Articles

Daphniphyllum Alkaloids. 16. Total Synthesis of (+)-Codaphniphylline[1]

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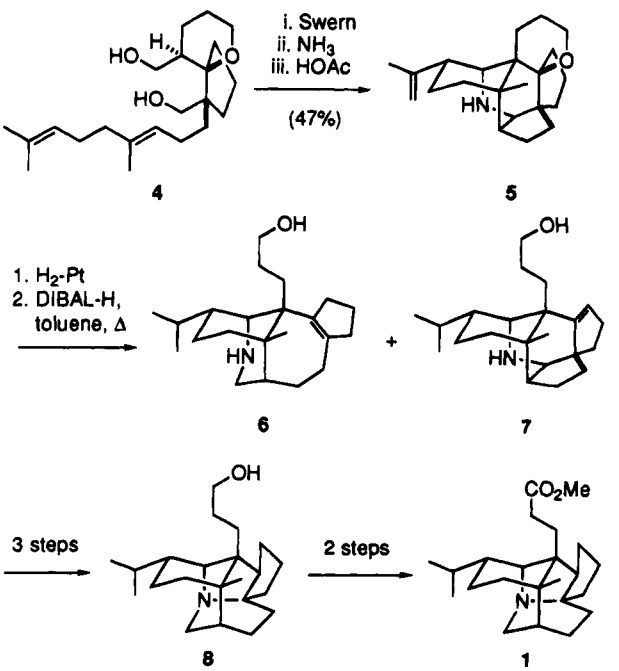
A total synthesis of (+)-codaphniphylline (**3**) has been developed. The synthesis begins with Noyori asymmetric reduction of methyl 2-oxocyclopentanecarboxylate (**15**), which gives the *trans*-β-hydroxy ester **16** (93% ee). Frater–Seebach alkylation of this material with homogeranyl iodide gives hydroxy esters **18** and **19** in a ratio of 15:1. This mixture is oxidized to keto ester **29**, which is converted into acetal **34**. Reduction of the ester function gives primary alcohol **35**, which is esterified by treatment with 2-bromo-4-chlorobutanoyl chloride. The resulting keto ester, **33**, is treated with unactivated zinc dust in the presence of 2 equiv of $ZnCl_2$ to obtain lactone ether **36**, which is reduced by lithium aluminum hydride to diol **9**. Serial treatment of this material with Swern oxidant, methylamine, and warm acetic acid provides the hexacyclic amino ether **10** in 63% overall yield. Reductive fragmentation to **11** results when **10** is treated with excess diisobutylaluminum hydride in hot toluene. Ring closure to the daphnane skeleton (**12**) occurs when the *N*,*O*-bis(phenylcarbamoyl) derivative **41** is treated with hot acetic acid, followed by KOH in methanol. Displacement of the tosyl group gives sulfide **50**, which is oxidized to sulfone **13**. This material is metalated and coupled with enantiomerically-pure aldehyde **46** to secure the codaphniphylline skeleton, as a mixture of four diastereomeric β-hydroxy sulfones (**51**). Oxidation gives a mixture of diastereomeric β-keto sulfones (**52**), which is desulfonated to obtain (+)-codaphniphylline (**3**). The synthesis requires 12 steps from homogeranyl iodide, the more precious starting material, and provides the enantiomerically pure alkaloid in 9% overall yield.

The *Daphniphyllum* alkaloids are squalene-derived amines that are found in extracts of fruit, bark, and leaves of *Daphniphyllum marcopodum*, *D. maxim*, and *D. teijsmanni*, trees native to Japan,[3] and *D. gracile*, a related tree found in New Guinea. In previous papers in this series, we have reported the development of a possibly biomimetic synthesis of the basic skeleton of the Daphniphyllum alkaloids and have employed this route for syntheses of methyl homosecodaphniphyllate (**1**),[4] secodaphniphylline (**2**),[5] and other *Daphniphyllum* alkaloids.[6] In this paper, we report a modification of our basic approach and application of this modified approach for the first total synthesis of (+)-codaphniphylline (**3**).[7]

Some of the key transformations in our synthesis of alkaloid **1** are outlined in Scheme 1. There were two problems with this synthesis. First, the cyclization

Scheme 1



process (**4** → **5**) proceeds in only 47% yield, much lower than the typical range of 75–95% for this process with other substrates we have employed. It was hypothesized that the reduced yield might result from the presence of the quaternary ether linkage in **4**. The other problem in Scheme 1 is that the reductive fragmentation of **5** to **6** is accompanied by about 15% simple elimination, giving **7**. We thought that both these problems might be

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(1) For an overview of previous work in this area, see: Heathcock, C. H. *Angew. Chem.* **1992**, *104*, 675. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 665.

(2) Current address: Pfizer Research Company; Groton, CT.

(3) For reviews of the *Daphniphyllum* alkaloids, see: (a) Yamamura, S.; Hirata, Y. In *The Alkaloids*, Manske, R. H. F., Ed., Academic Press: 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 Press: New York, **1986**, Vol. 29, p 265.

(4) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544.

(5) Heathcock, C. H.; Stafford, J. A. *J. Org. Chem.* **1992**, *57*, 2566.

(6) (a) Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3714. (b) Heathcock, C. H.; Piettre, S.; Ruggeri, R. B.; Ragan, J. A.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2554. (c) Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585. (d) Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575.

(7) Irakawa, H.; Sakabe, N.; Yamamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 5641.

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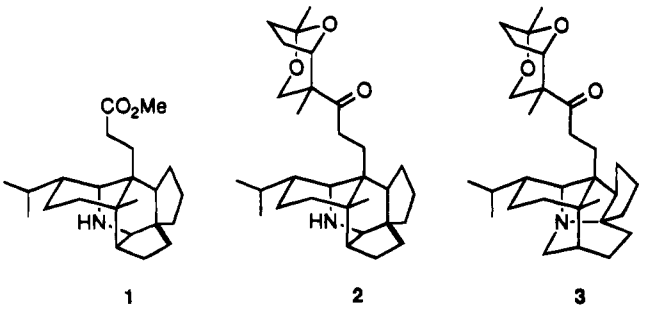
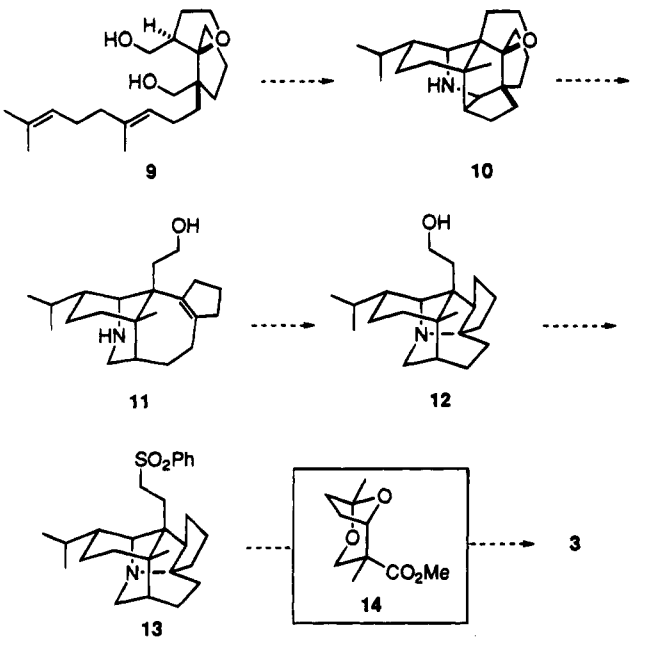


ameliorated by changing the tetrahydropyran in **4** to a tetrahydrofuran, as in **10** (Scheme 2). The rationale for this proposed modification was the nebulous belief that tetrahdrofurans, which are usually easier to form than tetrahydropyrans, might be less prone to undergo ring-opening reactions. The modified approach illustrated in Scheme 2 would, of course, deliver the required pentacyclic skeleton (**12**) with a two-carbon side-chain, rather than the three-carbon side-chain, as in intermediate **8** on the way to methyl homodaphniphyllate. However, we thought that **12** might serve as an appropriate precursor to codaphinphylline (**3**) as shown in Scheme 2.

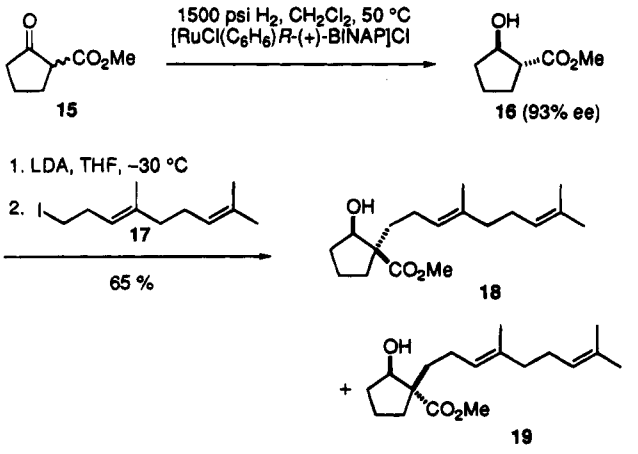
As shown in Scheme 3, the synthesis of codaphniphylline began with Noyori hydrogenation of methyl 2-oxocyclopentanecarboxylate (**15**).[8] The trans isomer **18** is obtained exclusively in 93% ee. The analogous ethyl ester derivative can be prepared in higher enantiomeric purity (99% ee) by lipase-mediated kinetic resolution of the acetate ester of racemic **16**.[9] However, in our hands, this procedure was difficult to scale up. The dianion of **16** was prepared and alkylated at −30 °C with homogeranyl iodide (**17**)[10] to obtain a chromatographically inseparable mixture of hydroxy esters **18** and **19** in a ratio of 15:1.[11] The cis relationship between the hydroxy and carbomethoxy groups of **18**, the major component of the mixture, was confirmed by the ^{1}H NMR resonance of the hydroxy proton, which is a sharp doublet due to coupling to the carbinol proton. The coupling is presumably due to the fact that the hydroxy proton is not exchanging because it is intramolecularly hydrogen bonded to the carbonyl of the methyl ester. In the minor diastereomer, the hydroxy and the carbomethoxy groups are trans, an intramolecular hydrogen bond is geometrically disfavored, and such coupling is not observed.

With the desired chirality established, we turned our attention to the intramolecular Reformatsky reaction that would be used to construct the desired tetrahydrofuran.[12] We anticipated a problem in this transformation. As shown in Scheme 4, the desired reaction pathway involves an intermediate bromozinc enolate (**20**) that can add to the ketone to give **21**, and thence intermediate **22** (path A). On the other hand, enolate **20** can also be expected to cyclize to cyclopropyl ester **23** (path B). This competing cyclopropane formation is an alternative that was not present in earlier applications

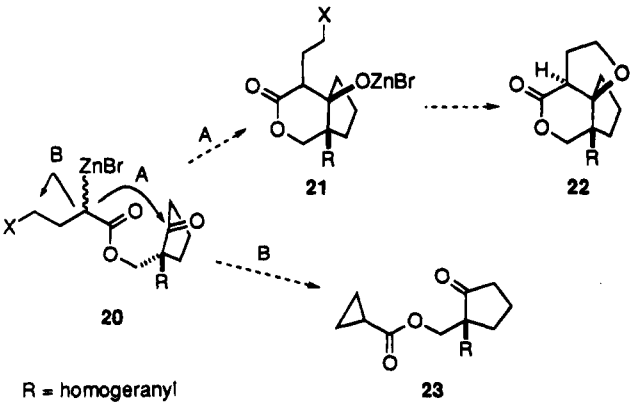
Scheme 2



Scheme 3



Scheme 4



of similar intramolecular Reformatsky reactions.[6a,c,12] To evaluate this possibility, a model study was carried out with the methyl-substituted dibromo esters **25a** and **25b**, which arise from acylation of alcohol **24** with 2,4-dibromobutanoyl chloride or 2-bromo-4-chlorobutanoyl chloride (Scheme 5). This study showed that our concerns had been justified. Addition of the 2,4-dibromo

(8) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taktoni, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.

