An Annelation Approach to the Synthesis of Eudesmane and Elemane Sesquiterpene Lactones. Total Synthesis of *dl*-Dihydrocallitrisin, *dl*-7,8-Epialantolactone, *dl*-7,8-Epiisoalantolactone, and *dl*-Atractylon

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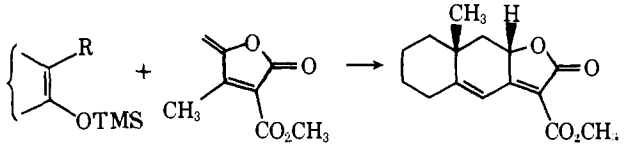
Abstract: An annelation approach to the synthesis of eudesmane sesquiterpenes is described. The 1,6-annelation reagent α-carbomethoxy-β-methyl-γ-methylidene-$\Delta^{\alpha,\beta}$-butenolide (**1**) is used to construct the linear tricyclic lactone 2,5,6,7,8,8a,9,9aβ-octahydro-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic acid methyl ester (**2**). The conversion of **2** to *dl*-dihydrocallitrisin (**3**), *dl*-7,8-epialantolactone (**4**), *dl*-7,8-epiisolantolactone (**5**), and *dl*-atractylon (**6**) is detailed. Studies directed toward synthesis of the elemane sesquiterpene lactones vernomenin and vernolepin also are presented.

Sesquiterpenes which possess an α-methylene-γ-butyrolactone ring often display considerable antitumor,[2-4] antibacterial,[5] allergenic,[6] and growth-inhibitory activity.[7] Consequently, a great deal of effort has been devoted to the development of methods for the construction of α-methylene-γ-butyrolactones and for the total synthesis of sesquiterpene lactones.[8]

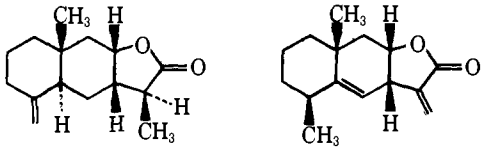
Herein, we report our efforts in the development of new, potentially general annelation methodology for the synthesis of eudesmane sesquiterpene lactones. Our approach features the 1,6-annelation reagent α-carbomethoxy-β-methyl-γ-methylidene-$\Delta^{\alpha,\beta}$-butenolide (**1**), which, in the present context, is used to construct the linear tricyclic lactone **2**. Thus,



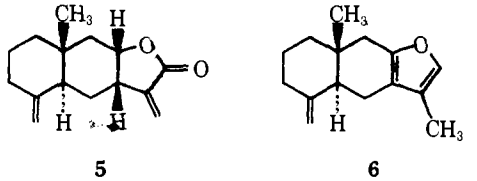
1 **2**

in relatively few synthetic operations, the essential carbon skeleton of the eudesmane sesquiterpenes can be assembled while simultaneously incorporating the γ-butyrolactone ring as well.

The method has been applied to the total synthesis of *dl*-dihydrocallitrisin (**3**), *dl*-7,8-epialantolactone (**4**), and *dl*-7,8-epiisoalantolactone (**5**).[9] We also describe the synthesis of the structurally related furanosesquiterpene *dl*-atractylon (**6**). It is interesting to note that diene lactone **2** serves as a



3 **4**

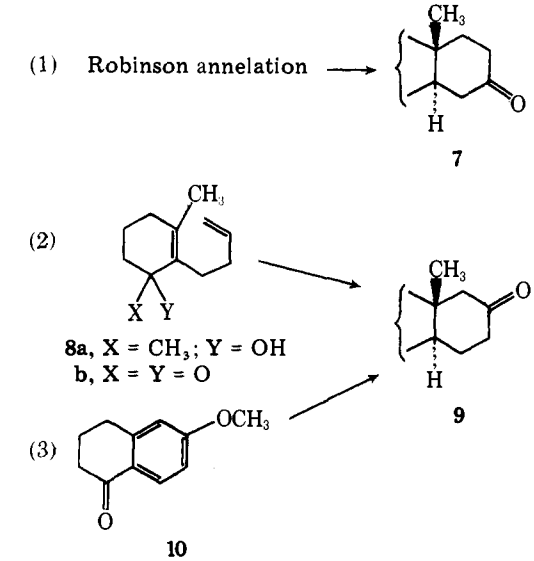


5 **6**

common intermediate to all these compounds. Studies directed toward synthesis of the elemane sesquiterpene lactones vernomenin and vernolepin also are presented.

Synthesis Perspective[8c]

A well-explored approach to synthesis of the eudesmane sesquiterpene lactones or furans involves elaboration of a basic 10-methyldecalin, followed by attachment of the lactone or furan ring. Decalin ring construction has generally taken three forms. The Robinson annelation approach provides a bicyclic ketone **7**, while cationic olefin cyclization of **8a**[10] or **8b**[11] leads to the isomeric ketone type **9**. Reduction of 6-methoxy-α-tetralone (**10**)[12,13] also provides access to **9**.



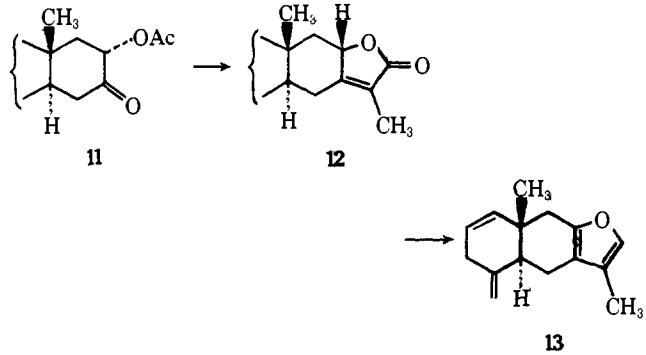
7

8a, X = CH_3; Y = OH
b, X = Y = O

9

10

A variety of methods have been developed for the introduction of the lactone ring components. In a total synthesis of *dl*-lindestrene (**13**), Minato uses a Robinson annelation approach to construct the α-acetoxy ketone **11**, from which lactone **12** is obtained by way of Reformatsky-based methodol-



11 **12** **13**

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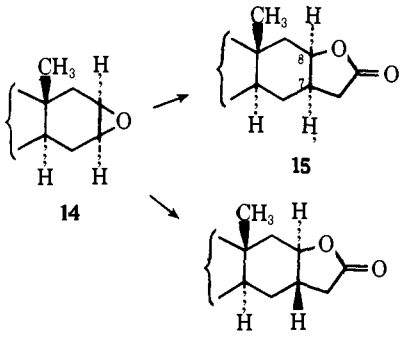
ogy.[14] Here, of course, stereochemical control at the lactone ring junction is not important to the synthesis; however, it is worth noting that stereochemistry in **12** is that resulting from equilibrium control.

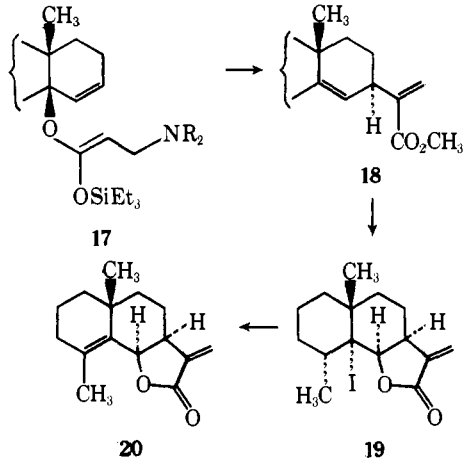
In principle, both ketone types **7** and **9** should be convertible to epoxide **14**. Marshall has demonstrated that **14** derived from decalone **7** is transformed to cis-fused lactone **15** by use of di-



14 **15** **16**

ethyl sodiomalonate as an acetic acid equivalent.[15] In the sequence **14** → **15**, the required inversion of configuration at C(7) was accomplished by epimerization of a C(8) ketonic intermediate. The method seems more advantageous for synthesis of trans-fused lactones **16**, and considerable recent progress in this area, stimulated by attempts at the total synthesis of vernolepin, are noted.[16]

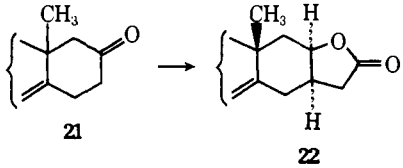
Still[17] has reported an imaginative synthesis of *dl*-frullanolide (**20**), in which Claisen rearrangement of **17** (prepared



17 **18** **19** **20**

by Wharton rearrangement of an octalone epoxide) provides the highly functionalized **18**. The cis-fused lactone **20** is available by an iodolactonization-dehydrohalogenation sequence.

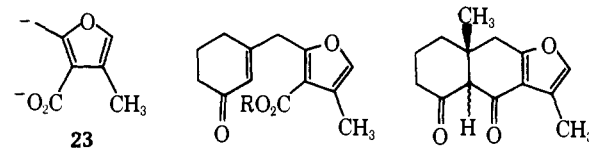
The last decalin-centered approach to be considered involves ketones of type **9**, in which the C(8) lactone ring oxygen atom is already correctly positioned. Thus, the lactone synthesis is carried forth by introduction of an acetic acid equivalent at C(7), and this is accomplished by alkylation of the enamine derived from **21** with ethyl bromoacetate.[10,13] Eventual re-



21 **22**

duction of the C(8) ketone carbonyl and lactonization gives the cis-fused lactone **22**. Here again, relative stereochemistry at C(7) is a result of equilibrium control via epimerization of a C(8) ketonic intermediate.

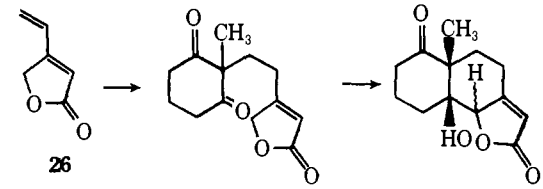
In a departure from the 10-methyldecalin strategy, Takahashi has very recently described a clever approach to tricyclic furan **25**.[18] The key step in the method involves condensation of the dianion of 2,4-dimethyl-3-furoic acid (**23**) with 3-methoxy-2-cyclohexenone to give **24a**; the annelation is completed



23 **24a**, R = H; **b**, R = CH_3 **25**

by internal acylation of the enolate resulting from lithium dimethylcuprate addition to **24b**. Because the furan ring can be oxidized directly to a lactone,[19] the method could provide a very direct approach to the eudesmane lactones.

After our research was already well underway, Yoshikoshi and co-workers reported an interesting and complementary annelation approach.[20a] For example, a 1,6-Michael addition of 2-methylcyclohexane-1,3-dione to butenolide **26** gives **27**,



26 **27** **28**

and this undergoes cyclization to give a diastereoisomeric mixture of hydroxy lactones **28**. Application of this methodology to sesquiterpene total synthesis has been reported very recently in a total synthesis of *dl*-frullanolide (**20**).[20b]

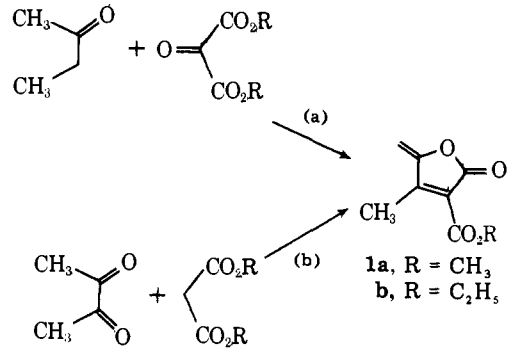
Results and Discussion

Butenolide Preparation. For an effective general approach to eudesmane sesquiterpene synthesis, we felt that an efficient preparation of the annelation reagent **1** was a necessity.[21] At the outset of this work, only α-arylidene analogues of butenolide **1** had been prepared,[22] but, because the methods used did not seem compatible with the anticipated instability of **1**, new synthetic methodology was explored.

In principle, the construction of **1** and related butenolides might be approached in two ways as diagrammed in Scheme I. We have, in fact, studied both and path (a) has already been detailed[23] and will not be considered here.

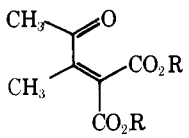
Biacetyl has been reported to undergo multiple condensations with aldehydes,[24] but no successful condensation between biacetyl and malonic acid derivatives has been reported. Initial attempts to perform this reaction using standard Knoevenagel methodology proved unsuccessful. However, the desired condensation of biacetyl with dialkyl malonates occurs with titanium tetrachloride[25] in pyridine-tetrahydrofuran solution to give keto diesters **29a** and **29b** in modest yield.

Scheme I

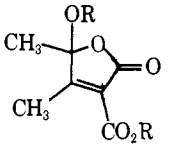


1a, R = CH_3; **b**, R = C_2H_5

We attempted to convert **29** to butenolide **1** by acid-catalyzed enol lactonization. Treatment of **29b** with *p*-toluenesulfonic acid in refluxing benzene gives only pseudoester **30b**; with **29b** and phosphorus pentoxide in methanesulfonic acid



29a, R = CH_3
b, R = C_2H_5



30a, R = R′ = CH_3
b, R = R′ = C_2H_5
c, R = R′ = H
d, R = CH_3; R′ = H

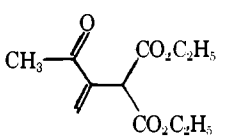
(1:10 solution by weight)[26] at room temperature a small amount of **1b** is formed (^{1}H NMR analysis) together with an intractable mixture of byproducts.

Limited success in preparation of **1** from pseudoester **30a** and **30b** was realized. Reaction of **30a** with phosphorus pentoxide–methanesulfonic acid (25 °C, 2 h) cleanly gives a mixture of butenolide **1a** and unreacted **30a** (1:3, respectively). Because of the instability of **1** (vide infra), attempts to force this reaction to completion by an increase in temperature or reaction time were not productive. Distillation of **30b** from sodium hydrogen sulfate[27] at reduced pressure gives a 70% recovery of a 1:4 mixture of butenolide **1b** and unreacted **30b**, respectively.

Subsequently, we developed an exceedingly simple preparation of butenolide **1a** from biacetyl and malonic acid. Whereas the $TiCl_4$-promoted condensation of biacetyl with malonic esters occurs in only moderate yield (24–30%), that with malonic acid gives the acid pseudoacid **30c** in 89% isolated yield.[28] Titration of an ether solution of **30c** with ethereal diazomethane gives the methyl ester pseudoacid **30d** (94%). Dehydration of **30d** in phosphorus pentoxide–methanesulfonic acid (25 °C, 1.5 h) gives butenolide **1a** in 95% isolated yield.

