Putative Diels–Alder-Catalyzed Cyclization during the Biosynthesis of Lovastatin

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A Diels–Alder cyclization proposed to occur during polyketide synthase assembly of the bicyclic core of lovastatin (**1**) (mevinolin) by *Aspergillus terreus* MF 4845 was examined *via* the synthesis of the *N*-acetylcysteamine (NAC) thioester of [2,11-^{13}C$_2$]-(*E,E,E*)-(*R*)-6-methyldodecatri-2,8,10-enoate (**5a**). *In vitro* Diels–Alder cyclization of the corresponding unlabeled NAC ester **5b**, ethyl ester **18b**, and acid **20b** yielded two analogous diastereomers in each case, under either thermal or Lewis acid-catalyzed conditions. The reaction of thioester **5** proceeds readily at 22 °C in aqueous media. For **18b**, one product is *trans*-fused ethyl (1R,2R,4aS, 6R,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalene-1-carboxylate (**30**) (*endo* product), and the other is *cis*-fused ethyl (1R,2S,-4aR,6R,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalene-1-carboxylate (**31**) (*exo* product). Isomer **21** with stereochemistry analogous to 4a,5-dihydromonacolin L (**2**), a precursor of **1**, was made by transformation of a tricyclic lactone, (1S,2S,4aR,6S,8S,8aS)-1-(ethoxycarbonyl)-1,2,-4a,5,6,7,8,8a-octahydro-2-methyl-6,8-naphthalenecarbolactone (**22**) using reduction and Barton deoxygenation. Comparison of **21** with **30** and **31** confirmed the structural assignments and showed that the nonenzymatic 4 + 2 cyclizations of **5**, **18**, and **20** proceed *via* chairlike *exo* and *endo* transition states with the methyl substituent pseudoequatorial. The proposed biosynthetic Diels–Alder leading to lovastatin (**1**) would require an *endo* conformation with the methyl substituent pseudoaxial. Intact incorporation of the labeled hexaketide triene **5a** into **1** was not achieved because of rapid degradation by *A. terreus* cells.

Introduction

Lovastatin (**1**) (also known as mevinolin, monacolin K, Mevacor) is a widely-prescribed cholesterol-lowering drug which was originally isolated from *Aspergillus terreus* by Merck researchers and from *Monascus ruber* by Endo and co-workers.[1–3] Studies on the biosynthesis of this fungal metabolite using incorporations of ^{13}C-, ^{2}H-, and ^{18}O-labeled acetates, ^{13}C-methionine, and ^{18}O$_2$ show that it is a polyketide having a main chain of nine intact acetate units linked head to tail (Scheme 1).[4] Examination of late stage transformations suggests that the first isolable intermediate and product of the lovastatin polyketide synthase (PKS) may be 4a,5-dihydromonacolin L (**2**).[5] The large array of structurally diverse polyketide metabolites produced by microorganisms all originate biochemically from repetitive connection of short chain fatty acids (e.g. acetate or propionate) by pathways that are very similar to fatty acid biosynthesis.[6–8] However, the polyketide synthases (PKS) can bypass particular reductive steps to generate a functionalized carbon skeleton containing keto, hydroxy, olefinic, or fully reduced carbons. The intermediates remain bound to the synthase complex until chain assembly is complete. After release from the protein, the product (e.g. **2**) may undergo further transformation (often oxidation or alkylation) by separate enzymes to produce the final metabolite (i.e. **1**). Genetic studies[6,7] and incorporations of partially-assembled intermediates (as their *N*-acetylcysteamine (NAC) thioesters)[8] support this hypothesis and promise rationally-engineered routes to a host of new biologically active metabolites. Cell-free biosynthesis of fully constructed natural polyketides has not been reported thus far, but

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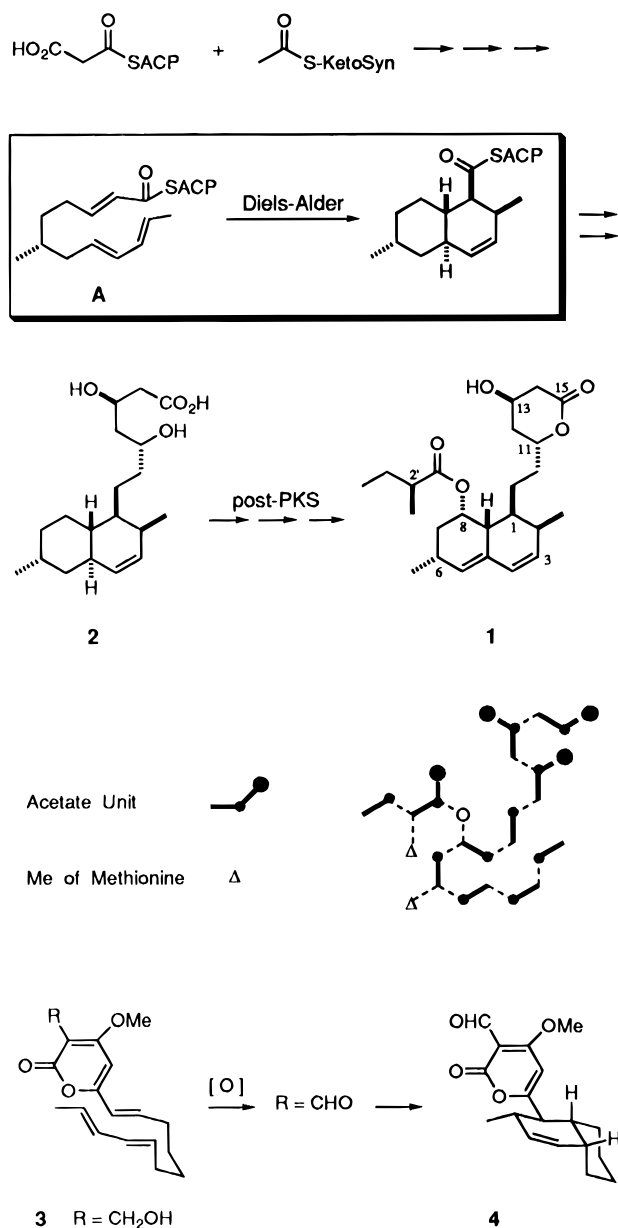
Scheme 1

A

2

1

Acetate Unit

Me of Methionine   Δ

3   R = CH$_2$OH

4

in vitro formation of a triketide lactone has recently been demonstrated using a genetically-modified protein derived from 6-deoxyerythronolide B synthase.[7a,b]

The stereochemistry of **2** supports the intriguing idea that an enzyme-catalyzed Diels–Alder reaction may occur during assembly of the polyketide chain.[4a,e] Such reactions have been proposed during biosynthesis of a number of other metabolites,[8i,9] and recent work shows that a partially purified oxidizing enzyme can catalyze *exo*-selective formation of optically active solanapyrone (**4**) from an achiral precursor, prosolanapyrone II (**3**), with high enantiomeric excess.[10] The process also proceeds

nonenzymatically to give racemic mixtures of *endo* and *exo* adducts if the participating double bond is made electron deficient by chemical oxidation of the allylic alcohol to an aldehyde. It thus appears that biological Diels–Alder reactions may be triggered by generation of reactive triene systems on an enzyme surface. Application of such reasoning to probable enzyme-bound PKS intermediates likely to be involved in formation of **2** enroute to **1** suggests that a hexaketide triene thioester **A** could undergo spontaneous 4 + 2 cyclization.[4a,e] In the present work, we describe the synthesis of such enantiomerically pure hexaketide derivatives of **A** and examine both their propensity to cyclize and the factors which influence the stereochemical outcome of the nonenzymatic Diels–Alder process. The synthetic approach is devised for facile formation of these hexaketides in doubly ^{13}C labeled form to test whether cultures of *A. terreus* to are able to incorporate them intact into lovastatin (**1**).

Results and Discussion

Hexaketide analogue **5** was chosen as the principal target for cyclization as well as incorporation studies with *A. terreus* cultures because *N*-acetylcysteamine (NAC) thioesters are known to enhance loading of precursors into PKS systems,[8] where they exist as enzyme-bound thioesters. Recently, α,β-unsaturated thioesters containing a diene system have been reported to undergo facile nonenzymatic intramolecular Diels–Alder reaction.[9i] Since β-oxidation[11] can rapidly degrade labeled precursors to short-chain fatty acids (e.g. acetate) prior to incorporation, double labeling with [13]C (as in **5a**) is essential[12] to detect intact utilization of the entire advanced precursor by fungal cultures.[8] Thus the synthesis of **5** was designed to incorporate ^{13}C labels at opposite ends of the molecule at a late stage in such a fashion that biological cyclization of the intact precursor would give rise to readily-detectable[12] coupling in the ^{13}C NMR spectrum of the product-(s).

Synthesis of the Hexaketide Precursor 5. Commercially available (*R*)-citronellol (**6**) is a readily available starting material that can be modified and extended in a two directional approach (Scheme 2). Its enantiomeric excess was determined to be ≥98% *via* derivatization to *N*-[(1*S*)-phenylethyl]-(*R*)-citronellamide and subsequent GC-MS.[13] Protection of the alcohol **6** as an acetate **7**,[14] followed by sequential treatment[15] with ozone and triphenylphosphine, delivers the aldehyde **8**. A second protection[16] with trimethyl orthoformate yields the acetal **9**. Hydrolysis of the acetate **9** and oxidation[17] of the

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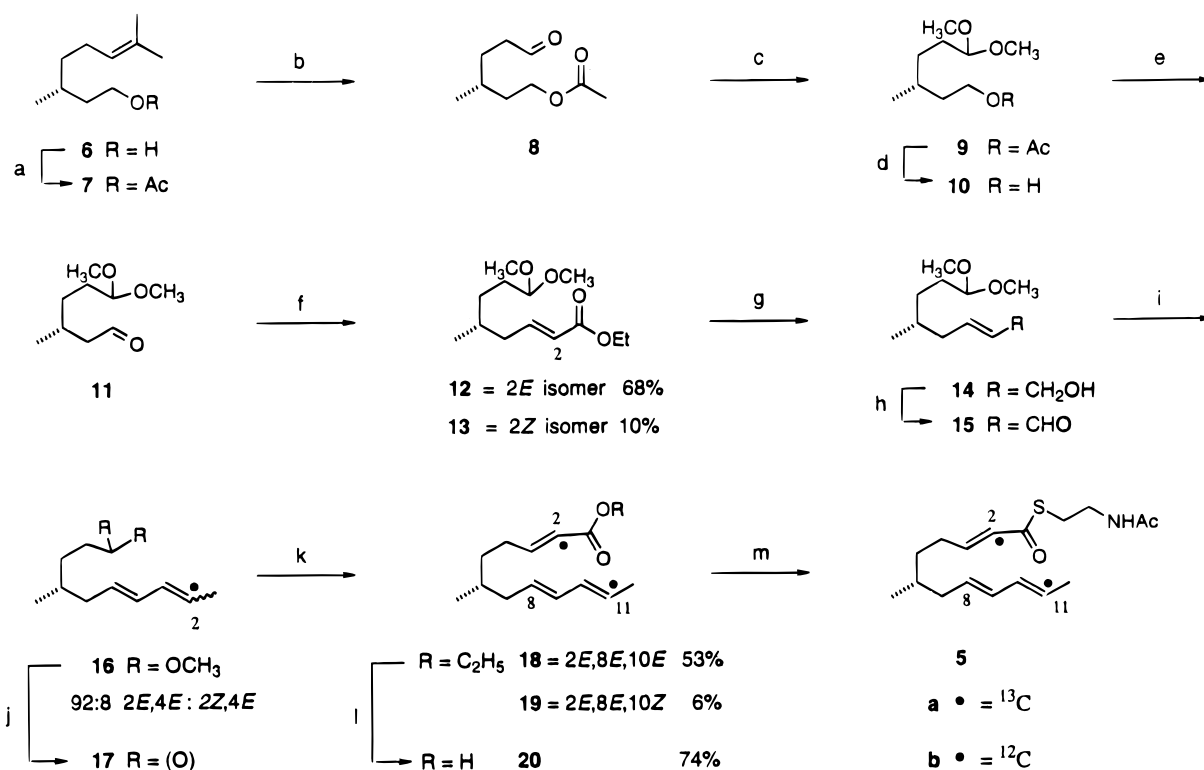
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Scheme 2[a]

[a] Reagents: (a) AcCl, Et₃N (95%); (b) O₃, Ph₃P (85%); (c) (CH₃O)₃CH, H⁺ (91%); (d) NaOMe, MeOH (89%); (e) Swern oxid (85%); (f) Ph₃P=CHCO₂Et (78%); (g) DIBAL (80%); (h) Swern oxid (94%); (i) (Ph₃P⁺)¹³CH₂CH₃(I⁻) and PhLi and then PhLi, HCl, (t-BuOK/t-BuOH) (85%); (j) saturated oxalic acid, THF; (k) Ph₃P=¹³CHCO₂Et (59%); (l) KOH (74%); (m) DCC, NAC, DMAP (61%).

resultant alcohol **10** generates the aldehyde **11**. The first olefin of the diene system is introduced by the reaction with Wittig reagent[18] to produce a mixture of *E*- and *Z*-isomers (87:13) (**12** and **13**, respectively) in 78% total yield. Separation of the major α,β-unsaturated ester **12** from the minor *Z*-isomer **13** and reduction[19] with DIBAL to the allylic alcohol **14**, followed by Swern oxidization[17] gives the aldehyde **15**. At this point the second *E*-double bond is introduced using the Schlosser modification[20] of the Wittig reaction.

