopy and the IR spectrum shows amide and ester carbonyl stretches. However, both the combustion analysis and the mass spectrum suggest that O_2 had been incorporated into the molecule. The structure of this impurity was not determined in spite of a significant effort. Less than 1% of this material was produced when distilled homogeranyl iodide was employed.

(17) The most simple solution to the problem, direct hemireduction of the ester–amide, was also explored using Red-Al and DIBAL. All attempts gave mixtures of products that included significant amounts of the fully reduced product, an amino alcohol. For details, see: Hansen, M. M. Dissertation, University of California at Berkeley, 1989.

(18) Some of these experiments are described in the supplementary material.

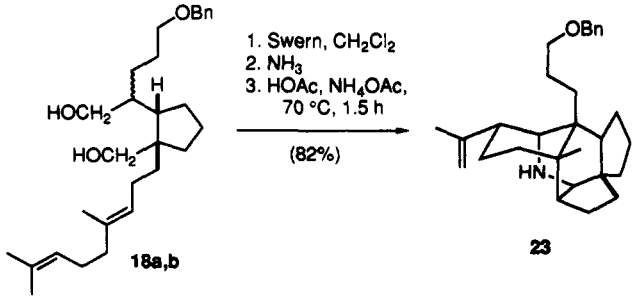
Scheme III



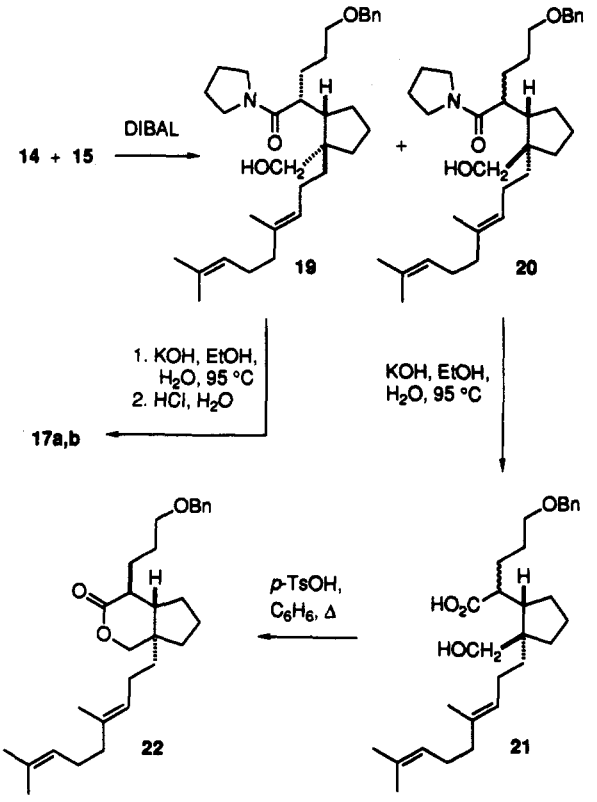
diastereomers in quantitative yield. Epimerization of the (benzyloxy)propyl center apparently occurs under the harsh alkaline conditions of the saponification. However, as will be seen, the stereochemistry at this position is of no consequence. Reduction of the lactone mixture with lithium aluminum hydride provided a 1:1 mixture of epimeric diols **18a** and **18b** in nearly quantitative yield. Although these diols could be separated by careful chromatography, the mixture was used in the subsequent tetracyclization protocol.

Conversion of amide **13** into lactones **17a,b** provided us with a method for assigning the stereochemistry of the amides **14** and **15**, the minor products in the convergent step (see Scheme II). A 2:1 mixture of **14** and **15** was reduced with DIBAL to afford a 3:1 mixture of hydroxy amides **19** and **20** (Scheme IV). These isomers were separated and individually hydrolyzed. Like **16**, hydroxy amide **19** gave a mixture of lactones **17a,b**, proving that **13** and **14** both resulted from alkylation cis to the hydrogen and are epimeric at the (benzyloxy)propyl side position. Hydrolysis of **20** gave a hydroxy acid (**21**) that did not spontaneously lactonize upon acidic workup. Treatment of **21** with *p*-toluenesulfonic acid in refluxing benzene provided trans-fused lactone **22** as a single diastereomer. The equatorial disposition of the (benzyloxy)propyl side chain was evident from the 12.2-Hz vicinal coupling constant of the methine proton at this stereocenter.

Diols **18a,b** were subjected to Swern oxidation[19] under normal conditions (oxalyl chloride, DMSO, Et_3N, CH_2Cl_2). After oxidation was complete, gaseous ammonia was passed over the surface of the stirring solution. Evaporation of the solvent and volatile byproducts gave a residue that was taken up in acetic acid containing NH_4OAc. The resulting solution was heated at 70 °C and worked up in the normal manner to obtain pentacyclic amine **23** in 82% yield.[20] The structure of amine **23** was originally deduced from its spectral data (500-MHz COSY and ^{13}C–^1H correlated NMR spectra); the validity of the assignment was eventually proven by the conversion of **23** into (±)-methyl homosecodaphniphyllate.



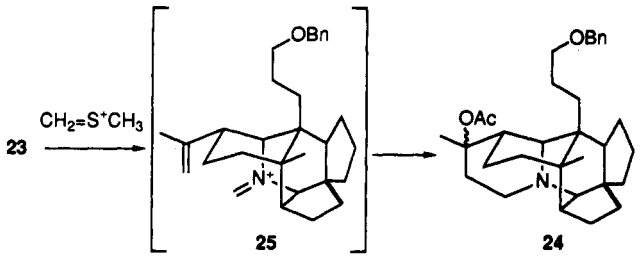
Scheme IV



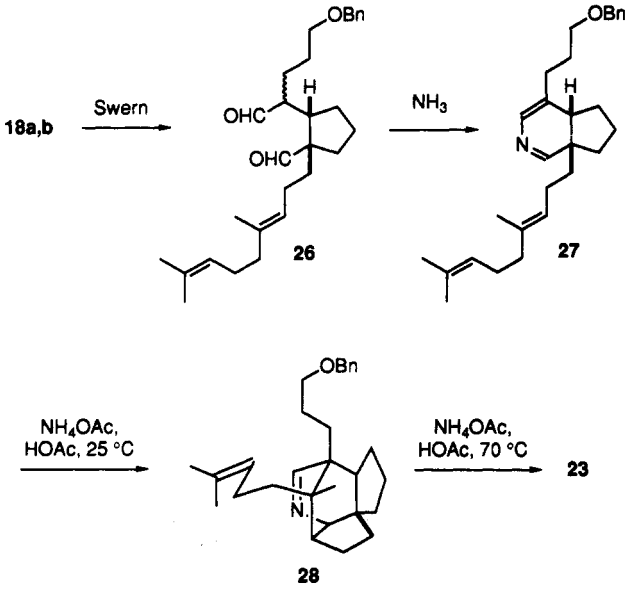
While optimizing the conditions for the tetracyclization process (**18** → **23**), we found that a significant byproduct was formed when we used 4 equiv of the Swern oxidant. This material, which was obtained in about 10% yield under conditions of excess oxidant, was assigned structure **24** on the basis of its spectral data. The ^1H NMR spectrum indicated the absence of a vinyl group and the presence of an acetate methyl group as well as two new proton resonances at 2.95 and 3.01 ppm. The protons responsible for these resonances were shown by a COSY experiment to be coupled to each other and to two other protons in the alkyl region. The ^{13}C NMR spectrum contained a resonance at 85.6 ppm, which can be assigned to the tertiary acetate carbon, and an extra resonance in the region expected for carbons attached to nitrogen. Structure **24** was confirmed by elemental analysis and mass spectrometry. However, the stereochemistry at the acetate carbon has not been assigned. Compound **24** is presumably formed from amine **23** via immonium ion **25**, which could result from the presence of some residual methylenating species that is left over from the Swern oxidation.

Several reaction intermediates in the conversion of **18a,b** into **23** have been isolated and characterized. Swern oxidation afforded the dialdehydes **26**, which were isolated in 55% yield by rapid chromatography of the crude re-

(19) Swern, D.; Mancusco, A. J. *Synthesis* **1981**, 165.
(20) In subsequent executions of this process, the overall yield has been improved to >95%.



