Construction of the Stemodane Nucleus by a Hydroxyl-Directed Intramolecular Ene Reaction. Total Synthesis of (±)-2-Desoxystemodinone

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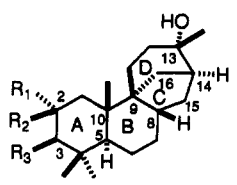
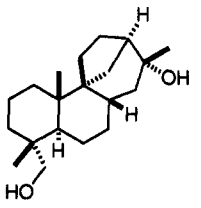
Abstract: A synthesis of the diterpene 2-desoxystemodinone was completed from the known tricyclic ketone **9** in eight steps and 35% overall yield. The key step involved a thermal intramolecular ene reaction of α-hydroxy aldehyde **21** which led to **24** in 94% yield. By contrast, a Lewis acid-catalyzed ene reaction of **21** gave oxetane **25** as the major product. The pivotal role of the hydroxyl substituent of **21** in facilitating the ene reaction was demonstrated and is rationalized by a hydrogen bond which orients the carbonyl in a favorable conformation for rearrangement.

Extracts of the leaves of *Stemodia maritima* L. (Scrophulariaceae),[1] a rare littoral plant found along shorelines in the West Indies, are reputed in Caribbean lore to be a treatment for venereal disease. Attracted by the reported medicinal properties of this shrub, known locally as Jamaican sea mint, Manchand et al. isolated and characterized two new diterpenoid natural products, stemodin (**1**) and stemodinone (**2**).[2] These were shown by chemical correlation and by X-ray crystallography to possess a new tetracyclic skeleton. Subsequently, 2-desoxystemodinone (**3**),[3] maritimol (**4**),[4] and stemarin (**5**)[5] were isolated from the same source, the latter exhibiting yet another new diterpene skeleton. A third structural variant possessing the C/D bicyclo-[3.2.1]octane ring system is represented by the fungal metabolite aphidicolin (**6**), isolated from *Cephalosporium aphidicola*[6] and later found to occur in *Nigrosporum sphaerica*. Aphidicolin, in spite of its relatively simple functionality, displays a wide range of interesting biological activities, including antiviral[7] and antitumor[8] properties.

The structural relationship between stemodanes **1–3** was demonstrated by chemical interconversion.[2] Thus, Jones' oxidation of stemodin (**1**) gave stemodinone (**2**), which could be reduced under Huang–Minlon conditions to afford 2-desoxystemodinone (**3**). Dehydration of the latter with phosphorus oxychloride gave the crystalline hydrocarbon **7**. Structurally, the stemodane and aphidicolane diterpenes are related through inversion at carbons 9, 13, and 14. The configurations at carbons 5, 8, and 10, however, are identical and, moreover, are the same as those found at the corresponding centers in the stemarane skeleton. This consistency led to a proposal for the biogenesis of these three tetracyclic diterpenes from a common intermediate.[9]



1, R_1 = OH, R_2 = R_3 = H
2, R_1 = R_2 = O, R_3 = H
3, R_1 = R_2 = R_3 = H
4, R_1 = R_2 = H, R_3 = OH



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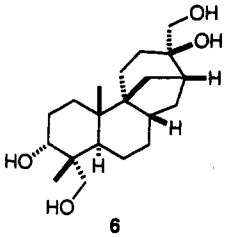

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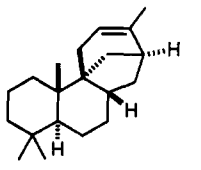

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The novel carbon skeleton and alleged medicinal properties of stemodin have drawn considerable attention to the total synthesis of stemodane diterpenes. Complete syntheses of members of this family have been reported by Corey,[10] Kelly,[11] Bettolo,[12] and Piers,[13] while cognate studies have opened routes to maritimol (**4**)[12,14] and stemarin (**5**).[15] An early report by Chatterjee[16] claiming synthesis of **3** has been challenged[10] and is made untenable by the present work. Herein we describe a synthesis of (±)-2-desoxystemodinone (**3**) which differs from previous approaches to this ring system in using an intramolecular ene process to fabricate the bicyclo[3.2.1]octane portion of the stemodane structure. This ene reaction is shown to be assisted by a proximal hydroxyl substituent.[17]

Results

The strategy envisioned for synthesis of (±)-2-desoxystemodinone is outlined in retrosynthetic form in Scheme 1. Discon-

* Abstract published in *Advance ACS Abstracts*, October 1, 1994.

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(10) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 7612.

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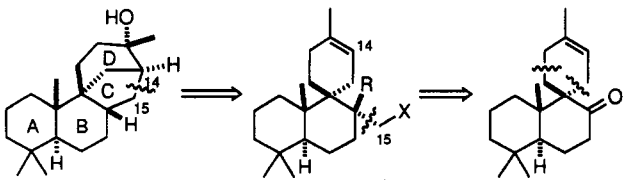
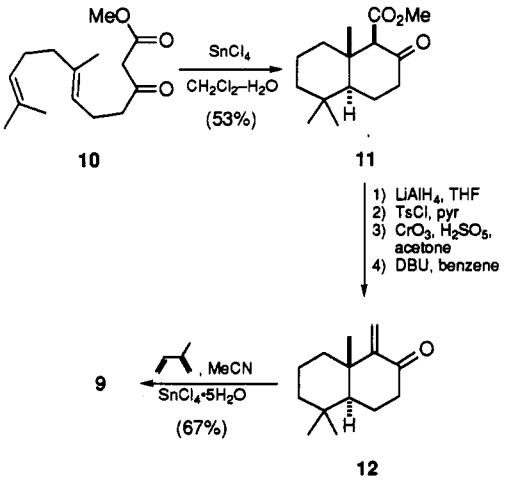
Scheme 1



3 8 9

nection of the C-14,15 bond would give a *seco*-stemodane **8** which could, in principle, be obtained by a one-carbon homologation of the spiroketone **9**, previously prepared in our laboratories.[18] It was initially hoped that closure of the C-14,15 bond could be accomplished through direct solvolysis of **8** (R = H, X = OTs) with participation by the $\Delta^{13,14}$ bond. This tactic was unsuccessful and led us to explore an alternative plan which made use of the spatial proximity of C14 and C15 in a different way.

The synthesis of spiroketone **9**, as originally developed,[18] employs a stannic chloride-mediated cyclization of keto ester **10** to the trans-fused bicyclic structure **11**. It was subsequently discovered that consistent yields of **11** are obtained only when methylene chloride *saturated with water* is used as the solvent.[19] Under anhydrous reaction conditions, the yield of **11** is greatly diminished and polymerization of **10** becomes the major pathway.

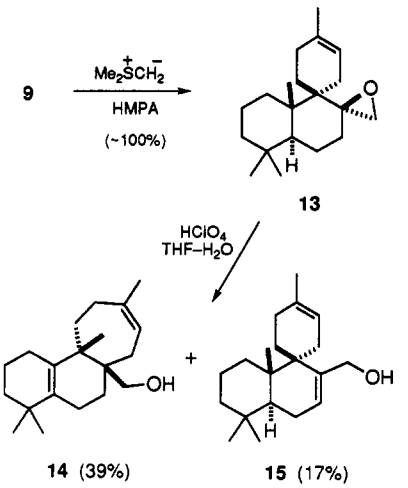


10 11 9 12

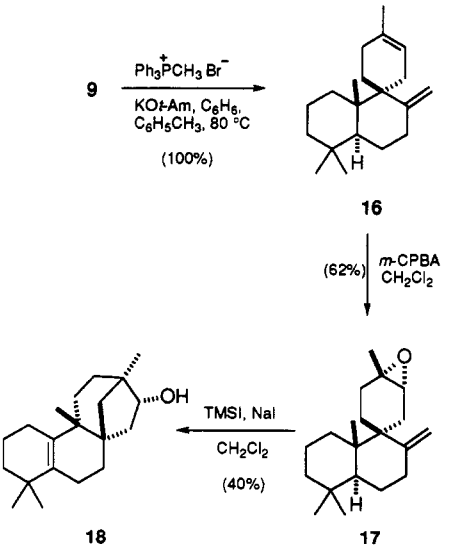
The conversion of **11** to methylene ketone **12** was accomplished by the four-step sequence shown, and **12** was subjected to a stannic chloride-catalyzed Diels–Alder reaction with isoprene to give **9**.

The synthesis of **9**, which requires eight steps from geraniol, proceeds in 20% overall yield and provided multigram quantities for subsequent synthetic studies.

It was expected that, due to the adjacent spiro carbon, the keto group of **9** would be too sterically hindered to react with most nucleophiles. Indeed, ketone **9** was inert to methyllithium and to phosphorane reagents under conventional Wittig conditions. Nevertheless, condensation of **9** with dimethylsulfonium methylide in hexamethylphosphoramide was found to give a nearly quantitative yield of epoxide **13**. Unfortunately, all attempts to effect acid-catalyzed rearrangement of **13** to an aldehyde afforded products that clearly had undergone deep-seated skeletal changes. For example, exposure of **13** to perchloric acid in aqueous tetrahydrofuran produced alcohols **14** and **15** in a 2:1 ratio, respectively.



Subsequently, it was found that application of rather unusual Wittig conditions[20] previously employed in the olefination of a sterically hindered ketone[21] produced a quantitative yield of diene **16** from **9**. Although hydroboration of **16** with 9-BBN or thexylborane failed to yield a useful result, epoxidation of **16** occurred selectively at the trisubstituted olefin to afford **17**. The



epoxide configuration of **17** is assigned on the assumption that approach by the peracid occurs at the more accessible face of the olefin. Treatment of **17** with trimethylsilyl iodide which, it was hoped, would lead to a substance with the stemodane framework gave instead a product that clearly possessed a quite different ring system. Spectral analysis supports the assignment of **18** to

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(17) Preliminary communication: White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424.

