Daphniphyllum Alkaloids. 12. A Proposed Biosynthesis of the Pentacyclic Skeleton. *proto*-Daphniphylline[1]

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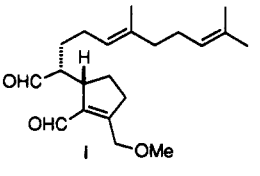
A biosynthetic proposal for the pentacyclic skeleton of the *Daphniphyllum* alkaloids is put forth (Scheme I) and various ramifications are examined experimentally. *proto*-Daphniphylline (11), the putative product of this hypothetical biogenesis, has been prepared by a convergent synthesis that starts with amide 14, α,β-unsaturated ester 15, and homogeranyl iodide (Scheme II) and employs a highly efficient tetracyclization process previously used for the synthesis of (±)-methyl homosecodaphniphyllate (30) (Scheme III). The structure of *proto*-daphniphylline was confirmed by converting it into 30. The mechanism of the first stage of the tetracyclization process was investigated with the bis-homoneryl analogues 36/37. Treatment of these aldehydes successively with ammonia and acetic acid provided tetracyclic imine 38, suggesting that the cyclization reaction is a concerted Diels–Alder reaction rather than a stepwise process. Dialdehydes 27/28 were converted into 1,2-dihydro-*proto*-daphniphylline (29) by a version of the tetracyclization process wherein methylamine (or glycine) is substituted for ammonia. *proto*-Daphniphylline has also been prepared in a one-pot, two-stage process from the acyclic dialdehydes 51 and 55. Several versions of this pentacyclization process have been worked out. In the simplest, 51 or 55 is treated successively with ammonia and hot acetic acid to afford 11 in 15 ± 2% yield. A slightly more elaborate protocol, a three-stage process that utilizes NaOH in benzene, ammonia in DMSO, and hot acetic acid, provided 11 in 49.4% overall yield. However, the most efficient pentacyclization process discovered employs successive reactions with methylamine (or glycine) and hot acetic acid. Under these conditions, 17,18-dihydro-*proto*-daphniphylline (29) is produced in 65% yield. The latter process is one of the most efficient reaction cascades ever discovered; it results in the formation of five rings, four carbon–carbon bonds, two carbon–nitrogen bonds, and concludes with the selective saturation of one of the three double bonds in *proto*-daphniphylline!

In the preceding paper in this series,[1] we described a simple protocol wherein the monocyclic dialdehyde 1 is converted into the pentacyclic unsaturated amine 2 by successive treatment with ammonia and acetic acid. Because of the exceptional ease with which the "tetracyclization reaction" occurs, it was speculated that the process may actually be biomimetic.[3] A possible biosynthesis is put forth in Scheme I. The rough outlines of this proposal are as follows: Step 1 is an oxidative transformation of squalene into a dialdehyde, 4.[4] In step 2 it is proposed that some primary amine, perhaps pyridoxamine[5] or an amino acid, condenses with one of the carbonyl groups of 4, giving imine 5. Step 3 is the prototopic rearrangement of a 1-aza diene to a 2-aza diene, a process that is well-precedented for the imines formed from α,β-unsaturated carbonyl compounds and benzylamine.[6] Although potassium *tert*-butoxide was used for the prototopic rearrangement of benzylimines, one can imagine that an imine derived from pyridoxamine or an amino acid would rearrange under much milder conditions. Because the 2-aza diene that would result from the foregoing prototopic rearrangement is an enimine, its double bond is not especially nucleophilic. However, if some nucleophilic species adds to the imine double bond, as in step 4, the product 7 is a nucleophilic enamine. The subsequent cyclization to give 8 has an exact in vitro precedent in the work of Schreiber, Meyers, and Wiberg.[7] In steps 6–9 the resulting bicyclic dihydropyran derivative 8 is transformed into a dihydropyridine derivative (9) similar to the intermediate in the in vitro conversion of 1 into 2. Other possible scenarios can be envisioned for the metamorphosis of 8 into 9. According to our biosynthetic supposition, 9 would then be converted into 10 by a catalyzed Diels–Alder process and the final ring would result from an ene-like cyclization, giving 11, the putative primordial *Daphniphyllum* alkaloid. Because of the likelihood that 11 is the first pentacyclic substance to occur in the biosynthesis of the *Daphniphyllum* alkaloids, we have named it *proto*-daphniphylline.[8,9]



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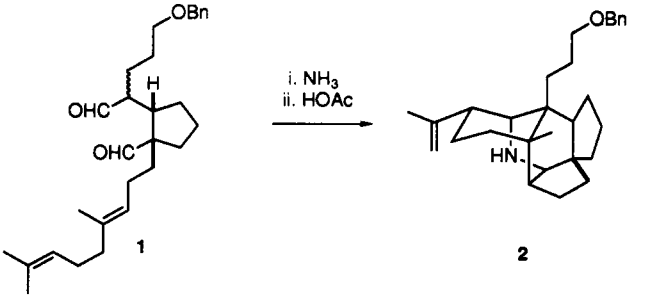

1 2

(1) For part 11, see: (a) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.*, preceding paper in this issue.

(2) (a) Present address: Marion Merrel Dow Research Institute; 16, rue d Ankara; B.P. 447 R/9; 67009 Strasbourg, France. (b) Present address: Department of Chemistry, Yale University, New Haven, CT 06511.

(3) Ruggeri, R. B.; Heathcock, C. H. *Pure Appl. Chem.* **1989**, *61*, 289.

(4) Terpenoids have been described in which two methyl groups are in the aldehyde oxidation state. Petrodial (*i*) is one example. Isoe, S.; Ge, Y.; Yamamoto, K.; Katsumura, S. *Tetrahedron Lett.* **1988**, *29*, 4591.

(5) Pyridoxamine is a well-known nitrogen donor in alkaloid biosynthesis: (a) Dalton, D. R. *The Alkaloids, A Biogenetic Approach*; Marcel Dekker: New York, 1976. (b) Akhtar, M.; Emery, V. C.; Robinson, J. A. In *The Chemistry of Enzyme Action*; Page, M. I., Ed.; Elsevier: Amsterdam, 1984; p 303.

(6) Malhotra, S. K.; Moakley, D. F.; Johnson, F. *J. Am. Chem. Soc.* **1967**, *89*, 2794.

(7) Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 8274.

(8) For a preliminary account of the synthesis of *proto*-daphniphylline, see: Piettre, S.; Heathcock, C. H. *Science (Washington D.C.)* **1990**, *248*, 1532.

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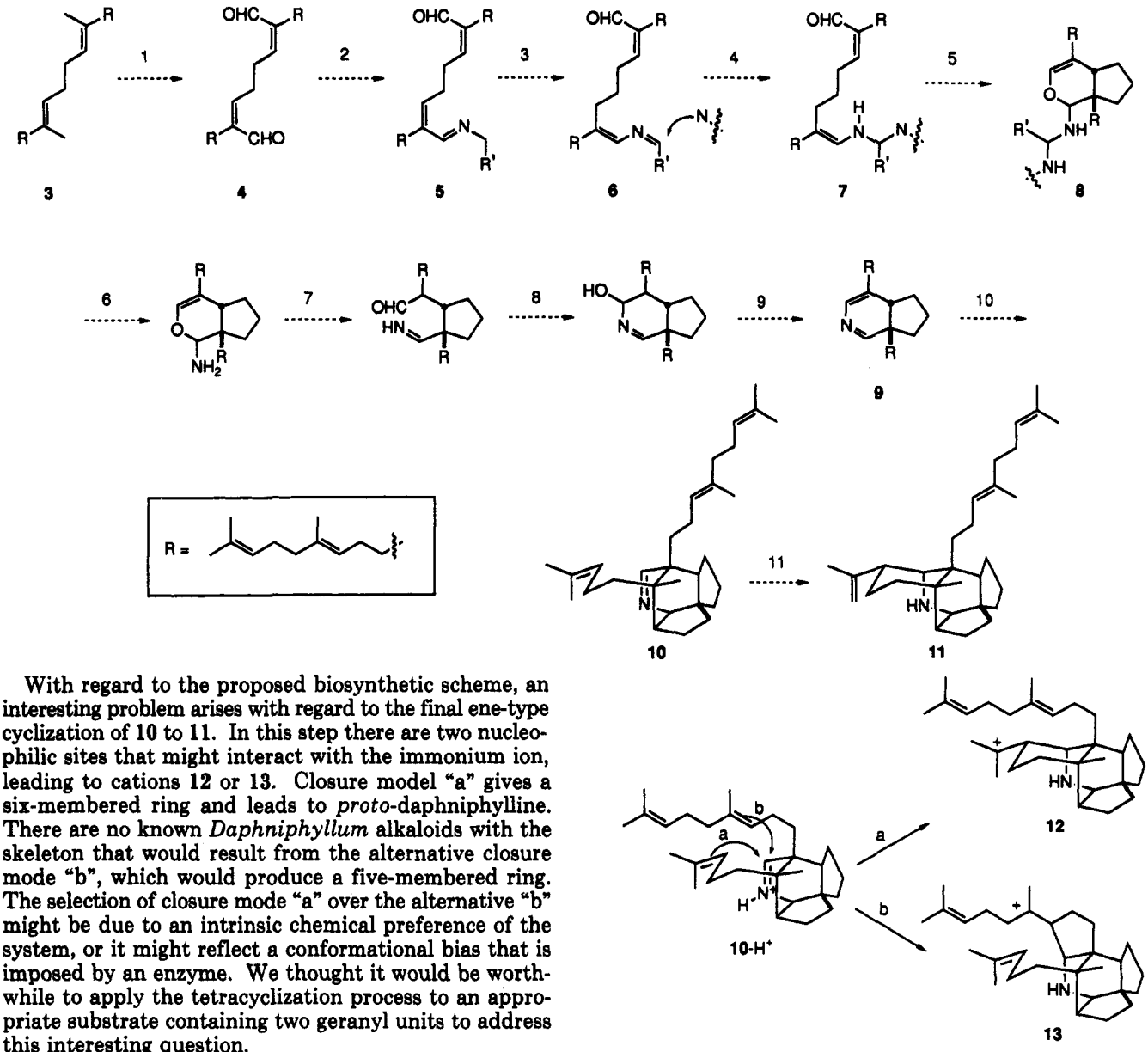
Scheme I

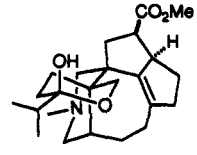


With regard to the proposed biosynthetic scheme, an interesting problem arises with regard to the final ene-type cyclization of **10** to **11**. In this step there are two nucleophilic sites that might interact with the immonium ion, leading to cations **12** or **13**. Closure model "a" gives a six-membered ring and leads to *proto*-daphniphylline. There are no known *Daphniphyllum* alkaloids with the skeleton that would result from the alternative closure mode "b", which would produce a five-membered ring. The selection of closure mode "a" over the alternative "b" might be due to an intrinsic chemical preference of the system, or it might reflect a conformational bias that is imposed by an enzyme. We thought it would be worthwhile to apply the tetracyclization process to an appropriate substrate containing two geranyl units to address this interesting question.

Our first synthesis of *proto*-daphniphylline began with the synthesis of amide **14** by alkylation of the lithium enolate of *N*-acetylpyrrolidine with homogeranyl iodide (**16**)[10] at −78 °C; compound **14** was obtained in 87% yield. Amide **14** was deprotonated with LDA and the resulting enolate treated successively with enoate **15** and halide **16** (Scheme II). There was obtained in a total yield of 94% a mixture of the four diastereomeric ester–amides **17**–**20** in an isomer ratio of 85:10:3:2. The major isomer **17** was isolated in 80% yield after chromatography on silica gel. The results of this convergent assembly of the entire *proto*-daphniphyline skeleton were quite analogous to those obtained in the previously reported synthesis of methyl homosecodaphniphyllate, except that the minor isomer corresponding to **20** was not observed in that reaction.[1]

As shown in Scheme III, amide–ester **17** was reduced with DIBAL in toluene at −78 °C to give hydroxy amide **21** in 86% yield, accompanied by 8% of amino alcohol **22**. The amide function was hydrolyzed with KOH in aqueous ethanol. Acidification of the alkaline hydrolysis mixture provided lactones **23** and **24** as a 1:1 mixture in a total isolated yield of 93%. The lactones were separately reduced to diols **25** and **26**, which were subjected to Swern oxidation conditions to obtain dialdehydes **27** and **28**. Because compounds **27** and **28** are quite fragile and decompose readily, they were always cyclized immediately after their preparation. The two dialdehydes were each subjected to the tetracyclization protocol[1] to obtain *proto*-daphniphylline in 78% yield. Careful examination of the reaction product revealed no trace of a product that would have resulted from closure mode "b".

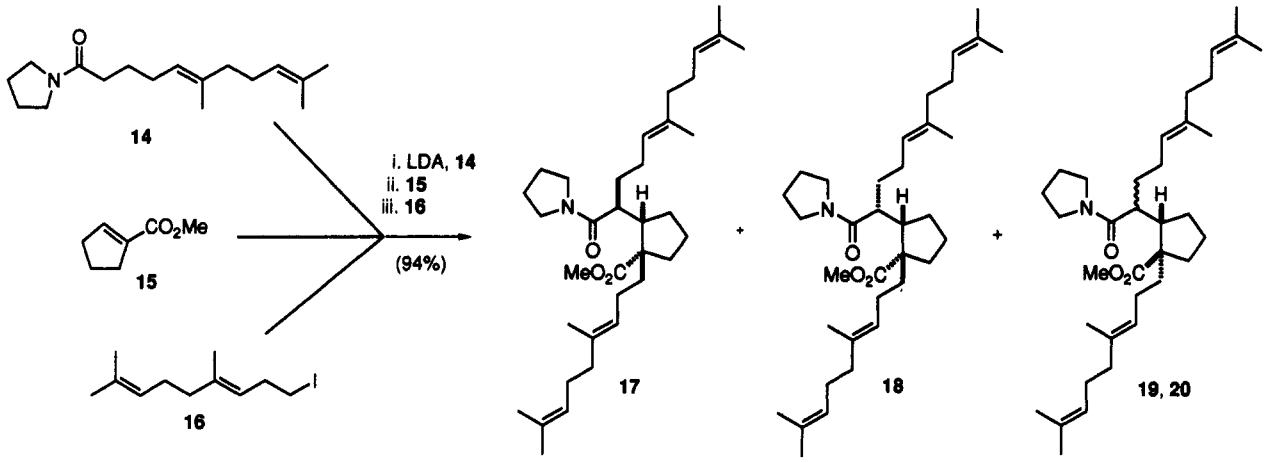
(9) There is a subset of *Daphniphyllum* alkaloids in which the final ene-like cyclization has not occurred. One example of this group is daphnigracine (**ii**): Yamamura, S.; Lamberton, J. A.; Irikawa, H.; Okumura, Y.; Hirata, Y. *Chem. Lett.* **1975**, 923. Yamamura, S.; Lamberton, J. A.; Irikawa, H.; Okumura, Y.; Toda, M.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1836. Thus, the proposed biosynthetic intermediate imine **10** is *proto*-daphnigracine.



