Daphniphyllum Alkaloids. 14. Total Synthesis of (±)-Bukittinggine[1]

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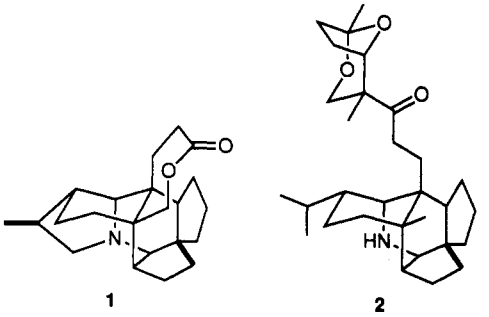
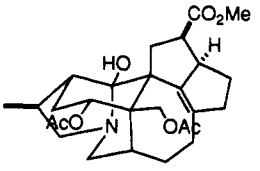
The unique heptacyclic *Daphniphyllum* alkaloid bukittinggine (1) has been prepared by total synthesis. The basic secodaphnane nucleus was fashioned in one step by application of the tetracyclization process to dihydroxy diether **5**. The pyrrolidine ring in **1** was formed by a Pd(II)-catalyzed oxidative cyclization of **19** to give hexacyclic amine **32**. Hydrogenation of **32** proceeded with little diastereoselectivity in establishing the final stereocenter in **1**. However, when **32** was treated to the sequence of hydroboration/oxidation, tosylation, and reduction, excellent control of stereochemistry was observed in the formation of **33**. Debenzylation of **33** (Na–liquid NH_3), followed by regiospecific oxidative lactonization of diol **36** (Fetizon's reagent), afforded (±)-bukittinggine (**1**). The synthesis required 18 steps (**9** → **10** → **11** → **12** → **13** → **14** → **15** → **8** → **16** → **17** → **18** → **5** → **19** → **32** → **35** → **33** → **36** → **1**) and delivered racemic bukittinggine in 3% overall yield.

The heptacyclic alkaloid bukittinggine (**1**) was recently isolated from the leaves and branches of *Sapium baccatum*, collected near the town of Bukittinggi in West Sumatra, Indonesia.[3] The substance has such an obvious relationship to the structurally unique *Daphniphyllum* alkaloids,[4] that it must derive from a very similar biosynthetic pathway, suggesting that *Sapium* and *Daphniphyllum* have similar phylogeny. As the only heptacyclic member of the 37 known *Daphniphyllum* alkaloids, bukittinggine possesses key structural elements of both secodaphniphylline (**2**) and yuzurimine (**3**). The preceding papers in this series described the development of a polycyclization process that is uniquely suited for quick formation of the secodaphniphylline skeleton and the application of this process to the synthesis of the simpler *Daphniphyllum* alkaloids. Because of the uniqueness of its heptacyclic structure and our interest in the synthesis of the more complex members of the *Daphniphyllum* alkaloid family, we initiated a total synthesis of **1**.



1 **2**



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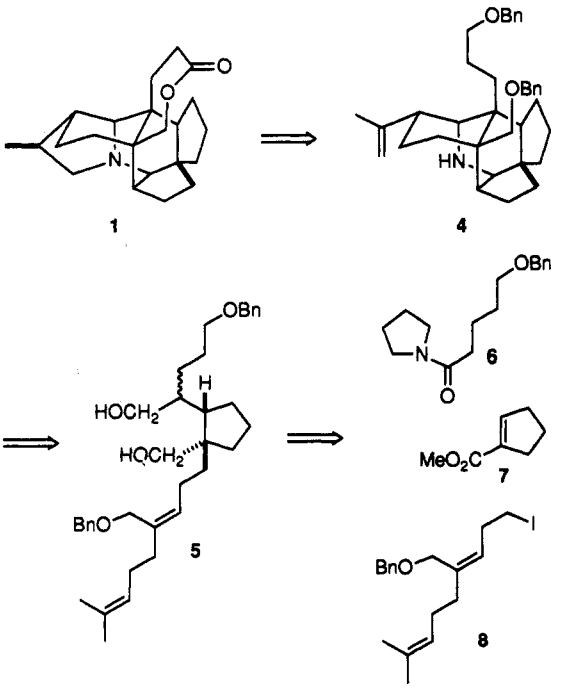
The tetracyclization reaction that forms the pentacyclic secodaphniphylline nucleus in one operation was planned to serve as the cornerstone in the assembly of bukittinggine.[5] The synthesis of **1** then becomes one of solving three problems: (1) incorporation of an additional oxygen atom into the skeleton, (2) formation of the fused pyrrolidine ring with control of stereochemistry at the methyl-bearing carbon, and (3) elaboration of the seven-membered lactone ring. Retrosynthetic analysis of **1** led us, by way of the tetracyclization reaction product **4**, back to dihydroxy diether **5**. The allylic ether in **5** is clearly pivotal to the successful execution of the synthesis. Not only does its role as the "dienophile" component in the tetracyclization reaction raise questions regarding the scope and mechanism of this process but it also becomes part of the seven-membered lactone found in bukittinggine. Finally, borrowing from the original methyl homosecodaphniphyllate synthesis,[5,6] diol **5** can be obtained in three steps from the adduct arising from Michael addition of pyrrolidine **6** to enolate **7**, followed by alkylation of the resulting enolate with the phenylmethoxy-substituted homogeranyl iodide **8**, which then becomes the initial synthetic target.



1 **4** **5** **6** **7** **8**

(1) For part 13, see: Heathcock, C. H.; Stafford, J. A. *J. Org. Chem.*, preceding paper in this issue.

(2) Current address: Glaxo, Inc.; Five Moore Drive; Research Triangle Park, NC 27709.

(3) Arbain, D.; Byrne, L. T.; Cannon, J. R.; Patrick, V. A.; White, A. H. *Aust. J. Chem.* **1990**, *43*, 185.

(4) (a) Yamamura, S.; Hirata, Y. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1975; Vol. 15, p 41. (b) Yamamura, S.; Hirata, Y. *Int. Rev. Sci., Org. Chem., Ser. 2* **1976**, *9*, 161. (c) Yamamura, S. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1986; Vol. 29, p 265.

(5) For an account on the development of the "tetracyclization reaction", see part 11 in this series: Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.*, second paper in the series in this issue.

(6) Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734.

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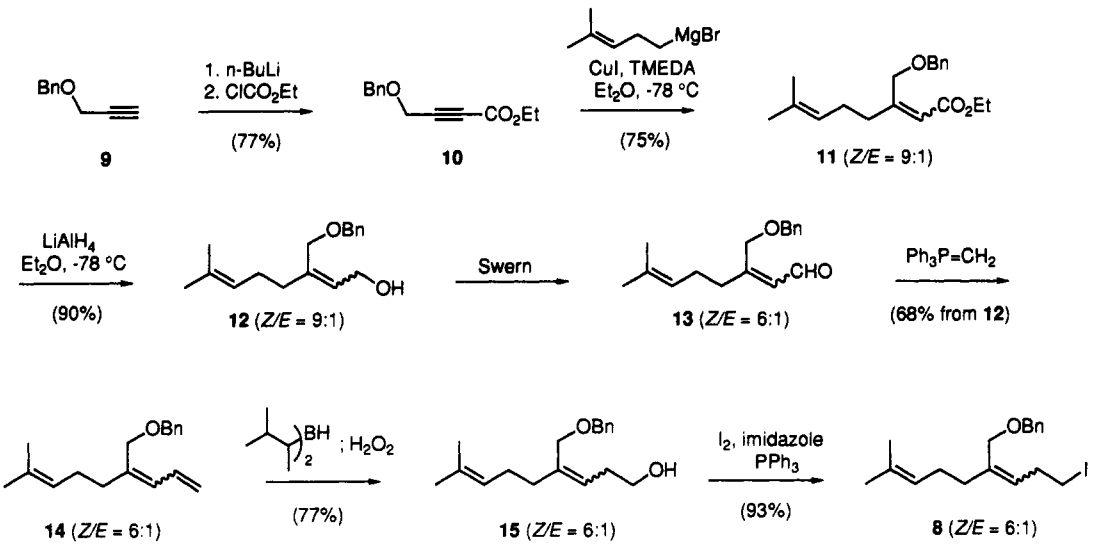
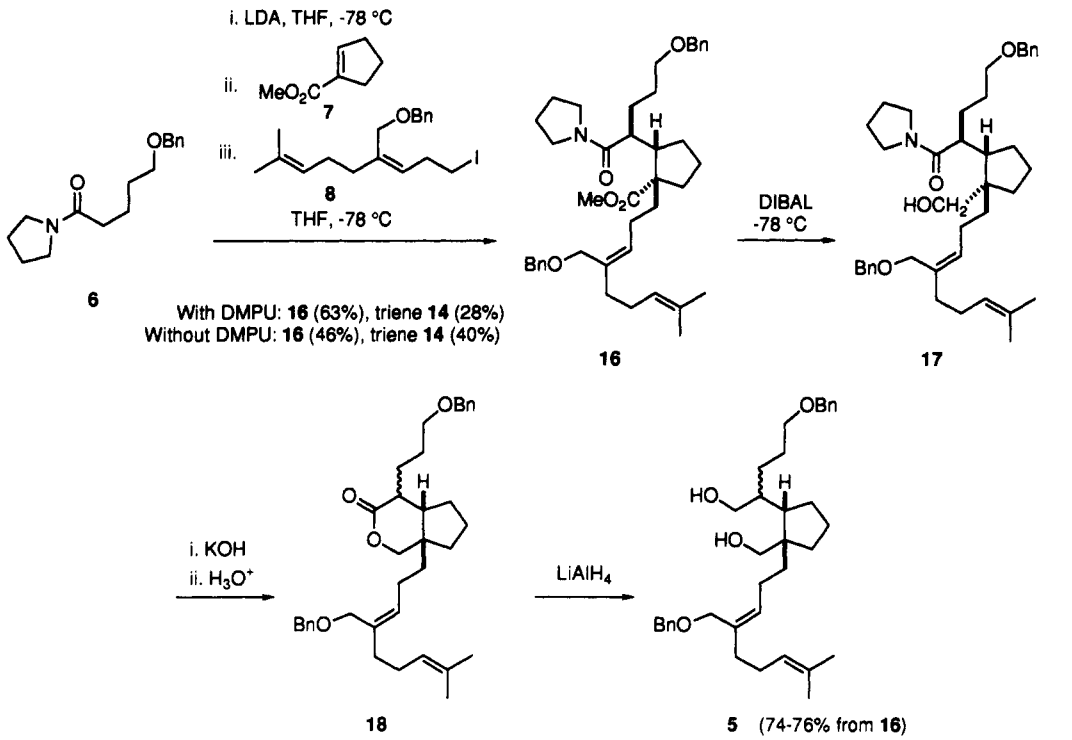
Scheme I



Scheme II



The synthesis of the homogeranyl fragment 8, shown in Scheme I started from 3-(phenylmethoxy)-1-propyne (9). Formation of the lithium acetylide with *n*-butyllithium, followed by treatment with ethyl chloroformate, afforded acetylenic ester 10 in 77% yield. Copper-assisted addition of the Grignard reagent derived from homoprenyl bromide to 10 gave in 75% yield unsaturated ester 11,[7] arising from expected cis addition of the organometallic to the triple bond. Analysis of this product by GC and ^{1}H NMR indicated that the ratio of double bond isomers was 9:1. Reduction of the ester functionality[7b] with $LiAlH_4$ at −78 °C afforded the (benzyloxy)geraniol 12 in 90% yield. With 12 in hand, all that was required to obtain 8 was a one-carbon homologation of the allylic alcohol,[8] followed by conversion to the corresponding iodide. To this end, Swern oxidation of 12 gave geranial 13, which on treatment with methylenetriphenylphosphorane afforded triene 14 in 68% yield for the two steps. ^{1}H and ^{13}C NMR analyses of the intermediate aldehyde indicated that the stereochemistry of the proximal double bond had been compromised to a 6:1 mixture during the course of the Swern oxidation. The geranyl and neryl isomers were homogeneous by TLC and flash chromatography, and the mixture was therefore used as such. Selective hydroboration/oxidation of the terminal double bond in 14 using a 3-fold excess of disiamylborane proceeded without incident to deliver the homogeraniol derivative 15 in 77% yield. Alcohol 15 was then converted into the corresponding iodide 8 by standard methodology.[9]

(7) (a) Anderson, R. J.; Corbin, V. L.; Cotterrell, G.; Cox, G. R.; Henrick, C. A.; Schaub, F.; Siddall, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 1197. (b) Poulter, C. D.; Wiggins, P. L.; Plummer, T. L. *J. Org. Chem.* **1981**, *46*, 1532.