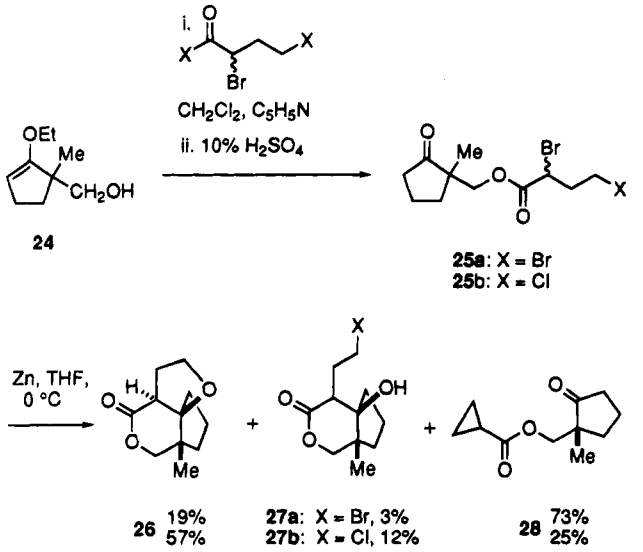
(9) Xie, Z.; Suemune, H.; Nakamura, I.; Sakai, K. *Chem. Pharm. Bull.* **1987**, *35*, 4454.

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

(11) (a) Herrmann, J. L.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2429. (b) Kraus, B. A.; Taschner, M. J. *Tetrahedron Lett.* **1977**, 4575. (c) Frater, G. *Helv. Chim. Acta.* **1979**, *62*, 2825. (d) Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1983**, *63*, 109.

(12) Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 5745.

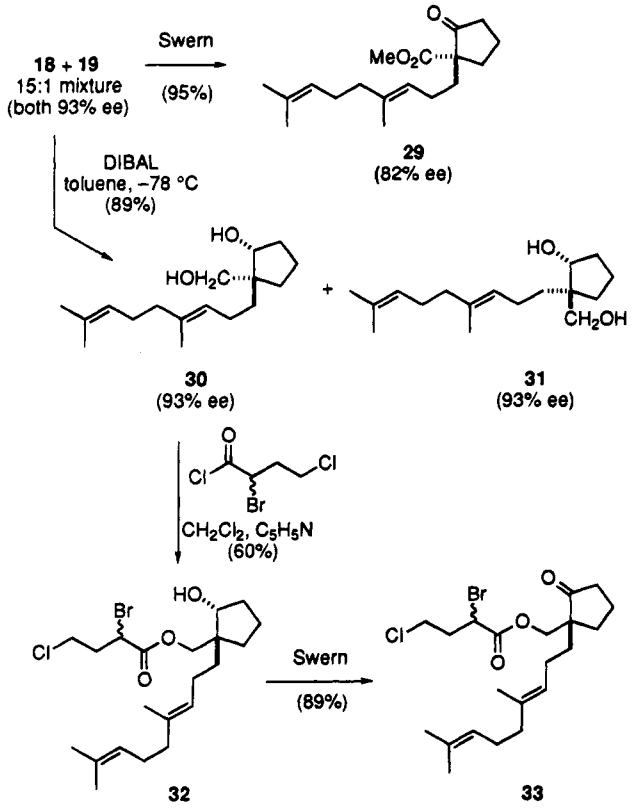
Scheme 5



ester **25a** to a suspension of highly active zinc[13] in THF at 0 °C resulted in rapid disappearance of starting material and appearance of three products, cyclopropyl ester **28** (73%), lactone **26** (19%), and lactone **27a** (3%). However, application of the same conditions to the 2-bromo-4-chloro ester **25b** gave a more agreeable mixture of the same three products. With this substrate, the desired lactone **26** was obtained in 57% yield, accompanied by 12% of the uncyclized bromo alcohol **27b** and only 25% of cyclopropyl ester **28**. The effect of the halo substituent at C-2 was also explored. However, not surprisingly, both the 2,4-dichloro and 2-iodo-4-chloro analogs of **25** gave essentially the same product ratio as **25b**.[14] When we eventually reached the intramolecular Reformatsky reaction in the course of our actual synthesis, we did discover a way to further improve the ratio of lactone to cyclopropyl ester (see later), but this improved procedure was not applied to the model substrate **25b**.

Oxidation of the 15:1 mixture of **18** and **19** provided keto ester **29** (Scheme 6). An unfortunate consequence of the fact that **18** and **19** could not be separated is revealed in this oxidation. The major enantiomer of the minor diastereomer **19** gives, upon oxidation, the minor enantiomer of the keto ester. As a result, the keto ester **29** produced in this manner has an enantiomeric purity of only 82% ee. That is, since **18** and **19** are each 93% ee, the mixture obtained in the Frater–Seebach alkylation has the composition 90.7% **18**, 3.3% ent-**18**, 5.8% **19**, and 0.2% ent-**19**. Upon oxidation, **18** and *ent*-**19** give **29** (90.9%), whereas *ent*-**18** and **19** give *ent*-**29** (9.1%). One attempt to circumvent this problem was only partly successful. Reduction of the mixture of **18** and **19** with diisobutylaluminum hydride afforded a mixture of diols **30** and **31**. It was possible to separate these isomers by careful silica gel chromatography and obtain the major isomer, **30**, in 89% yield. This diol presumably has the same enantiomeric purity (93% ee) as its precursor, hydroxy ester **18**. However, acylation of **30** with 3-bromo-4-chlorobutanoyl chloride proved not to be as regioselective as we had hoped. Although ester **32** is the major reaction product, it is accompanied by the bis-acylation product. Careful silica gel chromatography permitted the

Scheme 6



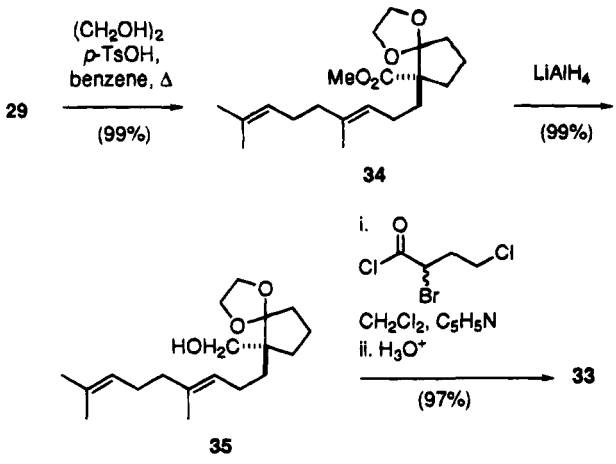
isolation of ester **32** in only 60% yield. Oxidation of this substance by the method of Swern[15] gave keto ester **33** in 89% yield.

In an attempt to increase the efficiency of this process we reversed the order of steps, first attempting to selectively oxidize the secondary hydroxy of **30**, then acylating the remaining primary alcohol. Two selective oxidation procedures (Fetizon's reagent,[16] Br_2 and Al_2O_3/PhCHO[17]) were investigated, but neither reagent accomplished selective oxidation. The low yield in acylation of **30** caused us to resort to a more conservative synthetic approach using keto ester **29** of 82% ee, with the hope that we could enhance the enantiomeric purity at a later stage of the synthesis. To this end, ketone **29** was protected as acetal **34** and the ester reduced with $LiAlH_4$ to provide primary alcohol **35** in 99% yield (Scheme 7). Treatment of **35** with 3-bromo-4-chlorobutanoyl chloride provided the acetal/ester that was deprotected by stirring in a 10:1 mixture of THF:10% H_2SO_4 for 48 h. The resulting product, bromo ester **33**, was isolated in 97% yield (90% for the four steps from the mixture of **18** and **19**).

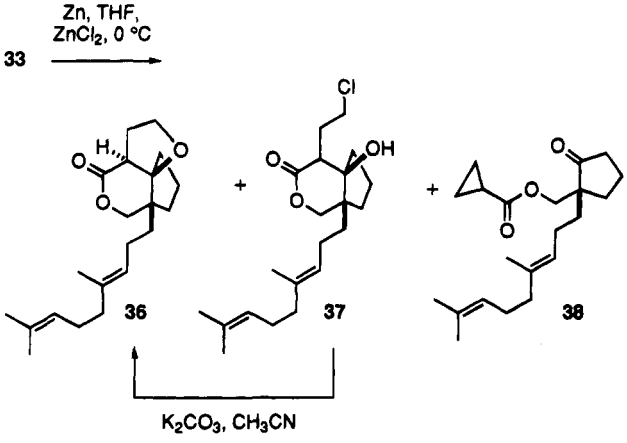
Application of the intramolecular Reformatsky conditions to keto ester **33** gave a mixture of lactone ether **36** (50%), uncyclized chlorohydrin **37** (14%), and cyclopropyl ester **38** (32%) (Scheme 8). Treatment of **37** with potassium carbonate in acetonitrile at room temperature gave additional **36**, for a total yield of this desired material of 64%. Thus, in this case, the ratio of the intramolecular Reformatsky reaction to cyclopropane formation is only 2:1, somewhat lower than was observed under the best conditions with the model keto ester **25b**

(13) Arnold, R. T.; Kulenovic, S. T. *Synth. Commun.* **1977**, *7*, 223.
(14) Harpp, D. N.; Bao, L. Q.; Black, C. J.; Smith, R. A. *Tetrahedron Lett.* **1974**, 3235.
(15) Swern, D.; Mancusco, A. J. *Synthesis* **1981**, 165.
(16) McKillop, A.; Young, D. W. *Synthesis.* **1979**, 401.
(17) Posner, G. H.; Perfetti, R. B.; Runquist, A. W. *Tetrahedron Lett.* **1976**, *39*, 3499.