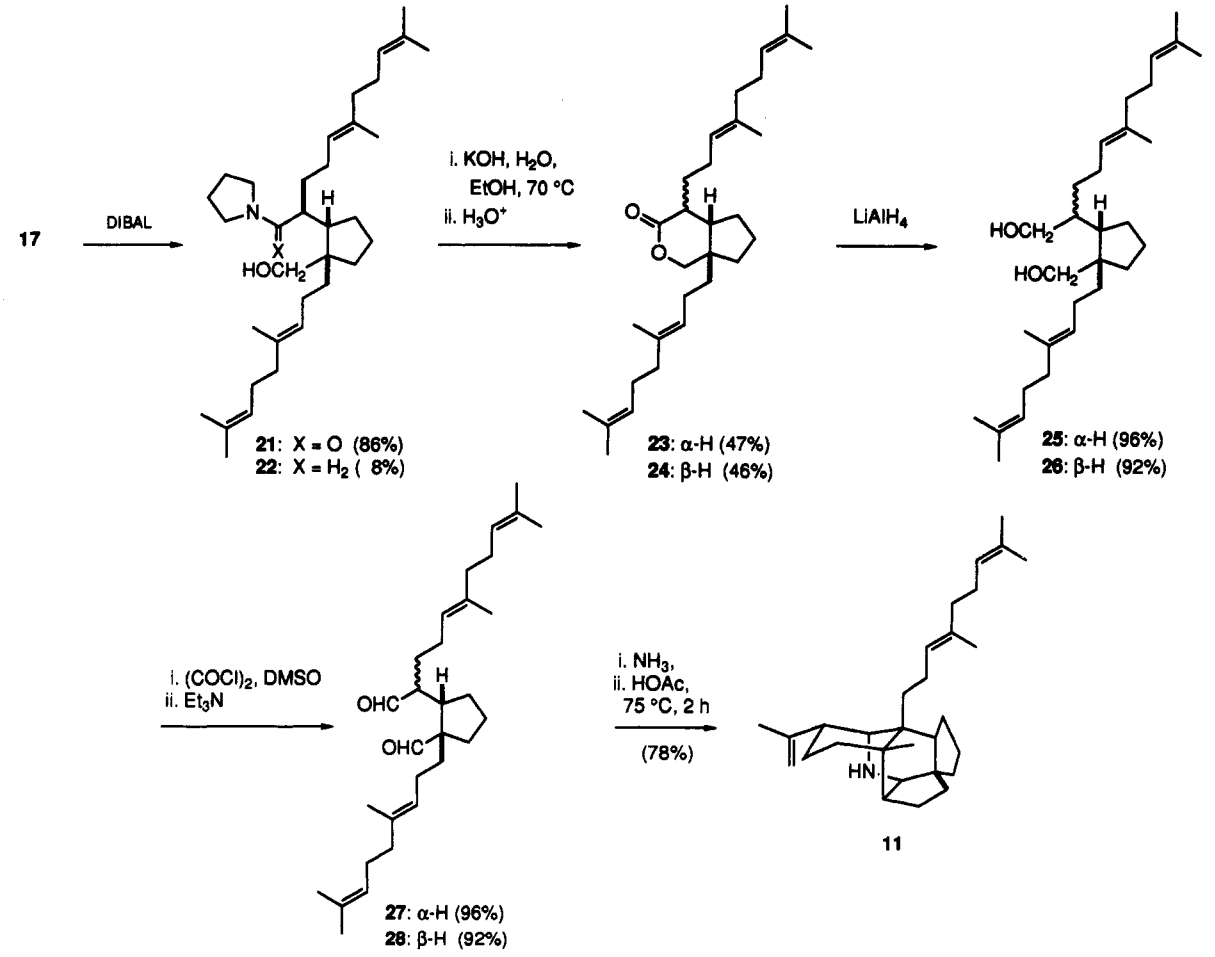
ii

(10) (a) Leopold, E. J. *Org. Synth.* **1985**, *64*, 164. (b) Kocienski, P.; Wadman, S. *J. Org. Chem.* **1989**, *54*, 1215.

Scheme II



Scheme III

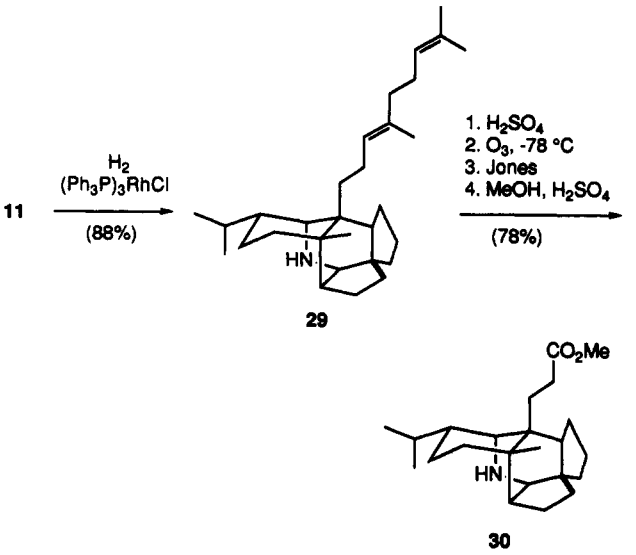


The structure of *proto*-daphniphylline was confirmed by converting it into (±)-methyl homosecodaphniphyllate (**30**). Careful hydrogenation of **11** with Wilkinson's catalyst[11] provided **29**. Ozonolysis of the sulfuric acid salt of this unsaturated amine, Jones oxidation of the resulting aldehyde,[12] and Fischer esterification gave **30** in 78% overall yield. Compound **30** was identified by comparison of its TLC mobility and NMR spectra with a sample prepared by the previously reported method.[1]

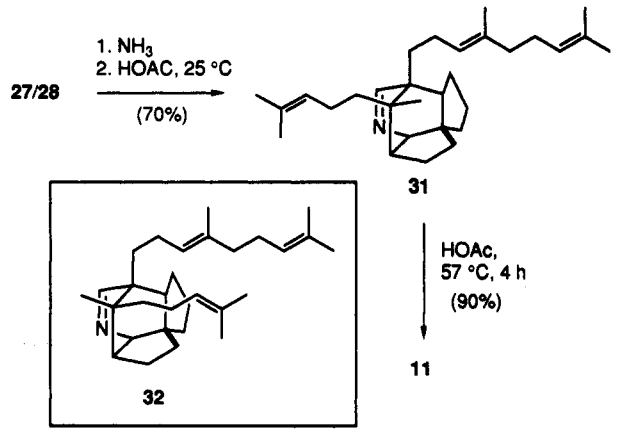
proto-Daphnigracine (**31**) was produced in 70% yield by passing gaseous ammonia through a CH_2Cl_2 solution of aldehydes **27** or **28**, removal of the solvent, and dissolution in acetic acid at room temperature. Treatment of **31** with acetic acid at 57 °C for 4 h gave *proto*-daphniphylline (**11**) in 90% yield. Careful examination of the crude product in the formation of **31** permitted the isolation of 4% of the isomeric tetracyclic imine **32**. The presence of this by-product was later traced to a small amount of contami-

(11) Young, J. F.; Osborn, J. A.; Jardine, F. H.; Wilkinson, G. *J. Chem. Soc., Chem. Commun.* **1965**, 131.

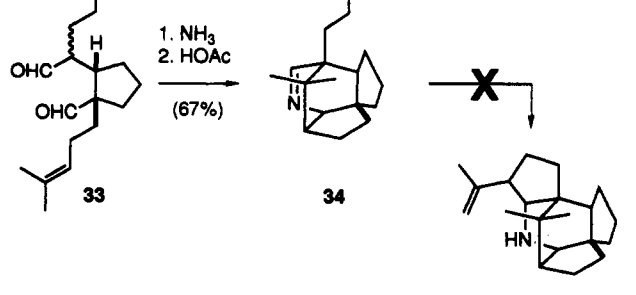
(12) Bowden K.; Heibron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39. (b) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548.



nating nerol in the geraniol used for the preparation of iodide **16** (vide infra).

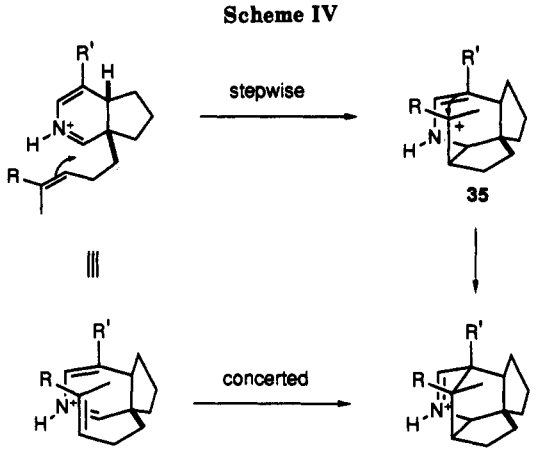


Our failure to observe any of the five-membered ring closure product in cyclization of immonium ion **10**-H^+ shows only that closure mode "a" has a lower activation energy than closure mode "b" by about 3.3 kcal/mol (assuming that we would have found as little as 3% of isomeric product). In order to examine the feasibility of five-membered ring closure more closely, we prepared dialdehyde **33** along the same lines as were used for the preparation of **27/28**.[13] Successive treatment of **33** with ammonia and acetic acid at room temperature gave tetracyclic imine **34**. However, under no conditions were we



(13) Details for this synthesis are given in the supplementary material.

Scheme IV

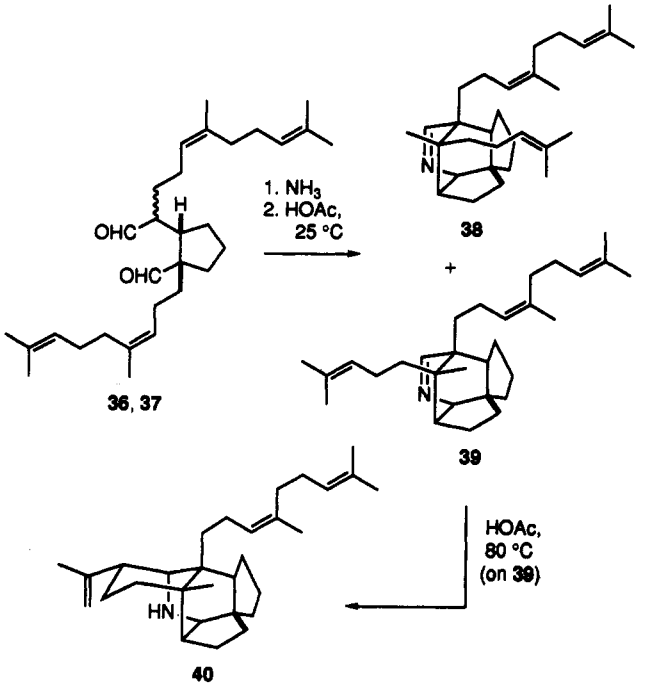


able to induce **34** to undergo a further cyclization. The material was recovered unchanged in 84% yield after being refluxed in acetic acid for 47 h.

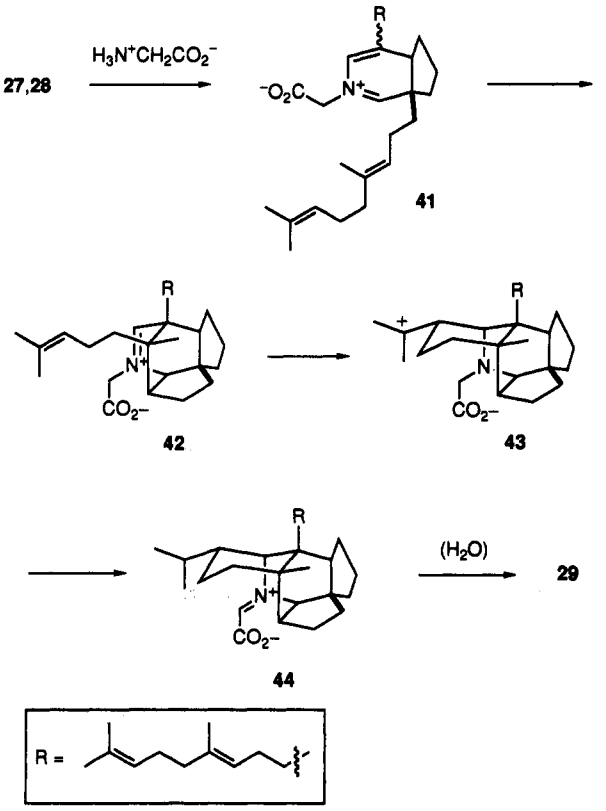
The cyclizations of dialdehydes **1**, **27/28**, and **33** proceed through intermediate dihydropyridines.[1] As shown in Scheme IV, the initial cyclization might be two-step, passing through an intermediate tricyclic enamino cation **35**, or concerted. Information on this point can be gained by investigating the stereochemistry of the reaction. To this end, the bis-neryl analogues **36** and **37** were prepared by the same method as has been previously described, starting with nerol instead of geraniol.[13] Because the nerol used was only 97% *Z*, the dialdehydes should be 94% *Z,Z*, 3% *Z,E*, and 3% *E,Z*. Treatment of **36** or **37** successively with ammonia and acetic acid at room temperature gave tetracyclic imine **38** in 79% yield, accompanied by 3.5% of isomer **39**. Isomer **39** presumably results from cyclization of the *E,Z* contaminant. Imine **38** was unchanged after being heated with ammonium acetate in acetic acid at 80 °C for 15 h, but imine **39** was smoothly converted into the pentacyclic product **40** by this treatment.[14] Thus, the cyclization process appears to be concerted and may be viewed as an inverse-electron-demand Diels–Alder reaction of the trisubstituted double bond with the protonated 2-aza diene.

Tetracyclization of dialdehydes **27/28** was readily achieved by the methylamine cyclization previously reported in connection with the total synthesis of methyl homosecodaphniphyllate.[1] Thus, treatment of dialdehydes **27** and **28** successively with methylamine at room temperature and acetic acid at 80 °C for 11 h provided dihydro-*proto*-daphniphylline (**29**) in 66% yield. This remarkable reductive cyclization also occurred when glycine was substituted for methylamine as a nitrogen source, providing **29** in 53% yield. Because the reaction with glycine can proceed through intermediates having no net charge (Scheme V, compounds **41**, **42**, **43**, and **44**), we had anticipated that cyclization might occur under even milder conditions than with ammonia or methylamine. However, subjection of dialdehydes **27** and **28** to several sets of nonacidic conditions (10 equiv of glycine in $CHCl_3$, EtOH, or aqueous EtOH, as well as 0.67 N $H_2NCH_2CO_2Na$ in aqueous EtOH) led only to recovered starting material or decomposition.