(18) (a) White, J. D.; Skeean, R. W.; Trammell, G. L. *J. Org. Chem.* **1985**, *50*, 1939. (b) Skeean, R. W.; Trammell, G. L.; White, J. D. *Tetrahedron Lett.* **1976**, 525.

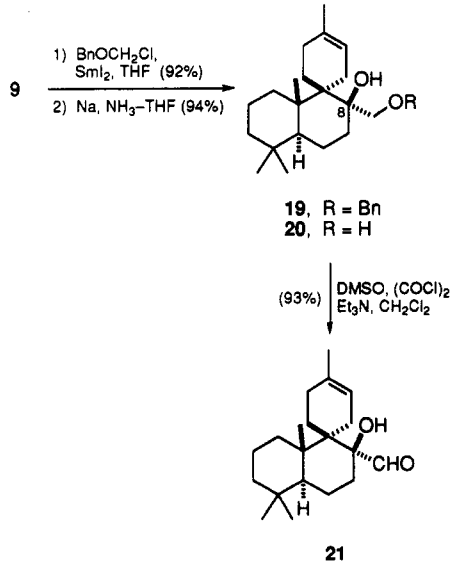
(19) We are grateful to Professor Weiler for this observation. See: Armstrong, R. J.; Weiler, L. *Can. J. Chem.* **1983**, *61*, 2530.

(20) Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760.

(21) Smith, A. B., III; Jerris, P. J. *J. Org. Chem.* **1982**, *47*, 1845.

this product, which results from a series of Wagner–Meerwein rearrangements reminiscent of those seen in the conversion of **13** to **14**. The ease with which **13** and **17** underwent skeletal rearrangement forced us to return to **9** and to adopt a quite different strategy based upon organosamarium chemistry for the requisite one-carbon homologation of this ketone.

Imamoto,[22] in an extension of Kagan's earlier work,[23] reported a method for hydroxymethylation of ketones using benzyl chloromethyl ether in the presence of samarium diiodide. The reaction is believed to proceed via electron transfer from an organosamarium halide and thus takes advantage of the powerful reducing properties of samarium(II). Subsequent cleavage of the resulting benzyl ether affords 1,2-diols. Although hindered substrates have not previously been examined, it was expected that spiroketone **9** would undergo reaction with this system to provide the glycol derivative **19**. In the event, a 92% yield of **19** was obtained which was assigned the configuration shown on the assumption that the bulky organosamarium complex attacks **9** at the less hindered α-face of the ketone, as observed previously with other reagents.[18a] This stereochemical assignment was subsequently confirmed by X-ray crystallographic analysis of a later synthetic intermediate. Attempts to reductively replace the C8 hydroxyl substituent of **19** in order to attain the oxidation level of **3** were unsuccessful due to the highly hindered environment of this axial alcohol which negated all conditions for mesylate or xanthate formation. In retrospect, this was a fortunate outcome since the C8 hydroxyl group was to play a pivotal role in the next phase of the synthesis.



21

Examination of a molecular model of hydroxy aldehyde **21** indicates that, if the aldehyde carbonyl adopts an internally hydrogen-bonded conformation, an ideal alignment for an intramolecular ene reaction[24] ensues. This formal [4 + 2] process would establish the bicyclo[3.2.1]octane system of the stemodanes and would also implant a D-ring double bond for further elaboration. It was unclear from models which of hydrogens a or b were better situated for transfer to the aldehyde oxygen at the transition state, and thus, the possibility existed for a mixture of exo and endo olefin isomers **22a** and **22b**. Molecular mechanics calculations on **21** using the MMX-MODEL program confirmed that the lowest energy structure did indeed contain an intramolecular hydrogen bond with the spiro-ring in a half-chair conformation. The energy minimized conformation of **21** derived from these calculations is shown in Figure 1a.

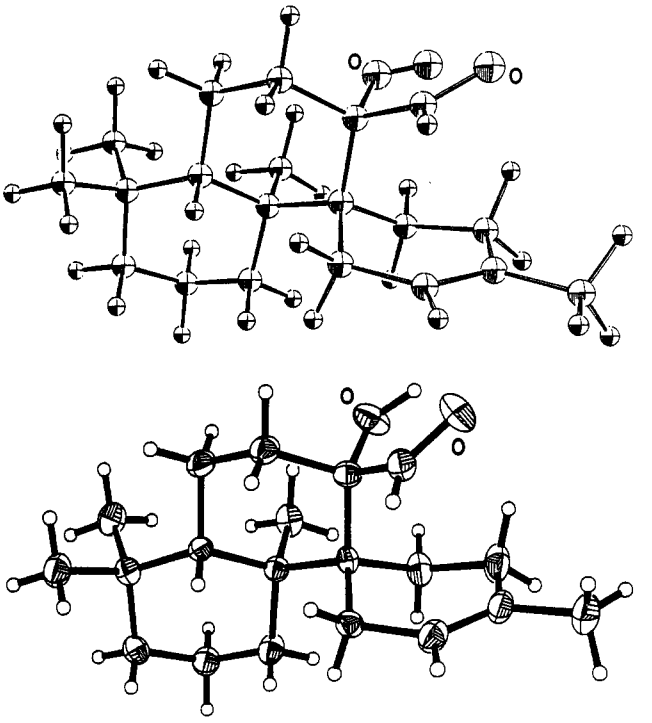
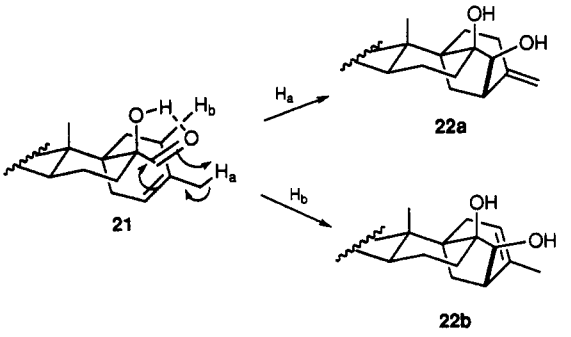


Figure 1. (Top) energy-minimized (MMX-MODEL) conformation of **21**. (Bottom) X-ray crystal structure of **21** confirming a hydrogen-bonded α-hydroxy aldehyde.

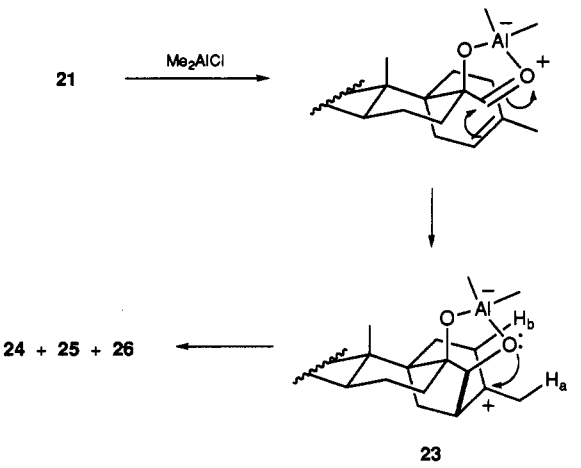


With the aim of testing these predictions, **19** was converted to **21** by cleavage of the benzyl ether with sodium in liquid ammonia followed by oxidation of diol **20** under Swern conditions.[25] The 400 MHz ^{1}H NMR spectrum of **21** displayed a 1.5 Hz coupling between the aldehyde (δ 9.33) and hydroxyl (δ 3.73) protons, clearly suggesting a stable, internal hydrogen bond. Infrared absorptions at 3437 (sharp) and 1704 cm^{-1} supported this conclusion. Final confirmation of the stereochemistry of **21** came from a single crystal X-ray analysis. An ORTEP plot derived from this structural analysis is shown in Figure 1 and is in excellent agreement with the energy-minimized structure of **21** from a molecular mechanics calculation (Figure 1).

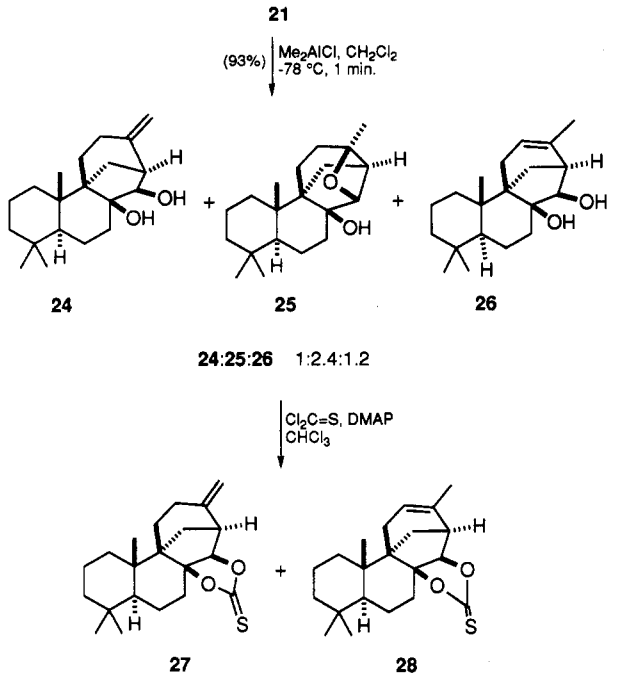
The conformation of **21**, as shown in Figure 1, is clearly conducive to a favorable ene reaction via path H_a, and in accord with this prognostication, aldehyde **21** was found to give **24** as a single product upon heating in toluene. The facility with which this ene reaction occurs is unusual and, as judged by subsequent experiments (vide infra), the process is greatly accelerated by the presence of the hydroxyl group in **21**. On the assumption that the hydrogen bond in the α-hydroxy aldehyde serves to activate the carbonyl group as well as to constrain it in a reactive conformation, Lewis acid-catalyzed versions of the ene reaction were also examined. The expectation of a successful outcome was reinforced by the observation that a small quantity of **24**