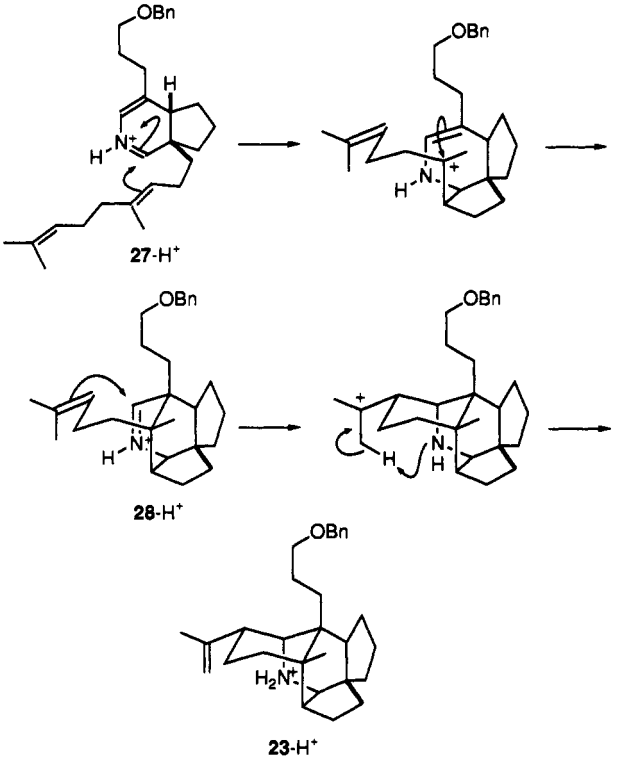
action mixture. The reaction was repeated without isolation to the dialdehydes and ammonia was added in the normal manner to afford aza diene **27**. Compound **27** was isolated in 44% yield by rapid chromatography of the residue remaining after addition of ammonia and removal of the solvent; the aza diene protons were observed at 6.5 and 7.3 ppm in the ^{1}H NMR spectrum. When the reaction was repeated and the residue containing aza diene **27** was dissolved in acetic acid for 10 min, imine **28** was isolated in 90% yield. Thin layer chromatographic analysis indicated that the Diels–Alder reaction was complete in less than 5 min. The catalysis of this reaction by acid is quite impressive; the corresponding thermal conversion of aza diene **27** to imine **28** in toluene has a half-life of approximately 2 h at 120 °C. If the acetic acid solution is heated at 70 °C for 1.5 h, pentacyclic amine **23** is obtained.



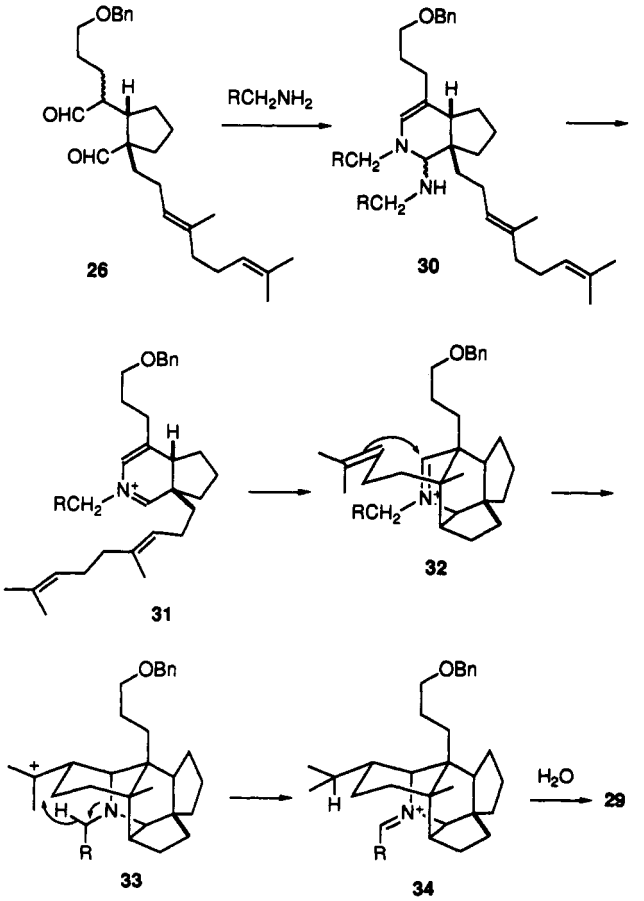
The mechanism of the tetracyclization process might be completely stepwise (Scheme V) or it could involve a concerted Diels–Alder reaction to give **28**-H$^+$ followed by a concerted ene reaction[21] to give **23**-H$^+$. Because subsequent mechanistic investigations[22] showed conclusively that the *E* stereochemistry of the homogeranyl double bond is preserved in the process, we think that **28**-H$^+$ is formed by a concerted, highly asynchronous, Diels–Alder reaction. It should be noted that the NH_4OAc used in the tetracyclization reaction is not necessary; however, the yield seems to be slightly improved when it is used. The excess acetate ion may stabilize the cationic intermediates in the reaction. An ancillary experiment also showed that the reaction proceeds well in the absence of the Et_3N·HCl which results from the Swern oxidation. Thus, NH_3 was added to purified dialdehydes **26** at 0 °C and the solvent was removed. Addition of acetic acid and NH_4OAc to the residue and heating for 1 h at 70 °C afforded amine **23** in 90% yield.

Further insight into the mechanism of the tetracyclization reaction came from a quite remarkable discovery. If the process is carried out as heretofore described,

Scheme V

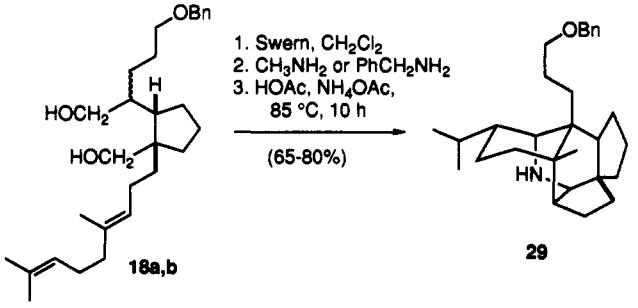


Scheme VI



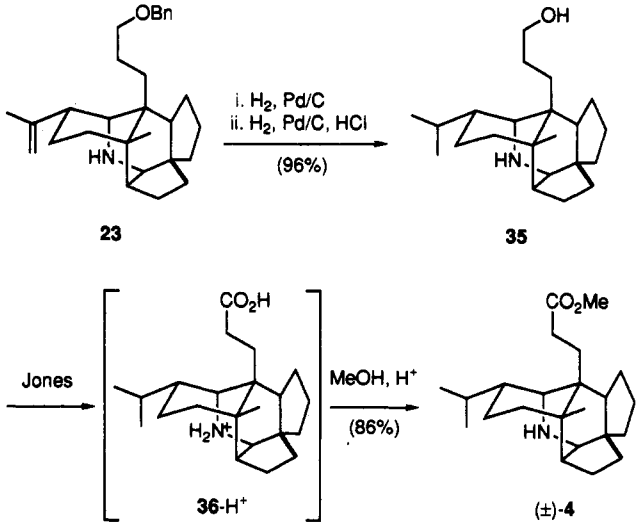
(21) (a) Oppolzer, W.; Snieckus, U. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (b) Lin, J.; KOch, K.; Fowler, F. W. *J. Org. Chem.* **1956**, *51*, 167.
(22) Heathcock, C. H.; Pietrre, S.; Ruggeri, R. B.; Ragan, J. A.; Kath, J. C. *J. Org. Chem.*, following paper in this issue.

but methylamine is used instead of ammonia, the pentacyclic *saturated* amine **29** is obtained in 75% yield.[23] The same product is obtained if benzylamine is used in the second stage of the tetracyclization protocol. A proposed mechanism for the formation of **29** is presented in Scheme VI.[24] Reaction of dialdehyde **26** with the primary amine is postulated to lead to **30**. An impure material having spectral properties consistent with this formulation is, in fact, isolated when the solvent is removed at high vacuum after treatment of **26** with methylamine. The ^1H NMR and ^{13}C NMR spectra of the crude product of this reaction show, in addition to the characteristic resonances of the homogeranyl and (benzyloxy)propyl chains, two *N*-methyl singlets with δ 2.4 and 2.8, a singlet with δ 5.55 which might be the enamine methine, and a quaternary carbon with δ 110.[25] When it is treated with acetic acid at room temperature, **30** is immediately transformed into a compound having NMR spectra consistent with the tetracyclic immonium salt **32**. The postulated intermediate *N*-methyldihydropyridinium salt **31** has not been observed, suggesting that it undergoes the intramolecular Diels–Alder reaction very rapidly. Further reaction of **32** occurs when the acetic acid solution is heated at 80 °C for 10 h or kept at room temperature for several days. Cyclization of **32** would in this series provide the amino cation **33**, which is ideally constructed to undergo intramolecular hydride transfer to give **34**.[26] Hydrolysis of **34** would give **29**. It is noteworthy that the final cyclization in this case (**32** → **34**) is considerably slower than in the acid-mediated cyclization of **28** to **23**. This difference in rate is probably steric in origin.