(14) Capillary GLC analysis of our synthetic *proto*-daphniphylline (**11**) revealed the presence of 2% of a compound having the same retention time as **40**. Like imine **32**, this isomer probably derives from a small amount (2–4%) of nerol in our starting geraniol.

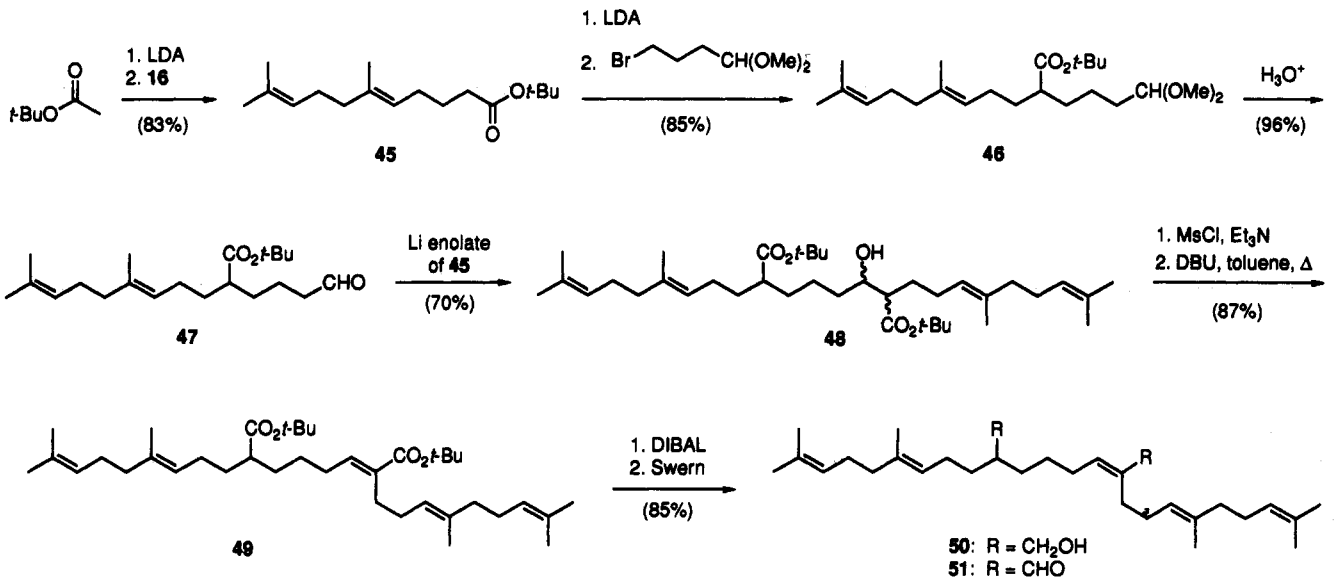


Scheme V

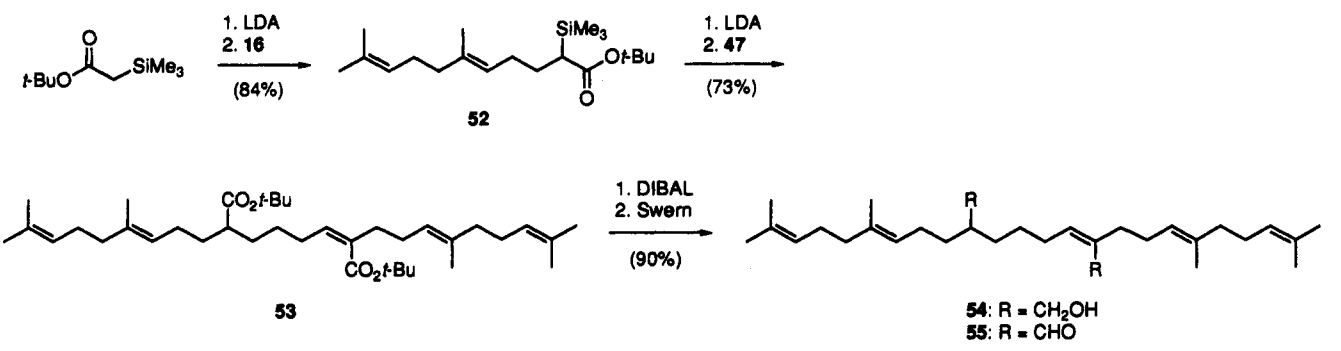


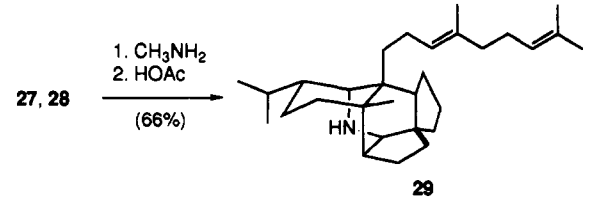
Because of the extraordinary efficiency of the tetracyclization process, we wondered if we could apply the procedure to an acyclic dialdehyde similar to 4 and thereby form all five of *proto*-daphniphylline's rings in one grand, biomimetic operation. To simplify the process somewhat,

Scheme VI



Scheme VII





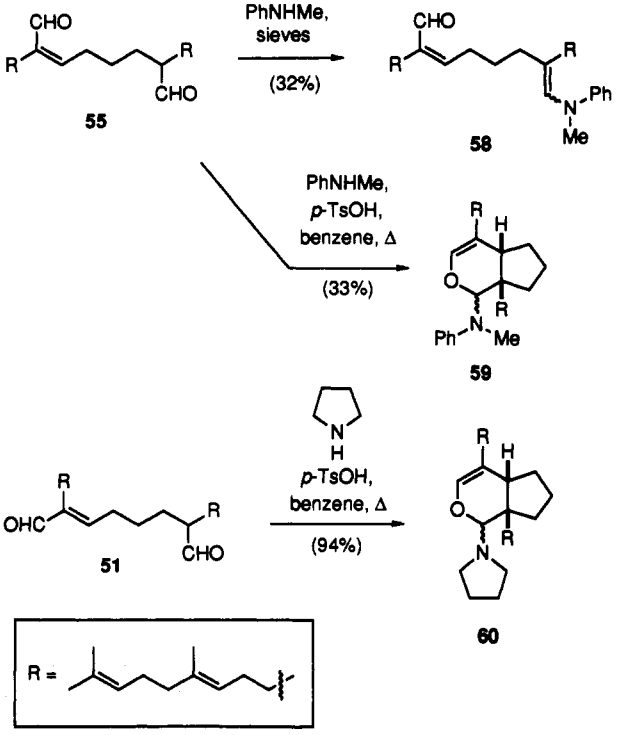
we decided to synthesize a dialdehyde in which one double bond has already been reduced. That is, we elected to intersect with the biosynthesis suggested in Scheme I at step 5. To this end, we prepared the *E* and *Z* isomers of 10,11-dihydrosqualene-27,28-dialdehyde (**51** and **55**) as shown in Schemes VI and VII. Alkylation of the lithium enolate of *tert*-butyl acetate with homogeranyl iodide (**16**) afforded ester **45**, which was alkylated with the dimethyl acetal of 4-bromobutanal[15] to obtain **46**. Hydrolysis of the acetal gave aldehyde **47**, which was condensed with the lithium enolate of **45** to obtain β-hydroxy esters **48** as a mixture of diastereomers. Elimination was accomplished by treatment of the methanesulfonate of **48** with DBU in toluene at 80 °C. Diester **49** was obtained in excellent yield, accompanied by approximately 10% of the *Z* isomer. After chromatographic separation of the stereoisomeric diesters, **49** was converted into the *E* dialdehyde **51** as shown in Scheme VI. To obtain the *Z* isomer in quantity, *tert*-butyl (trimethylsilyl)acetate was alkylated with iodide **16** to obtain the α-trimethylsilyl ester **52**. Treatment of the lithium enolate of **52** with aldehyde **47** afforded mainly the *Z* diester **53** (*Z*:*E* ratio = 7:3). The pure *Z* stereoisomer, obtained by silica gel chromatography of the mixture, was transformed into the *Z* dialdehyde **55** as shown in Scheme VII. Dialdehydes **51** and **55** are readily available by the routes shown; the overall yields are 35–45% from homogeranyl iodide. Both dialdehydes are somewhat labile and were partially destroyed by chromatography on silica gel. In addition, **55** is readily isomerized to **51**. Although we have carried out polycyclization experiments with both isomers, in most of our work we have used the *E* isomer **51**, which is more conveniently available in a pure form.

The pentacyclization process was first investigated using the conditions that had served for the tetracyclization of **27/28** to **11**. Thus, treatment of a CH_2Cl_2 solution of either **51** or **55** with ammonia and triethylamine hydrochloride at room temperature for 16 h resulted in disappearance in starting material, as shown by TLC. At this point the solvent was evaporated under vacuum and the resulting residue taken up in acetic acid and heated at 80 °C for 2 h. Workup gave *proto*-daphniphylline (**11**) in 15 ± 2% yield. A large amount of less polar material was also isolated in the chromatographic purification of **11**. This material was shown by NMR to be a complex mixture of compounds containing homogeranyl units; it is believed to consist of oligomers of the starting dialdehydes resulting from Michael or aldol reactions. Although the yield was low, this first pentacyclization was nevertheless very encouraging, as it represented the formation of six σ bonds and five rings in a single, simple process starting with acylic dialdehydes.

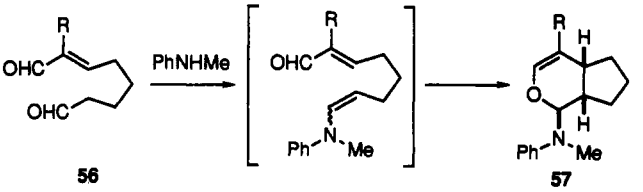
The difference in the yield of **11** obtained in the pentacyclization of **51/55** (15%) and the tetracyclization of **27/28** (78%) obviously reflects poor selectivity in formation of the first carbon–carbon bond. In an attempt to improve the yield of this part of the cyclization, we investigated various conditions that might accomplish the

(15) (a) Vedejs, E.; Arnost, M. J.; Hagen, J. P. *J. Org. Chem.* **1979**, *44*, 3234. (b) Petersen, J. S.; Tteberg-Kaulen, S.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 2948. (c) Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443.

Scheme VIII



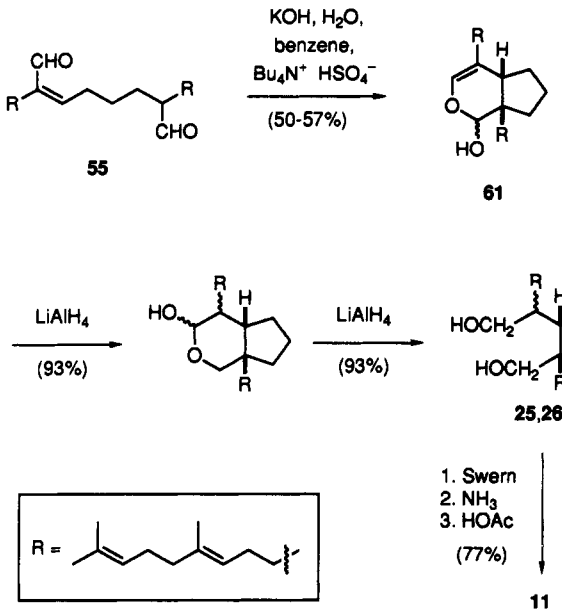
intramolecular Michael cyclization of **51/55**. Substituted oct-2-ene-1,8-dials are known to react with secondary amines to give enamines that undergo an overall [4 + 2] cycloaddition reaction to give aminodihydropyrans:[7]



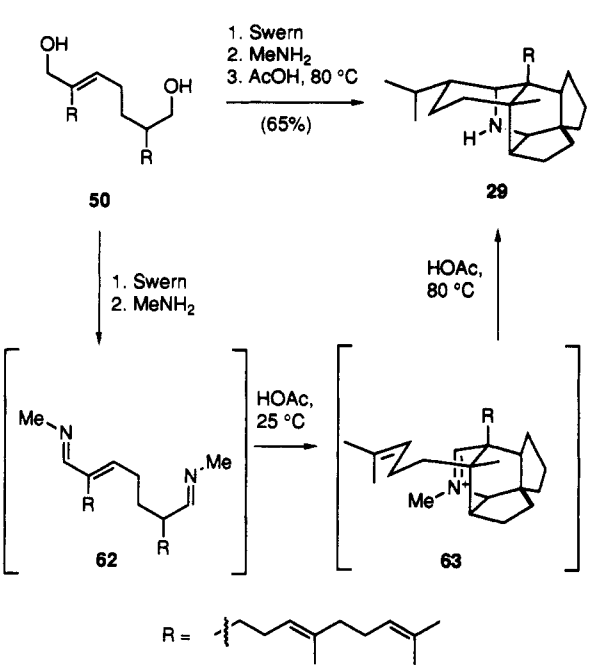
This precedent appears to offer an attractive way to form the first bond in the pentacyclization process, as dialdehyde **56** is but a simple analogue of **51** or **55**; upon treatment with ammonia, aminodihydropyran **59** might enter the pentacyclization manifold leading to **11**. To this end, we investigated the reactions of **51** and **55** with *N*-methylaniline and pyrrolidine. Under the conditions recommended by Schreiber and co-workers, aldehyde **55** was observed to isomerize to its *E* stereoisomer and enamines (*E*)- and (*Z*)-**58** were obtained in low yield (Scheme VIII). However, no aminodihydropyran was obtained. The fact that the enamine is formed but does not cyclize is presumably the result of steric hindrance; in our system the nucleophilic carbon of the enamine is fully substituted. More forcing conditions (*p*-toluenesulfonic acid, refluxing benzene, Dean–Stark trap) afforded aminodihydropyran **59** in an unoptimized yield of 33%. Treatment of dialdehyde **51** with pyrrolidine under similar conditions provided aminodihydropyran **60** in 94% yield. Both **59** and **60** were formed as an approximate 2:1 mixture at the anomeric center. Unfortunately, neither **59** nor **60** turned out to be a viable intermediate for the synthesis of *proto*-daphniphylline. Neither compound gave the tetracyclization reaction when treated successively with ammonia and acetic acid and neither could be hydrolyzed to dialdehydes **27/28**.[16]

(16) More details on the hydrolytic chemistry of these compounds are given in the supplementary material.

Scheme IX



Scheme X



While attempting to optimize the foregoing aminodihydropyran synthesis, one run in ether at room temperature unexpectedly gave a 2:1 mixture of hydroxydihydropyrans **61**. These compounds could be isolated by rapid chromatography on silica gel. Two-stage reduction with $LiAlH_4$ provided a mixture of diols **25** and **26**, identical with the compounds prepared from reduction of lactones **23** and **24**. The cis stereochemistry of the 6-5 ring fusion was confirmed by conversion of the diol mixture into *proto*-daphniphylline (Scheme IX). Optimization of this propitious discovery eventually led to a two-phase protocol wherein a benzene solution of the dialdehyde is stirred for 10 min at room temperature with 50% aqueous KOH in the presence of a catalytic amount of tetra-*n*-butylammonium bisulfate. Under these conditions, compounds **61** were obtained in 50–57% yield.