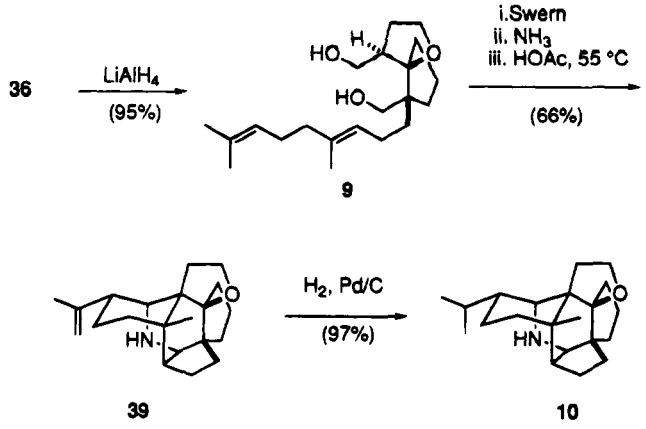
Scheme 7



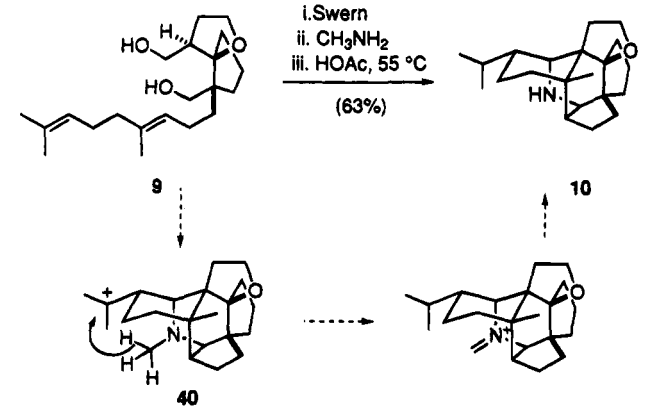
Scheme 8



Scheme 9



Scheme 10



(Scheme 5). In the process of optimizing the **36**:**38** ratio, we evaluated various other reducing agents, including SmI_2[18] and $VCl_3(THF)_3$,[19] neither of which gave detectable amounts of the Reformatsky products. The classical Reformatsky conditions,[20] heating **33** with unactivated zinc dust in THF for 6 h, gave solely the debrominated keto ester. Thus, under these conditions the zinc enolate apparently forms, but does not undergo intramolecular addition to the ketone. This was an intriguing result when compared with our original procedure, which employed activated zinc, generated by reduction of an excess of $ZnCl_2$ by sodium naphthalenide. Therefore, our previous intramolecular Reformatsky reactions had actually been carried out in the presence of excess of $ZnCl_2$. This discovery led to an improved procedure for the intramolecular Reformatsky reaction in which **33** was treated with unactivated zinc dust and 2 equiv of $ZnCl_2$ in refluxing THF. Under these conditions, lactone ether **36** is obtained in 67% yield, uncyclized chlorohydrin **37** in 9% yield, and cyclopropyl ester **38** in 11% yield. Chlorohydrin **37** was quantitatively cyclized to **36** by treatment with K_2CO_3 in acetonitrile, giving a total yield of **36** of 76%. A brief study revealed that the diethylaluminum chloride and BF_3 etherate both catalyzed the zinc dust Reformatsky reaction but neither of these Lewis acids provided an improvement of the yield or product ratio. With both of these Lewis acids, the uncyclized chlorohydrin was the major product.

As shown in Scheme 9, lactone ether **36** was reduced with lithium aluminum hydride in THF to obtain diol **9**, which was subjected to the "tetracyclization conditions" (sequential Swern oxidation, treatment with ammonia at room temperature, treatment with warm acetic acid).[4] This process provided hexacyclic amino ether **39** in 66% yield. Catalytic hydrogenation of the isopropenyl double bond gave **10** in essentially quantitative yield. Compound **10** can be obtained in the same yield by a simpler process wherein methylamine is substituted for ammonia in the tetracyclization reaction (Scheme 10). In this process, the tertiary cation resulting from the tetracyclization (**40**) undergoes intramolecular hydride transfer to give an immonium ion, which presumably undergoes hydrolysis during workup to deliver **10**.

Treatment of amino ether **10** with diisobutylaluminum hydride in refluxing toluene accomplished Eschenmoser-Grob fragmentation[21] and reduction of the initially-formed immonium ion to give unsaturated amino alcohol **11** in 86% yield (Scheme 11). It was gratifying to find that **11** was formed as the only product in this reaction, in contrast to the situation with the tetrahydropyran

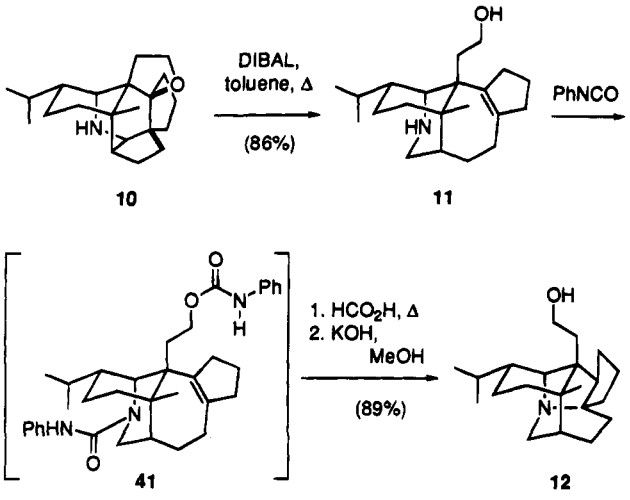
(18) (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556.

(19) (a) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014. (b) Takahara, P. M.; Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *Tetrahedron Lett.* **1989**, *30*, 7177.

(20) For a review of the Reformatsky reaction see: Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed., Pergamon: Oxford, 1991; Vol. 2, p 277.

(21) (a) Eschenmoser, A.; Frey, A. *Helv. Chim. Acta* **1952**, *35*, 1660. (b) Grob, C. A.; Baumann, W. *Ibid.* **1955**, *38*, 594. (c) Grob, C. A. *Experientia* **1957**, *13*, 126. (d) Grob, C. A.; Ostermayer, F. *Helv. Chim. Acta* **1962**, *45*, 1119. (e) Eschenmoser, A.; Felix, D.; Ohloff, G. *Ibid.* **1967**, *50*, 708, 2108. (f) Grob, C. A.; Schiess, P. W. *Angew. Chem. Int. Edn. Engl.* **1967**, *6*, 1. (g) Grob, C. A.; Kiefer, H. R.; Lutz, H. J.; Wilkens, H. J. *Helv. Chim. Acta* **1967**, *50*, 416. (h) Grob, C. A. *Angew. Chem. Int. Edn. Engl.* **1969**, *8*, 535.

Scheme 11

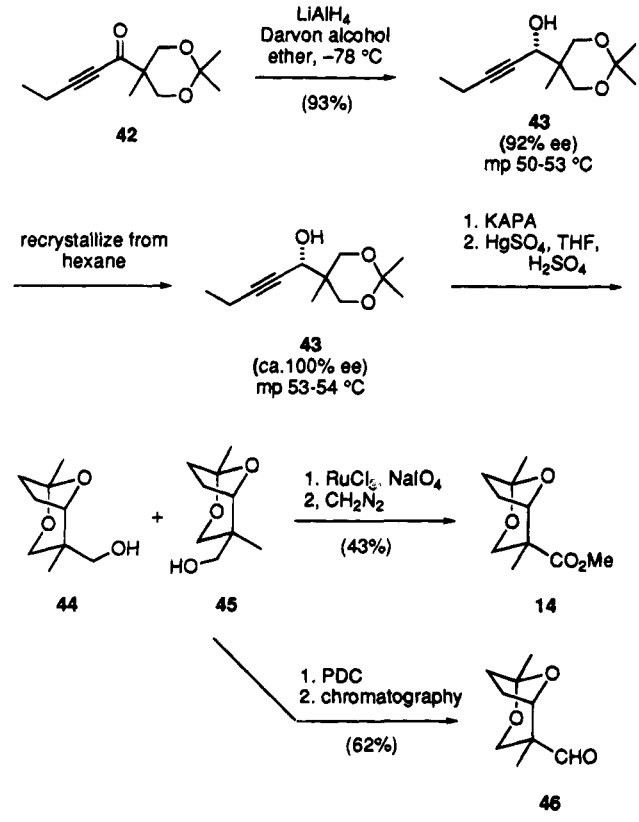


analog **5** (Scheme 1).[6c] Treatment of **11** with 2 equiv of phenyl isocyanate provided the *N,O*-bis(phenylcarbamoyl) derivative **41**, which was taken up in 97% formic acid and heated at reflux to accomplish cyclization to the daphniphylline skeleton.[22] The remaining *O*-phenylcarbamoyl group was removed by treatment with KOH in hot methanol to obtain the desired pentacyclic amino alcohol **12** in 89% yield.

The synthesis of amino alcohol **12** delivers material with an enantiomeric purity of only 82% because of the modest enantioselectivity of the Noyori hydrogenation and the fact that the two diastereomers that are produced in the Frater–Seebach alkylation could not be separated. However, for the synthesis of codaphniphylline, amino alcohol **12** will be joined with another chiral building block, ester **14** (Scheme 2). Therefore, we have another chance to improve the overall enantioselectivity of the synthesis. That is, if we employ **14** that has very high enantiomeric purity, the fragment assembly will give (+)-codaphniphylline of just as high enantiomeric purity, along with an unnatural diastereomer that arises from coupling of **14** with the 9% of minor enantiomer of the synthetic **12**.

As shown in Scheme 12, asymmetric carbonyl reduction of acetylenic ketone **42** with the $LiAlH_4$/Darvon alcohol complex[23] gave alcohol **43** in 93% yield. The enantioselectivity of this reduction was shown in our previous synthesis of (−)-secodaphniphylline to be only 92%.[5] However, in the present work, we have found that the enantiomeric purity of **43** can be improved by recrystallization from hexane to give white crystals, mp 53–54 °C. The enantiomeric purity of the propargyl alcohol was shown to be greater than 99% by the method of Mosher.[24] After isomerization of the propargyl to the terminal position (potassium aminopropylamide in 1,3-diaminopropane at −15 °C)[25] and hydration of the triple bond, a mixture of alcohols **44** and **45** was obtained. Oxidation of this mixture and esterification with diazomethane gave a mixture of diastereomeric esters that were separated by chromatography to give **14**. Alternatively, oxidation of the mixture of alcohols with pyridinium dichromate gave a mixture of aldehydes, from which the pure axial diastereomer **46** was obtained in 62% yield by silica gel chromatography.

Scheme 12



Two different methods were developed for assembly of the full codaphniphylline skeleton. The first is shown in Scheme 13. Treatment of amino alcohol **12** with *p*-toluenesulfonyl chloride in chloroform afforded tosylate **47** in nearly quantitative yield. Treatment of this material with sodium iodide in refluxing acetone provided the crystalline amino iodide **48**. It had been intended to metalate **48** and add the metallo derivative to either ester **14** or aldehyde **46**. However, metalation proved to be a capricious and irreproducible process. The crystalline iodide was dissolved in degassed ether and the solution cooled to −78 °C. Two equivalents of *tert*-butyllithium were added and the mixture was stirred for 1 h at −78 °C and 1 h at room temperature.[26] After recooling to −78 °C, aldehyde **46** was added. At best, the reaction provided a diastereomeric mixture of alcohols **49** in 63 % yield (Scheme 13), but at times the metalation did not occur and starting material was recovered. Modifying the procedure by use of different solvent systems (mixtures of pentane and ether), as well as using *t*-BuLi from different sources did not result in a reproducible procedure. There were also problems with the seemingly uncomplicated oxidation of **49** to the corresponding ketone. Several mild oxidants (Swern,[15] Dess–Martin,[27] and Oppenauer[28]) gave only recovered **49** in small-scale

(22) This protocol was adapted directly from our previous synthesis of (±)-methyl homosecodaphniphyllate, ref 6c. Treatment of **11** with various acids gives no cyclization, because of the basicity of the amine.

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

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(25) (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.