Butenolide **1a** is an extremely unstable crystalline material that does not exhibit a sharp melting point. The crystalline butenolide rapidly decomposes at room temperature to an as yet uncharacterized polymeric material; similar decomposition occurs in solution on treatment with amine bases or even sodium bicarbonate. Attempts to dry a chloroform solution of **1a** with anhydrous sodium sulfate result in rapid decomposition; however, magnesium sulfate may be used as a drying agent with essentially no decomposition. Dilute methylene chloride solutions of **1a** (5 mg/mL) may be stored (−15 °C) for several weeks with little decomposition.

Two other potentially useful annelation reagents (**31** and **34**) have also been prepared. Reaction of keto diester **29b** with triethylamine in refluxing ether solution gives a mixture of **29b** and vinyl ketone **31**[29] (1:3, respectively). From a preliminary



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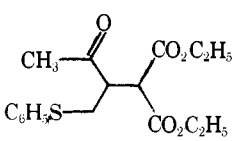

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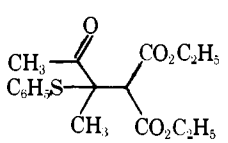

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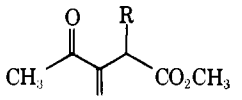
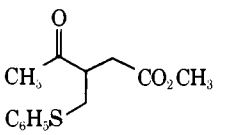
study of conjugate addition reactions with **29b** and **31**, we have determined that selective addition can be realized by simple control of reaction conditions. Treatment of keto diester **29b** with benzenethiol and triethylamine in refluxing ethanol gives only adduct **32**. In contrast, only adduct **33** is obtained on treatment of **29b** and benzenethiol with a catalytic amount of triethylamine. Heating an ethanol solution of **33** and triethylamine produces **32**, presumably through elimination of benzenethiol from **33**, isomerization to **31**, and readdition of benzenethiol. Thus, effective kinetic and equilibrium control in Michael addition to **29b–31** is possible.

Thermolysis of methyl ester pseudoacid **30d** under vacuum gives vinyl ketone **34** (76% distilled yield). A possible mechanism for this conversion involves isomerization of **30d** to **35** followed by decarboxylation of **35** to give **34**. As expected,



34, R = H
35, R = CO_2H



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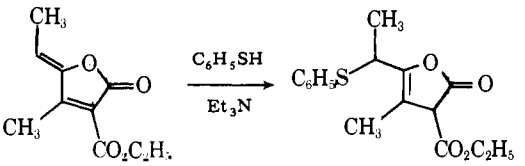
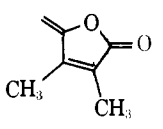
reaction of **34** with benzenethiol and a catalytic amount of triethylamine gives Michael adduct **36** in excellent yield.

Annelation Studies. Our approach to the synthesis of sesquiterpene lactones is centered on the ability of butenolide **1a** to function as a 1,6-Michael acceptor. Numerous 1,6-Michael additions to butadiene esters[30] have been reported; however, the extreme instability of butenolide **1a** to a variety of bases suggests that **1a** will not be useful in situations requiring classical Michael reaction conditions. In fact, even attempted addition of benzenethiol catalyzed by a trace of triethylamine results in instantaneous polymerization. By contrast, we have reported that butenolide **37** undergoes nearly instantaneous 1,6 addition of benzenethiol to give **38**.[23]



37 **38**

Nevertheless, we felt that base-catalyzed additions should not be excluded from consideration, and therefore butenolide **39**[31] was selected as a suitable model compound for 1,6-addition studies. Treatment of a solution of **39** and 2-methyl-1,3-cyclohexanedione in *tert*-butyl alcohol with tetramethylguanidine results in formation of the 1,6 adduct **40** in ~50%



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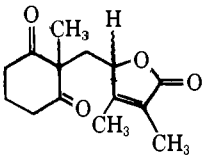


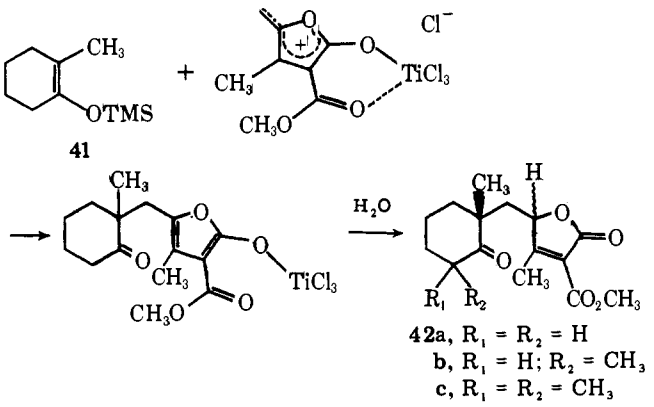
40

yield.[32] Attempts to perform a 1,6 addition with butenolide **1a** and 2-methyl-1,3-cyclohexanedione using similar conditions, and with a variety of nonnucleophilic amine bases, resulted in polymerization of **1a** and no trace of the corresponding adduct.

Mukaiyama and co-workers have shown that silyl enol ethers react with a variety of carbonyl-containing compounds in the presence of titanium tetrachloride; for example, ketones lead to β-hydroxy ketones and α,β-unsaturated ketones give 1,5-diketones.[33] We have found that butenolide **1a** and silyl enol ethers undergo a remarkably rapid reaction with titanium tetrachloride to give 1,7-dicarbonyl compounds. This is the first report of a 1,6-Michael addition promoted by titanium tetrachloride.[9]

Treatment of a methylene chloride solution of titanium tetrachloride and butenolide **1a** at −78 °C with silyl enol ether **41**,[34] followed by quenching the reaction mixture with aqueous

Scheme II



41

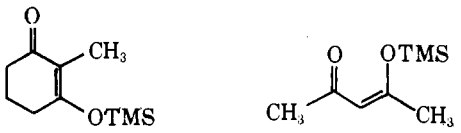
42a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$

potassium carbonate after 4 min, affords lactone **42a**, isolated as a crystalline mixture of diastereoisomers (55%, Scheme II).

In cases where Michael addition involves the use of sensitive compounds, Mukaiyama discovered that a mixed reagent derived from titanium tetrachloride and titanium tetraisopropoxide is advantageous.[35] Reaction of **1a** with **41** in the presence of titanium tetrachloride and titanium isopropoxide gives lactone **42a** in approximately 50% yield. Since there was no particular advantage in using the mixed reagent, titanium tetrachloride alone was used in further studies with **1a**.

We have examined the utility of silyl enol ether additions to butenolide **1a** within the context of eudesmane sesquiterpene total synthesis. Whereas silyl enol ethers of alkyl-substituted cyclohexanones give good results, those derived from β-dicarbonyl or β-ketonitrile compounds do not lead to addition. Thus, **42b** and **42c** are available from reaction of **1a** with the silyl enol ethers of 2,6-dimethylcyclohexanone and 2,2,6-trimethylcyclohexanone, respectively.

Silyl enol ethers **43**,[36] **44**,[37] and **45** are prepared by a procedure similar to that reported by House and co-workers;[34] **46** is prepared by addition of isoxazole **47** to a solution of lithium



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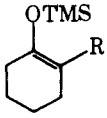
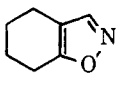


45, R = $CO_2C_2H_5$
46, R = CN



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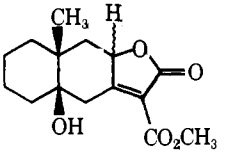
diisopropylamide in THF. Using a variety of conditions, silyl enol ethers **43–46** failed to give the corresponding adducts when reacted with **1a** and titanium tetrachloride. The failure of these silyl enol ethers to undergo the desired additions lends support for the mechanism of 1,6 addition proposed in Scheme II. The electron-withdrawing substituent (carbonyl group or nitrile) on the silyl enol ether double bond apparently makes the double bond much less susceptible to electrophilic attack by the proposed butenolide-$TiCl_4$ intermediate. In this regard, it is interesting to note that silyl enol ether **43** will not undergo $TiCl_4$-promoted 1,4 addition to chalcone (see Experimental Section).[35]

The annelation of the cyclohexanone ring is completed by treatment of **42a** with potassium carbonate in aqueous methanol to afford a crystalline mixture of diastereoisomeric alcohols **48** in nearly quantitative yield. The stereochemistry of **48** is proposed in accord with the well-documented stereochemical outcome of the Robinson annelation products from α-substituted cyclohexanones and vinyl ketones.[38]

Dehydration of **48** in phosphorus pentoxide-methanesulfonic acid (1:10 solution by weight) at room temperature gives a mixture of diastereoisomeric diene lactones **49** and **49a** in 60% yield. Treatment of this mixture with a trace of potassium carbonate in anhydrous methanol gives mainly one diaste-



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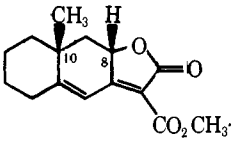

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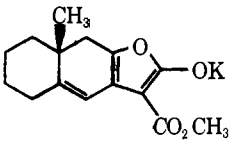


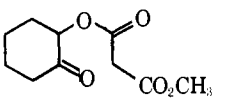
50

reoisomer **49** (95:5) in nearly quantitative yield. The epimerization undoubtedly proceeds via enolate **50** because complete exchange of the proton at C(8) is observed when diene lactone is treated with a trace of potassium carbonate in methanol-d_1.

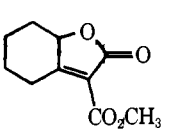
The stereochemical assignment in **49** is based on a large nuclear Overhauser effect observed in a ^1H NMR double resonance experiment.[39] Irradiation of the C(10) methyl resonance in the spectrum of **49** results in a 25% enhancement of the intensity of the resonance due to the methine hydrogen at C(8), indicating a cis relationship between these two substituents.

A more efficient procedure for preparation of large quantities of diene lactone **49** was developed. Extension of the $TiCl_4$-promoted Michael reaction from 4 to 30 min, and reaction of the resulting adduct **42a** without purification with potassium carbonate in methanol, gives diol mixture **48** in 65% yield. Dehydration of **48** with acetic anhydride-sodium acetate produces a mixture of diene lactones in which **49** largely predominates. Recrystallization of **49** followed by epimerization of the material retained in the mother liquor gives an 80% yield of pure **49**. Thus, the linear tricyclic lactone **49** can be obtained in 52% overall yield from equivalent amounts of butenolide **1a** and silyl enol ether **41**.

An alternative approach to the synthesis of fused-ring α-carbalkoxy-$\Delta^{\alpha,\beta}$-butenolides was briefly explored. In analogy with a reported synthesis of 3,5,5-trisubstituted 2(5*H*)-furanones,[40] α-bromocyclohexanone[41] reacts with potassium methyl malonate[42] in refluxing benzene solution with 18-crown-6 to give lactone **52** in 63% yield. Presumably, keto ester **51** is an intermediate and subsequent cyclization-dehydration



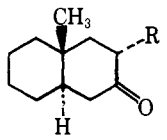
51



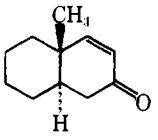
52

gives **52**.

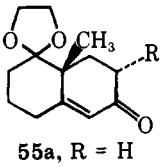
This relatively simple methodology could not successfully be applied to more structurally complex systems. Reaction of bromo ketone **53a**[43] with potassium methyl malonate under conditions used to prepare **52** resulted in none of the desired tricyclic lactone; similar results were obtained with bromo ketone **55b**. It is noteworthy that bromo ketone **53a** reacts with potassium acetate in the presence of 18-crown-6 to give a mixture of α-acetoxy ketone **53b**[44] and enone **54**[45] (85:15, respectively).



53a, R = Br
b, R = $OCOCH_3$

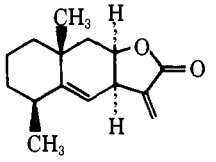


54



55a, R = H
b, R = Br

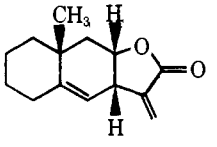
Eudesmane Sesquiterpene Total Synthesis. Dihydrocallitrisin (**3**) is a new sesquiterpene lactone isolated by Carman and Brecknell from the heartwood of *Callitris columellaris*.[46] The structure of **3** is extremely interesting because of the novel stereochemical relationship between C(7), C(8), and C(10), which differs from that usually associated with the eudesmane series as noted for alantolactone (**4a**).[10] However, definitive



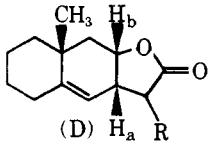
4a

evidence for assignment of stereochemistry to dihydrocallitrisin was not available. A total synthesis of **3** would, therefore, provide a desirable confirmation of structure and, further, demonstrate the efficacy of our annelation approach to the sesquiterpene lactones. In this regard, the tricyclic lactone **49** appeared to be a particularly useful intermediate for a total synthesis of **3**. Also envisioned was the conversion of **49** to the stereochemically related and potentially active[47] 7,8-epialantolactone (**4**) and 7,8-epiisoalantolactone (**5**).

Synthesis of *dl*-7,8-Epialantolactone (4). The synthesis of *dl*-7,8-epialantolactone (**4**) from **49** or a related compound required the development of a cis-fused α-methylene-γ-butyrolactone ring system. To this end, we studied the conversion of **49** to **56**. The conjugate reduction of alkylidenemalonic esters has been carried out with sodium borohydride,[48] lithium aluminum hydride,[49] and sodium cyanoborohydride,[50]



56



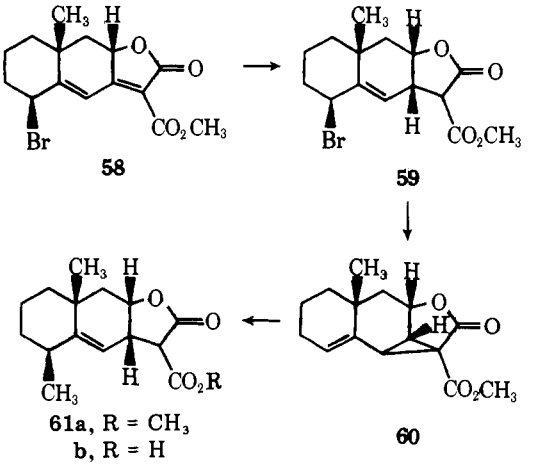
57a, R = CO_2CH_3
b, R = CO_2H
c, R = CH_2OH

and indeed treatment of **49** with sodium borohydride gives lactone **57a** in essentially quantitative yield. Furthermore, exclusive incorporation of deuterium at C(7) in **57** can be achieved by reduction with sodium borodeuteride. Diene lactone **49** also undergoes conjugate reduction with sodium bis(2-methoxyethoxy)aluminum hydride, diisobutylaluminum hydride, and lithium tri-*tert*-butoxyaluminum hydride.