With an efficient synthesis of amine **23** in hand, we investigated its conversion to methyl homosecodaphniphyllate. The alkene was readily hydrogenated on small scale using 25 mass percent of Pd/C and 1 atm of H_2 over 2 h. ^1H NMR spectroscopy indicated that amine **29** was produced, along with a small amount of amino alcohol **35**. Addition of 5–10 equiv of concentrated HCl increased the rate of hydrogenolysis considerably; 12–24 h were required for complete conversion to **35**. On large scale (2 g of amine **23**) a larger catalyst ratio (100 mass percent Pd/C) and a longer reaction time (47 h) were necessary for the hydrogenation step. Addition of 5 equiv of HCl and further reaction for 60 h completed the hydrogenolysis to afford **35**-H$^+$, the HCl salt of amino alcohol **35**, in 96% yield from amine **23**.[27] Amino alcohol **35** was isolated by neutralization of the HCl salt. Both **35** and its HCl salt are highly insoluble in most solvents, including $CDCl_3$, so a ^{13}C NMR spectrum could not be obtained. However, the assigned structure is fully supported by IR and ^1H NMR spectroscopy, combustion analysis, and a 500-MHz COSY NMR spectrum.

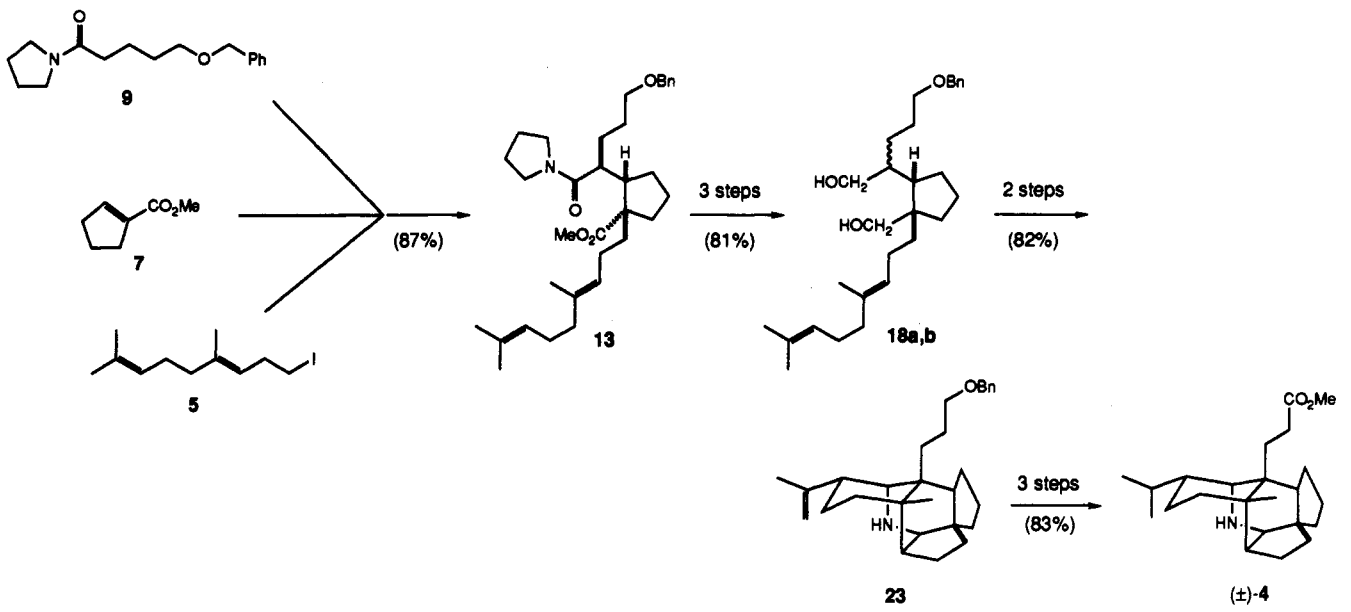
Salt **35**-H$^+$ was directly converted to amino acid **36** by oxidation with excess Jones reagent.[28] The HCl salt was not soluble in acetone; however, addition of 15 equiv of 9 M H_2SO_4 to the HCl salt afforded a cloudy solution. Excess Jones reagent (29 mol of Cr(VI) per mole of substrate) was added at 0 °C and after 30 min the excess oxidant was quenched with isopropyl alcohol. The solvent was removed to give the crude amino acid salt (**36**-H$^+$), which was taken up in methanol. After being stirred overnight at room temperature, the reaction mixture was worked up to obtain (±)-methyl homosecodaphniphyllate (**4**) in 86% yield from **35**-H$^+$. The chromatographed material was slightly tan colored but was analytically pure. Recrystallization from hexanes afforded a colorless solid but this material was slightly lower melting than the chromatographed material (62.5–63.5 °C vs 63–65 °C). Methyl homosecodaphniphyllate (**4**) was initially identified by its IR, ^1H NMR, and ^{13}C NMR spectral data and combustion analysis. The synthetic material was identical by ^1H NMR spectroscopy and TLC mobility with an authentic sample of the natural alkaloid, generously provided Professor S. Yamamura.[29]



The total synthesis of (±)-methyl homosecodaphniphyllate (**4**) is summarized in Scheme VII. The synthesis requires nine steps and proceeds in 48% overall yield from the simple starting materials **5**, **7**, and **9**. Amide **9** and enoate **7** are each made in two steps from commercially available materials. The synthesis of iodide **5** is more complicated, requiring four steps from geraniol. The longest linear sequence requires 13 steps from geraniol and proceeds in 18% overall yield. The key steps in the synthesis are the tandem Michael addition–alkylation process, which assembles all of the carbons necessary for the skeleton, and the tetracyclization reaction, which provides the complete pentacyclic skeleton in one operation. The only disappointing sequence is the conversion of amide **13** to diol **18**; three steps are expended for what would appear

(23) This serendipitous discovery resulted from use of a lecture bottle of methylamine that was mislabeled as ammonia by the vendor.
(24) We thank Professor Steven Pedersen for first suggesting this mechanism to us.
(25) The NMR spectra of this crude reaction intermediate are presented in the supplementary material.
(26) Such intramolecular hydride shifts are precedented: Cohen, T.; Onopchenko, A. *J. Org. Chem.* **1983**, *48*, 4531.
(27) These reaction were not monitored closely, so the reaction times given here are unnecessarily long. Furthermore, the activity of the palladium catalyst used on large scale seemed to be inferior to the catalyst used in the small-scale hydrogenations.
(28) Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.
(29) We thank Prof. S. Yamamura (Keio University) for providing us with two samples of natural methyl homosecodaphniphyllate. The first sample was compared with our racemic material and the second sample was used to determined the optical rotation of the natural material: $[\alpha]_D$ −97.5 (c = 0.79 g/100 mL $CHCl_3$).