(22) Imamoto, T.; Takeyama, T.; Yokoyama, M. *Tetrahedron Lett.* **1984**, *25*, 3225.
(23) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
(24) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476.
(25) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

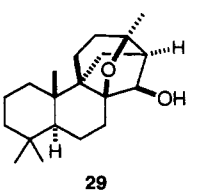
could be seen even when **21** was subjected to chromatography on silica gel. However, when **21** was exposed to dimethylaluminum



chloride[26] the major product was oxetane **25**. Lesser quantities of the exo and endo ene products **24** and **26** were also present which accounted for virtually the entire reaction mixture. Separation of the mixture proved difficult but was facilitated by its treatment with thiophosgene, which removed **24** and **26** from **25** as thionocarbonates **27** and **28**, respectively. This derivatization



concomitantly established the configuration of the 1,2-diol moieties in **24** and **26** as cis. The structure of **25** was conclusively proven by means of an X-ray crystallographic analysis (Figure 2) which thereby ruled out the alternative candidate **29**. The



formation of **25**, along with the mixture of olefin isomers **24** and **26** under Lewis acid catalysis, can be rationalized by a process

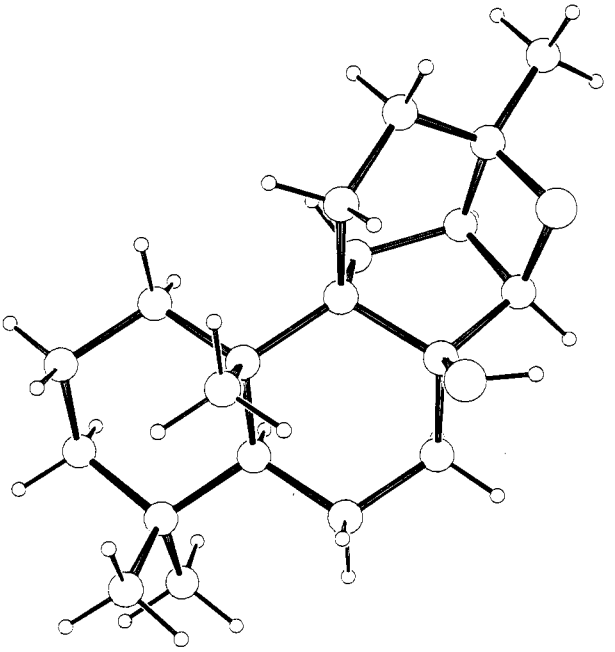
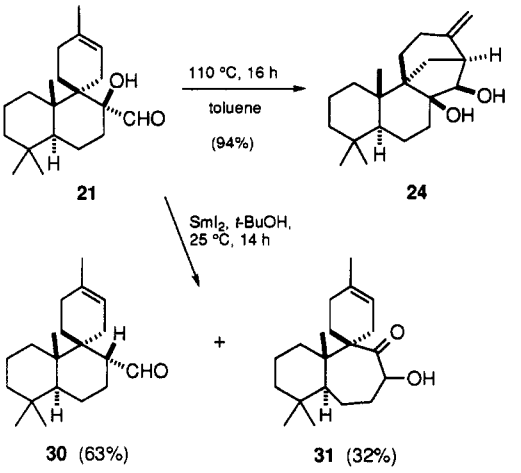


Figure 2. X-ray crystal structure of **25** confirming the oxetane structure.

which passes through carbocation **23** and which terminates by loss of protons H_a or H_b or by ring closure at oxygen to give the oxetane.[27]

The crucial role of the hydroxyl function in the ene reaction of **21** was established through its reductive removal with samarium diiodide in the presence of 2-methyl-2-propanol. The reduction proceeded at room temperature to give **30** in which the aldehyde was assigned an equatorial orientation on the basis of a comparison of measured ^1H chemical shift values with those reported for a closely related system.[10] A byproduct isolated from this reaction was shown to be the ring-expanded α-hydroxy ketone **31** formally derived from a samarium-induced α-ketol rearrangement of **21**.

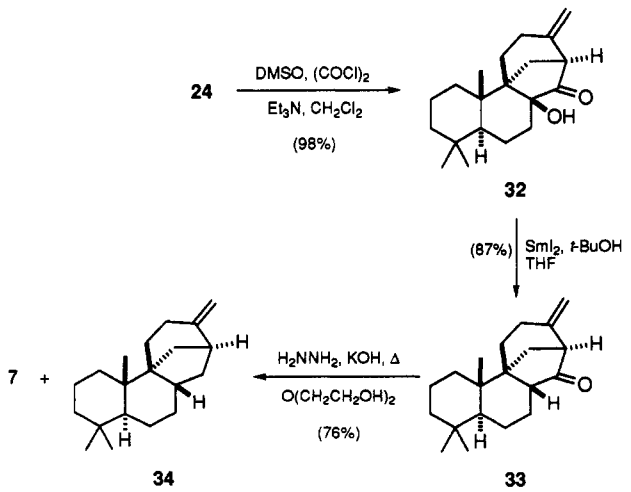


Although Molander has reported a related, general procedure for reductive removal of heteroatom substituents α to a ketone,[28] poor yields are generally obtained with α-hydroxy ketones. Our results indicate that, with 2-methyl-2-propanol as the proton source in a 0.1 M solution of samarium diiodide in tetrahydrofuran, efficient reduction of a free hydroxyl group can be achieved. The use of concentrated samarium diiodide with methanol as the source of protons caused rapid reduction of the aldehyde function of **21**, and only diol products were obtained. That the 8β-hydroxyl group of **21** was necessary for the successful intramolecular ene reaction

(26) (a) Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555. (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.
(27) Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160.
(28) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

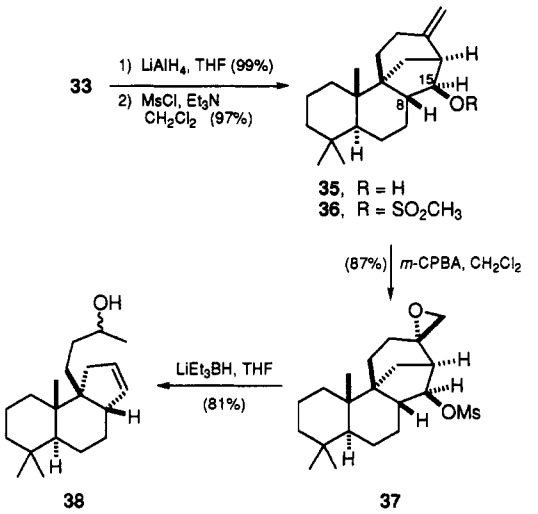
was confirmed by the complete failure of **30** to yield any trace of an ene product under either thermal conditions or in the presence of a Lewis acid. Whether this is due to an insurmountable activation barrier for the ene reaction or to the adoption by the aldehyde of a conformation which does not permit the reaction is unclear.

With an efficient route to a substance possessing the stemodane framework in hand, attention was turned to functional group modification in the C and D rings of **24**. Specifically, completion of a route to **3** required reductive removal of the hydroxyl groups at carbons 8 and 15 along with introduction of the tertiary alcohol at C-13, and our initial efforts along these lines focused on thionocarbonate **27**. However, reduction of **27** with tri-*n*-butyltin hydride[29] gave complex mixtures containing no trace of dehydro-2-desoxystemodinone. This failure necessitated a more circuitous route from **24** to **3**, and to this end, **24** was oxidized under Swern conditions to α-hydroxy ketone **32**. As with **21**, the tertiary hydroxyl group was cleanly removed from **32** by reduction with samarium diiodide in the presence of 2-methyl-2-propanol. This gave **33** in which the stereochemical assignment at C-8 is supported by several observations. First, the gross similarities seen in the ^{1}H and ^{13}C NMR spectra of **32** and **33** are consistent with a close structural correspondence between these compounds. If protonation of the intermediate enolate, formed during the samarium diiodide reduction of **32**, had occurred at the α-face, the resulting configuration at C-8 would have forced major conformational changes upon the A and B rings. In particular, the B-ring would be confined to a highly strained boat conformation to which the five-membered ring would necessarily be trans-fused. Second, the failure to detect any stereoisomer of **33** from the reaction of **32** with samarium(II), or during subsequent reduction of **33**, supports the view that the 8β-hydrogen configuration is thermodynamically more stable and that this is the configuration produced directly during samarium(II) reduction of **32**. The chemical shift correspondence between major signals in the ^{1}H NMR spectra of **33** and **7** argues against the possibility that the 8α epimer of **33** was produced and that isomerization occurred under the basic conditions of its reduction to yield the natural stemodane stereochemistry.