The assignment of stereochemistry of the lactone ring fusion in **57a** rests on ^1H NMR spectral data and inferential crystallographic analysis of a related compound (vide infra, **4**). Herz and co-workers report that the vicinal coupling constant for bridgehead protons in ring-fused γ-lactones is generally $\leq$8–9 Hz for a cis fusion and >10 Hz for a trans fusion.[51] The vicinal coupling constant, $J_{a,b}$ of 7.5 Hz in the ^1H NMR spectrum of **57a** strongly suggests the presence of a cis-lactone fusion.

A variety of methods are available for the conversion of α-carboalkoxy lactones to α-methylene lactones.[8a,b] Here, the method of choice initially involves hydrolysis of **57a** with aqueous methanolic sodium hydroxide followed by acidification to give lactone acid **57b**. Treatment of **57b** with formalin-diethylamine followed by sodium acetate-acetic acid[52]

Scheme III



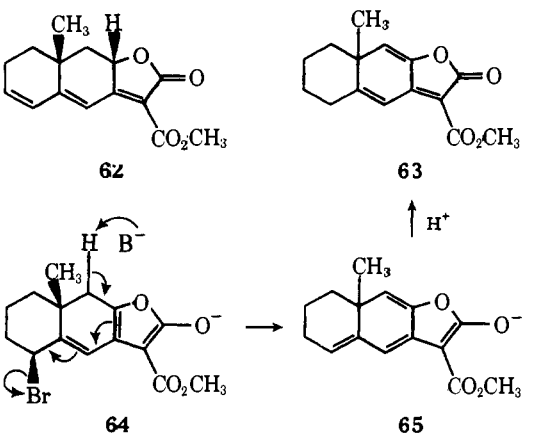
gives α-methylene-γ-butyrolactone **56** in an overall yield of 70% from diene lactone **49**. In a related experiment, reduction of **57b** with sodium borohydride in ethanol solution, followed by acidification, gives α-hydroxymethyl lactone **57c** in high yield; the conversion of **57c** to **56** using a literature procedure should be possible.[8a,b]

An obvious approach to *dl*-7,8-epialantolactone (**4**) would involve the previously discussed Michael adduct **42b**; however, cyclization of **42b** to the required linear tricyclic lactone proved impossible, presumably as a result of unfavorable steric interaction centered around the additional methyl substituent at C(4). Fortunately, we discovered that diene lactone **49** undergoes selective bromination at C(4) with *N*-bromosuccinimide[53] in refluxing carbon tetrachloride to give bromo diene **58** in 99% yield. The stereochemistry at C(4) follows from a comparison of chemical shift data for the C(10) methyl substituent in **58** (δ 1.66) and **49** (1.34); the dramatic downfield shift of the C(10) methyl resonance in **58** must be the result of deshielding by the axial bromine atom.

Bromo diene **58** undergoes an elimination of HBr when treated with 1,5-diazabicyclo[4.3.0]non-5-ene to give enol lactone **63** instead of the fully conjugated triene **62**. Presumably HBr elimination occurs from enolate **64** as shown and protonation of the resulting enolate **65** gives **63**. Enol lactone **63** may prove useful in future studies of eudesmanolide synthesis; inversion of stereochemistry at C(8) in **49** should be possible by stereoselective reduction of **63** or a derivative.

The cis-fused lactone **59** is obtained by conjugate reduction of bromo diene **58**. In this case, the instability of **58** to base (in retrospect, also the instability of the product; cf. **59** → **60**) suggested the use of sodium cyanoborohydride in ethanolic hydrogen chloride–THF solution and under these conditions **59** is isolated in 97% yield (Scheme III).

Bromocyclohexanes have been reported to undergo substitution with lithium dimethylcuprate.[54] However, the reaction



is nonstereospecific and competing elimination and reduction also occur. Treatment of allylic bromide **59** with lithium dimethylcuprate in ether solution gives a complex mixture of products which contains little if any **61**.

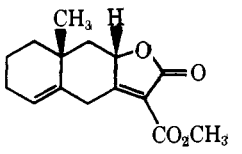
Activated vinylcyclopropanes undergo vinylogous homoconjugate addition with lithium dialkylcuprates.[55] The conversion of **59** to vinylcyclopropane **60** requires an internal S_N2'-like displacement of bromide ion from the enolate of **59**. This overall elimination does indeed occur on reaction of **59** with 1,5-diazabicyclo[4.3.0]non-5-ene in benzene solution at room temperature to give highly crystalline **60** in 95% isolated yield.[56] The preparation of activated, fused-ring vinylcyclopropanes by this method complements the well-explored diazo ester addition to proximate olefins.[57]

Addition of lithium dimethylcuprate to vinylcyclopropane **60** gives the desired 1,7-addition product **61a** in 75% yield. Conversion of **61a** to *dl*-7,8-epialantolactone (**4**) is accomplished by hydrolysis to the lactone acid **61b** and α-methylenation of **61b** (formalin-diethylamine followed by sodium acetate-acetic acid). The structure of **4**, thus obtained in 70% yield, was firmly established by an X-ray crystallographic study.[9b]

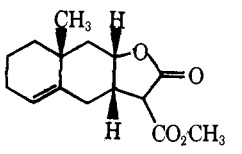
The stereochemistry of addition of lithium dimethylcuprate to **60** is especially noteworthy. Prior to this work, we were not aware of any test of stereochemistry in the addition of organocuprates to activated vinylcyclopropanes. On the other hand, there is a good deal of experimental evidence suggesting that the preferred mode of addition of organocuprates to α,β-unsaturated ketones is that favoring antiparallel approach of the reagent to the π system of the enone.[58] In cyclohexenone ring systems, the stereochemical result is generally axial substitution.[59] We note that the addition of lithium dimethylcuprate to vinylcyclopropane **60** results in apparently exclusive axial substitution at C(4).

Synthesis of *dl*-Dihydrocallitrisin (3) and *dl*-Epiisoalantolactone (5). With functionalization at C(4) already present, bromo diene **58** seemed to be an attractive intermediate for synthesis of **3** and **5**. We planned to convert the C(4) bromide to a ketone carbonyl group, from which the exo-methylene carbon would be introduced via a Wittig reaction. To this end, **58** was subjected to reductive debromination[60] with zinc dust in THF containing acetic acid. Under these conditions, the unconjugated diene lactone **66** can be isolated reproducibly in 97% yield with only 3–4% contamination by the fully conjugated diene lactone **49**.

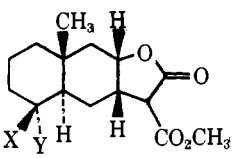
Hydroboration of **66** with borane-methyl sulfide (BMS) in ethyl acetate followed by oxidation with hydrogen peroxide-sodium acetate gives trans decalol **68a** as the major product (32%), together with cis decalol **69a** (~5%) and an isomeric alcohol (~5%), which is assigned structure **70** on the basis of its unreactivity to Jones reagent. These alcohols are separated by silica gel chromatography and Jones oxidation of **68a** so purified gives trans-fused ketone **68b** in 93% yield.



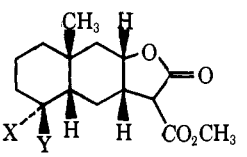
66



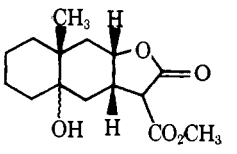
67



68a, X = H; Y = OH
b, X = Y = O



69a, X = H; Y = OH
b, X = Y = O



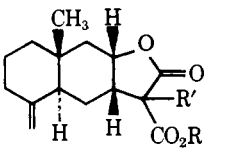
70

We were pleased to find that the major product of hydroboration of **66** is the trans-fused decalol **68a**; however, the attendant difficult separation of products and low yield necessitated a search for a more efficient reaction sequence to **68b**.[61] Olefinic lactone **67**, in which the axial substituent at C(7) should effectively block the β face of the remaining carbon-carbon double bond, was expected to provide a route to the cis-fused ketone **69b**.

Conjugate reduction of **66** with sodium cyanoborohydride gives the desired olefinic lactone in 95% yield and hydroboration-oxidation of **66** affords cis decalol **69a** (61% isolated) and only a trace of the trans decalol **68a**. The cis-fused keto lactone **69b** is obtained in 94% yield by Jones oxidation of **69a**. Epimerization of **69b** with sodium methoxide in refluxing methanol solution gives a mixture of **68b** and **69b** (5:1, respectively) in nearly quantitative yield.[62] Treatment of pure **68b** under identical conditions gives the same 5:1 mixture of **68b** and **69b**, indicating that this ratio is the equilibrium mixture.

The stereochemistry of the decalin ring fusion in **68a**, **68b**, **69a**, and **69b** can be assigned with a high degree of confidence by consideration of ^{1}H NMR chemical shift for the C(10) methyl resonance. Generally, the position of the C(10) methyl resonance in a *trans*-10-methyldecalin is at higher field (δ 0.73–0.90) than that of a *cis*-10-methyldecalin (1.05–1.20).[63] Thus, the C(10) methyl resonances of **68a** (0.85) and **68b** (0.82) indicate a *trans*-decalin junction, while those of **69a** (1.05) and **69b** (1.08) suggest a *cis*-decalin junction.

Treatment of keto lactone **68b** with methylenetriphenylphosphorane (3.5 equiv) in THF-HMPA gives the ene lactone **71a** in 86% isolated yield. ^{1}H NMR data is again used to assign



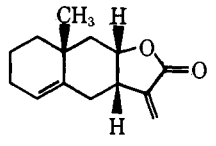
71a, R = CH_3; R' = H
b, R = R' = CH_3
c, R = R' = H

stereochemistry to the decalin ring junction of **71a**. Spectral data for model compounds are available in the literature; the C(10) methyl resonance of 1-methylene-*cis*-10-methyldecalin is δ 0.87, while that of 1-methylene-*trans*-10-methyldecalin is δ 0.73.[63a] For **71a**, the C(10) methyl resonance appears at δ 0.74, suggesting that a trans ring fusion is present.

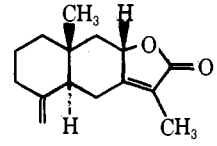
A mixture of diastereoisomers **71b** is obtained on methylation of the enolate of **71a** (NaH, CH_3I) in THF solution. Decarbomethoxylation of **71b** with sodium cyanide in HMPA (80 °C, 1 h)[64] directly affords *dl*-dihydrocallitrisin (**3**) in 85% overall yield from ene lactone **71a**. The ^{1}H NMR ($CDCl_3$ and C_6D_6 solvents) and infrared spectra together with the low-resolution mass spectral fragmentation pattern (electron impact) of synthetic **3** are identical with those of the natural material kindly supplied by Dr. R. M. Carman. In addition, synthetic and natural dihydrocallitrisin have identical retention times on three GLC columns, namely, SE-30 (180 °C), DC 710 (220 °C), and DEGS (190 °C, retention time ~50 min).[65] Thus, the novel structure of dihydrocallitrisin is confirmed by total synthesis.[9c] The overall isolated yield of **3** from diene lactone **49** is 36%.

Ene lactone **71a** also can be converted to *dl*-7,8-epiisoalantolactone (**5**) in 73% yield by hydrolysis to the lactone acid

71c (aqueous methanolic sodium hydroxide followed by acidification) and the usual α-methylenation sequence. In a similar fashion, olefinic lactone **67** is converted to the tricyclic α-methylene-γ-lactone **72**.



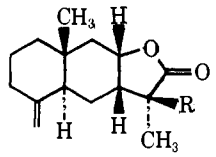
72



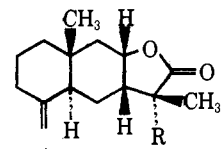
73

Synthesis of Atractylon (6). A total synthesis of the furanosesquiterpene atractylon (**6**)[66] has been accomplished by reduction of lactone **73**.[12b] Conversion of *dl*-dihydrocallitrisin (**3**) to lactone **73** would, therefore, constitute a total synthesis of **6**. In this regard, we expected that sulfenylation of the enolate derived from **3** would occur mainly from the sterically more accessible approach to give **74a**.[67] Conversion of **74a** to sulfoxide **74b** and elimination would then be expected to give mainly the endocyclic ene lactone **73**.[68]

Dihydrocallitrisin (**3**) was added to a THF solution of LDA at −78 °C and, after 1 h, diphenyl disulfide (2 equiv) in THF containing HMPA (1.2 equiv) was added. These reaction conditions give a crystalline mixture of α-phenylsulfinyl lactones **74a** and **75a** (70:30, respectively) in 95% isolated yield.



74a, R = SPh
b, R = SOPh

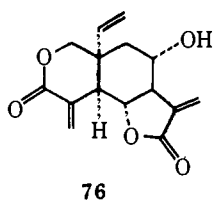


75a, R = SPh
b, R = SOPh

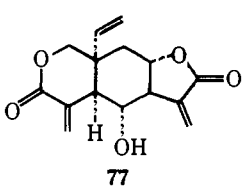
Unfortunately, this product distribution could not be improved by modification of reaction conditions; substitution of phenyl phenylthiosulfonate[69] for diphenyl disulfide gives a 60:40 mixture of **74a** and **74b**, respectively.

Oxidation of the mixture of sulfides **74a** and **75a** with excess sodium metaperiodate[70a] in aqueous THF solution at 25 °C gives not only the expected mixture of sulfoxides **74b** and **75b**, but also lactone **73**. Pyrolysis of this mixture in refluxing benzene solution containing powdered calcium carbonate[70b] followed by chromatography on alumina gives *dl*-7,8-epiisolantolactone (**5**) and lactone **73** (60% isolated yield; mp 101–102 °C, lit. 102–103 °C).[12b] The ^{1}H NMR and IR spectra of **73** were in full accord with published spectra.[66] Reduction of lactone **73** with diisobutylaluminum hydride by the method of Minato and co-workers[12b] gives *dl*-atractylon (**6**), for which the ^{1}H NMR spectrum is identical with that of the natural material.[71]

Studies Directed toward a Synthesis of Vernolepin and Vernomenin. Vernolepin (**76**) and vernomenin (**77**), isolated from *Vernonia hymemolepis*, show significant cytotoxicity.