Scheme VII



to be straightforward functional group manipulations. However, this is the only workable method that we could find for this conversion and the overall yield for the three steps is quite respectable. All of the steps in the sequence can be efficiently carried out on gram scale. We have synthesized more than 3.5 g of (±)-methyl homosecodaphniphyllate using this route. Because the tetracyclization process is so efficient and proceeds under such mild conditions with common reagents, we believe that it is probably biomimetic. Further explorations of this basic idea are presented in succeeding papers in this series.

Experimental Section

General. Unless otherwise noted, reagent solutions were added using a syringe. Chromatography was carried out using Merck 60 230–400-mesh silica gel according to the procedure described by Still[30] unless otherwise noted. Reactions and chromatography fractions were analyzed using Analtech 250-μm silica gel GF plates. When an R_f is reported for a compound, the solvent used is the chromatography solvent unless otherwise indicated. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Ether and tetrahydrofuran (THF) were distilled under N_2 from Na/benzophenone immediately prior to use. Toluene, xylenes, triethylamine (Et_3N), and diisopropylamine (i-Pr_2NH) were distilled from CaH_2 and stored over 3- or 4-Å molecular sieves. CH_2Cl_2 was distilled from P_2O_5 immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled from BaO and stored over 3-Å molecular sieves. When necessary, the densities of compounds that were oils were determined by weighing 50 μL of the material in a 100-μL syringe. In this manner the densities of the following frequently used compounds were determined (g/mL): enoate **7**, 1.03; amide **9**, 1.1; iodide **10**, 1.5. The concentration of commercially available solutions of n-butyllithium in hexanes was periodically checked by titration using diphenylacetic acid.[31] Unless otherwise noted, extracts were dried over $MgSO_4$ and solvents were removed with a rotary evaporator at aspirator pressure. Unless otherwise indicated, IR spectra were recorded as films on NaCl plates and NMR spectra were measured in $CDCl_3$. J values are in hertz. In some cases Distortionless Enhancement by Polarization Transfer (DEPT)[32] was used to assign the ^{13}C NMR resonances as CH_3, CH_2, CH, or C. When ^{13}C NMR spectra were obtained on mixtures of stereoisomers, some of the resonances overlapped. Therefore, the correct number of resonances may not be listed. Also, when carbons are equivalent (e.g., ortho and meta protons of a benzyl group) no special notation is used. Gas chromatography was performed with 4% Carbowax 20M on a 60/80-mesh Chromosorb G column.

1-[1-Oxo-5-(phenylmethoxy)pentyl]pyrrolidine (9). To 19.8 g (95.0 mmol) of 5-(phenylmethoxy)pentanoic acid[33] in 200 mL of dry CH_2Cl_2 was added 17.0 g (105 mol) of 1,1′-carbonyldiimidazole in portions over 10 min. (Vigorous evolution of CO_2!) The reaction flask was immersed in a cool water bath after the addition was begun to minimize refluxing of the solvent. The mixture was stirred at room temperature under N_2 for 10 min and again cooled with a water bath as 17.5 mL (209 mmol) of pyrrolidine was added over 2 min. After 15 min the cooling bath was removed and the mixture was allowed to warm to room temperature overnight. The reaction flask was immersed in an ice/H_2O bath and 200 mL of 2 M HCl was added. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were washed with a 4:1 mixture of saturated $NaHCO_3$ and brine. The aqueous layer was backwashed with 20 mL of CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$). The solvent was removed with a rotary evaporator and the residue was distilled to afford 24.5 g (99%) of amide **9** as a colorless oil, bp 125–182 °C, 0.02 mmHg. IR: 3100–2750, 1641 cm^{-1}. ^1H NMR (250 MHz): δ 1.59–2.00 (m, 8), 2.29 (br t, 2, J = 7), 3.37 (t, 2, J = 6.6), 3.45 (t, 2, J = 6), 3.50 (t, 2, J = 6), 4.49 (s, 2), 7.20–7.40 (m, 5). ^{13}C NMR (125 MHz): δ 21.62 (CH_2), 24.29 (CH_2), 26.00 (CH_2), 29.36 (CH_2), 34.33 (CH_2), 45.45 (CH_2), 46.45 (CH_2), 70.08 (CH_2), 72.78 (CH_2), 127.37 (CH), 127.52 (CH), 128.22 (CH), 138.50 (C), 171.35 (C). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.27; H, 8.60; N, 5.23.

Methyl [1a,1(*E*),2a(*S)]-(±)-1-(4,8-Dimethyl-3,7-nonadienyl)-2-[4-(phenylmethoxy)-1-(1-pyrrolidinylcarbonyl)butyl]cyclopentanecarboxylate (13).** Into a 500-mL flask under N_2 at 0 °C were placed 17 mL of THF, 3.5 mL (25 mmol) of i-Pr_2NH, and 11.7 mL (23 mmol) of a 1.97 M solution of n-butyllithium in hexanes. After 15 min, the solution was cooled to −78 °C and 5.53 g (23 mmol) of amide **9** in 17 mL of THF was added over 5 min. The flask and syringe were rinsed with 5 mL of THF. After 30 min, enoate **7** in 14 mL of THF was added over 5 min. The flask and syringe were rinsed with 4 mL of THF. After 15 min, 5.3 g (19 mmol) of homogeranyl iodide (**5**) in 5 mL of THF was added. The resulting yellow solution was allowed to warm slowly with the dry ice/acetone bath to −10 °C over 3 h. The dry ice/acetone bath was then replaced with an ice/NaCl/H_2O bath (ca. −8 °C) and the mixture was allowed to warm slowly to room

(30) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(31) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
(32) Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon: New York, 1987; p 143.
(33) Hoye, T. R.; Kurth, M. J.; Vincent, L. *Tetrahedron Lett.* **1981**, *22*, 815.

temperature over 13 h. Saturated aqueous NH_4Cl (80 mL) and saturated aqueous $Na_2S_2O_3$ (40 mL) were added and the mixture was transferred to a separatory funnel with 200 mL of ether. The layers were agitated and separated and the aqueous layer was washed with ether (2 × 100 mL). The combined organic layers were washed with brine (50 mL) and dried. Removal of the solvent afforded a colorless oil. Chromatography on 300 g of silica gel with 1:3 ethyl acetate/hexanes afforded 8.87 g (87%) of amide **13** as a colorless oil (R_f 0.6, 1:1 ethyl acetate/hexanes). There was also obtained 1.25 g (12%) of material that was about a 2:1 mixture of amide **14** (R_f 0.36) and amide **15** (R_f 0.32), respectively. Amides **14** and **15** could only be partially separated by silica gel chromatography. The mixture of **14** and **15** also contained a small amount (10%) of two impurities with methyl ester peaks.

Amide 13. IR: 1725, 1641 cm^{-1}. ^1H NMR (400 MHz): δ 1.24 (m, 1), 1.38–2.12 (m, 20), 1.56 (s, 3), 1.59 (s, 3), 1.68 (d, 3, J = 0.9), 2.15–2.29 (m, 2), 2.63 (br ddd, 1, J = 3, 8, 11), 3.32–3.52 (m, 5), 3.64 (s, 3), 3.74 (m, 1), 4.46 (s, 2), 5.07 (m, 2), 7.20–7.40 (m, 5). ^{13}C NMR (100 MHz): δ 15.80 (CH_3), 17.61 (CH_3), 21.48 (CH_2), 24.26 (CH_2), 24.74 (CH_2), 25.63 (CH_3), 26.12 (CH_2), 26.66 (CH_2), 27.56 (CH_2), 27.90 (CH_2), 28.09 (CH_2), 34.33 (CH_2), 37.87 (CH_2), 39.63 (CH_2), 43.12 (CH), 45.69 (CH_2), 46.25 (CH_2), 51.33 (CH_3), 52.14 (CH), 56.63 (C), 70.51 (CH_2), 72.91 (CH_2), 124.11 (CH), 124.29 (CH), 127.45 (CH), 127.64 (CH), 128.28 (CH), 131.22 (C), 135.01 (C), 138.45 (C), 173.91 (C), 176.77 (C). Anal. Calcd for $C_{34}H_{51}NO_4$: C, 75.94; H, 9.56; N, 2.60. Found: C, 75.74; H, 9.48; N, 2.73.