Treatment of a DMSO solution of **61** with NH_3 and NH_4OAc at 80 °C for 3 h and then with acetic acid at the same temperature for 3 h gave *proto*-daphniphylline in 86% yield. The three steps from **51** or **55** to *proto*-daphniphylline were most effectively carried out as a two-stage process, without purification of intermediates. Thus, the heterogeneous transformation to **61** was carried out as described in the previous paragraph. After removal of the benzene, a DMSO solution of the crude hydroxydihydropyrans was placed in a pressure bottle and saturated with ammonia. The solution was heated at 80 °C for 3 h. After brief cooling, acetic acid was added and the solution was heated at 80 °C for an additional 3 h. In this manner, *proto*-daphniphylline was obtained in 49.4% overall yield. The process can also be carried out in "one pot." Thus, a solution of **51** or **55** in DMSO was treated sequentially with (1) 1 molar equiv of powdered NaOH at 25 °C for 3.5 h, (2) saturated NH_3 at 80 °C for 3 h, and (3) acetic acid at 80 °C for 3 h; *proto*-daphniphylline was produced in 44% yield on a scale of 132 mg. It is important that the foregoing process be carried out under strictly anhydrous conditions, as the presence of water seems to have a distinctly adverse effect on yield. For example, use of 1 molar equiv of tetra-*n*-butylammonium hydroxide (10% w/w in water) for the first step gave **11** in only 17% yield, and powdered 85% KOH gave an overall yield of only 35%.

Based on the reductive cyclization of dialdehydes **27** and **28** to dihydro-*proto*-daphniphylline (**29**) with methylamine, we next investigated the pentacyclization of dialdehyde **51** with methylamine. Because the low yield in the pentacyclization of **51** and **55** with ammonia was presumably due to poor selectivity in the formation of the first carbon–carbon bond, we reasoned that the more nucleophilic *N*-methyl enamine derived from methylamine might improve upon the 15% yield observed with ammonia. Indeed, we were gratified to find that subjection of diol **50** to the sequence (i) Swern oxidation, (ii) treatment of the Swern reaction mixture with methylamine for 2–3 h, and (iii) concentration followed by treatment of the residue thus obtained with acetic acid at 80 °C for 11 h provided dihydro-*proto*-daphniphylline (**29**) in 65% yield. Since the tetracyclization of **27** and **28** with methylamine proceeds in essentially the same yield (66%), it would seem that cyclization to form the first five-membered ring is highly efficient in this case.

Although the reductive pentacyclization of **51** was generally performed as described above, an early experiment involved isolation of two of the intermediates (Scheme X). If the residue obtained following Swern oxidation and methylamine treatment was triturated with ether and filtered, concentration of the filtrate provided a clear, pale yellow oil, spectral analysis of which (IR, ^1H and ^{13}C NMR) showed it to be bis(*N*-methylimine) **62**. Treatment of this material with acetic acid at room temperature for 5 h followed by concentration from several portions of toluene provided an oily yellow solid, the ^1H NMR of which was consistent with the *N*-methylimmonium ion **63**, presumably as its acetate salt. Finally, treatment of this material with acetic acid at 80 °C provided dihydro-*proto*-daphniphylline (**29**).

As discussed earlier, we had hoped that amino acids would cause the reductive cyclization to occur under even milder conditions, as the cationic nitrogen would be balanced by a carboxylate anion within the same molecule, providing an overall neutral species (Scheme V). While we were unable to discover neutral or basic conditions which led to cyclization, we did find that glycine is a suitable nitrogen source under the same conditions used with methylamine (i.e. acetic acid, 80 °C). Thus, subjection of diol **50** to the sequence (i) Swern oxidation, (ii) concentration of the Swern reaction mixture, followed by treatment of the residue thus obtained with glycine (10

equivalents) in acetic acid at room temperature, and (iii) warming to 80 °C for 6–8 h provided dihydro-*proto*-daphniphylline (**29**) in 38% isolated yield. The lower yield relative to methylamine (65%) is presumably due to the more hindered nature of glycine, which probably renders several steps in the sequence less selective (especially the final intramolecular hydride transfer).

We also investigated several chiral amines to see what magnitude of asymmetric induction could be realized. Two α-amino acids were used in the sequence described above for glycine: (*S*)-(+)-alanine led to a 32% yield of dihydro-*proto*-daphniphylline (**29**) with only minimal optical activity (1–2% ee) and (*S*)-(+)-valine provided a 13% yield of **29** with moderate optical activity (20–25% ee). (*R*)-(+)-α-Phenylethylamine was also investigated, and although the corresponding bis-*N*-phenylethylimine was formed cleanly, treatment of this material with acetic acid at 80 °C led to no characterizable products. Apparently this amine is simply too sterically hindered to undergo the cyclization sequence.

Finally, an aspect of the temperature dependence of the reductive cyclization warrents mentioning. As described above (Scheme X), treatment of the bis(*N*-methylimine) with acetic acid at room temperature leads to the *N*-methylimmonium ion **63**; the subsequent ene reaction/hydride migration occurs upon heating to 80 °C. It was found that running the sequence in the fashion just described or subjecting the bis(*N*-methylimine) **62** *immediately* to 80 °C acetic acid had no measurable effect on the yield of dihydro-*proto*-daphniphylline (**29**) with methylamine. However, in the tetracyclization of aldehydes **27** and **28** with glycine, a significant temperature dependence was observed: direct treatment with 80 °C acetic acid gave **29** in 32% yield, whereas treatment with room temperature acetic acid for 6–8 h followed by heating to 80 °C for another 6–8 h gave **29** in 53% yield. This observation suggests that at least one of the intermediates derived from glycine is more prone to destructive side reactions in hot acetic acid than are the analogous intermediates derived from methylamine.

Experimental Section

General. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Benzene, diethyl ether, and THF were distilled from Na/benzophenone immediately prior to use. Triethylamine (Et_3N) was distilled from CaH_2 prior to use. Dimethyl sulfoxide (DMSO) and hexamethylphosphoric triamide (HMPA) were sequentially dried[17] and stored over 4-Å molecular sieves. All reactions involving oxygen- or moisture-sensitive compounds were performed under a dry N_2 atmosphere. THF/hexane solutions of lithium diisopropylamide (LDA) were prepared at 0 °C from diisopropylamine (1 mmol), THF (2 mL), and a 1.5 M solution of butyllithium in hexane (1 mmol, 0.667 mL). Unless indicated organic extracts were dried with $MgSO_4$. Unless otherwise stated all chromatography was carried out with E. Merck silica gel 60 (230–400 mesh ASTM) using a described procedure[18] and all products were isolated as colorless oils. Thin layer chromatography (TLC) was performed with Analtech silica gel (SiO_2) GF (250 μm) or Macherey-Nagel Plygram Al_2O_3 (200 μm) TLC plates. ^1H NMR and ^{13}C NMR spectra were measured using $CDCl_3$ as solvent. *J* values are in hertz. Infrared spectra were measured in CH_2Cl_2. All mass spectra (MS) were measured using the electron-impact method; data are reported as *m/z* (relative intensity).

1-[(5*E*)-6,10-Dimethyl-1-oxo-5,9-undecadienyl)pyrrolidine (14). *N*-Acetylpyrrolidine (113.5 mg, 1.0 mmol) was added dropwise to a solution of LDA (1 mmol) in THF (1.5 mL) at −78 °C and the mixture was stirred for 45 min. Homogeranyl iodide (278.3 mg, 1.0 mmol) in 0.5 mL of THF was added dropwise and stirring was continued for 3 h at −78 °C. The resulting mixture was warmed to room temperature, stirred for 12 h, and poured into brine (15 mL). Extraction with CH_2Cl_2, drying of the combined organic layers, and evaporation of the solvents gave a crude material that was chromatographed using a 7:3 mixture of hexanes–EtOAc as eluent to afford 231 mg (88%) of **14** as a colorless liquid, bp 135–140 °C (0.05 Torr). IR: 1645 cm^{-1}. ^1H NMR (400 MHz): δ 1.59 (s, 3), 1.60 (s, 3), 1.67 (s, 3), 1.67–2.07 (m, 12), 2.25 (t, 2, *J* = 7.8), 3.40 (t, 2, *J* = 6.8), 3.46 (t, 2, *J* = 6.9), 5.08 (br t, 1, *J* = 1.4), 5.09 (br t, 1, *J* = 1.4). ^{13}C NMR (125 MHz): δ 15.86, 17.51, 24.27, 24.83, 25.51, 25.98, 26.54, 27.34, 33.95, 36.56, 45.38, 46.41, 123.71, 124.15, 131.12, 135.60, 171.54. HMRS: calcd for $C_{17}H_{29}NO$ 263.2249, found 263.2254.

Tandem Michael Addition–Alkylation of Enoate 15. A solution of amide **14** (263.3 mg, 1.0 mmol) in 0.5 mL of THF was added dropwise to a stirring solution of LDA (1.0 mmol) at −78 °C. After 30 min a solution of ester **15** (126.15 mg, 1.0 mmol) in 1 mL of THF was added and stirring was continued for another 15 min. Homogeranyl iodide (278.3 mg, 1.0 mmol) in 1.0 mL of THF was then added slowly and the resulting mixture was stirred for 1 h at −78 °C, at 0 °C for 3 h, and at room temperature for 12 h. The solution was poured into water (15 mL), extracted with CH_2Cl_2 (3 × 10 mL), and dried. Evaporation of the solvents yielded the crude products as a yellowish oil. Chromatography and elution with a 4:1 mixture of hexane–EtOAc gave 14 mg (2.6%) of an isomer of **17** having a neryl group in place of one of the geranyl groups. IR: 1742, 1630 cm^{-1}. ^1H NMR (400 MHz): δ 1.2–2.26 (m, 27), 1.56 (s, 3), 1.60 (s, 6), 1.66 (s, 3), 1.68 (s, 6), 2.59–2.64 (m, 1), 3.36–3.74 (m, 4), 3.67 (s, 3), 5.03–5.08 (m, 4). ^{13}C NMR (125 MHz): δ 15.83, 17.59, 17.63, 21.58, 23.39, 24.32, 24.72, 25.46, 25.65, 25.68, 26.18, 26.51, 26.68, 27.80, 31.45, 31.95, 34.21, 38.00, 39.65, 42.97, 45.70, 46.26, 51.31, 52.08, 56.75, 124.11, 124.21, 124.30, 124.96, 131.26, 131.50, 135.06, 135.44, 173.94, 176.81. HRMS: calcd for $C_{35}H_{57}NO_3$ 539.4338, found 539.4356.

Further elution gave 432 mg (80%) of ester **17**. IR: 1744, 1629 cm^{-1}. ^1H NMR (400 MHz): δ 1.2–2.24 (m, 27), 1.55 (s, 3), 1.56 (s, 3), 1.59 (s, 6), 1.67 (s, 6), 2.61–2.66 (m, 1), 3.38–3.72 (m, 4), 3.67 (s, 3), 5.04–5.10 (m, 4). ^{13}C NMR (125 MHz): δ 15.78, 15.96, 17.58, 21.56, 24.28, 24.66, 25.59, 26.15, 26.60, 26.62, 27.72, 31.10, 34.17, 37.99, 39.60, 42.88, 45.66, 46.22, 51.25, 52.10, 56.65, 124.06, 124.10, 124.25, 131.17, 131.25, 135.00, 135.27, 173.95, 176.73. HRMS: calcd for $C_{35}H_{57}NO_3$ 539.4338, found 539.4329.

Finally there was isolated 75 mg (14%) of a 2:1 mixture of diastereomeric esters **19** and **20**. IR: 1740, 1632 cm^{-1}. ^1H NMR (400 MHz): δ (major isomer) 1.38–2.28 (m, 45), 2.45–2.55 (m, 1), 3.32–3.50 (m, 4), 3.65 (s, 3), 5.05–5.12 (m, 4); δ (minor isomer) 1.15–2.28 (m, 45), 2.58–2.64 (m, 1), 3.32–3.55 (m, 4), 3.65 (s, 3), 5.05–5.17 (m, 4). HRMS: calcd for $C_{35}H_{57}NO_3$ 539.4338, found 539.4343. Anal. Calcd for $C_{35}H_{57}NO_3$: C, 77.86; H, 10.64; N, 2.59. Found: C, 77.25; H, 10.55; N, 2.56.

DIBAL Reduction of Amide 17. Diisobutylaluminum hydride (DIBAL) (4.0 mmol, 2.67 mL of a 1.5 M solution in toluene) was added dropwise to a stirring solution of amides **17** (1 mmol) in toluene (2 mL) at −78 °C. Stirring was continued for 60 min and 2 M NaOH (7 mL) was then slowly added. The mixture was warmed to room temperature and poured into brine (25 mL). Extraction with CH_2Cl_2 (3 × 15 mL), drying of the extract, and evaporation of the solvents furnished the crude material, which was chromatographed. Elution with a 4:1 mixture of hexane–EtOAc gave 428 mg (86%) of hydroxy amide **21**. IR: 3619, 1639 cm^{-1}. ^1H NMR (400 MHz): δ 1.20–2.14 (m, 28), 1.56 (s, 3), 1.61 (s, 3), 1.60 (s, 6), 1.68 (s, 6), 2.63–2.69 (m, 1), 3.40–3.59 (m, 6), 5.06–5.14 (m, 4). ^{13}C NMR (125 MHz): δ 15.87, 15.94, 17.54, 21.51, 22.99, 24.16, 25.26, 25.56, 26.16, 26.56, 26.65, 29.14, 32.29, 36.37, 39.56, 39.62, 45.73, 46.58, 48.26, 48.90, 53.32, 65.83, 124.13, 124.17, 124.32, 125.08, 131.07, 131.19, 131.50, 135.29, 175.00. HRMS: calcd for $C_{34}H_{57}NO_2$ 511.4515, found 511.4517.

Further elution gave 40 mg (8%) of amino alcohol **22**, resulting from overreduction. IR 3400–2500 cm^{-1}. ^1H NMR (400 MHz): δ 1.17–2.19 (m, 30), 1.60 (s, 9), 1.62 (s, 3), 1.68 (s, 6), 2.38–2.44 (m, 2), 2.60–2.66 (m, 2), 2.82 (dd, 1, *J* = 6.9, 12.7), 3.29 (d, 1, *J* = 11.5), 3.65 (d, 1, *J* = 11.4), 5.07–5.11 (m, 3), 5.17 (t, 1, *J* = 6.8). ^{13}C NMR (125 MHz): δ 15.16, 15.77, 15.95, 17.56, 20.80, 23.08, 23.46, 23.87, 25.58, 26.62, 26.65, 30.75, 35.01, 37.57, 38.37, 38.73,

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39.60, 39.61, 49.28, 52.28, 53.77, 60.59, 64.61, 65.73, 124.20, 124.34, 124.41, 131.00, 131.15, 134.41, 134.95. Anal. Calcd for $C_{34}H_{59}NO$: C, 82.03; H, 11.95; N, 2.81. Found: C, 81.73; H, 11.97; N, 2.81.

