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.

Acknowledgment. This work was supported by a research grant from the National Science Foundation (CHE-84-18437). We are grateful to the following agencies and companies for support in the form of fellowships: Merck, Sharp & Dohme for a postdoctoral fellowship to S.P., Pfizer for a predoctoral fellowship to R.R., the American Cancer Society for a postdoctoral fellowship to J.R., and the United States Department of Education for a predoctoral fellowship to J.K.

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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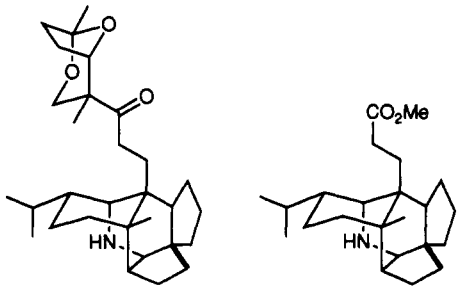
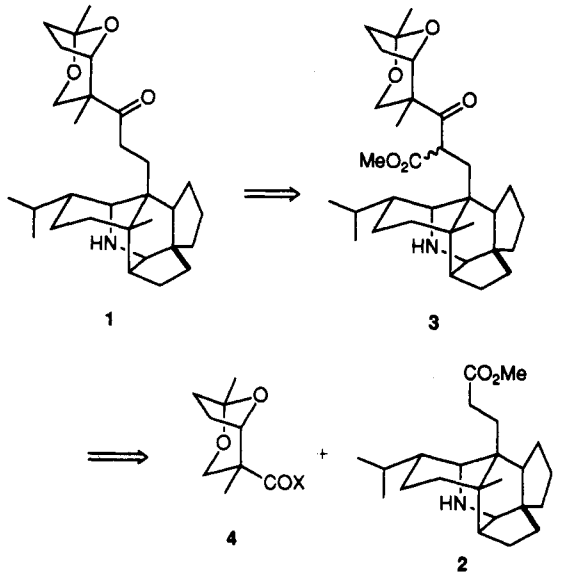
phylline is one of the nine *Daphniphyllum* alkaloids that has retained the entire C_{30} complement of squalene. These C_{30} alkaloids are fashioned on a common structural motif: a bicyclic ketal or lactone that is tethered by a three-carbon chain to a pentacyclic, nitrogen-containing core. The remaining members of the alkaloid family have truncated structures that contain only 22 of the original 30 squalene carbons. In a previous installment in this series of papers, we described the total synthesis of (±)-methyl homosecodaphniphyllate (**2**), the 22-carbon analogue of secodaphniphylline.[5] In this paper we describe an extension of this work to the synthesis of (−)-secodaphniphylline itself.[6]



1 **2**

We envisioned secodaphniphylline as arising from simple decarbomethoxylation of β-keto ester **3**, which might be prepared by a mixed Claisen condensation of (−)-methyl homosecodaphniphyllate (**2**) with **4**, a carboxylic acid derivative with the characteristic 2,8-dioxabicyclo[3.2.1]octane structure commonly found in the *Daphniphyllum* alkaloids. There are two significant advantages of this plan. It is highly convergent, with the convergent step being the penultimate step of the synthesis, and it employs methyl homosecodaphniphyllate (**2**), which, in its racemic form, is available in good overall yield by the previous synthesis that we have developed. The major obstacle to overcome in this mixed Claisen coupling strategy is the need for an enantioselective route to both **2** and **4**.



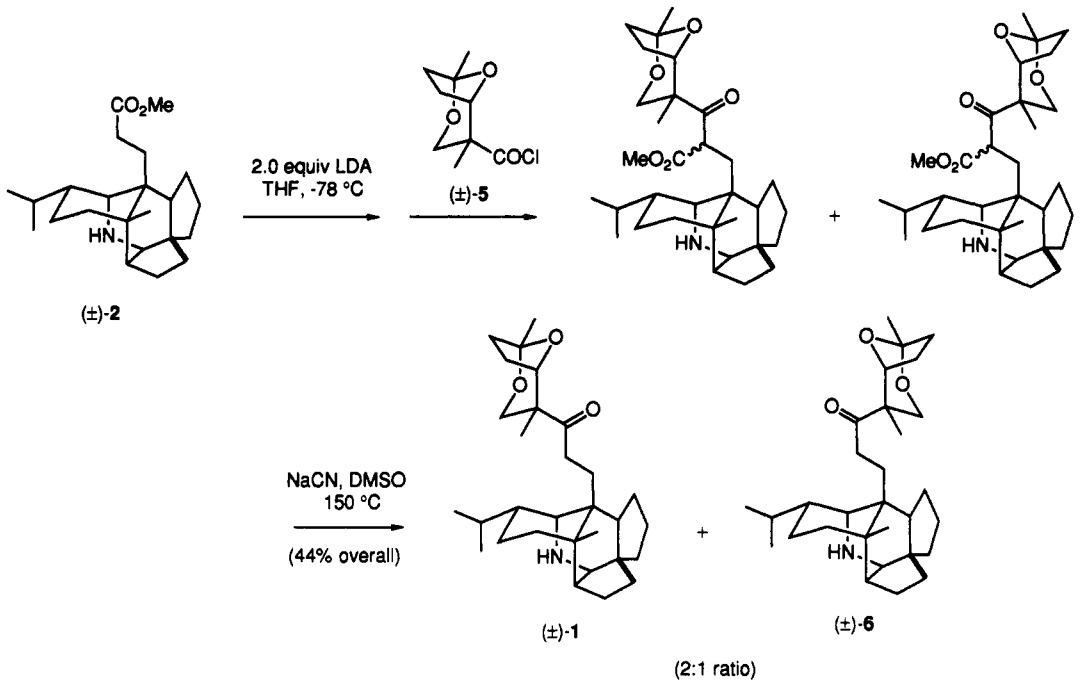
1 **3** **4** **2**

Before launching enantioselective syntheses of **2** and **4**, we decided to test the viability of the mixed Claisen condensation strategy with the more easily prepared racemic components (Scheme I). Along these lines, acid chloride **5** was prepared in seven steps from commercially available 1,1,1-tris(hydroxymethyl)ethane in a route that featured a Wacker oxidation reaction in the construction of the bicyclic ketal.[7] When (±)-**5** was added to the lithium enolate of (±)-methyl homosecodaphniphyllate at −78 °C, a mixture of diastereomeric β-keto esters was formed. The crude mixture was treated directly with sodium cyanide in dimethyl sulfoxide at 150 °C[8] to provide in 44% yield a 2:1 mixture of (±)-secodaphniphylline (**1**) and "(±)-isosecodaphniphylline" (**6**), resulting from coupling of the "natural" enantiomer of **2** with the "unnatural" enantiomer of **5** (and vice versa).[9] The mass balance in the coupling step was excellent and the ^{1}H NMR spectrum of the crude mixture of diastereomeric products showed no major impurities. Therefore, we believe that the unaccounted mass balance in the two-step process is due to material lost under the forcing conditions required in the decarboxylation step. Attempts were also made to use the ester of the bicyclic ketal in the coupling process but we were unable to detect any β-keto ester formation by this procedure. The low reactivity of the enolate of methyl homosecodaphniphyllate toward the methyl ester corresponding to **5** is probably due to steric hindrance.

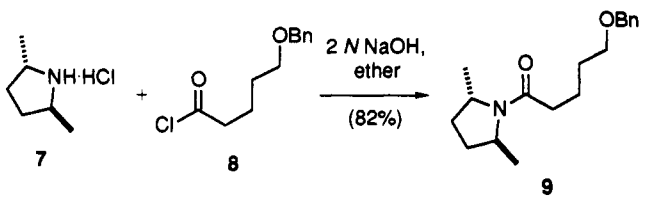
The mixed Claisen reaction shows a modest mutual kinetic enantioselection[10] that favors formation of the secodaphniphylline relative stereochemistry over the isosecodaphniphylline stereochemistry. This small difference presumably stems from a slight difference in nonbonded steric interactions in the diastereomeric transition states. However, the magnitude of the difference is not sufficient to be preparatively useful because the secodaphniphylline diastereomers were found to be totally inseparable by chromatography. To have stereocontrol over the synthesis of secodaphniphylline, then, it is necessary to carry out the Claisen coupling with scalemic (enantiomerically enriched) **2** and **5**.[11] Our first priority in selecting a route to (−)-methyl homosecodaphniphyllate was to preserve the key elements of the highly efficient synthesis of the racemic alkaloid, most notably the tetracyclization reaction and the convergent Michael addition/alkylation protocol that brings together in one step all the carbons necessary to assemble the alkaloid. The most direct modification would be to find an asymmetric version of the initial Michael addition reaction. The amide of a C_2-symmetric pyrrolidine appealed to us for a variety of reasons. First, the use of a C_2-symmetric auxiliary on the amide would obviate