[1α,1(*E*),2α(*S)]-(±)-1-(4,8-Dimethyl-3,7-nonadienyl)-2-[4-(phenylmethoxy)-1-(1-pyrrolidinylcarbonyl)butyl]-cyclopentanemethanol (16).** To 8.85 g (16.4 mmol) of amide **13** in a dry 250-mL flask under N_2 was added 35 mL of dry toluene (distilled from CaH_2). The solution was cooled to −78 °C and 43.9 mL (65.8 mmol) of a 1.5 M solution of diisobutylaluminum hydride in toluene was added with a syringe over 12 min. After 1.5 h at −78 °C, a large gas vent needle was added and 120 mL of 2 M aqueous NaOH was added over 10 min. The cooling bath was removed and the mixture was allowed to warm to room temperature. The mixture was partitioned between ether (250 mL) and H_2O (75 mL). The layers were separated and the aqueous layer was washed with ether (2 × 100 mL). The combined organic layers were washed with brine (50 mL) and the aqueous layer was back-washed with ether (50 mL). The combined organic layers were dried and the solvent was removed first with a rotary evaporator and then with a static high vacuum (14 h) to afford 9.30 g of a colorless oil. Chromatography on 250 g of silica gel with 1:2 ethyl acetate/hexanes afforded 6.94 g (83%) of alcohol **16** as a colorless oil. IR (neat): 3660–3100, 1620 cm^{-1}. ^1H NMR (400 MHz): δ 1.18 (m, 1), 1.33–2.15 (m, 22), 1.60 (s, 3), 1.61 (s, 3), 1.68 (s, 3), 2.35 (br s, 1), 2.70 (br dt, 1 J = 3, 9) 3.33–3.52 (m, 7), 3.53–3.62 (m, 1), 4.47 (s, 2), 5.11 (m, 2), 7.22–7.42 (m, 5). ^{13}C NMR (100 MHz): δ 15.95 (CH_3), 17.62 (CH_3), 21.58 (CH_2), 23.08 (CH_2), 24.17 (CH_2), 25.64 (CH_3), 26.18 (CH_2), 26.72 (CH_2), 27.10 (CH_2), 28.65 (CH_2), 29.07 (CH_2), 33.78 (CH_2), 36.45 (CH_2), 39.69 (CH_2), 45.80 (CH_2), 46.62 (CH_2), 48.39 (CH), 48.89 (C), 65.96 (CH_2), 70.44 (CH_2), 72.88 (CH_2), 124.38 (CH), 125.08 (CH), 127.48 (CH), 127.65 (CH), 128.29 (CH), 131.19 (C), 134.68 (C), 138.45 (C), 174.93 (C). Anal. Calcd for $C_{33}H_{51}NO_3$: C, 77.75; H, 10.08; N, 2.75. Found: C, 77.48; H, 9.92; N, 2.81.

[4α,4aβ,7aβ(*E*)]- and [4α,4aα,7aα(*E*)]-(±)-7a-(4,8-Dimethyl-3,7-nonadienyl)hexahydro-4-[3-(phenylmethoxy)-propyl]cyclopenta[*c*]pyran-3(1*H*)-one (17a,b). To 6.94 g (13.6 mmol) of alcohol **16** in 190 mL of ethanol was added 46 mL of 5 M aqueous KOH. The mixture was heated at 95 °C for 2 h and then cooled to 0 °C. Methylene chloride (150 mL) and 125 mL of 2 M aqueous HCl were added (pH 1). After being warmed to room temperature, the mixture was transferred to a separatory funnel with 50 mL of CH_2Cl_2. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL) and the aqueous layer was back-washed with 50 mL of CH_2Cl_2. The combined organic layers were dried, and the solvent was removed first with a rotary evaporator and then by a static high vacuum (23 h) to afford 5.97 g (100%) of lactones **17a** and **17b** as a yellow oil. Lactones **17a** and **17b** were isolated as a 1:1 mixture of stereoisomers. This material was suitable for use in the subsequent reaction. An analytical sample of the 1:1 isomeric mixture was obtained by chromatography on silica gel with 1:4 ethyl acetate/hexanes. IR: 1750 cm^{-1}. ^1H NMR (400 MHz): δ 1.13 (m, 1), 1.18–2.12 (m, 37), 1.59 (s, 6), 1.60 (s, 6), 1.68 (d, 6, J = 1.0), 2.19 (br ddd, 1, J = 3, 8, 11), 2.50 (dd, 1 J = 6.7, 12.8), 3.50 (m, 4), 3.88 (d, 1, J = 11.4), 3.95 (d, 1, J = 11.5), 3.98 (d, 1, J = 11.5), 4.11 (d, 1, J = 11.4), 4.50 (s, 4), 5.08 (m, 4), 7.23–7.44 (m, 10). ^{13}C NMR (100 MHz): δ 15.94, 15.97, 17.62, 22.83, 23.03, 24.23, 24.78, 25.30, 25.62, 26.28, 26.56, 26.59, 27.32, 27.61, 30.59, 33.83, 34.85, 35.42, 38.51, 38.94, 39.57, 41.73, 43.57, 44.88, 45.80, 46.06, 48.33, 70.16, 70.23, 71.10, 72.76, 72.90, 73.47, 123.59, 123.64, 124.08, 124.19, 127.41, 127.48, 127.59, 127.62, 128.26, 128.29, 131.28, 131.38, 135.37, 135.65, 138.43, 138.53, 175.12, 175.57. Anal. Calcd for $C_{29}H_{42}O_3$: C, 79.41; H, 9.65. Found: C, 79.03; H, 9.57.

[1α(*R),2α,2(*E*)]- and [1a(*S**),2α,2(*E*)]-(±)-2-(4,8-Dimethyl-3,7-nonadienyl)-2-(hydroxymethyl)-β-[3-(phenylmethoxy)propyl]cyclopentaneethanol (18a,b).** To 5.97 g (13.6 mmol) of crude lactones **17a,b** in a 1-L flask immersed in a cool tap water bath was added 140 mL of dry ether, followed by 1.55 g (40.8 mmol) of $LiAlH_4$ over 1 min. After the vigorous foaming had subsided the mixture was allowed to warm to room temperature. After 5 h, the mixture was cooled in an ice/H_2O bath and 1.6 mL of H_2O, 1.6 mL of 15% aqueous NaOH, and 4.6 mL of H_2O were added sequentially.[34] The cooling bath was removed and the mixture was allowed to warm to room temperature to afford a white suspension (20 min). A scoopula of $MgSO_4$ was added and the mixture was filtered through a fine glass frit. The filtrate was concentrated with a rotary evaporator followed by high vacuum (12 h) to afford 6.12 g of a colorless oil. Chromatography on 150 g of silica gel with 1:2 ethyl acetate/hexanes (1 L) followed by 1:1 ethyl acetate/hexanes (1 L) afforded 5.88 g (98%) of diols **18** as a colorless oil. Diols **18a,b** were used as a 1:1 mixture of stereoisomers in subsequent reactions. Careful chromatography of a sample of the diols on silica gel with 1:3 ethyl acetate/hexanes afforded the individual isomers **18a** and **18b**.

Less Polar Isomer. ^1H NMR (400 MHz): δ 1.18–1.32 (m, 2), 1.37–1.87 (m, 12), 1.60 (s, 6), 1.68 (d, 3, J = 0.7), 1.93–2.09 (m, 6), 2.15 (br s, 2), 3.38–3.66 (m, 6), 4.50 (s, 2), 5.09 (tt, 1, J = 1.4, 7.0), 5.14 (dt, 1, J = 1.1, 1.7), 7.20–7.40 (m, 5). ^{13}C NMR (100 MHz): δ 15.99 (CH_3), 17.67 (CH_3), 22.22 (CH_2), 23.34 (CH_2), 25.67 (CH_3), 26.05 (CH_2), 26.71 (CH_2), 27.03 (CH_2), 28.52 (CH_2), 35.03 (CH_2), 37.25 (CH_2), 39.693 (CH_2), 40.02 (CH), 48.14 (CH), 48.28 (C), 65.48 (CH_2), 65.84 (CH_2), 70.56 (CH_2), 72.93 (CH_2), 124.34 (CH), 124.90 (CH), 127.56 (CH), 127.69 (CH), 128.35 (CH), 131.30 (C), 134.86 (C), 138.37 (C). Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.39; H, 10.59.