(8) We adapted the homologation sequence that has been described for the conversion of geraniol to homogeraniol: Leopold, E. J. *Org. Synth.* **1985**, *64*, 164.

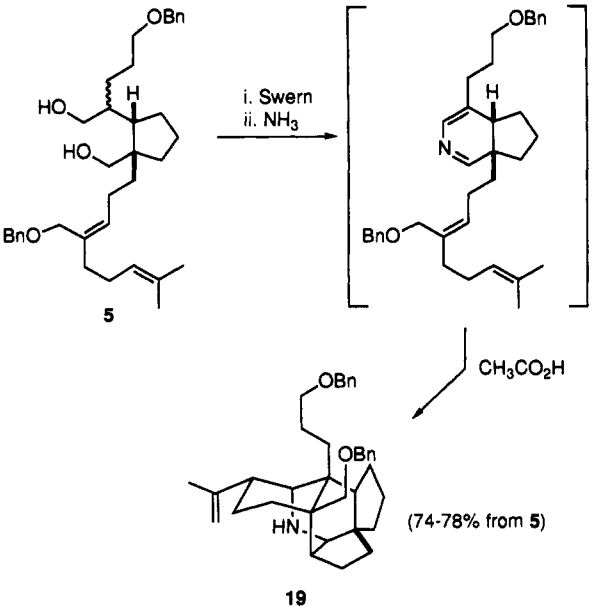
(9) Marshall, J. A.; DeHoff, B. S. *Tetrahedron* **1987**, *43*, 4849.

The Michael addition/alkylation sequence using **8** as the alkylating agent proved to be more difficult than anticipated (Scheme II). Under the standard procedure developed previously,[6b] iodide **8** showed an increased propensity to undergo elimination, giving triene **14** in 40% yield, along with the expected product **16** in 46% yield. The mass recovery from this process was >95% with the only other products being the expected Michael addition/alkylation minor diastereomers and unalkylated Michael adduct stereoisomers. It is possible that the benzyl ether in **8** interferes with the course of alkylation, either by a simple inductive effect that renders the protons next to the iodide more acidic or perhaps by formation of a less reactive aggregate form of the intermediate ester enolate. Nevertheless, we found that addition of *N,N'*-dimethyl-*N,N'*-propyleneurea (DMPU)[10] with the iodide suppressed the elimination pathway and provided greater amounts of alkylated material. Accounting for the modest 6:1 ratio of homogeranyl:homoneryl iodide isomers, the yield of the desired amide ester **16** was 63%.

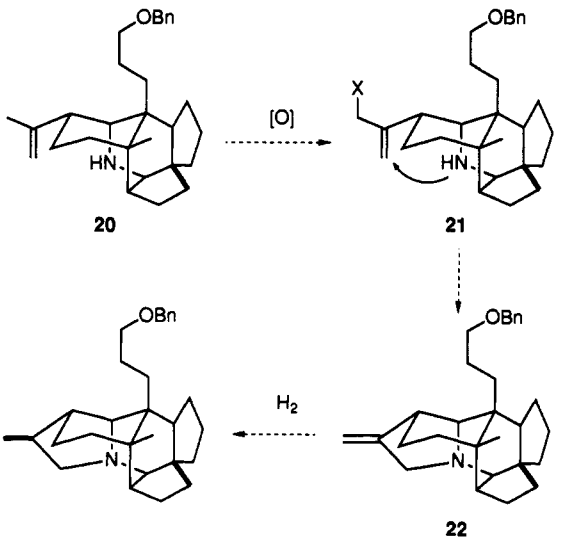
Selective reduction of the ester function with diisobutylaluminum hydride provided hydroxy amide **17**, which was saponified by treatment with alcoholic KOH. Upon acidification, lactone **18** was obtained as a mixture of diastereomers. Reduction of this material with $LiAlH_4$ afforded a diastereomeric mixture of dihydroxy diethers **5**. Each of the intermediates in this three-step sequence can be purified by silica gel chromatography to provide an analytically pure product. However, the overall yield of this process is higher if chromatographic purification is postponed until after the $LiAlH_4$ reduction. In this manner, **5** was routinely obtained from **16** in 74–76% overall yield.

Diol **5** was subjected to the conditions of the tetracyclization process (i, Swern oxidation;[11] ii, NH_3; iii, acetic acid) to obtain pentacyclic unsaturated amine **19** in 74–78% yield. It is of interest that the allylic benzyl ether of diol **5** in no way affected the tetracyclization reaction. It has been suggested by others that the actual mechanism of the tetracyclization reaction involves a series of π-cyclizations onto intermediate immonium ions.[12] Although this constitutes a reasonable mechanism, one might expect that the inductive effect of an allylic ether could decelerate a Mannich-type process, yet we observe no difference in rate or stereoselectivity in the reaction of **5**. From experimental evidence gathered in earlier studies we have suggested that the intramolecular reaction between the internal double bond on the homogeranyl side chain and the 2-aza diene intermediate is a concerted, asynchronous, inverse-electron-demand Diels–Alder reaction and not a polar, Mannich-type process involving discrete cationic intermediates.[13] The facility and stereoselectivity with which the present tetracyclization reaction occurs lends additional support to this hypothesis.

With the (benzyloxy)methyl group in place on the alkaloid nucleus, our first goal in the bukittinggine synthesis was met, and we directed our attention to the second task in the synthesis, formation of the pyrrolidine ring with stereocontrol at the methyl-bearing carbon. For this study



we used as a model compound the simpler and more readily available pentacyclic amine **20**, an intermediate in the earlier (±)-methyl homosecodaphniphyllate synthesis.[5] Our plan was to activate the isopropenyl group in **20** by an allylic oxidation leading to a suitable intermediate (**21**), which could undergo an intramolecular nucleophilic displacement by the secondary amine to close the pyrrolidine ring and form the exocyclic olefin **22**. Molecular models of **22** convinced us that hydrogenation of the exocyclic double bond would come from the α-face, thus establishing the correct relative stereochemistry at the methyl-bearing carbon.

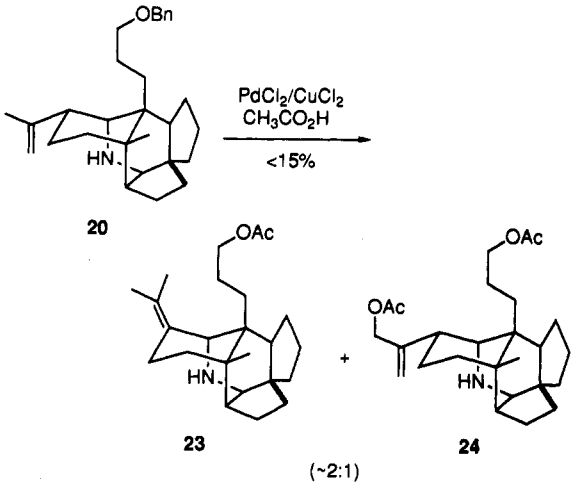


Our first attempt to oxidize the allylic position of the isopropenyl group was encouraging, albeit not totally successful. Treatment of **20** with $PdCl_2$ and $CuCl_2$ in refluxing acetic acid[14] led to a low yield (<15%) of an approximately 2:1 mixture of two compounds, tentatively assigned **23** and **24** on the basis of ^1H NMR analysis.[15] Specifically, the ^1H NMR spectrum of **23** showed one of the bridgehead protons next to nitrogen shifted downfield to 3.8 ppm. A methyl singlet at 2.0 ppm and two-proton

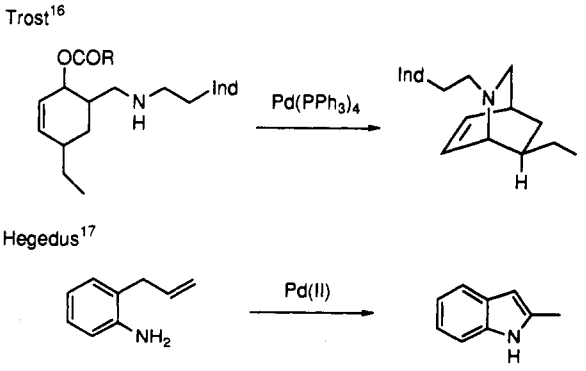
(10) Mukhopadhyay, T.; Seebach, D. *Helv. Chem. Acta* **1982**, *65*, 385.
(11) (a) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329. (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(12) (a) Overman, L. E.; Ricca, D. J. In "Intramolecular Mannich and Related Reactions," *Comprehensive Organic Synthesis*, Vol. 2; Heathcock, C. H., Ed.; Pergamon: Oxford, 1991. (b) Marson, C. M.; Grabowska, U.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J. Org. Chem.* **1991**, *56*, 2603 (ref 14c).
(13) (a) Heathcock, C. H.; Piettre, S.; Kath, J. *Pure Appl. Chem.* **1990**, *62*, 1911. (b) Heathcock, C. H.; Piettre, S.; Ruggeri, R. B.; Ragan, J. A.; Kath, J. C. *J. Org. Chem.*, third paper in the series in this issue.

(14) Horiuchi, C. A.; Satoh, J. Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2595. A milder procedure to effect Pd-catalyzed allylic oxidation has been reported: McMurry, J. E.; Kocovsky, P. *Tetrahedron Lett.* **1984**, *25*, 4187.
(15) The ^1H NMR spectra of **23** and **24** are shown in the supplementary material.

triplet at 3.9 ppm accounted for the acetate, and the presence of methyl resonances at 1.68 and 1.69 ppm, together with the absence of olefinic resonances, suggested as isopropylidene group. The ^{1}H NMR spectrum of **24** showed two singlets at about 2.1 ppm for the acetate methyls and both an AB pattern (4.5 ppm and 4.6 ppm) and singlets at 5.0 and 5.2 ppm, indicative of an allylic acetate and a geminally disubstituted double bond.