Use of Schlosser conditions with aldehyde **15** and ¹³C-labeled phosphonium iodide[21] produces the 2*E*,4*E*-diene **16** with typically 5−15% of the 2*Z*,4*E*-isomer. The *E,E* geometry of **16** is evident from the characteristic 14.2 Hz coupling constants seen between both H-2 and H-3, as well as H-4 and H-5. This mixture is difficult to separate and is therefore best carried through to the subsequent steps. The removal of the acetal in saturated aqueous oxalic acid and THF[22] gives the highly volatile aldehyde **17**. It is most effective to condense this directly with the ¹³C-labeled Wittig reagent without purification. Initially, the full synthetic scheme involved a 1,2-ethylene glycol acetal as the protecting group for the original aldehyde **8**, but acetal deprotection at the diene stage generates a high preponderance of decomposition products. The side reactions were circumvented using the more labile dimethoxy acetal. Condensation of **17** with ¹³C-labeled

Wittig reagent gives a mixture of triene isomers. The major *trans*-isomer **18a** can be partially purified by flash chromatography, but it is still contaminated by the 2*E*,8*E*,10*Z*-triene **19a**. This unwanted byproduct, originating from *cis*-olefin formation in the Schlosser reaction, can be separated from the desired 2*E*,8*E*,10*E*-isomer **18a** by MPLC with AgNO₃ impregnated silica gel.[23] Hydrolysis[24] of the ester **18a** with aqueous KOH in THF followed by simultaneous treatment[25] of the resulting acid **20a** with *N*-acetylcysteamine (NAC)[26] and a mixture of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) affords the NAC ester of the hexaketide **5a**. The methodology used to generate labeled hexaketide **5a** was accomplished initially with unlabeled reagents. This allowed the construction of unlabeled ethyl ester **18b**, free acid **20b**, and NAC triene **5b**.

Compound **5a** from the NAC coupling reaction contained small amounts of an impurity which displays two sets of doublets in the ¹³C NMR spectrum at 58.6 and 33.6 ppm ($J = 31.2$ Hz) and 56.5 and 34.2 ppm ($J = 33.2$ Hz). The quantity of this material increased after normal flash chromatography and the impurity still persisted in samples purified by reverse phase HPLC. Although the ¹H NMR spectrum appears to indicate presence of only a single product **5a**, it is clear that small amounts of the triene cyclized spontaneously at room temperature to

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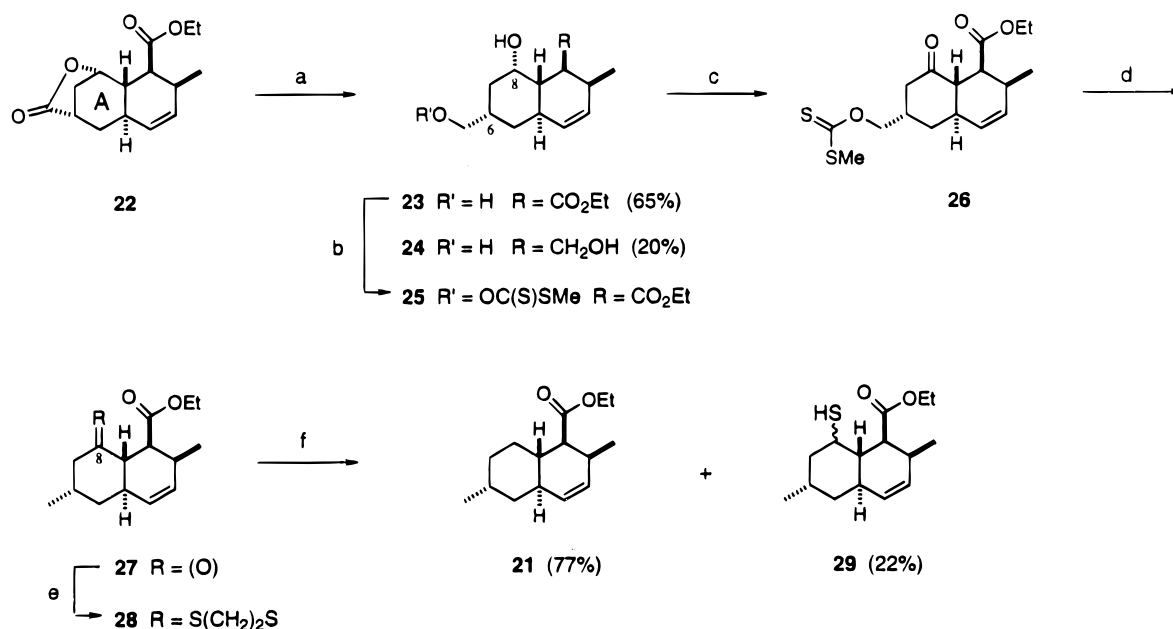
Scheme 3[a]

22 → a → 23 R' = H R = CO₂Et (65%)

b

23 R' = H R = CO₂Et (65%)

24 R' = H R = CH₂OH (20%)

25 R' = OC(S)SMe R = CO₂Et

→ c → 26 → d →

27 R = (O)

e

28 R = S(CH₂)₂S

→ f → 21 (77%) + 29 (22%)

[a] Reagents: (a) LiBEt₃H, 0 °C (85%); (b) Bu₄N⁺ ⁻HSO₄, CS₂, CH₃I, NaOH, PhH (85%); (c) PDC (80%); (d) Bu₃SnH, cymene, 150 °C (63%); (e) HS(CH₂)₂SH, BF₃·OEt₂ (66%); (f) neat Bu₃SnH, AIBN, 120 °C, 4 days (99%).

form two bicyclic Diels−Alder reaction products. This process is much more easily detectable with the ¹³C-labeled material **5a** than with unlabeled **5b**.

Bicyclic Reference Compound 21. To unambiguously confirm whether one of the spontaneous cyclization products is the *endo* Diels−Alder adduct with stereochemistry analogous to that in the lovastatin precursor, 4a,5-dihydromonacolin L (**2**), the corresponding decalin derivative **21** was synthesized by an independent route (Scheme 3). The total synthesis of **2** represents a challenge undertaken by many research groups,[27] and our route to reference compound **21** begins with the tricyclic lactone **22** employed as an intermediate by Lewis and co-workers.[27e] Compound **22** contains the required stereochemistry and requires only cleavage of the lactone and its oxygens from the A-ring to give **21**. Reduction of **22** with lithium triethylborohydride generates the diol **23** and the triol **24**. However, the seemingly straightforward removal of the hydroxyl groups proved unexpectedly difficult. Several unsuccessful routes were tried involving formation of the tosylate or halogenation and subsequent elimination, as well as Barton deoxygenation *via* methyl xanthates[28] and phenoxythiocarbonates.[29] The hydroxyl group at C-8 is axial, and this orientation presents a problem. Its juxtaposition with the axial methylene group at C-6 facilitates the formation of a tricyclic ether, and the antiperiplanar relationship to vicinal hydrogens allows facile elimination to an olefin.

The interference caused by the C-8 hydroxyl could be circumvented first protecting the primary alcohol as a

methyl xanthate **25** *via* a two-phase system[30] followed by oxidation of the troublesome secondary alcohol to the corresponding ketone **26**. Deoxygenation[31] of the methyl xanthate **26** occurs at 150 °C to produce the keto-ester **27**, which is subsequently protected[32] as the dithioketal **28**. Attempts to remove the ketal with Raney-nickel were unsuccessful. Activated Raney-nickel causes over-reduction whereas deactivated reagent leads to either complex mixtures or isolation of starting material. However, reaction of dithioketal **28** in neat tri-*n*-butyltin hydride and catalytic AIBN at elevated temperatures[33] produces the desired reference compound **21** in good yield along with a partially-reduced species **29** which could be converted into desired reference compound **21** by further reaction.

***In Vitro* Intramolecular Diels−Alder Reactions**. The intramolecular Diels−Alder reactions of 1,7,9-decatrienes forming bicyclo[4.4.0]decenes have been reviewed by several authors in the past 10 years[34] and are actively being used to make natural products.[35] Comparison of the *exo* and *endo* transition states with the connecting chain in its chairlike form can sometimes allow prediction of the stereochemical outcome, with the major adducts being those generated from the conformers with the least bond-angle strain and fewest nonbonded interactions.[34b] Consideration of transition states for intramolecular Diels−Alder reaction of unlabeled triene ethyl ester **18b**, free acid **20b**, and NAC thioester **5b** suggests that both *endo* and *exo* cyclizations are likely and could each give two diastereomers (i.e. four isomers total), depending on whether the methyl at C-6 is

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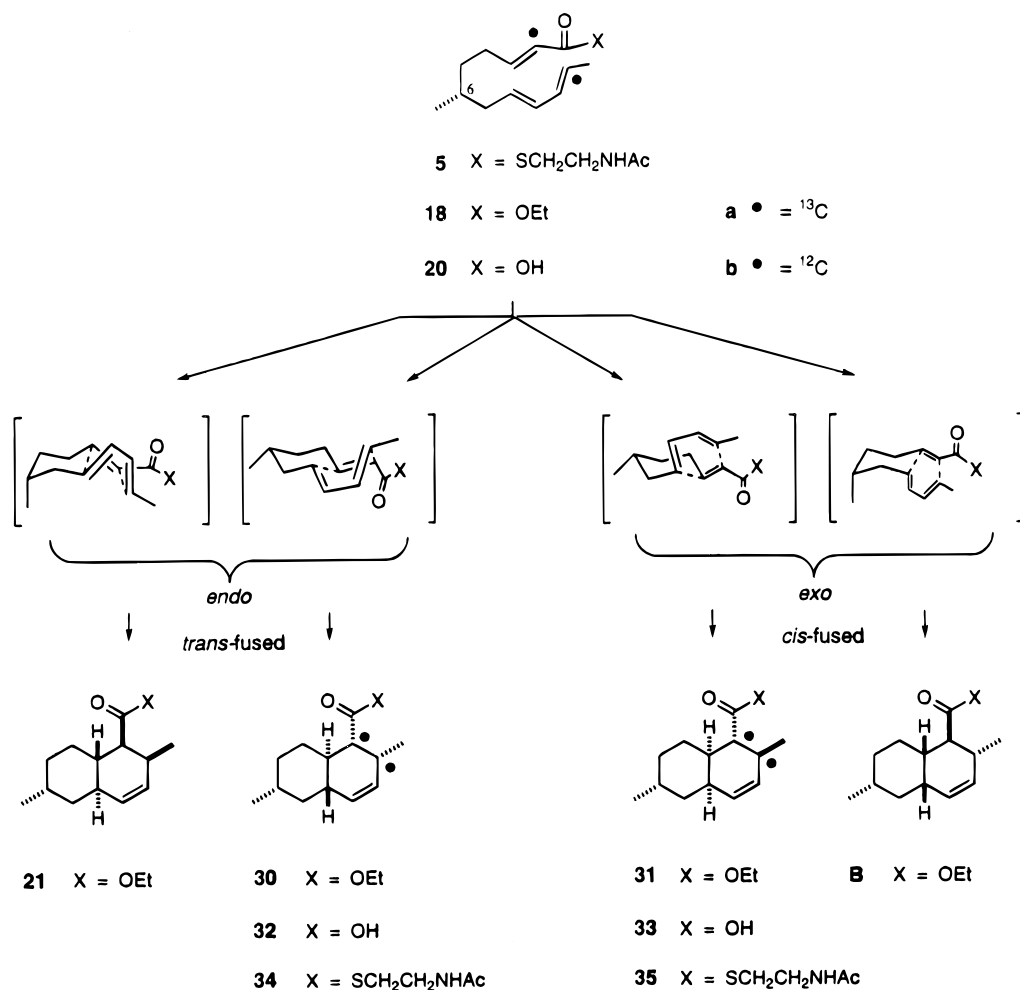(31) Barton, D. H. R.; Motherwell, W. B; Stange, A. *Synthesis* **1981**, 743−745.
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Scheme 4

5   X = SCH$_2$CH$_2$NHAc

18   X = OEt   **a** ● = ^{13}C

20   X = OH   **b** ● = ^{12}C

endo

trans-fused

exo

cis-fused

21   X = OEt

30   X = OEt
32   X = OH
34   X = SCH$_2$CH$_2$NHAc

31   X = OEt   **B**   X = OEt
33   X = OH
35   X = SCH$_2$CH$_2$NHAc

pseudoaxial or pseudoequatorial (Scheme 4). To determine the outcome, the trienes were individually subjected to both thermal and Lewis acid (EtAlCl$_2$)[36]-catalyzed cyclization conditions.