(1) For part 12, see: Heathcock, C. H.; Piettre, S.; Ruggeri, R. B.; Ragan, J. A.; Kath, J. C. *J. Org. Chem.*, preceding paper in this issue.
(2) Current address: Glaxo, Inc., Five Moore Drive, Research Triangle Park, NC 27709.
(3) (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.
(4) Irikawa, H.; Toda, M.; Yamamura, S.; Hirata, Y. *Tetrahedron Lett.* **1969**, *9*, 1821.
(5) (a) Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734. (b) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.*, second paper in the series in this issue.
(6) A preliminary account of this work has appeared: Stafford, J. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5433.
(7) Details of the synthesis of *racemic* acid chloride **5** are provided in the supplementary material.
(8) Krapcho, A. J.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, *8*, 215.
(9) The ^{1}H NMR spectrum of this material is provided in the supplementary material.
(10) The term "kinetic enantioselection" has the same meaning as the more familiar term "kinetic resolution", except that it can be applied to situations like the one being discussed here, where two racemates react and an actual resolution, in the traditional sense of the term, does not result. The term was suggested by E. L. Eliel and was first used in a review article on the stereochemistry of enolate Michael additions: Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227.
(11) The term scalemic has been defined by James Brewster (Purdue University) to describe an unequal mixture of enantiomers. Thus, scalemic and racemic are macroscopic analogues of chiral and achiral, adjectives that can only be applied to single objects.

Scheme I



the complication of amide rotamers in the ^1H NMR spectra of products from the Michael addition/alkylation reaction mixture. Second, the use of C_2-symmetric pyrrolidine auxiliaries to impart high levels of asymmetric induction in such varied processes as alkylation,[12] Michael addition,[13] radical addition,[14] Diels–Alder,[15] and aldol chemistry[16] is well documented. Because it is the prototypical C_2-symmetric pyrrolidine, we chose (*S,S*)-2,5-dimethylpyrrolidine (**7**)[17] as the chiral amine auxiliary. Compound **7**, prepared from L-alanine by a modification of the procedure of Schlessinger and Iwanowicz,[17b] was coupled under Schotten-Baumann conditions with acid chloride **8**, derived from 5-(phenylmethoxy)pentanoic acid,[18] to obtain amide **9** (82% from the acid).



Our initial attempts to use amide **9** in the Michael addition/alkylation sequence, following the previously developed protocol, were disappointing, affording the adduct in yields ranging between 30 and 40%. Careful experimentation revealed that the rates of both the Michael addition to the enoate **10** and the alkylation of the resulting ester enolate by homogeranyl iodide (**11**) are considerably slower with the 2,5-dimethylpyrrolidine amide than with the unsubstituted analogue. However, by extending the time of the Michael addition step to 45 min and by adding HMPA during the alkylation step, we were able to obtain a mixture of stereoisomeric Michael addition/alkylation adducts in reasonable yield. Chromatographic separation of what appeared to be a single, major product (homogeneous by TLC using several solvent systems) actually afforded, as evidenced by ^1H and ^{13}C NMR spectroscopy, a 92:8 mixture of two very similar diastereomers in a yield of 64%. As will be shown in the sequel, the fact that this mixture of diastereomers was converted into (−)-methyl homosecodaphniphyllate of 84% ee shows that these two diastereomers are **12** and **13**. Other isomers that were not fully characterized were formed in lesser amount (<10%). The stereochemical assignment of **12** is based on its spectroscopic and chromatographic similarity to the related major product from the racemic synthesis, which in turn was assigned by analogy to earlier work by Yamaguchi on the Michael addition reactions of pyrrolidine amide enolates to α,β-unsaturated esters[19] and on its eventual conversion into (−)-methyl homosecodaphniphyllate. The observed diastereomeric excess of approximately 84% is in close agreement to that previously reported in similar Michael addition/alkylations.[13]

The stereoselectivity in the Michael addition/alkylation sequence can be understood by considering the transition-state structures represented below. We believe that the Michael addition leading to formation of **12** occurs through the eight-membered closed transition state **A**.[20] Reaction from the other diasteroface of the amide enolate, represented by transition state **B**, gives rise to the minor diastereomer **13**. The fact that the enolate prefers to react on the diastereoface represented by structure **A** suggests that the repulsive interaction between the pyrrolidine methyl and the cyclopentane ring is favored over that with

(12) (a) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857. (b) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 2463. (c) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755.

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

(14) Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, *31*, 1675.

(15) (a) Defoin, A.; Brouillard-Poichet, A.; Streith, *J. Helv. Chem. Acta* **1991**, *74*, 103. (b) Gouverneur, V.; Ghosez, L. *Tetrahedron: Asymmetry* **1990**, *1*, 363. (c) Kawanami, Y.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4190.

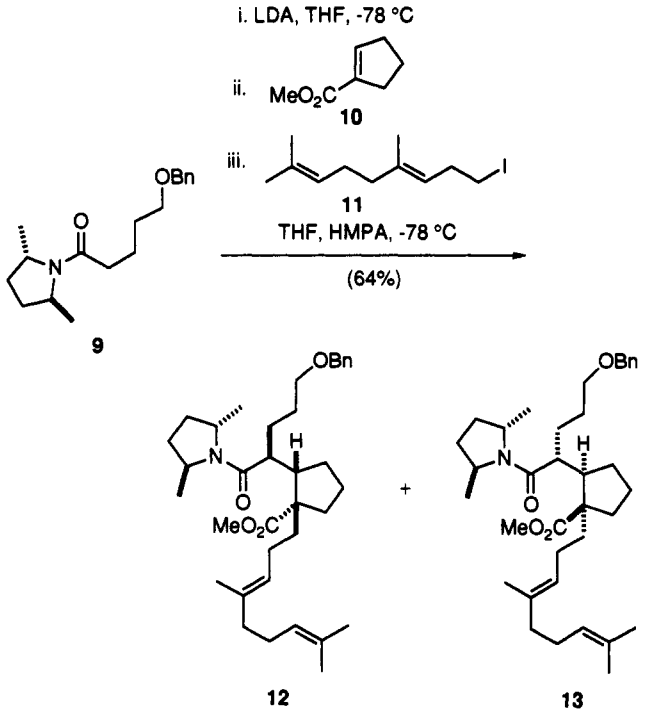
(16) (a) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 5807. (b) Schlessinger, R. H.; Iwanowicz, E. J.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 3070. (c) Whitesell, J. K.; Minton, M. A.; Chen, K. M. *J. Org. Chem.* **1988**, *53*, 5383.

(17) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663. (b) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083.

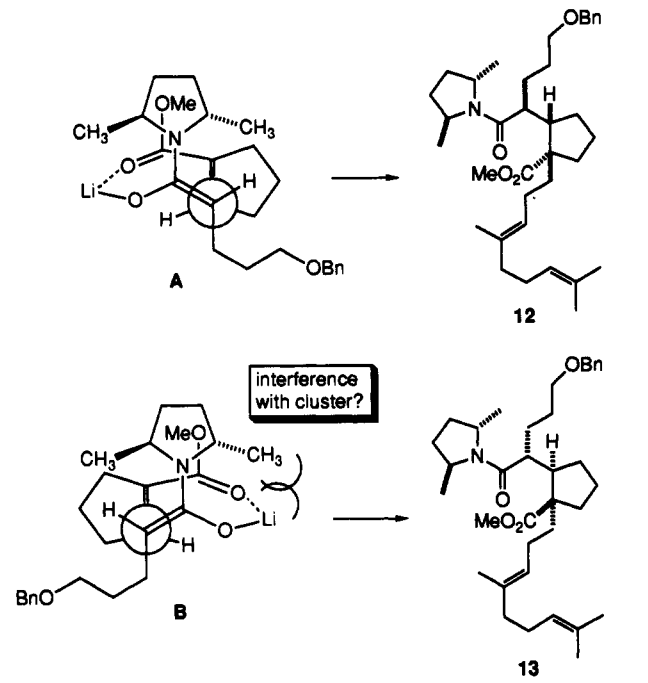
(18) Hoye, T. R.; Kurth, M. J.; Lo, V. *Tetrahedron Lett.* **1981**, *22*, 815.

(19) Yamaguchi, M. *Yuki Gosei Kagaka* **1986**, *44*, 405.