The formation of **23** can be accounted for by acid-catalyzed removal of the benzyl ether, Fisher esterification of the alcohol to give an acetate, and an acid-catalyzed isomerization of the disubstituted double bond to the tetrasubstituted double bond. The formation of allylic acetate **24**, however, is more interesting and suggested to us that the Pd(II) in fact reacts with **20** to give an intermediate π-allyl complex that undergoes capture by acetic acid to form **24**. With this in mind we planned to consolidate the Pd-assisted oxidation and subsequent cyclization into one step. By using a nonnucleophilic solvent we anticipated that the π-allyl complex could be directly intercepted by the internal nitrogen nucleophile to give **22** directly. An oxidative ring closure such as this bears a qualitative resemblance to the work of Trost and Hegedus:[16,17]



When **20** was treated with stoichiometric palladium trifluoroacetate in THF,[18] with a small amount of triphenylphosphine added as an external ligand, **22** was obtained in 27% yield. Initial assignment of **22** came from

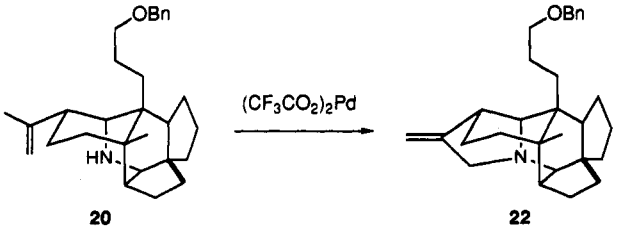
(16) (a) Trost, B. M.; Genet, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 8516. (b) Trost, B. M.; Cossy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6881.
(17) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800.
(18) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572. The $Pd(OCOCF_3)_2$ was purchased from the Aldrich Chemical Co. and used without further purification.

Table I. Optimization of the Pd(II)-Mediated Cyclization of Unsaturated Amine 20

entry	solvent	equiv Pd(II)	additives (equiv)	% yield[a]
1	THF	1.0	PPh_3 (0.2)	27
2	CH_3CN	1.0	PPh_3 (0.2)	31
3	CH_3CN	1.0	PPh_3 (2.0)	32
4	CH_3CN	1.0	PBu_3 (1.5)	0
5	CH_3CN	1.0	PPh_3 (2.0), triethylamine (1.0)	trace
6	CH_3CN	1.0	PPh_3 (1.0)	44
7	CH_3CN	0.15	PPh_3 (0.1), benzoquinone (1.0)	74
8	CH_3CN	0.2	PPh_3 (0.3), benzoquinone (1.0)	69
9	CH_3CN	0.075	PPh_3 (0.05), benzoquinone (1.1)	57
10	CH_3CN	0.1	PPh_3 (0.2), benzoquinone (1.2)	71
11	CH_3CN	0.15	PPh_3 (0.1), benzoquinone (1.1)	70

[a] All yields refer to isolated and purified products.

inspection of its ^{1}H NMR spectrum. An AB pattern with δ = 3.4 and 3.7 is suggestive of a methylene group adjacent to nitrogen. Furthermore, one of the bridgehead methines adjacent to the nitrogen, a singlet at 2.95 ppm in **20**, became a doublet (J = 4.1 Hz) at 3.00 ppm in **22**. The corresponding methine in bukittinggine appears as a doublet (J = 4.0 Hz). Starting material was not recovered from this reaction, and the mass balance was due only to intractable materials. An effort was made to optimize this process, and some of the conditions that were examined are shown in Table I. The best yield for this oxidative cyclization was realized by carrying out the reaction in acetonitrile at room temperature using 15 mol % palladium trifluoroacetate, 1.1 equiv of benzoquinone, and 10 mol % triphenylphosphine. These conditions routinely delivered the desired product in yields ranging from 65 to 74%. It should be noted that the best results were observed with catalytic rather than stoichiometric Pd. When a full equivalent of Pd(II) is used, an equivalent amount of trifluoroacetic acid is produced on formation of the π-allyl complex. The lower yields in these cases may suggest that the basic secondary nitrogen is protonated by the trifluoroacetic acid, thereby making it unavailable as a nucleophile. The use of catalytic amounts of Pd(II) avoids this problem. Furthermore, the quality of the benzoquinone appears to be critically important in this cyclization reaction. We were unable to effect this transformation with unrecrystallized benzoquinone, and even recrystallized benzoquinone appeared to lose its effectiveness after prolonged (>3 months) storage at room temperature. Our best results were obtained when using benzoquinone that was freshly recrystallized from benzene (hot charcoal filtration method) and stored in the refrigerator.



Although the end result of this cyclization appears to be an additional example of the Trost/Hegedus methodology, a distinction deserves to be made. The probable mechanism of the Trost reaction begins with formation of a π-allyl complex by treatment of the allylic acetate with Pd(0), followed by capture of the π-allyl intermediate with the internal nitrogen nucleophile. On the other hand, the accepted mechanism of the Hegedus reaction does not involve nucleophilic addition to a π-allyl complex but rather to a simple olefin–Pd complex, formed by reaction

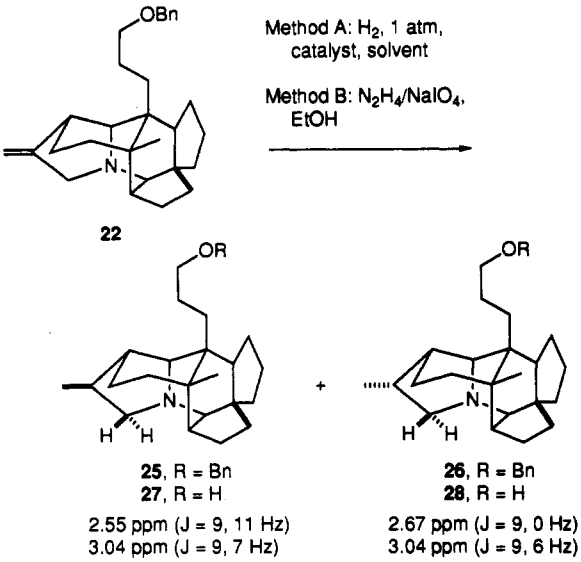
of the olefin with a Pd(II) salt. In this regard, the Hegedus indole synthesis is mechanistically related to a Wacker oxidation. Hegedus and co-workers have pointed out, however, that nonaromatic, aliphatic nitrogens fail to undergo this reaction, presumably because the nitrogen atom binds too tightly to the palladium, thereby eliminating its effectiveness as a nucleophile. It is a consequence of the mild basicity of the aniline nitrogen that allows this process to be successful.

When a simple olefin reacts with Pd(II) one of two scenarios can occur: (a) formation of a π-allyl complex, rendering the olefin electrophilic at the two allyl termini; (b) formation of an olefin–Pd complex, rendering the olefin electrophilic at the carbons of the double bond. The confusion surrounding this duality of mechanisms when using Pd(II) salts was removed when Trost and Metzner found that palladium trifluoroacetate reacts rapidly and quantitatively with simple, isolated olefins to form π-allyl complexes.[18] In the cyclization of **20** to **22** the formation of a π-allyl complex from the reaction of **20** with palladium trifluoroacetate is followed by nucleophilic addition of the internal nitrogen to one of the allylic termini. This is a rare example of successful amination of a π-allyl complex formed from the reaction of an olefin with catalytic Pd(II).[19] Since Hegedus and co-workers have found that nonaromatic nitrogens normally do not aminate olefins under catalytic Pd(II) conditions, we think that the successful conversion of **20** to **22** is due both to the hindered nature of the secondary amine nitrogen, which prevents its coordination with Pd(II), and to the superiority of palladium trifluoroacetate for the formation of π-allyl complexes with isolated double bonds.

When exocyclic olefin **22** was hydrogenated at 1 atm over 10% Pd–C in ethyl acetate–ethanol, we were surprised to obtain a 1:1 mixture of diastereomers **25** and **26** (R = Bn), epimeric at the methyl-bearing carbon. The assignment of diastereomer stereochemistry was straightforward. In bukittinggine both of the methylene protons on the five-membered ring and adjacent to the nitrogen appear as doublets of doublets, having chemical shifts of 2.55 and 3.03 ppm, respectively. In addition there is a methyl doublet at 0.96 ppm. Nearly identical resonances were found in one of the diastereomeric hydrogenation products, while the other diastereomer had slightly different chemical shifts and coupling data. The eventual synthesis of bukittinggine showed the stereochemical assignment to be correct.

Some attempts to improve this hydrogenation ratio by varying the catalyst and solvent are summarized in Table 2, which is contained in the supplementary material. Different hydrogenation conditions did result in different diastereomer ratios. The best results were obtained with 10% Pd–C in acetic acid with a small amount of concentrated HCl. Under these conditions we obtained acetylated derivatives (R = Ac) resulting from reductive debenzylation followed by Fisher esterification; the diastereomer ratio was 3:1. Omission of the HCl resulted in a slightly lower diastereomer ratio (2:1) of alcohols **27** and **28** (R = H). Homogeneous reduction with $(Ph_3P)_3RhCl$ (Wilkinson's catalyst), known for its sensitivity to steric effects,[20] afforded a disappointing 1:1 ratio of diastereomers.

Because catalytic hydrogenation gave poor stereoselectivity, we investigated diimide as a reducing agent. Best



results were obtained by slight modification of Schlessinger's procedure, which generates diimide by oxidation of hydrazine with sodium periodate.[21] Using this procedure we consistently obtained the reduced material **25** and **26** in an approximately 4:1 ratio. Although this ratio of isomers was greater than any obtained by catalytic hydrogenation, diethers **25** and **26** were quite difficult to separate, so we continued our search for a more selective reduction protocol.

When **22** was hydroborated with 2 equiv of BH_3·THF (presumably 1 equiv of BH_3 is consumed by formation of the amine borane), followed by oxidation and workup, primary alcohol **29** was obtained. The ^1H NMR spectrum of the crude reaction product revealed that the reaction proceeded with excellent diastereoselectivity. Proton resonances arising from the minor diastereomer were not discernible. An attempt was made to effect protonolysis of the intermediate organoborane **30** by treatment with propionic acid at 150 °C;[22] however, only uncharacterized material was obtained upon workup. Although it is known that protonolysis of σ-bonded organozirconium compounds can be effected with dilute acid,[23] conditions that are considerably less destructive than those required for protonolysis of their organoboron counterparts, we were unable to hydrozirconate **22** by treatment with Cp_2ZrHCl in benzene.[23]

Molecular models of **22** clearly suggest that the favorable approach of a reagent should be from the α-face if the reaction is governed exclusively by steric effects (Figure 1). Therefore, the preferential formation of isomer **25** by diimide reduction and of **29** by hydroboration is expected. However, it is puzzling that catalytic hydrogenation of **22** gives so much **26** and **28**. The mechanism of hydrogenation using Pd/C is uncertain but is generally believed to be a stepwise process[24] and the mechanism of reduction using Wilkinson's catalyst is better understood, with strong evidence pointing to a stepwise process involving σ-bonded Rh–C species.[25] There are numerous reports in the literature that show stereoselectivity in catalytic hydrogen-

(19) For reviews on organopalladium chemistry, see: (a) Huttel, R. *Synthesis* **1970**, 225. (b) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. (c) Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415.

(20) (a) Brown, M.; Piszkiewicz, L. W. *J. Org. Chem.* **1967**, *32*, 2013. (b) Djerassi, C.; Gutzwiller, J. *J. Am. Chem. Soc.* **1966**, *88*, 4537.

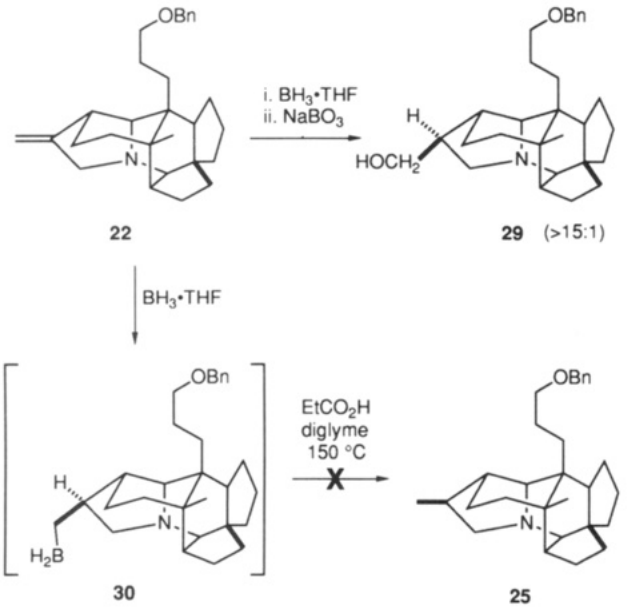
(21) Hoffman, J. M.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1971**, 1245.