A solution of the triene ethyl ester **18b** in toluene heated to 160 °C for 4 days in a sealed tube generated a 1:1 mixture of **30** and **31** (72%), which are separable by flash chromatography, along with a small amount (6%) of unreacted starting material **18b**. The free acid triene **20b** and NAC ester triene **5b** also cyclize under the thermal conditions and produce 1:1 mixtures of cycloadducts **32-33** (83%), and **34–35** (81%), respectively. Both mixtures are difficult to separate. Hence, the cyclized ethyl esters **30** and **31** were reduced[37] to their corresponding alcohols **36** (80%) and **37** (86%), respectively, with lithium aluminum hydride (Scheme 5). The two mixtures of cyclized products from the NAC ester **5b** and free acid **20b** reactions were also reduced to their alcohols (79% and 81%, respectively). Comparison of the ^{1}H NMR data of the alcohols **36** and **37**, generated from each ethyl ester reduction, with the mixture of alcohols from the NAC ester and free acid reductions demonstrates that each of the Diels–Alder reactions (of **18b**, **20b**, and **5b**) has the same stereochemical outcome and produces two analogous products. To further confirm this, the purified alcohol **36** derived from the higher R_f ethyl ester **30** was oxidized to the acid **32** (51%).

To examine the effects of a Lewis acid on the cyclization, both the ethyl ester **18b** and NAC ester **5b** were

Scheme 5

30 and **31**   X = OEt   **36**   **37**

32 and **33**   X = OH

34 and **35**   X = S(CH$_2$)$_2$NHAc
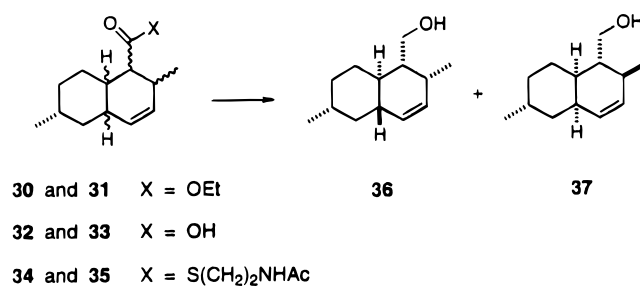
treated with 0.9 equiv of ethylaluminum dichloride (EtAlCl$_2$) at room temperature. Each reaction was complete in less than 3 h. Each ester generates the same two cycloadducts as produced from their respective thermal reactions, except the product mixtures are no longer in a 1:1 ratio. The ethyl ester produces a 9:1 mixture of **30:31** (58%), and the NAC ester affords **34:35** (80%) in a ratio of 19:1. Although the same two products result from the thermal reaction, the Lewis acid cyclizations proceed rapidly at room temperature and show significant *endo* selectivity.

Since incorporation experiments were done with cells in aqueous media (see below), which are known to accelerate Diels–Alder reactions,[38] the influence of solvent on cyclization of **18b** was also examined. The half-life for cyclization of **18b** to **30** and **31** in chloroform at 22 °C is about 10 days. In water:acetonitrile:methanol (ca 5:5:1) at 28 °C (fermentation temperature for *A. terreus*) the half-life for reaction drops to about 2 days

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(37) VanMiddlesworth, F. L. *J. Org. Chem.* **1986**, *51*, 5019–5021.
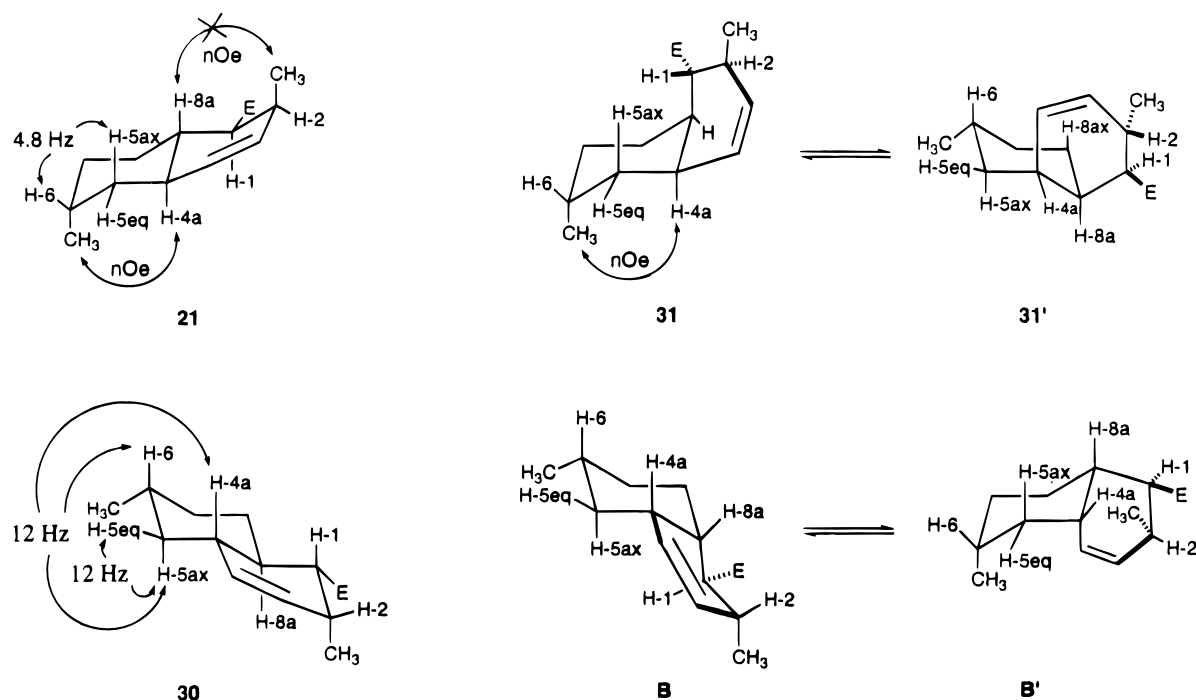
Figure 1. Possible conformations adopted by cycloadducts **21**, **30**, **31**, and **B**. Relevant NMR data is indicated.

at either pH 5 or 7. Nearly identical accelerations are seen in cell-free fermentation media used for incorporation experiments.

Chromatographic analysis of Diels−Alder reactions and spectral comparison with **30** and **31** clearly demonstrate that compound **21** is not one of the products of thermal or Lewis acid cyclization of ethyl ester **18b**. The full stereochemical assignments of the cycloadducts required combined use of ^{1}H, ^{13}C, COSY, HMQC, and ^{1}H-decoupled NMR experiments.[39] The ^{1}H COSY spectrum of the higher R_f diastereomer **30** allows complete assignment of the ^{1}H signals. Irradiation experiments show a characteristic *trans*-fused coupling constant of 12.0 Hz between H-8a and H-4a, thus eliminating the two potential *cis*-fused adducts as possible structures (Figure 1). The distinction between the *trans*-fused adducts, **21** and **30**, is also clear from the coupling pattern seen for H-5ax. In the two most probable conformations for the *trans*-fused products, only the conformer shown in Figure 1 allows for an axial−axial arrangement between H-5ax and H-4a, and H-5ax and H-6. The H-5ax signal is an apparent quartet arising from three doublets each having a coupling constant of 12.0 Hz. Two of the three doublets result from two axial−axial vicinal couplings and the third is from geminal coupling with H-5eq. Spectral analysis of **21** exhibits two large coupling constants for H-4a which suggests a 180° relationship with H-5ax and H-8a as shown. The peak for its H-5ax proton displays only two large coupling constants corresponding to the axial−axial relationship of H-5ax and H-4a and the geminal coupling with H-5eq. The third doublet in this signal shows only a 4.8 Hz coupling constant between H-5ax and H-6. The results define the preferred conformations of **21** and **30**.

NMR analysis of the cis-fused *exo* adduct **31** is hindered by the complexity of the angular hydrogen signals which obscures the magnitude of the coupling constant between H-4a and H-8a. However, difference ^{1}H NOE spectra in which the overlapping C-6 and C-2 methyl protons are irradiated show an enhancement of the H-4a but not the H-8a signal, which clearly eliminates the *cis*-fused product **B** as a possible structure, since no conformation of this isomer would allow an NOE enhancement between the H-4a and H-8a and the bicyclic methyl substituents. This enhancement also indicates the *cis*-fused conformer **31** is preferred over **31′**.

Incorporation Experiments and Conclusions. In order to test whether the labeled hexaketide derivative **5a** could be incorporated intact into lovastatin (**1**), it was added under a variety of conditions to growing cultures of *Aspergillus terreus* MF 4845 both in the presence and absence of various ω- and β-oxidation inhibitors.[8d,f] Use of protoplasts,[40] saponin,[41] and 2,6-*O*-dimethyl-β-cyclodextrin[8g] to assist the incorporation was also attempted. None of these experiments gave any detectable carbon−carbon coupling in the ^{13}C NMR spectrum of the resulting **1**. In addition, incoporations with intact cells typically allowed less than 1% recovery of the labeled precursor **5a**. Attempts to incorporate a number of shorter NAC esters which would be expected to be on the pathway, including doubly ^{13}C-labeled diketides such as NAC acetoacetate, NAC β-hydroxybutyrate, and NAC 2-butenoate, gave similar results.[42] Apparently very rapid degradation of the precursors in *A. terreus* prevents their loading into the lovastatin PKS system. Fortunately, the availability of both nonenzymatic Diels−Alder products **34** and **35** from cyclization of **18** as well as the putative enzymatic product, the NAC ester corresponding

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(40) Ventura, L.; Ramón, D. *FEMS Microbiol. Lett.* **1991**, *82*, 189−194.

(41) Meiners, S.; Gharyal, P. K.; Schlinder, M. *Planta* **1991**, *184*, 443−447.

(42) Attempts to incorporate the stereochemically correct triketide, NAC (*E,E*)-2,4-hexadienoate, and the tetraketide, NAC (*2S*)-(*E,E*)-2-methyl-4,6-octadienoate, into **1** were also unsuccessful: Yoshizawa, Y.; Vederas, J. C. unpublished results.

to diastereomer **21**, affords a convenient assay for the "Diels−Alderase" (most likely a lovastatin PKS) in cell free experiments that are currently being investigated.