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(27) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

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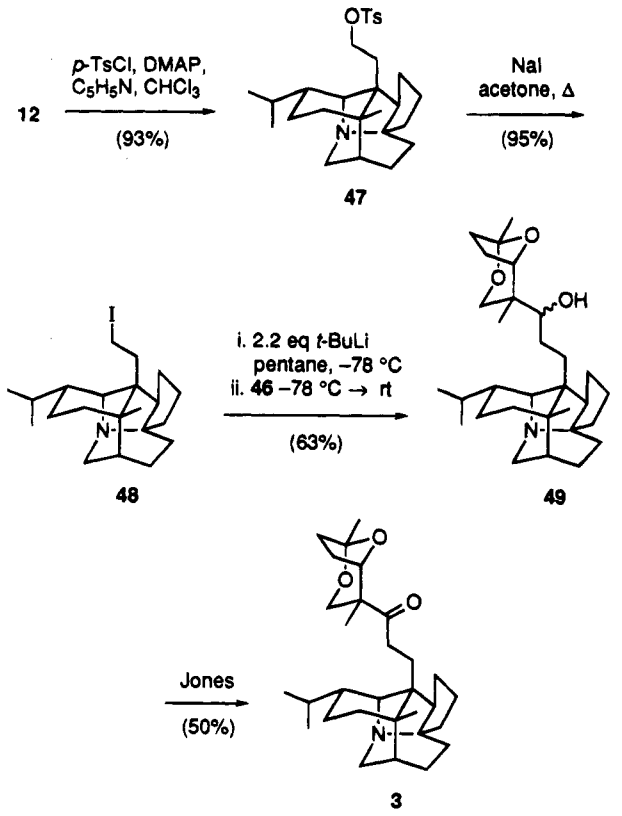
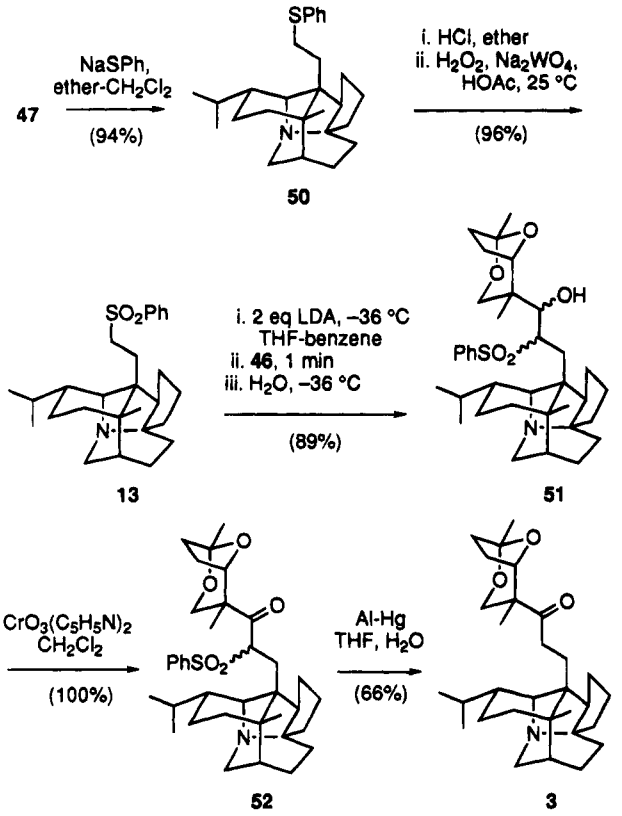
Scheme 13



Scheme 14



exploratory runs. Success was finally realized with the Jones oxidation protocol, but the isolated yield of (+)-codaphniphylline was only 50%, probably because the rather acidic conditions of the Jones oxidation[29] causes some degradation of the bicyclic acetal portion of the molecule.

Because of the erratic nature of the metalation process and the poor overall yield of this direct assembly, we developed the somewhat longer but more reliable protocol summarized in Scheme 14. Treatment of tosylate **47** with sodium thiophenoxide in a mixture of ether and methylene chloride provided sulfide **50**, which was protonated (to protect the nitrogen) and then oxidized with hydrogen peroxide in the presence of a catalytic amount of sodium tungstate. Sulfone **13** was obtained in this manner in excellent yield (84% overall from alcohol **12**). Our original plan had been to add the dianion of **13** to ester **14** to obtain a β-keto sulfone with the skeleton of codaphniphylline. However, we encountered unexpected solubility problems. Sulfone **13** is only sparingly soluble in THF at room temperature and is virtually insoluble at −78 °C. Attempts to form and trap the sulfone dianion by treating a slurry of the sulfone with *n*-butyllithium or LDA in THF were uniformly unsuccessful, even if the reaction was carried out in the presence of HMPA or TMEDA. In these experiments, there was visual evidence that a metalated species was formed, but in no cases were any coupling products seen.

After much experimentation, we discovered that sulfone **13** is rather soluble in a 2:3 mixture of benzene and THF. In this solvent, a 0.2 M solution of **13** is homogeneous, even at −78 °C. Furthermore, metalation occurs at a reasonable rate at −36 °C and the resulting anion is soluble at this temperature. The method that we used to define these very specific conditions was to treat the benzene:THF solution of **13** with base at a constant temperature for a predetermined period of time. The reaction mixture was then quenched at low temperature with an excess of pivalaldehyde to mimic aldehyde **46**. This protocol must be followed precisely, including the low-temperature (e.g., below −20 °C) quench; if the reaction is quenched by addition of aqueous $NaHCO_3$ at room temperature, the anion of the β-hydroxy sulfone appears to revert to sulfone and aldehyde and no product is obtained. Having worked out these precise conditions, we were able to convert sulfone **13** smoothly into adduct **51**, which was obtained in 89% yield, as a mixture of four diastereomers along with a small amount (5%) of unreacted sulfone **13** (Scheme 14).

Oxidation of **51** was accomplished by a modified Sarrett procedure.[30] However, just as was the case with alcohols **49**, oxidation of **51** was found to be slow. Use of a more-or-less standard reaction time of 15 min at room temperature gave mostly recovered starting material. However, by extending the reaction time to 3 h we were able to obtain β-keto sulfones **52** in quantitative yield. The synthesis was completed by treatment of **52** with aluminum amalgam[31] in refluxing THF/H_2O to obtain (+)-codaphniphylline in an overall yield of 57% for the three-step procedure.

As was expected, spectral analysis of the synthetic natural product showed the presence of a minor contaminant, which is presumed to be the a mismatched diastereomer (isocodaphniphylline, **53**) arising from the minor enantiomer of **13**, which has an enantiomeric purity of only 82%. The identity of this minor contaminant was confirmed by coupling (±)-**13** with enantiomerically homogeneous **46**, using the same procedure as

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(30) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

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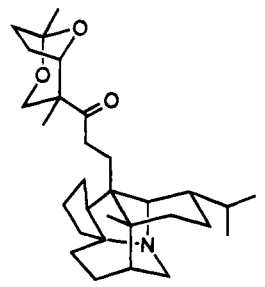
shown in Scheme 14. This coupling provided a 1:1 mixture of diastereomers and the unique NMR spectral lines of the mismatched diastereomer corresponded exactly with those of the contaminant in the synthetic natural product.



53

To remove the small amount of diastereomer **53** from the synthetic codaphniphylline, we prepared the hydrochloride salt by treatment of a dichloromethane solution of **3** with excess ethereal HCl. The residue that remained after removal of the solvents was recrystallized from chloroform–ether to obtain fine white crystals that melted at 266–267 °C in a sealed tube (lit. mp 266–267 °C[7]). The optical rotation of the recrystallized salt ($[\alpha]^{25}_D$ +4.4 (c = 0.68, $CHCl_3$)) also matched that of a natural sample graciously provided to us by Professor Yamamura ($[\alpha]^{25}_D$ +4.6 (*c* = 0.39, $CHCl_3$), lit. $[\alpha]^{25}_D$ +4.2 (*c* = 2.4, $CHCl_3$)[7]). Finally, a dichloromethane solution of the recrystallized salt was extracted with 2 N KOH. The ^1H NMR spectrum of the resulting free base showed no remaining isocodaphniphylline.

In summary, we have worked out a route for the total synthesis of enantiomerically pure (+)-codaphniphylline (**3**) in 12 steps and 9% overall yield from homogeranyl iodide (**17**).

Experimental Section

General: All reactions involving oxygen- or moisture-sensitive compounds were carried out under a dry N_2 (or Ar where noted) atmosphere. Unless otherwise noted, reagents were added by syringe. Organic extracts were dried over anhydrous $MgSO_4$, filtered through a fritted glass funnel, and concentrated with a rotary evaporator at aspirator pressure (30–40 mm). Column chromatography was performed with Merck 60 (230–400 mesh) silica gel using the procedure of Still.[32] Thin layer chromatography (TLC) was performed with Merck F-254 silica gel plates.

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and ether were distilled under N_2 from Na/benzophenone immediately prior to use. Dichloromethane (CH_2Cl_2), benzene, toluene, triethylamine, diisopropylamine and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) were distilled from CaH_2 immediately prior to use. Dimethyl sulfoxide (DMSO) and hexamethylphosphoric triamide (HMPA) were dried and stored over 4 Å molecular sieves.[33] The concentrations of commercially available solutions of *n*-butyllithium and *t*-butyllithium were checked by titration using diphenylacetic acid[34] or BHT/fluorene.[35]

All NMR spectra were measured as solutions in $CDCl_3$, and chemical shifts are expressed in ppm relative to internal $CHCl_3$ (7.26 ppm). In most cases distortionless enhancement by polarization transfer (DEPT) was used to assign carbon resonances as CH_3, CH_2, CH, or C. When ^{13}C NMR spectra were obtained on mixtures of stereoisomers, some of the resonances overlap and the correct number of resonances may not be listed. Mass spectra were measured using fast atom bombardment (FAB) unless otherwise noted.

Methyl (1*R*,2*R*)-2-Hydroxyl-1-(4,8-dimethyl-3,7-nonadienyl)cyclopentanecarboxylate (18). A 25-mL round-bottomed flask was charged with 10 mL of THF and diisopropylamine (1.07 mL, 7.63 mmol) and cooled to 0 °C. A 2.15 M solution of *n*-BuLi in hexanes (3.23 mL, 6.94 mmol) was added with a syringe. The solution was allowed to stir for 15 min and cooled to −30 °C, and hydroxy ester **16**[8] (500 mg, 3.47 mmol) was added neat with a syringe. The yellow dianion solution was allowed to stir for 1 h. Homogeranyl iodide[4] (1.64 g, 5.90 mmol) was added neat with a syringe, and the mixture was stirred at −30 °C for 48 h. A solution of saturated aqueous NH_4Cl (2.5 mL) was added at −30 °C, and the mixture was diluted with 50 mL of ether. The aqueous phase was extracted with 2.5 mL of ether, the combined organic layers were dried, and the solvent was removed to obtain a yellow oil. Chromatography on silica gel (60 g), eluting with 600 mL of 6:1 hexanes:ethyl acetate and 200 mL of 2:1 hexanes:ethyl acetate, gave 640 mg (63%) of hydroxy ester **18** as a pale yellow oil. ^1H NMR spectroscopy and GC analysis showed the ester to be contaminated with about 6% of its diastereomer, **19**. $[\alpha]^{25}_D$ −39.6 (*c* = 0.42, CH_3OH). IR ($CHCl_3$): 3460, 2950, 1720, 1440, 1170 cm^{-1}. ^1H NMR (500 MHz): δ 1.45 (m, 1), 1.57–1.67 (m, 13), 1.80–2.07 (m, 8), 2.22 (m, 1), 2.84 (d, 1, *J* = 4.8), 3.72 (s, 3), 4.06 (m, 1), 5.05 (t, 1, *J* = 8.1), 5.07 (t, 1, *J* = 8.2). ^{13}C NMR (125 MHz): δ 15.98, 17.66, 20.47, 23.78, 25.68, 26.61, 31.26, 32.19, 36.43, 39.63, 51.72, 58.54, 79.11, 123.33, 124.19, 131.41, 135.82, 176.65. Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.11; H, 10.44.