More Polar Isomer. ^1H NMR (400 MHz): δ 1.14 (br ddd, 1, J = 6, 11, 13), 1.60 (s, 6), 1.68 (s, 3), 1.32–1.85 (m, 13), 1.87–2.10 (m, 6), 2.88 (br s, 2), 3.43 (d, 1, J = 11.8), 3.46 (t, 2, J = 6.6), 3.53 (dd, 1, J = 5.0, 10.5), 3.55 (d, 1, J = 11.8), 3.66 (dd, 1, J = 7.0, 10.5), 4.50 (s, 2), 5.09 (tt, 1, J = 1.4, 7.0), 5.12 (dt, 1, J = 1.4, 7.0), 7.23–7.42 (m, 5). ^{13}C NMR (100 MHz): δ 15.99 (CH_3), 17.68 (CH_3), 22.11 (CH_2), 23.49 (CH_2), 25.68 (CH_3), 26.70 (CH_2), 27.17 (CH_2), 27.38 (CH_2), 30.28 (CH_2), 34.35 (CH_2), 37.60 (CH_2), 37.96 (CH), 39.70 (CH_2), 48.02 (C), 50.55 (CH), 64.93 (CH_2), 65.95 (CH_2), 70.67 (CH_2), 72.98 (CH_2), 124.34 (CH), 124.89 (CH), 127.54 (CH), 127.68 (CH), 128.35 (CH), 131.31 (C), 134.83 (C), 138.43 (C). Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.47; H, 10.44.

(±)-17,18-Didehydro-23-(phenylmethoxy)-12,16-cyclo-1,12-secodaphnane (23). Into a dry 500-mL flask under N_2 (17 gauge inlet needle) was placed 50 mL of dry CH_2Cl_2. After cooling to −78 °C, 1.3 mL (14.6 mmol) of distilled oxalyl chloride was added. An outlet needle (17 gauge) was added to vent CO and CO_2 as 2.4 mL (33 mmol) of DMSO in 7 mL of CH_2Cl_2 was added over 5 min. After 5 min the gas outlet needle was removed and 2.94 g (6.6 mmol) of diols **18** in 10 mL of CH_2Cl_2 was added with a syringe. The flask and syringe were rinsed with CH_2Cl_2 (2 × 3 mL). The resulting white suspension was stirred for 15 min at −78 °C and then 11 mL (80 mmol) of Et_3N (freshly distilled from CaH_2) was added. After 5 min the dry ice bath was removed; after 10 min the reaction vessel was immersed in an ice/H_2O bath. Analysis by TLC showed that the oxidation to dialdehydes **26** was complete after ca. 25 min at 0 °C. After a total of 50 min, a stream of NH_3 gas was blown over the reaction mixture for 10

(34) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1; Wiley: New York, 1967; p 584.

min. The ice/H_2O bath was then removed and the excess NH_3 was allowed to evaporate as the mixture warmed to room temperature (45 min). The solvent was removed with a rotary evaporator and the white solid residue was dried under high vacuum (2 h). The residue was placed under N_2 and 5.2 g (66 mmol) of NH_4OAc was added followed by 130 mL of CH_3CO_2H (from bottle). The solid was completely suspended by vigorous stirring and swirling around the sides of the flask. After 30 min, the mixture was heated in an oil bath at 70 °C for 1.5 h. After being cooled to room temperature, the mixture was transferred to a separatory funnel containing 450 mL of H_2O and 200 mL of CH_2Cl_2. The layers were agitated and separated and the aqueous layer was washed with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with 475 mL of 2 M NaOH (pH aqueous layer = 10). The aqueous layer was back-washed with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were dried (K_2CO_3). The solvent was removed with a rotary evaporator to afford a brown oil that was directly chromatographed on 175 g of silica gel with 1:5 ethyl acetate/hexanes to afford 2.29 g (82%) of amine **23** as a yellow oil. ^1H NMR (500 MHz): δ 0.80 (s, 3), 1.19 (ddd, 1, J = 2.4, 4.2, 13.5), 1.23–1.95 (m, 20), 1.76 (s, 3), 2.01 (br d, 1, J = 11.8), 2.53 (d, 1, J = 4.5), 3.00 (br s, 1), 3.41 (t, 2, J = 6.7), 4.50 (s, 2), 4.73 (s, 1), 4.86 (s, 1), 7.15–7.50 (m, 5). ^{13}C NMR (100 MHz): δ 20.21 (CH_2), 21.52 (CH_3), 22.62 (CH_3), 22.82 (CH_2), 25.38 (CH_2), 26.67 (CH_2), 29.22 (CH_2), 29.60 (CH_2), 36.31 (CH_2), 36.49 (C), 36.93 (C), 38.46 (CH_2), 39.53 (CH_2), 42.30 (CH), 47.77 (CH), 49.54 (CH), 50.73 (C), 53.56 (CH), 60.10 (CH), 71.55 (CH_2), 72.78 (CH_2), 110.18 (CH_2), 127.43 (CH), 127.51 (CH), 128.30 (CH), 138.66 (C), 147.68 (C). Anal. Calcd for $C_{29}H_{41}NO$: C, 83.00; H, 9.85; N, 3.34. Found: C, 82.80; H, 9.70; N, 3.49.

[1α(*R),2α,2(*E*)]- and [1α(*S**),2α,2(*E*)]-2-(4,8-Dimethyl-3,7-nonadienyl)-2-formyl-α-[3-(phenylmethoxy)propyl]-cyclopentaneacetaldehyde (26a,b).** Into a dry 25-mL flask under N_2 were placed 5 mL of CH_2Cl_2 and 0.080 mL (0.90 mmol) of oxalyl chloride. The solution was cooled to −78 °C and 0.17 mL (2.3 mmol) of dimethyl sulfoxide in 0.5 mL of CH_2Cl_2 was added. After 5 min, a solution of 100 mg (0.23 mmol) of diols **18a,b** in 0.5 mL of CH_2Cl_2 was added. The flask and syringe were rinsed with 0.5 mL of CH_2Cl_2. After 15 min at −78 °C, 0.64 mL (4.6 mmol) of Et_3N was added. The dry ice/acetone bath was replaced with an ice/H_2O bath after 5 min. After 2 h at 0 °C, the solvent was removed with an N_2 flow followed by high vacuum. The residue was suspended in 1:7 ethyl acetate/hexanes and rapidly chromatographed on 7 g of silica gel to afford 55 mg (55%) of dialdehydes **26** as a colorless oil. IR: 1725 cm^{-1}. ^1H NMR (500 MHz): δ 1.27–1.42 (m, 2), 1.42–2.22 (m, 36), 1.55 (s, 3), 1.57 (s, 3), 1.60 (s, 6), 1.68 (s, 6), 2.43 (m, 1), 2.53 (m, 1), 3.44 (m, 4), 4.46 (s, 2), 4.48 (s, 2), 5.05 (m, 4), 7.24–7.36 (m, 10), 9.51 (d, 1, J = 3.7), 9.62 (d, 1, J = 3.8), 9.64 (s, 1), 9.66 (s, 1). ^{13}C NMR (500 MHz): δ 15.95, 15.97, 17.62, 22.39, 23.30, 23.94, 24.08, 25.12, 25.64, 26.05, 26.51, 26.55, 27.08, 27.47, 29.24, 29.30, 31.15, 31.69, 35.93, 36.56, 39.56, 39.58, 49.67, 50.50, 51.40, 52.21, 59.04, 59.12, 69.45, 69.54, 72.82, 72.87, 123.29, 123.45, 124.16, 127.52, 127.57, 127.58, 128.32, 131.34, 135.95, 136.01, 138.34, 203.80, 204.13, 205.76, 206.49. Anal. Calcd for $C_{29}H_{42}O_3$: C, 79.41; H, 9.65. Found: C, 79.52; H, 9.64.