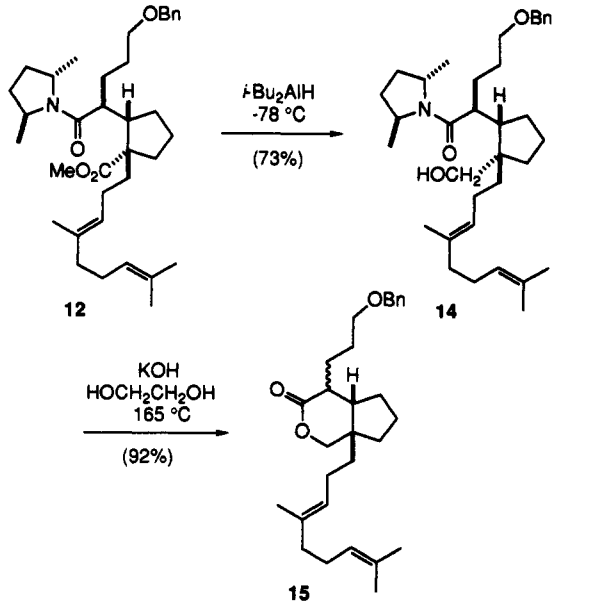
(20) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132.



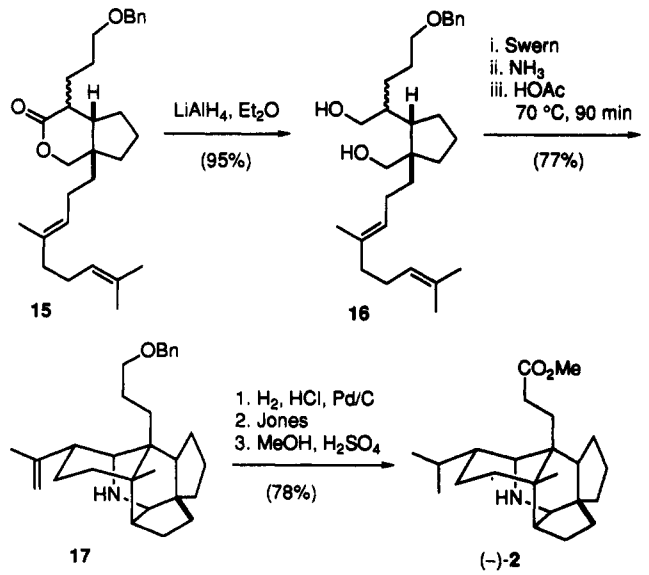
the enolate cluster (structure **B**). The observed ratio of 11:1, of course, corresponds to only a modest difference of 1.1 kcal mol^{-1} in free energies of the two diastereomeric transition states.



The mixture of amide ester diastereomers (for clarity, only **12** is depicted) was treated with DIBAL in toluene at −78 °C to obtain amide alcohol **14** (with diastereomer) in 73% yield. As in the synthesis of (±)-methyl homosecodaphniphyllate, **14** was treated with alcoholic KOH at 90 °C to saponify the amide. However, the two additional methyl groups cause **14** to be much more resistant to hydrolysis than its unsubstituted analogue and it was completely unchanged under these conditions. Treatment of **14** with KOH/ethylene glycol at 165 °C for 2–3 days did affect hydrolysis and acidification of the mixture afforded lactones **15**, an approximate 1:1 mixture of diastereomers at the (benzyloxy)propyl side-chain position, in a total yield of 92%.



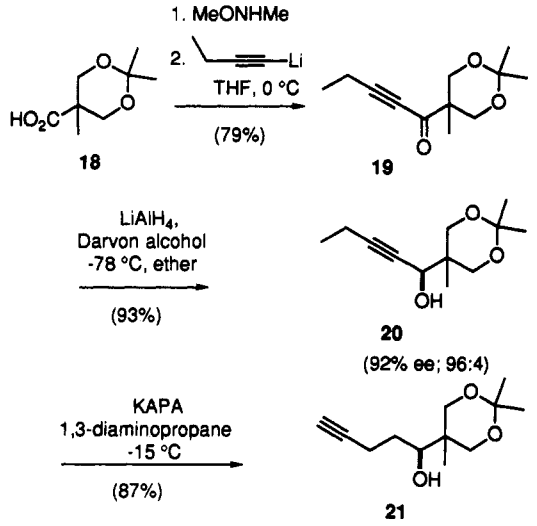
The remainder of the synthesis of (−)-methyl homosecodaphniphyllate followed exactly the same route as was used in the racemic synthesis. Reduction of **15** afforded the mixture of diols **16**, which were subjected to the conditions of the tetracyclization reactions: (1) Swern oxidation to the dialdehyde, (2) exposure to ammonia gas to form a 2-aza diene, and (3) treatment with acetic acid to effect both the Diels–Alder and aza-Prins cyclizations. The advanced alkaloid intermediate **17** was consistently produced in an overall yield of approximately 80%. The synthesis of (−)-methyl homosecodaphniphyllate (**2**) was then completed by catalytic hydrogenation, Jones oxidation, and Fischer esterification. The material so obtained had mp 77–80 °C and $[\alpha]_D = -82$ ($c = 1.12$, $CHCl_3$), corresponding to 84% ee. Recrystallization from *n*-hexane gave material with mp 98–99 °C and $[\alpha]_D = -88$ ($c = 0.31$, $CHCl_3$), corresponding to 90% ee.



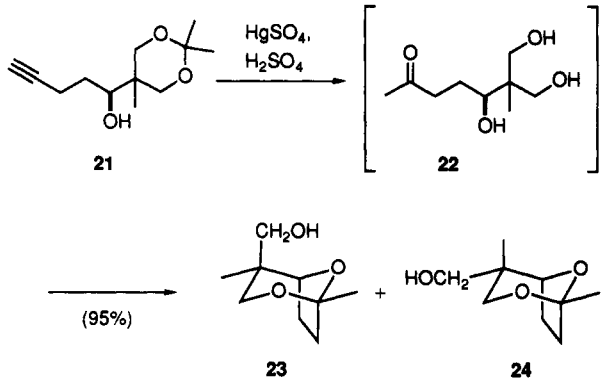
With the synthesis of (−)-**2** completed, we turned our attention to the enantioselective preparation of the bicyclic ketal unit. The synthesis of **4** began with the known carboxylic acid **18**.[21] Formation of the *N*-methoxy-*N*-methylamide,[22] followed by treatment with 1-butynyl-

(21) Bruice, T. C.; Piszkiewicz, D. *J. Am. Chem. Soc.* **1967**, *89*, 3568.
(22) Nahm, S.; Weinreb, S. *Tetrahedron Lett.* **1981**, *22*, 3815.

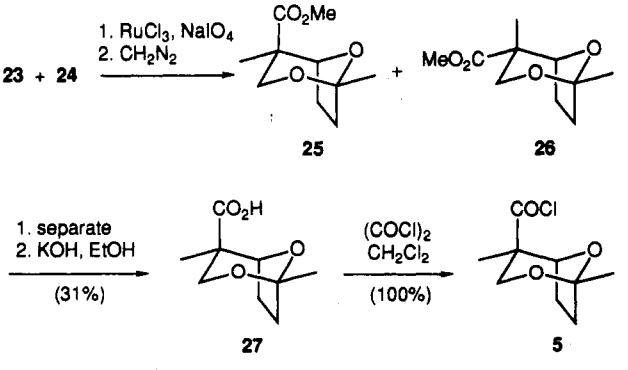
lithium in THF, afforded the acetylenic ketone **19** (79%, 2 steps). Asymmetric carbonyl reduction of **19** by the $LiAlH_4$/Darvon alcohol complex[23] gave alcohol **20** in 93% yield. The enantiomeric purity of **20** was found to be 92% ee by formation of the Mosher ester[24] and analysis by GLC and ^1H NMR. Reduction of ketone **19** by Alpine-borane under high pressure (Midland procedure)[25] also led to the desired propargylic alcohol (55% yield, 90% ee). However, it was more difficult to obtain a pure product with this method upon scale-up to multigram quantities. Having served one of its functions by serving as the controlling element in the establishment of the carbinol absolute stereochemistry, the triple bond was then isomerized to the terminus where it could again be used to our advantage. To this end, treatment of **20** with potassium aminopropylamide (KAPA)[26] in 1,3-diaminopropane at −15 °C cleanly isomerized the triple bond to the terminal position to afford **21** (87%). For confirmation that no racemization had taken place in the course of this isomerization, the Mosher ester was formed and again the enantiomeric purity was found to be 92%.