(22) Brown, H. C.; Murray, K. *J. Am. Chem. Soc.* **1959**, *81*, 4108.

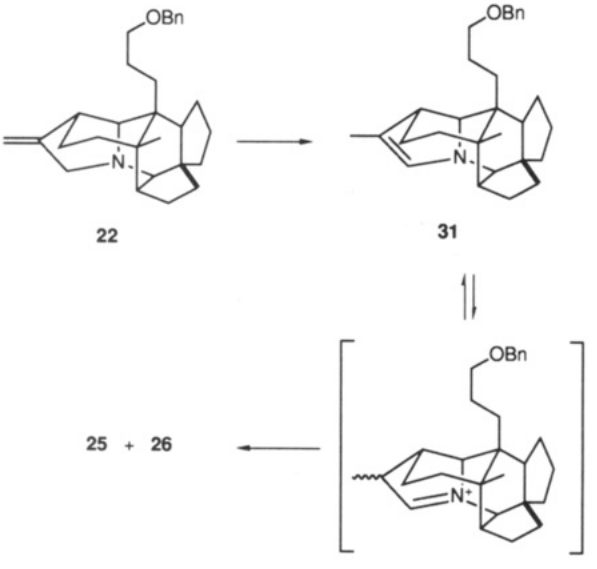
(23) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.

(24) For a brief discussion and leading references on the mechanism of catalytic hydrogenation, see: House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin/Cummings: Menlo Park, 1972; pp 19–23.

(25) (a) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711. (b) Jardine, F. H.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. A* **1967**, 1574.



ation being influenced by the choice of catalyst, solvent, pressure, and/or the amount of catalyst.[26] The varying selectivity that we observe in the hydrogenation of **22**, either by homogeneous or heterogeneous catalysis, might be due to rapid double-bond isomerization to the endocyclic isomer **31**. Since this isomer is an enamine, there could be some unusual process at work. One possibility is that the hypothetical isomerization product undergoes protonation by solvent to an immonium ion, which undergoes hydrogenation. In this scenario, the stereochemistry at the methyl-bearing stereocenter might even be established on thermodynamic grounds, if the enamine–immonium ion equilibrium is rapid.



With these model studies behind us, we turned our attention back to the bukittinggine synthesis. Using the Pd-catalyzed cyclization procedure developed with **20**, reaction with pentacyclic amine **19** afforded amine **32** in 70% yield. As in the model study, diimide reduction of **32** delivered a 4:1 mixture of saturated amines **33** and **34** in 87% yield. Chromatographic separation of this mixture proved to be difficult, and the cost of recovering pure **33** was a large sacrifice of material to mixed fractions off the

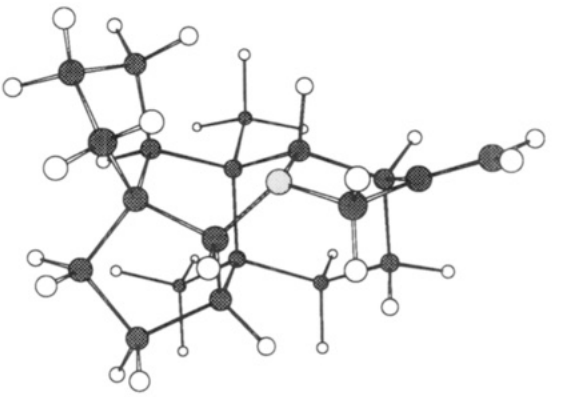
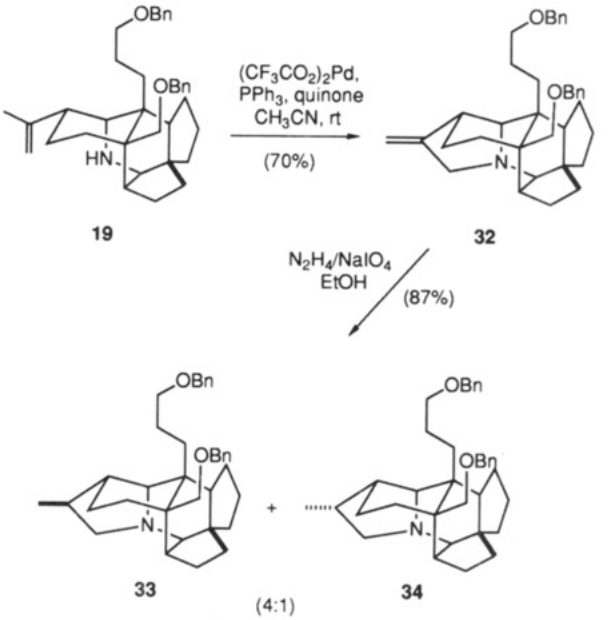


Figure 1. Molecular model of an analogue of unsaturated amine **22** with the (benzyloxy)propyl group replaced by methyl for clarity.

column. The modest selectivity of the diimide reduction limited the amount of diastereomerically pure **33** available to complete the synthesis, and we were again forced to an alternative method of reducing the double bond in **32**.



Since the hydroboration/oxidation of model compound **22** gave almost exclusively alcohol **29**, we decided to use this method for the conversion of **32** to **33**. To this end, **32** was treated with two equivalents of BH_3·THF; oxidation of the intermediate organoborane with sodium perborate[27] provided alcohol **35** (Scheme III). The mass recovery of **35** was quantitative, and the material was deemed sufficiently pure by ^1H NMR spectroscopy (>95%) to carry on without purification. The primary alcohol was treated with *p*-toluenesulfonyl chloride in pyridine–$CHCl_3$ to provide an intermediate tosylate, which was treated directly with lithium triethylborohydride[28] to provide a mixture of **33** and the corresponding α-methyl isomer **34**. The ratio of isomers was determined by ^1H NMR spectroscopy to be >15:1, reflecting the selectivity of the hydroboration/oxidation reaction of **32**.

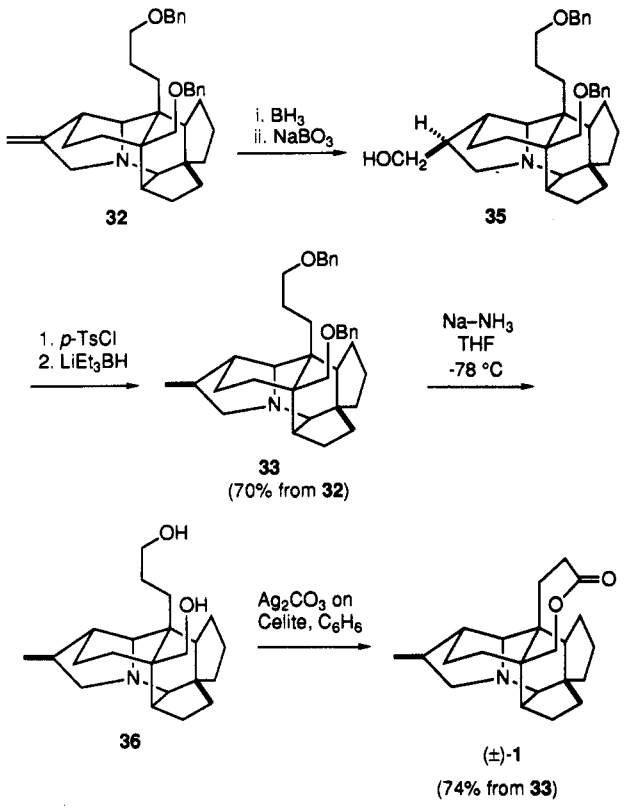
Completion of the bukittinggine synthesis required removal of the two benzyl-protecting groups from **33** and formation of the seven-membered lactone ring. Removal of the benzyl groups was straightforward; treatment of **33**

(26) Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967; pp 89–107.

(27) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.

(28) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064.

Scheme III



with Na in ammonia[29] at −78 °C for a brief period led to the amino diol **36** as a white solid. The crude NMR of the reaction product indicated the presence of 1,2-diphenylethane as a byproduct contaminant, which was, however, conveniently removed by sublimation under high vacuum. Oxidation of **36** with Ag_2CO_3–Celite (Fetizon's reagent)[30] gave (±)-bukittinggine (**1**); the other possible lactone was not detected in the crude ^1H NMR spectrum. The selectivity observed in this oxidation undoubtedly results from a subtle steric difference between the two hydroxyl groups. One of the hydroxyl groups is neopentyl and therefore less accessible to the solid-supported oxidant. After chromatography, bukittinggine was obtained in 52% overall yield for the five steps from hexacyclic amine **32**. The (±)-bukittinggine so obtained was identical (^1H NMR, ^{13}C NMR, IR, TLC) with a natural sample provided by Dr. Dayar Arbain (Universitas Andalas, Indonesia).

Experimental Section

General. All starting materials were obtained from commercial suppliers and used without purification. THF and ether were distilled from potassium immediately prior to use. Triethylamine (Et_3N), *N,N,N′,N′*-tetramethylenediamine, and CH_2Cl_2 were distilled from CaH_2 prior to use. All reactions involving oxygen- or moisture-sensitive compounds were performed under a dry N_2 atmosphere. When reactions were worked-up by extraction with ether or CH_2Cl_2, organic solutions were dried with $MgSO_4$ or K_2CO_3 (amine products) and concentrated with a rotary evaporator. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$. *J* values are in hertz. IR spectra were measured as thin films on NaCl plates unless otherwise indicated. Mass spectra (MS) were determined using the electron-impact method; data are reported as *m/z* (relative intensity).

Ethyl 4-(Phenylmethoxy)-2-butynoate (10). To 3-(phenylmethoxy)-1-propyne (**9**) (1.00 g, 6.58 mmol) in THF (15 mL), cooled to −70 °C, was added a 1.58 M solution of *n*-butyllithium in hexanes (4.8 mL, 7.58 mmol, 1.1 equiv) dropwise over 3 min. The resulting solution was allowed to stir for 2 h while being slowly warmed to 5 °C. The solution was cooled to −70 °C and ethyl chloroformate (0.80 mL, 8.37 mmol) was added in one portion. The resulting solution was allowed to stir for 110 min while being slowly warmed to 5 °C and quenched by addition of saturated aqueous NH_4Cl (15 mL). The aqueous layer was extracted with ether (2 × 15 mL). The combined organic solutions were dried and concentrated. The resulting oil was purified by chromatography (9:1 hexanes–ethyl acetate) to give 1.15 g (77%) of **10** as a colorless oil. IR: 3000, 2240, 1700 cm^{-1}. TLC: R_f 0.33 (10:1 hexanes–ethyl acetate). ^1H NMR (400 MHz): δ 7.35–7.33 (m, 5), 4.59 (s, 2), 4.26 (s, 2), 4.23 (q, 2, *J* = 7.1), 1.30 (t, 3, *J* = 7.1). ^{13}C NMR (100 MHz): δ 13.79, 56.55, 61.95, 71.84, 77.32, 82.97, 127.90, 127.94, 127.99, 128.23, 128.32, 136.58, 152.93. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.31; H, 6.66.

Ethyl (*Z*)-7-Methyl-3-[(phenylmethoxy)methyl]octa-2,6-dienoate (11). To 600 mg (24.7 mmol) of magnesium turnings in 5 mL of ether was added 0.5 mL of a solution of homoprenyl bromide (4.23 g, 25.9 mmol) in ether (20 mL). The mixture was briefly heated with a heat gun to initiate reaction and the remainder of the homoprenyl bromide solution was added dropwise over 20 min at a rate sufficient to maintain reflux without external heating. The resulting solution was allowed to stir at room temperature for 70 min and placed into a refrigerator at 0 °C overnight.