76

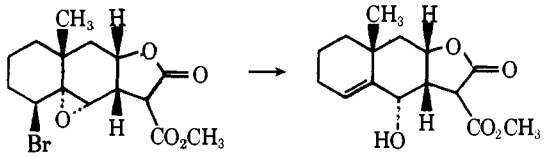


77

Vernolepin has demonstrated in vivo tumor-inhibitory activity against Walker intramuscular carcinosarcoma in rats.[72] Intense synthetic activity directed toward **76** has resulted in reports of four total syntheses of vernolepin (**76**).[73]

In order to utilize the annelation approach in a synthesis of **76** and **77**, it is necessary to develop the means for efficient introduction of the C(6) oxygen functionality. This we have accomplished in model studies which center on the conversion of allylic bromide **59** to transposed allylic alcohols **79** and **83a** with complete stereochemical control. The results of our study follow.

Epoxidation of **59** with *m*-chloroperbenzoic acid in methylene chloride solution gives bromo epoxide **78** in 91% yield. The epoxidation is presumed to occur from the least hindered side of the C(5,6) double bond to provide the stereochemistry indicated in formula **78**. Reductive elimination of **78** by



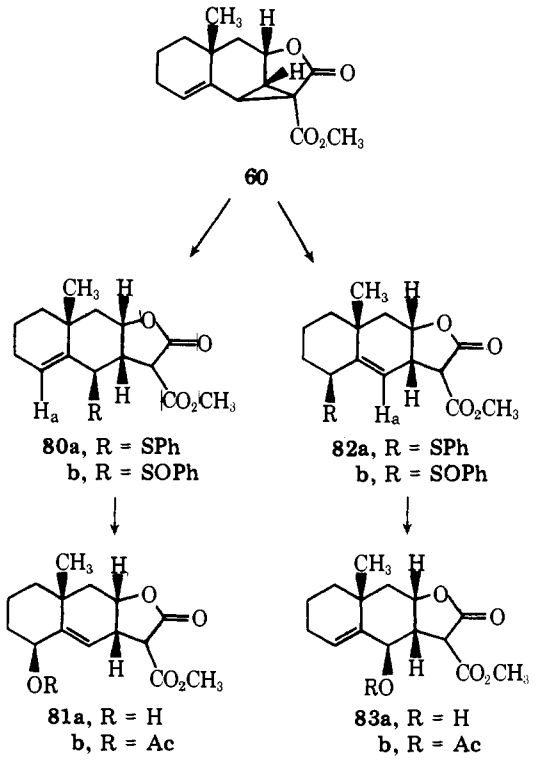
78 → **79**

treatment with zinc-silver couple[74] in THF solution containing acetic acid gives the expected allylic alcohol **79** in essentially quantitative yield.

We have already detailed the conversion of **59** to vinylcyclopropane **60**. With regard to the desired conversion of **59** to allylic alcohol **83a** we note that mercaptans undergo homoconjugate and vinylogous homoconjugate addition to activated vinylcyclopropanes depending upon the reaction conditions; base catalysis results in 1,5 addition, while free-radical conditions lead to 1,7 addition.[75]

As expected, treatment of **60** with benzenethiol and 1,5-diazabicyclo[4.3.0]non-5-ene in benzene solution gives 1,5 adduct **80a** in excellent yield (Scheme IV). The ^{1}H NMR spectrum of **80a** displays a triplet at δ 5.69 (J = 3.6 Hz) for H_a, which serves to confirm the 1,5 mode of addition. Oxidation of **80a** with *m*-chloroperbenzoic acid at −78 °C gives a mixture of diastereoisomeric sulfoxides **80b** and treatment of **80b** with trimethyl phosphite in methanol solution at 50 °C results in [2,3]-sigmatropic rearrangement and formation of allylic alcohol **81a**. Acetylation of **81a** with acetic anhydride in pyridine solution provides allylic acetate **81b** in 67% overall yield from **60**. Because the [2,3]-sigmatropic rearrangement of allylic

Scheme IV



60

80a, R = SPh
b, R = SOPh

82a, R = SPh
b, R = SOPh

81a, R = H
b, R = Ac

83a, R = H
b, R = Ac

sulfoxide proceeds in syn fashion,[76] the stereochemistry of **81b** must be as formulated.

Addition of benzenethiol to **60** in benzene solution in the presence of a trace of 2,2′-azobisisobutyronitrile gives exclusively the 1,7 adduct **82a**. The 1,7 mode of addition is confirmed by the presence of a broadened doublet at δ 5.12 (J = 4 Hz) for H_a in the ^{1}H NMR spectrum of **82a**. Stereochemistry at C(4) follows from a comparison of the ^{1}H NMR chemical shift for the C(10) methyl group in **57a** (δ 1.12) and **82a** (δ 1.42); the downfield shift of the C(10) methyl resonance for **82a** relative to that for **57a** must be the result of deshielding by the axial phenylthiol group. Thus, 1,7 addition of benzenethiol to **60** results in axial substitution as did the addition of lithium dimethylcuprate.

In the manner described for **80a**, oxidation of **82a** and reductive rearrangement of the resulting mixture of diastereoisomeric sulfoxides **82b** gives allylic alcohol **83a**. Acetylation of **83a** and chromatography affords allylic acetate **83b** in 50% overall yield from **60**. Inspection of a Drieding stereomodel of **83b** reveals that the proton at C(6) is orthogonal to that at C(7); in accord with this observation, we find that the resonance for the proton at C(6) appears as a singlet at δ 5.26.

Conclusion

The annelation approach to eudesmane sesquiterpenes, for which butenolide **1a** serves as the annelation reagent, has been demonstrated to be highly effective. In its present state of development, the method appears particularly suited to synthesis of sesquiterpenes with the relative stereochemistry at C(7), C(8), and C(10) that is present in dihydrocallitrisin (**3**). Adaptation of these methods to the synthesis of the structurally more complex vernolepin (**76**) and vernomenin (**77**) seems promising.

Experimental Section

General. ^{1}H NMR spectra were obtained on a Varian A-60A or a Varian EM-390 NMR spectrometer using tetramethylsilane as an internal standard. ^{1}H NMR decoupling experiments were recorded on a Varian EM 390 NMR spectrometer. Low-resolution chemical ionization or electron impact mass spectra were obtained with a Finnigan 3300 gas chromatograph–mass spectrometer or an AEI-MS-902 mass spectrometer, while high-resolution mass measurements were obtained with an AEI-MS-902 mass spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 137-B infrared spectrophotometer as a thin film (film) or in chloroform solution ($CHCl_3$).

Melting-point determinations were performed using a Thomas-Hoover capillary melting point apparatus in open capillaries and are uncorrected. Microanalyses were carried out by Spang Microanalytical Laboratory, Eagle Harbor, Mich., or Galbraith Laboratories, Inc., Knoxville, Tenn.

Tetrahydrofuran (THF) was predried over molecular sieves and deaerated with a stream of prepurified nitrogen gas before distillation from potassium metal under a nitrogen atmosphere using benzophenone ketyl as indicator.

Hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure and stored over 4 A molecular sieves under a nitrogen atmosphere. Ethyl acetate was distilled from calcium hydride and stored over 4 A molecular sieves. Triethylamine was distilled from lithium aluminum hydride and stored over 4 A molecular sieves. Methylene chloride was distilled from phosphorus pentoxide and stored over 4 A molecular sieves. Pyridine was distilled from barium hydroxide and stored over 3 A sieves.

Commercially available "absolute" ether was used without further purification and methanol was distilled from magnesium turnings.

Preparation of Methyl 2-Carbomethoxy-3-methyl-4-oxo-2-pentenoate (29a). A solution of titanium tetrachloride (22 mL, 0.20 mol) in absolute carbon tetrachloride (50 mL) was added dropwise to dry THF (400 mL) under a calcium sulfate drying tube with efficient mechanical stirring and ice-bath cooling over 1 h. To the resulting bright yellow suspension was added a solution of dimethyl malonate (0.1 mol) and 2,3-butanedione (0.11 mol) in dry THF (50 mL) over 1.5 h, after which a solution of dry pyridine (0.4 mol) in THF (70 mL) was added over 4 h. The resulting mixture was stirred at ice-bath temperature for an additional 12 h and then at room temperature for 52 h. The reaction mixture was quenched with water (100 mL) and ether (100 mL) and the layers were separated. The aqueous layer was extracted with ether and the combined organic fractions were washed with 0.5 N hydrochloric acid and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue fractionally distilled to give **29a** (4.7 g, 24%): bp 87–90 °C (0.15 mm); IR (film) 5.78 and 6.05 μ; ^{1}H NMR δ ($CDCl_3$) 2.07 (3 H, singlet), 2.36 (3 H, singlet), 3.77 (3 H, singlet), and 3.87 (3 H, singlet).

Preparation of Ethyl 2-Carbethoxy-3-methyl-4-oxo-2-pentenoate (29b). Keto diester **29b** was prepared from diethyl malonate and 2,3-butanedione by the method described for the preparation of keto diester **29a**. Fractional distillation gave **29b** (30%): bp 98–100 °C (0.10 mm); IR (film) 5.78 and 6.05 μ; ^{1}H NMR δ ($CDCl_3$) 1.25 (3 H, triplet, J = 7 Hz), 1.31 (3 H, triplet, J = 7 Hz), 2.03 (3 H, singlet), 2.33 (3 H, singlet), 4.20 (2 H, quartet, J = 7 Hz), and 4.30 (2 H, quartet, J = 7 Hz); electron impact mass spectrum m/e 228.

Preparation of 2,5-Dihydro-5-hydroxy-4,5-dimethyl-2-oxo-3-furancarboxylic Acid (30c). A solution of titanium tetrachloride (44 mL, 0.4 mol) in absolute carbon tetrachloride (100 mL) was added dropwise to THF (800 mL, Aldrich, 99.5%, Gold Label, stored over 4 A molecular sieves) under a calcium sulfate drying tube with efficient mechanical stirring and ice-bath cooling over 1 h. To the resulting bright yellow suspension was added a solution of malonic acid (0.20 mol) and freshly distilled 2,3-butanedione (0.22 mol) in THF (100 mL) over 2 h, after which a solution of dry pyridine (0.8 mol) in THF (140 mL) was added, via syringe pump, over 4–5 h. The resulting mixture was stirred at ice-bath temperature for an additional 8 h and then at room temperature for 72 h. The reaction was quenched with water (200 mL) and ether (200 mL) and the layers were separated. The aqueous layer was saturated with sodium chloride and extracted with THF (2 × 150 mL). The combined organic fractions were washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure and recrystallization of the residue from water (decolorized with Norit A) gave **30c** as a colorless solid (30.6 g, 89%): mp 101–117 °C; IR (Nujol) 2.94, 3.12, and 5.80 μ; ^{1}H NMR δ (Me_2SO-d_6) 1.54 (3 H, singlet) and 2.23 (3 H, singlet).

Anal. Calcd for $C_7H_9O_5$: C, 48.84; H, 4.68; O, 46.67. Found: C, 46.29, 46.20; H, 4.99, 4.94. Analysis correct for $C_7H_8O_5 \cdot {}^1/_2H_2O$.

Preparation of 2,5-Dihydro-5-hydroxy-4,5-dimethyl-2-oxo-3-furancarboxylic Acid Methyl Ester (30d). To a stirred suspension of pseudoacid **30c** (10.0 g, 58 mmol) in ether (100 mL) was slowly added an ethereal solution of diazomethane (1.0 equiv). This esterification reaction can be conveniently followed by ^{1}H NMR analysis. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give **30d** as a very viscous oil which crystallized upon standing. Keto diester **29a**, if present, can be removed by washing the crystalline material with pentane to give **30d** (10.15 g, 94%) of sufficient purity for further operations. Recrystallization from water gave **30d**: mp 56 °C; IR ($CHCl_3$) 2.83, 5.58, 5.75, and 5.93 μ; ^{1}H NMR δ ($CDCl_3$) 1.68 (3 H, singlet), 2.38 (3 H, singlet), and 3.38 (3 H, singlet), and 4.47 (1 H, broad singlet, variable, replaceable on addition of deuterium oxide).

Anal. ($C_8H_{10}O_5$) C, H.

Preparation of 2,5-Dihydro-4-methyl-5-methylene-2-oxo-3-furancarboxylic Acid Methyl Ester (1a). To a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid[26] (25 mL) was added pseudoacid methyl ester **30d** (1.10 g, 5.91 mmol). The resulting mixture was stirred at room temperature under a calcium sulfate drying tube for 1.5 h and then added slowly to water (115 mL). After stirring for 10 min, the resulting mixture was extracted with chloroform (4 × 30 mL) and the combined chloroform fractions were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure, at or below 25 °C, to give butenolide **1a** as a yellow, highly unstable, crystalline solid which does not exhibit a melting point (0.94 g, 95%): IR ($CHCl_3$) 5.58, 5.80, 6.08, and 6.17 μ; ^{1}H NMR δ ($CDCl_3$) 2.50 (3 H, singlet), 3.93 (3 H, singlet), 5.30 (1 H, doublet, J = 4 Hz), and 5.43 (1 H, doublet, J = 4 Hz); electron impact mass spectrum m/e 168.0426.

Preparation of 2,5-Dihydro-4,5-dimethyl-5-methoxy-2-oxo-3-furancarboxylic Acid Methyl Ester (30a). A solution of pseudoacid

30c (14.79 g, 86 mmol) in anhydrous methanol (100 mL) was saturated with hydrogen chloride gas at room temperature. After the solution was stirred overnight, the solvent was removed at reduced pressure, the residue taken up in ether, and the resulting solution washed with 1 N sodium bicarbonate and brine. After the solution was dried over anhydrous magnesium sulfate, removal of the solvent at reduced pressure and distillation gave **30a** which crystallized upon standing (bp 88–90 °C (0.04 mm), 10.2 g, 59%). Recrystallization from aqueous methanol gave an analytical sample: mp 52–53 °C; IR ($CHCl_3$) 5.60, 5.78, and 5.96 μ; ^1H NMR δ ($CDCl_3$) 1.62 (3 H, singlet), 2.32 (3 H, singlet), 3.20 (3 H, singlet), and 3.90 (3 H, singlet).

Anal. ($C_9H_{12}O_5$) C, H.