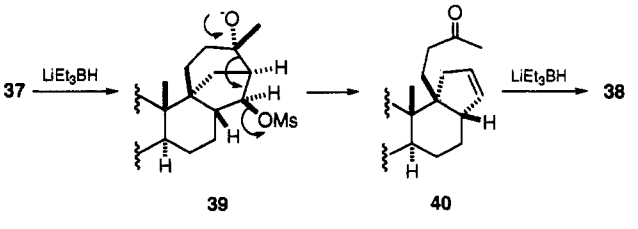


Huang-Minlon reduction[30] of **33** gave a 2.5:1 mixture of exo and endo olefins **34** and **7**, respectively. Although these isomers could not be separated, the latter exhibited distinctive ^{1}H NMR, IR, and mass spectral properties which were identical to those recorded on a sample of **7** prepared by dehydration of natural 2-desoxystemodinone. Attempts were made to avoid the double bond isomerization that occurred under the strongly basic conditions of this reduction but without success, and we therefore resorted to a different tactic for removal of the keto group from **33**. The revision to our plan was motivated, in part, by an examination of a molecular model of **34** which suggested that epoxidation of the exo olefin would exhibit little stereoselectivity. On the other hand, a β oriented substituent at C15 would effectively shield the top face of the double bond and should lead to the desired α epoxide.

Accordingly, **33** was reduced with lithium aluminum hydride and was found to give **35** as the only detectable stereoisomer. Assignment of configuration to this alcohol was made on the assumption that attack at the keto group occurs from the more accessible face exo to the bicyclo[3.2.1]octane framework and from the ^{1}H NMR spectrum of **35** which showed a small coupling constant between protons at C8 and C15. The latter is in agreement with a dihedral angle close to 90°. The mesylate **36** derived from **35** was epoxidized to give in excellent yield a 10:1 mixture of epimeric epoxides in which the major product was assumed on steric grounds to possess the configuration shown in **37**. It was hoped that reduction of the epoxide and mesylate of

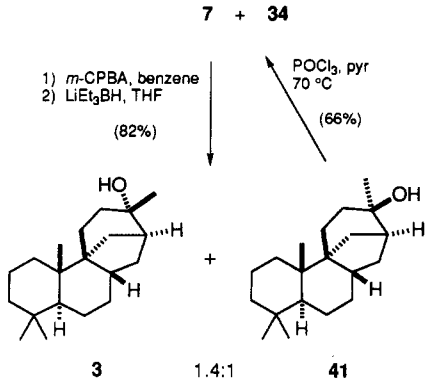


37 could be accomplished in a single operation.[31,32] However, treatment of **33** with excess lithium triethylborohydride did not give the expected 2-desoxystemodinone (**3**). Instead, a 1:1 mixture of two stereoisomeric secondary alcohols was obtained for which structure **38** was deduced by spectral methods. This fragmentation of the stemodane nucleus probably occurs after initial reduction of the epoxide to the tertiary alkoxide **39** which then undergoes Grob scission[33] to ketone **40**. The ketone is rapidly reduced by a second equivalent of the hydride reagent to a mixture of alcohols **38**.



The unfavorable outcome of our detour through **35** forced us to return to the exo and endo olefins obtained from the reduction of **33**, and as expected, treatment of **7** and **34** with *m*-chloroperbenzoic acid yielded a mixture of epoxides. This mixture was reduced with lithium triethylborohydride to afford an easily separable 1.4:1 mixture of (±)-2-desoxystemodinone (**3**) and its C-13 epimer **41**. The latter could be recycled to a mixture of **7** and **34** (1:1.7, respectively) by dehydration with phosphorus

(29) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718.
(30) Todd, D. *Org. React.* **1948**, *4*, 378.
(31) Krishnamurthy, S.; Schubert, R. M.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 8486.
(32) Holder, R. W.; Matturro, M. G. *J. Org. Chem.* **1977**, *42*, 2166.
(33) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.



oxychloride in pyridine, thereby providing a route which converts **33** to **3** in 55% overall yield. Synthetic (±)-2-desoxystemodinone (**3**) displayed TLC behavior and ^{1}H NMR, ^{13}C NMR, IR, and mass spectra which were identical to those of a sample of natural material. However, the measured melting point of (±)-**3**, 108–109.5 °C, is in serious disagreement with two values, 144 °C[16] and 146–147 °C,[12] reported in the literature for the racemic compound. We are unable to explain this discrepancy but point out that, coincidentally, the melting point recorded for naturally occurring (+)-**3** is 144 °C.[2] A final single crystal X-ray structure determination of (±)-**3** left no doubt as to the identity of our synthetic material (Figure 3).

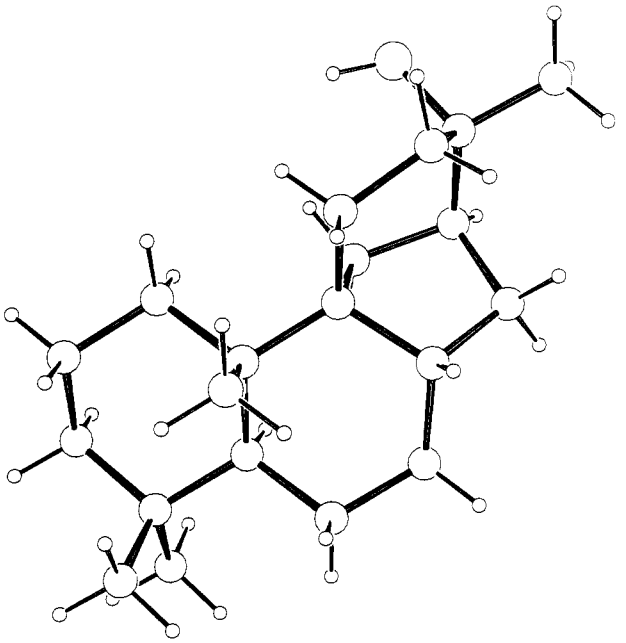


Figure 3. X-ray crystal structure of synthetic (±)-2-desoxystemodinone (**3**).

Experimental Section

Solvents were dried by distillation shortly before use from an appropriate drying agent. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Analytical thin layer chromatography (TLC) was carried out on 2.5 × 7.0 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.2 mm) manufactured by E. Merck. Flash chromatography was carried out with E. Merck silica gel 60 (230–400 mesh ASTM). Melting points were measured on a Büchi melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on either a Perkin-Elmer 727B or a Nicolet 5DXB FT-IR spectrometer. Nuclear magnetic resonance spectra (NMR) were recorded on either an IBM NR-80F or a Bruker AM-400 spectrometer. Carbon NMR spectra were measured on a Bruker AM-400 spectrometer. Chemical shifts are reported downfield from internal Me_4Si on the δ scale. Mass spectra (MS) were obtained with either a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were determined on a Kratos MS-50. Elemental analyses were performed by Desert Analytics (formerly MicAnal), Tucson, AZ. Molecular mechanics calculations were performed using MODEL version KS 2.9 and MMK version 87 available from Serena Software and were run on a VAX 11-750 computer.

(±)-(1′α,4′aα,8′aβ)-3′,4′,4′a,5′,6′,7′,8′,8′a-Octahydro-4,5′,5′,8′a-tetramethyl-2′-oxiranylspiro[3-cyclohexene-1,1′(2′*H*)-naphthalene] (13). Sodium hydride (117 mg, 2.91 mmol, 60% dispersion in mineral oil) was washed with two 10 mL portions of hexane, and 7 mL of HMPA was added. To the stirred suspension was added 520 mg (2.55 mmol) of trimethylsulfonium iodide, and after the mixture was stirred at room temperature for 5 min, a solution of 110 mg (0.401 mmol) of **9** in 2 mL of benzene was added dropwise. The mixture was stirred for 12 h, diluted with 10 mL of water, and extracted with ether (2 × 50 mL). The ethereal extract was washed with water, 10% aqueous sodium carbonate, and brine and was dried over sodium sulfate. Evaporation of the solvent left 117 mg (100%) of virtually pure **13** as an unstable colorless oil: IR (neat) 2960 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (1H, m), 2.72 (1H, d, J = 4.0 Hz), 2.45 (1H, m), 2.19 (1H, d, J = 4.0 Hz), 1.65 (3H, s), 1.06 (3H, s), 0.93 (3H, s), 0.89 (3H, s); HRMS m/z 288.2454 (calcd for $C_{20}H_{32}O$ 288.2453). Attempts to chromatograph **13** on silica gel and on Florisil led to decomposition.

Acid-Catalyzed Rearrangement of 13. To a solution of 40.0 mg (0.139 mmol) of **13** in 2 mL of THF was added 1 mL of 5% aqueous perchloric acid. The solution was stirred for 24 h and diluted with 10 mL of ether. The ethereal layer was separated, washed with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a pale yellow oil which was separated by HPLC on a Porisil column. Elution with ethyl acetate–hexane (1:8) gave 15.7 mg (39%) of **14** and 6.6 mg (17%) of **15**.

14: IR (neat) 3600 (broad) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (1H, t, J = 6.7 Hz), 3.63 (1H, d, J = 10.7 Hz), 3.45 (1H, d, J = 10.7 Hz), 2.38 (1H, dd, J = 6.2, 14.4 Hz), 1.71 (3H, s), 1.00 (3H, s), 0.98 (3H, s), 0.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 135.8, 132.8, 121.4, 76.4, 44.0, 40.0, 39.9, 34.5, 32.4, 30.5, 29.8, 28.2, 27.2, 25.9, 24.7, 22.5, 21.4, 20.2; MS m/z 288 (M^+), 273, 257. Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.28. Found: C, 82.94; H, 11.36.

15: IR (neat) 3500 (broad) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (1H, m), 5.41 (1H, m), 4.06 (2H, s), 2.29 (1H, d, J = 16.0 Hz), 1.66 (3H, s), 0.93 (3H, s), 0.91 (3H, s), 0.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 133.8, 125.1, 122.0, 65.8, 43.3, 42.0, 40.8, 33.8, 33.4, 33.2, 29.4, 24.9, 24.0, 23.4, 22.3, 19.0, 16.1; MS m/z 288 (M^+), 242, 220, 91.