In summary, the synthesis of doubly ^{13}C-labeled hexaketide NAC thioester **5a** in optically pure form can be achieved in 13 steps from commercially available (*R*)-citronellol with an overall yield of 4.0%, with the labels added at a late stage. The nonenzymatic Diels−Alder reactions of unlabeled triene NAC thioester **5b**, its ethyl ester **18b**, and its free acid **20b** yield two analogous diastereomers in each case (derived from *exo* and *endo* transition states), under either thermal or Lewis acid conditions. As expected,[9i,38] reaction is most facile for the thioester **18b** in aqueous media. The synthesis of reference compound **21**, which has stereochemistry analogous to lovastatin precursor **2**, confirms the configurational assignment and demonstrates that **21** is not produced in the nonenzymatic cyclization. Thus, the conventional *exo* and *endo* Diels−Alder reactions both proceed through chairlike transition states that place the side chain methyl pseudoequatorial, whereas the proposed enzymatic Diels−Alder enroute to lovastatin (**1**) requires an intermediate *endo* conformation with this methyl group pseudoaxial. One function of the PKS enzyme may be to correctly control the conformation of the acyclic triene thioester, which is naturally prone to cyclization, through hydrophobic interactions. It may also assist the ring formation through Lewis acid catalysis, either by simple site specific protonation or coordination of a metal ion.[43] It seems likely that the cyclization occurs spontaneously upon formation of the appropriate skeleton **A** in the polyketide synthase active site and may be enhanced by carbonyl protonation expected to assist normal acyl transfer reaction required by PKS enzymes.[6,7] This, together with the observation that enzymatic oxidation of **3** spontaneously incites formation of chiral solanapyrone (**4**),[10] suggests that other proteins normally not involved in cyclization reactions may become "Diels−Alderases" by formation of the appropriate precursor on an enzyme surface.[44,45] Experiments to test this hypothesis and to confirm the involvement of hexaketide **A** in formation of **2** are in progress.

Experimental Section

General. General procedures and instrumentation can be obtained from the supporting information. Published procedures, which have been modified and used, are cited.

(6*R*)-*E,E,E*-6-Methyldodeca-2,8,10-trienoic Acid *N*-Acetylcysteamine Thioester (5b). A solution of the acid **20b** (860 mg, 4.13 mmol) in dry CH$_2$Cl$_2$ (7 mL) was treated simultaneously with a solution of *N*-acetylcysteamine (581 mg, 4.87 mmol) in CH$_2$Cl$_2$ (7 mL), and a solution of DCC (1.02 g, 4.95 mmol) and 4-(dimethylamino)pyridine (19.6 mg) in CH$_2$-Cl$_2$ (7 mL) over 5 min at −15 °C.[25] The resultant cloudy white

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(44) (a) Hilvert, D.; Hill, K. W.; Nared, K. D.; Auditor, M.-T. M. *J. Am. Chem. Soc.* **1989**, *111*, 9261−9262. (b) For a review of catalytic antibodies see: Schultz, P. A.; Lerner, R. A. *Science* **1995**, *269*, 1835−1842.

(45) For selected references to Diels−Alder studies with nonprotein hosts see: (a) Morris, K. N.; Tarasow, T. M.; Julin, C. M.; Simons, S. L.; Hilvert, D.; Gold, L. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 13028−13032. (b) Walter, C. J.; Sanders, J. K. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 217−219.

solution was stirred overnight at room temperature. The mixture was concentrated *in vacuo* to afford a yellow oil, which was purified by flash chromatography (SiO$_2$; 40 × 120 mm, 100% EtOAc, R_f 0.33) to yield **5b** (970 mg, 76%) as a white solid: mp 38−39 °C; [α]^{20}$_D$ −7.41° (*c* 0.081, CH$_2$Cl$_2$); IR (CH$_2$-Cl$_2$ cast) 3321 (br s), 1657 (s), 1626 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.90 (dt, 1H, *J* = 15.5, 7.4 Hz), 6.11 (dt, 1H, *J* = 15.5, 1.5 Hz), 6.01 (ddq, 1H, *J* = 14.2, 10.2, 1.5 Hz), 5.95 (ddt, 1H, *J* = 14.2, 10.2, 1.2 Hz), 5.57 (dq, 1H, *J* = 14.2, 6.6 Hz), 5.91−5.83 (br s, 1H), 5.48 (dt, 1H, *J* = 14.2, 7.2 Hz), 3.44 (dt, 2H, *J* = 6.3, 5.9 Hz), 3.07 (t, 2H, *J* = 6.3 Hz), 2.31−2.12 (m, 2H), 2.06 (ddd, *J* = 13.7, 7.2, 6.1 Hz), 1.94 (ddd, *J* = 13.7, 7.4, 7.2 Hz), 1.95 (s, 3H), 1.72 (d, 3H, *J* = 6.6 Hz), 1.55−1.45 (m, 2H), 1.30−1.25 (m, 1H), 0.87 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 190.36, 170.34, 146.77, 131.97, 131.55, 129.66, 128.27, 127.20, 39.86, 39.84, 34.55, 32.87, 29.92, 28.26, 23.20, 19.32, 17.99; MS (CI, NH$_3$) 327 (MNH$_4$$^+$, 8), 310 (MH$^+$, 14). Anal. Calcd for C$_{17}H_{26}NO_2$S: C, 65.98; H, 8.79. Found: C, 66.24; H, 9.03.

[2,11-^{13}C$_2$]-Labeled 5 (5a). The same method as for the preparation of **5b** was employed. The spectral and chromatographic properties were similar to those of **5b** except for the following: ^{1}H NMR (200 MHz, CDCl$_3$) δ 6.92 (dtd, 1H, *J* = 15.6, 7.0, 1.0 Hz), 6.12 (ddt, 1H, *J* = 161.0, 15.6, 1.5 Hz), 6.05−5.85 (m, 2H), 5.57 (ddq, 1H, *J* = 150.2, 14.2, 6.7 Hz), 1.73 (dd, 3H, *J* = 6.7, 6.7 Hz); ^{13}C NMR (50 MHz, CDCl$_3$) δ 190.30 (d, *J* = 76.0 Hz), 146.72 (d, *J* = 70.0 Hz), 131.66 (d, *J* = 72.5 Hz), 34.50 (d, *J* = 3.5 Hz), 17.96 (d, *J* = 44.3 Hz); MS (CI, NH$_3$) 329 (MNH$_4$$^+$, 25), 312 (MH$^+$, 100). Anal. Calcd for ^{13}C$_2$^{12}C$_{15}$H$_{26}$NO$_2$S: C, 66.20; H, 8.74. Found: C, 66.00; H, 9.08.

(3*R*)-Methyl-6-oxohexyl Acetate (8). Ozonized oxygen, cooled by passage through a glass coil immersed in a cold-bath at −78 °C, was bubbled into a cold (−78 °C) solution of **7**[14] (6.17 g, 31.1 mmol) in dry CH$_2$Cl$_2$ (60 mL) until the solution had acquired a blue tint (1.5 h).[15] Triphenylphosphine (8.98 g, 34.2 mmol) was added, and the reaction mixture was stirred at −78 °C for a further 30 min. The cooling bath was then removed and stirring was continued for 2 h. The solution was evaporated *in vacuo*, and the residue was purified by flash chromatography (SiO$_2$; 30% Et$_2$O in pentane, R_f 0.25) to yield **8** (4.56 g, 85%) as a colorless volatile oil: [α]^{20}$_D$ +1.87° (*c* 7.18, CHCl$_3$); IR (CHCl$_3$ cast) 1740 (s), 1725 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.74 (br s, 1H), 4.12−4.01 (m, 2H), 2.50−2.35 (m, 2H), 2.00 (s, 3H), 1.71−1.57 (m, 2H), 1.60−1.50 (m, 1H), 1.49−1.40 (m, 2H), 0.89 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.34, 171.09, 62.53, 41.44, 35.19, 29.43, 28.69, 20.59, 19.08; MS (CI, NH$_3$) 190 (MNH$_4$$^+$, 100), 173 (MH$^+$, 4.2). Anal. Calcd for C$_9$H$_{16}$O$_3$: C, 62.77; H, 9.36. Found: C, 62.72; H, 9.59.

(3*R*)-6,6-Dimethoxy-3-methylhexyl Acetate (9). A solution of aldehyde **8** (24.3 g, 141 mmol), trimethyl orthoformate (100 mL), and acetyl chloride (0.26 mL, 3.62 mmol) in dry MeOH (100 mL) was heated to reflux overnight using a Dean−Stark apparatus.[16] After the solution was allowed to cool, and brine (75 mL) and 5% aqueous NaHCO$_3$ (75 mL) were added. Most of the MeOH was removed *in vacuo*, and the mixture was extracted with Et$_2$O (2 × 350 mL). The Et$_2$O layer was washed with H$_2$O (50 mL) and brine (50 mL), and these aqueous washings were combined and back-extracted with Et$_2$O (3 × 250 mL). The combined Et$_2$O fractions were dried (MgSO$_4$) and concentrated *in vacuo* to a clear colorless oil (31.8 g), which can be used without further purification. A small portion (0.638 g) was removed and purified by Kugelrohr distillation to yield a clear oil **9** (0.580 g, 91%): bp 109−111 °C (0.2 mmHg); [α]^{20}$_D$ +2.23° (*c* 2.38, CHCl$_3$); IR (CHCl$_3$ cast) 1741 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.32 (t, 1H, *J* = 4.7 Hz), 4.13−4.04 (m , 2H), 3.30 (s, 6H), 2.03 (s, 3H), 1.70−1.50 (m, 4H), 1.49−1.32 (m, 2H), 1.24−1.14 (m, 1H), 0.90 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.18, 104.86, 62.91, 52.69, 35.47, 31.58, 30.01, 29.81, 21.02, 19.41; MS (CI, NH$_3$) 236 (MNH$_4$$^+$, 6). Anal. Calcd for C$_{11}H_{22}O_4$: C, 60.51; H, 10.16. Found: C, 60.20; H, 10.40.

(3*R*)-6,6-Dimethoxy-3-methylhexanol (10). Freshly prepared sodium methoxide (0.47 g, 8.7 mmol) was added to a solution of acetate **9** (20.0 g, 91.5 mmol) in dry MeOH (200 mL). After stirring at room temperature overnight, the mixture was treated with H$_2$O (120 mL), and the solvent

volume was reduced *in vacuo* to give an aqueous residue, which was extracted with Et$_2$O (3 × 330 mL). The combined Et$_2$O fractions were washed with H$_2$O (2 × 100 mL) and brine (200 mL), and these aqueous washings were back-extracted with Et$_2$O (3 × 50 mL). The combined Et$_2$O fractions were again washed with H$_2$O (2 × 50 mL) and brine (50 mL), dried (MgSO$_4$), and concentrated *in vacuo* to yield a clear colorless oil (14.4 g), which could be used without further purification. A small portion (0.948 g) was removed and purified by Kugelrohr distillation to yield a clear oil **10** (0.844 g, 89%): bp 125 °C (0.1 mmHg); [α]^{20}$_D$ +2.75° (*c* 2.22, CHCl$_3$); IR (CHCl$_3$ cast) 3409 cm^{-1}; ^{1}H NMR (400 MHz, benzene-*d$_6$*) δ 4.26 (t, 1H, *J* = 5.7 Hz), 3.57–3.40 (m, 2H), 3.13 (s, 6H), 1.70–1.49 (m, 4H), 1.49–1.32 (m, 1H), 1.32–1.12 (m, 2H), 0.83 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, benzene-*d$_6$*) δ 104.91, 60.61, 52.25, 52.10, 40.10, 32.08, 30.24, 29.60, 19.73; MS (CI, NH$_3$) 194 (MNH$_4$$^+$, 2.7), 177 (MH$^+$, 0.1), 130 (100). Anal. Calcd for C$_9$H$_{20}$O$_3$: C, 61.31; H, 11.44. Found: C, 60.94; H, 11.29.

(3R)-6,6-Dimethoxy-3-methylhexanal (11). Dry DMSO (2.11 mL, 29.8 mmol) was added dropwise over 5 min to a stirred cooled (−78 °C) solution of distilled oxalyl chloride (1.36 mL, 15.6 mmol) in CH$_2$Cl$_2$ (30 mL).[17] After 10 min, a solution of the alcohol **10** (2.72 g, 15.6 mmol) in CH$_2$Cl$_2$ (15 mL) was added over 30 min. The resultant slurry was stirred for 20 min at −78 °C, and then dry triethylamine (7.43 mL, 53.3 mmol) was injected dropwise over 30 min. Stirring was continued at −78 °C for 20 min and the cold bath removed, and after a further 30 min, H$_2$O (10 mL) was added. The mixture was stirred for a further 10 min, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic layers were washed with 10% v/v aqueous HCl (2 × 7 mL), saturated aqueous NaHCO$_3$ (2 × 10 mL), and brine (1 × 10 mL), dried over MgSO$_4$, and evaporated *in vacuo*. The residue was purified by flash chromatograghy (SiO$_2$; 25% Et$_2$O in pentane, R_f 0.25) to yield **11** (2.31 g, 85%) as an oil: [α]^{20}$_D$ +13.23° (*c* 1.41, CHCl$_3$); IR (neat) 2720 (m), 1725 (s) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.71 (t, 1H, *J* = 2.2 Hz), 4.30 (t, 1H, *J* = 5.6 Hz), 3.27 (s, 6H), 2.38 (ddd, 1H, *J* = 16.0, 5.8, 2.2 Hz), 2.21 (ddd, 1H, *J* = 16.0, 7.8, 2.2 Hz), 2.04 (br p, 1H, *J* = 6.6 Hz), 1.71–1.48 (m, 2H), 1.41–1.12 (m, 2H), 0.93 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.54, 104.55, 52.78, 52.74, 50.92, 31.52, 29.99, 27.94, 19.80; MS (CI, NH$_3$) 192 (MNH$_4$$^+$, 8), 175 (MH$^+$, 0.4), 75 (100). Anal. Calcd for C$_9$H$_{18}$O$_3$: C, 62.04; H, 10.41. Found: C, 61.89; H, 10.14.