Preparation of 5-Ethoxy-2,5-dihydro-4,5-dimethyl-2-oxo-3-furancarboxylic Acid Ethyl Ester (30b). A solution of pseudoacid **30c** (2.10 g, 12 mmol) in absolute ethanol (40 mL) was saturated with hydrogen chloride gas at room temperature. After the solution was stirred overnight, water (50 mL) was added and the resulting mixture extracted with ether. The combined ether fractions were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent at reduced pressure and distillation gave **30b** as a pale yellow oil (2.78 g, 63%): bp 87–89 °C (0.05 mm); IR (film) 5.60, 5.80, and 5.98 μ; ^1H NMR δ ($CDCl_3$) 1.20 (3 H, triplet, J = 7 Hz), 1.38 (3 H, triplet, J = 7 Hz), 1.65 (3 H, singlet), 2.33 (3 H, singlet), 3.41 (2 H, multiplet), and 4.37 (2 H, quartet, J = 7 Hz); electron impact mass spectrum m/e 213 ($M^+ - 15$).

Preparation of Ethyl 2-Carbethoxy-3-methylene-4-oxopentanoate (31). A solution of keto diester **29b** (115 mg, 0.5 mmol) and triethylamine (7 μL, 0.1 equiv) in anhydrous ether (1.5 mL) under nitrogen was heated at reflux for 2 h. The solvent was removed at reduced pressure to give an inseparable mixture of keto diester **29b** and vinyl ketone **31** (1:3, respectively) in quantitative yield: ^1H NMR δ ($CDCl_3$) 1.30 (6 H, triplet, J = 7 Hz), 2.42 (3 H, singlet), 4.28 (4 H, quartet, J = 7 Hz), 4.75 (1 H, broad singlet), 6.16 (1 H, broad singlet), and 6.40 (1 H, singlet).

Preparation of Ethyl 2-Carbethoxy-4-oxo-3-(phenylthiomethyl)-pentanoate (32). A solution of keto diester **29b** (1.02 g, 4.47 mmol), benzenethiol (0.50 mL, 1.1 equiv), and triethylamine (0.12 mL, 0.2 equiv) in absolute ethanol (11 mL) under nitrogen was heated at reflux for 11 h. Removal of the solvent at reduced pressure and distillation gave **32** as a nearly colorless oil (1.24 g, 82%): bp 143–146 °C (0.005 mm); IR (film) 5.72, 5.78, 6.28, 13.50, and 14.55 μ; ^1H NMR δ ($CDCl_3$) 1.17 (3 H, triplet, J = 7 Hz), 1.20 (3 H, triplet, J = 7 Hz), 2.26 (3 H, singlet), 2.90–3.71 (3 H, multiplet), 3.92 (1 H, doublet, J = 9 Hz), 4.09 (2 H, quartet, J = 7 Hz), 4.15 (2 H, quartet, J = 7 Hz), and 7.10–7.50 (5 H, multiplet).

Preparation of Ethyl 2-Carbethoxy-3-methyl-4-oxo-3-(phenylthio)pentanoate (33). To a mixture of keto diester **29b** (1.03 g, 4.51 mmol) and benzenethiol (0.70 mL, 1.5 equiv) under nitrogen was added triethylamine (0.30 mL, 0.05 equiv). The resulting mixture was stirred at room temperature for 1 h. Fractional distillation gave **33** as a slightly yellow oil (1.18 g, 77%): IR (film) 5.68, 5.75, 5.84, 13.30, and 14.50 μ; ^1H NMR δ $CDCl_3$) 1.16 (3 H, triplet, J = 7 Hz), 2.40 (3 H, singlet), 4.05 (1 H, singlet), 4.07 (2 H, quartet, J = 7 Hz), 4.32 (2 H, quartet, J = 7 Hz), and 7.23–7.63 (5 H, multiplet).

Conversion of 33 to 32. A solution of **33** (222 mg, 0.66 mmol) and triethylamine (15 μL, 0.15 equiv) in absolute ethanol (4 mL) under nitrogen was heated at reflux for 16 h. Removal of the solvent at reduced pressure gave only **32** in quantitative yield.

Preparation of Methyl 3-Methylene-4-oxopentanoate (34). While under vacuum, methyl ester pseudoacid **30d** (720 mg, 3.88 mmol) was heated to approximately 140 °C, after which **34** distilled as a colorless liquid (420 mg, 76%): bp 40 °C (0.05 mm); IR (film) 5.74, 5.96, and 6.13 μ; ^1H NMR δ ($CDCl_3$) 2.37 (3 H, singlet), 3.31 (2 H, doublet, J = 1 Hz), 3.69 (3 H, singlet), 5.98 (1 H, triplet, J = 1 Hz), and 6.21 (1 H, singlet).[77]

Anal. ($C_7H_{10}O_3$) C, H.

Preparation of Methyl 4-Oxo-3-(phenylthiomethyl)pentanoate (36). To a solution of vinyl ketone **34** (0.70 g, 4.93 mmol) and benzenethiol (0.59 g, 5.42 mmol) in anhydrous ether (5 mL) under nitrogen was added triethylamine (0.50 g, 0.49 mmol). A mildly exothermic reaction ensued and the resulting mixture was stirred at room temperature for 5 h. The solvent was removed at reduced pressure and the residue distilled to give **36** as a nearly colorless oil (1.05 g, 84%): bp 143–146 °C (0.02 mm); IR (film) 5.75, 5.81, 6.29, 13.45, and 14.50 μ; ^1H NMR δ ($CDCl_3$) 2.33 (3 H, singlet), 2.53–3.33 (5 H, multiplet), 3.65 (3 H, singlet), and 7.13–7.50 (5 H, multiplet); electron impact mass spectrum m/e 252.

Attempted 1,6 Addition of Benzenethiol into Butenolide 1a. A solution of butenolide **1a** (70 mg, 0.42 mmol), absolute methanol (17 μL, 1 equiv), benzenethiol (43 μL), and deuteriochloroform (0.5 mL) was placed in an NMR tube. The ^1H NMR spectrum of this mixture verified that each component was still intact. Triethylamine (0.6 μL, 0.01 equiv) was added and the ^1H NMR spectrum, recorded immediately after the addition of triethylamine, indicated that butenolide **1a** decomposed and none of the expected 1,6-addition product was present.

Attempted 1,6 Addition of 2-Methyl-1,3-cyclohexanedione to Butenolide 1a. A mixture of butenolide **1a** (144 mg, 0.86 mmol), 2-methyl-1,3-cyclohexanedione (120 mg, 0.95 mmol), and tetramethylguanidine (10 μL) in dry *tert*-butyl alcohol (2.5 mL) under nitrogen was heated at reflux for 12 h. After cooling, the mixture was extracted with ether and the combined ether fractions were washed with saturated sodium carbonate and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a residue whose ^1H NMR spectrum indicated that decomposition of butenolide **1a** had occurred.

Preparation of 2,5-Dihydro-4-methyl-5-[(1-methyl-2-oxocyclohexyl)methyl]-2-oxo-3-furancarboxylic Acid Methyl Ester (42a). Procedure A. To a solution of titanium tetrachloride (0.98 mL, 8.92 mmol) in dry methylene chloride (50 mL) at −78 °C under nitrogen was rapidly added a solution of butenolide **1a** (1.50 g, 8.92 mmol) in methylene chloride (8 mL). After 2 min, a solution of silyl enol ether **41**[34] (1.64 g, 8.92 mmol) in methylene chloride (5 mL) was rapidly added. After stirring at −78 °C for 4 min, the deep blue mixture was quenched with aqueous potassium carbonate (1.12 g in 50 mL of water). Ether was added and the resulting mixture was filtered through a Celite pad. The filtrate was extracted with ether and the combined ether fractions were washed with water. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed on silica gel (chloroform) to give **42a** as a colorless, crystalline mixture of diastereomers (1.23 g, 50%): IR ($CHCl_3$) 5.62, 5.80, 5.85, and 6.05 μ; ^1H NMR δ ($CHCl_3$) 1.24 (1.2 H, singlet), 1.37 (1.8 H, singlet), 1.47–2.77 (10 H, multiplet), 2.47 (3 H, singlet), 3.87 (3 H, singlet), 4.86 (0.4 H, doublet of doublet, J = 1.7, 9.5 Hz), and 5.07 (0.6 H, doublet of doublet, J = 1.7, 9.5 Hz); electron impact mass spectrum m/e 280.

Procedure B. To a solution of titanium tetrachloride (0.33 mL, 3.0 mmol) in dry methylene chloride (15 mL) under nitrogen was added titanium tetraisopropoxide (0.89 mL, 3.0 mmol). After stirring at room temperature for 25 min, the solution was cooled to −78 °C and a solution of butenolide **1a** (0.50 g, 3.0 mmol) in methylene chloride (3.5 mL) was rapidly added. After 7 min, a solution of silyl enol ether **41** (0.55 g, 3.0 mmol) in methylene chloride (3 mL) was added. The resulting dark brown mixture was stirred at −78 °C for 1 h and quenched with aqueous potassium carbonate (0.80 g in 15 mL of water). Ether was added and the mixture was acidified with concentrated hydrochloric acid and extracted with ether. The combined ether fractions were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure and the residue chromatographed on silica gel (chloroform) to give keto lactone **42a** (approximately 50% yield).

Preparation of 2,5-Dihydro-4-methyl-5-[(1,3-dimethyl-2-oxocyclohexyl)methyl]-2-oxo-3-furancarboxylic Acid Methyl Ester (42b). Keto lactone **42b** was prepared from butenolide **1a** in the manner described for the preparation of keto lactone **42a** (procedure A). Chromatography on silica gel (chloroform) gave keto lactone **42a**, a mixture of diastereomers, as a colorless oil (32%): IR ($CHCl_3$) 5.62, 5.81, 5.87, and 6.05 μ; ^1H NMR δ ($CDCl_3$) 0.88–2.83 (18 H, multiplet), 3.90 (3 H, singlet), 4.89 (0.5 H, broadened doublet, J = 8.8 Hz), and 5.15 (0.5 H, broadened doublet, J = 8.3 Hz).

Preparation of 2,5-Dihydro-4-methyl-5-[(1,3,3-trimethyl-2-oxocyclohexyl)methyl]-2-oxo-3-furancarboxylic Acid Methyl Ester (42c). Keto lactone **42c** was prepared from butenolide **1a** in the manner described for the preparation of keto lactone **42a** (procedure A). Chromatography on silica gel (chloroform) gave **42c** as a crystalline mixture of diastereomers (37%): IR ($CHCl_3$) 5.62, 5.81, 5.92, and 6.03 μ; ^1H NMR δ ($CDCl_3$) 1.00–2.60 (20 H, multiplet), 3.88 (3 H, singlet), 4.64 (0.5 H, doublet of doublet, J = 2, 9.5 Hz), and 5.11 (0.5 H, doublet of doublet, J = 3, 9.5 Hz).

Attempted Addition of Silyl Enol Ether 43 to Chalcone. To a solution of titanium tetrachloride (0.11 mL, 1 mmol) in dry methylene chloride

at −78 °C under nitrogen was added a solution of chalcone (208 mg, 1 mmol) in methylene chloride (3 mL). To the resulting dark brown mixture was added a solution of silyl enol ether **43** (198 mg, 1 mmol) in methylene chloride (3 mL).[35] After stirring at −78 °C for 1.25 h, the reaction mixture was quenched with aqueous potassium carbonate (0.7 g in 15 mL of water) and filtered with the aid of ether. The filtrate was extracted with ether and the combined ether fractions were washed with water and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give chalcone and no trace of the desired adduct.

Preparation of 1-Carbethoxy-2-trimethylsilyloxy-1-cyclohexene (45). To a solution of diisopropylamine (4.06 mL, 28.6 mmol) in dry THF (30 mL) at 0 °C under nitrogen was added 2.5 M *n*-butyllithium (11.47 mL, 28.6 mmol). After 30 min, a solution of ethyl 2-cyclohexanonecarboxylate (4.78 g, 28.1 mmol) in THF (12 mL) was added over 10 min. After the solution was stirred at 0 °C for 30 min, chlorotrimethylsilane (4.28 mL, 33.6 mmol) was added and the mixture was warmed to room temperature for 12 h and heated at reflux for 1 h. The solvent was removed at reduced pressure, pentane was added, and the resulting solution was filtered to remove lithium chloride. Removal of the solvent at reduced pressure and distillation gave silyl enol ether **45** (3.75 g, 55%): bp 115 °C (8 mm); ^{1}H NMR δ ($CDCl_3$) 0.21 (9 H, singlet), 1.27 (3 H, triplet, J = 7 Hz), 1.44–2.47 (8 H, multiplet), and 4.08 (2 H, quartet, J = 7 Hz).

Preparation of 2-Cyano-1-trimethylsilyloxy-1-cyclohexene (46). To a solution of diisopropylamine (3.56 mL, 25 mmol) in dry THF (22 mL) at 0 °C under nitrogen was added 2.45 M *n*-butyllithium (10.25, 25 mmol). After 30 min, a solution of isooxazole **47**[78] (3.0 g, 24.4 mmol) in tetrahydrofuran (12 mL) was added. The resulting deep orange mixture was stirred for 45 min and chlorotrimethylsilane (3.87 mL, 30.5 mmol) was added. The mixture was stirred at 0 °C for 15 min and at room temperature for 3 h. The solvent was removed at reduced pressure, pentane was added, and the resulting solution was filtered to remove lithium chloride. Removal of the solvent at reduced pressure and distillation gave silyl enol ether **46** (3.63 g, 76%): bp 58 °C (0.05 mm); IR (film) 4.52, 6.10, 10.75, and 11.78 μ; ^{1}H NMR δ ($CDCl_3$) 0.20 (9 H, singlet), 1.32–1.88 (4 H, multiplet), and 1.88–2.37 (4 H, multiplet).

Preparation of 2,4,4a,5,6,7,8a,9,9a-Decahydro-4aβ-hydroxy-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (48). To a solution of keto lactone **42a** (0.48 g, 1.73 mmol) in methanol (20 mL) containing water (0.13 mL) under nitrogen was added anhydrous potassium carbonate (0.48 g, 3.46 mmol) and the resulting mixture stirred at room temperature for 14 h. Water (20 mL) was added and the mixture extracted with ether (ether extracts were discarded). The aqueous fraction was acidified with concentrated hydrochloric acid and extracted with chloroform. The combined chloroform fractions were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure to give **48** as a crystalline mixture of diastereomers (0.45 g, 93%): IR ($CHCl_3$) 2.88, 5.65, 5.80, and 6.02 μ; ^{1}H NMR δ ($CDCl_3$) 1.08 (1.2 H, singlet), 1.16 (1.8 H, singlet), 1.30–2.21 (11 H, multiplet), 2.83 (0.6 H, doublet, J = 14.3 Hz), 3.06 (0.4 H, doublet, J = 15 Hz), 3.43 (0.4 H, doublet, J = 15 Hz), 3.53 (0.6 H, doublet, J = 14.3 Hz), 3.88 (3 H, singlet), 4.96 (0.4 H, doublet of doublet, J = 7, 11.4 Hz), and 5.04 (0.6 H, doublet of doublet, J = 7.5, 11.4 Hz).