(±)-(1′α,4′aα,8′aβ)-3′,4′,4′a,5′,6′,7′,8′,8′a-Octahydro-4,5′,5′,8′a-tetramethyl-2′-methylenespiro[3-cyclohexene-1,1′(2′*H*)-naphthalene] (16). Methyltriphenylphosphonium bromide (1.25 g, 3.50 mmol) was placed in a 10 mL two-neck flask equipped with a reflux condenser and argon inlet. The apparatus was purged with argon and preheated in an oil bath to 85 °C. Potassium *tert*-amylate in benzene (2.69 mL, 1.30 M, 3.50 mmol) was added in one portion, followed by 0.5 mL of dry toluene. After being heated at 85 °C for 30 min, the orange solution became homogeneous. A solution of **9** (121 mg, 0.442 mmol) in 0.2 mL of toluene was added via syringe, and the solution was maintained at reflux for 4 h. After cooling, 2 mL of water was added and the mixture was diluted with ether. The organic layer was separated and washed with two 25 mL portions of water and brine and was dried over magnesium sulfate. After the crude mixture was concentrated it was redissolved in pentane and filtered through silica gel (5 g). Evaporation afforded 120 mg (99%) of **16** as a colorless oil: IR (neat) 2950, 1635, 890, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (1H, bs), 4.88 (1H, s), 4.73 (1H, s), 2.4–2.1 (5H, m), 1.9–1.8 (2H, m), 1.59 (3H, bs), 0.87 (6H, s), 0.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 133.0, 119.4, 108.2, 46.0, 45.4, 42.1, 41.7, 34.1, 33.6, 33.5, 32.7, 28.7, 28.3, 24.6, 23.3, 23.1, 22.0, 19.5, 16.0; MS m/z 272 (M^+), 257, 154, 134 (100); HRMS m/z 272.2496 (calcd for $C_{20}H_{32}$ 272.2506). Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.21; H, 11.88.

(±)-[1′α,3′β(4aS*,8aS*),6′α]-Octahydro-5,5,6′,8a-tetramethyl-2-methylenespiro[naphthalene-1(2*H*),3′-bicyclo[4.1.0]-7-oxaheptane] (17). To a stirred solution of **16** (114 mg, 0.418 mmol) in 2 mL of dry methylene chloride at 0 °C was added portionwise 89 mg (0.516 mmol) of *m*-chloroperbenzoic acid (85%). After 3 h the suspension was warmed to room temperature and 10% aqueous sodium sulfite was added. The mixture was transferred to a separatory funnel, was washed with water and brine, and was dried over magnesium sulfate. Concentration of the solution gave an oil which was chromatographed (20 g of silica gel, ethyl acetate–hexane 1:30) to afford 74.8 mg (62%) of **17** as a glass: IR ($CHCl_3$) 3050, 2900, 1615, 1380, 1210, 900, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (1H, s); 4.63 (1H, s), 2.93 (1H, bs), 2.35 (1H, m), 2.15

(3H, m), 2.00 (1H, m), 1.80 (1H, m), 1.26 (3H, s), 0.87 (3H, s), 0.81 (3H, s), 0.80 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 110.0, 59.5, 56.9, 45.4, 44.5, 42.3, 41.9, 34.1, 33.8, 33.5, 32.6, 28.8, 27.3, 24.3, 23.0, 22.0, 20.2, 19.3, 16.0; MS *m/z* 288 (M^+), 270, 177, 151, 137 (100); HRMS *m/z* 288.2453 (calcd for $C_{20}H_{32}O$ 288.2453).

(±)-(6aα,8β,9α,11aα)-1,2,3,4,5,6,7,8,9,10,11,11a-Dodecahydro-4,4,9,-11a-tetramethyl-6a,9-methano-6a*H*-cyclohepta[*a*]naphthalen-8-ol (18). To a stirred solution of **17** (74.8 mg, 0.259 mmol) in 5 mL of dry methylene chloride was added 390 mg (2.60 mmol) of sodium iodide and 184 μL (1.30 mmol) of trimethylsilyl iodide. After 10 min, water and ether were added, and the organic phase was separated, washed with water, 5% aqueous sodium thiosulfate, and brine, and dried over magnesium sulfate. Concentration gave a dark oil which was chromatographed (20 g of silica gel, ethyl acetate–hexane 1:10) to afford 30.3 mg (40%) of **18** as an oil: IR (neat) 3335, 2921, 2858, 1457, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (1H, dd, J = 10.7, 4.3 Hz), 1.01 (3H, s), 0.96 (3H, s), 0.93 (3H, s), 0.91 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 133.1, 79.2, 45.7, 44.1, 43.2, 42.7, 40.6, 40.0, 34.0, 31.2, 30.5, 30.3, 29.1, 27.8, 25.6, 24.8, 22.6, 21.2, 20.0; MS *m/z* 288 (M^+), 274, 273 (100), 255, 232, 213, 199; HRMS *m/z* 288.2452 (calcd for $C_{20}H_{32}O$ 288.2453). Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.04; H, 10.99.

(●)-(1'α,2'β,4'aα,8'aβ)-3',4',4'a,5',6',7',8',8'a-Octahydro-4,5',5',8'a-tetramethyl-2'-[(phenylmethoxy)methyl]spiro[3-cyclohexene-1,1'(2'*H*)-naphthalen]-2'-ol (19). Freshly prepared samarium diiodide in dry tetrahydrofuran (0.1 M, 33 mL, 3 equiv) was added via cannula to a stirred solution of **9** (300 mg, 1.09 mmol) and benzyl chloromethyl ether (205 mg, 1.31 mmol, 1.2 equiv) in 5 mL of tetrahydrofuran under an argon atmosphere. The dark blue solution was stirred at ambient temperature for 22 h after which 10 mL of 0.1 M aqueous hydrochloric acid was added to dissolve the inorganic precipitate. The mixture was diluted with ether, and the organic phase was separated, washed successively with hydrochloric acid, water, and 10% aqueous sodium sulfite, and dried over magnesium sulfate. Concentration of the solution gave 455 mg of a viscous yellow oil which was chromatographed (60 g of silica gel, ethyl acetate–hexane 1:20) to afford 396 mg (92%) of **19** as a colorless solid: mp 81.5–82.0 °C (hexane); IR (KBr) 3553, 2949, 2868, 1454, 1095, 611 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (5H, m), 5.30 (1H, m), 4.49 (2H, s), 3.48 (1H, d, J = 8.8 Hz, *A*B), 3.19 (1H, d, J = 8.8 Hz, A*B*), 2.57 (1H, s), 2.25 (1H, m), 1.60 (3H, bs), 1.22 (3H, s), 0.87 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 133.8, 128.4, 127.7, 127.6, 121.7, 77.6, 76.2, 73.4, 47.0, 44.3, 43.5, 41.7, 34.6, 34.4, 34.2, 33.3, 29.6, 27.5, 23.3, 22.2, 21.9, 18.7, 18.4, 17.3; MS *m/z* 396 (M^+), 378, 275, 270, 257, 183, 149, 136, 91 (100), 69; HRMS *m/z* 396.3030 (calcd for $C_{27}H_{40}O_2$ 396.3028). Anal. Calcd for $C_{27}H_{40}O_2$: C, 81.77; H, 10.17. Found: C, 82.06; H, 10.29.

(±)-(1'α,2'β,4'aα,8'aβ)-3',4',4'a,5',6',7',8',8'a-Octahydro-2'-hydroxy-4,5',5',8'a-tetramethylspiro[3-cyclohexene-1,1'(2'*H*)-naphthalene]-2'-methanol (20). To 20 mL of distilled ammonia at –78 °C under an argon atmosphere was added 462 mg (1.16 mmol) of **19** in 10 mL of dry tetrahydrofuran. Sodium metal (54.0 mg, 2.33 mmol) was added in one portion, and after 5 min the stirred solution turned deep blue. The cooling bath was removed, and the mixture was allowed to reflux for 0.5 h, at which time the blue color had dissipated. Solid ammonium chloride was added, and the ammonia was removed under a stream of argon. The mixture was dissolved in a combination of ether, ethyl acetate, and water (2:1:3), and the aqueous phase was separated and extracted with ether. The combined organic solution was washed with water and brine and was dried over anhydrous sodium sulfate. Concentration of the solution gave a colorless glass which was chromatographed (30 g of silica gel, ethyl acetate–hexane 1:4) to afford 337 mg (94%) of **20** as a colorless solid. An analytical sample was prepared by recrystallization from methylene chloride–hexane: mp 99.5–100.5 °C (needles); IR (Nujol) 3430, 2923 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (1H, bm), 3.62 (1H, dd, J = 10.7, 4.9 Hz), 3.32 (1H, dd, J = 10.7, 7.1 Hz), 2.30 (1H, bd, J = 10 Hz), 1.64 (3H, bs), 1.21 (3H, s), 0.88 (3H, s), 0.87 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 121.6, 78.3, 68.2, 46.8, 44.5, 43.5, 41.7, 34.2, 34.1, 33.3, 33.0, 29.6, 27.5, 23.3, 22.1, 21.9, 18.6, 18.3, 17.4; MS *m/z* 306 (M^+), 288, 275 (100), 270, 257, 163, 150, 137, 95, 69. Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.39; H, 11.18. Found: C, 78.63; H, 11.18.