Preparation of Lactones 23 and 24. A mixture of hydroxy amide **21** and 3.2 mL of 5 M KOH in 12 mL of ethanol was heated at 80 °C for 100 min. After cooling to 0 °C, CH_2Cl_2 (20 mL) was added followed by 2 M HCl until pH = 1. The mixture was stirred for 5 min at 25 °C, poured into brine (40 mL), and extracted with CH_2Cl_2 (3 × 20 mL). Drying of the organic extracts, evaporation of the solvents, and medium-pressure chromatography (MPLC) on silica gel using a 7:3 mixture of hexanes–EtOAc as eluent afforded 207 mg (47%) of lactone **23** and 203 mg (46%) of lactone **24**.

[4α,4aα(*E*),7aβ(*E*)]-(±)-4,7a-Bis(4,8-dimethyl-3,7-nonadienyl)hexahydrocyclopenta[*c*]pyran-3(1*H*)-one (23). IR: 1745 cm^{-1}. ^1H NMR (400 MHz): (400 MHz): δ 1.25–2.23 (m, 24), 1.59 (s, 6), 1.60 (s, 6), 1.68 (s, 6), 3.90 (d, 1, *J* = 11.4), 4.13 (d, 1, *J* = 11.4), 5.06–5.14 (m, 4). ^{13}C NMR (125 MHz): δ 15.87, 15.97, 17.55, 22.99, 25.25, 25.56, 25.88, 26.54, 26.65, 29.54, 33.82, 34.84, 38.48, 39.06, 39.59, 42.96, 45.77, 48.34, 71.04, 123.63, 124.14, 124.18, 124.48, 131.17, 135.27, 136.05, 175.10. Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.62; H, 10.82.

[4α,4aα(*E*),7aα(*E*)]-(±)-4,7a-Bis(4,8-dimethyl-3,7-nonadienyl)hexahydrocyclopenta[*c*]pyran-3(1*H*)-one (24). IR: 1744 cm^{-1}. ^1H NMR (400 MHz): δ 1.03–1.10 (m, 1), 1.33–1.44 (m, 4), 1.60–2.15 (m, 18), 1.60 (s, 9), 1.61 (s, 3), 1.68 (s, 6), 2.47–2.52 (m, 1), 3.97–4.03 (m, 2), 5.07–5.14 (m, 4). ^{13}C NMR (125 MHz): δ 15.84, 15.94, 17.51, 22.75, 24.17, 25.07, 25.53, 26.47, 26.57, 27.58, 30.58, 35.38, 38.89, 39.01, 39.48, 39.55, 40.93, 44.77, 45.69, 73.73, 123.34, 123.60, 124.08, 131.14, 131.20, 135.52, 135.96, 175.54. Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.72; H, 10.96.

Preparation of Diols 25 and 26. To a solution of 440.7 mg (1 mmol) of lactone **23** or **24** in 12 mL of ether was added 114 mg (3 mmol) of $LiAlH_4$. The solution was stirred for 3 h, cooled to 0 °C, and quenched by the dropwise addition of water (0.153 mL), 15% w/w aqueous NaOH (0.153 mL), and water (0.460 mL). The slurry was stirred at 0 °C for 30 min and $MgSO_4$ (1 g) was added. Filtration and evaporation of the solvent furnished the pure diol. The analytical sample was further purified by rapid chromatography and elution with CH_2Cl_2–EtOAc (95:5).

[1α(*S),1α(*E*),2α(*E*)]-β,2-Bis(4,8-dimethyl-3,7-nonadienyl)-2-(hydroxymethyl)cyclopentanemethanol (25)** (1,281 mg, 96%). IR: 3680–3080, 3625, 3050–2750 cm^{-1}. ^1H NMR (400 MHz): δ 1.16–1.23 (m, 1), 1.24–1.34 (m, 1), 1.44–1.79 (m, 10), 1.60 (s, 12), 1.68 (s, 6), 1.96–2.11 (m, 12), 3.49, 3.58 (d, 1 each, *J* = 11.0), 3.58 (dd, 1, *J* = 6.0, 10.7), 3.70 (dd, 1, *J* = 4.0, 10.7), 5.07–5.17 (m, 4). ^{13}C NMR (125 MHz): δ 15.88, 15.92, 17.56, 22.05, 23.24, 25.24, 25.57, 26.65, 28.65, 30.19, 35.16, 37.05, 39.63, 40.34, 48.13, 48.46, 65.37, 65.59, 124.26, 124.29, 124.46, 124.88, 131.14, 131.16, 134.70, 135.03. HRMS: calcd for $C_{30}H_{52}O_2$ 444.3967, found 444.3984.

[1α(*R),1α(*E*),2α(*E*)]-β,2-Bis(4,8-dimethyl-3,7-nonadienyl)-2-(hydroxymethyl)cyclopentanemethanol (26)** (1,227 mg, 92%). IR: 3700–3080, 3621, 3055–2785 cm^{-1}. ^1H NMR (400 MHz): δ 1.13–1.22 (m, 1), 1.30–1.38 (m, 1), 1.39–1.47 (m, 1), 1.48–1.76 (m, 10), 1.60 (s, 12), 1.68 (s, 6), 1.88–1.94 (m, 1), 1.97–2.10 (m, 12), 3.46, 3.58 (d, 1, *J* = 11.5), 3.59 (dd, 1, *J* = 4.6, 10.5), 3.70 (dd, 1, *J* = 7.0, 10.5), 5.07–5.16 (m, 4). ^{13}C NMR (125 MHz): δ 15.90, 16.00, 17.59, 22.08, 23.41, 25.61, 25.71, 26.66, 26.82, 34.18, 34.45, 37.36, 37.63, 39.66, 47.89, 51.00, 64.92, 65.75, 124.88, 124.32, 124.90, 131.18, 134.61, 135.11. HRMS: calcd for $C_{30}H_{52}O_2$ 444.3967, found 444.3961.

General Procedure for Swern Oxidation of Diols. A solution of 381 mg (3 mmol) of oxalyl chloride in 6 mL of dry CH_2Cl_2 was cooled to −78 °C and 469 mg (6 mmol) of DMSO in 2 mL of CH_2Cl_2 was added dropwise. After 5 min a solution of 444.7 mg (1 mmol) of the diol in 2 mL of CH_2Cl_2 was added over a 3-min period. After 15 min, 506 mg (5 mmol) of triethylamine in 3 mL of CH_2Cl_2 was added slowly and stirring continued at −78 °C for 10 min. The clear solution was warmed to 0 °C, stirred for 1 h, and poured into 30 mL of water. Rapid extraction with CH_2Cl_2 (3 × 15 mL), drying of the extract (K_2CO_3), and evaporation of the solvent gave the pure dialdehyde in yields varying from 95 to 99%.

[1α(*S),1α(*E*),2α(*E*)]-β,2-Bis(4,8-dimethyl-3,7-nonadienyl)-2-formylcyclopentaneacetaldehyde (27).** IR: 2725, 1725 cm^{-1}. ^1H NMR (400 MHz): δ 1.25–2.25 (m, 23), 1.56, 1.60, 1.68 (s, 6 each), 2.40–2.52 (m, 1), 5.01–5.10 (m, 4), 9.65 (d, 1), 9.65 (s, 1).

[1α(*R),1α(*E*),2α(*E*)]-β,2-Bis(4,8-dimethyl-3,7-nonadienyl)-2-formylcyclopentaneacetaldehyde (28).** IR: 2738, 1728 cm^{-1}. ^1H NMR (400 MHz): δ 1.40–2.12 (m, 23), 1.57, 1.58 (s, 3 each), 1.60, 1.68 (s, 6 each), 2.48–2.53 (m, 1), 5.05 (t, 1, *J* = 6.5), 5.06–5.10 (m, 3), 9.53 (d, 1, *J* = 3.5), 9.66 (s, 1). ^{13}C NMR (125 MHz): δ 16.01, 16.09, 17.66, 23.41, 23.95, 25.67, 25.71, 26.60, 29.44, 31.78, 36.57, 39.61, 39.64, 50.30, 51.36, 59.01, 122.76, 123.48, 124.16, 124.18, 131.42, 135.99, 136.65, 203.99, 205.68.

[2*E*,2(*E*),7(*E*)]-2,7-Bis(4,8-dimethyl-3,7-nonadienyl)-2-octenedial (51). IR: 2725, 1726, 1685, 1646 cm^{-1}. ^1H NMR (400 MHz): δ 1.48–1.76 (m, 6), 1.57 (s, 6), 1.58 (s, 6), 1.60 (s, 3), 1.68 (s, 3), 1.93–2.08 (m, 12), 2.24–2.39 (m, 5), 5.04–5.12 (m, 4), 5.41 (t, 1, *J* = 7.4), 9.37 (s, 1), 9.59 (d, 1, *J* = 2.7). ^{13}C NMR (125 MHz): δ 15.91, 15.97, 17.61, 24.17, 25.26, 25.62, 26.15, 26.50, 25.60, 25.86, 28.34, 39.60, 39.64, 51.16, 123.03, 123.18, 124.10, 124.18, 131.27, 131.34, 135.99, 136.40, 143.61, 154.01, 194.92, 204.56. Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.24; H, 11.27.

[2*Z*,2(*E*)]-,7(*E*)]-2,7-Bis(4,8-dimethyl-3,7-nonadienyl)-2-octenedial (55). IR: 2725, 1725, 1675 cm^{-1}. ^1H NMR (400 MHz): δ 1.43–1.75 (m, 6), 1.57 (s, 3), 1.58 (s, 3), 1.60 (s, 6), 1.68 (s, 6), 1.94–2.29 (m, 15), 2.55–2.61 (m, 2), 5.05–5.10 (m, 4), 6.41 (t, 1, *J* = 8.1), 9.58 (d, 1, *J* = 2.7), 10.10 (s, 1). ^{13}C NMR (125 MHz): δ 15.86, 15.92, 17.56, 24.12, 25.20, 25.58, 26.10, 26.45, 26.55, 26.81, 28.29, 28.87, 28.89, 39.55, 39.59, 51.09, 122.98, 123.13, 124.06, 124.14, 131.20, 131.27, 135.92, 136.33, 143.54, 154.00, 194.27, 204.51. Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.26; H, 10.68.

Tricyclization Process. Preparation of Imines 31 and 39. Ammonia gas was bubbled through a mixture of 220.4 mg (0.5 mmol) dialdehydes **27/28** or **36/37** and 137.5 mg (1 mmol) of triethylammonium hydrochloride in 12 mL of CH_2Cl_2 at 0 °C for 3 min. The mixture was allowed to warm to 25 °C and stirred for 1 h. The solvent was then evaporated and 77 mg (1 mmol) of NH_4OAc and 10 mL of acetic acid were added. The solution was stirred at 25 °C for 30 min, poured into 75 mL of water, and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with 50 mL of 2 M NaOH. After separation of the two layers, the basic aqueous phase was extracted with another 15 mL of CH_2Cl_2. The combined extracts were dried over K_2CO_3. Filtration, evaporation of the solvent, and chromatography using hexane–EtOAc (8:2) as eluent afforded the colorless, oily imine. Application of this procedure to dialdehydes **27/28** gave 148 mg (70%) of imine **31** and 9 mg (4%) of the isomeric imine **32**.

[3α,3aβ,6α(*E*),6aα,9a*R,10*S**]-(±)-2,3,3a,6,6a,7,8,9-Octahydro-10-methyl-10-(4-methyl-3-pentenyl)-6-(4,8-dimethyl-3,7-nonadienyl)-3,6-methano-1*H*-dicyclopenta[*b*,*c*]pyridine (31).** IR: 1625 cm^{-1}. ^1H NMR (400 MHz): δ 0.86 (s, 3), 1.56 (s, 3), 1.61 (s, 3), 1.63 (s, 3), 1.64 (s, 3), 1.69 (s, 3), 0.88–0.96 (m, 1), 1.04–1.18 (m, 1), 1.22–1.91 (m, 16), 1.98–2.03 (m, 2), 2.06–2.11 (m, 2), 2.17–2.26 (m, 2), 4.11 (d, 1, *J* = 4.6), 4.99 (t, 1, *J* = 7.0), 5.10, 5.15 (t, 1 each, *J* = 6.9), 8.10 (s, 1). ^{13}C NMR (125 MHz): δ 16.02, 16.87, 17.57, 22.03, 23.11, 24.68, 25.53, 25.57, 26.57, 31.16, 32.61, 36.96, 38.49, 39.01, 39.55, 43.02, 43.76, 48.31, 53.81, 54.15, 69.10, 124.14, 124.65, 124.83, 130.97, 131.19, 134.87, 178.39. Anal. Calcd for $C_{30}H_{47}N$: C, 85.44; H, 11.23; N, 3.32. Found: C, 85.33; H, 11.02; N, 3.22.

[3α,3aβ,6α(*E*),6aα,9a*R,10*R**]-(±)-2,3,3a,6,6a,7,8,9-Octahydro-10-methyl-10-(4-methyl-3-pentenyl)-6-(4,8-dimethyl-3,7-nonadienyl)-3,6-methano-1*H*-dicyclopenta[*b*,*c*]pyridine (32).** ^1H NMR (400 MHz): δ 0.78 (s, 3), 0.79–2.12 (m, 24), 1.55, 1.59, 1.63 (s, 3 each), 1.69 (s, 6), 4.12 (d, 1, *J* = 4.9), 5.05–5.18 (m, 3), 8.17 (s, 1). HRMS: calcd for $C_{30}H_{47}N$ 421.3708, found 421.3698.

Application of the procedure to dialdehydes **36/37** gave 167 mg (79%) of imine **38** and 7 mg (3%) of imine **39**.

[3α,3aβ,6α(*Z*),6aα,9a*R,10*R**]-(±)-2,3,3a,6,6a,7,8,9-Octahydro-10-methyl-10-(4-methyl-3-pentenyl)-6-(4,8-dimethyl-3,7-nonadienyl)-3,6-methano-1*H*-dicyclopenta[*b*,*c*]pyridine (38).** IR: 1625 cm^{-1}. ^1H NMR (400 MHz): δ 0.77 (s, 3), 1.00–1.07 (m, 1), 1.20–1.41 (m, 4), 1.45–1.83 (m, 11), 1.60 (s, 3), 1.61 (s, 3), 1.71 (s, 3), 1.68 (s, 6), 1.98–2.10 (m, 6), 2.17–2.30 (m, 2), 4.12 (d, 1, *J* = 4.9), 5.06–5.18 (m, 3), 8.16 (s, 1). ^{13}C NMR (125 MHz): δ 17.56, 17.68, 23.30, 23.53, 24.05, 24.78, 24.97, 25.67, 25.56, 31.77, 31.92, 32.03, 33.05, 36.20, 37.53, 44.04, 45.82, 48.63, 52.36, 54.88,

68.39, 124.09, 124.77, 125.72, 131.05, 131.55, 135.16, 178.57. Anal. Calcd for $C_{30}H_{47}N$: C, 85.44; H, 11.23; N, 3.32. Found: C, 85.05; H, 10.97; N, 3.27.