Preparation of the Diastereomeric Mixture of Diene Lactones 49 and 49a. To a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid (44 mL) was added lactone **48** (1.84 g, 6.57 mmol). The resulting mixture was stirred at room temperature under a calcium sulfate drying tube for 40 min and then slowly added to water (180 mL). After stirring for 10 min, the mixture was extracted with chloroform and the combined fractions were washed with water, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a crystalline mixture of diastereomers **49** and **49a** (1.20 g, 70%, crude): IR ($CHCl_3$) 5.66, 5.84, and 6.13 μ; ^{1}H NMR δ ($CDCl_3$) 1.26 (1.2 H, singlet), 1.34 (1.8 H, singlet), 1.40–2.50 (10 H, multiplet), 3.89 (3 H, singlet), 4.98 (0.4 H, doublet of doublet, J = 6, 13.8 Hz), 5.08 (0.6 H, doublet of doublet, J = 5.4, 13.6 Hz), 6.85 (0.4 H, singlet), and 6.89 (0.6 H, singlet).

Preparation of 2,5,6,7,8,8a,9,9aβ-Octahydro-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (49). To a solution of the diastereomeric mixture of diene lactones **49** and **49a** (108 mg, 0.38 mmol) in anhydrous methanol (2.4 mL) under nitrogen was added anhydrous potassium carbonate (2.6 mg, 0.05 equiv). After stirring for 18 h at room temperature, the mixture was acidified with 1 N hydrochloric acid and extracted with chloroform. The combined chloroform fractions were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure to give, in 95% yield, mainly one diastereomer, **49** (95%), which can be obtained pure by recrystallization from ether: mp 143–144 °C; IR ($CHCl_3$) 5.66, 5.84, and 6.13 μ; ^{1}H NMR δ ($CDCl_3$) 1.34 (3 H, singlet), 1.40–2.12 (7 H, multiplet), 2.27 (1 H, doublet of doublet, J = 5.4, 12 Hz), 2.42 (2 H, multiplet), 3.89 (3 H, singlet), 5.08 (1 H, doublet of doublet, J = 5.4, 13.6 Hz), and 6.89 (1 H, singlet); electron impact mass spectrum *m/e* 262.1203.

Anal. ($C_{15}H_{18}O_4$) C, H.

Preparative-Scale Preparation of 2,4,4a,5,6,7,8,8a,9,9a-Decahydro-4aβ-hydroxy-8aβ-methyl-2-oxonaphtho[2,3-*b*]-furan-3-carboxylic Acid Methyl Ester (48). To a cold (−78 °C) solution of titanium tetrachloride (1.8 mL, 15.7 mmol) in dry methylene chloride (60 mL) under nitrogen was rapidly added a cold (−78 °C) solution of butenolide **1a** (2.63 g, 15.7 mmol) in methylene chloride (25 mL). After 45 s, a cold (−78 °C) solution of silyl enol ether **41** (2.89 g, 15.7 mmol) in methylene chloride (17 mL) was added. The resulting deep blue mixture was stirred at −78 °C for 30 min and quenched with aqueous potassium carbonate (5.4 g in 110 mL of water). The cold bath was removed and the reaction mixture acidified with concentrated hydrochloric acid and extracted with chloroform. The combined chloroform fractions were washed with 1 N sodium bicarbonate and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a mixture of lactone **42a** and 2-methylcyclohexanone, which crystallized upon standing.

The crude keto lactone **42a**, being washed with pentane to remove most of the 2-methylcyclohexanone, was dissolved in methanol (40 mL). To the resulting solution under nitrogen were added water (4 mL) and anhydrous potassium carbonate (3.35 g, 24.2 mmol). After the mixture was stirred for 12 h, water was added until the mixture became homogenous; the mixture was extracted with ether (ether fractions discarded). The aqueous fraction was acidified with concentrated hydrochloric acid and extracted with chloroform. The combined chloroform fractions were washed with 1 N sodium bicarbonate (aqueous washes are red in color) and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give **48** (2.86 g, 65% overall yield), as a crystalline mixture of diastereomers, which can be used without further purification.

Preparative-Scale Preparation of 2,5,6,7,8,8a,9,9aβ-Octahydro-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (49). A mixture of **48** (10.0 g, 35.7 mmol) and sodium acetate (0.4 g) in acetic anhydride (120 mL) under nitrogen was heated at 105 °C for 8 h, after which thin layer chromatography (silica gel, ether) indicated that no **48** remained. After the mixture was cooled, the acetic anhydride was removed by distillation (0.05 mm) and the brown, crystalline residue was dissolved in chloroform. The resulting solution was washed with water, twice with 1 N sodium bicarbonate, and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and recrystallization from methanol–ether gave pure **49** (6.10 g, 65%).

The mother liquors, which contained a mixture of diastereomeric diene lactones **49** and **49a**, were concentrated at reduced pressure and the residue was dissolved in anhydrous methanol (50 mL). To the resulting solution under nitrogen was added anhydrous potassium carbonate (0.18 g). After stirring at room temperature for 20 h, the mixture was acidified with 1 N hydrochloric acid and extracted with chloroform. The combined chloroform fractions were washed with water, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue passed through a short column of silica gel (chloroform). Recrystallization from methanol–ether gave an additional 1.42 g of **49** (total yield 80%).

Preparation of 2,4,5,6,7,7a-Hexahydro-2-oxobenzofuran-3-carboxylic Acid Methyl Ester (52). A mixture of α-bromocyclohexanone[41] (1.20 g, 6.73 mmol), potassium methyl malonate[42] (1.0 g, 6.41 mmol), and 18-crown-6 (0.42 g, 1.6 mmol) in benzene (90 mL) under nitrogen was heated at reflux in a water separator for 7 h. The mixture was passed through a short column of silica gel to remove the 18-crown-6. The solvent was removed at reduced pressure and the residue distilled to give **52** as a light yellow oil (0.78 g, 63%): bp 128 °C (0.03 mm); IR (film) 5.62, 5.80, and 6.04 μ; ^{1}H NMR δ ($CDCl_3$) 1.16–2.78 (8

H, multiplet), 3.90 (3 H, singlet), and 4.78 (1 H, multiplet).

Preparation of 3α-Bromo-4,4a,5,6,7,8-hexahydro-4aβ-methyl-5-(1,3-dioxolane)-2(3*H*)-naphthalenone (55b). Bromo enone **55b** was prepared by the general procedure described by Stotter and Hill.[79] To a solution of hexamethyldisilazane (1.81 mL, 9.31 mmol) in dry THF (15 mL) at 0 °C under nitrogen was added 2.5 M *n*-butyllithium (3.72 mL, 9.31 mmol). After 15 min, the solution was cooled to −78 °C and a solution of enone **55a** (2.02 g, 8.87 mmol) in THF (6 mL) was added over 30 min. After the solution was stirred for 15 min, a methylene chloride solution of bromine (1 equiv) was rapidly added. After 75 s, the reaction mixture was quenched with 1 N sodium bicarbonate (15 mL) and extracted with ether. The combined ether fractions were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure and the residue chromatographed on neutral alumina (benzene). Recrystallization from isopropyl ether gave **55b** as colorless crystals (1.50 g, 55%): mp 116–119 °C; IR ($CHCl_3$) 5.95 and 6.16 μ; ^1H NMR δ ($CDCl_3$) 1.46 (3 H, singlet), 1.56–3.02 (8 H, multiplet), 4.02 (4 H, singlet), 4.83 (1 H, doublet of doublet, J = 6, 9.3 Hz), and 5.90 (1 H, broad singlet); electron impact mass spectrum *m/e* 300, 302.

Reaction of Bromo Ketone 53a with Potassium Acetate. A mixture of bromo ketone **53a**[43] (95 mg, 0.39 mmol), anhydrous potassium acetate (38 mg, 0.39 mmol), and 18-crown-6 (15 mg, 0.15 equiv) in acetonitrile (3.5 mL) under nitrogen was heated at reflux for 2 h and extracted with ether. The combined ether fractions were washed with water and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a mixture of α-acetoxy ketone **53b**[44] and enone **54**[45] (85:15, respectively).

Preparation of 2,3,3aβ,5,6,7,8,8a,9,9aβ-Decahydro-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (57a). To a cold (0 °C) solution of diene lactone **49** (1.39 g, 5.31 mmol) in dry THF (32 mL) under nitrogen was added sodium borohydride (0.40 g, 10.6 mmol). The mixture was stirred at 0 °C for 2 h, quenched rapidly with 1 N hydrochloric acid, and extracted with chloroform. The combined chloroform fractions were washed with water and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give **57a** (1.38 g, 99%). Recrystallization from benzene–pentane gave an analytical sample: mp 92–94 °C; IR ($CHCl_3$) 5.61 and 5.75 μ; ^1H NMR δ ($CDCl_3$) 1.12 (3 H, singlet), 1.13–2.40 (10 H, multiplet), 3.40 (2 H, multiplet), 3.82 (3 H, singlet), 4.82 (1 H, doublet of doublet of doublet, J = 4.8, 7.5, 12 Hz), and 5.30 (1 H, multiplet); electron impact mass spectrum *m/e* 264.

Anal. ($C_{15}H_{20}O_4$) C, H.

Diene lactone **49** also undergoes efficient conjugate reduction to give lactone **57a** in THF solution with diisobutylaluminum hydride (−25 °C, 45 min), sodium bis(2-methoxyethoxy)aluminum hydride (−40 to −20 °C, 45 min), and lithium tri-*tert*-butoxyaluminum hydride (0 °C, 2 h).

Preparation of 3aβ,5,6,7,8,8a,9,9aβ-Octahydro-8aβ-methyl-3-methylenenaphtho[2,3-*b*]furan-2(3*H*)-one (56). To a solution of lactone ester **57a** (1.38 g, 5.22 mmol) in methanol (16 mL) containing water (10 mL) was added 5 N sodium hydroxide (14 mL). After stirring for 7 h at room temperature, the mixture was cooled to 0 °C, acidified with concentrated hydrochloric acid, and extracted with ether. The aqueous solutions were saturated with sodium chloride and extracted with ether. The combined ether fractions were washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure to give lactone acid **57b.**

Lactone acid **57b** from above was treated at 60 °C with a solution prepared from 37% aqueous formaldehyde (11 mL) and diethylamine (5.0 mL). After 30 min, sodium acetate (1.0 g) and acetic acid (10 mL) were added and the resulting mixture was heated at 75 °C for 20 min and extracted with ether. The combined ether fractions were washed with 10% hydrochloric acid, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed to give **56** (794 mg, 70%). Recrystallization from benzene–hexane gave an analytical sample: mp 98–99 °C; IR ($CHCl_3$) 5.70 and 6.02 μ; ^1H NMR δ ($CDCl_3$), 1.10 (3 H, singlet), 1.20–2.30 (10 H, multiplet), 3.50 (1 H, multiplet), 4.83 (1 H, doublet of doublet of doublet, J = 4.8, 7.8, 12 Hz), 5.42 (1 H, doublet of triplet, J = 4.5, 1.4 Hz), 5.56 (1 H, doublet, J = 3.2 Hz), and 6.26 (1 H, doublet, J = 3.6 Hz); electron impact mass spectrum *m/e* 218.

Anal. ($C_{14}H_{18}O_2$) C, H.

Preparation of 3aβ,5,6,7,8,8a,9,9aβ-Octahydro-3β-hydroxymethyl-8aβ-methylnaphtho[2,3-*b*]furan-2(3*H*)-one (57c). To a cold (0 °C) solution of lactone acid **57b** (0.79 g, 3.16 mmol) in absolute ethanol (25 mL) was added sodium borohydride (0.60 g, 5 equiv) in small portions during 35 min. The mixture was then stirred at room temperature for 45 min, cooled to 0 °C, quenched with 1 N hydrochloric acid, and extracted with ether. The combined ether fractions were washed with 1 N sodium bicarbonate (save these washes) and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give **57c** as a colorless oil (0.624 g): IR ($CHCl_3$) 2.93 and 5.71 μ; ^1H NMR δ ($CDCl_3$) 1.00–2.30 (10 H, multiplet), 1.10 (3 H, singlet), 2.63 (1 H, broad singlet, replaceable on addition of deuterium oxide), 2,90 (1 H, doublet of triplet, J = 10.5, 6.7 Hz), 3.23 (1 H, multiplet), 3.86 (2 H, doublet, J = 6.7 Hz), 4.80 (1 H, doublet of doublet of doublet, J = 4.5, 7.5, 9.0 Hz), and 5.20 (1 H, broad doublet, J = 3.7 Hz).

The basic washes were acidified with concentrated hydrochloric acid and extracted with ether to give **57b** (0.14 g); therefore, the yield of **57c** based on recovered starting material was 97%.

Preparation of 5β-Bromo-2,5,6,7,8,8a,9,9aβ-octahydro-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (58). A mixture of diene lactone **49** (1.02 g, 3.9 mmol) and *N*-bromosuccinimide (723 mg, 4.06 mmol) in dry carbon tetrachloride (30 mL) under nitrogen was heated in an 85 °C oil bath until dissolution of **49** was achieved. The mixture was then irradiated with a 240-W sunlamp while being maintained at reflux temperature for 20 min. The mixture was cooled and filtered with the aid of addition carbon tetrachloride, and the filtrate was washed with 1% sodium thiosulfate, water, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressured to give **58** as a light yellow, crystalline solid (1.33 g, 99%), which must be stored under refrigeration (−15 °C). Recrystallization from ether–chloroform gave a colorless sample: mp 118–119 °C; IR ($CHCl_3$) 5.68, 5.84 and 6.13 μ; ^1H NMR δ ($CDCl_3$) 1.66 (3 H, singlet), 1.35–2.40 (9 H, multiplet), 3.87 (3 H, singlet), 5.08 (1 H, broad singlet), 5.19 (1 H, doublet of doublet, J = 13.5, 5.7 Hz), and 7.15 (1 H, singlet); chemical ionization mass spectrum *m/e* 341, 343.