(±)-(1'α,2'β,4'aα,8'aβ)-3',4',4'a,5',6',7',8',8'a-Octahydro-2'-hydroxy-4,5',5',8'a-tetramethylspiro[3-cyclohexene-1,1'(2'*H*)-naphthalene]-2'-carboxaldehyde (21). To a flame-dried flask which had been purged with argon was added 154 μL (1.76 mmol) of oxalyl chloride and 2.5 mL of dry methylene chloride. The solution was cooled to –60 °C, and 261 μL (3.68 mmol) of dimethyl sulfoxide was added dropwise. After 5 min a solution of 246 mg (0.801 mmol) of **20** in 5 mL of methylene chloride was added, followed after 3 min by 1.06 mL (7.61 mmol) of triethylamine. The mixture was warmed to ambient temperature and was quenched by the addition of 15 mL of water. The aqueous phase was separated and extracted with methylene chloride, and the combined organic layers were washed with water and concentrated in vacuo. The resultant light yellow solid (257 mg) was chromatographed (25 g of silica gel, ethyl acetate–hexane 1:10) to afford 226 mg (93%) of **21** as a colorless crystalline solid: mp 100.5–101.5 °C (prisms, hexane); IR (Nujol) 3437 (sharp), 2953, 1704, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (1H, d, J = 1.5 Hz), 5.47 (1H, m), 3.73 (1H, d, J = 1.5 Hz, –OH), 2.56 (1H, bd, J = 19.0 Hz), 2.24 (1H, bd, J = 19.0 Hz), 2.05 (2H, m), 1.51 (3H, bs), 1.27 (3H, s), 0.91 (3H, s), 0.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 134.4, 122.2, 80.1, 45.9, 45.8, 41.7, 41.7, 34.2, 33.4, 33.2, 32.3, 27.3, 27.2, 23.0, 22.5 (×2), 18.6, 18.2, 17.1; MS *m/z* 304 (M^+), 275 (100), 257, 163, 149, 137, 109, 95, 69; HRMS *m/z* 304.2402 (calcd for $C_{20}H_{32}O_2$ 304.2402). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.69; H, 10.82.

Compound **21** crystallized in space group $P2_12_12_1$ with a = 6.392(1) Å, b = 10.974(2) Å, c = 24.922(2) Å, V = 1748.2(6) Å^3, Z = 4, d_{calc} = 1.16 g/cm^3, d_{obsd} = 1.14 g/cm^3. All nonequivalent reflections in the range 3.5° < 2θ < 45.0° were measured by the θ – 2θ technique on a Nicolet R3m/V diffractometer with graphite-monochromated Mo Kα radiation. The structure was solved with SHELXTL PLUS using 1109 unique reflections with $F > 3\sigma(F)$. Full-matrix least-squares refinement with anisotropic temperature factors and calculated hydrogen atom positions led to final discrepancy indices of R = 0.0591 and R_w = 0.0655.

Thermal Ene Reaction of 21: (±)-(4aα,6aβ,7β,8α,11aα,11bβ)-Dodecahydro-4,4,11b-trimethyl-9-methylene-8,11a-methano-11aH-cyclohepta[*a*]naphthalene-6a(7*H*),7-diol (24). A solution of 106 mg (0.348 mmol) of **21** in 20 mL of dry toluene was heated at reflux under an argon atmosphere for 16 h. The solvent was removed in vacuo, and the resultant solid was chromatographed (19 g of silica gel, cyclohexane–acetone 5:1) to afford 100 mg (94%) of **24** as a colorless crystalline solid: mp 162–163 °C (plates, methylene chloride–hexane); IR (KBr) 3500 (broad), 2935, 2867, 1446, 1102, 909, 895 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (1H, bs), 4.69 (1H, bs), 3.66 (1H, dd, J = 5.6, 7.3 Hz), 2.93 (1H, dd, J = 7.3, 5.6 Hz), 2.81 (1H, s, –OH), 2.33 (1H, d, J = 5.6 Hz, –OH), 2.25 (2H, m), 1.90 (3H, m), 1.09 (3H, s), 0.90 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 109.5, 78.8, 76.5, 52.0, 48.1, 47.2, 42.8, 41.8, 38.9, 35.8, 34.6, 33.3, 33.1, 28.9, 25.5, 22.8, 19.5, 18.4, 16.8; MS *m/z* 304 (M^+), 286, 271, 268, 253, 205, 189, 150, 123, 69 (100). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.97; H, 10.78.

Lewis Acid Mediated Ene Reaction of 21: 24, (±)-(4aα,6aβ,6bα,8β,-8aα,9aβ,9bβ)-Decahydro-4,4,8,9b-tetrahydro-8*H*-8,9a-ethanobenz[4,5]-indeno[1,2-*b*]oxet-6a(6b*H*)-ol (25), and (±)-(4aα,6aβ,7β,8aα,11aα,-11bβ)-1,2,3,4,4a,5,6,8,11,11b-Decahydro-4,4,9,11b-tetramethyl-8,11a-methano-11a*H*-cyclohepta[*a*]naphthalene-6a(7*H*),7-diol (26). To a stirred solution of 102.3 mg (0.336 mmol) of **21** in 2 mL of dry methylene chloride under argon at –78 °C was added dropwise 0.70 mL (0.70 mmol, 1.0 M in hexane) of dimethylaluminum chloride. After 1 min 2 mL of water was added, the frozen mixture was warmed to room temperature, and 1.0 M hydrochloric acid was added until the solution was acidic to litmus. The mixture was extracted with methylene chloride, and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated to give 113 mg of a light yellow oil. Chromatography of this oil (25 g of silica gel, ethyl acetate–hexane 1:4) gave 95.4 mg (93%) of a mixture of **24**, **25**, and **26** (1:2.4:1.2). A pure sample of **25** was obtained by crystallization from hexane.

25: mp 149.5–150.5 °C; IR (Nujol) 3300, 2854, 2923, 1490 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (1H, d, J = 5.9 Hz), 3.20 (1H, d, J = 1.8 Hz, –OH), 2.76 (1H, dd, J = 5.9, 5.4 Hz), 1.36 (3H, s), 1.08 (3H, s), 0.89 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.7, 84.0, 78.1, 49.9, 48.1, 42.1, 40.2, 38.8, 35.2, 34.5, 33.4, 33.1, 31.1, 28.2, 27.4, 22.4, 20.2, 18.6, 18.4, 14.1; MS *m/z* 304 (M^+), 289, 286, 271, 228, 179, 163, 109, 94, 81, 69. Compound **25** crystallized in space group $P2_{1/c}$ with a = 12.804(1) Å, b = 63.13(2) Å, c = 21.64(1) Å, β = 102.15(1)°, Z = 4, d_{calc} = 1.183 g/cm^3. The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, ω – 2θ scans). Of the 3512 independent reflections for θ < 75°, 2964 were considered to be observed [$I > 3.0\sigma(I)$]. The structure was solved by a multiple-solution procedure and was refined by full-matrix least-squares. Two reflections which were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement, anisotropic thermal parameters were used for the non-hydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The final discrepancy indices are R = 0.052 and R_w = 0.076 for the remaining 2962 observed reflections. The final difference map has no peaks greater than 0.3 e/Å^3.

26: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (1H, b), 3.55 (1H, dd, J = 7.3, 11.2 Hz), 2.73 (1H, s, –OH), 2.53 (1H, dd, J = 7.3, 5.2 Hz), 2.40 (1H, bd, J = 16.7 Hz), 2.33 (1H, d, J = 11.2 Hz, –OH), 1.97 (1H, bd, J = 16.7 Hz), 1.87 (1H, dd, J = 5.2, 12.2 Hz), 1.69 (3H, b), 1.03 (3H, s), 0.89 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 124.7, 80.5, 76.8, 51.2, 48.3, 43.1, 42.0, 41.5, 38.8, 35.1, 34.5, 33.4, 31.3, 28.9, 23.9, 22.7, 19.2, 18.5, 15.5.

(±)-(4aα,4bβ,8β,8aβ,11aR*,13aβ)-Dodecahydro-1,1,4a-trimethyl-7-methylene-5*H*-4b,8-methanonaphtho[2′,1′:1,7]cyclohepta[1,2-*d*][1,3]dioxole-10-thione (27) and (±)-(4aα,4bβ,8β,8aβ,11aR*,13aβ)-1,2,3,4,4a,8,8a,-12,13,13a-Decahydro-1,1,4a,7-tetramethyl-5*H*-4b,8-methanonaphtho[2′,1′:1,7]cyclohepta[1,2-*d*][1,3]dioxole-10-thione (28). To an ice-cooled solution of 61.6 mg (0.202 mmol) of a mixture of **24**, **25**, and **26** and 130 mg (1.06 mmol) of 4-(dimethylamino)pyridine in 2 mL of chloroform was added 28.5 μL (0.506 mmol) of thiophosgene. The orange solution was warmed to room temperature over 5 h, 1 g of silica gel was added, and the solvent was removed in vacuo. The resultant solid was placed on a column of 10 g of silica gel and eluted with methylene chloride–hexane (1:1) to afford 23.1 mg (56% based on recovered **25**) of a 1:2 mixture of **27** and **28**, respectively: IR (KBr) 3017, 2924, 1443, 1300, 909, 800, 658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, bs), 4.72 (2.5H, m), 3.10 (0.5H, bt, J = 6.5 Hz), 2.64 (1H, bt, J = 6.0 Hz), 1.68 (3H, bs), 1.06 (1.5H, s), 1.01 (3H, s), 0.92 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 192.3, 144.9, 135.6, 121.9, 110.2, 96.5, 95.6 (×2), 93.7, 55.8, 53.3, 47.3, 47.2, 45.5, 42.1, 41.5, 41.4, 38.3 (×2), 37.9, 37.1, 35.7, 35.3, 34.4, 34.3, 33.6, 33.4, 33.3, 29.8, 26.7, 25.3, 23.4, 22.8, 22.7, 19.0, 18.8, 18.4, 18.3 (×2), 17.6, 17.1. Further elution with ethyl acetate gave 25.3 mg of **25**.