To CuI (2.05 g, 10.76 mmol) in ether (35 mL) was added TMEDA (2.40 mL, 15.9 mmol). The mixture was cooled to −78 °C and homoprenyl magnesium bromide (10.00 mL of the above prepared solution) was added dropwise over 10 min. The resulting orange solution was allowed to stir for 2.5 h at −78 °C at which time a solution of ester **10** (1.21 g, 5.57 mmol) in ether (3 mL, 1-mL rinse) was added dropwise over 10 min. This mixture was stirred for 3.5 h at −78 °C prior to quenching at this temperature with MeOH (2 mL). After being warmed to room temperature, the mixture was poured onto 9:1 saturated NH_4Cl–saturated NH_4OH (150 mL). The aqueous phase was extracted with ether (3 × 30 mL). The combined organic layers were washed with 9:1 saturated NH_4Cl–saturated NH_4OH (3 × 50 mL) and brine (50 mL), dried, and concentrated to give a yellow oil. Silica gel chromatography (9:1 hexanes–ethyl acetate) provided 1.28 g (75%) of **11**, homogeneous by TLC. GC analysis showed that this material was a 9:1 mixture of *Z* and *E* stereoisomers.[31] IR: 1725, 1650, 750, 700 cm^{-1}. ^1H NMR (400 MHz): δ 1.25 (t, 3, *J* = 7.1), 1.57 (s, 3), 1.67 (s, 3), 2.18 (q, 2, *J* = 7.5), 2.36 (t, 2, *J* = 7.6), 4.12 (q, 2, *J* = 7.1), 4.51 (s, 2), 4.67 (s, 2), 5.10 (t, 1, *J* = 1.33), 5.74 (s, 1), 7.30–7.33 (m, 5). ^{13}C NMR (100 MHz): δ 14.14, 17.54, 25.51, 26.43, 34.86, 59.68, 68.14, 72.75, 116.70, 123.51, 127.44, 127.54, 127.61, 128.20, 128.31, 132.21, 138.22, 159.77, 165.96. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.49; H, 8.57.

(*Z*)-7-Methyl-3-[(phenylmethoxy)methyl]octa-2,6-dien-1-ol (12). To $LiAlH_4$ (65 mg, 1.71 mmol), in ether (2 mL), cooled to −78 °C, was added a solution of ester **11** (340 mg, 1.13 mmol) in ether (2 mL, 2-mL rinse) dropwise over 10 min. The resulting grey suspension was allowed to warm to room temperature over 5 h. At this time, the reaction was quenched by sequential and cautious addition of H_2O (100 μL), 15% NaOH (100 μL), and H_2O (300 μL). After being stirred over $MgSO_4$ (2 scoops) for 30 min, the mixture was filtered and concentrated to give an oil, which upon purification by silica gel chromatography (3:1, 1:1 hexanes–ethyl acetate) provided 263 mg (90%) of alcohol **12** as a colorless oil. The ^1H NMR spectrum indicated that **12** was a 9:1 mixture of *Z* and *E* diastereomers. IR: 3360, 2900, 1075, 1000 cm^{-1}. ^1H NMR (400 MHz): δ 1.58 (s, 3), 1.68 (s, 3), 1.93 (b, 1), 2.09–2.17 (m, 4), 4.02 (s, 2), 4.13 (t, 2, *J* = 5.7), 4.49 (s, 2), 5.10–5.11 (m, 1), 5.66 (t, 1, *J* = 6.9), 7.25–7.35 (m, 5). ^{13}C NMR (100 MHz):

(29) (a) Reist, E. J.; Bartuska, V. J.; Goodman, L. *J. Org. Chem.* **1964**, *29*, 3725. (b) Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2776.

(30) (a) Fetizon, M.; Golfier, M.; Louis, J.-M. *J. Chem. Soc., Chem. Commun.* **1969**, 1118. (b) Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, 171. (c) A convenient procedure that we used to prepare the oxidizing reagent can be found in the following review: McKillop, A.; Young, D. W. *Synthesis* **1979**, 401.

(31) The data given are for the major stereoisomer.

δ 17.67, 25.63, 26.58, 35.80, 58.75, 67.74, 72.45, 123.67, 127.79, 128.12, 128.33, 128.40, 131.85, 137.91, 139.89. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.10; H, 9.21.

(*Z*)-7-Methyl-3-[(phenylmethoxy)methyl]-2,6-octadienal (13). To a stirring solution of oxalyl chloride (0.76 mL, 8.75 mmol) in CH_2Cl_2 (30 mL) cooled to −78 °C was slowly added a solution of DMSO (1.3 mL, 18.2 mmol) in CH_2Cl_2 (1.0 mL). The resulting solution was stirred for 10 min and treated with a solution of **12** (1.75 g, 6.73 mmol) in CH_2Cl_2 (5 mL). After stirring at −78 °C for 25 min, triethylamine (5 mL) was added dropwise. After an additional 25 min at −78 °C, the dry ice/acetone bath was replaced with an ice water bath, and the reaction mixture was stirred at 0 °C for 20 min. The mixture was transferred to a separatory funnel containing 25 mL of brine–H_2O (1:1). The layers were separated, and the organic layer was washed successively with 1% HCl (20 mL), saturated $NaHCO_3$ (2 × 20 mL), and brine (20 mL). The organic layer was dried, filtered, and concentrated to afford a yellow oil. Silica gel chromatography (9:1 hexanes–ethyl acetate) yielded 1.43 g (82%) of **13** as a yellow oil, shown by its ^1H NMR spectrum to be a 6:1 mixture of *Z* and *E* diasteromers. IR: 1670, 1100, 740, 700 cm^{-1}. ^1H NMR (400 MHz): δ 1.58 (s, 3), 1.67 (s, 3), 2.19 (m, 2), 2.34 (m, 2), 4.42 (s, 2), 4.55 (s, 2), 5.05–5.09 (m, 1), 5.95 (dt, 1, *J* = 7.7, 1.0), 7.29–7.37 (m, 5), 10.04 (d, 1, *J* = 7.7). ^{13}C NMR (100 MHz): δ 17.64, 25.57, 25.99, 35.75, 67.74, 72.86, 122.55, 127.72, 127.91, 128.47, 128.86, 132.87, 137.29, 161.37, 191.07. Although judged to be pure by ^1H NMR, ^{13}C NMR, and TLC, satisfactory combustion analysis data could not be obtained for aldehyde **13**.

(*Z*)-8-Methyl-4-[(phenylmethoxy)methyl]-1,3,7-nonatriene (14). A stirring suspension of methyltriphenylphosphonium bromide (2.66 g, 7.45 mmol) in THF (15 mL) was cooled to 0 °C and treated dropwise with phenyllithium (4.5 mL of a 7:3 mixture of 1.7 M solution in cyclohexane and ether, 7.58 mmol). The cold bath was removed and the orange-brown solution was stirred at room temperature for 50 min. This ylide solution was cooled to 0 °C and treated dropwise with a solution of aldehyde **13** (1.43 g, 5.54 mmol) in THF (4 mL). The cold bath was removed and stirring was continued at room temperature for 4 h, at which time the reaction was quenched by addition of methanol (1.0 mL). Removal of most of the solvent left an orange slurry, which was triturated with hexanes (20 mL). The solids were allowed to settle and the hexanes were carefully pipeted from the residue into another round-bottomed flask. This extraction procedure was repeated with hexanes (4 × 20 mL). The combined hexanes extracts were concentrated to a solid–oil residue. Kugelrohr distillation (0.05 Torr) of this residue afforded 1.18 g (68% from **12**) of **14** as a nearly colorless oil. IR: 3420, 1070, 740, 700 cm^{-1}. ^1H NMR (500 MHz): δ 1.60 (s, 3), 1.68 (s, 3), 2.13–2.21 (m, 2), 2.22–2.27 (m, 2), 4.14 (s, 2), 4.47 (s, 2), 5.06 (dd, 1, *J* = 10.2, 1.7), 5.12 (m, 1), 5.19 (dd, 1, *J* = 16.7, 1.5), 6.06 (d, 1, *J* = 11.0), 6.61 (dt, 1, *J* = 16.7, 10.4), 7.25–7.35 (m, 5). ^{13}C NMR (125 MHz): δ 17.65, 25.64, 26.67, 35.41, 67.17, 71.84, 117.01, 123.88, 127.51, 127.73, 128.28, 129.41, 131.70, 132.20, 138.32, 138.80. Anal. Calcd for $C_{18}H_{24}O$: C, 84.31; H, 9.44. Found: C, 84.53; H, 9.28.

(*Z*)-8-Methyl-4-[(phenylmethoxy)methyl]-3,7-nonadien-1-ol (15). A 1 M solution of BH_3·THF (14.6 mL, 14.6 mmol) in a pear-shaped flask was cooled to −15 °C (ice–acetone bath), and 2-methyl-2-butene (3.43 mL, 2.2 equiv, 32.3 mmol, dried over K_2CO_3 prior to use) was added rapidly. The resulting solution was warmed to 0 °C with an ice–water bath and allowed to stand at that temperature for 2 h. After this time the resulting chilled solution of disiamylborane was slowly cannulated into a cooled (0 °C) and stirring solution of triene **14** (1.07 g, 4.18 mmol) in THF (1.7 mL). Upon completion of addition the resulting solution was stirred for 16 h, gradually warming to room temperature. Ethanol (1.5 mL) was added, the solution was cooled to 0 °C, and 3 N NaOH (4.4 mL) was added rapidly. To this resulting solution was slowly cannulated a chilled (0 °C) solution of 30% H_2O_2 (4.4 mL). The cold bath was removed, and the mixture was stirred at room temperature for 4 h. The mixture was transferred to a separatory funnel containing ether and brine. The layers were separated, and the ether layer was dried, filtered, and concentrated to a colorless oil. Silica gel chromatography (4:1 hexanes–ethyl acetate) afforded 883 mg (77%) of **15** as a colorless oil. IR: 3400, 3020, 750, 700 cm^{-1}. ^1H NMR (500 MHz): δ 1.58 (s, 3), 1.68 (s, 3), 2.08–2.12 (m, 2), 2.15–2.18 (m, 2), 2.29–2.33 (m, 2), 3.59 (t, 2, *J* = 6.1), 3.99 (s, 2), 4.49 (s, 2), 5.08 (t, 1, *J* = 1.27), 5.41 (t, 1, *J* = 7.8), 7.25–7.36 (m, 5). ^{13}C NMR (125 MHz): δ 17.65, 25.63, 26.73, 31.19, 36.02, 61.76, 67.16, 72.41, 124.00, 125.75, 127.63, 127.70, 127.82, 128.34, 131.72, 138.07, 139.19, 156.41. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.78; H, 9.55. Found: C, 78.54; H, 9.26.