Ethyl (5R)-(E)-8,8-Dimethoxy-5-methyloct-2-enoate (12). A solution of aldehyde **11** (31.2 g, 179 mmol) and (carbethoxymethylene)triphenylphosphorane (77.1 g, 221 mmol) in dry benzene (1500 mL) was heated to reflux at 85 °C for 12 h.[24] The mixture was cooled, the solvent was removed *in vacuo*, and the residue was purified by repeated flash chromatography (SiO$_2$; 15% Et$_2$O in pentane) to yield the desired *E*-isomer **12** (29.9 g, 68%, R_f 0.14) together with the minor, *Z*-isomer **13** (5.29 g, 10%, R_f 0.19). A small portion of the *E*-isomer **12** was removed and purified further by Kugelrohr distillation to give a clear oil: bp 148–151 °C (0.75 mmHg); [α]^{20}$_D$ +2.98° (*c* 1.98, CHCl$_3$); IR (CH$_2$Cl$_2$ cast) 1722 (s), 1654 (m) cm^{-1}; ^{1}H NMR (400 MHz, benzene-*d$_6$*) δ 7.03 (dt, 1H, *J* = 15.5, 7.7 Hz), 5.87 (dt, 1H, *J* = 15.5, 1.2 Hz), 4.19 (t, 1H, *J* = 5.7 Hz), 4.04 (q, 2H, *J* = 7.1 Hz), 3.12 (s, 6H), 1.85 (dddd, 1H, *J* = 13.0, 7.7, 5.3, 1.2 Hz), 1.67 (dddd, 1H, *J* = 13.0, 7.7, 7.7, 1.2 Hz), 1.60–1.50 (m, 1H), 1.50–1.40 (m, 1H), 1.32–1.20 (m, 2H), 1.11–1.02 (m, 1H), 0.98 (t, 3H, *J* = 7.1 Hz), 0.67 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, benzene-*d$_6$*) δ 166.05, 147.70, 123.11, 104.66, 59.97, 52.21, 39.57, 32.49, 31.64, 30.26, 19.39, 14.30; MS (CI, NH$_3$) 262 (MNH$_4$$^+$, 27), 198 (100). Anal. Calcd for C$_{13}$H$_{24}$O$_4$: C, 63.89; H, 9.91. Found: C, 63.92; H, 9.92.

(5R)-(E)-8,8-Dimethoxy-5-methyloct-2-enol (14). A solution of ester **12** (1.27 g, 5.24 mmol) in CH$_2$Cl$_2$ (13 mL) was treated with DIBAL (2.23 g, 15.7 mmol) in CH$_2$Cl$_2$ (9 mL) over 10 min at −78 °C.[19] The reaction mixture was stirred for 2 h at −78 °C and then for 30 min at −30 °C, at which point MeOH (2 mL) was added to quench the excess of DIBAL. The mixture was diluted with Et$_2$O (300 mL), and the layers were separated. The Et$_2$O phase was washed with saturated aqueous potassium–sodium tartrate (4 × 100 mL) and brine (2 × 100 mL), dried (MgSO$_4$), and concentrated *in vacuo* to give a clear oil. The residue was purified by flash chromatography (SiO$_2$;

50 × 250 mm, 75% Et$_2$O in pentane, R_f 0.31) to yield **14** (0.85 g, 80%) as a clear oil: [α]^{20}$_D$ +3.42° (*c* 2.93, CHCl$_3$); IR (CH$_2$Cl$_2$ cast) 3420 (br m), 2952 (s) cm^{-1}; ^{1}H NMR (400 MHz, benzene-*d$_6$*) δ 5.55–5.49 (m, 2H), 4.27 (t, 1H, *J* = 5.6 Hz), 3.91 (br s, 2H), 3.14 (s, 6H), 1.99–1.90 (m, 1H), 1.84–1.75 (m, 1H), 1.70–1.50 (m, 3H) 1.45–1.33 (m, 2H), 1.22–1.12 (m, 1H), 0.82 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, benzene-*d$_6$*) δ 131.57, 130.19, 104.88, 63.41, 52.24, 39.91, 33.12, 31.53, 30.36, 19.59; MS (CI, NH$_4$) 220 (MNH$_4$$^+$, 6), 203 (MH$^+$, 0.3). Anal. Calcd for C$_{11}$H$_{22}$O$_3$: C, 65.30; H, 10.97. Found: C, 65.40; H, 11.07.

(5R)-(E)-8,8-Dimethoxy-5-methyloct-2-enal (15). The same method as for the preparation of aldehyde **11** was employed. Thus, oxidation of alcohol **14** (4.66 g, 23.1 mmol) with DMSO (3.11 mL, 43.8 mmol) and oxalyl chloride (2.41 mL, 27.7 mmol) afforded **15** (4.04 g, 94%, based on 7% recovered starting material) as a clear oil after flash chromatography (SiO$_2$; 50% Et$_2$O in pentane, R_f 0.35): [α]^{20}$_D$ −0.20° (*c* 2.50, CHCl$_3$); IR (CH$_2$Cl$_2$ cast) 2725 (w), 1693 (s), 1636 (w) cm^{-1}; ^{1}H NMR (400 MHz, benzene-d$_6$) δ 9.30 (d, 1H, *J* = 7.7 Hz), 6.09 (dt, 1H, *J* = 15.5, 7.7 Hz), 5.90 (ddt, 1H, *J* = 15.5, 7.7, 1.0 Hz), 4.21 (t, 1H, *J* = 5.5 Hz), 3.14 (s, 6H), 1.76 (ddd, 1H, *J* = 13.4, 7.7, 5.8 Hz), 1.59 (ddd, 1H, *J* = 13.4, 7.7, 7.4 Hz), 1.56–1.40 (m, 2H), 1.28–1.15 (m, 2H), 1.10–0.99 (m, 1H), 0.61 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, benzene-*d$_6$*) δ 192.57, 155.71, 134.51, 104.65, 52.35, 39.77, 32.37, 31.53, 30.76, 19.33; MS (CI, NH$_3$) 218 (MNH$_4$$^+$, 25), 201 (MH$^+$, 0.1), 75 (100). Anal. Calcd for C$_{11}$H$_{20}$O$_3$: C, 65.95; H, 10.07. Found: C, 65.81; H, 10.09.

(7R)-(E,E)-10,10-Dimethoxy-7-methyldeca-2,4-diene (16b). Ethyltriphenylphosphonium iodide (0.295 g, 0.704 mmol) was suspended in dry THF (1.4 mL) and dry Et$_2$O (1.1 mL) and was stirred with phenyllithium (1.8 M in cyclohexane/Et$_2$O (70/30); 0.39 mL, 0.704 mmol) for 10 min at room temperature.[20] After the white slurry turned a clear red color, the solution was cooled to −78 °C and a solution of the aldehyde **15** (0.140 g, 0.704 mmol) in Et$_2$O (0.6 mL) was added with vigorous stirring. After 5 min, an additional portion of phenyllithium (1.8 M in cyclohexane/Et$_2$O (70/30); 0.39 mL, 0.704 mmol) was added to the orange slurry. The red solution was stirred for 5 min, and ethereal HCl (5.3 M, 0.147 mL, 0.775 mmol) was slowly added followed by a quick addition of potassium *tert*-butoxide (1:1 complex with *tert*-butyl alcohol, 0.197 g, 1.06 mmol). The mixture was warmed to room temperature, stirred for 2 h, and then diluted with Et$_2$O (50 mL), washed with H$_2$O (4 × 10 mL) until neutral and then brine (1 × 10 mL), and dried (MgSO$_4$). Concentration of the filtrate *in vacuo* gave a yellow liquid, which was purified by flash chromatography (SiO$_2$; 20% Et$_2$O in pentane, R_f 0.50) to afford **16b** (111 mg, 75%) as a clear oil. This material was contaminated with 2Z,4E-isomer (8% by ^{1}H NMR integration), which was not easily removed. Data for the mixture: [α]^{20}$_D$ −3.22° (*c* 2.39, CHCl$_3$); IR (CH$_2$Cl$_2$ cast) 3016 (m), 2952 (s) cm^{-1}; MS (CI, NH$_3$) 230 (MNH$_4$$^+$, 1.0), 213 (MH$^+$, 0.1). Anal. Calcd for C$_{13}$H$_{24}$O$_2$: C, 73.52; H, 11.40. Found: C, 73.76; H, 11.46. Data for the desired *E*,*E*-diene: ^{1}H NMR (400 MHz, benzene-*d$_6$*) δ 6.12–5.99 (m, 2H), 5.53–5.43 (m, 2H), 4.28 (t, 1H, *J* = 5.7 Hz), 3.15 (s, 6H), 2.04 (ddd, 1H, *J* = 13.8, 7.0, 7.0 Hz), 1.87 (ddd, 1H, *J* = 13.8, 7.0, 6.5 Hz), 1.72–1.52 (m, 2H), 1.62 (d, 3H, *J* = 6.7 Hz), 1.48–1.38 (m, 2H), 1.27–1.18 (m, 1H), 0.83 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, benzene-*d$_6$*) δ 132.46, 132.40, 130.34, 126.68, 104.88, 52.07, 40.38, 33.55, 31.73, 30.48, 19.65, 18.08.

[2-^{13}C]-Labeled 16 (16a). The same method as for the preparation of **16b** was employed. The spectral and chromatographic properties were similar to those of **16b** except for: Data for the *E*,*E*-isomer: ^{1}H NMR (400 MHz, benzene-*d$_6$*) δ 5.49 (m, 1H, H-5), 5.52–5.46 (ddd, 1H, *J* = 150.5, 14.1, 6.7 Hz), 1.62 (dd, 3H, *J* = 6.7, 6.7 Hz); ^{13}C NMR (100 MHz, benzene-*d$_6$*) δ 132.42 (d, *J* = 71.4 Hz), 130.30 (d, *J* = 10.0 Hz), 18.03 (d, *J* = 43.3 Hz).

(4R)-E,E-4-Methyldeca-6,8-dienal (17b). Distilled THF (21.5 mL) and saturated aqueous oxalic acid (15 mL) were added to the protected aldehyde **16b** (1.07 g, 5.02 mmol), and the resultant mixture was stirred at room temperature for 24 h, then treated with a further portion of saturated aqueous oxalic acid (2 mL), and stirred for an additional 6 h.[22] The reaction mixture was partitioned between Et$_2$O (250 mL) and

H_2O (50 mL), and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with 5% $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL) and then dried ($MgSO_4$). Partial concentration *in vacuo* gave a volatile pale yellow liquid (0.794 g), which could be used without further purification. A portion of the crude aldehyde (0.200 g) was chromatographed on silica (30% CH_2Cl_2 in pentane, R_f 0.25) to afford **17b** (0.156 g, 78%), which still contained the difficult to separate 2*Z*,4*E*-isomer (8% by ^{1}H NMR integration). Data for the mixture: $[\alpha]^{20}_D$ −8.27° (*c* 1.28, CH_2Cl_2); IR (CH_2Cl_2 cast) 3015 (m), 2725 (m), 1723 (s) cm^{−1}; MS (EI) calcd for $C_{11}H_{18}O$ 166.1358, found 166.1357 (M[+], 21), 109.0650 (24). Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.92. Found: C, 79.25; H, 10.88. Data for the desired *E,E*-dienal: ^{1}H NMR (400 MHz, benzene-d_6) δ 9.30 (t, 3H, *J* = 1.7 Hz), 6.10−5.95 (m, 2H), 5.49 (dq, 1H, *J* = 14.2, 7.1 Hz), 5.38 (dt, 1H, *J* = 14.1, 7.0 Hz), 1.95−1.67 (m, 4H), 1.58 (d, 3H, *J* = 7.0 Hz), 1.44−1.35 (m, 1H), 1.25−1.15 (m, 1H), 1.15−1.07 (m, 1H), 0.67 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, benzene-d_6) δ 200.62, 132.55, 132.25, 129.76, 126.98, 41.58, 40.31, 32.97, 28.58, 19.19, 18.04.