(±)-(1′α,2′α,4′aβ,8′aβ)-3′,4′,4′a,5′,6′,7′,8′,8′a-Octahydro-4,5′,5′,8′a-tetramethylspiro[3-cyclohexene-1,1′(2′*H*)-naphthalene]-2′-carboxaldehyde (30) and (±)-(4aα,5β,9aβ)-2,3,4,4a,7,8,9,9a-Octahydro-7-hydroxy-1,1,4′,4a-tetramethylspiro[5*H*-benzocycloheptene-5,1′-cyclohex-3-en]-6(1*H*)-one (31). To a solution of 22.3 mg (73.2 μmol) of **21** in 2 mL of dry tetrahydrofuran containing 28.0 μL (0.293 mmol) of 2-methyl-2-propanol under argon was added 2.9 mL (0.293 mmol, 0.1 M in tetrahydrofuran) of freshly prepared samarium diiodide. The resultant deep-blue solution was stirred at room temperature for 14 h, and 0.1 M hydrochloric acid was added to dissolve the precipitate. The mixture was diluted with ether, and the organic phase was separated, washed with 0.1 M hydrochloric acid, 10% aqueous sodium sulfite, water, and brine, and dried over anhydrous magnesium sulfate. Concentration of the solution gave a colorless oil which was chromatographed (9 g of silica gel, methylene chloride–hexane 2:1) to afford 13.3 mg (63%) of **30**: IR (neat) 2945, 1697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (1H, s), 5.36 (1H, b), 1.66 (3H, b), 0.87 (3H, s), 0.86 (3H, s), 0.80 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 132.6, 120.6, 47.7, 45.4, 43.2, 41.9, 40.8, 34.0, 33.2, 32.3, 30.2, 27.8, 23.7, 22.9, 21.9, 19.9, 18.9, 18.7, 16.4; MS m/z 288 (M$^+$), 270, 231, 205, 177, 163, 137, 105, 95 (100), 79, 67, 55; HRMS m/z 288.2453 (calcd for $C_{20}H_{32}O$ 288.2453). Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.16; H, 11.22.

Further elution gave 7.1 mg (32%) of **31**: mp 106–108 °C (hexane); IR (KBr) 3469 (sharp), 2932, 1681, 1392, 1099, 801 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (1H, m), 4.37 (1H, bd, J = 7.1 Hz), 4.12 (1H, d, J = 2.5 Hz), 2.62 (1H, bd, J = 18 Hz), 2.43 (1H, bd, J = 18 Hz), 1.55 (3H, bs), 0.93 (3H, s), 0.85 (3H, s), 0.79 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.8, 135.5, 119.9, 73.9, 56.1, 51.3, 42.0, 41.6, 35.2, 34.7, 34.2, 33.7, 28.4, 27.4, 25.6, 23.0, 22.1, 21.7, 18.9, 15.6; MS m/z 304 (M$^+$, 100), 286, 162, 149, 136, 123, 107, 93, 69; HRMS m/z 304.2402 (calcd for $C_{20}H_{32}O_2$ 304.2402).

(±)-(4aα,6aβ,8α,11aα,11bβ)-Dodecahydro-6a-hydroxy-4,4,11b-trimethyl-9-methylene-8,11a-methano-11a*H*-cyclohepta[*a*]naphthalen-7-one (32). To a solution of 79 μL (0.898 mmol) of oxalyl chloride in 2 mL of dry methylene chloride at –60 °C under argon was added 133 μL of dry dimethyl sulfoxide (1.88 mmol). A solution of **24** (124 mg, 0.408 mmol) in 4 mL of dry methylene chloride was added after 5 min, followed by triethylamine (0.54 mL, 3.88 mmol). The suspension was warmed to room temperature and was quenched by the addition of 20 mL of water. The aqueous phase was separated and extracted twice with methylene chloride, and the combined organic extracts were concentrated in vacuo to leave a yellow solid. Chromatography of this material (20 g of silica gel, ethyl acetate–hexane 1:5) afforded 121 mg (98%) of **32**: mp 197–198 °C (needles, hexane); IR (KBr) 3449 (sharp), 2938, 1738, 885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (1H, s), 4.67 (1H, d, J = 1.0 Hz), 3.12 (1H, d, J = 5.8 Hz), 2.40 (1H, s, –OH), 2.37 (1H, m), 2.22 (2H, m), 2.12 (1H, m), 1.16 (3H, s), 0.93 (3H, s), 0.91 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.0, 147.8, 107.3, 80.0, 53.1, 51.0, 47.4, 41.7, 37.9, 34.6 (×2), 34.1, 33.5, 33.3, 30.0, 26.9, 22.5, 18.2, 17.8, 16.3; MS m/z 302 (M$^+$), 274 (100), 259, 256, 207, 136, 93, 55. Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.55; H, 10.15.

(±)-(4aα,6aβ,8α,11aα,11bβ)-Dodecahydro-4,4,11b-trimethyl-9-methylene-8,11a-methano-11a*H*-cyclohepta[*a*]naphthalen-7(6a*H*)-one (33). To a stirred solution of **32** (87.7 mg, 0.289 mmol) in 2 mL of dry tetrahydrofuran under an argon atmosphere at room temperature was added via syringe 82 μL (0.869 mmol) of dry 2-methyl-2-propanol and 8.70 mL (0.1 M in tetrahydrofuran, 0.869 mmol) of freshly prepared samarium diiodide. The deep-blue solution was stirred for 12 h and then was opened to the atmosphere to destroy excess samarium(II). The resultant yellow suspension was transferred to a separatory funnel, diluted with 30 mL of ether, and washed with 0.1 M hydrochloric acid, 10% aqueous sodium sulfite, water, and brine. After being dried over anhydrous magnesium sulfate, the solution was concentrated to give a colorless solid which was chromatographed (16 g of silica gel, ethyl acetate–hexane 1:10) to afford 71.8 mg (87%) of **33** as a colorless crystalline solid: mp 110.5–111.0 °C (prisms, hexane); IR (KBr) 2960, 2929, 2866, 1735, 1652, 895 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, bs), 4.65 (1H, bs), 3.04 (1H, d, J = 5.8 Hz), 2.47 (1H, dd, J = 5.8, 11.7 Hz), 2.25 (3H, m), 1.97 (1H, m), 1.73 (2H, m), 1.00 (3H, s), 0.91 (3H, s), 0.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.2, 147.4, 107.1, 56.4, 49.7, 48.6, 46.9, 41.7, 37.8, 35.2, 34.5, 33.9, 33.2, 31.3, 30.5, 26.0, 22.6, 21.0, 19.4, 18.1; MS m/z 286 (M$^+$, 100), 268, 163, 135, 119, 105, 93; HRMS m/z 286.2296 (calcd for $C_{20}H_{30}O$ 286.2297). Anal. Calcd for $C_{20}H_{30}O$: C, 83.85; H, 10.56. Found: C, 84.16; H, 10.65.

(±)-*exo*- (34) and (±)-*endo*-Dehydro-2-desoxystemodinone (7). Method A. A stirred solution of 137.4 mg (0.479 mmol) of **33**, 1.0 g (17.8 mmol) of powdered potassium hydroxide and 1.5 mL (30.9 mmol) of hydrazine monohydrate in 10 mL of diethylene glycol was heated to 140 °C under argon during 30 min. The mixture was maintained at 140 °C for 30 min and then heated to 205 °C as the excess hydrazine and water were collected in a Dean-Stark trap. After 2 h at 205 °C the solution was cooled to room temperature, diluted with 10 mL of water, and poured into 20 mL of brine. The aqueous solution was extracted with three portions of ether, and the combined organic extracts were washed twice with brine and dried over magnesium sulfate. Concentration of the solution gave a light yellow oil which was chromatographed on 5 g of silica gel with pentane as eluent to afford 98.9 mg (76%) of a colorless oil as a 1:2.5 mixture of **7** and **34**. This material was used in subsequent transformations without further purification.

Method B. A solution of 35.9 mg (0.124 mmol) of **41** in 5 mL of dry pyridine under argon was treated with excess phosphorus oxychloride (0.23 mL, 2.48 mmol) and warmed to 70 °C for 15 min. The solution was cooled to room temperature, poured into 30 mL of water, and extracted with three portions of pentane. The combined organic extracts were washed with saturated aqueous copper(II) sulfate, water, and brine and dried over magnesium sulfate. Concentration of the solution gave 23.7 mg of an oil which was eluted from 1 g of silica gel with pentane to afford 22.2 mg (66%) of a 1.7:1 mixture of **7** and **34**, respectively.

7: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (1H, b), 1.64 (3H, d, J = 1.4 Hz), 0.95 (3H, s), 0.88 (3H, s), 0.87 (3H, s).

34: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (1H, m), 4.36 (1H, m), 2.69 (1H, bt, J = 6.6 Hz), 2.28 (1H, m), 2.10 (2H, m), 0.96 (3H, s), 0.88 (3H, s), 0.87 (3H, s).