2-Bromo-4-chlorobutyryl Chloride. A 250-mL round-bottomed flask was equipped with a reflux condenser and a N_2 bubbler filled with 2 N KOH solution. The flask was charged with 4-chlorobutyryl chloride (48.1 g, 34.0 mmol) and bromine (54.5 g, 341.0 mmol). Five drops of 48% HBr was added with a pipet, resulting in the immediate evolution of HBr. The mixture was heated at 65 °C for 4 h under a strong sweep of N_2, heated to 120 °C for 1 h, and cooled to 85 °C for 12 h. After cooling, the orange liquid was transferred to a 100-mL round-bottomed flask and distilled at aspirator pressure (35 mm). A forerun was collected from 80–116 °C, and the acyl halide was collected from 116–121 °C as a pale yellow liquid (63.2 g, 70%). IR (neat): 2965, 1787, 1445, 1427, 1310, 1282, 1230, 995 cm^{-1}. ^1H NMR (500 MHz): δ 2.42 (m, 1), 2.61 (m, 1), 3.73 (m, 2), 4.86 (dd, 1, *J* = 9.2, 4.7). ^{13}C NMR (125 MHz): δ 36.76, 40.66, 55.53, 165.05.

Methyl (*R*)-2-Oxo-1-(4,8-dimethyl-3,7-nonadienyl)cyclopentanecarboxylate (29). Oxalyl chloride (35 μL, 0.41 mmol) in 1 mL of CH_2Cl_2 was cooled to −78 °C. A solution of dimethyl sulfoxide (60 μL, 0.85 mmol) in 200 μL of CH_2Cl_2 was added dropwise, and the resulting solution was stirred for 5 min at −78 °C. The mixture of hydroxy esters **18** and **19** (100 mg, 0.34 mmol) in 200 μL of CH_2Cl_2 was added dropwise. After 15 min, triethylamine (240 μL, 1.70 mmol) was added and the reaction mixture was warmed to 0 °C. After 30 min the mixture was transferred to a separatory funnel, diluted with 5 mL of CH_2Cl_2, and washed with 1 mL each of 10% HCl, saturated $NaHCO_3$, and brine solutions. The organic layer was dried and the solvent was removed to obtain a yellow oil. Chromatography on silica gel (6 g), eluting with 6:1 hexanes:ethyl acetate, provided keto ester **29** (98 mg, 98%) as a pale yellow oil. $[\alpha]^{25}_D$ −21.1 (*c* = 0.73, CH_3OH). IR (neat): 2950, 1760, 1720, 1450, 1225, 160, 845 cm^{-1}. ^1H NMR (400 MHz): δ 1.57 (s, 3), 1.58 (m, 1), 1.59 (s, 3), 1.67 (s, 3), 1.89–2.05 (m, 10), 2.26 (m, 1), 2.37 (m, 1), 2.55 (m, 1), 3.70 (s, 3), 5.07 (m, 2). ^{13}C NMR (100 MHz): δ 15.91, 17.64, 19.59, 23.49, 25.64, 26.60, 32.66, 34.01, 37.92, 39.61, 52.45, 60.49, 122.97, 124.19, 131.39, 136.19, 171.36, 214.65. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.73; H, 9.73.

(1*R*,2*S*)-2-Hydroxy-1-(4,8-dimethyl-3,7-nonadienyl)cyclopentane-1-methanol (30). A solution of the 15:1 mixture of hydroxy esters **18** and **19** (105 mg, 0.36 mmol) in 2 mL of

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THF was cooled to −78 °C. A 1.5 M solution of DIBAL in toluene (950 μL, 1.43 mmol) was added dropwise with a syringe. The mixture was stirred, slowly allowed to warm to rt over 12 h, and then quenched with 500 μL of a 15% NaOH solution. The two-phase mixture was diluted with ether (3 mL), and the aqueous phase was extracted with ether (2 × 500 μL). The combined organic layers were dried, and the solvent was removed to obtain a colorless oil. Chromatography on silica gel (30 g), eluting with 2:1 hexanes:ethyl acetate, provided 84 mg (89%) of diol **30** as a colorless oil. IR (film): 3490, 2960, 2920, 1455, 1155 cm^{-1}. ^1H NMR (400 MHz): δ 1.22(m, 1), 1.41−1.76 (m, 6), 1.60 (s,3), 1.61 (s, 3), 1.69 (s, 3), 1.93−2.10 (m, 7), 2.57 (d, 1, J = 3.8), 2.75 (t, 1, J = 5.6), 3.61 (dd, 1, J = 11.2, 6.1), 3.73 (dd, 1, J = 11.2, 4.5), 3.98 (m, 1), 5.10 (t, 1, J = 5.5), 5.14 (t, 1, J = 7.0). ^{13}C NMR (100 MHz): δ 15.97, 17.67, 21.05, 22.95, 25.68, 26.66, 31.78, 34.41, 36.07, 39.66, 48.50, 65.87, 81.66, 124.27, 124.49, 131.38, 135.15. Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.54; H, 11.30.

Methyl (*R*)-2-(Ethylenedioxy)-1-(4,8-dimethyl-3,7-nonadienyl)cyclopentanecarboxylate (34). A 50-mL round-bottomed flask equipped with a Dean−Stark trap and condenser was charged with keto ester **29** (450 mg, 1.54 mmol), ethylene glycol (956 mg, 15.4 mmol), *p*-toluenesulfonic acid (29 mg, 0.15 mmol), and 30 mL of benzene. The mixture was heated at reflux for 20 h, cooled, and diluted with 20 mL of ether. The ethereal solution was washed with 10 mL of saturated $NaHCO_3$ and 5 mL of brine and dried, and the solvent was removed to obtain analytically-pure acetal **34** (513 mg, 99%) as a colorless oil. $[\alpha]^{25}_D$ −19.7 (c = 0.85, CH_3OH). IR (neat): 2960, 1730, 1450, 1310, 1050 cm^{-1}. ^1H NMR (400 MHz): δ 1.29 (m, 1), 1.52 (s, 3), 1.54 (s, 3),1.56−1.70 (m, 4), 1.62 (s, 3), 1.75 (m, 2), 1.90 (m, 3), 2.00 (m, 3), 2.37 (m, 1), 3.63 (s, 3), 3.74 (m, 1), 3.82−3.94 (m, 3), 5.04 (m, 2). ^{13}C NMR (100 MHz): δ 15.57 (CH_3), 17.49 (CH_3), 19.30 (CH_2), 23.61 (CH_2), 25.51 (CH_3), 26.54 (CH_2), 30.87 (CH_2), 33.41 (CH_2), 35.77 (CH_2), 39.53 (CH_2), 51.33 (CH_3), 58.53 (C), 64.53 (CH_2), 65.34 (CH_2), 118.68 (C), 123.63 (CH), 124.20 (CH), 131.09 (C), 135.26 (C), 174.19 (C). Anal. Calcd for $C_{20}H_{32}O_4$: C: 71.39; H: 9.59. Found: C, 71.39; H, 9.47.

(*S*)-2-(Ethylenedioxy)-1-(4,8-dimethyl-3,7-nonadienyl)-cyclopentane-1-methanol (35). A solution of ester **34** (513 mg, 1.52 mmol) in 20 mL of ether was cooled to 0 °C. Lithium aluminum hydride (116 mg, 3.05 mmol) was added slowly with a spatula. The reaction mixture was stirred at rt for 30 min, cooled to 0 °C, and quenched by the dropwise addition of 250 μL of water, 250 μL of a 15% NaOH solution, and 750 μL of water. Excess $MgSO_4$ was added, and the white slurry was stirred for 1 h. Filtration of the solids and evaporation of the solvent gave a colorless oil that was purified on silica gel (30 g), eluting with 4:1 hexanes:ethyl acetate to give alcohol **35** (464 mg, 99%) as a clear colorless oil. $[\alpha]^{25}_D$ −1.8 (c = 2.4, $CHCl_3$). IR (CH_2Cl_2): 3550, 2920, 1450, 1147, 1060 cm^{-1}. ^1H NMR (400 MHz): δ 1.34 (m, 1), 1.52−1.78 (m, 7), 1.59 (s, 3), 1.60 (s, 3), 1.67 (s, 3), 1.83−2.08 (m, 6), 2.97 (dd, 1, J = 8.5, 4.2), 3.47 (dd, 1, J = 11.7, 8.5), 3.65 (dd, 1, J = 11.7, 4.2), 3.87−3.97 (m, 4), 5.08 (t, 1, J = 6.8), 5.14 (t, 1, J = 6.0). ^{13}C NMR (100 MHz): δ 15.88 (CH_3), 17.61 (CH_3), 18.89 (CH_2), 22.91 (CH_2), 25.62 (CH_3), 26.64 (CH_2), 30.35 (CH_2), 30.75 (CH_2), 34.10 (CH_2), 39.64 (CH_2), 49.36 (C), 64.18 (CH_2), 64.58 (CH_2), 65.35 (CH_2), 120.58 (C), 124.34 (CH), 124.77 (CH), 131.18 (C), 134.74 (C). Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 74.08; H, 10.42.

[(1*S*)-(4,8-Dimethyl-3,7-nonadienyl)-2-oxocyclopentyl]-methyl 2-Bromo-4-chlorobutanoate (33). A solution of alcohol **35** (226 mg, 0.73 mmol) and pyridine (150 μL, 1.76 mmol) in 5 mL of CH_2Cl_2 was cooled to 0 °C, and 2-bromo-4-chlorobutanoyl chloride (193 mg, 0.88 mmol) was added dropwise with a pipet. The resulting yellow solution was stirred for 1 h at rt and the solvent removed to give an oily residue that was dissolved in 5.5 mL of 10:1 THF:10% H_2SO_4. After stirring for 60 h, the mixture was diluted with 20 mL of ether and 2 mL of water. The layers were separated, and the aqueous phase was extracted with ether (2 × 4 mL). The combined organic phases were washed with 2 mL of saturated $NaHCO_3$ and 2 mL of brine. The ether layer was dried and the solvent removed to obtain a pale yellow oil. Chromatography on silica gel (45 g), eluting with 500 mL of 19:1 hexanes:ethyl acetate, followed by 250 mL of 3:1 hexanes:ethyl acetate gave bromo ester **17** (328 mg, 97%), as a pale yellow oil. IR (neat): 1745 cm^{-1}. ^1H NMR (400 MHz): δ 1.45−1.55 (m, 2), 1.56 (s, 6), 1.68 (s, 3), 1.83−2.12 (m, 10), 2.27−2.54 (m, 4), 3.69 (t, 2, J = 6.1), 4.17 (d, 1, J = 10.6), 4.23 (d, 1, J = 10.6), 4.50 m, 1), 5.02−5.10 (m, 2). ^{13}C NMR (100 MHz): δ 15.93, 15.96, 17.61, 18.83, 22.50, 25.62, 26.48, 30.72, 30.89, 33.19, 33.26, 36.69, 36.78, 38.30, 39.50, 41.54, 42.22, 51.52, 68.35, 68.48, 122.94, 124.01, 131.29, 136.03, 136.06, 168.60, 168.71, 219.64, 219.90. Anal. Calcd for $C_{21}H_{32}BrClO_3$: C, 56.32; H, 7.20. Found: C, 56.19; H, 7.09.