Hydration of the triple bond in **21** was effected by treatment with $HgSO_4$ and 10% H_2SO_4 in THF. The resulting methyl ketone, however, was not observed. The acidic conditions of the reaction mixture were sufficient to hydrolyze the ketal, and the intermediate keto triol **22** cyclized to the mixture of bicyclic ketal alcohols **23** and **24** in a ratio of approximately 5:1 favoring the desired isomer.[27] The thermodynamic preference in favor of **23** may be due to the fact that this isomer can form an internal hydrogen bond between the axial hydroxymethyl group and one of the dioxane ring oxygens.[28] However, attempts to characterize this intramolecular hydrogen bond by solution IR spectroscopy at different concentrations were unsuccessful. Furthermore, we were unable to improve this ratio by treatment of the ketal mixture under a variety of acidic conditions in nonpolar media where intramolecular hydrogen bonding might be favored over intermolecular hydrogen bonding. That the ratio of ketal isomers is under thermodynamic and not kinetic control was confirmed by resubjecting either isomer[29] to the reaction conditions and isolating the same 5:1 mixture.



Because diastereomeric alcohols **23** and **24** are only separable with difficulty, we chose to proceed with the mixture and separate at a later stage. Direct oxidation of **23**/**24** to the corresponding carboxylic acids proved to be more difficult than originally anticipated. Attempts at this conversion using such standard procedures as $KMnO_4$/NaOH, $KMnO_4$/18-crown-6/benzene, PDC/DMF, or Jones reagent were unsuccessful because they caused decomposition of the ketal. However, it was found that biphasic oxidation with $RuCl_3/NaIO_4$ (Sharpless procedure),[30] followed by immediate esterification of the crude acids with diazomethane, afforded the esters **25** and **26** in reasonable yield. Silica gel chromatography on the ester mixture was quite convenient, the esters having an R_f difference of approximately 0.5 in a solvent system of 20% ethyl acetate/hexanes. Saponification of **25** then delivered the carboxylic acid **27** in an overall yield of 43%. Acid **27** was converted to acid chloride **5** by treatment with oxalyl chloride in dichloromethane.



With the synthesis of both components completed we were prepared to carry out the mixed Claisen condensation

(23) (a) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870. (b) Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 582.

(24) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(25) Midland, M. M.; McLoughlin, J. I.; Gabriel, J. *J. Org. Chem.* **1989**, *54*, 159.

(26) (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891. (b) Midland, M. M.; Halterman, R. L.; Brown, C. A.; Yamaichi, A. *Tetrahedron Lett.* **1981**, *22*, 4171.

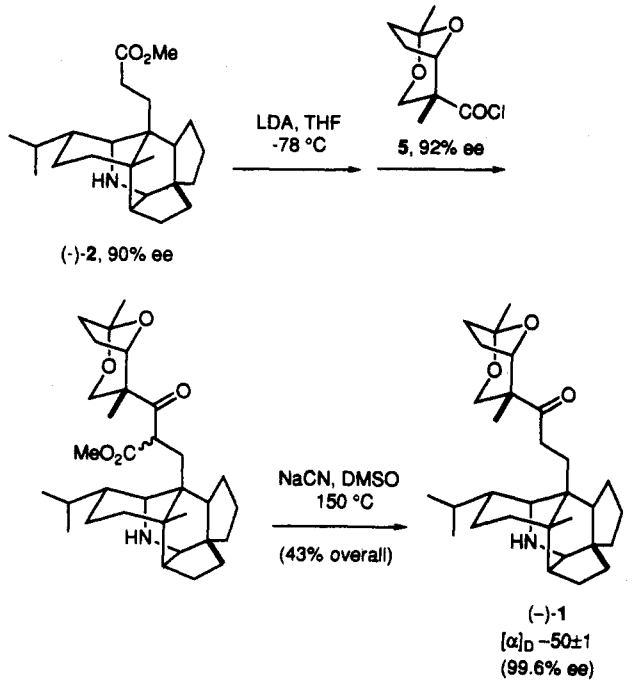
(27) (a) The assignment of stereochemistry was made by the eventual conversion of the major isomer to its corresponding carboxylic acid and comparison of its proton NMR to the published spectrum of authentic material, obtained by degradation of daphniphylline: Irikawa, H.; Sakabe, N.; Yamamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 5691. (b) Bicyclic ketal alcohol **23** has been prepared in racemic form by a synthesis also involving the intermediacy of keto triol **22** (Irikawa, H.; Ishikura, T.; Okumura, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2811). Although these authors do not report the formation of minor diastereomer **24**, we obtained the same 5:1 ratio of **23** and **24** when we subjected pure **23** to conditions that mimic their cyclization procedure.

(28) The position of conformational equilibrium in 1,3-dioxanes is known to be influenced by polar substituents at the 5 position. See, for example: Alonso, J. A.; Wilson, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 1248.

(29) Pure samples of **23** and **24** were obtained by standard $LiAlH_4$ reduction (Et_2O, r.t.) on esters **25** and **26**, respectively.

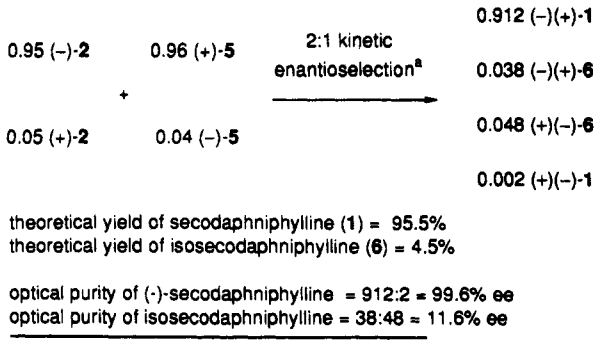
(30) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

leading to the secodaphniphylline skeleton. As before in the racemic series, (−)-methyl homosecodaphniphyllate (90% ee) was treated with LDA, and the acid chloride **5** (92% ee) was added to the resulting enolate solution. After workup, the crude mixture of β-keto esters[31] was subjected to the Krapcho decarboxylation procedure[8] (NaCN, DMSO, 150 °C) to afford, after chromatography (−)-secodaphniphylline (**1**) in 43% yield for the two steps. The synthetic secodaphnipylline was identical in all respects (^{1}H NMR, ^{13}C NMR, IR, TLC mobility) with natural material kindly supplied by Professor Yamamura.[32]



The specific rotation of the synthetic (−)-secodaphniphylline indicated that the optical purity of the material was quite high, even though the two components of the coupling process were of only 92% and 90% ee. This result is a clear demonstration of a stereochemical principle that is perhaps not obvious and certainly not well appreciated by synthetic organic chemists. The principle was first enunciated by Kogure and Eliel in connection with a synthesis of (−)-malyngolide[33] and later recognized by Midland and Gabriel in connection with a synthesis of (−)-talaromycin A.[34] In brief, when two chiral, enantiomerically enriched reactants are coupled, one diastereomeric product will always be of enhanced enantiomeric purity, relative to either of the reactants. The other diastereomeric product in such a coupling reaction can be of higher enantiomeric purity than one of the reactants, but often will be of lower enantiomeric purity than either of the reactants. If there is no kinetic enantioselection, the major diastereomeric product will be the one with enhanced enantiomeric purity.[35] As applied to the synthesis of

Scheme II



[a]The effect of the kinetic enantioselection is only felt in the chemical yield and has no effect on the optical purity.

(−)-secodaphniphylline, the situation is as follows (Scheme II): The two reactants had enantiomeric compositions of 95/5 for **2** and 96/4 for **5**. Thus, the enantiomeric purity of the secodaphniphylline is (0.95 × 0.96)/(0.05 × 0.04) = 456/1, corresponding to 99.6% ee, and that of isosecodaphniphylline is (0.95 × 0.04)/(0.96 × 0.05) = 38/48, corresponding to 11.6% ee. On top of this statistical factor is superimposed the intrinsic kinetic enantioselection of the coupling reaction. This was seen in the reaction of the two racemates to be 2:1, favoring secodaphniphylline over isosecodaphniphylline. Thus, the 1:6 ratio is calculated to be 2 × [(0.95 × 0.96) + (0.05 × 0.04)]/[(0.95 × 0.04) + (0.96 × 0.05)] = 95.5/4.5. Of course, the kinetic enantioselection is mutual; just as (−)-**2** reacts twice as fast with (−)-**5** as it does with (+)-**5**, so also does (+)-**2** react twice as fast with (+)-**5** as it does with (−)-**5**. Therefore, the mutual kinetic enantioselection does not affect the enantiomeric purity of either diastereomer. However, it still results in a doubling of the 1:6 ratio over what would be expected from a purely statistical assembly of the two reactants.