(*Z*)-1-Iodo-8-methyl-4-[(phenylmethoxy)methyl]-3,7-nonadiene (8). In a 25-mL round-bottomed flask was placed alcohol **15** (873 mg, 3.19 mmol), followed by triphenylphosphine (937 mg, 3.60 mmol) and imidazole (277 mg, 4.1 mmol). The flask was flushed with N_2, and CH_3CN (1.6 mL) and THF (4.8 mL) were added. The resulting solution was cooled to −10 °C (ice/acetone bath), and to this stirring solution was added I_2 (1.10 g, 4.30 mmol) in one portion. Stirring was continued at −15 °C for 2 h, at which time 2 mL of saturated $Na_2S_2O_3$ was added, and the mixture was stirred an additional 5 min. The mixture was transferred to a separatory funnel containing ether and H_2O. The layers were separated, and the aqueous layer was extracted three times with ether. The combined ether extracts were washed 1:1 brine–saturated $Na_2S_2O_3$, dried, filtered, and concentrated to a solid. The solid was triturated with 10 mL of hexanes and the supernatant solution was drawn off the remaining white solid with a pipet and placed in a round-bottomed flask. This procedure was repeated three times to wash the triphenylphosphine oxide. The combined hexanes were concentrated to a pale oil. Silica gel chromatography (5% ethyl acetate–hexanes) of this oil afforded 1.14 g (93%) of **8**. IR: 2920, 1070, 750, 710 cm^{-1}. ^1H NMR (400 MHz): δ 1.59 (s, 3), 1.68 (s, 3), 2.13 (m, 4), 2.62 (m, 2), 3.12 (m, 2), 3.99 (s, 2), 4.47 (s, 2), 5.11 (m, 1), 5.34 (t, 1, *J* = 7.3), 7.27–7.35 (m, 5). ^{13}C NMR (100 MHz): δ 5.68 , 17.72, 25.69, 26.59, 31.85, 35.41, 67.25, 72.18, 123.96, 127.59, 127.72, 128.31, 128.36, 131.64, 138.27, 138.66. Anal. Calcd for $C_{18}H_{25}IO$: C, 56.24; H, 6.56. Found: C, 56.35; H, 6.58.

Methyl [1α,1(*Z*),2α(*S)]-(±)-1-[8-Methyl-4-[(phenylmethoxy)methyl]-3,7-nonadienyl]-2-[4-(phenylmethoxy)-1-(1-pyrrolidinylcarbonyl)butyl]cyclopentanecarboxylate (16).** To a stirring solution of freshly distilled diisopropylamine (0.30 mL, 2.14 mmol) in THF (1.4 mL) cooled to 0 °C was added *n*-butyllithium (0.94 mL of 2.06 M solution in hexanes, 1.95 mmol). The solution was stirred at 0 °C for 10 min and cooled to −78 °C over 10 min. To this solution was added a solution of amide **6** (508 mg, 1.95 mmol) in THF (1.4 mL). After stirring for 45 min, a solution of enoate **7** (245 mg, 1.95 mmol) in THF (10 mL) was added. Stirring was continued at −78 °C for 15 min, and a solution of iodide **8** (623 mg, 1.62 mmol) in *N,N'*-dimethyl-*N,N'*-propyleneurea (DMPU) (0.7 mL) was added. The resulting yellow solution was stirred at −78 °C for 1.5 h and warmed to −15 °C (ice/acetone bath). This solution was allowed to warm to room temperature gradually over 12 h. The mixture was partitioned in a separatory funnel between ether and saturated $Na_2S_2O_3$. The layers were separated, and the aqueous layer was three times extracted with ether. The combined ether extracts were dried, filtered, and concentrated to afford 1.40 g of a yellow oil. Chromatography on silica gel (gradient elution: 15% ethyl acetate–hexanes, 30% ethyl acetate–hexanes, 50% ethyl acetate–hexanes) led to, in order of elution: triene **14** (118 mg, 28%), amide ester **16** (560 mg, 63%), other Michael addition/alkylation stereoisomers (137 mg, 13%), and unalkylated Michael addition stereoisomers (152 mg, 20%). Data for **16**. IR: 1730, 1645, 1100 cm^{-1}. ^1H NMR (400 MHz): δ 1.22–1.27 (m, 1), 1.40–2.24 (m, 18), 1.58 (s, 3), 1.67 (s, 3), 2.09 (bs, 4), 2.56–2.60 (m, 1), 3.32–3.68 (m, 6), 3.61 (s, 3), 3.98 (d, 2, *J* = 1.3), 4.43 (s, 2), 4.46 (s, 2), 5.09 (bs, 1), 5.33 (t, 1, *J* = 7), 7.12–7.33 (m, 10). ^{13}C NMR (100 MHz): δ 17.59, 21.48, 24.17, 24.45, 25.58, 26.03, 26.76, 27.42, 27.99, 28.12, 34.35, 35.15, 38.00, 43.14, 45.64, 46.19, 51.30, 51.98, 56.43, 66.99, 70.42, 71.71, 72.84, 124.18, 127.34, 127.39, 127.57, 127.61, 128.19, 128.22, 129.17, 131.27, 135.64, 138.38, 138.50, 173.71, 176.58. Anal. Calcd for $C_{41}H_{57}NO_5$: C, 76.40; H, 8.93; N, 2.18. Found: C, 76.22; H, 8.91; N, 2.03.

[1α,1(*Z*),2α(*S)]-(±)-1-[8-Methyl-4-[(phenylmethoxy)methyl]-3,7-nonadienyl]-2-[4-(phenylmethoxy)-1-(1-pyrrolidinylcarbonyl)butyl]cyclopentanemethanol (17).** To a solution of **16** (1.11 g, 1.73 mmol) in toluene (4 mL) cooled to −78 °C was added dropwise DIBAL (4.6 mL of a 1.5 M solution in toluene, 6.90 mmol). The resulting solution was stirred for 3.5 h at −78 °C, at which time 12 mL of 2 N NaOH was added slowly. After addition was complete the cold bath was removed and the

mixture was stirred vigorously for 35 min while being warmed to room temperature. The mixture was transferred to a separatory funnel containing ether (20 mL) and brine (10 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 15 mL). The combined ether extracts were dried, filtered, and concentrated under reduced pressure to afford, after placement under high vacuum for 12 h, alcohol **17** as a colorless oil (1.08 g, 100% crude yield). This material was typically taken on to the next step without further purification. An analytical sample was prepared by chromatography (1:2 ethyl acetate–hexanes). IR: 3400, 1620, 1460 cm^{-1}. ^1H NMR (400 MHz): δ 1.18–2.21 (m, 20), 1.59 (s, 3), 1.68 (s, 3), 2.09 (bs, 4), 2.66–2.70 (m, 1), 3.37–3.58 (m, 8), 4.47 (d, 2, J = 2.1), 4.47 (s, 2), 4.48 (s, 2), 5.11 (bs, 1), 5.41 (t, 1, J = 7.2), 7.27–7.35 (m, 10). ^{13}C NMR (100 MHz): δ 17.62, 21.53, 22.89, 24.12, 25.59, 26.13, 26.91, 27.05, 28.72, 29.08, 33.82, 35.38, 36.66, 43.21, 45.77, 46.57, 48.28, 48.81, 65.83, 67.29, 70.45, 71.79, 72.85, 124.35, 127.34, 127.45, 127.61, 127.69, 128.20, 128.27, 130.30, 131.24, 135.24, 138.48, 138.69, 174.82. Anal. Calcd for $C_{40}H_{57}NO_4$: C, 77.99; H, 9.33; N, 2.28. Found: C, 77.95; H, 9.59; N, 2.18.

[4α,4aβ,7aβ(*Z*)]- and [4α,4aα,7aα(*Z*)]-(±)-7a-[8-Methyl-4-[(phenylmethoxy)methyl]-3,7-nonadienyl]hexahydro-4-[3-(phenylmethoxy)propyl]cyclopenta[*c*]pyran-3(1*H*)-one (18). To a stirring solution of alcohol **17** (1.03 g, 1.67 mmol) in 95% ethanol (13 mL) was added 5 N KOH (10 mL). The resulting solution was heated at 95 °C for 1 h, at which time TLC analysis of the mixture indicated complete consumption of **17**. Upon cooling to 0 °C, CH_2Cl_2 (30 mL) was added, and 4 N HCl was added though a pipet until pH ≈ 1. The cold bath was removed, and the two-phase mixture was stirred vigorously for 30 min. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were washed with 1:1 saturated $NaHCO_3$–H_2O, dried, filtered, and concentrated under reduced pressure to afford 905 mg (99% crude) of lactones **18** as a yellow oil, which was typically used directly in the next step. An analytical sample of the diastereomer mixture was prepared by silica gel chromatography (1:4 ethyl acetate–hexanes). IR: 1755, 1105, 750 cm^{-1}. The 400-MHz ^1H NMR spectrum of this material, which was approximately a 1:1 mixture of diastereomers, was too complex to evaluate. Similarly, we were not able to assign individual resonances in the ^{13}C NMR spectrum to either isomer. ^{13}C NMR (100 MHz): δ 17.69, 22.69, 22.87, 24.25, 24.79, 25.31, 25.68, 26.29, 26.76, 27.38, 27.65, 30.58, 33.80, 34.81, 35.28, 35.41, 35.58, 38.71, 39.15, 41.73, 43.55, 44.79, 45.81, 46.08, 48.31, 67.05, 67.08, 70.21, 70.23, 70.97, 71.96, 72.11, 72.79, 72.94, 73.36, 124.02, 124.12, 127.47, 127.49, 127.53, 127.67, 127.76, 128.30, 128.34, 128.36, 128.63, 128.76, 131.52, 131.61, 136.16, 136.47, 138.28, 138.43, 138.46, 138.52, 175.12, 175.58. Anal. Calcd for $C_{36}H_{48}O_4$: C, 79.36; H, 8.89. Found: C, 79.00; H, 8.91.

[1α(*R),2α,2(*Z*)]- and [1α(*S**),2α,2(*Z*)]-(±)-2-[8-Methyl-4-[(phenylmethoxy)methyl]-3,7-nonadienyl]-2-(hydroxymethyl)-β-[3-(phenylmethoxy)propyl]cyclopentaneethanol (5).** To a stirring solution of lactones **18** (905 mg, 1.66 mmol) in ether (16 mL) cooled to 0 °C was added $LiAlH_4$ (190 mg, 5.01 mmol). After stirring at 0 °C for 15 min, the ice water bath was removed, and the mixture was stirred at room temperature for 4.5 h. The mixture was again cooled to 0 °C and diluted with ether (10 mL). A gas vent needle was placed in the rubber septum, and H_2O (190 μL) was slowly added. This was followed by sequential, dropwise addition of 15% NaOH (190 μL) and H_2O (0.60 mL). After the resulting mixture was stirred for 45 min at room temperature, anhydrous $MgSO_4$ was added, and the white solids were filtered through a vacuum-adapted, fritted glass funnel. Solvent removal led to a colorless oil, which was chromatographed on silica gel (2:1 hexanes–ethyl acetate) to afford 721 mg of diol **5** as a mixture of diastereomers (76% overall yield from **16**). IR: 3390, 1460, 740 cm^{-1}. ^1H NMR (400 MHz): δ 1.09–1.75 (m, 8), 1.58 (s, 3), 1.67 (s, 3), 1.86 (bs, 1), 1.98–2.13 (m, 6), 3.36–3.66 (m, 6), 4.00 (d, 2, J = 6.8), 4.02 (s, 2), 4.46 (s, 2), 4.47 (s, 2), 4.49 (s, 2), 4.50 (s, 2), 5.10 (bs, 1), 5.42 (dd, 1, J = 7, 13), 7.26–7.37 (m, 10). ^{13}C NMR (100 MHz): δ 17.67, 21.92, 22.12, 23.14, 23.34, 25.63, 26.13, 26.78, 26.83, 26.86, 27.03, 27.38, 28.40, 30.34, 34.29, 35.04, 35.52, 35.60, 37.31, 37.76, 39.99, 47.92, 47.94, 48.20, 50.79, 64.80, 65.26, 65.46, 65.58, 67.24, 70.55, 70.63, 71.85, 71.88, 72.87, 72.93, 124.22, 127.46, 127.49, 127.52, 127.61, 127.64, 127.74, 127.78, 128.26, 128.31, 130.20, 130.36, 131.38, 135.28, 135.36, 138.37, 138.45. Anal. Calcd for $C_{36}H_{52}O_4$: C, 78.78; H, 9.56. Found: C, 78.50; H, 9.93.