(1-Methyl-2-oxocyclopentyl)methyl 2,4-Dibromobutanoate (25a). Alcohol **24** (1.47 g, 9.41 mmol) was treated in the foregoing manner using 2,4-dibromobutanoyl bromide (3.40 g, 11.0 mmol). The crude product was purified by column chromatography on silica (75 g), eluting with 10:90 ether−hexanes, to obtain 2.60 g (78%) of the keto ester as a viscous golden oil. The product was obtained as a nearly equal mixture of diastereomers. IR: 1750 (s), 1470 (s). ^1H NMR: δ 1.06 + 1.08 (s, 3), 1.80−2.60 (m, 8), 3.53 (t, 2, J = 6.2), 4.09 (d, 0.5, J = 10.8), 4.16 (s, 1), 4.23 (d, 0.5, J = 10.8), 4.45−4.55 (m, 1). ^{13}C NMR: δ 18.60, 18.62, 19.46, 29.70, 32.95, 33.18, 36.63, 36.72, 37.83, 37.85, 43.38, 48.32, 68.96, 69.02, 168.49, 168.60, 219.80, 220.01. Anal. Calcd for $C_{11}H_{16}Br_2O_3$: C, 37.11; H, 4.53. Found: C, 37.14; H, 4.53.

(1-Methyl-2-oxocyclopentyl)methyl 2-Bromo-4-chlorobutanoate (25b). Alcohol **24** (1.31 g, 8.39 mmol) was treated in the foregoing manner using 2-bromo-4-chlorobutanoyl chloride (2.42 g, 11.0 mmol). The crude product was purified by column chromatography on silica (75 g), eluting with 10:90 ether-hexanes, to obtain 2.09 g (80%) of the keto ester as a very viscous golden oil. The product was obtained as a nearly equal mixture of diastereomers. IR: 1740 (s), 1460 (s). ^1H NMR: δ 1.06 + 1.08 (s, 3), 1.80−2.55 (m, 8), 3.69 (t, 2, J = 6.1), 4.09 (d, 0.5, J = 10.9), 4.16 (s, 1), 4.23 (d, 0.5, J = 10.9), 4.48−4.55 (m, 1). ^{13}C NMR: δ 18.54, 18.55, 19.39, 32.89, 33.12, 36.60, 36.69, 37.76, 37.78, 41.52, 42.20, 42.24, 48.25, 68.89, 68.95, 168.48, 168.60, 219.72, 219.92. Anal. Calcd for $C_{11}H_{16}BrClO_3$: C, 42.40; H, 5.18. Found: C, 42.33; H, 5.13.

(4aα,7aβ,(*E*),10a*S*)-7a-(4,8-Dimethyl-3,7-nonadienyl)octahydro-5*H*,7*H*-cyclopenta[*c*]furano[2,3-*d*]pyran-5-one (36). A flame-dried 10-mL round-bottomed flask was charged with keto ester **33** (411 mg, 0.91 mmol), zinc dust (120 mg, 1.82 mmol), 1.8 mL of THF, and 1.8 mL (1.80 mmol) of a 1 M solution of $ZnCl_2$ in ether. The mixture was refluxed for 6.5 h and then quenched with 2 mL of saturated NH_4Cl solution. The two-phase mixture was transferred to a separatory funnel and diluted with 15 mL of ether. The layers were separated, and the aqueous phase was extracted with ether (3 × 2 mL). The combined organic layers were dried, and the solvent was removed to obtain a pale yellow oil. Chromatography on silica gel (60 g), eluting with 500 mL of 19:1 hexanes:ethyl acetate and 500 mL of 9:1 hexanes:ethyl acetate, provided (in order of elution) a mixture of cyclopropyl ester **38** (34 mg), chloride **37** (29 mg, 9%), and the desired lactone ether **36** (205 mg, 67%). The chloride **37** was converted to lactone ether **36** in quantitative yield by stirring with an excess of K_2CO_3 in acetonitrile for 10 h to obtain an overall 76% yield of lactone ether as a colorless oil. IR (neat): 1740 cm^{-1}. ^1H NMR (500 MHz): δ 1.38−1.55 (m, 3), 1.58 (s, 3), 1.74−1.82 (m, 2), 1.88−1.97 (m, 4), 1.99−2.06 (m, 3), 2.16 (m, 1), 2.51 (m, 1), 2.79 (dd, 1, J = 8.5, 3.7), 3.76−3.87 (m, 3), 4.12 (d, 1, J = 11.7), 5.06 (t, 1, J = 6.7), 5.11 (t, 1, J = 6.3). ^{13}C NMR (125 MHz): δ 15.84 (CH_3), 17.53 (CH_3), 22.57 (CH_2), 23.09 (CH_2), 25.53 (CH_3), 26.53 (CH_2), 27.37 (CH_2), 30.48 (CH_2), 33.35 (CH_2), 39.52 (CH_2), 40.14 (CH_2), 47.23 (C), 47.55 (CH), 66.48 (CH_2), 70.20 (CH_2), 92.03 (C), 123.87 (CH), 124.19 (CH), 131.16 (C), 135.13 (C), 173.20 (C). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.04; H, 9.65.

(+)-(4aα,7aβ,(*E*),10a*S*)-7a-(4,8-Dimethyl-3,7-nonadienyl)-1-oxaspiro[4.4]nonane-4,6-dimethanol (9). To a cold (0 °C), stirring solution of lactone ether **36** (671 mg, 2.02 mmol) in 10 mL of ether was added gradually with a spatula $LiAlH_4$ (227 mg, 6.06 mmol). After 6 h, 230 μL of water, 230 μL of a

15% NaOH solution, and 690 μL of water were added slowly with a syringe. Excess $MgSO_4$ was added until a white slurry resulted. The slurry was vigorously stirred for 1 h, and the solids were filtered and rinsed with ether. Concentration of the filtrate gave a clear colorless oil that was purified on silica gel (21 g), eluting with 500 mL each of 1:1 hexanes:ethyl acetate and 3:1 hexanes:ethyl acetate to give 642 mg (95%) of diol **9** as a white solid, mp 58–59 °C. $[\alpha]^{25}_D$ +25.4 (c = 1.3, $CHCl_3$). IR (neat): 3300, 1455, 1080, 1040 cm^{-1}. ^1H NMR (400 MHz): δ 1.43–2.24 (m, 19), 1.59 (s, 6), 1.66 (s, 3), 3.43 (m, 3), 3.59 (s, 2), 3.94 (dd, 1, J = 10.8, 7.1), 5.07 (t, 1, J = 6.9), 5.14 (t, 1, J = 7.0). ^{13}C NMR (125 MHz): δ 15.97 (CH_3), 17.66 (CH_3), 18.56 (CH_2), 24.02 (CH_2), 25.65 (CH_3), 26.67 (CH_2), 29.98 (CH_2), 30.65 (CH_2), 34.58 (CH_2), 35.69 (CH_2), 39.69 (CH_2), 46.96 (CH), 52.38 (C), 62.60 (CH_2), 63.30 (CH_2), 65.81 (CH_2), 94.65 (C), 124.35 (CH), 125.23 (CH), 131.31 (C), 134.83 (C). Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.01; H, 10.83.

17,18-Didehydro-8,22-epoxy-23-nor-12,16-cyclo-1,12-secodaphnane (39). A solution of oxalyl chloride (4.73 mL of a 1.0 M solution in CH_2Cl_2, 4.73 mmol) in 20 mL of CH_2Cl_2 was stirred in a 100-mL round-bottomed flask, cooled by a dry ice/acetone bath, as dimethyl sulfoxide (9.46 mL of a 1.0 M solution in CH_2Cl_2, 9.46 mmol) was added dropwise by syringe. After 5 min, diol **9** (637.0 mg, 1.89 mmol in 20 mL of CH_2Cl_2) was added by a cannula to the cooled solution. After 30 min, triethylamine (3.30 mL, 23.6 mmol) was added to the resulting white slurry by syringe, and after 5 min, the clear colorless solution was warmed in an ice/water bath. After 1 h, the septum was removed and the chilled dialdehyde solution was stirred vigorously as a rapid stream of ammonia gas was passed into the reaction vessel, resulting in the formation of a copious white precipitate. After the solution had been saturated (approximately 15 s), the cooling bath was removed and the excess ammonia allowed to evaporate as the stirring mixture warmed to rt. After 1 h, the stirring bar was removed, rinsing with $CHCl_3$ into the flask (adding several mL reduces "bumping" at the end of solvent removal). The solvent was evaporated and the white solid was placed under vacuum for 1 h. The residue was combined with NH_4OAc (1.54 g, 20.0 mmol) and suspended in 40 mL of glacial acetic acid. The reaction vessel was equipped with a reflux condenser, purged with N_2, and the solution was stirred in an oil bath (temp = 70 °C) for 2 h and then at rt for 14 h. The dark reaction mixture was diluted with 100 mL of water and extracted with CH_2Cl_2 (4 × 50 mL). The extracts were washed with 100 mL of a 3 N NaOH, and the aqueous wash (still be basic to litmus) was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried, filtered, and concentrated to give 0.640 g of a dark tar. This crude product was purified by column chromatography on silica (10 g), eluting with 10:90 ether–hexanes, to obtain 0.390 g (66%) of the amine as a pale yellow oil. To obtain an analytical sample, this material was purified again by the same procedure to give 0.384 g (65%) of the product as a faintly yellow oil. IR: 3360 (s), 1640 (m). ^1H NMR: δ 0.93 (s, 3), 1.18–2.00 (m, 18), 1.75 (s, 3), 2.17–2.25 (m, 1), 2.71 (d, 1, J = 4.3), 3.09 (s, 1), 3.75–3.85 (m, 2), 4.74 (s, 1), 4.85 (s, 1). ^{13}C NMR: δ 20.35, 22.53, 23.84, 24.15, 24.21, 28.42, 28.48, 34.97, 35.08, 38.44, 39.96, 46.07, 46.43, 47.28, 51.72, 55.81, 65.27, 65.41, 96.66, 110.28, 146.75. Anal. Calcd for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.35; H, 9.77; N, 4.39.

(−)-8,22-Epoxy-23-nor-12,16-cyclo-1,12-secodaphnane (10). A solution of oxalyl chloride (300 μL, 3.44 mmol) in 15 mL of CH_2Cl_2 was cooled to −78 °C. Dimethyl sulfoxide (658 mg, 7.82 mmol) in 3 mL of CH_2Cl_2 was added dropwise with a syringe, and the mixture was stirred for 5 min. Diol **9** (523 mg, 1.56 mmol) in 2 mL of CH_2Cl_2 was added, and the flask and syringe were rinsed with 1 mL of CH_2Cl_2, which was added to the mixture. After 30 min, triethylamine was added dropwise and the mixture was allowed to warm to 0 °C over 1 h. Methylamine was blown over the crude reaction mixture for 30 s, the ice/water bath was removed, and the reaction was warmed to rt over 1 h. The stirring bar was removed, and the solvent was removed in vacuo to obtain a yellow solid that was placed under high vacuum for 2 h. The residue was then dissolved in 20 mL of acetic acid and the resulting solution stirred for 11 h at rt followed by heating at 65 °C for 10 h. The reaction mixture was poured into a separatory funnel with 15 mL of water and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with 120 mL of 3 N NaOH, and the basic aqueous phase was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried, and the solvent was removed to obtain a black oil. Chromatography on silica gel (30 g), eluting with 67:33:5 ether:hexanes:triethylamine, gave amino ether **10** (313 mg, 63%) as a pale yellow solid, mp 68–68.5 °C. $[\alpha]^{25}_D$ −34.7 (c = 2.2, $CHCl_3$): IR (CH_2Cl_2): 3380, 1470 cm^{-1}. ^1H NMR (400 MHz): δ 0.68–0.80 (m, 1), 0.88–0.91 (m, 9), 1.15–2.00 (m, 18), 2.18–2.28 (m, 1), 2.72 (d, 1, J = 4.2), 3.09 (d, 1, J = 1.6), 3.77 (m, 2). ^{13}C NMR (125 MHz): δ 20.93 (CH_2), 20.98 (CH_3), 21.07 (CH_3), 23.94 (CH_2), 24.22 (CH_2), 24.32 (CH_3), 28.47 (CH_2), 28.65 (CH_2), 28.67 (CH), 34.95, (C), 35.44 (CH_2), 38.59 (CH_2), 40.62 (CH_2), 46.31 (C), 46.51(CH), 47.28 (CH), 51.94(C), 55.44 (CH), 65.34 (CH_2), 65.52 (CH), 96.55 (C). Anal. Calcd for $C_{21}H_{33}NO$: C, 79.95; H, 10.54; N, 4.44. Found: C, 79.65; H, 10.85; N, 4.29.