Preparation of 2,5,6,7,8,8a-Hexahydro-8a-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (63). To a solution of bromo diene **58** (121 mg, 0.35 mmol) in dry benzene (7 mL) under nitrogen was added 1,5-diazabicyclo[4.3.0]non-5-ene (0.13 mL, 3 equiv). After stirring for 20 min at room temperature, the mixture was diluted with additional benzene and washed with 1 N hydrochloric acid and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed (silica gel, ether) to give **63** as a colorless solid (40.2 mg, 43%, low yield may be due, in part, to decomposition on silica gel): mp 129–131 °C (without recrystallization); IR ($CHCl_3$) 5.65, 5.84, 5.95, and 6.23 μ; ^1H NMR δ ($CDCl_3$) 1.10–2.30 (6 H, multiplet), 1.31 (3 H, singlet), 2.56 (2 H, multiplet), 3.88 (3 H, singlet), 6.13 (1 H, singlet), and 7.23 (1 H, singlet); electron impact mass spectrum *m/e* 260.

Preparation of 5β-Bromo-2,3,3aβ,5,6,7,8,8a,9,9aβ-decahydro-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (59). To a solution of bromo diene **58** (585 mg, 1.71 mmol) in THF (30 mL) containing ethanol (10 mL) were added 1 N ethanolic hydrogen chloride (0.75 mL) and a small amount of bromocresol green indicator followed by just enough water to allow the indicator to function. Sodium cyanoborohydride (860 mg, 8 equiv) was added and the mixture stirred at room temperature for 1 h while a yellow color was maintained by the addition of 1 N ethanolic hydrogen chloride when necessary. The mixture was added to chloroform and the resulting solution washed with water, 1 N hydrochloric acid, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give **59** (576 mg, 97%). Recrystallization from benzene–ether gave an analytical sample: mp 121–122 °C dec; IR ($CHCl_3$) 5.62 and 5.75 μ; ^1H NMR δ ($CDCl_3$) 1.03–2.43 (8 H, multiplet), 1.46 (3 H, singlet), 3.33 (1 H, doublet, J = 12 Hz), 3.60 (1 H, doublet of doublet of doublet, J = 4.2, 7.5, 12 Hz), 3.83 (3 H, singlet), 4.92 (1 H, doublet of doublet of doublet, J = 4.5, 7.5, 12.5 Hz), 5.00 (1 H, multiplet), and 5.76 (1 H, doublet, J = 4.2 Hz); chemical ionization mass spectrum *m/e* 343, 345.

Anal. ($C_{15}H_{19}BrO_4$) C, H.

Attempted Preparation of 61a. To a cold (0 °C), stirred suspension of cuprous iodide (124 mg, 0.652 mmol) in anhydrous ether (3 mL) was added a 1.8 M ethereal solution of methyllithium (0.73 mL, 1.31

mmol). After the solution was stirred for 10 min, a solution of bromo olefin **59** (45 mg, 0.13 mmol) in anhydrous ether (0.6 mL) containing dry THF (0.3 mL) was added. The resulting mixture was stirred for 2 h at 0 °C, quenched with saturated ammonium chloride, and extracted with ether. The combined ether fractions were washed with saturated ammonium chloride, water, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a complex mixture of products which contained little if any **61a.**

Preparation of 2bβ,2cβ,4,5,6,6a,7,7aβ-Octahydro-6aβ-methyl-2-oxocyclopropa[*cd*]naphtho[2,3-*b*]furan-2a(2*H*)-carboxylic Acid Methyl Ester (60). To a solution of bromo olefin **59** (440 mg, 1.28 mmol) in dry benzene (18 mL) under nitrogen was added 1,5-diazabicyclo[4.3.0]non-5-ene (0.32 mL, 2 equiv). The resulting mixture was stirred at room temperature for 75 min and added to ether, and the ether solution was washed with 1 N hydrochloric acid, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give **60** which crystallized upon standing (320 mg, 95%). Recrystallization from ethyl acetate–hexane gave an analytical sample: mp 112–113 °C; IR ($CHCl_3$) 5.65 and 5.79 μ; ^1H NMR δ ($CDCl_3$) 1.20 (3 H, singlet), 1.30–2.30 (8 H, multiplet), 2.93 (2 H, multiplet), 3.83 (3 H, singlet), 4.81 (1 H, multiplet), and 5.97 (1 H, doublet of triplet, J = 3.9, 1.5 Hz); electron impact mass spectrum *m/e* 262 (4.8%), 230 (100%).

Anal. ($C_{15}H_{18}O_4$) C, H.

Preparation of 2,3,3aβ,5,6,7,8,8a,9,9aβ-Decahydro-5β,8aβ-dimethyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (61a). To a cooled (0 °C), stirred suspension of cuprous iodide (97 mg, 0.52 mmol) in anhydrous ether (3.5 mL) under nitrogen was added a 1.77 M ethereal solution of methyllithium (0.57 mL, 1.0 mmol). After stirring for 10 min, the mixture was cooled to −20 °C and a solution of vinylcyclopropane **60** (90 mg, 0.34 mmol) in anhydrous ether (2.0 mL) was added. The resulting mixture was stirred for 40 min, while warming from −20 to −5 °C, quenched with saturated ammonium chloride, and extracted with ether. The combined ether fractions were washed with saturated ammonium chloride, water, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed on silica gel (chloroform–ethyl acetate, 95:5) to give **61a** as a colorless oil (72 mg, 75%): IR ($CHCl_3$) 5.62 and 5.75 μ; ^1H NMR δ ($CDCl_3$) 1.12 (3 H, doublet, J = 7 Hz), 1.18 (3 H, singlet), 1.15–2.20 (8 H, multiplet), 2.50 (1 H, multiplet, 3.43 (2 H, multiplet), 3.82 (3 H, singlet), 4.88 (1 H, multiplet), and 5.35 (1 H, doublet, J = 3.6 Hz).

Preparation of 3aβ,5,6,7,8,8a,9,9aβ-Octahydro-5β,8aβ-dimethyl-3-methylenenaphtho[2,3-*b*]furan-2(3*H*)-one or *dl*-7,8-Epialantolactone (4). Lactone **4** was prepared from **61a** in 70% yield by the procedure described for the preparation of lactone **56.** Recrystallization from ethyl acetate–hexane gave an analytical sample: mp 109–110 °C; IR ($CHCl_3$) 5.69 μ; ^1H NMR δ 1.13 (3 H, doublet, J = 7 Hz), 1.17 (3 H, singlet), 1.18–2.00 (8 H, multiplet), 2.56 (1 H, multiplet), 3.53 (1 H, multiplet), 4.90 (1 H, doublet of doublet of doublet, J = 5.1, 8.4, 12 Hz), 5.50 (1 H, doublet, J = 4.2 Hz), 5.58 (1 H, doublet, J = 3.3 Hz), and 6.28 (1 H, doublet, J = 3.6 Hz); electron impact mass spectrum *m/e* 232.

Anal. ($C_{15}H_{20}O_2$) C, H.

Preparation of 2,4,6,7,8,8a,9,9aβ-Octahydro-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (66). To a solution of bromo diene **58** (550 mg, 1.61 mmol) in dry THF (20 mL) containing glacial acetic acid (1.0 mL, 10 equiv) under nitrogen was added zinc dust (1.05 g, 10 equiv). After stirring for 1 h at room temperature, the mixture was filtered with the aid of chloroform and the filtrate was washed with water and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give diene lactone **66** containing only 3–4% of diene lactone **49** (410 mg, 97%). Recrystallization from ether–chloroform gave an analytical sample: mp 107–110 °C; IR ($CHCl_3$) 5.66, 5.81, 6.04, and 9.65 μ; ^1H NMR δ ($CDCl_3$) 1.25 (3 H, singlet), 1.26–2.20 (7 H, multiplet), 2.38 (1 H, doublet of doublet, J = 6.3, 12.3 Hz), 3.31 (1 H, doublet of multiplet, J = 15.6 Hz), 3.89 (3 H, singlet), 4.12 (1 H, doublet, J = 15.6 Hz), 5.06 (1 H, doublet of doublet, J = 6.3, 12.0 Hz), and 5.63 (1 H, multiplet).

Anal. ($C_{15}H_{18}O_4$) C, H.

Preparation of 2,3,3aβ,4,4aα,5,6,7,8,8a,9,9aβ-Dodecahydro-5α-hydroxy-8aβ-methylnaphtho[2,3-*d*]furan-3-carboxylic Acid Methyl Ester (68a). To a solution of diene lactone **66** (320 mg, 1.23 mmol) in dry ethyl acetate (8 mL) under nitrogen was added borane–methyl sulfide complex (0.23 mL, 2 equiv). The resulting mixture was stirred at room temperature for 2 h and cooled to 0 °C, and absolute ethanol (8 mL), 2.5 M sodium acetate (4 mL), and 30% hydrogen peroxide (2.6 mL) were added successively. The reaction mixture was warmed to room temperature, stirred for 6 h, and extracted with ether. The combined ether fractions were washed with water, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed (silica gel, ether) to give a mixture of trans decalol **68a** and cis decalol **69a** (6.4:1, respectively) as a colorless solid (128 mg, 37%). Recrystallization from ethyl acetate–heptane gave an analytical sample of **68a:** mp 150–151 °C; IR ($CHCl_3$) 2.88, 5.61, and 5.74 μ; ^1H NMR δ ($CDCl_3$) 0.85 (3 H, singlet), 1.01–2.32 (12 H, multiplet, 1 H replaceable on addition of deuterium oxide), 3.28 (2 H, multiplet), 3.57 (1 H, doublet, J = 14.2 Hz), 3.80 (3 H, singlet), and 4.76 (1 H, doublet of doublet of doublet, J = 6.9, 6.9, 11.4 Hz).

Anal. ($C_{15}H_{22}O_5$) C, H.

Preparation of 2,3,3aβ,4,4aα,5,6,7,8,8a,9,9aβ-Dodecahydro-8aβ-methyl-2,5-dioxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (68b). To a cold (0 °C) solution of trans decalol **68a** (120 mg, 0.42 mmol) in acetone (8 mL) was added Jones reagent (1 mL). The mixture was stirred at 0 °C for 1 h, quenched with excess 2-propanol, and extracted with chloroform. The combined chloroform fractions were washed with water, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give trans keto lactone **68b** (110 mg, 93%). Recrystallization from ethyl acetate–heptane gave an analytical sample: mp 188–189 °C; IR ($CHCl_3$) 5.61, 5.75, and 5.85 μ; ^1H NMR δ ($CDCl_3$) 0.82 (3 H, singlet), 1.18–2.86 (11 H, multiplet), 3.26 (1 H, multiplet), 3.49 (1 H, doublet, J = 13.5 Hz), 3.80 (3 H, singlet), and 4.76 (1 H, doublet of doublet of doublet, J = 6.6, 6.6, 11.3 Hz).

Anal. ($C_{15}H_{20}O_5$) C, H.

Preparation of 2,3,3aβ,4,6,7,8,8a,9,9aβ-Decahydro-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (67). To a solution of diene lactone **66** (421 mg, 1.61 mmol) in THF (18 mL) containing ethanol (6 mL) were added 1 N ethanolic hydrogen chloride (0.5 mL) and a small amount of bromocresol green indicator followed by just enough water to allow the indicator to function. Sodium cyanoborohydride (800 mg, 8 equiv) was added and the mixture stirred at room temperature for 1 h while a yellow color was maintained by the addition of 1 N ethanolic hydrogen chloride when necessary. The mixture was then added to chloroform and the resulting solution washed with water, 1 N hydrochloric acid, 1 N sodium bicarbonate, and brine. After the solution was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give **67** (406 mg, 95%). Recrystallization from methanol gave an analytical sample: mp 98–99 °C; IR ($CHCl_3$) 5.62 and 5.75 μ; ^1H NMR δ ($CDCl_3$) 1.05 (3 H, singlet), 1.06–2.20 (9 H, multiplet), 2.66 (1 H, doublet of multiplet, J = 18 Hz), 3.22 (1 H, multiplet), 3.44 (1 H, doublet, J = 12 Hz), 3.82 (3 H, singlet), 4.85 (1 H, doublet of doublet of doublet, J = 6.5, 6.6, 10.5 Hz), and 5.53 (1 H, multiplet).

Anal. ($C_{15}H_{20}O_4$) C, H.

Preparation of 2,3,3aβ,4,4aβ,5,6,7,8,8a,9,9aβ-Dodecahydro-5β-hydroxy-8aβ-methylnaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (69a). To a solution of olefinic lactone **67** (119 mg, 0.45 mmol) in dry ethyl acetate (3 mL) under nitrogen was added borane–methyl sulfide complex (0.13 mL, 3 equiv). The resulting mixture was stirred for 3 h at room temperature and cooled to 0 °C, and absolute ethanol (3 mL), 2.5 M sodium acetate (1.5 mL), and 30% hydrogen peroxide (1 mL) were added successively. The reaction mixture was warmed to room temperature, stirred for 3 h, and extracted with ether. The combined ether fractions were washed successively with water, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed (silica gel, ether) to give cis decalol **69a,** containing a trace of trans decalol **68a,** as a colorless oil (78 mg, 61%): IR ($CHCl_3$) 2.82, 5.63, and 5.75 μ; ^1H NMR δ ($CDCl_3$) 1.06 (3 H, singlet), 1.12–2.30 (12 H, multiplet, 1 H replaceable on addition of deuterium oxide), 3.06 (1 H, multiplet), 3.56 (1 H, doublet, J = 10.8 Hz), 3.72 (1 H, multiplet), 3.82 (3 H, singlet), 4.88 (1 H, doublet of doublet of doublet, J = 7.5,

7.5, 7.5 Hz).

Preparation of 2,3,3aβ,4,4aβ,5,6,7,8,8a,9,9aβ-Dodecahydro-8aβ-methyl-2,5-dioxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (69b). Keto lactone **69b** was prepared from cis decalol **69a** in 94% yield by the procedure described for the preparation of keto lactone **68b.** Recrystallization from ethyl acetate–hexane gave an analytical sample: mp 135–136 °C; IR ($CHCl_3$) 5.63, 5.77, and 5.88 μ; ^1H NMR δ ($CDCl_3$) 1.08 (3 H, singlet), 1.50–2.51 (11 H, multiplet), 3.01 (H, multiplet), 3.65 (1 H, doublet, J = 9 Hz), 3.83 (3 H, singlet), and 4.82 (1 H, doublet of doublet of doublet, J = 6.8, 6.8, 6.8 Hz).