[9-^{13}C]-Labeled 17 (17a). The same method as for the preparation of unlabeled aldehyde **17b** was employed. Thus, reaction of labeled acetal **16a** (2.39 g, 11.2 mmol) with saturated aqueous oxalic acid (10 mL) in THF (30 mL) afforded crude **17a** still containing some solvent. Due to the high volatility of the product, this material was used in the next reaction without further purification.

Ethyl (6*R*)-(*E,E,E*)-6-Methyldodeca-2,8,10-trienoate (18b). A solution of aldehyde **17b** (1.25 g, 7.54 mmol) and (carbethoxymethylene)triphenylphosphorane (3.15 g, 9.04 mmol) in dry benzene (150 mL) was heated to reflux at 85 °C for 17 h.[24] The mixture was cooled to room temperature, and the solvent was removed *in vacuo* to give a pale yellow slurry. The slurry was partially purified on flash silica (40 × 220 mm, 5% Et_2O in pentane, R_f 0.41) to yield a mixture of trienes (1.42 g, 80%). This oil was separated using MPLC with $AgNO_3$-stained silica gel, to give the 2*Z*,8*E*,10*Z*-triene impurity **19b** (126 mg, 7%), the desired *E,E,E*-triene **18b** (1.11 g, 62%), and some mixed material (95.8 mg, 5%). The *E,E,E*-triene was further purified on flash silica (5% Et_2O in pentane, R_f 0.41) to yield **18b** (834 mg, 47%) as a clear oil: $[\alpha]^{20}_D$ −7.59° (*c* 1.1, CHCl_3); IR (CHCl_3 cast) 1722 (s), 1655 (m) cm^{−1}; ^{1}H NMR (400 MHz, CDCl_3) δ 6.95 (dt, 1H, *J* = 15.6, 6.9 Hz), 6.02 (ddq, 1H, *J* = 14.2, 10.4, 1.5 Hz), 5.97 (ddt, 1H, *J* = 14.4, 10.4, 1.3 Hz), 5.81 (dt, 1H, *J* = 15.6, 1.6 Hz), 5.58 (dq, 1H, *J* = 14.2, 6.9 Hz), 5.50 (dt, 1H, *J* = 14.4, 7.3 Hz), 4.17 (q, 2H, *J* = 6.5 Hz), 2.29−2.10 (m, 2H), 2.06 (ddd, 1H, *J* = 13.5, 7.3, 6.1 Hz), 1.93 (ddd, 1H, *J* = 13.5, 7.3, 7.0 Hz), 1.73 (d, 3H, *J* = 6.9 Hz), 1.56−1.43 (m, 2H), 1.28−1.19 (m, 1H), 1.28 (t, 3H, *J* = 6.5 Hz), 0.90 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 166.81, 149.48, 131.89, 131.60, 129.90, 127.14, 121.23, 60.16, 39.93, 34.69, 32.79, 29.86, 19.32, 18.02, 14.31; MS (EI) calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1775 (M[+], 9), 190.1353 (6). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.21; H, 10.24. Found: C, 76.40; H, 10.22.

[2,11-[13]C_2]-Labeled 18 (18a). The same method as for the preparation of **18b** was employed. The spectral and chromatographic properties were similar to those of **18b** except for: ^{1}H NMR (400 MHz, benzene-d_6) δ 7.03 (dtd, 1H, *J* = 15.7, 7.0, 2.0 Hz), 6.08−5.96 (m, 2H, H-9 and H-10), 5.87 (ddt, 1H, *J* = 161.1, 15.7, 1.6 Hz), 5.52 (ddq, 1H, *J* = 150.5, 14.2, 7.0 Hz), 1.92−1.70 (m, 4H, H-4 and H-7), 1.60 (dd, 3H, *J* = 7.0, 7.0 Hz, H-12); ^{13}C NMR (100 MHz, benzene-d_6) δ 166.81 (d, *J* = 75.5 Hz), 149.10 (d, *J* = 69.4 Hz), 132.31 (d, *J* = 71.4 Hz), 34.88 (d, *J* = 3.0 Hz), 18.04 (d, *J* = 43.3 Hz); MS (EI) calcd for $^{13}C_2{}^2C_{13}H_{24}O_2$ 238.1843, found 238.1834 (M[+], 7), 209.1447 (1.1), 165.1548 (30). Anal. Calcd for $^{13}C_2{}^2C_{13}H_{24}O_2$: C, 76.42; H, 10.15. Found: C, 76.21; H, 10.14.

(6*R*)-*E,E,E*-6-Methyldodeca-2,8,10-trienoic Acid (20b). A solution of triene ethyl ester **18b** (1.00 g, 4.23 mmol) in distilled THF (50 mL) was treated with aqueous 3 M KOH (10 mL), and the mixture was stirred for 18 h at 50 °C.[24] Most of the THF was removed *in vacuo*, and the cloudy solution was stirred at 50 °C until it became clear. After cooling, H_2O (500 mL) was added and this solution was washed with pentane (2 × 50 mL). The aqueous layer was acidified to pH 7 (1 N HCl) and then extracted with Et_2O (3 × 200 mL). The combined

organic fractions were dried ($MgSO_4$) and concentrated to yield a clear oil (855 mg, 97%), which could be used without further purification. The acid could be purified by flash chromatography (SiO_2; 20 × 250 mm, 100% Et_2O, R_f 0.50) to yield **20b** (656 mg, 75%) as a clear oil: $[\alpha]^{20}_D$ −7.37° (*c* 0.095, CHCl_3); IR (CHCl_3 cast) 3400−2300 (br), 1696 (s), 1650 (s) cm^{−1}; ^{1}H NMR (400 MHz, CDCl_3) δ 11.2 (br s, 1H), 7.08 (dt, 1H, *J* = 15.6, 6.9 Hz), 6.02 (ddq, 1H, *J* = 14.2, 10.4, 1.5 Hz), 5.98 (ddt, 1H, *J* = 14.4, 10.4, 1.3 Hz), 5.82 (dt, 1H, *J* = 15.6, 1.6 Hz), 5.58 (dq, 1H, *J* = 14.2, 6.9 Hz), 5.50 (dt, 1H, *J* = 14.4, 7.3 Hz), 2.34−2.14 (m, 2H), 2.05 (ddd, 1H, *J* = 13.8, 7.3, 6.4 Hz), 1.93 (ddd, 1H, *J* = 13.8, 7.3, 7.0 Hz), 1.73 (d, 3H, *J* = 6.9 Hz), 1.57−1.45 (m, 2H), 1.32−1.22 (m, 1H), 0.88 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 172.28, 152.49, 131.96, 131.59, 129.76, 127.16, 120.63, 39.90, 34.50, 32.82, 29.98, 19.30, 18.03; MS (CI, NH_3) 226 (MNH_4^{+}, 81), 209 (MH[+], 6). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.61; H, 9.73.

[2,11-[13]C_2]-Labeled 20 (20a). The same method as for the preparation of **20b** was employed. The spectral and chromatographic properties were similar to those of **20b** except for the following: ^{1}H NMR (300 MHz, CDCl_3) δ 7.07 (dtd, 1H, *J* = 15.6, 7.0, 1.9 Hz), 6.05−5.92 (m, 2H), 5.82 (ddt, 1H, *J* = 162.8, 15.6, 1.4 Hz), 5.59 (ddq, 1H, *J* = 150.2, 14.2, 6.9 Hz), 1.73 (dd, 3H, *J* = 6.9, 6.8 Hz); ^{13}C NMR (75.5 MHz, CDCl_3) δ 172.30 (d, *J* = 69.8 Hz), 152.46 (d, *J* = 69.4 Hz), 131.64 (d, *J* = 70.9 Hz), 34.54 (d, *J* = 3.5 Hz), 18.01 (d, *J* = 43.8 Hz); MS (EI) calcd for $^{13}C_2{}^2C_{11}H_{20}O_2$ 210.1536, found 210.1527 (M[+], 4.3), 165.1548 (19). Anal. Calcd for $^{13}C_2{}^2C_{11}H_{20}O_2$: C, 75.20; H, 9.59. Found: C, 74.91; H, 9.44.

Ethyl (1*S*, 2*S*, 4a*R*, 6*R*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalene-1-carboxylate (21). Tributyltin hydride (0.5 mL, 1.86 mmol) and freshly recrystallized α,α′-azobis(isobutyronitrile) (AIBN, ∼5 mg) were stirred with thioketal **28** (55.4 mg, 0.170 mmol) at 120 °C for 4 days.[33] After cooling, the mixture was purified by flash chromatograhy (SiO_2; 2% Et_2O in pentane) to give the desired fully reduced product **21** (30.8 mg, 77%, R_f 0.20), and the mercapto intermediate **29** (8.8 mg, 22%, R_f 0.16) as clear oils. Data for **21**: $[\alpha]^{20}_D$ +143.3° (*c* 0.72, CHCl_3); IR (CH_2Cl_2 cast) 1736 (s) cm^{−1}; ^{1}H NMR (400 MHz, CDCl_3) δ 5.56 (ddd, 1H, *J* = 9.9, 4.0, 3.0 Hz), 5.33 (br d, 1H, *J* = 9.9 Hz), 4.15 (q, 2H, *J* = 7.2 Hz), 2.61−2.49 (m, 2H), 2.10−2.00 (m, 1H), 1.93 (dddm, 1H, *J* = 12.8, 12.5, 2.6 Hz), 1.72 (dddd, 1H, *J* = 12.5, 3.9, 3.9, 3.7 Hz), 1.63 (dddd, 1H, *J* = 13.2, 12.9, 3.9, 3.9 Hz), 1.56−1.53 (m, 1H), 1.53−1.48 (m, 1H), 1.45−1.35 (m, 1H), 1.33 (ddd, 1H, *J* = 13.0, 12.8, 4.8 Hz), 1.26 (t, 3H, *J* = 7.0 Hz), 1.10 (dddd, 1H, *J* = 12.9, 12.9, 11.9, 3.7 Hz), 0.99 (d, 3H, *J* = 7.2 Hz), 0.91 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 173.88, 131.24, 131.21, 59.76, 49.60, 38.73, 37.20, 35.66, 32.35, 31.94, 27.63, 24.49, 18.37, 17.79, 14.40; MS (EI) calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1778 (M[+], 10), 191.1428 (7), 162.1410 (100). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.50; H, 10.19.

Ethyl (1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8,8a-Octahydro-8-hydroxy-6-(hydroxymethyl)-2-methylnaphthalene-1-carboxylate (23). A solution of the lactone **22** (0.476 g, 1.80 mmol) in dry THF (20 mL) was cooled to 0 °C, and lithium triethylborohydride (LiBEt_3H; 1.0 M in THF, 2.34 mmol) was added slowly (15 min).[27e] Further portions of lithium triethylborohydride (1.26 mmol) were added to react with intermediates generated, but the additions were limited so as to not fully reduce the starting material (TLC monitoring). H_2O (0.5 mL) was carefully added to destroy excess reagent, followed by 2 N NaOH(aq) (1 mL) and 30% H_2O_2 solution (1 mL) dropwise. The resulting cloudy mixture was stirred vigorously for 1 h at room temperature and then poured into Et_2O (100 mL). The organic layer was washed with brine (20 mL), and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (SiO_2; 10% pentane in Et_2O) of the resultant oil yielded two products: the desired product **23** (312 mg, 65%, R_f 0.20) and the triol **24** (9.88 mg, 20%, R_f 0.07) as a colorless solids. Data for diol **23**: mp 100−100.5 °C; $[\alpha]^{20}_D$ +142.0° (*c* 0.29, CHCl_3); IR (CH_2Cl_2 cast) 3350 (br m), 1732 (s), 1712 (s) cm^{−1}; ^{1}H NMR (400 MHz, CDCl_3) δ 5.53 (ddd, 1H, *J* = 9.8, 4.2, 2.8 Hz), 5.39 (br d, 1H, *J* = 9.8 Hz), 4.24 (br d, 1H, *J* = 2.1 Hz), 4.20−4.10 (m, 2H), 3.78−3.69 (m, 2H), 3.30

(br s, 2H), 2.82 (dd, 1H, $J = 11.9$, 6.6 Hz), 2.65−2.54 (m, 1H), 2.52−2.42 (m, 1H), 2.01−1.95 (m, 1H), 1.95−1.83 (m, 2H), 1.83−1.75 (m, 1H), 1.47 (ddd, 1H, $J = 11.4$, 11.0, 1.7 Hz), 1.35 (ddd, 1H, $J = 13.4$, 13.4, 6.1 Hz), 1.26 (t, 3H, $J = 7.1$ Hz), 0.91 (d, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.91, 131.19, 130.54, 67.98, 65.69, 60.00, 45.12, 39.85, 35.73, 35.04, 33.99, 32.46, 30.52, 17.63, 14.31; MS (CI, NH$_3$) 286 (MNH$_4^+$, 10), 269 (MH$^+$, 100). Anal. Calcd for C$_{15}$H$_{24}$O$_4$: C, 67.14; H, 9.01. Found: C, 66.74; H, 9.36.