[4aα,7aα(*E*)]-(±)-7a-(4,8-Dimethyl-3,7-nonadienyl)-4a,6,7,7a-tetrahydro-4-[3-(phenylmethoxy)propyl]-5*H*-2-pyrindine (27). Into a dry 50-mL flask under N_2 was placed 8 mL of CH_2Cl_2. The flask was cooled to −78 °C and 0.12 mL (1.4 mmol) of oxalyl chloride was added, followed by 0.23 mL (3.2 mmol) of DMSO in 1 mL of CH_2Cl_2. After 5 min at −78 °C, 0.20 g (0.45 mmol) of diols **18a,b** in 1.2 mL of CH_2Cl_2 was added. After 15 min, 0.94 mL (6.8 mmol) of Et_3N was added. After 5 min, the dry ice/acetone bath was replaced with an ice/H_2O bath. After 1 h at 0 °C, a slow stream of NH_3 was blown over the reaction mixture for 2 min. The ice bath was removed and the excess NH_3 was allowed to evaporate as the mixture warmed to room temperature (30 min). The solvent was removed to obtain a solid residue that was dried under vacuum (1 h). The residue was suspended in ether and chromatographed on 5 g of silica gel with ether to obtain 130 mg of a colorless oil. This crude product was rechromatographed on 5 g of silica gel with 1:2 ethyl acetate/hexanes to afford 85 mg (44%) of reasonably pure aza diene **27**. Further chromatography on 6 g of silica gel with 1:3.5 ethyl acetate/hexanes afforded 23.0 mg (12%) of analytically pure **27**. Significant decomposition of the aza diene occurred during the multiple chromatographies used in its purification. IR: 1670, 1646 cm^{-1}. ^1H NMR (500 MHz): δ 1.15–2.25 (m, 19), 1.56 (s, 3), 1.59 (s, 3), 1.67 (s, 3), 3.50 (dt, 2, J = 1.8, 6.4), 4.51 (s, 2), 5.04 (br dt, 1, J = 1.7), 5.08 (tt, 1, J = 1.4, 6.9), 6.47 (s, 1), 7.26 (s, 1), 7.25–7.36 (m, 5). ^{13}C NMR (125 MHz): δ 15.93 (CH_3), 17.65 (CH_3), 22.62 (CH_2), 23.32 (CH_2), 25.66 (CH_3), 26.62 (CH_2), 27.67 (CH_2), 30.28 (CH_2), 34.86 (CH_2), 38.92 (CH_2), 39.30 (CH_2), 39.61 (CH_2), 43.49 (CH), 46.24 (C), 69.85 (CH_2), 72.98 (CH_2), 123.98 (CH), 124.24 (CH), 127.53 (CH), 127.58 (CH), 127.63 (CH), 128.35 (CH), 131.33 (C), 132.03 (C), 135.38 (C), 138.45 (C), 165.34 (CH). LRMS (EI), m/z (relative intensity): 419 (M^+, 3), 328 (10), 284 (9), 91 (100), 69 (76). HRMS (EI): exact mass calcd for $C_{29}H_{41}NO$ 419.3190, found 419.3189.

(3α,3aβ,6α,6aα,9a*R,10*S**)-(±)-2,3,3a,6,6a,7,8,9-Octahydro-10-methyl-10-(4-methyl-3-pentenyl)-6-[3-(phenylmethoxy)propyl]-3,6-methano-1*H*-dicyclopenta[*b*,*c*]pyridine (28).** Into a dry 50-mL flask under N_2 was placed 8 mL of CH_2Cl_2. The flask was cooled to −78 °C and 0.12 mL (1.4 mmol) of oxalyl chloride was added, followed by 0.23 mL (3.2 mmol) of DMSO in 1 mL of CH_2Cl_2. After 5 min at −78 °C, 0.20 g (0.45 mmol) of diols **18a,b** in 1.2 mL of CH_2Cl_2 was added. The flask and syringe were rinsed with 1 mL of CH_2Cl_2. After 15 min, 0.94 mL (6.8 mmol) of Et_3N was added. After 5 min, the dry ice/acetone bath was replaced with an ice/H_2O bath. After 1 h at 0 °C, NH_3 was blown over the reaction mixture for 2 min. The ice bath was removed and the excess NH_3 was allowed to evaporate as the mixture warmed to room temperature (30 min). The solvent was removed to obtain a solid residue that was dried under vacuum (3 h). The vacuum was replaced with N_2 and 0.35 g of NH_4OAc, followed by 9 mL of acetic acid was added. The suspension was stirred vigorously for 8 min and a nearly homogeneous yellow mixture was formed. The mixture was added to 25 mL of H_2O and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with 50 mL of 3 M aqueous KOH. The aqueous layer was back-washed with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (K_2CO_3) and the solvent was removed first with a rotary evaporator and then with static high vacuum to obtain a brown oil. Chromatography on 10 g of silica gel with 1:4 ethyl acetate/hexanes afforded 171 mg (90%) of imine **28** as a colorless oil that turned yellow on standing. IR: 1629 cm^{-1}. ^1H NMR (500 MHz): δ 0.84 (s, 3), 0.92 (m, 1), 1.04 (m, 1), 1.26 (m, 1), 1.38 (m, 1), 1.47 (m, 1), 1.50–1.93 (m, 15), 1.56 (s, 3), 1.65 (s, 3), 3.49 (t, 2, J = 6.3), 4.11 (d, 1, J = 4.7), 4.53 (s, 2), 4.98 (tt, 1, J = 1.3, 7.0), 7.25–7.37 (m, 5), 8.06 (s, 1). ^{13}C NMR (125 MHz): δ 17.10 (CH_3), 17.61 (CH_3), 22.10 (CH_2), 23.17 (CH_2), 25.58 (CH_2), 25.62 (CH_3), 26.38 (CH_2), 27.31 (CH_2), 32.63 (CH_2), 37.00 (CH_2), 38.58 (CH_2), 39.12 (CH_2), 43.09 (CH), 43.85 (C), 48.24 (C), 53.59 (CH), 54.28 (C), 69.17 (CH), 71.41 (CH_2), 72.94 (CH_2), 124.73 (CH), 127.50 (CH), 127.55 (CH), 128.33 (CH), 131.11 (C), 138.51 (C), 178.56 (C). Anal. Calcd for $C_{29}H_{41}NO$: C, 83.00; H, 9.85; N, 3.34. Found: C, 82.84; H, 9.86; N, 3.29.

(±)-23-(Phenylmethoxy)-12,16-cyclo-1,12-secodaphnane (29). To a solution of 0.059 mL (0.68 mmol) of oxalyl chloride in 5 mL of CH_2Cl_2, cooled to −78 °C, was added a solution of 0.12 mL (1.70 mmol) of DMSO in 0.5 mL of CH_2Cl_2. After 5 min a solution of 75 mg (0.17 mmol) of diols **18a,b** in 0.5 mL of CH_2Cl_2 was added. The flask and syringe were rinsed with 0.5 mL of CH_2Cl_2, which was added to the reaction mixture. After 30 min at −78 °C, 0.47 mL (3.39 mmol) of triethylamine was added and the dry ice/acetone bath was replaced by an ice/water bath. After 1 h at 0 °C, methylamine was blown over the reaction mixture for 1 min. The ice bath was removed and the excess methylamine allowed to evaporate over 1 h. The solvent was removed to provide a solid residue that was dried at high vacuum for 2 h. The residue was taken up in 5 mL of acetic acid and 150 mg of NH_4OAc was added. The resulting solution was heated at 85 °C for 10 h, diluted with 10 mL of H_2O, and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with 3 N NaOH (2 × 10 mL). The combined base washes were back-extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried and then concentrated to obtain a brown oil. Chromatography on silica gel with 3.7:0.05 ethyl acetate/hexanes/triethylamine afforded 52 mg (75%) of amine **29** as a pale yellow oil. Repetition of the foregoing procedure on a scale of 89 mg (0.20 mmol) of diols **18a,b**, using 0.180 mL (1.61 mmol) of benzylamine instead of methylamine, provided 55 mg (66%) of amine **29**. ^1H NMR (500 MHz):

δ 0.76 (s, 3), 0.87 (d, 3, J = 6.6), 0.88 (d, 3, J = 6.6), 1.12–1.72 (m, 22), 1.88 (t, 1, J = 5.2), 2.51 (d, 1, J = 4.5), 2.99 (s, 1), 3.84 (t, 2, J = 6.7), 4.49 (s, 2), 7.26–7.36 (m, 5). ^{13}C NMR (125 MHz): δ 20.81 (CH_2), 20.99 (CH_3), 21.09 (CH_3), 21.51 (CH_3), 22.92 (CH_2), 25.31 (CH_2), 26.74 (CH_2), 28.80 (CH), 29.32 (CH_2), 29.78 (CH_2), 36.42 (CH_2), 36.78 (C), 39.20 (CH_2), 39.80 (CH_2), 42.87 (CH), 48.69 (CH), 50.45 (C), 53.36 (CH), 60.20 (CH), 71.63 (CH_2), 72.75 (CH_2), 127.42 (CH), 127.52 (CH), 128.30 (CH), 138.75 (C). Anal. Calcd for $C_{29}H_{43}NO$: C, 82.61; H, 10.28; N, 3.32. Found: C, 82.29; H, 10.11; N, 3.17.