[3α,3aβ,6α(*Z*),6aα,9a*R,10*S**]-(±)-2,3,3a,6,6a,7,8,9-Octahydro-10-methyl-10-(4-methyl-3-pentenyl)-6-(4,8-dimethyl-3,7-nonadienyl)-3,6-methano-1*H*-dicyclopenta[*b*,*c*]pyridine (39).** ^{1}H NMR (400 MHz): δ 0.85 (s, 3), 0.86–0.97 (m, 1), 1.04–1.11 (m, 1), 1.19–1.88 (m, 14), 1.56, 1.61 (s, 3), 1.64 (s, 3), 1.68 (s, 3), 1.71 (s, 3), 1.99–2.10 (m, 6), 2.18–2.24 (m, 2), 4.11 (d, 1, *J* = 4.7), 4.96–5.00 (m, 1), 5.10–5.18 (m, 2), 8.10 (s, 1).

***proto*-Daphniphylline (11). Method A.** The foregoing procedure was followed except that the acetic acid solution of the imine **31** was heated at 75 °C for 2 h prior to the workup. There was thus isolated 329 mg (78%) of *proto*-daphniphylline. IR: 1648 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.81 (s, 3), 1.16–1.22 (m, 1), 1.25–2.12 (m, 26), 1.60 (s, 6), 1.68 (s, 6), 1.78 (s, 6), 2.54 (d, 1, *J* = 4.5), 2.74 (br s, 1), 4.74 (s, 1), 4.86, (s, 1), 5.06–5.12 (m, 2). ^{13}C NMR (125 MHz): δ 16.07, 17.63, 20.19, 21.35, 22.59, 22.81, 23.61, 25.63, 26.64, 26.69, 29.76, 33.11, 36.29, 36.62, 36.87, 38.43, 39.52, 39.64, 42.35, 47.76, 49.22, 50.76, 53.76, 60.07, 110.16, 124.28, 125.30, 131.17, 134.30, 147.65. Anal. Calcd for $C_{30}H_{47}N$: C, 85.44; H, 11.23; N, 3.32. Found: C, 85.08; H, 10.85; N, 3.40.

Method B. Compound **11** was also obtained by heating a solution of 172 mg (0.41 mmol) of imine **31** and 314 mg (4.1 mmol) of NH_4OAc in 8 mL of acetic acid at 75 °C for 2 h. Application of the foregoing workup procedure gave 155 mg (90%) of *proto*-daphniphylline.

Method C. Ammonia gas was bubbled for 3 min through a solution of dialdehyde **55** (110 mg, 0.25 mmol), NH_4OAc (19.3 mg, 0.25 mmol), and triethylamine hydrochloride (34.4 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) at room temperature and the resulting mixture was stirred for 16 h. The solvent was then evaporated and NH_4OAc (193 mg, 2.5 mmol) and AcOH (5 mL) were added. The mixture was heated at 80 °C for 3 h, cooled, and poured into water (25 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with 2 M NaOH. The layers were separated and the aqueous phase was extracted with additional CH_2Cl_2 (10 mL). The CH_2Cl_2 extract was dried and evaporated and the residue chromatographed to give 18 mg (17%) of *proto*-daphniphylline (**11**). The same procedure when applied to dialdehyde **51** gave 12.5 mg (13%) of **11**.

Method D. Dialdehyde **55** (132 mg, 0.31 mmol) in dry DMSO (0.5 mL) was added at 25 °C to a suspension of finely powdered NaOH (98% grade, 12.4 mg, 0.31 mmol) in DMSO (2 mL) in a pressure bottle equipped with a rubber ring and a Teflon screw-cap. The resulting mixture was stirred for 3.5 h, NH_4OAc (48 mg, 0.62 mmol) was added, and ammonia was bubbled through the mixture for 3 min. The bottle was closed and heated at 80 °C in an oil bath for 3 h. Acetic acid (5 mL) was added and the solution heated at 80 °C for 2.5 h. Workup and purification as above gave 58 mg (44%) of *proto*-daphniphylline. Use of KOH instead of NaOH gave the product in only 35% yield.

Method E. Tetra-*n*-butylammonium bisulfate (3.3 mg, 0.0096 mmol) was added to a vigorously stirring mixture of 50% KOH (0.193 mL), dialdehyde **51** or **55** (85 mg, 0.193 mmol), and benzene (3 mL) at 25 °C. After 10 min[19] the mixture was poured into water (3 mL) and extracted with ether (3 × 2 mL). The extract was dried over K_2CO_3, the solvents were evaporated, and the residue was placed in a pressure bottle along with NH_4OAc (92 mg, 1.193 mmol) and DMSO (6 mL). Ammonia gas was bubbled through the solution for 3 min and the flask was closed with a Teflon screw-cap and heated at 80 °C for 3 h. Acetic acid (8 mL) was then added and heating continued for 3 h. Workup and purification as above furnished 40.2 mg (49.4%) of pure **11**.

1,2-Dihydro-*proto*-daphniphylline (29). Method A. Tris(triphenylphosphine)rhodium(I) chloride (160 mg, 0.173 mmol) was suspended in 12 mL of dry benzene that had been degassed (freeze–pump–thaw cycle). The suspension was stirred at 25 °C for 45 min under an atmosphere of H_2 (the catalyst dissolved). *proto*-Daphniphylline (243 mg, 0.576 mmol) in C_6H_6 (1 mL) was added with a syringe and stirring was continued for 8 h. The solvent was evaporated and the residue chromatographed on silica gel using 9:1 hexane–EtOAc as eluent to give 213 mg (88%) of amine **29**, contaminated with a small amount of dihydrogenated product. ^{1}H NMR (400 MHz): δ 0.78 (s, 3), 0.89 (d, 3, *J* = 6.7), 0.91 (d, 3, *J* = 6.7), 0.90–0.97 (m, 1), 1.13–1.18 (m, 1), 1.21–1.78 (m, 19), 1.59 (s, 3), 1.61 (s, 3), 1.68 (s, 3), 1.86–1.91 (m, 2), 1.93–2.00 (m, 2), 2.03–2.10 (m, 2), 2.52 (d, 1, *J* = 4.5), 3.02 (s, 1), 5.03–5.11 (m, 2). ^{13}C NMR (125 MHz): δ 16.05, 17.62, 20.75, 21.00, 21.03, 21.33, 22.89, 23.55, 25.63, 26.65, 26.75, 28.75, 29.91, 33.20, 36.37, 36.49, 36.67, 39.13, 39.65, 39.77, 42.87, 47.75, 48.34, 50.42, 53.49, 60.12, 124.30, 125.46, 131.11, 134.09. Anal. Calcd for $C_{30}H_{49}N$: C, 85.04; H, 11.66; N, 3.31. Found: C, 84.74; H, 11.79; N, 3.31.

Method B. To a −78 °C solution of DMSO (66 μL, 0.93 mmol) in 0.8 mL of CH_2Cl_2 was added 206 μL of a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (0.412 mmol). After 15 min, diols **25** and **26** (45.8 mg, 0.103 mmol) were added via cannula as a solution in 0.8 mL of CH_2Cl_2, followed by a 0.8-mL rinse. The resulting cloudy solution was stirred at −78 °C for 15 min and then treated with triethylamine (0.10 mL, 0.72 mmol). The dry ice bath was replaced with an ice water bath, and the solution was allowed to warm to 0 °C over a period of 80 min. A stream of anhydrous methylamine was then passed over the solution for 3 min. The flask was sealed tightly and allowed to warm to ambient temperature over a period of 2 h. The clear solution was concentrated by passing a stream of dry nitrogen over it for a period of 10 min. The resulting white, oily solid was then placed on a vacuum pump for 4 h. The resulting solid was taken up in 5 mL of acetic acid and stirred at room temperature for 5 h and then placed in an 80 °C oil bath for 11 h. After cooling to 0 °C, the mixture was partitioned between CH_2Cl_2 and 15 mL of 6 N NaOH and stirred vigorously for 15 min. The layers were separated, and the aqueous phase was extracted with three portions of CH_2Cl_2. The combined organic phases were than washed with brine and dried over $MgSO_4$. Filtration and concentration provided 57.5 mg of a brown oil, which was purifed by flash chromatography (gradient elution with 10:1 to 5:1 hexanes/ethyl acetate) to provide the desired product as a clear, pale yellow oil (28.7 mg, 65.8%).

Method C. To a −78 °C solution of DMSO (45 μL, 0.63 mmol) in 1 mL of CH_2Cl_2 was added 140 μL of a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (0.280 mmol). After 10 min, diols **25** and **26** (31.1 mg, 0.0699 mmol) were added via cannula as a solution in 1 mL of CH_2Cl_2, followed by two 0.5-mL rinses. The resulting cloudy solution was stirred at −78 °C for 15 min and then treated with triethylamine (0.070 mL, 0.50 mmol). The dry ice bath was replaced with an ice water bath, and the solution was allowed to warm to 0 °C over a period of 60 min. The solvent was then removed under a stream of dry nitrogen to provide a white, oily solid, which was triturated with ether and filtered through a plug of cotton. Concentration of the resulting colorless solution provided 40.8 mg of a clear, pale yellow oil. The crude bisaldehyde was then treated with 1.5 mL of acetic acid and 51 mg of glycine (0.68 mmol) and stirred for 10 h at room temperature, followed by 16 h in an 80 °C oil bath. After being cooled to room temperature, the solution was partitioned between 5 mL each of CH_2Cl_2 and 2 N NaOH and stirred vigorously for 2 h. The layers were separated, the aqueous phase was extracted with two portions of CH_2Cl_2, and the combined organic phases were dried over K_2CO_3. Filtration and concentration provided 27.3 mg of a pale, orange-brown oil. Flash chromatography of this material (gradient elution with 10:1 to 5:1 hexanes/ethyl acetate) provided the desired product as a clear, pale yellow oil (15.8 mg, 53.4%).

Method D. To a −78 °C solution of DMSO (88 μL, 1.2 mmol) in 1 mL of CH_2Cl_2 was added 276 μL of a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (0.552 mmol). After 20 min, diol **50** (61.3 mg, 0.138 mmol) was added via cannula as a solution in 1 mL of CH_2Cl_2, followed by a 1-mL rinse. The resulting cloudy solution was stirred at −78 °C for 20 min and then treated with triethylamine (0.14 mL, 1.0 mmol). The dry ice bath was removed, and the solution was allowed to warm to ambient temperature over a period of 50 min. After cooling to 0 °C, a stream of anhydrous methylamine was passed over the solution for 3 min. The flask was then sealed tightly and allowed to warm to ambient temperature over a period of 5 h. The clear solution was concentrated by passing a stream of dry nitrogen over it for a period of 10 min. The resulting white, oily solid was triturated with ether, filtered, and concentrated (high vacuum for 4 h) to provide 84.0

(19) The reaction can be monitored by TLC on Al_2O_3 plates with a 9:1 mixture of hexane–EtOAc as eluent.

mg of a clear, pale yellow oil. Although generally utilized immediately in the next reaction, spectral analysis of this material was consistent with the bis(*N*-methylimine) **62**. IR (thin film): 2960, 2920, 2840, 1665, 1640, 1450, 1395, 1345. ^{1}H NMR (400 MHz, selected signals listed): δ 7.72 (s, 1), 7.43 (d, 1), 5.77 (t, 1), 5.15–5.05 (m, 4), 3.35 (s, 3), 3.26 (s, 3). ^{13}C NMR (100 MHz): δ 15.91, 15.95, 16.00, 17.58, 25.41, 25.60, 25.98, 26.70, 26.80, 26.93, 27.09, 28.43, 31.69, 32.40, 39.65, 44.62, 47.82, 47.86, 123.99, 124.23, 124.35, 124.43, 131.10, 131.17, 135.08, 135.31, 139.85, 141.34, 166.12, 169.63.

The crude bisimine was taken up in 1 mL of acetic acid and placed in an 80 °C oil bath for 11 h. After being cooled to 0 °C, the mixture was partitioned between 5 mL each of CH_2Cl_2 and 2 N NaOH and stirred vigorously for 15 min. The layers were separated, and the aqueous phase was extracted with three portions of CH_2Cl_2. The combined organic phases were then washed with brine and dried over $MgSO_4$. Filtration and concentration provided 68.0 mg of a brown oil. Purification by flash chromatography (gradient elution with 10:1 to 5:1 hexanes/ethyl acetate) provided the desired product as a clear, pale yellow oil (38.2 mg, 65.4%).

Method E. To a −78 °C solution of DMSO (60 μL, 0.85 mmol) in 1 mL of CH_2Cl_2 was added 190 μL of a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (0.380 mmol). After 20 min, diol **50** (41.9 mg, 0.0942 mmol) was added via cannula as a solution in 1 mL of CH_2Cl_2, followed by two 0.5-mL rinses. The resulting cloudy solution was stirred at −78 °C for 20 min and then treated with triethylamine (0.10 mL, 0.72 mmol). The dry ice bath was removed, and the solution was allowed to warm to room temperature over a period of 60 min. The solvent was then removed under a stream of dry nitrogen to provide a white, oily solid, which was triturated with ether and filtered through a plug of cotton. Concentration of the resulting colorless solution provided 47.5 mg of a clear, pale yellow oil. The crude bisaldehyde was then treated with 1.5 mL of acetic acid and 70 mg of glycine (0.93 mmol) and stirred for 9 h at room temperature, followed by 9 h in an 80 °C oil bath. After being cooled to room temperature, the solution was partitioned between 15 mL each of CH_2Cl_2 and 2 N NaOH and stirred vigorously for 90 min. The layers were separated, the aqueous phase was extracted with two portions of CH_2Cl_2, and the combined organic phases were dried over K_2CO_3. Filtration and concentration provided 72 mg of a brown, cloudy oil. Flash chromatography of this material (gradient elution with 10:1 to 5:1 hexanes/ethyl acetate) provided the desired product as a clear, colorless oil (15.0 mg, 37.6%).

Attempted Cyclization of Imines 31 and 38. A solution of 4.2 mg (0.01 mmol) of imine **31** or **38** and 7.7 mg (0.1 mmol) of NH_4OAc in 0.2 mL of acetic acid was heated at 80 °C for 15 h. Workup as usual gave a brown oil. Analysis by TLC (SiO_2, hexane–EtOAc (7:3)), GC, or ^{1}H NMR spectrometry indicated no change.