(±)-17,18-Didehydro-20,23-bis(phenylmethoxy)-12,16-cyclo-1,12-secodaphnane (19). A stirring solution of oxalyl chloride (98 μL, 143 mg, 1.12 mmol) in CH_2Cl_2 (3.8 mL), cooled to −78 °C, was treated dropwise with a solution of DMSO (0.18 mL, 198 mg, 2.53 mmol) in CH_2Cl_2 (0.5 mL). The resulting solution was stirred for 7 min, and a solution of **5** (274 mg, 0.50 mmol) in CH_2Cl_2 (0.75 mL) was added dropwise. The temperature was maintained at −78 °C for 15 min, at which time triethylamine (0.80 mL) was added to the mixture. After 5 min the cold bath was removed, and after an additional 10 min an ice water bath (0 °C) was placed under the reaction flask. Stirring was continued for 45 min at 0 °C. The rubber septum was removed, and a stream of NH_3 gas was passed into the reaction vessel (over the surface!) through a 9-in. disposable Pasteur pipet for approximately 5 min. The cold bath was removed, and the milky white mixture was allowed to warm gradually to room temperature over a period of 40 min. The solvent was evaporated, and the white solid residue was placed under high vacuum for 2 h. The flask was vented with N_2 and solid NH_4OAc (390 mg) was added, followed by glacial acetic acid (9 mL). This mixture was stirred at room temperature for 30 min and was placed in an oil bath preheated to 75 °C. After 2 h at this temperature the orange mixture was transferred to a separatory funnel containing H_2O (35 mL) and CH_2Cl_2 (15 mL). The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined CH_2Cl_2 extracts were washed with 2 N NaOH (40 mL). The layers were separated, the base was extracted with CH_2Cl_2 (2 × 10 mL), and the combined extracts were dried (K_2CO_3), filtered, and concentrated under reduced pressure to leave 270 mg of a garlic-scented, amber oil. Silica gel chromatography (3:7 ethyl acetate–hexanes) of this oil led to 198 mg (76%) of **19** as a pale yellow oil. IR: 2940, 1100, 745 cm^{-1}. ^1H NMR (400 MHz): δ 1.22–2.02 (m, 22), 1.74 (s, 3), 2.55 (d, 1, J = 4.5), 2.95 (s, 1), 3.22 (d, 1, J = 8.6), 3.35 (dt, 2, J = 1.7, 6.7), 3.44 (d, 1, J = 8.7), 4.39 (d, 1, J = 11.9), 4.46 (s, 2), 4.46 (d, 1, J = 11.9), 4.73 (s, 1), 4.85 (s, 1), 7.25–7.35 (m, 10). ^{13}C NMR (100 MHz): δ 19.47, 22.42, 23.09, 25.39, 26.46, 29.21, 29.46, 32.36, 36.26, 39.17, 41.49, 41.85, 45.98, 49.80, 50.61, 52.65, 59.65, 71.21, 72.68, 73.09, 74.13, 110.28, 127.22, 127.33, 127.37, 127.42, 128.10, 128.21, 138.49, 138.58, 147.36. Anal. Calcd for $C_{36}H_{47}NO_2$: C, 82.23; H, 9.02; N, 2.67. Found: C, 82.46; H, 9.28; N, 2.28.

(1α,3aβ,5aβ,6α,8aα,11aβ,11bβ,11cβ,12*R)-(±)-Tetradecahydro-3-methylene-5a-[(phenylmethoxy)methyl]-11b-[3-(phenylmethoxy)propyl]-1,6,8a-metheno-2*H*-azuleno[5,4-*g*]indole (32).** A solution was prepared by dissolving **19** (157 mg, 0.29 mmol) in CH_3CN (4.2 mL, dried over K_2CO_3 immediately before use). To this solution was added, in order, triphenylphosphine (7.8 mg, 0.03 mmol, 10 mol %) and *p*-benzoquinone (35.4 mg, 0.33 mmol, 1.1 equiv, freshly recrystallized by hot charcoal filtration from benzene). The flask was purged with N_2, and palladium bis(trifluoroacetate) (14.8 mg, 0.044 mmol, 15 mol %) was added. The flask was wrapped with aluminum foil, and the amber solution was stirred at room temperature for 24 h, at which time TLC analysis (50% ether–hexanes) indicated complete consumption of **19**. The solution was diluted with ether, transferred to a separatory funnel, and washed successively with saturated $NaHCO_3$, H_2O, and brine. The combined washings were back-extracted with ether (2×). The combined ether extracts were dried (K_2CO_3), filtered, and concentrated to afford 216 mg of a black residue, which was immediately chromatographed on silica gel (55% hexanes–ether) to yield 109 mg (70%) of **32** as a pale amber oil. IR (CCl_4): 2960, 1110 cm^{-1}. ^1H NMR (400 MHz): δ 1.28–1.73 (m, 16), 1.81–1.89 (m, 2), 1.92–1.99 (m, 1), 2.20 (t, 1, J = 5), 2.26–2.32 (m, 1), 2.38 (d, 1, J = 4.0), 3.00 (d, 1, J = 4.1), 3.25 (d, 1, J = 8.8), 3.37 (t, 2, J = 6.6), 3.48 (d, 1, J = 15.1), 3.49 (d, 1, J = 8.5), 3.63 (d, 1, J = 13.8), 4.41 (d, 1, J = 11.9), 4.48 (s, 2), 4.48 (d, 1, J = 11.8), 4.75 (s, 1), 4.85 (s, 1), 7.27–7.39 (m, 10). ^{13}C NMR (100 MHz): δ 23.16, 23.59, 26.03, 26.38, 29.14, 29.63, 29.78, 35.49, 36.42, 38.86, 40.18, 41.07, 41.19, 51.43, 53.53, 55.47, 59.82, 67.25, 71.52, 72.84, 73.19, 74.24, 102.95, 127.32, 127.46, 127.56, 128.21, 128.31, 138.59, 138.69, 154.66. Although this material appeared to be analytically pure by ^1H NMR and ^{13}C NMR, satisfactory values from combustion analysis were not obtained until after additional chromatography (3:7 ethyl acetate–hexanes). Anal. Calcd for $C_{36}H_{45}NO_2$: C, 82.56; H, 8.66; N, 2.67. Found: C, 82.72; H, 8.73; N, 2.48.

(1α,3aα,3aβ,5aβ,6α,8aα,11aβ,11bβ,11cβ,12R*)-(●)-Tetradecahydro-5a-[(phenylmethoxy)methyl]-11b-[3-(phenylmethoxy)propyl]-1,6,8a-metheno-2H-azuleno[5,4-g]-indole-3-methanol (35). To a cooled (0 °C) and stirring solution of olefin **32** (70 mg, 0.13 mmol) in THF (1.9 mL) was added dropwise a solution of BH_3·THF (2 equiv, 0.26 mL of a 1 M solution). The ice–water bath was removed, and the resulting colorless solution was stirred at room temperature for 2 h, at which time 2 mL of H_2O was added dropwise, followed by 119 mg (6.0 equiv) of solid $NaBO_3$·$4H_2O$. The mixture was stirred vigorously at room temperature for 3 h and transferred to a separatory funnel containing 10 mL of ether and 6 mL of water. The layers were agitated and separated, and the aqueous layer was extracted with ethyl acetate (3 × 8 mL). The combined organic extracts were dried, filtered, and concentrated to obtain 72 mg of **35** as a colorless oil. An ^1H NMR spectrum of this material indicated that the material was sufficiently pure to be used without further purification. IR: 3380, 1460, 1230, 1110 cm^{-1}. ^1H NMR (400 MHz, (characteristic peaks only):[32] δ 1.21–1.99 (m), 2.11 (t, 1, J = 5), 2.32 (d, 1, J = 3.7), 2.58 (t, 1, J = 10), 2.94 (d, 1, J = 3.5), 3.07 (t, 1, J = 8), 3.22 (d, 1, J = 8.8), 3.34 (t, 2, J = 6.5), 3.44 (d, 1, J = 8.8), 3.57–3.70 (m, 2), 4.39 (d, 1, J = 12), 4.45 (d, 1, J = 12), 4.45 (s, 2). EIMS: 541 (M^+, 28), 525 (21), 450 (35), 434 (56), 91 (100).

(1α,3aα,3aβ,5aβ,6α,8aα,11aβ,11bβ,11cβ,12R*)-(±)-Tetradecahydro-3-methyl-5a-[(phenylmethoxy)methyl]-11b-[3-(phenylmethoxy)propyl]-1,6,8a-metheno-2H-azuleno[5,4-g]indole (33). Method A. Diimide Reduction of 32. In a 50-mL round-bottomed flask, a solution of **32** (230 mg, 0.44 mmol) in 95% ethanol (10 mL) and THF (3.0 mL) was treated with hydrazine (1.37 mL, 40 equiv), cooled to 0 °C, and treated dropwise with a solution of $NaIO_4$ (940 mg, 4.4 mmol, 10 equiv) in H_2O (2.7 mL). It was necessary to warm the flask with a hot air gun to dissolve completely the $NaIO_4$. The cold bath was removed, a reflux condenser was attached, and the slurry was heated in an oil bath at 75 °C for 21 h with the top of the condenser left open to the atmosphere, over which time the reaction mixture became a homogeneous yellow solution. Upon cooling to room temperature the solution was transferred to a separatory funnel containing 1 N NaOH (40 mL) and CH_2Cl_2 (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried (K_2CO_3), filtered, and concentrated to afford 220 mg of **33** and **34** as a yellow oil. Chromatography on 15.5 g silica gel (8% methanol–$CHCl_3$) gave the following fractions: 54 mg of **33**/**34** (1:1), 66 mg of **33**/**34** (5:1), 37 mg of **33**/**34** (10:1), and 43 mg of pure **33** (87% total yield of reduced material). Ratios were determined by ^1H NMR and are approximate. Analytical data for **33**. IR: 1455, 1365, 1270, 1100, 740 cm^{-1}. ^1H NMR (400 MHz): δ 0.93 (d, 3, J = 6.8), 1.20–1.96 (m, 20), 2.09–2.16 (m, 2), 2.27 (d, 1, J = 3.8), 2.51 (dd, 1, J = 9.3, 11.0), 2.95 (d, 1, J = 3.3), 2.98 (t, 1, J = 8), 3.22 (d, 1, J = 8.8), 3.34 (t, 2, J = 6.6), 3.44 (d, 1, J = 8.8), 4.39 (d, 1, J = 11.9), 4.45 (s, 2), 4.46 (d, 1, J = 11.9), 7.23–7.39 (m, 10). ^{13}C NMR (100 MHz): δ 11.91, 16.99, 23.53, 25.95, 26.35, 29.18, 29.40, 29.80, 35.69, 36.37, 37.01, 37.47, 39.14, 39.36, 41.44, 50.99, 53.52, 57.39, 61.09, 66.87, 71.57, 72.81, 73.12, 74.27, 127.26, 127.40, 127.44, 127.55, 128.17, 128.29, 138.56, 138.73. Anal. Calcd for $C_{36}H_{47}NO_2$: C, 82.23; H, 9.02; N, 2.67. Found: C, 82.21; H, 9.21; N, 2.74.