Ethyl (1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8,8a-Octahydro-8-hydroxy-2-methyl-6-[[[(methylthio)thiocarbonyl]oxy]methyl]naphthalene-1-carboxylate (25). A solution of tetrabutylammonium hydrogen sulfate (691 mg, 2.04 mmol) and diol **23** (497 mg, 1.85 mmol) in distilled benzene (15 mL) was treated (with vigorous stirring), with 4 N NaOH(aq) (15 mL), followed by a quick addition of carbon disulfide (0.23 mL, 3.70 mmol) and methyl iodide (0.173 mL, 2.78 mmol).[30] After 10 min, ice (30 g) and Et$_2$O (30 mL) were added to quench the reaction. The aqueous layer was extracted with Et$_2$O (2 × 30 mL) and the combined organic layers were washed with brine (15 mL), dried (MgSO$_4$), and evaporated *in vacuo*. The resultant pale orange oil was purified by flash chromatography (SiO$_2$; 30% Et$_2$O in pentane, R_f 0.30) to give **25** (564 mg, 85%) as a colorless oil: [α]$^{20}_D$ +162.9° (*c* 0.42, CHCl$_3$); IR (CH$_2$Cl$_2$ cast) 3500 (br m) 1731 (s), 1714 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.57 (ddd, 1H, $J = 9.8$, 4.6, 2.6 Hz), 5.39 (br d, 1H, $J = 9.8$ Hz), 4.90 (dd, 1H, $J = 10.9$, 9.3 Hz), 4.76 (dd, 1H, $J = 10.9$, 6.1 Hz), 4.31 (dd, 1H, $J = 2.6$, 2.5 Hz), 4.21−4.09 (m, 2H), 2.85 (dd, 1H, $J = 11.6$, 5.9 Hz), 2.66−2.59 (m, 1H), 2.56 (s, 3H), 2.51−2.41 (m, 1H), 2.41−2.33 (m, 1H), 1.92-1.76 (m, 2H), 1.60−1.50 (m, 2H), 1.33 (ddd, 1H, $J = 13.4$, 13.4, 5.1 Hz), 1.26 (t, 3H, $J = 7.1$ Hz), 0.92 (d, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 215.94, 173.69, 131.14, 130.66, 77.18, 66.52, 60.04, 44.99, 40.02, 34.86, 33.42, 32.48, 31.88, 28.98, 18.96, 17.54, 14.33; MS (CI, NH$_3$) 376 (MNH$_4^+$, 10), 359 (MH$^+$, 6), 268 (100). Anal. Calcd for C$_{17}$H$_{26}$O$_4$S$_2$: C, 56.95; H, 7.31. Found: C, 57.16; H, 7.52.

Ethyl (1S,2S,4aR,6S,8aS)-1,2,4a,5,6,7,8,8a-Octahydro-2-methyl-6-[[[(methylthio)thiocarbonyl]oxy]methyl]-8-oxonaphthalene-1-carboxylate (26). A solution of alcohol **25** (1.14 g, 3.18 mmol) and pyridinium dichromate (1.79 g, 4.76 mmol) in dry CH$_2$Cl$_2$ (5 mL) was stirred at room temperature for 36 h.[46] The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (SiO$_2$; 40% Et$_2$O in pentane, R_f 0.30) to yield the desired keto-ester **26** (0.908 g, 80%) as a colorless waxy solid: mp 82-82.5 °C; [α]$^{20}_D$ +160.5°(*c* 1.19, CHCl$_3$); IR (CH$_2$Cl$_2$) 1733 (s), 1717 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.66 (ddd, 1H, $J = 9.8$, 4.5, 2.6 Hz), 5.45 (ddd, 1H, $J = 9.8$, 1.6, 1.5 Hz), 4.52 (dd, 1H, $J = 11.1$, 7.9 Hz), 4.45 (dd, 1H, $J = 11.1$, 6.9 Hz), 4.22−4.09 (m, 2H), 2.90−2.60 (m, 5H), 2.73 (s, 3H), 2.38 (ddd, 1H, $J = 13.7$, 1.8, 1.8 Hz), 2.29 (ddm, 1H, $J = 11.8$, 11.8 Hz), 1.97 (dm, 1H, $J = 14.1$ Hz), 1.79 (ddd, 1H, $J = 13.4$, 13.4, 5.3 Hz), 1.26 (t, 3H, $J = 7.2$ Hz), 0.89 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 215.75, 209.03, 173.51, 132.50, 128.03, 74.47, 60.30, 49.24, 42.99, 42.63, 38.03, 35.40, 32.92, 31.15, 19.15, 17.72, 14.26; MS (EI) calcd for C$_{17}$H$_{24}$O$_4$S$_2$ 356.1116, found 356.1110 (M$^+$, 18), 310.0696 (16), 202.0989 (100). Anal. Calcd for C$_{17}$H$_{24}$O$_4$S$_2$: C, 57.28; H, 6.79. Found: C, 56.98; H, 6.42.

Ethyl (1S,2S,4aR,6S,8aS)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethyl-8-oxonaphthalene-1-carboxylate (27). A solution of tributyltin hydride (0.133 mL, 0.496 mmol) in dry cymene (2 mL) was slowly added to a solution of methyl xanthate **26** (22.1 mg, 0.062 mmol) in cymene (2 mL) at 150 °C over 1.25 h.[31] The mixture was allowed to stir overnight at 150 °C. The solvent was removed *in vacuo* and the resultant oil purified by flash chromatography (SiO$_2$; 40% Et$_2$O in pentane, R_f 0.40) to yield **27** (9.75 mg, 63%) as a clear colorless solid: mp 34−35 °C; [α]$^{20}_D$ +80.8° (*c* 0.13, CHCl$_3$); IR (CH$_2$Cl$_2$ cast) 1736 (s), 1718 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.64 (ddd, 1H, $J = 9.8$, 4.5, 2.8 Hz), 5.45 (ddd, 1H, $J = 9.8$, 1.6, 1.5 Hz), 4.23−4.09 (m, 2H), 2.82 (dd, 1H, $J = 11.5$, 6.6 Hz), 2.75 (dd, 1H, $J = 12.6$, 6.6 Hz), 2.70−2.50 (m, 3H), 2.37−2.28 (m, 1H), 2.15 (ddd, 1H, $J = 12.6$, 1.9, 1.9 Hz), 1.78 (ddd, 1H, $J =$

12.9, 12.9, 4.9 Hz), 1.69 (dp, 1H, $J = 13.3$, 1.8 Hz), 1.26 (t, 3H, $J = 7.1$ Hz), 0.98 (d, 3H, $J = 7.2$ Hz), 0.89 (d, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 210.50, 173.76, 132.15, 128.87, 60.22, 49.53, 48.11, 42.83, 38.01, 37.82, 31.35, 31.26, 19.39, 17.80, 14.28; MS (EI) calcd for C$_{15}$H$_{22}$O$_3$ 250.1569, found 250.1567 (M$^+$, 22), 204.1149 (76), 176.1198 (100). Anal. Calcd for C$_{15}$H$_{22}$O$_3$: C, 71.97; H, 8.86. Found: C, 71.71; H, 8.87.

Ethyl (1S,2S,4aR,6S,8aS)-1,2,4a,5,6,7,8,8a-Octahydro-8-(dimethylenedithio)-2,6-dimethylnaphthalene-1-carboxylate (28). A solution of ketone **27** (0.244 g, 0.977 mmol) in dry CH$_2$Cl$_2$ (8 mL) was treated with 1,2-ethanedithiol (0.164 mL, 1.95 mmol) and boron trifluoride etherate (0.120 mL, 0.977 mmol) at 0 °C.[32] The mixture was then warmed to room temperature and stirred overnight. The reaction mixture was diluted with CH$_2$Cl$_2$ (50 mL) and washed with 1 N NaOH (10 mL), 1 N HCl (10 mL), H$_2$O (10 mL), and brine (10 mL). The solvent was removed *in vacuo*, and the resultant oil was purified by flash chromatography (SiO$_2$; 10% Et$_2$O in pentane, R_f 0.22) to yield **28** (212 mg, 66%) as a clear colorless oil: [α]$^{20}_D$ +84.3° (*c* 0.22, CHCl$_3$); IR (CH$_2$Cl$_2$ cast) 1730 (s) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.64 (br s, 2H), 4.11 (dm, 2H, $J = 3.0$ Hz), 3.43−3.33 (m, 1H), 3.33−3.28 (m, 1H), 3.28−3.20 (m, 2H), 3.10 (dd, 1H, $J = 7.8$, 6.2 Hz), 2.47 (br dq, 1H, $J = 7.8$, 7.4 Hz), 2.32−2.22 (m, 2H), 2.21 (dd, 1H, $J = 10.9$, 6.2 Hz), 2.20−2.10 (m, 1H), 2.12−2.00 (br t, 1H, $J = 12.3$ Hz), 1.75 (dm, 1H, $J = 13.3$ Hz), 1.62 (ddd, 1H, $J = 12.7$, 12.7, 5.3 Hz), 1.24 (t, 3H, $J = 7.2$ Hz), 1.21 (d, 3H, $J = 7.5$ Hz), 1.10 (d, 3H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 176.20, 134.15, 133.37, 72.68, 59.95, 54.22, 50.91, 49.74, 40.97, 38.50, 37.99, 33.71, 31.93, 29.50, 20.46, 17.64, 14.33; MS (EI) calcd for C$_{17}$H$_{26}$O$_2$S$_2$ 326.1374, found 326.1369 (M$^+$, 60), 298.1050 (68), 219.0844 (27), 159.1168 (100). Anal. Calcd for C$_{17}$H$_{26}$O$_2$S$_2$: C, 62.54; H, 8.03. Found: C, 62.81; H, 8.34.

Diels−Alder Cyclization. (A) Thermal Reaction: A solution of triene (20.0 mg, 84.9 μmol) in dry toluene (1 mL) was placed in a thick-walled glass tube, and the solution was degassed with a stream of argon for 5 min.[36] The tube was sealed under argon and then heated in an oil bath at 160 °C for 43 h. The tube was cooled and opened, and the solvent was removed *in vacuo*. Flash chromatography of the clear residue yielded the *trans*-fused product, the *cis*-fused product, and unreacted starting material as clear oils. **(B) Lewis Acid-Catalyzed Reaction:** Ethylaluminum dichloride (240 μL, 54.0 μmol, 1.8 M in toluene) was slowly added to a solution of triene (13.4 mg, 56.8 μmol) in dry toluene (0.5 mL), and the mixture was stirred at room temperature for 3 h.[36] The reaction mixture was then poured into 1 N HCl (1.0 mL), and the aqueous layer was extracted with Et$_2$O (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaHCO$_3$ (2 mL), dried (MgSO$_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography to yield the *trans*-fused product, the *cis*-fused product, and unreacted starting material.