[7(*Z*)]-17,18-Didehydro-7-(4,8-dimethyl-3,7-nonadienyl)-12,16-cyclo-21,22,23-trinor-1,12-secodaphnane (40). A solution of 172 mg (0.41 mmol) of imine **39** and 314 mg (4.1 mmol) of NH_4OAc in 8 mL of acetic acid was heated at 80 °C for 2 h. The normal workup gave 155 mg (90%) of amine **40**. ^{1}H NMR (400 MHz): δ 0.80 (s, 3), 0.81–0.90 (m, 1), 1.16–2.10 (m, 25), 1.55 (s, 3), 1.61 (s, 3), 1.68 (s, 3), 1.77 (s, 3), 2.53 (d, 1, J = 4.5), 3.02 (s, 1), 4.74 (s, 1), 4.86 (s, 1), 5.05–5.12 (m, 2). HRMS: calcd for $C_{30}H_{47}N$ 421.3708, found 421.3707.

(±)-Methyl Homosecodaphniphyllate (30). Ozone was bubbled for 3 min through a solution of 150 mg (0.354 mmol) of amine **29**, 69.4 mg (0.71 mmol) of concd H_2SO_4, 4 mL of CH_2Cl_2, and 4 mL of MeOH, cooled to −78 °C. The blue solution was discolored by bubbling N_2 through it and warmed to 25 °C. The solvents were evaporated and the residue placed under high vacuum for 10 min. Acetone (8 mL) was added followed by 1.59 mL of a 2.67 M solution of CrO_3 in concd H_2SO_4 at 0 °C. The mixture was stirred for 30 min at 0 °C and for 10 min at 25 °C. Filtration through a plug of Celite and washing with acetone (15 mL) afforded a clear solution. Evaporation of the solvent gave an oily residue that was dissolved in 25 mL of methanol and treated with 0.5 mL of concd H_2SO_4. The solution was stirred at 25 °C for 40 h, poured into 50 mL of water, and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$ and dried, and the solvents were evaporated. The residue was purified by chromatography and eluted with a 8:2 mixture of hexane–EtOAc to furnish 99 mg (78%) of **30**, identical by ^{1}H NMR, ^{13}C NMR, and TLC with an authentic sample.[1]

***tert*-Butyl (5*E*)-6,10-Dimethylundeca-5,9-dienoate (45).** A solution of 116.2 mg (1 mmol) of *tert*-butyl acetate in 0.8 mL of dry THF was added dropwise to a stirring solution of 1 mmol of LDA at −78 °C. After 45 min, a mixture of 179.2 mg (1 mmol) of HMPA and 0.2 mL of THF (0.2 mL) was added followed *immediately* by a solution of 250 mg (0.9 mmol) of homogeranyl iodide in 1 mL of THF. After 4 h at −78 °C the mixture was warmed to 25 °C, poured into 20 mL of brine, and extracted with CH_2Cl_2 (3 × 10 mL). Drying of the extracts, filtration, and evaporation of the solvents left a residue that was chromatographed. Elution with hexane–EtOAc (99:1) afforded 213 mg (83%) of ester **45**, bp 74–78 °C (0.1 Torr). IR: 1725 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.42 (s, 9), 1.56 (s, 3), 1.57 (s, 3), 1.56–1.62 (m, 2), 1.65 (s, 3), 1.94–2.07 (m, 6), 2.17 (t, 2, J = 7.5), 5.04–5.08 (m, 2). ^{13}C NMR (125 MHz): δ 15.85, 17.58, 25.10, 25.60, 26.53, 27.10, 28.02, 34.83, 39.65, 79.77, 123.56, 124.23, 131.20, 135.73, 173.16. Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.25; H, 11.32.

Further elution gave 28 mg (9%) of a byproduct resulting from Claisen condensation of **45** with *tert*-butyl acetate. IR: 1735, 1714 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.47 (s, 9), 1.59 (s, 3), 1.60 (s, 3), 1.68 (s, 3), 1.60–1.67 (m, 2), 1.96–2.15 (m, 6), 2.51 (t, 1, J = 7.4), 3.33 (s, 2), 5.06–5.10 (m, 2). ^{13}C NMR (125 MHz): δ 15.71, 17.37, 23.29, 25.41, 26.39, 26.79, 27.65, 39.45, 41.90, 50.34, 81.33, 123.23, 124.03, 130.91, 135.74, 166.19, 202.94. Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 74.09; H, 10.59.

(5*E*)-*tert*-Butyl 2-(4,4-Dimethoxybutyl)-6,10-dimethyl-5,9-undecadienoate (46). A solution of 266.4 mg (1 mmol) of ester **45** in 0.8 mL of THF was added dropwise to a stirring solution of LDA (1.2 mmol) at −78 °C. After 45 min of stirring, a solution of 236.5 mg (1.2 mmol) of 1,1-dimethoxy-4-bromobutane in 1 mL of THF was added dropwise, followed by a mixture of 179.2 mg (1 mmol) of HMPA and 0.2 mL of THF. Stirring was continued for 3 h at −78 °C and the mixture was warmed to 25 °C overnight, poured into 20 mL of water, and extracted with CH_2Cl_2. The combined extracts were dried over K_2CO_3 and the solvents evaporated. The residue was chromatographed and eluted with a 97:3 mixture of hexane–EtOAc and finally distilled under reduced pressure to afford 327 mg (85%) of acetal **46**, bp 119–121 °C (0.01 Torr). IR: 1725 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.13–1.64 (m, 8), 1.46 (s, 9), 1.59 (s, 3), 1.60 (s, 3), 1.68 (s, 3), 1.94–2.10 (m, 6), 2.19–2.27 (m, 1), 3.29 (s, 3), 3.30 (s, 3), 4.34 (t, 1, J = 5.8), 5.06–5.10 (m, 2). ^{13}C NMR (125 MHz): δ 15.82, 17.55, 22.32, 25.57, 25.65, 26.54, 28.00, 32.27, 32.53, 39.59, 45.88, 52.37, 52.47, 79.75, 104.17, 123.65, 124.20, 131.10, 135.37, 175.45. Anal. Calcd for $C_{23}H_{42}O_4$: C, 72.21; H, 11.07. Found: C, 72.40; H, 11.22.

(5*E*)-*tert*-Butyl 6,10-Dimethyl-2-(4-oxobutyl)-5,9-undecadienoate (47). A mixture of 3.826 g (10 mmol) of acetal **46**, 380 mg (2 mmol) of *p*-toluenesulfonic acid, and 3.5 mL of water (3.5 mL) in 24 mL of acetone was stirred for 16 h at 25 °C. The solution was poured into 50 mL of brine and extracted with CH_2Cl_2 (3 × 25 mL). Drying of the extract, filtration, and evaporation of the solvent gave a residue that was purified by chromatography (eluant: CH_2Cl_2) and bulb-to-bulb distillation (117–119 °C at 0.02 Torr) to furnish 3.31 g (98%) of aldehyde **47**. IR: 2726, 1724 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.37–1.47 (m, 2), 1.46 (s, 9), 1.58–1.66 (m, 4), 1.59, 1.60 (s, 3), 1.68 (s, 3), 1.93–2.02 (m, 4), 2.05–2.10 (m, 2), 2.23–2.27 (m, 1), 2.42–2.46 (m, 2), 5.06–5.11 (m, 2), 9.75 (t, 1, J = 1.6). ^{13}C NMR (125 MHz): δ 15.86, 17.56, 19.81, 25.59, 26.55, 28.02, 31.79, 32.52, 39.60, 43.60, 45.72, 80.06, 123.49, 124.18, 131.19, 135.57, 175,17, 202.01. Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.60; H, 10.53.

[2(*E*),7(*E*)]-Di-*tert*-butyl 2,7-Bis(4,8-dimethyl-3,7-nonadienyl)-3-hydroxyoctanedioate (48). To a solution of diisopropylamine (0.46 mL, 3.3 mmol) in 3 mL of THF at 0 °C was added 1.39 mL of a 2.33 M *n*-butyllithium solution. After 20 min, the solution was cooled to −78 °C, and ester **45** (785 mg, 2.95 mmol) was added via cannula in 3 mL of THF, followed by a 2-mL rinse. The solution was stirred at −78 °C for 50 min and then treated with aldehyde **47** (815 mg, 2.42 mmol), which was added via cannula in 3 mL of THF, followed by a 2-mL rinse. The solution was stirred for an additional 50 min and then quenched at −78 °C by the addition of approximately 5 mL of aqueous NH_4Cl

solution. After being warmed to room temperature, the solution was extracted with three portions of ether. The combined organic phases were washed with brine and dried over $MgSO_4$. Filtration and concentration provided 1.783 g of a clear, colorless oil. Purification by flash chromatography (gradient elution with 100 to 50 to 20 to 10:1 hexanes/ethyl acetate) provided recovered ester **45** (204 mg, 0.766 mmol), followed by the desired β-hydroxy ester **48** as a clear, colorless oil (1.199 g, 1.989 mmol, 82%). Anal. Calcd for $C_{38}H_{68}O_5$: C, 75.70; H, 11.03. Found: C, 75.90; H, 10.78.

[2*E*,2(*E*),7(*E*)]-Di-*tert*-butyl 2,7-Bis(4,8-dimethyl-3,7-nonadienyl)-2-octenedioate (49). To a 0 °C solution of β-hydroxy esters **48** (1.643 g, 2.725 mmol) and triethylamine (1.52 mL, 10.9 mmol) in 8 mL of CH_2Cl_2 was added 0.42 mL (5.5 mmol) of methanesulfonyl chloride. The ice bath was removed, and the solution was allowed to stir at room temperature for 3 h. After dilution with 20 mL of CH_2Cl_2, the solution was washed with aqueous $NaHCO_3$ (2×), 0.1 N HCl, and brine. The aqueous phases were extracted once with CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$. Filtration and concentration provided a granular, orange-brown oil, which was taken up in 8 mL of toluene, treated with 1,8-diazabicyclo[5.4.0]undecene (DBU) (1.2 mL, 8.2 mmol), and heated in an 80 °C oil bath for 12 h. After being cooled to room temperature, the solution was diluted with ether, washed with 0.1 N HCl (2×), aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. Filtration and concentration provided 1.701 g of a clear pale yellow oil. Purification by flash chromatography (gradient elution with 40 to 30:1 hexanes/ethyl acetate) provided the 14*Z* isomer **53** (0.134 g, 0.23 mmol, 8.4%) and the 14*E* isomer **49** (1.402 g, 2.397 mmol, 88.0%), both as clear, colorless oils. IR: 1725, 1710 cm^{-1}. ^1H NMR (400 MHz): δ 1.40–1.68 (m, 4), 1.45 (s, 9), 1.49 (s, 9), 1.58 (s, 3), 1.59 (s, 3), 1.60 (s, 6), 1.68 (s, 6), 1.96–2.46 (m, 19), 5.07–5.10 (m, 3), 5.11–5.16 (m, 1), 6.62 (t, 1, *J* = 7.5). ^{13}C NMR (125 MHz): δ 15.90, 15.91, 17.62, 25.64, 25.71, 26.61, 26.66, 26.97, 27.71, 28.09, 28.10, 28.21, 28.47, 32.31, 32.60, 39.66, 39.69, 45.92, 79.82, 79.90, 123.58, 123.66, 124.25, 124.30, 131.22, 133.65, 135.51, 141.01, 167.21, 175.43. Anal. Calcd for $C_{38}H_{64}O_4$: C, 78.03; H, 11.03. Found: C, 78.20; H, 11.06.

(6*E*,14*Z*,18*E*)-10,11-Dihydrosqualene-27,28-diol (50). A 1.0 M solution of DIBAL in toluene (30 mL, 30 mmol) was added dropwise to a solution of 1.939 g (3.315 mmol) of diester **49** in 16 mL of CH_2Cl_2 at −78 °C. After 3 h, the reaction was quenched by slow addition of 2 mL of methanol. After warming to room temperature, 50 mL each of ether and saturated aqueous sodium potassium tartrate were added, and the resulting solution was stirred vigorously until two clear phases resulted. The layers were then separated, and the aqueous phase was extracted with three portions of ether. The combined organic phases were washed with brine and dried. Filtration and evaporation of the solvents gave a crude mixture of compounds that was resubjected to further reduction by being dissolved in 16 mL of CH_2Cl_2, cooled to −78 °C, and treated with another 30-mL portion of 1.0 M DIBAL in toluene (30 mmol) for 3 h at −78 °C. Workup as before provided a clear, pale yellow oil, which was purified by flash chromatography (gradient elution with 3 to 2:1 hexanes/ethyl acetate) to provide diol **50** as a clear, colorless oil (1.413 g, 96%). IR: 3700–3250, 3615 cm^{-1}. ^1H NMR (400 MHz): δ 1.24–1.58 (m, 7), 1.59 (s, 12), 1.68 (s, 6), 1.95–2.14 (m, 16), 3.45 (dd, 1, *J* = 5.9, 10.5), 4.06 (d, 1, *J* = 11.8), 4.13 (d, 1, *J* = 11.8), 5.06–5.13 (m, 4), 5.29 (t, 1, *J* = 6.3). ^{13}C NMR (125 MHz): δ 15.83, 15.88, 17.50, 25.13, 25.52, 26.57, 26.59, 26.71, 26.81, 27.50, 30.11, 30.81, 34.91, 39.58, 59.68, 65.09, 123.97, 124.21, 124.40, 128.37, 131.03, 134.83, 135.02, 138.24. Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.78. Found: C, 80.86; H, 11.90.

***tert*-Butyl (5*E*)-2-(Trimethylsilyl)-6,10-dimethylundeca-5,9-dienoate (52).** A solution of 188.4 mg (1 mmol) of *tert*-butyl (trimethylsilyl)acetate[20] in 0.5 mL of THF was added slowly into a stirring solution of 1.1 mmol of LDA in THF/hexane at −78 °C. The resulting mixture was stirred for 30 min at −78 °C and 15 min at −42 °C. The solution was cooled to −78 °C, a solution of 278.3 mg (1 mmol) of iodide **16** in 1 mL of THF was added dropwise, and the solution was stirred for 3 h. The mixture was then warmed to room temperature and stirring continued for 16 h. The crude solution was poured into 25 mL of brine, extracted with CH_2Cl_2 (3 × 15 mL), and dried. Filtration, evaporation of the solvent, and chromatography (95:5 hexane–EtOAc) furnished 286 mg (84%) of **52**. IR: 1705 cm^{-1}. ^1H NMR (400 MHz): δ 0.006 (s, 9), 1.29–1.67 (m, 2), 1.44 (s, 9), 1.60 (s, 6), 1.68 (s, 3), 1.76–2.12 (m, 7), 5.04–5.12 (m, 2). ^{13}C NMR (125 MHz): δ −2.67, 15.88, 17.59, 25.62, 26.61, 26.96, 28.26, 28.44, 38.07, 39.70, 79.20, 123.83, 124.31, 131.10, 135.61, 174.50. Anal. Calcd for $C_{20}H_{38}SiO_2$: C, 70.94; H, 11.31. Found: C, 71.03; H, 11.25.