Of course, if the stereochemical enrichment that follows from this logical analysis is to be realized, it is of critical importance that the minor diastereomer be separable from the major diastereomer. In our racemic model study secodaphniphylline and isosecodaphniphylline were found to be inseparable. However, when the scalemic components were used the product secodaphniphylline readily crystallized. In part, at least, this ready physical separation of the two diastereomers was due to the fact that the amount of isosecodaphniphylline formed in the coupling was very small. However, the high enantiomeric purity of the secodaphniphylline probably conferred on it a higher melting point than that of the racemate, whereas the low enantiomeric purity of the minor product resulted in its having a relatively low melting point. Therefore, this purely statistical effect, itself a consequence of the enantiomeric enrichment of the coupling reaction, played an important role in providing synthetic (−)-secodaphniphylline of exceptional enantiomeric purity.

Experimental Section

General. All starting materials were obtained from commercial suppliers and used without purification. THF was distilled from potassium immediately prior to use. Triethylamine (Et_3N) was 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 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. ^{1}H 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 de-

(31) ^{1}H NMR analysis of this β-keto ester mixture showed it to be an approximately 2:1 ratio of diastereomers. The ^{1}H NMR spectrum of this material is provided in the supplementary material.

(32) The ^{1}H NMR and IR spectra of both (−)-secodaphniphylline and synthetic (−)-secodaphniphylline are provided in the supplementary material.

(33) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576.

(34) Midland, M. M.; Gabriel, J. *J. Org. Chem.* **1985**, *50*, 1143.

(35) A more explicit discussion of the phenomenon, accompanied by a series of nomographs depicting the yields and enantiomeric purities of the diastereomeric products of such coupling reactions as a function of the enantiomeric purities of the reactants, is provided in the supplementary material.

termined using the electron-impact method; data are reported as m/z (relative intensity). Elemental analyses were performed at the Berkeley Microanalytical Lab, University of California.

(2*S*-*trans*)-2,5-Dimethyl-1-[1-oxo-5-(phenylmethoxy)-pentyl]pyrrolidine (9). To a solution of 5-(phenylmethoxy)-pentanoic acid[18] (1.78 g, 8.58 mmol) in 15 mL of CH_2Cl_2, cooled to 0 °C, was added oxalyl chloride (0.82 mL, 9.4 mmol). After addition was complete, the ice bath was removed, and the solution was allowed to stand until the bubbling ceased. The CH_2Cl_2 was removed, and the resulting yellow oil was placed under high vacuum. After 1 h this acid chloride was dissolved in 7 mL of ether and pipeted into a vigorously stirring, cooled (0 °C), biphasic mixture of (*S,S*)-dimethylpyrrolidine hydrochloride (890 mg, 6.6 mmol), 10 mL of 2 N NaOH, and 20 mL of ether. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The layers were separated, and the ether layer was washed with H_2O and brine, dried, and concentrated to afford a colorless oil. Chromatography on silica gel (25% ethyl acetate/hexanes) yielded 1.57 g (63%) of **9** as a colorless oil. $[\alpha]_D$ + 13.0 (*c* 3.3, CH_2Cl_2). IR: 1635, 1110 cm^{-1}. ^1H NMR (400 MHz): δ 1.11 (d, 3, J = 6.3), 1.13 (d, 3, J = 6.3), 1.47–1.50 (m, 1), 1.53–1.57 (m, 1), 1.63–1.76 (m, 4), 2.03–2.15 (m, 2), 2.26–2.31 (m, 2), 3.48 (t, 2, J = 6.3), 3.95 (q, 1, J = 6.6), 4.19 (q, 1, J = 6.8), 4.48 (s, 2), 7.24–7.32 (m, 5). ^{13}C NMR (100 MHz): δ 19.18, 21.67, 22.40, 28.97, 29.36, 30.76, 34.38, 52.86, 53.48, 70.21, 72.87, 127.43, 127.59, 127.70, 128.28, 138.52, 171.33. TLC: R_f 0.12 (30% ethyl acetate/hexanes). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.69; H, 9.40; N, 4.84. Found: C, 74.32; H, 9.22; N, 4.74.

Methyl [2*S*-[1[*S[1*R**,1(*E*),2*S**]],2α,5β]]-1-(4,8-Dimethyl-3,7-nonadienyl)-2-[1-[(2,5-dimethyl-1-pyrrolidinyl)-carbonyl]-4-(phenylmethoxy)butyl]cyclopentanecarboxylate (12).** A solution of diisopropylamine (124 μL, 0.88 mmol) in 0.48 mL of THF was cooled to 0 °C, and *n*-BuLi (0.76 mmol, 0.52 mL 1.45 M in hexanes) was added dropwise. The resulting solution was stirred for 15 min at 0 °C and then cooled to −78 °C. After 10 min a solution of amide **9** (183 mg, 0.63 mmol) in 0.48 mL of THF was added dropwise to the stirring solution of LDA. The pale yellow solution was stirred for 40 min, and the enoate **10** (79.9 mg, 0.63 mmol) in 0.39 mL of THF was added dropwise. This solution was stirred for 35 min and a solution of homogeranyl iodide (264 mg, 0.95 mmol) in 0.30 mL of HMPA was added. The yellow solution was stirred for 5.5 h at −78 °C and for 12 h at −10 °C. After warming to room temperature, 5 mL of saturated NH_4Cl and 10 mL of ether were added. The layers were separated and the aqueous layer was extracted with ether (3 × 5 mL). The combined ether extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to yield 561 mg of an orangish brown oil. Chromatography on silica gel (15% ethyl acetate/hexanes) gave 228 mg (64%) of **12**, contaminated with approximately 10% of diastereomer **13**. IR: 1730, 1640 cm^{-1}. ^1H NMR (400 MHz): δ 1.16 (d, 3, J = 6.4), 1.18 (d, 3, J = 6.4), 1.36–1.81 (m, 12), 1.59 (s, 3), 1.60 (s, 3), 1.69 (s, 3), 1.90–2.24 (m, 11), 2.41 (ddd, 1, J = 3.1, 10.4, 10.4), 3.37–3.43 (m, 2), 3.69 (s, 3), 3.99 (q, 1, J = 6.7), 4.19 (q, 1, J = 6.7), 4.48 (d, 2, J = 1.8), 5.09 and 5.11 (m, 2), 7.23–7.31 (m, 5). ^{13}C NMR (125 MHz): δ 15.95, 17.67, 18.37, 22.43, 23.16, 24.76, 25.69, 26.64, 28.52, 28.72, 29.03, 30.79, 30.89, 35.87, 39.34, 39.65, 44.86, 51.35, 53.29, 53.45, 54.05, 56.46, 70.77, 72.82, 124.04, 124.28, 127.42, 127.64, 128.28, 131.32, 135.26, 138.60, 173.28, 177.33. TLC: R_f 0.35 (30% ethyl acetate/hexanes). Although homogeneous by TLC, satisfactory values for combustion analysis could not be obtained for this highly viscous oil. MS: 565 (M^+, 12), 496 (11), 474 (12), 289 (57), 91 (100). HRMS: calcd for $C_{36}H_{55}NO_4$ 565.4131; found 565.4151. Other lower R_f materials were not characterized.

[2*S*-[1[*R[1*R**,2*S**,2(*E*)]],2α,5β]]-1-[2-[2-(4,8-Dimethyl-3,7-nonadienyl)-2-(hydroxymethyl)cyclopentyl]-1-oxo-5-(phenylmethoxy)pentyl]-2,5-dimethylpyrrolidine (14).** Amide ester **12** (1.01 g, 1.78 mmol) was dissolved in 6 mL of toluene, and the solution was cooled to −78 °C under N_2. To this solution was added DIBAL (5.90 mL of a 1.5 M solution in toluene, 8.85 mmol) dropwise over several minutes. The resulting solution was stirred at −78 °C for 2 h. A gas vent needle was placed in the rubber septum, and the reaction mixture was quenched by slow addition of 13 mL of 2 N NaOH. The dry ice–acetone bath was removed, and the mixture was stirred while being warmed to room temperature over 30 min. The reaction mixture was poured into a separatory funnel containing ether (20 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted twice with ether. The combined ether extracts were washed with brine, and the brine was back-extracted with ether. The combined ether extracts were dried and concentrated to obtain 941 mg of a pale yellow oil. Silica gel chromatography of this oil (30% ethyl acetate/hexanes) afforded 695 mg (73%) of **14** as a colorless, viscous oil that solidified after continuous concentration under high vacuum to give a white solid, mp 60–62 °C. $[\alpha]_D$: −3.39 (*c* 2.77, $CHCl_3$). IR: 3410, 1620 cm^{-1}. ^1H NMR (500 MHz): δ 1.16 (d, 3, J = 4.8), 1.17 (d, 3, J = 4.8), 1.23–2.14 (m, 23), 1.57 (s, 6), 1.65 (s, 3), 2.85 (dd, 1, J = 8.4, 14.4), 3.35–3.49 (m, 4), 4.13–4.20 (m, 2), 4.45 (s, 2), 5.07 and 5.08 (overlapping t, 2, J = 7.1), 7.22–7.30 (m, 5). ^{13}C NMR (125 MHz): δ 15.99, 17.66, 18.48, 22.44, 23.18, 23.34, 25.67, 26.67, 28.47, 28.57, 29.10, 30.92, 31.49, 35.20, 38.75, 39.66, 43.39, 47.57, 49.75, 53.35, 53.48, 67.72, 70.85, 72.88, 124.29, 124.58, 127.42, 127.65, 128.27, 131.29, 135.02, 138.56, 174.61. TLC: R_f 0.24 (30% ethyl acetate/hexanes). Anal. Calcd for $C_{35}H_{55}NO_3$: C, 78.16; H, 10.31; N, 2.61. Found: C, 78.08; H, 10.27; N, 2.35.