8,12-Didehydro-23-nor-1,12-secodaphnan-22-ol (11). The amino ether **10** (800 mg, 2.54 mmol) was dissolved in a solution of DIBAL (55.8 mL of a 1.0 M solution in toluene, 55.80 mmol). The resulting solution was stirred vigorously and heated at reflux for 70 h. The mixture was cooled to 0 °C and the excess DIBAL was quenched by slow dropwise addition of 2.5 mL of methanol. Stirring was continued at rt for 1 h, and the solution was transferred to a 1-L round-bottomed flask. Addition of 200 mL of a saturated solution of Rochelle's salt and 200 mL of ether followed by vigorous stirring for 1.5 h provided a clean two-phase solution. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried, and the solvent was removed to obtain a pale yellow oil. Chromatography on silica gel (40 g), eluting with 15:85:5 ether:hexanes:triethylamine, gave the unsaturated amino alcohol **11** (700 mg, 86%) as a pale yellow solid, mp 119–121 °C. IR ($CHCl_3$): 3680, 3620, 1600 cm^{-1}. ^1H NMR (400 MHz): δ 0.90 (m, 9), 1.30–2.16 (m, 15), 2.30–2.42 (m, 6), 2.45 (d, 1, J = 4.0), 2.69 (d, 1, J = 15.0), 3.35 (dd, 1, J = 15.0, 6.7), 3.53 (dt, 1, J = 9.9, 2.8), 3.87 (ddd, 1, J = 9.9, 8.7, 7.7). ^{13}C NMR (100 MHz): δ 20.95 (CH_3), 21.01 (CH_3), 21.78 (CH_2), 27.53 (CH_2), 27.64 (CH_3), 28.52 (CH_2), 29.20 (CH_2), 31.55 (CH), 36.12 (CH_2), 37.24 (C), 39.23 (CH_2), 39.94 (CH_2), 40.33 (CH), 41.49 (CH_2), 43.00 (CH), 47.07 (CH_2), 49.07 (C), 55.48 (CH), 61.96 (CH_2), 137.23 (C), 140.17 (C). HRMS (FAB): exact mass calcd for $C_{21}H_{36}NO$ (MH^+), 318.2797. Found 318.2793.

(−)-23-Nordaphnan-22-ol (12). To a solution of amino alcohol **11** (796 mg, 2.50 mmol) in 40 mL of CH_2Cl_2 was added phenyl isocyanate (652 μL, 6.00 mmol) dropwise with a syringe. The mixture was stirred for 1 h and then concentrated to a solid that was dissolved in 50 mL of 97% HCO_2H. The resulting solution was heated for 2 h at 100 °C, and the HCO_2H was removed with a stream of N_2. To the remaining oily residue was added 60 mL of 2 N methanolic KOH. The resulting mixture was heated at reflux for 3 h, concentrated to 5 mL, and diluted with 10 mL of water. The solution was extracted with ether (3 × 50 mL), and the combined organic layers were dried. The solvent was removed in vacuo to obtain a yellow oil. Chromatography on silica gel (30 g), eluting with 50:50:5 ether:hexanes:triethylamine gave 706 mg (89%) of amino alcohol **12** as a white solid, mp 196–197 °C. $[\alpha]^{25}_D$ −2.8 (c = 2.5; $CHCl_3$). IR (CH_2Cl_2): 3300 cm^{-1}. ^1H NMR (500 MHz): δ 0.81 (s, 3), 0.89 (d, 3, J = 6.6), 0.99 (d, 3, J = 6.6), 1.12–2.14 (m, 20), 2.72 (m, 2), 3.22 (m, 1), 3.67 (m, 1), 3.82 (m, 1). ^{13}C NMR (125 MHz): δ 21.06 (CH_3), 21.47 (CH_3), 22.66 (CH_2), 25.33 (CH_2), 25.53 (CH_3), 27.07 (CH_2), 28.61 (CH_2), 28.98 (CH_2), 30.95 (CH), 35.72 (CH_2), 36.62 (CH_2), 36.67 (C), 38.15 (CH), 41.30 (CH), 41.73 (CH_2), 47.17 (CH_2), 47.40 (C), 51.34 (CH), 61.29 (CH_2), 62.95 (CH), 72.32 (C). Anal. Calcd for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.65; H, 10.91; N; 4.59.

(1*R*-*exo*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octane-4-carboxaldehyde (46). A suspension of powdered 4 Å sieves (9.6 g) and pyridinium dichromate (PDC) (9.69 g, 25.75 mmol) in 113 mL of CH_2Cl_2 was prepared and set to stir under N_2. A

mixture of alcohols **44** and **45** (2.21 g, 12.87 mmol) in 37 mL of CH_2Cl_2 was added dropwise with a syringe. The resulting mixture was stirred vigorously for 1 h and diluted with 250 mL of ether. After stirring an additional hour, the dark brown suspension was filtered through a plug of Florisil. The remaining solids were rinsed with 50 mL of ether. The filtrate was concentrated in vacuo to obtain a pale yellow liquid that is a mixture of isomeric aldehydes. The aldehydes were separated by chromatography on silica gel (100 g), eluting with 1000 mL of 9:1 hexanes:ethyl acetate in that order. Axial aldehyde **46** (1.36 g, 62%) was obtained as a pale yellow liquid that was stored under Ar at −5 °C. Spectral data were in accordance with previous reported values.[5] Immediately prior to use, optically pure **46** was distilled bulb to bulb (86−90 °C, 0.02 mm). IR (neat): 2710, 1730, 1390 cm-1. ^{1}H NMR (500 MHz): δ 0.74 (s, 3), 1.43 (s, 3), 1.87−1.93 (m, 2), 2.05−2.08 (m, 2), 3.56 (d, 1, J = 11.9), 4.07 (dd, 1, J = 11.9, 1.7), 4.52 (dd, 1, J = 6.7, 1.6), 9.85 (d, 1, J = 1.1). ^{13}C NMR (125 MHz): δ 14.66, 23.57, 24.59, 33.52, 48.21, 64.68, 79.78, 105.22, 204.34.

(−)-22-(*p*-Toluenesulfonyloxy)-23-nordaphnane (47). Alcohol **12** (501 mg, 1.57 mmol), *p*-toluenesulfonyl chloride (2.40 g, 12.59 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (30 mg, 0.25 mmol) were combined in a 10-mL round-bottomed flask and dissolved in a mixture of 3 mL of $CHCl_3$ and 2 mL of pyridine. The solution was stirred for 48 h and then transferred to a separatory funnel and diluted with 20 mL of CH_2Cl_2. The organic layer was washed with water (5 mL) and the aqueous phase extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were washed with 10 mL of a 5% Na_2CO_3 solution, and this basic layer was extracted with 2 mL of CH_2Cl_2. The combined organic layers were dried, and the solvent was removed to obtain a black oil. Purification by silica gel chromatography eluting with 50:50:5 ether:hexanes:triethylamine provided tosylate **47** (688 mg, 93%) as a sticky foam. $[\alpha]^{25}_D$ −8.7 (c = 1.3, $CHCl_3$). IR ($CHCl_3$): 2960, 1480, 1460, 1370, 1175, 1110, 960 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.73 (s, 3), 0.86 (d, 3, J = 6.5), 0.95 (d, 3, J = 6.5), 1.19−1.28 (m, 10), 1.33−1.85 (m, 10), 2.04 (m, 2), 2.44 (s, 3), 2.65 9d, 1, J = 3.8), 2.71 (d, 1, J = 14.3), 3.19 (d, 1, J = 14.3), 4.05 (m, 1), 4.23 (m, 1), 7.34 (d, 2, J = 8.1), 7.77 (d, 2, J = 8.1). ^{13}C NMR (125 MHz): δ 21.02 (CH_3), 21.38 (CH_3), 21.62 (CH_3), 22.59 (CH_2), 25.31 (CH_2), 25.56 (CH_3), 26.91 (CH_2), 28.49 (CH_2), 28.77 (CH_2), 30.98 (CH), 31.22 (CH_2), 36.46 (CH_2), 36.58 (C), 38.12 (CH), 41.19 (CH), 41.56 (CH_2), 47.13 (CH_2), 47.40 (C), 51.03 (CH), 62.94 (CH), 69.47 (CH_2), 72.55 (C), 127.85 (CH), 129.80 (CH), 133.34 (C), 144.69 (C). Anal. Calcd for $C_{28}H_{41}NO_3S$: C, 71.20; H, 8.76; N, 2.97. Found: C, 70.87; H, 8.90; N, 2.88.

23-Iodo-23-nordaphnane (48). Tosylate **47** (192 mg, 0.41 mmol) was dissolved in 1.5 mL of acetone, NaI (487 mg, 3.25 mmol) was added in one portion, and the resulting mixture was heated at reflux for 35 h. The mixture was transferred to a separatory funnel and diluted with 6 mL of ethyl acetate and 4 mL of water. The layers were separated, and the aqueous phase was back-washed with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried, and the solvent was removed to give a brown oil. Purification by chromatography on silica gel, eluting with 50:50:5 ether:hexanes:triethylamine gave iodide **48** (170 mg, 95%) as a cream colored solid mp 68−70 °C. IR(CH_2Cl_2): 2900, 1470, 1450, 1375, 1170, 935, 910 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.90 (d, 3, J = 6.3), 0.91 (s, 3), 1.00 (d, 3, J = 6.3), 1.25−1.47 (m, 8), 1.51−1.92 (m, 10), 2.17 (dd, 1, J = 7.2,3.0), 2.42 (m, 1), 2.71 (s, 1), 2.74 (d, 1, J = 11.0), 3.23 (m, 1), 3.27 (m, 1), 3.36 (m, 1). ^{13}C NMR (100 MHz): δ 4.21 (CH_2), 21.02 (CH_3), 21.39 (CH_3), 22.67 (CH_2), 25.39 (CH_2), 26.29 (CH_3), 27.03 (CH_2), 28.56 (CH_2), 28.96 (CH_2), 31.06 (CH), 36.66 (CH_2), 36.89 (C), 38.08 (CH), 38.64 (CH_2), 41.60 (CH_2), 41.68 (CH), 47.12 (CH_2), 51.04 (CH), 51.48 (C), 62.93 (CH), 72.41 (C). Anal. Calcd for $C_{21}H_{34}NI$: C, 59.01; H, 8.02; N, 3.28. Found: C, 58.71; H, 8.03; N, 2.84.