[2*Z*,2(*E*),7(*E*)]-Di-*tert*-butyl 2,7-Bis(4,8-dimethyl-3,7-nonadienyl)-2-octenedioate (53). A solution of 2.71 g (8 mmol) of ester **52** in 8 mL of THF was added dropwise to a solution of 8 mmol of LDA in THF/hexane at −78 °C. After 3.5 h, 2.69 g (8 mmol) of aldehyde **47** was added over a 5-min period and stirring was continued for 15 min. The solution was warmed to 0 °C, stirred for an additional 10 min, and quenched with 100 mL of water. Extraction with CH_2Cl_2, drying of the combined organic extracts, filtration, and evaporation of the solvents gave a crude oil. Chromatographic purification, eluting with 95:5 hexane–EtOAc, gave 2.42 g of 14*Z* isomer **53**, followed by 1.39 g of 14*E* isomer **49** (total yield, 73%). IR: 1720 cm^{-1}. ^1H NMR (400 MHz): δ 1.37–1.68 (m, 6), 1.45 (s, 9), 1.50 (s, 9), 1.58 (s, 3), 1.59 (s, 3), 1.60 (s, 6), 1.68 (s, 6), 1.93–2.23 (m, 15), 2.35–2.39 (m, 2), 5.07–5.14 (m, 4), 5.70 (t, 1, *J* = 7.4). ^{13}C NMR (125 MHz): δ 15.86, 15.92, 17.59, 25.61, 25.71, 26.58, 26.66, 27.21, 27.58, 28.05, 28.17, 29.30, 32.19, 32.59, 34.96, 39.64, 45.94, 79.73, 80.16, 123.46, 127.71, 124.26, 131.12, 133.53, 135.38, 135.44, 139.30, 167.49, 175.51. Anal. Calcd for $C_{38}H_{64}O_4$: C, 78.03; H, 11.03. Found: C, 78.13; H, 11.21.

(6*E*,14*E*,18*E*)-10,11-Dihydrosqualene-27,28-diol (54). The procedure described for the preparation of diol **50** was followed with 935 mg (1.6 mmol) of diester **53** to obtain 700 mg (87%) of diol **54**. IR: 3720–3240, 3620 cm^{-1}. ^1H NMR (400 MHz): δ 1.28–1.75 (m, 7), 1.60 (s, 12), 1.68 (s, 6), 1.95–2.16 (m, 16), 3.51–3.57 (m, 2), 4.03 (s, 2), 5.06–5.17 (m, 4), 5.43 (t, 1, *J* = 6.6). ^{13}C NMR (125 MHz): δ 15.95, 17.63, 25.20, 25.64, 26.62, 26.65, 26.92, 26.98, 27.79, 28.14, 30.53, 30.91, 39.66, 40.00, 65.32, 67.14, 123.87, 124.25, 124.28, 124.43, 127.08, 131.27, 131.32, 135.08, 135.47, 138.98. Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.78. Found: C, 80.76; H, 11.76.

1,5-Bis(4,8-dimethylnona-3,7-dienyl)-2-hydroxy-3-oxabicyclo[4.3.0]-4-nonenes (61). Tetra-*n*-butylammonium bisulfate (8.5 mg, 0.025 mmol) was added to a vigorously stirring mixture of dialdehyde **55** (220 mg, 0.5 mmol), C_6H_6 (7.75 mL), and 50% w/w aqueous KOH (0.5 mL) at room temperature. The reaction was monitored by TLC (Al_2O_3; 9:1 mixture of hexane–EtOAc). After about 10 min the mixture was quenched with water (25 mL) and extracted with ether (3 × 15 mL). Drying over K_2CO_3 and evaporation of the solvents gave a residue containing about 57% of the desired products. Chromatography on Al_2O_3 and elution with 93:7 hexane–EtOAc afforded 48 mg (22%) of hydroxydihydropyran **61** as a 2:1 mixture of epimers (extensive decomposition occured upon chromatography). IR: 3585, 1727, 1667 cm^{-1}. ^1H NMR (400 MHz): δ (major isomer) 1.31–1.68 (m, 6), 1.60 (s, 12), 1.68 (s, 6), 1.86–2.18 (m, 17), 4.75 (d, 1, *J* = 6.6), 5.06–5.15 (m, 4), 6.06 (s, 1); δ (minor isomer) 4.98 (d, 1, *J* = 6.7), 6.02 (s, 1). ^{13}C NMR (125 MHz): δ 15.95, 15.96, 16.08, 17.65, 22.35, 23.03, 23.33, 23.42, 25.65, 26.53, 26.63, 26.70, 30.81, 30.93, 30.98, 31.11, 31.76, 32.27, 32.38, 38.16, 39.66, 43.47, 43.51, 46.45, 47.68, 96.55, 96.81, 117.09, 117.64, 123.89, 123.92, 124.29, 124.33, 124.49, 124.75, 131.27, 131.29, 133.88, 134.94, 134.97, 135.05, 135.21, 135.31. Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.50; H, 11.00.

(*E*,*E*)-1,5-Bis(4,8-dimethylnona-3,7-dienyl)-2-(methylphenylamino)-3-oxabicyclo[4.3.0]-4-nonenes (59). A mixture of *N*-methylaniline (32.4 mg, 0.302 mmol), dialdehyde **51** (133 mg, 0.302 mmol), and 3 mg of *p*-toluenesulfonic acid in benzene (3 mL) was refluxed for 35 min in a flask equipped with a Dean–Stark apparatus containing molecular sieves. The solvent was evaporated and the oily residue was chromatographed on Al_2O_3. Elution with a 9:1 mixture of hexane and ether delivered 53 mg (33%) of colorless products. ^1H NMR (CD_2Cl_2): δ (major isomer) 1.39–2.26 (m), 2.70–2.71 (m, 1), 2.96 (s, 3), 5.00–5.18 (m, 5), 6.21 (s, 1), 6.82 (t, 1, *J* = 7.2), 6.95 (d, 2, *J* = 8.0), 7.21–7.26 (m, 2); δ (minor isomer) 2.30–2.33 (m, 1), 3.01 (s, 1), 6.27 (s, 1). ^{13}C NMR (125 MHz, CD_2Cl_2): δ (major isomer) 151.73, 138.94, 135.59, 135.42, 131.63, 131.55, 129.29, 124.73, 124.70, 124.68, 124.50, 119.56, 116.63, 116.02, 90.02, 49.98, 45.70, 40.16, 40.03, 37.08, 35.43, 34.62, 31.26, 30.32, 27.26, 27.05, 26.94, 25.80, 22.89, 22.85, 17.78, 16.27 15.72;

(20) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67.

δ (minor isomer) 152.02, 138.76, 135.57, 135.24, 131.60, 131.58, 125.13, 124.54, 119.28, 116.41, 115.53, 89.12, 47.94, 44.53, 40.09, 35.14, 34.19, 32.29, 31.59, 27.11, 27.08, 25.54, 22.95, 22.54, 17.75, 16.20, 15.96.

(*E*,*E*)-1,5-Bis(4,8-dimethylnona-3,7-dienyl)-2-pyrrolidino-3-oxabicyclo[4.3.0]-4-nonenes (60). A 10-mL round-bottom flask equipped with a Dean–Stark trap and reflux condenser was charged with bisaldehyde **51** (31.2 mg, 0.071 mmol), pyrrolidine hydrochloride (20 mg, 0.186 mmol), and 1 mL of benzene. The solution was treated with 3 drops of triethylamine and heated to reflux for 2 h. After being cooled to room temperature, the solution was diluted with ether and washed with aqueous NH_4Cl. The layers were separated, and the organic phase was washed with brine. The aqueous phases were then back-extracted with two portions of ether, and the combined organic phases were dried over $MgSO_4$. Filtration and concentration provided 33.1 mg of a clear, yellow oil, which ^1H NMR showed to be the desired aminodihydropyrans (0.067 mmol, 94%). An analytical sample was obtained by filtration through a plug of basic alumina in 10:1 hexanes/ethyl acetate. IR (thin film): 3045, 2960, 2925, 2910, 2870, 2845, 1660, 1450, 1440, 1140 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) (signals for the minor isomer are in parentheses): δ 6.17 (6.24) (s, 1), 5.15–5.09 (m, 4), 4.52 (4.23) (s, 1), 2.94–2.87 (m, 4), 2.53 (br d, J = 5.7, 1), 2.15–1.90 (m, 14), 1.69 (s, 6), 1.61 (s, 12), 1.80–1.20 (m, 12). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) 138.89, 135.04, 134.90, 134.59, 131.28, 125.16, 124.91, 124.41, 124.37, 115.48, 90.84, 49.06, 47.98, 44.23, 39.75, 39.71, 37.61, 34.34, 30.61, 30.16, 26.81, 26.76, 26.72, 26.68, 25.69, 24.70, 22.56, 22.47, 17.67, 16.10, 15.84, 15.66; δ (minor isomer) 138.58, 135.02, 124.39, 124.27, 124.25, 92.2, 49.71, 46.60, 43.82, 39.69, 34.65, 31.40, 25.95, 24.66, 22.50. Anal. Calcd for $C_{34}H_{55}NO$: C, 82.70; H, 11.23; N, 2.84. Found: C, 82.88; H, 11.55; N, 2.85.

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Registry No. (±)-**11**, 138409-27-5; **14**, 138409-29-7; **15**, 25662-28-6; **16**, 22339-13-5; (±)-**17**, 138512-25-1; (±)-**18**, 138512-26-2; (±)-**19**, 138512-27-3; (±)-**20**, 138512-28-4; (±)-**21**, 138409-30-0; (±)-**22**, 138513-32-3; (±)-**23**, 138409-31-1; (±)-**24**, 138512-29-5; (±)-**25**, 138409-32-2; (±)-**26**, 138512-30-8; (±)-**27**, 138409-33-3; (±)-**28**, 138512-31-9; (±)-**29**, 138409-34-4; (±)-**30**, 118099-25-5; (±)-**31**, 138409-35-5; (±)-**32**, 138512-32-0; (±)-**34**, 138409-36-6; (±)-**36**, 138512-33-1; (±)-**37**, 138512-34-2; (±)-**38**, 138512-35-3; (±)-**39**, 138512-36-4; (±)-**40**, 138409-37-7; **45**, 131938-67-5; **45** (α-acetyl derivative), 138409-53-7; (±)-**46**, 138409-38-8; (±)-**47**, 138409-39-9; **48**, 131979-62-9; (±)-**49**, 138409-40-2; (±)-**50**, 138409-41-3; (±)-**51**, 138409-42-4; (±)-**52**, 138409-43-5; (±)-**53**, 138409-44-6; (±)-**54**, 138409-45-7; (±)-**55**, 138409-46-8; (±)-**59** (isomer 1), 138409-47-9; (±)-**59** (isomer 2), 138512-37-5; (±)-**60** (isomer 1), 138409-48-0; (±)-**60** (isomer 2), 138512-38-6; (±)-**61** (isomer 1), 138409-49-1; (±)-**61** (isomer 2), 138512-39-7; (±)-**62**, 138409-50-4; S1, 138409-22-0; (±)-S3, 138409-23-1; (±)-S4, 138409-24-2; (±)-S5 (isomer 1), 138409-25-3; (±)-S5 (isomer 2), 138512-22-8; (±)-S6 (isomer 1), 138409-26-4; (±)-S6 (isomer 2), 138512-23-9; S10, 69405-40-9; S11, 138409-51-5; (±)-S12, 138409-28-6; (±)-S13, 138512-24-0; (±)-S14, 138512-40-0; (±)-S14 amino-alcohol, 138409-52-6; (±)-S15, 138513-33-4; (±)-S16, 138513-34-5; (±)-s17, 138512-41-1; (±)-S18, 138512-42-2; *t*-BuO$COCH_3$, 540-88-5; $Br(CH_2)_3CH(OMe)_2$, 24157-02-6; *t*-Bu$OCOCH_2SiMe_3$, 41108-81-0; *N*-acetylpyrrolidine, 4030-18-6.

Supplementary Material Available: Descriptions of the preparation of dialdehydes **33**, **36**, and **37** and a more detailed discussion of the hydrolytic chemistry of aminodihydropyran **60**, including 13 additional experimental procedures, mass spectral data for compounds **14**, **17**, **21**, **25**, **26**, **32**, and **40**, and ^1H NMR spectra of compounds **14**, **17**, **25**, **26**, **27**, **28**, **32**, **39**, **40**, **59**, and **62** (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. 13. Asymmetric Total Synthesis of (−)-Secodaphniphylline[1]

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(−)-Secodaphniphylline (**1**) has been prepared by total synthesis. The early stages of the synthesis were an asymmetric version of the previously published synthesis of methyl homosecodaphniphyllate (**2**). The necessary chirality was secured by an asymmetric Michael addition reaction of the lithium enolate of the C_2-symmetric amide **9** to α,β-unsaturated ester **10** to give ester amide **12**. The conversion of **12** into (−)-**2** was modelled after the previously reported synthesis in the analogous racemic series, although there were quantitative differences in the reaction conditions required for some of the succeeding transformations of the relatively hindered 2,5-dimethylpyrrolidine amides. The (−)-**2** produced in this synthesis was of 84% ee, which represents the enantioselectivity of the initial Michael addition. Recrystallization of this material provided (−)-**2** of 90% ee. The required 2,8-dioxabicyclo[3.2.1]octanecarboxylic acid chloride **5** was assembled in an eight-step synthesis starting with acid **18**. The necessary chirality was acquired by an asymmetric reduction of acetylenic ketone **19** with the $LiAlH_4$–Darvon alcohol complex. Alcohol **20**, of 92% ee, was obtained and was isomerized to isomer **21** without loss of enantiomeric purity. Concomitant hydration of the triple bond, hydrolysis of the ketal, and cyclization of the resulting keto triol provided a 5:1 mixture of alcohols **23** and **24**. After conversion to a similar mixture of methyl esters **25** and **26**, the isomers were separated and the major carboxylic acid **27** was converted into acid chloride **5**. Ester (−)-**2** and acid chloride **5** were joined by a mixed Claisen condensation and the resulting diastereomeric β-keto esters demethylated and decarboxylated by treatment with NaCN in hot DMSO to obtain (−)-secodaphniphylline (**1**). Although the two components in the Claisen reaction were enantiomerically enriched only to a modest extent (90% ee and 92% ee), the product alkaloid was >99% ee.

Secodaphniphylline (**1**) is the parent member of one of the five major structural classes of *Daphniphyllum* alkaloids, a family of secondary metabolites that now has 37 known members.[3] First described in 1969,[4] secodaphni-

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