Method B. Deoxygenation of Alcohol 35. To a solution of alcohol **35** (72 mg, 0.13 mmol) in pyridine (0.2 mL) and $CHCl_3$ (0.3 mL), cooled to 0 °C, were added 4-(dimethylamino)pyridine (20 mg) and *p*-toluenesulfonyl chloride (8 equiv, 202 mg). The cold bath was removed, and the resulting orange solution was stirred at room temperature for 46 h. The mixture was diluted with CH_2Cl_2 (6 mL) and transferred to a separatory funnel containing H_2O (5 mL). The layers were separated, and the layer was extracted with CH_2Cl_2 (5 mL). The combined orange layers were washed with saturated $NaHCO_3$ (7 mL). The $NaHCO_3$ was extracted with CH_2Cl_2 (2 × 6 mL). The combined extracts were dried over K_2CO_3 and concentrated to afford a brown oil (189 mg) that was taken directly to the next step.

The brown oil was dissolved in THF (1.5 mL) and cooled to 0 °C, and a solution of $LiEt_3BH$ (10 equiv, 1.3 mL of a 1 M solution in THF) was added dropwise. The cold bath was removed, and the solution was allowed to stir at room temperature for 4 h. H_2O (1.1 mL) was added, the mixture was cooled to 0 °C, and $NaBO_3$·$4H_2O$ (1.2 g) was added. The mixture was stirred vigorously at room temperature for 2.5 h and transferred to a separatory funnel containing ether and H_2O. The layers were separated, and the layer was extracted with ethyl acetate (3×). The combined organic layers were washed with saturated NaCl, dried (K_2CO_3), and concentrated to afford a mixture of **33** and **34** as a brown oil (87 mg). An ^1H NMR spectrum of this material indicated an isomer ratio of approximately 16:1 favoring **33**. Silica gel chromatography (40% ethyl acetate–hexanes) of this oil led to the bis(benzyl ether) **33** (47 mg, 70% from **32**) as a colorless oil. The IR, ^1H NMR, and ^{13}C NMR spectra of this material were identical with those of the material as prepared by method A.

(±)-Bukittinggine (1). Approximately 2 mL of gaseous ammonia was condensed into a 10-mL, two-necked, round-bottomed flask cooled to −78 °C, and Na metal (12 equiv, 1.67 g-atoms, 38 mg) was added in small pieces to form a deep-blue color solution. To this solution was added the bis(benzyl ether) **33** (73 mg, 0.14 mmol) in THF (0.3 mL). Stirring was continued for an additional 20 min at −78 °C, at which time additional THF (1.5 mL) was added followed by solid NH_4Cl (250 mg) and a small amount of isoprene to consume the excess Na metal. The cold bath was removed, and the solution was allowed to warm slowly to room temperature, evaporating the NH_3. The residue was diluted with ether and water and poured into a separatory funnel containing CH_2Cl_2 and dilute NaOH. After shaking, the layers were separated and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated to yield 48 mg of a white solid. The ^1H NMR spectrum of this material indicated the presence of a small amount of 1,2-diphenylethane, which was removed by sublimation at room temperature under high vacuum (<0.5 Torr) for several hours.

The white solid was dissolved in methanol–$CHCl_3$ (1:1) and the solvent was removed with a rotary evaporator to leave a colorless oil (the trace amounts of methanol and $CHCl_3$ that remained helped to solubilize the material in the next reaction). Benzene (9 mL) was added, followed by freshly prepared Fetizon's reagent (Ag_2CO_3 on Celite, 1.0 g), and the mixture was heated to reflux. After 5 h TLC analysis (ethyl acetate) indicated total consumption of diol **36**. The black mixture was cooled to room temperature and filtered through Celite ($CHCl_3$). Solvent removal led to 46 mg of a yellow oil, which after silica gel chromatography on 3.0 g of silica gel (5% methanol–ethyl acetate) provided 23 mg (52% from **32**) of (±)-bukittinggine as a white solid, mp 99–102 °C. IR (CCl_4): 2950, 1741, 1463, 1297, 1217, 1062 cm^{-1}. ^1H NMR (500 MHz): δ 0.96 (d, 3, J = 6.8), 1.25–1.29 (m, 1), 1.34–1.59 (m, 10), 1.66–1.88 (m, 5), 1.97–2.10 (m, 2), 2.11–2.16 (m, 1), 2.18 (dd, 1, J = 4.2, 6.0), 2.32 (d, 1, J = 3.8), 2.41 (ddd, 1, J = 1.2, 7.0, 14.1), 2.55 (dd, 1, J = 9.3, 11.0), 2.73 (dt, 1, J = 1.7, 14.1), 2.81 (d, 1, J = 3.6), 3.03 (dd, 1, J = 7.3, 8.7), 3.85 (d, 1, J = 12.7), 4.39 (d, 1, J = 12.7). ^{13}C NMR (125 MHz): δ 11.94, 16.97, 20.82, 24.90, 26.21, 27.32, 28.57, 29.27, 35.57, 36.04, 36.82, 37.52, 37.72, 38.71, 40.48, 49.94, 50.63, 57.43, 61.98, 67.67, 70.76, 175.47. EIMS: 341 (M^+, 100), 268 (16.7), 254 (17.0), 214 (10.4). HRMS: calcd for $C_{22}H_{31}NO_2$ 341.2355, found 341.2354.

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Registry No. (±)-**1**, 138435-38-8; (±)-**5** (isomer 1), 138435-39-9; (±)-**5** (isomer 2), 138513-46-9; **6**, 117959-71-4; **7**, 25662-28-6; (*Z*)-**8**, 138435-40-2; (*E*)-**8**, 138435-41-3; **9**, 4039-82-1; **10**, 138435-42-4; (*Z*)-**11**, 138435-43-5; (*E*)-**11**, 138435-44-6; (*Z*)-**12**, 138435-45-7; (*E*)-**12**, 138435-46-8; (*Z*)-**13**, 138435-47-9; (*E*)-**13**, 138435-48-0; (*Z*)-**14**, 138435-49-1; (*E*)-**14**, 138435-50-4; (*Z*)-**15**, 138435-51-5; (*E*)-**15**, 138435-52-6; (±)-**16**, 138435-53-7; (±)-**17**, 138435-54-8; (±)-**18** (isomer 1), 138435-55-9; (±)-**18** (isomer 2), 138513-47-0; (±)-**19**, 138458-91-0; (±)-**22**, 138458-92-1; (±)-**25**, 138435-56-0; (±)-**26**, 138513-48-1; (±)-**32**, 138435-57-1; (±)-**33**, 138435-58-2; (±)-**34**, 138513-49-2; (±)-**35**, 138435-59-3; (±)-**36**, 138435-60-6; homoprenyl bromide, 2270-59-9.

(32) The ^1H NMR spectrum of this material is provided in the supplementary material.

Supplementary Material Available: General experimental procedure for the hydrogenation of **22**; experimental procedure for the cyclization of **20**; ^{1}H NMR spectra of compounds **23**, **24**, **26**, and **32**; ^{1}H NMR spectrum of unpurified **25**/**26** mixture (4:1) from diimide reduction of **22**; ^{1}H NMR spectrum of unpurified alcohol **35**; ^{1}H NMR and IR spectra of synthetic and natural bukittinggine; ^{1}H NMR spectra of expanded region (0.6–4.8 ppm) of synthetic and natural bukittinggine; and the ^{1}H NMR spectrum of aldehyde **13** (15 pages). This material is found 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. 15. Total Syntheses of (±)-Methyl Homodaphniphyllate and (±)-Daphnilactone A[1]

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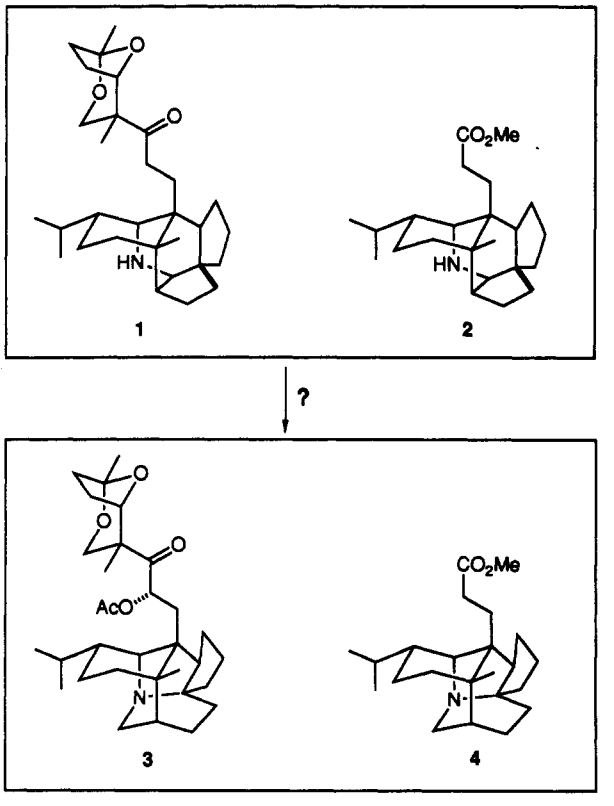
Biomimetic total syntheses of (±)-daphnilactone A (**6**) and (±)-methyl homodaphniphyllate (**4**) have been carried out. The syntheses began with the preparation of tricyclic lactone ether **18d**, which was reduced to diol **19d** with $LiAlH_4$. Oxidation of **19d** gave a sensitive dialdehyde (**20d**), which was treated sequentially with ammonia and warm acetic acid to obtain the hexacyclic amino ether **22d**. The tetracyclization process leading from **19d** to **22d** proceeded in 47% yield and resulted in the formation of five new σ-bonds and four new rings. After hydrogenation of the double bond, the saturated amino ether **7** was fragmented by treatment with diisobutylaluminum hydride in refluxing toluene. Unsaturated amino alcohol **23** was obtained in 71% yield, accompanied by a smaller amount of the simple elimination product **24**. Compound **23** was converted into (±)-daphnilactone A (**6**) by oxidation to the unsaturated amino acid, which was cyclized by treatment with aqueous formaldehyde at pH 7. For the preparation of **4**, compound **23** was oxidized and the resulting amino acid esterified to obtain **26**. Treatment of this compound with phenyl isocyanate gave a urea derivative (**27**) that underwent smooth cyclization to (±)-methyl homodaphniphyllate (**4**) in refluxing formic acid. From homogeranyl iodide, the limiting starting material, compound **6** was obtained in 11 steps and 8% overall yield and compound **4** was obtained in 13 steps and 11% overall yield.

Although the secodaphnane skeleton, as embodied in secodaphniphylline (**1**) and the C-22 *Daphniphyllum* alkaloid methyl homosecodaphniphyllate (**2**), is probably the initial skeleton biosynthesized,[3] the daphnane skeleton, as typified by daphniphylline (**3**) and methyl homodaphniphyllate (**4**), is by far more common. It has been proposed[4] that the daphnane skeleton might arise from the secodaphnane skeleton by way of the unknown fragmentation product **5**. Intramolecular addition of the N—H bond to the C=C bond would give the daphnane skeleton (e.g., **3**, **4**, etc.). The possible intervention of a biosynthetic intermediate such as **5** is further suggested by the occurrence of the minor *Daphniphyllum* alkaloid daphnilactone A (**6**), since this compound could arise from **5** by a Mannich-type process involving formaldehyde or its equivalent. The purpose of the present work was to find a way to simulate the process outlined schematically, that is, to convert a secodaphnane intermediate into **5** and show that this material provides alkaloids **4** and **6**.[5] The basic plan of the project is outlined in Scheme I. Thus, we thought we could use the tetracyclization reaction[6] to prepare an angularly functionalized secodaphnane **A**, which would undergo Eschenmoser–Grob fragmentation[7] to an imine **B**; reduction of the latter intermediate would provide **C**, the putative biosynthetic link between the secodaphnanes and daphnanes.



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