[4*R*,4a*R*,7a*S*(*E*)]- and [4*S*,4a*R*,7a*S*(*E*)]-(±)-7a-(4,8-Dimethyl-3,7-nonadienyl)hexahydro-4-[3-(phenylmethoxy)-propyl]cyclopenta[*c*]pyran-3(1*H*)-one (15). To a solution of hydroxy amide **14** (205 mg, 0.38 mmol) in 4 mL of ethylene glycol was added 2 mL of 5 N KOH. A reflux condenser was attached to the flask and the solution was heated to 167 °C. TLC analysis (ethylene glycol was evaporated from the plate with a hot air gun) of the reaction mixture after 50 h indicated complete consumption of **14**. After cooling to room temperature, 5 mL of CH_2Cl_2 was added. The stirring mixture was cooled to 0 °C, and 2 N HCl was added until the aqueous layer was adjusted to a pH of about 1. An additional 15 mL of CH_2Cl_2 was added, and the mixture was transferred to a larger flask for more efficient mixing. After vigorous stirring for 20 min, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, dried, and concentrated to obtain 176 mg of a yellow oil. Chromatography on silica gel (20% ethyl acetate/hexanes) yielded 152 mg (92%) of the lactones **15** identical by ^1H NMR and IR with the racemic lactones previously described.[5]

(−)-17,18-Didehydro-23-(phenylmethoxy)-12,16-cyclo-1,12-secodaphnane (17). A stirring solution of oxalyl chloride (82 μL, 118 mg, 0.93 mmol) in CH_2Cl_2 (3.2 mL) cooled to −78 °C was treated dropwise with a solution of DMSO (0.15 mL, 165 mg, 2.00 mmol) in CH_2Cl_2 (0.44 mL). The resulting solution was stirred for 7 min, and a solution of **16** (186 mg, 0.42 mmol) in CH_2Cl_2 (0.64 mL) was added dropwise. The temperature was maintained at −78 °C for 15 min, at which time triethylamine (0.70 mL) was added to the reaction 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 round-bottomed 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 flask and over the surface of the reaction 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 removed with a rotary evaporator, and the white solid residue was placed under high vacuum for 2 h. The flask was vented with N_2, and solid NH_4OAc (330 mg) was added, followed by glacial acetic acid (8.3 mL). This mixture was stirred at room temperature for 30 min and then was placed in an oil bath preheated to 75 °C. After 2 h at this temperature the orange reaction mixture was transferred to a separatory funnel containing H_2O (25 mL) and CH_2Cl_2 (15 mL). The layers were separated, and aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined CH_2Cl_2 extracts were washed with 2 N NaOH (30 mL). The layers were separated, the aqueous 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 172 mg of garlic-scented, amber oil. Silica gel chromatography (30% ethyl acetate/hexanes) of this oil led to 135 mg (77%) of **17** as a pale yellow oil. $[\alpha]_D$: −62 (*c* 0.02). ^1H NMR, ^{13}C NMR, and IR were identical with those previously described.[5]

(−)-Methyl Homosecodaphniphyllate (2). Pentacyclic amine **17** (88 mg, 0.21 mmol) was converted to (−)-**2** by the method previously described.[5] Silica gel chromatography (35% ethyl

acetate/hexanes) of the crude product from this procedure led to 59 mg (78%) of (−)-**2** as a tan solid (mp 77–80 °C, $[\alpha]_D$ = −81.5 (c = 1.12, $CHCl_3$); lit. 102–103 °C, $[\alpha]_D$ = −97.5).[36] This material was recrystallized from *n*-hexanes by being allowed to stand in the refrigerator (−2 °C) for 8 d. The crystalline material so obtained (mp 98–99 °C, $[\alpha]_D$ = −88 (c 0.31, $CHCl_3$)) had 90% ee.

1-(2,2,5-Trimethyl-1,3-dioxan-5-yl)-2-pentyn-1-one (19). To a solution of **18** (476 mg, 2.73 mmol) in 5 mL of CH_2Cl_2 was added 1,1-carbonyldiimidazole (443 mg, 2.73 mmol) in one portion. After the bubbling ceased the resulting solution was allowed to stand for 10 min, and *N,O*-dimethylhydroxylamine hydrochloride (268 mg, 5.46 mmol) was added. The reaction mixture was stirred at room temperature for 20 h, diluted with ether, and transferred to a separatory funnel. The ether solution was washed with H_2O, saturated NH_4Cl, and brine. After drying over $MgSO_4$, the solution was filtered and concentrated to afford 552 mg of a clear oil. Kugelrohr bulb-to-bulb distillation of this oil (ot 60–70 °C, 0.05 Torr) yielded 543 mg (92%) of the *N*-methoxy-*N*-methylamide. IR: 1650 cm^{-1}. ^1H NMR (500 MHz): δ 1.39 (s, 3), 1.41 (s, 3), 1.42 (s, 3), 3.18 (s, 3), 3.69 (s, 3), 3.77 (d, 2, J = 11.8), 4.19 (d, 2, J = 11.8). ^{13}C NMR (125 MHz): δ 18.04, 20.94, 26.28, 33.18, 42.23, 60.85, 65.76, 97.96, 174.79. TLC: R_f 0.47 (50% ethyl acetate/hexanes). Anal. Calcd for $C_{10}H_{19}O_4$: C, 55.27; H, 8.82; N, 6.45. Found: C, 55.31; H, 8.81; N, 6.38.

A solution of the *N*-methoxy-*N*-methylamide (120 mg, 0.55 mmol) in 4 mL of THF was cooled to 0 °C and treated with a solution of butynyllithium (1.1 mmol), which was prepared by addition of *n*-BuLi (1.11 mmol, 0.82 mL 1.35 M in hexanes) to a solution of butyne (119 mg, 2.20 mmol) in 5 mL of THF at 0 °C. After addition of the butynyllithium solution, the reaction mixture was warmed to room temperature and stirred for 30 min. After addition of 1 mL of 5% aqueous HCl, the reaction mixture was concentrated and the residue was partitioned in a separatory funnel between 15 mL of ether and 10 mL of H_2O. The layers were separated, and the ether layer was washed with saturated NH_4Cl and brine, dried, and concentrated to a colorless oil. Bulb-to-bulb distillation (ot 75 °C, 0.05 Torr) of this oil afforded 100 mg (86%) of **19**. IR: 2210, 1670 cm^{-1} ^1H NMR (400 MHz): δ 1.13 (s, 3), 1.21 (t, 3, J = 7.5), 1.36 (s, 3), 1.42 (s, 3), 2.40 (q, 2, J = 7.5), 3.67 (d, 2, J = 11.8), 4.28 (d, 2, J = 11.8). ^{13}C NMR (100 MHz): δ 12.71, 12.74, 17.98, 22.11, 24.97, 47.24, 65.43, 77.76, 97.79, 98.02, 189.83. TLC: R_f 0.59 (30% ethyl acetate/hexanes). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.62. Found: C, 68.68; H, 8.62.