(±)-(4aα,6aβ,7β,8α,11aα,11bβ)-Tetradecahydro-4,4,11b-trimethyl-9-methylene-8,11a-methano-11a*H*-cyclohepta[*a*]naphthalen-7-ol (35). To a solution of 35.0 mg (0.122 mmol) of **33** in 3 mL of dry tetrahydrofuran under argon at 0 °C was added 2.3 mg (61 μmol) of lithium aluminum hydride. After 5 min 4 drops of saturated aqueous Rochelle's salt was added, and the mixture was diluted with ether, washed with water and brine, and dried over magnesium sulfate. Concentration of the solution gave 34.7 mg (99%) of **35** as a colorless crystalline solid: mp (prisms, hexane) 120–121 °C; IR (KBr) 3277, 2917, 878 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (1H, bs), 4.64 (1H, bs), 3.88 (1H, dd, J = 1.8, 6.9 Hz), 2.85 (1H, dd, J = 6.1, 6.4 Hz), 2.46 (1H, m), 2.22 (2H, m), 2.04 (1H, ddd, J = 2.4, 5.5, 11.8 Hz), 0.95 (3H, s), 0.88 (3H, s), 0.87 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 108.6, 83.1, 49.6, 49.5, 48.1, 47.3, 41.9, 38.6, 35.5, 35.2, 34.4, 33.8, 33.3, 31.8, 28.6, 22.8, 21.7, 18.6; MS m/z 288 (M$^+$, 100), 270, 257, 255, 201, 190, 175, 161, 147, 132, 119, 105, 95, 69. Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.40; H, 11.48.

Methyl (±)-(4aα,6aβ,7β,8α,11aα,11bβ)-Tetradecahydro-4,4,11b-trimethyl-9-methylene-8,11a-methano-11a*H*-cyclohepta[*a*]naphthalen-7-yl Sulfate (36). A solution of 10.6 mg (36.7 μmol) of **35**, 10.2 μL (73.4 μmol) of triethylamine, and 1 mL of dry methylene chloride at 0 °C under argon was treated with 4.3 μL (55.0 μmol) of methanesulfonyl chloride. After 20 min water was added and the aqueous layer was

separated and extracted with methylene chloride. The combined organic extracts were concentrated to afford 13.2 mg (97%) of **36**: ^{1}H NMR (80 MHz, $CDCl_3$) δ 4.80–4.50 (3H, m), 2.94 (3H, s), 0.97 (3H, s), 0.87 (6H, s). This material was used without further purification.

(±)-(4aα,6aβ,7β,8α,11aα,11bβ)-Dodecahydro-4,4,11b-trimethylspiro-[8,11a-methano-11a*H*-cyclohepta[*a*]naphthalene-9(2*H*),2′-oxiran]-7-yl Methyl Sulfate (37). To a solution of 13.2 mg of **36** (35.9 μmol) in 1 mL of dry methylene chloride under argon was added 11.6 mg (54.0 μmol, 80–85%) of *m*-chloroperbenzoic acid in one portion. After 45 min the mixture was warmed to ambient temperature for 3 h and diluted with water and ether. The organic phase was separated, washed with water and brine, and dried over magnesium sulfate. The solution was evaporated, and the resultant colorless solid was dissolved in ethyl acetate–hexane (1:1) and filtered through a plug of silica gel. Concentration of the filtrate afforded 11.9 mg (86%) of **37** accompanied by ca. 1 mg of the diastereomeric epoxide: ^{1}H NMR (80 MHz, $CDCl_3$) δ 4.70 (1H, m), 3.08 (0.3H, $-OSO_2CH_3$ of minor diastereomer), 2.99 (3H, s), 2.71 (2H, s), 0.99 (3H, s), 0.89 (6H, s). This was used without further purification.

(±)-(3aα,6aβ,9aα,9bα)-Dodecahydro-α,6,6,9a-tetramethyl-9b*H*-benz-[*e*]indene-9b-propanol (38). A solution of **37** (11.9 mg, 31.0 μmol) in 1 mL of dry tetrahydrofuran under argon was treated with 310 μL (310 μmol, 1.0 M in tetrahydrofuran) of lithium triethylborohydride in tetrahydrofuran. After 1 h at room temperature the solution was heated at reflux for 5 h and then was cooled, and the excess hydride was quenched by addition of water. Five drops of 1 M potassium hydroxide were added, followed by 3 drops of 50% hydrogen peroxide, and after the initially exothermic reaction had subsided water and ether were added. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. Concentration of the solution gave 11.3 mg of a solid which was chromatographed (5 g of silica, ethyl acetate–hexane 1:3) to afford 7.3 mg of **38** (1:1 mixture of diastereomers) as a colorless oil: IR (neat) 3354 (broad), 2934, 2866, 1457, 1377, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, m), 5.49 (1H, m), 3.59 (1H, m), 2.47 (1H, bd, J = 16.4 Hz), 2.14 (1H, m), 1.98 (1H, m), 1.88 (1H, dd, J = 2.3, 16.2 Hz), 1.14 (3H, d, J = 5.8 Hz), 1.01 (1.5H, s), 1.00 (1.5H, s), 0.90 (3H, s), 0.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 137.7, 126.9, 126.8, 69.6, 69.5, 52.5, 48.2, 46.6, 46.5, 41.9, 39.3, 38.0, 37.9, 37.8, 35.7, 34.4, 33.2, 33.0, 32.9, 23.6, 23.5, 22.8, 19.6, 18.6; MS *m/z* 290 (M^+), 257, 219, 217, 152, 147, 137, 123, 119, 105, 94 (100%), 81, 69, 55; HRMS *m/z* 290.2610 (calcd for $C_{20}H_{34}O$ 290.2610).

(±)-2-Desoxystemodinone (3) and (±)-13-*epi*-2-Desoxystemodinone (41). A stirred solution of 98.9 mg (0.363 mmol) of a 1:2.5 mixture of **7** and **34** in 5 mL of dry benzene was treated with 102 mg of *m*-chloroperbenzoic acid (80–85%, 0.472 mmol) for 12 h under an argon atmosphere in the dark. The mixture was diluted with methylene chloride, washed with 10% aqueous sodium sulfite and water, and concentrated to give 109.4 mg of a colorless solid. This material was dissolved in 5 mL of dry tetrahydrofuran, lithium triethylborohydride (1.14 mL, 1.14 mmol, 1.0 M in tetrahydrofuran) was added via syringe, and the solution was stirred at ambient temperature under argon for 4 h. A few drops each of 1.0 M potassium hydroxide and 30% hydrogen peroxide were added, and after 5 min the mixture was transferred to a separatory funnel and diluted with ether. The ether layer was separated, washed with water and brine, and dried over magnesium sulfate. Concentration of the solution gave 122 mg of an oil which was chromatographed (25 g of silica gel, ethyl acetate–hexane 1:5) to afford 50.5 mg (48%) of (±)-2-desoxystemodinone (**3**), identical with a sample of natural material by IR, MS, ^{1}H and ^{13}C NMR, and thin layer chromatographic behavior in three solvent systems: mp 108.0–109.5 °C (prisms, hexane); IR (KBr) 3382, 2942, 2866, 1454, 1216, 964, 923, 910, 896 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (2H, m), 1.12 (3H, s), 0.95 (3H, s), 0.88 (3H, s), 0.87 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.5, 50.1, 47.3, 46.2, 41.9, 38.4, 38.2, 37.2, 36.7, 36.3, 34.6, 33.2, 32.9, 30.0, 28.2, 27.7, 22.8, 22.3, 18.9, 18.8; MS *m/z* 290 (M^+), 257, 219, 218, 149, 123, 109, 94 (100), 81, 69.

Compound **3** crystallized from hexane in space group $P2_1$ with a = 12.874(2) Å, b = 21.345(4) Å, c = 12.887(2) Å, β = 93.38(1)°, Z = 8, and d_{calc} = 1.091 g/cm^3. The intensity data were measured on a Hilger–Watts diffractometer (Ni-filtered Cu Kα radiation, θ-2θ scans, pulse-height discrimination). Of the 6758 accessible reflections for $\theta < 70°$, 4934 were considered to be observed [$I < 2.5\sigma(I)$].

The structure was solved by a multiple-solution procedure and was refined by block-diagonal least squares in which the matrix was partitioned into four blocks. Seven reflections which were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement, anisotropic thermal parameters were used for the hydrogen atoms. The final discrepancy indices are R = 0.064 and R_w = 0.067 for the remaining 4927 observed reflections. The final difference map has no peaks greater than ±0.2 A^{-3}.

Further elution gave 35.0 mg (33%) of (±)-13-*epi*-2-desoxystemodinone (**41**): mp 182.5–183.5 °C (needles, hexane); IR (KBr) 3300, 2936, 2865, 1469, 1451, 1129, 1116, 949, 930 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (1H, bdd, J = 8.3, 14.0 Hz), 1.90 (3H, m), 1.23 (3H, s), 0.95 (3H, s), 0.88 (3H, s), 0.87 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.8, 50.5, 47.4, 47.1, 41.9, 38.3, 27.6, 36.7, 36.2, 35.8, 34.6, 33.9, 33.2, 32.8, 29.1, 26.2, 22.8, 22.3, 19.1, 18.8; MS *m/z* 290 (M^+), 257, 219, 149, 133, 123, 94 (100), 69. Anal. Calcd for $C_{20}H_{34}O$: C, 82.70; H, 11.80. Found: C, 83.10; H, 12.16.

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Supplementary Material Available: X-ray crystallographic data for **3**, **21**, and **25**, including atomic coordinates, bond lengths, and bond angles (31 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.