Ethyl (1R,2R,4aS, 6R,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalene-1-carboxylate (30): [α]$^{20}_D$ −89.5° (*c* 1.40, CHCl$_3$); IR (CH$_2$Cl$_2$ cast) 1737 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.53 (ddd, 1H, $J = 9.9$, 4.0, 2.7 Hz), 5.38 (br d, 1H, $J = 9.9$ Hz), 4.13 (q, 2H, $J = 7.1$ Hz), 2.55 (m, 1H), 2.53 (m, 1H), 1.95 (dddd, 1H, $J = 12.0$, 3.2, 3.0, 2.9 Hz), 1.77−1.68 (m, 3H), 1.52−1.43 (m , 1H), 1.35 (dddd, 1H, $J = 12.0$, 12.0, 12.0, 3.0 Hz), 1.27 (t, 3H, $J = 7.1$ Hz), 1.04 (dddd, 1H, $J = 12.0$, 12.0, 12.0, 3.0 Hz), 1.00−0.95 (m, 1H), 0.93 (d, 3H, $J = 6.7$ Hz), 0.90 (d, 3H, $J = 6.8$ Hz), 0.80 (ddd, 1H, $J = 12.0$, 12.0, 12.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.97, 130.93, 130.92, 59.79, 49.51, 41.89, 41.63, 36.20, 35.27, 33.10, 32.46, 29.94, 22.53, 17.75, 14.40; MS (EI) calcd for C$_{15}$H$_{24}$O$_2$ 236.1776, found 236.1775 (M$^+$, 11), 191.1429 (7), 162.1406 (100). Anal. Calcd for C$_{15}$H$_{24}$O$_2$: C, 76.23; H, 10.23. Found: C, 76.20; H, 10.20.

Ethyl (1R,2S,4aR,6R,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalene-1-carboxylate (31): [α]$^{20}_D$ +6.95° (*c* 0.81, CHCl$_3$); IR (CH$_2$Cl$_2$ cast) 1732 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.54 (ddd, 1H, $J = 10.0$, 4.2, 2.4 Hz), 5.42 (ddd, 1H, $J = 10.0$, 1.6, 1.5 Hz), 4.17 (q, 1H, $J = 7.1$ Hz), 4.16 (q, 1H, $J = 7.07$ Hz), 2.52 (dqdd, 1H, $J = 8.7$, 6.1, 4.2, 1.6 Hz), 2.37 (dd, 1H, $J = 10.0$, 8.7 Hz), 2.29 (m, 1H), 2.05 (m, 1H), 1.94−1.83 (m , 1H), 1.74−1.64 (m, 2H), 1.48−1.35 (m, 2H), 1.38−1.29 (m, 1H), 1.28 (t, 3H, $J = 7.1$ Hz), 1.18 (ddd, 1H, J

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= 9.7, 6.0, 5.0 Hz), 0.99 (d, 3H, J = 6.1 Hz), 0.97 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 176.22, 131.31, 130.83, 60.08, 47.92, 36.31, 36.19, 34.04, 31.01, 28.06, 27.41, 24.03, 20.61, 18.66, 14.43; MS (EI) calcd for C$_{15}$H$_{24}$O$_2$ 236.1776, found 236.1776 (M$^+$, 13), 162.1410 (100). Anal. Calcd for C$_{15}$H$_{24}$O$_2$: C, 76.23; H, 10.23. Found: C, 76.07; H, 10.01.

(1R,2R,4aS, 6R,8aR)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalene-1-carboxylic acid (32): [α]^{20}$_D$ −68.0° (c 0.10, CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$ cast) 3600−2400 (br m), 1705 (s) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.55 (ddd, 1H, J = 10.0, 4.1, 2.8 Hz), 5.39 (br d, 1H, J = 10.0 Hz), 2.65−2.50 (m, 2H), 2.08−2.00 (m, 1H), 1.80−1.68 (m, 3H), 1.54−1.42 (m, 1H), 1.42−1.28 (m, 1H), 1.10−0.90 (m, 2H), 0.95 (d, 3H, J = 6.7 Hz), 0.90 (d, 3H, J = 6.8 Hz), 0.79 (ddd, 1H, J = 12.0, 12.0, 12.0 Hz); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 180.77, 130.92, 130.62, 49.39, 41.73, 41.56, 35.96, 35.22, 33.05, 32.33, 29.91, 22.49, 17.65; MS (EI) calcd for C$_{13}$H$_{22}$O$_2$ 208.1463, found 208.1469 (M$^+$, 26), 163.1488 (100). Anal. Calcd for C$_{13}$H$_{22}$O$_2$: C, 74.96; H, 9.68. Found: C, 74.72; H, 9.41.

(1R,2S,4aR,6R,8aR)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalene-1-carboxylic acid (33): IR (CH$_2$Cl$_2$ cast) 3600−2400 (br m), 1704 (s) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.55 (ddd, 1H, J = 10.0, 4.1, 2.8 Hz), 5.44 (ddd, 1H, J = 10.0, 2.0, 2.0 Hz), 2.58−2.50 (m, 1H), 2.39 (dd, 1H, J = 9.5, 8.0 Hz), 2.37−2.29 (m, 1H), 2.11−2.05 (m, 1H), 1.89−1.80 (m, 1H), 1.75−1.65 (m, 2H), 1.48−1.35 (m, 2H), 1.30−1.25 (m, 1H), 1.20.1.11 (m, 1H), 1.04 (d, 3H, J = 6.2 Hz), 0.98 (d, 3H, J = 6.1 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 182.89, 131.17, 130.46, 48.05, 36.43, 36.05, 33.46, 30.91, 28.63, 27.34, 24.37, 20.74, 18.94; MS (EI) calcd for C$_{13}$H$_{22}$O$_2$ 208.1463, found 208.1461 (M$^+$, 21), 163.1488 (100). Anal. Calcd for C$_{13}$H$_{22}$O$_2$: C, 74.96; H, 9.68. Found: C, 74.85; H, 9.80.

(1R,2R,4aS, 6R,8aR)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalene-1-carboxylic acid, *N*-acetylcysteamine thioester (34): mp 94−95 °C; [α]^{20}$_D$ −31.5° (c 0.41, CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$ cast) 3550−3100 (br m), 1687 (s), 1657 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.83 (br s, 1H), 5.53 (ddd, 1H, J = 10.0, 4.2, 2.7 Hz), 5.38 (br d, 1H, J = 10.0 Hz), 3.49−3.41 (m, 2H), 3.03 (t, 2H, J = 6.3 Hz), 2.85 (dd, 1H, J = 11.2, 5.8 Hz), 2.63−2.55 (m, 1H), 1.95 (s, 3H), 1.83−1.65 (m, 4H), 1.50−1.45 (m, 2H), 1.09−0.90 (m, 2H), 0.89 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 7.1 Hz), 0.78 (ddd, 1H, J = 12.0, 12.0, 12.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.00, 171.80, 130.92, 130.62, 58.62, 42.07, 41.48, 40.23, 36.81, 35.12, 33.59, 33.00, 29.46, 28.28, 23.28, 22.46, 17.42; MS (EI) calcd for C$_{17}$H$_{27}$NO$_2$S 309.1763, found 309.1760 (M$^+$, 1.4), 190.1359 (24), 163.1487 (100). Anal. Calcd for C$_{17}$H$_{27}$NO$_2$S: C, 65.98; H, 8.79. Found: C, 65.70; H, 9.28.

(1R,2S,4aR,6R,8aR)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalene-1-carboxylic acid, *N*-acetylcysteamine thioester (35): IR (CH$_2$Cl$_2$ cast) 3550−3100 (br m) 1683 (s), 1655 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.83 (br s, 1H), 5.53 (ddd, 1H, J = 10.0, 4.2, 2.4 Hz), 5.43 (ddd, 1H, J = 10.0, 2.0, 2.0 Hz), 3.50−3.40 (m, 2H), 3.06 (t, 1H, J = 6.4 Hz), 2.62 (dd, 1H, J = 9.3, 8.4 Hz), 2.61−2.50 (m, 1H), 2.34−2.27 (m, 1H), 2.13−2.07 (m, 1H), 1.92−1.82 (m, 1H), 1.73−1.63 (m, 2H), 1.48−1.35 (m, 2H), 1.38−1.32 (m, 1H), 1.22−1.15 (m, 1H), 1.02 (d, 3H, J = 7.1 Hz), 0.96 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 201.42, 170.24, 131.26, 130.62, 56.55, 40.22, 40.07, 36.99, 36.31, 34.27, 33.59, 31.15, 28.39, 28.28, 23.27, 22.46, 20.61; MS (EI) calcd for C$_{17}$H$_{27}$NO$_2$S 309.1763, found 309.1760 (M$^+$, 1.7), 190.1355 (19), 163.1482 (100); MS (CI, NH$_3$) 327 (MNH$_4$$^+$, 21), 310 (MH$^+$, 100). Anal. Calcd for C$_{17}$H$_{27}$NO$_2$S: C, 65.98; H, 8.79. Found: C, 65.82; H, 8.95.

(1R,2R,4aS, 6R,8aR)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethyl-1-(hydroxymethyl)naphthalene (36). The same method as for the preparation of alcohol **37** was employed. Thus, reduction of ethyl ester **30** (40.8 mg, 0.173 mmol) with LiAlH$_4$ (26.2 mg, 0.690 mmol) afforded **36** (26.9 mg, 80%): mp 64−65 °C; [α]^{20}$_D$ +70.37° (c 0.054, CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$ cast) 3600−3100 (br m), 3008 (m), 1455 (m) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.58 (ddd, 1H, J = 9.7, 4.6, 2.7 Hz), 5.36 (br d, 1H, J = 9.7 Hz), 3.83 (dd, 1H, J = 10.7, 5.5 Hz), 3.53 (dd, 1H, J = 10.7, 9.3 Hz), 2.50−2.38 (m, 1H), 1.80−1.63 (m, 5H), 1.51−1.36 (m , 2H), 1.11−0.92 (m, 3H), 0.92 (d, 3H, J = 7.1 Hz), 0.89 (d, 3H, J = 6.6 Hz), 0.73 (ddd, 1H, J = 12.2, 12.2, 12.2 Hz); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 132.34, 131.19, 63.21, 44.13, 43.34, 41.83, 37.34, 35.53, 32.82, 31.65, 29.16, 22.61, 15.51; MS (EI) calcd for C$_{13}$H$_{22}$O 194.1671, found 194.1669 (M$^+$, 10), 163.1487 (100). Anal. Calcd for C$_{13}$H$_{22}$O: C, 80.35; H, 11.41. Found: C, 80.15; H, 11.44.

(1R,2S,4aR,6R,8aR)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethyl-1-(hydroxymethyl)naphthalene (37). A solution of ethyl ester **31** (45.4 mg, 0.192 mmol) in dry Et$_2$O (0.7 mL) was added to a slurry of LiAlH$_4$ (29.2 mg, 7.68 mmol) in Et$_2$O (1.7 mL) at 0 °C.^{37} After stirring at room temperature for 2 h, the reaction mixture was cooled to 0 °C and treated sequentially with H$_2$O (33 μL), 3 M NaOH (33 μL), and H$_2$O (100 μL). The mixture was allowed to warm to room temperature and was stirred for an additional 1 h. MgSO$_4$ was added to the stirring solution, and the mixture was filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography (SiO$_2$; 30% Et$_2$O in pentane, R_f 0.35) to yield the desired alcohol **37** (32.0 mg, 86%) as a colorless solid: mp 59.5−60 °C; [α]^{20}$_D$ +28.6° (c 0.028, CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$ cast) 3600−3100 (br m), 1454 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.50 (ddd, 1H, J = 10.1, 2.8, 2.8 Hz), 5.40 (ddd, 1H, J = 10.0, 2.0, 2.0 Hz), 3.58 (d, 2H, J = 6.8 Hz), 2.35−2.28 (m, 1H), 2.00−1.90 (m, 1H), 1.82−1.75 (m, 1H), 1.69−1.57 (m, 3H), 1.57−1.42 (m, 2H), 1.39−1.32 (m, 1H), 1.25−1.19 (m, 1H), 1.09 (d, 3H, J = 7.5 Hz), 0.99−0.90 (m, 1H), 0.87 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 131.60, 129.80, 65.51, 46.13, 39.59, 34.79, 34.35, 31.07, 30.66, 28.15, 27.78, 22.17, 21.92; MS (EI) calcd for C$_{13}$H$_{22}$O 194.1671, found 194.1668 (M$^+$, 9), 163.1485 (100). Anal. Calcd for C$_{13}$H$_{22}$O: C, 80.35; H, 11.41. Found: C, 80.07; H, 11.52.

Supporting Information Available: Full spectral assignments for listed compounds, data for compounds **13**, **16**, **17** (2*Z*,4*E*-isomer), **19a,b**, **24**, and **29** and general experimental procedures (13 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.