(-)-22-(Phenylthio)-23-nordaphnane (50). Sodium thiophenoxide (379 mg, 2.87 mmol) was suspended in 1.5 mL of ether at rt. Tosylate **47** (113 mg, 0.24 mmol) in 500 μL of CH_2Cl_2 was added with a syringe, and the flask and syringe were rinsed with 250 μL of CH_2Cl_2, which was added to the reaction mixture. The mixture was stirred vigorously for 48 h and then transferred to a separatory funnel with 10 mL of CH_2Cl_2 and 2 mL of 15% NaOH. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were dried, and the solvent was removed to give a gray oil. Chromatography on silica gel (8 g), eluting with 50 mL of 1:1 ether:hexanes and then 100 mL of 50:50:5 ether:hexanes:triethylamine, provided thioether **53** (92 mg, 94%) as a colorless oil. $[\alpha]^{25}_D$ −1.9 (c = 2.6, $CHCl_3$). IR ($CHCl_3$), 2940, 2900, 2860, 1470 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.88 (d, 3, J = 6.5), 0.93 (s, 3), 0.98 (d, 3, J = 6.5), 1.19−1.42 (m, 8), 1.51−1.88 (m, 10), 2.07 (m, 1), 2.18 (t, 1, J = 7.0), 2.70 (m, 2), 2.98 (dt, 1, J = 12.1, 3.9), 3.08 (dt, 1, J = 12.1, 5.6), 3.21 (d, 1, J = 14.3), 7.15−7.33 (m, 5). ^{13}C NMR (125 MHz): δ 21.00 (CH_3), 21.40 (CH_3), 22.75 (CH_2), 25.44 (CH_2), 26.10 (CH_3), 27.06 (CH_2), 28.63 (CH_2), 29.05 (CH_2), 31.07 (CH), 32.10 (CH_2), 32.15 (CH_2), 36.72 (CH_2), 37.07 (C), 38.06 (CH), 41.69 (CH), 41.73 (CH_2), 47.22 (CH_2), 48.90 (C), 51.45 (CH), 62.97 (CH), 72.38 (C), 125.82 (CH), 128.81 (CH), 129.13 (CH), 137.97 (C). Anal. Calcd for $C_{27}H_{39}NS$: C, 79.16; H, 9.60; N, 3.42. Found: C, 78.89; H, 9.73; N, 3.15.

(−)-22-(Phenylsulfonyl)-23-nordaphnane (13). Thioether **50** (157 mg, 0.38 mmol) was dissolved in 3 mL of CH_2Cl_2, and an excess of ethereal HCl was added. The solvents were removed in vacuo to obtain a white foam that was combined with sodium tungstate (1mg) in 600 μL of acetic acid. Hydrogen peroxide (70 μL of a 30% aqueous solution) was added dropwise with a syringe. The mixture was stirred for 30 min and transferred to a separatory funnel with 10 mL of CH_2Cl_2 and 4 mL of 15% NaOH. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic layers were dried, and the solvent was removed to obtain sulfone **13** (162 mg, 96%) as a white solid, mp: 202−204 °C. $[\alpha]^{25}_D$ −9.0 (c = 1.0, $CHCl_3$). IR ($CHCl_3$): 2950, 1480, 1450, 1312, 1160 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.80 (s, 3), 0.90 (d, 3, J = 6.5), 0.97 (d, 3, J = 6.5), 1.17−1.28 (m, 4), 1.31−1.41 (m, 3), 1.47−1.88 (m, 11), 2.02 (t, 1, J = 7.3), 2.14 (m, 1), 2.68 (m, 2), 3.19 (m, 2), 3.30 (dt, 1, J = 13.0, 5.2), 7.57 (m, 2), 7.67 (t, 1, J = 7.3), 7.91 (dd, 2, J = 8.0, 0.5). ^{13}C NMR (100 MHz): δ 20.99 (CH_3), 21.37 (CH_3), 22.63 (CH_2), 23.42 (CH_2), 25.44 (CH_2), 25.92 (CH_3), 26.91 (CH_2), 28.50 (CH_2), 28.74 (CH_2), 31.09 (CH), 36.51 (CH_2), 37.12 (C), 38.00 (CH), 41.57 (CH_2), 41.64 (CH), 47.12 (CH_2), 47.81 (C), 51.13 (CH), 55.18 (CH_2), 62.90 (CH), 72.53 (C), 128.04 (CH), 129.31 (CH), 133.70 (CH), 139.21 (C). Anal. Calcd for $C_{27}H_{39}NO_2S$: C, 73.42; H, 8.90; N, 3.17. Found: C, 73.10; H, 9.07; N, 2.97.

(+)-Codaphniphylline (3). Method A. Iodide **48** (49 mg, 0.12 mmol) in 600 μL of degassed ether was cooled to −78 °C under argon. A solution of *tert*-butyllithium (150 μL of a 1.71 M solution in pentane, 0.25 mmol) was added dropwise with a syringe. The mixture was stirred at −78 °C for 1 h, warmed to rt for 1 h, and then cooled back to −78 °C. Aldehyde **46** (48 mg, 0.28 mmol) was added in 100 μL of degassed ether with a syringe. The flask and syringe were rinsed with an additional 100 μL of ether, which was added to the reaction mixture. The solution was slowly warmed to rt over 12 h, quenched with 2 mL of saturated NH_4Cl, transferred to a separatory funnel, and extracted with ether (4 × 5 mL). The combined ether layers were washed with 2 mL of 5% Na_2CO_3 and dried. The solvent was removed in vacuo to obtain a pale yellow solid. Purification on silica gel (10 g), eluting with 50 mL of 1:1 hexanes:ethyl acetate and then 150 mL of 50:50:5 ether: hexanes:triethylamine, provided 34 mg (63%) of alcohol **49** as a 1:1 mixture of diastereomers. The mixture was immediately taken on to the next step.

Alcohol **49** (34 mg, 0.07 mmol) was dissolved in 7.5 mL of acetone in a 20-mL round-bottomed flask. Celite (300 mg) was added, and the resulting suspension cooled to 0 °C. Jones reagent (10 drops) was added with a pipet and the orange suspension stirred for 30 min at 0 °C. The reaction mixture was quenched by back titration with 2-propanol until an olive green color persisted and then stirred at rt for 10 min. The solids were filtered away through a small plug of Celite and washed thoroughly with acetone. The filtrate was condensed to obtain a green oil that was dissolved in 10 mL of CH_2Cl_2 and transferred to a separatory funnel containing 2 mL of 5% Na_2CO_3. The basic aqueous phase was extracted with 2 mL of CH_2Cl_2. The combined organic layers were dried (K_2CO_3),

and the solvent was removed to obtain a yellow oil that was purified by chromatography on silica gel (5 g, elution with 50 mL of 1:1 ether:hexanes followed by 100 mL of 50:50:5 ether:hexanes:triethylamine). This provided codaphniphylline (**3**) as a colorless oil (16 mg, 48%) whose spectral data were identical with that of natural codaphniphylline provided by Professor Yamamura.

Method B. To sulfone **13** (34 mg, 0.076 mmol) in a 10-mL round-bottomed flask under Ar was added benzene (180 μL), THF (230 μL) and diisopropylamine (21 μL, 0.153 mmol). The resulting mixture was maintained at −36 °C with a Cryocool bath and *n*-butyllithium (77 μL of a 1.99 M solution in hexanes, 0.153 mmol) was added dropwise with a syringe. The reaction was stirred for 2.5 h. A solution of freshly-distilled aldehyde **46** (26 mg, 0.153 mmol) in THF (75 μL) was added dropwise with a syringe. The flask and syringe were washed with 50 μL of THF, which was added to the reaction mixture. After 1 min, the mixture was quenched with 500 μL of saturated NH_4Cl and warmed to rt. After dilution with 5 mL of CH_2Cl_2 and 1 mL of water, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 1 mL). The organic layers were washed with saturated $NaHCO_3$ (1 mL) and dried. The solvent was removed in vacuo to give an oil that was purified by chromatography on silica gel (7 g), eluting with 1:1 ether:hexanes (100 mL) and 50:50:5 ether:hexanes:triethylamine. This provided alcohol **51** (43 mg) as a colorless oil that was taken directly to the next step.

To a solution of pyridine (74 μL, 0.915 mmol) in 1.1 mL of CH_2Cl_2 under Ar was added CrO_3 (46 mg, 0.458 mmol). The resulting solution was stirred for 15 min at rt and alcohol **51** in 200 μL of CH_2Cl_2 was added dropwise with a syringe. The flask and syringe were rinsed with 100 μL of CH_2Cl_2, which was added to the mixture. After stirring for 3.5 h, the black solution was diluted with 3 mL of CH_2Cl_2 and silica gel (750 mg) was added. Stirring was continued for 15 min before the solvent was removed in vacuo. The remaining slurry was placed atop silica gel (8 g), and the chromium salts were removed by eluting with 50:50:5 ether:hexanes:triethylamine to obtain keto sulfone **52** (41 mg). Keto sulfone **52** was then dissolved in 1.3 mL of 9:1 THF:water. Aluminum amalgam[30] was cut directly into the reaction mixture and the resulting suspension heated at reflux for 2.5 h. The solids were filtered off and silica gel (750 mg) was added to the filtrate. The solvent was removed, and the resulting slurry was placed atop a silica gel column (13 g). Elution with 8:4:1 hexanes:CH_2Cl_2:ethyl acetate with 4% triethylamine provided codaphniphylline (**3**) (21 mg, 57%). IR ($CHCl_3$): 2920, 1710, 1475, 1455, 1390, 1144 cm^{-1}. ^1H NMR (400 MHz): δ 0.79 (s, 3), 0.90 (d, 3, J = 6.4), 0.91 (s, 3), 1.01 (d, 3, J = 6.4), 1.22−2.20 (m, 24), 1.44 (s, 3), 2.76 (m, 2), 2.91 (m, 2), 3.27 (d, 1, J = 13.7), 3.51 (d, 1, J = 12.1), 4.30 (dd, 1, J = 12.1, 1.8), 4.71 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 17.73 (CH_3), 21.06 (CH_3), 21.42 (CH_3), 22.82 (CH_2), 23.59 (CH_3), 23.66 (CH_2), 24.62 (CH_2), 25.45 (CH_2), 25.90 (CH_3), 27.17 (CH_2), 28.70 (CH_2), 28.84 (CH_2), 31.14 (CH), 33.79 (CH_2), 36.76 (CH_2), 37.03 (CH_2), 37.19 (C), 37.97 (CH), 41.68 (CH), 41.83 (CH_2), 47.34 (CH_2), 47.98 (C), 49.64 (C), 51.58 (CH), 63.11 (CH), 65.43 (CH_2), 72.25 (C), 80.76 (CH), 105.17 (C), 212.36 (C). Anal. Calcd for $C_{30}H_{47}NO_3$: C, 76.71; H, 10.09; N, 2.98. Found: C, 76.96; H, 9.90; N, 3.03.

To compare the foregoing sample with reported literature values, the amine hydrochloride salt was prepared by addition of an excess of ethereal HCl to a CH_2Cl_2 solution of synthetic **3**. The solvents were removed in vacuo and the remaining residue was recrystallized with $CHCl_3$:ether to remove the small amount of the undesired diastereomer, isocodaphniphylline (**53**). The resulting white crystals melted at 266−267 °C in a sealed tube (lit. mp 266−267 °C).[7] In addition, these crystals displayed an optical rotation ($[\alpha]^{25}_D$ +4.4 (c = 0.68, $CHCl_3$) that matched favorably with material provided to us by Professor Yamamura ($[\alpha]^{25}_D$ +4.6 (c = 0.39, $CHCl_3$) as well as with the reported value ($[\alpha]^{25}_D$ +4.2 (c = 2.4, $CHCl_3$).[7]

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