(±)-23-Hydroxy-12,16-cyclo-1,12-secodaphnane (35). To 2.07 g (4.94 mmol) of amine **23** in a 500-mL flask was added 120 mL of absolute ethanol. The mixture was stirred until amine **23** dissolved completely and then 2 g of 10% Pd/C was added. The reaction vessel was attached to a hydrogenation apparatus and the atmosphere was replaced with H_2 by applying aspirator vacuum and then back-filling with H_2 (repeat 3 times). The mixture was stirred vigorously under H_2 (slightly over 1 atm) for 47 h or until amine **23** was consumed as indicated by TLC. (In general a 24-h period should suffice.) The mixture was carefully opened to the atmosphere, 2.1 mL (25 mmol) of 12 M HCl was added with a syringe, and the mixture was resubjected to H_2 as above. After 60 h (the disappearance of the intermediate amino benzyl ether **29** can be followed by TLC), the mixture was carefully exposed to the atmosphere and the excess H_2 was expelled with an N_2 flow. The catalyst was removed by filtration through ca. 1 cm of Celite in a 150-mL course glass frit. The filter pack was washed repeatedly with ethanol (350 mL total) and the filtrate was concentrated with a rotary evaporator. The residue was dried by evaporating benzene from the sample with a rotary evaporator (4 × 50 mL), and the resulting white solid was placed under high vacuum (23 h). In this manner, 1.75 g (96%) of the crude amine salt of amino alcohol **35** was obtained. This material was used directly in the subsequent Jones oxidation reaction. The free amine was prepared for characterization purposes by partitioning the amine salt between 1 M aqueous NaOH and CH_2Cl_2. The layers were separated and the organic layer was dried (K_2CO_3). The solvent was removed to give a grey solid that was recrystallized from CH_2Cl_2 to afford amino alcohol **35** as white crystals, mp 195–196 °C. ^{1}H NMR (500 MHz): δ 0.77 (s, 3), 0.88 (d, 3, J = 6.6), 0.89 (d, 3, J = 6.6), 1.13–1.77 (m, 23), 1.90 (t, 1, J = 5.2), 2.53 (d, 1, J = 4.5), 3.00 (s, 1), 3.58 (t, 2, J = 6.6). Anal. Calcd for $C_{22}H_{37}NO$: C, 79.70; H, 11.25; N, 4.22. Found: C, 79.92; H, 11.35; N, 4.20.

(±)-Methyl Homosecodaphniphyllate (4). To 1.75 g (4.74 mmol) of crude amino alcohol **35** in a 1-L flask was added 400 mL of acetone and 8.2 mL of 9 M H_2SO_4. After 20 min all the solid had dissolved to afford a cloudy solution. Celite (15 g) was added and the mixture was cooled in an ice/H_2O bath as 11 mL of Jones reagent was added dropwise over 6 min. The brown mixture was stirred at 0 °C for 30 min and 11 mL of ispropyl alcohol was added. After being warmed to room temperature, the gelatinous mixture was filtered through 1 cm of Celite on a 350-mL coarse glass frit. The cloudy brown filtrate was concentrated with a rotary evaporator. Excess isopropyl alcohol and water were removed by thrice adding 50 mL of acetone and concentrating with a rotary evaporator. The resulting green-black oil was placed under high vacuum for 20 min and then dissolved in 300 mL of methanol. After being stirred under N_2 for 22 h, this mixture was poured slowly into a separatory funnel containing 500 mL of saturated aqueous $NaHCO_3$, 100 mL of H_2O, and 300 mL of CH_2Cl_2. The layers were agitated and separated; the aqueous layer was washed with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried (K_2CO_3) and the solvent was removed to obtain a tan oil. Chromatography on silica gel with 1:3 ethyl acetate/hexanes afforded 1.47 g (86%) of (±)-methyl homosecodaphniphyllate (**4**), mp 63–65 °C. IR: 3100–2700, 1742 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.79 (s, 3), 0.90 (d, 6, J = 6.6), 1.18 (br dt, 1, J = 13, 3), 1.33–1.85 (m, 19 H), 1.90 (t, 1, J = 5.2), 2.24 (ddd, 1, J = 5.3, 12.5, 15.5), 2.39 (ddd, 1, J = 4.5, 13.0, 15.5), 2.53 (d, 1, J = 4.5), 2.96 (s, 1), 3.67 (s, 3). ^{13}C NMR (125 MHz):[35] δ 20.69 (CH_2), 20.93 (CH_3), 21.02 (CH_3), 21.40 (CH_3), 22.84 (CH_2), 26.74 (CH_2), 27.90 (CH_2), 28.75 (CH), 29.56 (CH_2), 30.17 (CH_2), 36.27 (CH_2 + C), 36.82 (C), 39.02 (CH_2), 39.71 (CH_2), 42.90 (CH), 47.74 (CH), 48.48 (CH), 50.54 (C), 51.51 (CH_3), 53.20 (CH), 60.06 (CH), 174.90 (C). Anal. Calcd for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37; N, 3.90. Found: C, 76.68; H, 10.50; N, 4.09.

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Registry No. (±)-**4**, 118099-25-5; **5**, 22339-13-5; **6** acid, 6740-39-2; **7**, 25662-28-6; **9**, 117959-71-4; (±)-**11**, 138336-57-9; (±)-**13**, 118015-92-2; (±)-**14**, 117959-72-5; **15**, 138383-32-1; (±)-**16**, 138336-58-0; (±)-**17a**, 118015-93-3; (±)-**17b**, 117959-73-6; (±)-**18a**, 118015-94-4; (±)-**18b**, 117959-74-7; (±)-**19**, 138383-33-2; **20**, 138383-34-3; (±)-**22**, 138383-35-4; (±)-**23**, 117959-76-9; **24**, 138336-59-1; (±)-**26** (isomer 1), 118015-95-5; (±)-**26** (Isomer 2), 117959-75-8; (±)-**27**, 117959-77-0; (±)-**28**, 117959-78-1; (±)-**29**, 138336-60-4; (±)-**35**, 138336-61-5; (±)-s,1, 138336-54-6; (±)-s,2 (isomer 1), 138336-55-7; (±)-s,2 (isomer 2), 138383-31-0; (±)-s,3, 138336-56-8; (±)-s,4a, 138336-63-7; (±)–s,5a, 138383-36-5; (±)-s,5b, 138336-62-6; (±)-s,7, 138336-64-8; pyrrolidine, 123-75-1.

Supplementary Material Available: Background studies for the development of the tandem Michael addition–alkylation process, model studies with amide ester **11**, experimental procedures for the preparation of compounds **5**, **11**, **19**, **20**, **22**, and **24**, ^{1}H and ^{13}C NMR spectra of the postulated intermediate **30**, additional spectral data for (±)-methyl homosecodaphniphyllate (C_6D_6 solution), 500-MHz ^{1}H NMR spectra of natural and synthetic methyl homosecodaphniphyllate, and the ^{1}H NMR spectrum of aza diene **27** (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

(35) The ^{13}C NMR spectrum in C_6D_6 solution is recorded in the supplementary material.