(*S*)-α-1-Butynyl-2,2,5-trimethyl-1,3-dioxane-5-methanol (20). To a stirring suspension of $LiAlH_4$ (265 mg, 6.98 mmol) in ether (172 mL) at 0 °C was added dropwise a solution of Darvon alcohol (4.94 g, 17.4 mmol) in ether (28 mL). After addition was complete the resulting solution was stirred at 0 °C for 2 min and then cooled to −78 °C, at which time a thick white precipitate formed. A solution of ketone **19** (1.22 g, 5.81 mmol) in ether (28 mL) was then added slowly to the cooled (−78 °C) Darvon alcohol/$LiAlH_4$ complex. The resulting colorless solution was maintained at −78 °C for 5 h. The dry ice–acetone bath was removed, and the solution was allowed to warm gradually to room temperature overnight. The resulting clear solution was quenched by slow addition of water (70 mL) and allowing the resulting mixture to stir for 30 min. The layers were separated and the organic layer was washed with 1 N HCl (3 × 30 mL) and brine (30 mL). The ether solution was dried and concentrated to obtain 1.14 g (93%) of **20** as colorless, viscous oil that solidified on standing to give a white solid, mp 50–53 °C $[\alpha]_D$: −4.87 (c 1.72, $CHCl_3$). IR (CCl_4): 3610, 3450, 1200 cm^{-1}. ^1H NMR (500 MHz): δ 0.87 (s, 3), 1.12 (t, 3, J = 7.5), 1.38 (s, 3), 1.42 (s, 3), 2.20 (d, 1, J = 2.0), 2.21 (dq, 2, J = 2.0, 7.5), 3.59 (dd, 2, J = 10.2, 11.8), 3.82 (dd, 2, J = 1.9, 11.8), 4.75 (t, 1, J = 2.5). ^{13}C NMR (125 MHz): δ 12.37, 13.83, 14.72, 20.57, 26.75, 37.79, 63.99, 65.17, 67.23, 77.74, 88.58, 98.04. TLC: R_f 0.45 (30% ethyl acetate/hexanes). Anal. Calcd for $C_{15}H_{20}O_3$: C, 67.89; H, 9.49. Found: C, 67.50; H, 9.53.

(*S*)-α-3-Butynyl-2,2,5-trimethyl-1,3-dioxane-5-methanol (21). A solution of potassium aminopropylamide was prepared by addition of 1,3-diaminopropane (12 mL) to KH (1.60 mg of a 35% mineral oil dispersion prewashed three times with hexanes, 560 mg of KH, 13.9 mmol). The resulting suspension was stirred at room temperature for 3 h, during which time the reaction mixture became a homogeneous, amber-colored solution. This solution was cooled to −10 °C (ice/acetone), and a solution of **20** (561 mg, 2.65 mmol) in 1,3-diaminopropane (3 mL) was added rapidly. After 45 min the reaction mixture was poured into a 100-mL Erlenmeyer flask containing 35 mL of a saturated NH_4Cl solution cooled to 0 °C. This mixture was stirred vigorously for 5 min at 0 °C and then at room temperature for 20 min. Extraction with ether (4 × 20 mL), drying of the combined extracts, and concentration led to a colorless oil that was chromatographed on silica gel (30% ethyl acetate/hexanes) to obtain 488 mg (87%) of the terminal acetylene **21**. IR: 3460, 2120 cm^{-1}. ^1H NMR (500 MHz): δ 0.83 (s, 3), 1.39 (s, 3), 1.43 (s, 3), 1.55–1.62 (m, 1), 1.68–1.74 (m, 1), 2.00 (t, 1, J = 2.7), 2.32–2.47 (m, 3), 3.55 (d, 2, J = 11.9), 3.72 (dd, 1, J = 1.7, 11.9), 3.93 (dd, 1, J = 1.6, 11.8), 3.96 (bs, 1). ^{13}C NMR (125 MHz): δ 15.28, 15.78, 21.97, 25.39, 29.81, 37.08, 66.49, 67.18, 68.99, 72.23, 84.07, 98.09. TLC: R_f 0.32 (30% ethyl acetate/hexanes). MS: 212 (M^+, 0.15), 197 (59). HRMS: calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1416.

(1*R*-*exo*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octane-4-methanol (23). Acetylene **21** (481 mg, 2.27 mmol) was dissolved in a solution of THF (8 mL) and 10% H_2SO_4 (4 mL), cooled to 0 °C, and stirred vigorously as $HgSO_4$ (67 mg, 0.23 mmol) was added. The resulting solution was allowed to warm to room temperature while being stirred over a period of 12 h. The reaction mixture was then diluted with ether (15 mL) and washed with brine (10 mL). The aqueous layer was extracted twice with ether, and the combined ether extracts were dried and concentrated to give a colorless oil (378 mg). Silica gel chromatography (35% ethyl acetate/hexanes) of this oil provided 370 mg (95%) of a mixture of bicyclic alcohols **23** and **24**. GLC and NMR analysis of this mixture indicated an approximately 5:1 ratio of isomers.

Compound 23 (major isomer). IR: 3450, 2970, 1395 cm^{-1}. $[\alpha]_D$: −1.13 (c 2.04, CH_2Cl_2). IR (CCl_4, 0.3 M): 3650, 3500, 2980, 1400 cm^{-1}. ^1H NMR (400 MHz): δ 0.74 (s, 3), 1.48 (s, 3), 1.80–1.86 (m, 1), 1.99–2.09 (m, 3), 2.32 (br s, 1), 3.52 (d, 1, J = 11.9), 3.59 (dd, 1, J = 1.6, 11.9), 3.78 (d, 1, J = 10.6), 3.88 (d, 1, J = 10.6), 4.22 (d, 1, J = 6.2). ^{13}C NMR (100 MHz): δ 17.11, 23.71, 24.88, 33.21, 37.40, 66.48, 67.11, 80.44, 104.94. TLC: R_f 0.16 (30% ethyl acetate/hexanes). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.81; H, 9.75.

Compound 24 (minor isomer). IR: 3440, 1465, 1395 cm^{-1}. ^1H NMR (400 MHz): δ 1.30 (s, 3), 1.45 (s, 3), 1.77–1.83 (m, 1), 1.92–2.01 (m, 3), 3.27 (d, 1, J = 10.9), 3.34 (d, 1, J = 10.9), 3.37 (dd, 1, J = 1.8, 11.4), 3.57 (d, 1, J = 11.5), 4.07 (dd, 1, J = 1.5, 6.7). ^{13}C NMR (100 MHz): δ 19.25, 23.79, 24.99, 33.03, 37.69, 66.86, 67.15, 80.89, 105.17.

Methyl (1*R*-*exo*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octane-4-carboxylate (25 and 26). Alcohols **23** and **24** (380 mg, 2.21 mmol) and $NaIO_4$ (1.92 g, 9.01 mmol) were partitioned between a biphasic mixture of CH_3CN (4.4 mL), CCl_4 (4.4 mL), and H_2O (6.6 mL), and the mixture was cooled to 0 °C in an ice bath. This cooled mixture was stirred vigorously as $RuCl_3 \cdot 3H_2O$ (10 mg, 2.2 mol %) was added in one portion. The resulting brown mixture was maintained at 0 °C for 15 min. The cold bath was removed and the mixture was stirred at room temperature for 5 min, at which time the mixture was diluted with CH_2Cl_2 (10 mL) and stirred for an additional 20 min. The layers were separated and the aqueous layer was extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were dried and evaporated. The black residue was taken up in ether and filtered though Celite. Concentration afforded 343 mg of a dark oil that was dissolved in 5 mL of ether and cooled to 0 °C. To this cold ether solution was added a solution of CH_2N_2 in ether until a slight yellow color persisted and bubbling ceased. After 1 h the solvent was removed to leave 331 mg of the crude ester as a green-black oil. Chromatography on silica gel (20% ethyl acetate/hexanes) gave 191 mg (43%) of ester **25** and 44 mg (10%) of ester **26** as colorless oils.

Compound 25. IR: 1740 cm^{-1}. ^1H NMR (400 MHz): δ 0.89 (s, 3), 1.41 (s, 3), 1.81–1.87 (m, 2), 1.98–2.04 (m, 2), 3.43 (d, 1, J = 11.8), 3.74 (s, 3), 4.24 (dd, 1, J = 1.9, 11.8), 4.66 (dd, 1, J = 1.8, 7.2). ^{13}C NMR (100 MHz): δ 18.06, 23.57, 24.22, 33.49, 45.62, 52.24, 65.52, 80.34, 104.99, 175.02. TLC: R_f 0.40 (30% ethyl acetate/

(36) The optical rotation of natural methyl homosecodaphniphyllate was measured at Berkeley with a sample provided by Professor Yamamura.

hexanes). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.66; H, 8.22.

Compound 26. IR: 1740 cm^{-1}. ^1H NMR (400 MHz): δ 1.43 (s, 3), 1.46 (d, 3, J = 0.7), 1.64–1.78 (m, 2), 1.97–2.09 (m, 2), 3.58 (dd, 1, J = 1.7, 12.1), 3.63 (s, 3), 3.99 (d, 1, J = 12.0), 4.34 (dd, 1, J = 1.4, 7.9). ^{13}C NMR (100 MHz): δ 20.61, 23.53, 27.53, 32.69, 43.91, 51.71, 65.11, 80.05, 105.36, 174.53. TLC: R_f 0.60 (30% ethyl acetate/hexanes).

(1*R*-*exo*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octane-4-carboxylic Acid (27). A solution of **25** (191 mg, 0.95 mmol), 5 N KOH (2 mL), and absolute ethanol (5 mL) was heated to 70 °C for 2.5 h. The solution was cooled to room temperature and extracted with ether (2 × 10 mL). The aqueous layer was cooled to 0 °C, CH_2Cl_2 (10 mL) was added, and the resulting mixture was stirred vigorously as concd HCl was added until pH <2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried and evaporated to obtain 128 mg (72%) of acid **27** as colorless needles, mp 105–7 °C. This material was recrystallized from 1:1 benzene/hexanes to obtain material of slightly greater purity, mp 111–13 °C (lit. mp[37] 122–23 °C). $[\alpha]_D$: +5.3 (c 0.38, CH_2Cl_2). IR (CCl_4): 3000, 1720 cm^{-1}. ^1H NMR (500 MHz): δ 0.99 (s, 3), 1.48 (s, 3), 1.86–1.94 (m, 2), 2.03–2.10 (m, 2), 3.50 (d, 1, J = 11.9), 4.22 (dd, 1, J = 1.7, 11.9), 4.68 (d, 1, J = 5.9). ^{13}C NMR (125 MHz): δ 17.99, 23.64, 24.39, 33.38, 45.42, 65.53, 80.29, 105.41, 179.66. MS: 186 (M^+, 3.7), 168 (3.6), 136 (65), 121 (100). HRMS: calcd for $C_9H_{14}O_4$ 186.0892, found 186.0885. Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.58. Found: C, 58.34; H, 7.92.

(1*R*-*exo*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octane-4-carbonyl Chloride (5). A solution of 20.2 mg (0.11 mmol) of **27** and 28 μL (0.33 mmol) of oxalyl chloride in 0.3 mL of CH_2Cl_2 in a pear-shaped flask was kept at room temperature for 2 h and then concentrated under vacuum to obtain 22.1 mg (100%) of acid chloride **5**. After 1 h under high vacuum the flask was vented with N_2 and capped with a white rubber septum; the yellow solid so obtained was used directly in the next step. ^1H NMR (400 MHz): δ 1.08 (s, 3), 1.47 (s, 3), 1.86–1.94 (m, 2), 2.04–2.15 (m, 2), 3.55 (d, 1, J = 12.2), 4.25 (dd, 1, J = 2.1, 12.2), 4.82 (dd, 1, J = 1.4, 7.0).

(−)-Secodaphniphylline (1). To a solution of freshly distilled diisopropylamine (32 μL, 0.23 mmol) in 0.2 mL of dry THF at 0 °C under N_2 was added dropwise 138 μL of a 1.31 M solution of n-butyllithium in hexanes (0.18 mmol). The resulting solution was stirred at 0 °C for 10 min and then cooled to −78 °C over 15 min. To this stirring solution was added dropwise a solution of 32.5 mg (0.09 mmol) of (−)-methyl homosecodaphniphyllate (**2**) in 0.2 mL of THF. The resulting solution was stirred at −78 °C for 45 min and a solution of 22.1 mg (0.11 mmol) of **5** in 0.2 mL of THF was added. After being stirred for 1 h at −78 °C, the reaction mixture was quenched by addition of 0.5 mL of 1:1 saturated NH_4Cl/brine. The mixture was transferred to a separatory funnel, extracted with CH_2Cl_2 (4 × 5 mL), dried (K_2CO_3), filtered, and concentrated to obtain 49.8 mg of a brown oil. This oil was passed though a plug of silica gel in a Pasteur pipet (50% ethyl acetate/hexanes elute) to yield 41.4 mg of the β-keto ester mixture as a clear amber oil.[31]

This oil was dissolved in 2.5 mL of DMSO in a 10-mL round-bottomed flask, and 56 mg (1.1 mmol) of NaCN and 6 drops of water were added. The flask was immersed in a oil bath preheated to 150 °C and the solution was stirred at this temperature for 2 h, at which time 10 drops of 10% H_2SO_4 were added. The solution was stirred an additional 20 min at 150 °C and then cooled to room temperature. Water (3 mL) was added, followed by solid K_2CO_3, until the pH was greater than 7. The mixture was transferred to a separatory funnel containing ether and water. The aqueous layer was extracted five times with ether and the combined ether extracts were dried (K_2CO_3), filtered, and concentrated to give a yellow oil. This oil was passed through a plug of silica gel (50% CH_2Cl_2/ethyl acetate) to yield 19 mg (44%) of secodaphniphylline (**1**) as a clear, colorless oil that was crystallized by treatment with n-hexanes. The crystalline material had mp 124–25 °C (lit. mp[4] 129–30 °C) and $[\alpha]_D$ −50 ± 1 (c 0.35, $CHCl_3$).[38] IR (CCl_4): 2950, 1715, 1390, 1185, 1145, 1060 cm^{-1}. ^1H NMR (500 MHz): δ 0.78 (s, 3), 0.80 (s, 3), 0.88 (d, 3, J = 6.7), 0.91 (d, 3, J = 6.6), 1.16 (br dt, 1, J = 3.0, 13.1), 1.38–1.74 (m, 19), 1.43 (s, 3), 1.83–1.94 (m, 3), 2.04–2.09 (m, 2), 2.54 (d, 1, J = 4.4), 2.63 (m, 1), 2.89 (m, 1), 3.03 (s, 1), 3.51 (d, 1, J = 12.1), 4.26 (dd, 1, J = 1.9, 12.1), 4.67 (d, 1, J = 5.5). ^{13}C NMR (125 MHz): δ 17.66, 20.72, 20.96, 21.07, 21.38, 22.86, 23.61, 24.59, 25.74, 26.73, 28.75, 29.72, 33.79, 34.11, 36.02, 36.24, 36.87, 38.98, 39.76, 42.84, 47.72, 48.45, 49.76, 50.47, 53.39, 59.99, 65.39, 80.87, 105.19, 213.19. MS: 469 (M^+, 70), 426 (20), 328 (19), 316 (32), 300 (39), 286 (100). HRMS: calcd for $C_{30}H_{47}NO_3$ 469.3556, found 469.3562.

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Registry No. (−)-**1**, 28606-61-3; (−)-**2**, 28519-09-7; **3** (isomer 1), 138517-56-3; **3** (isomer 2), 138604-20-3; **5**, 129570-17-8; **7**, 138133-34-3; **8** acid, 64740-39-2; **9**, 129539-96-4; **10**, 25662-28-6; **11**, 22339-13-5; **12**, 138517-50-7; **13**, 129645-69-8; **14**, 129539-98-6; **15** (isomer 1), 138604-13-4; **15** (isomer 2), 138604-14-5; **16** (isomer 1), 138604-15-6; **16** (isomer 2), 138604-16-7; **17**, 138517-51-8; **18**, 16837-14-2; **18** (*N*-methoxy-*N*-methylamide), 138517-57-4; **19**, 129539-99-7; **20**, 129540-00-7; **21**, 129540-01-8; **23**, 129645-66-5; (±)-**23**, 138604-18-9; **24**, 129645-67-6; (±)-**24**, 138604-19-0; **25**, 138517-52-9; **26**, 138604-17-8; **27**, 129645-68-7; (±)-**27**, 65337-04-4; S1, 3663-46-5; S2, 138517-53-0; (±)-S3, 138517-54-1; (±)-S4, 138517-55-2; 1-butyne, 107-00-6.

Supplementary Material Available: A more thorough discussion of the enantiomeric enhancement that results from coupling two enantiomerically enriched reactants, along with 11 nomographs for estimating the % yield and % ee of the major and minor products in various cases; a description, including full experimental details, for the preparation of (±)-**5**; ^1H NMR and IR spectra of natural and synthetic secodaphniphylline; ^1H NMR spectra of the scalemic β-keto ester mixture and the (±)-secodaphniphylline and (±)-isosecodaphniphylline mixture; an overlay of the expanded ^1H NMR spectra (downfield region) of the (±)-secodaphniphylline and (±)-isosecodaphniphylline mixture, synthetic (−)-secodaphniphylline, and natural (−)-secodaphniphylline (25 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.

(37) Irikawa, H.; Sakabe, N.; Yamamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 5691.

(38) Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron Lett.* **1972**, *28*, 1477. We observed $[\alpha]_D$ = −51 ± 0.5 (c = 1.06, $CHCl_3$) for an authentic sample of secodaphniphylline kindly provided by Professor Yamamura.