Anal. ($C_{15}H_{20}O_5$) C, H.

Conversion of Keto Lactone 69b to Keto Lactone 68b. A solution of cis keto lactone **69b** (21 mg, 0.075 mmol) and sodium methoxide (0.4 mg, 0.1 equiv) in anhydrous methanol (3 mL) under nitrogen was heated at reflux for 16 h, cooled, acidified with 1 N hydrochloric acid, and extracted with chloroform. The combined chloroform fractions were washed with water and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a mixture of **68b** and **69b** (5:1, respectively) in 95% yield. The trans keto lactone **68b** can be obtained pure by recrystallization from ether.

Treatment of pure trans keto lactone **68b** with sodium methoxide in methanol, as above, gave the 5:1 mixture of **68b** and **69b,** respectively.

Attempted Selective Hydroboration–Oxidation of Diene Lactone 66. A. To a solution of **66** (50 mg, 0.19 mmol) in dry ethyl acetate (1.5 mL) under nitrogen was added borane–methyl sulfide complex (18 μL, 0.19 mmol). The resulting mixture was stirred at room temperature for 2 h and then cooled to 0 °C, after which absolute ethanol (1.5 mL), 2.5 M sodium acetate (0.8 mL), and 30% hydrogen peroxide (0.2 mL) were added successively. The mixture was warmed to room temperature, stirred for 6 h, and extracted with ether. The combined ether fractions were washed with water, 1 N sodium bicarbonate, and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a mixture of **68a** and **67.**

B. To a solution of **66** (50 mg, 0.19 mmol) in dry THF (2 mL) under nitrogen was added a 0.5 M solution of 9-borabicyclo[3.3.1]nonane in tetrahydrofuran (0.38 mL, 0.19 mmol). The resulting solution was heated to reflux for 1 h and cooled to room temperature, after which absolute ethanol (2 mL), 2.5 M sodium acetate (1.0 mL), and 30% hydrogen peroxide (0.25 mL) were added successively. The solution was then heated to 50 °C for 1 h, cooled, and extracted with chloroform. The combined chloroform fractions were washed with water and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a complex mixture, in which **67** was the major, identifiable component.

Preparation of 2,3,3aβ,4,4aα,5,6,7,8,8a,9,9aβ-Dodecahydro-8aβ-methyl-5-methylenenaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (71a). To a cold (0 °C), stirred suspension of methyltriphenylphosphonium bromide (1.0 g, 2.80 mmol) in dry THF (7.5 mL) containing dry HMPA (5 mL) under nitrogen was added 2.4 M *n*-butyllithium dropwise (1.17 mL, 2.80 mmol). The resulting solution was stirred at 0 °C for 15 min and at room temperature for 45 min.

To the deep red solution of methylenetriphenylphosphorane from above was added a solution of keto lactone **68b** (226 mg, 0.807 mmol) in THF (3.5 mL) and the resulting mixture stirred for 17 h at room temperature. The reaction mixture was quenched with saturated ammonium chloride and extracted with benzene. The combined benzene fractions were washed with water, 1 N hydrochloric acid, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed on silica gel (chloroform–ethyl acetate, 95:5) to give **71a** (195 mg, 86%). Recrystallization from *n*-heptane gave an analytical sample: mp 113–114 °C; IR ($CHCl_3$) 5.61, 5.74, 6.04, 10.02, and 11.24 μ; ^1H NMR δ ($CDCl_3$) 0.74 (3 H, singlet), 1.03–2.53 (11 H, multiplet), 3.26 (1 H, multiplet), 3.59 (1 H, doublet, J = 13.4 Hz), 3.80 (3 H, singlet), 4.50 (1 H, broad singlet), 4.75 (1 H, doublet of doublet of doublet, J = 6.9, 6.9, 11 Hz), and 4.81 (1 H, broad singlet).

Anal. ($C_{16}H_{22}O_4$) C, H.

Preparation of 2,3,3aβ,4,4aα,5,6,7,8,8a,9,9aβ-Dodecahydro-3,8aβ-dimethylnaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (71b). To a suspension of sodium hydride (51 mg, 2.12 mmol), obtained from a 50% oil dispersion after three washings with dry pentane, in dry THF (2 mL) at 0 °C under nitrogen was added a solution of lactone **71a** (110 mg, 0.39 mmol) in THF (5 mL). The mixture was warmed to room temperature and stirred for 6 h, after which methyl iodide (0.5 mL, 20 equiv) was added. After 6 h, the reaction mixture was cooled to 0 °C, quenched with saturated ammonium chloride, and extracted with chloroform. The combined chloroform fractions were washed with water, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed to give **71b** as a nearly equal mixture of diastereomers (107 mg, 93%): IR ($CHCl_3$) 5.68, 5.79, and 6.10 μ; ^1H NMR δ ($CDCl_3$) 0.73 (1.5 H, singlet), 0.75 (1.5 H, singlet), 1.10–2.50 (11 H, multiplet), 1.50 (1.5 H, singlet), 1.56 (1.5 H, singlet), 2.71 (0.5 H, multiplet), 3.32 (0.5 H, multiplet), 3.72 (1.5 H, singlet), 3.76 (1.5 H, singlet), 4.50 (1 H, broad singlet), 4.73 (1 H, multiplet), and 4.78 (1 H, broad singlet).

Preparation of 3aβ,4,4aα,5,6,7,8,8a,9,9aβ-Decahydro-3β,8aβ-dimethyl-5-methylenenaphtho[2,3-*b*]furan-2(3*H*)-one or *dl*-Dihydrocallitrisin (3). A solution of lactone **71b** (107 mg, 0.36 mmol) and sodium cyanide (52 mg, 1.06 mmol) in dry HMPA (9 mL) under argon was heated at 80 ° for 1 h and cooled, after which 10% hydrochloric acid (30 mL) was added. The mixture was extracted with ether and the combined ether fractions were washed successively with water, 10% hydrochloric acid, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed (silica gel, chloroform) to give **3** (78 mg, 91%). Recrystallization from hexane gave an analytical sample: mp 125–126 °C: IR ($CHCl_3$) 5.64, 6.03, 10.07, and 11.26 μ; ^1H NMR δ ($CDCl_3$) 0.74 (3 H, singlet), 1.09–2.74 (13 H, multiplet), 1.20 (3 H, doublet, J = 6.7 Hz), 4.53 (1 H, broad singlet), 4.65 (1 H, doublet of doublet of doublet, J = 6.6, 6.6, and 11.1 Hz), 4.81 (1 H, broad singlet); ^1H NMR δ (C_6D_6) 0.40 (3 H, singlet), 0.77–2.36 (13 H, multiplet), 0.94 (3 H, doublet, J = 6.0 Hz), 4.15 (1 H, doublet of doublet of doublet, J = 6.6, 6.6, 11.1 Hz), 4.40 (1 H, broad singlet), and 4.75 (1 H, broad singlet); electron impact mass spectrum *m/e* 234; see Results and Discussion section for additional data.

Anal. ($C_{15}H_{22}O_2$) C, H.

Preparation of 3aβ,4,4aα,5,6,7,8,8a,9,9aβ-Decahydro-8aβ-methyl-3,5-bis(methylene)naphtho[2,3-*b*]furan-2(3*H*)-one or 7,8-Epiisolantolactone (5). Lactone **5** was prepared from **71a** in 73% yield by the manner described for the preparation of lactone **56.** Recrystallization from hexane gave an analytical sample: mp 103.5–104.5 °C; IR ($CHCl_3$) 5.68, 6.07, and 11.2 μ; ^1H NMR δ ($CDCl_3$) 0.73 (3 H, singlet), 0.93–2.50 (11 H, multiplet), 3.30 (1 H, multiplet), 4.56 (1 H, broad singlet), 4.80 (1 H, multiplet), 4.81 (1 H, broad singlet), 5.51 (1 H, doublet, J = 3.5 Hz), and 6.31 (1 H, doublet of doublet, J = 0.8, 3.6 Hz).

Anal. ($C_{15}H_{20}O_2$) C, H.

Preparation of 3aβ,4,6,7,8,8a,9,9aβ-Octahydro-8aβ-methyl-2-methylenenaphtho[2,3-*b*]furan-2(3*H*)-one (72). Lactone **72** was prepared from **67** in 67% yield by the manner described for the preparation of lactone **56.** Recrystallization from ethyl acetate–hexane gave an analytical sample: mp 60–61 °C; IR ($CHCl_3$) 5.68 and 6.02 μ; ^1H NMR δ ($CDCl_3$) 1.09 (3 H, singlet), 1.13–1.73 (8 H, multiplet), 2.27 (1 H, doublet of doublet, J = 1.5, 14.4 Hz), 2.78 (1 H, doublet of multiplet, J = 14.4 Hz), 3.23 (1 H, multiplet), 4.85 (1 H, doublet of doublet of doublet, J = 5.4, 7.5, 9.0 Hz), 5.41 (1 H, multiplet), 5.50 (1 H, doublet, J = 2.9 Hz), and 6.27 (1 H, doublet, J = 3.1 Hz).

Anal. ($C_{14}H_{18}O_2$) C, H.

Preparation of 3aβ,4,4aα,5,6,7,8,8a,9,9aβ-Decahydro-3α,8aβ-dimethyl-5-methylene-3β-(phenylthio)naphtho[2,3-*b*]furan-2(3*H*)-one (74a) and 3aβ,4,4aα,5,6,7,8,8a,9,9aβ-Decahydro-3β,8aβ-dimethyl-5-methylene-3α-(phenylthio)naphtho[2,3-*b*]furan-2(3*H*)-one (75a). To a solution of diisopropylamine (30 μL, 0.21 mmol) in dry THF (1.2 mL) at 0 °C under nitrogen was added 2.45 M *n*-butyllithium (86 μL, 0.21 mmol). The solution was stirred for 20 min and cooled to −78 °C, after which a solution of *dl*-dihydrocallitrisin (**3**, 41 mg, 0.175 mmol) in THF (0.8 mL) was added over 10 min. After 1 h, a solution of diphenyl disulfide (76 mg, 0.35 mmol) in THF (0.8 mL) containing HMPA (36 μL, 0.21 mmol) was added. The resulting mixture was stirred at −78 °C for 1 h, −20 °C for 30 min, and finally at room temperature for 2 h, after which the mixture was extracted with ether. The combined ether fractions were washed successively with 1 N hydrochloric acid, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed (silica gel, chloroform) to give a crystalline mixture of **74a** and **75a** (70:30,

respectively) which was not separated (57 mg, 95%): IR ($CHCl_3$) 5.58 and 8.30 μ; ^1H NMR δ ($CDCl_3$) 0.70 (2.1 H, singlet), 0.76 (0.9 H, singlet), 1.10–3.00 (12 H, multiplet), 1.35 (0.9 H, singlet), 1.51 (2.1 H, singlet), 4.41–4.83 (1 H, multiplet), 4.56 (1 H, broad singlet), 4.83 (1 H, broad singlet), and 7.23–7.73 (5 H, multiplet).

Preparation of 4aα,5,6,7,8,8a,9,9aβ-Octahydro-3-methyl-5-methylenenaphtho[2,3-*b*]furan-2(4*H*)-one (73). To a solution of the mixture of sulfides **74a** and **75a** (70:30, respectively, 57 mg, 0.166 mmol) in THF (4 mL) containing water (0.5 mL) was added sodium metaperiodate (285 mg, 8 equiv). After stirring at room temperature for 48 h, the mixture was diluted with ether and the resulting solution washed with water and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a mixture of sulfoxides **74b** and **75b** plus lactone **73.**

The crude mixture from above was heated at reflux in benzene (10 mL) containing powdered calcium carbonate (200 mg) under nitrogen for 18 h. Ether was added and the resulting solution was washed with 1 N hydrochloric acid, 1 N sodium bicarbonate, and brine. After the solution was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a mixture of lactone **73** and *dl*-7,8-epiisolantolactone (**5**). Chromatography on alumina gave pure lactone **73** (23 mg, 60%) whose ^1H NMR and infrared spectra were in full agreement with the published spectra:[66] mp 101–102 °C (from ethyl acetate–hexane) (lit. 102–103 °C);[12b] IR ($CHCl_3$) 5.74, 5.93, and 6.06 μ; ^1H NMR δ ($CDCl_3$) 0.87 (3 H, singlet), 1.79 (3 H, triplet, J = 1.5 Hz), 1.05–2.83 (11 H, multiplet), 4.58 (1 H, broad singlet), 4.80 (1 H, multiplet), and 4.87 (1 H, broad singlet); electron impact mass spectrum *m/e* 232.

Preparation of 4,4aα,5,6,7,8,8a,9-Octahydro-3,8aβ-dimethyl-5-methylenenaphtho[2,3-*b*]furan or *dl*-Atractylon (6). Atractylon (**6**) was prepared from lactone **73** by the method of Minato.[12b] To a cold (−25 °C) solution of lactone **73** (8 mg, 3.44×10^{-2} mmol) in dry THF (1 mL) under nitrogen was added a 1 M solution of diisobutylaluminum hydride in hexane (45 μL, 1.3 equiv). After the mixture was stirred at −25 °C for 1.75 h, 2 N sulfuric acid (0.3 mL) was added and the resulting mixture was stirred at 0 °C for 1 h. Ether was added and the resulting solution was washed with water, 1 N sodium bicarbonate, and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a nearly equal mixture of atractylon (**6**) and lactone **73.** The ^1H NMR spectrum of **6** was identical with the spectrum of the natural material kindly supplied by Dr. I. Yosioka.[71]

Preparation of 5β-Bromo-2,3,3aβ,4,4a,5,6,7,8,8a,9,9aβ-dodecahydro-8aβ-methyl-4α,4aα-oxido-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (78). To a solution of bromo olefin **59** (1.02 g, 2.97 mmol) in methylene chloride (40 mL) was added 85% *m*-chloroperbenzoic acid (0.90 g, 1.5 equiv). The resulting mixture was stirred in the dark for 40 h, after which the mixture was diluted with chloroform and the resulting solution washed successively with 1% sodium thiosulfate (twice), 1 N sodium bicarbonate (twice), and brine. After the solution was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give **78** as a colorless solid (0.97 g, 91%). Recrystallization from ethyl acetate–hexane gave an analytical sample: mp 117–118 °C; IR ($CHCl_3$) 5.62 and 5.75 μ; ^1H NMR δ ($CDCl_3$) 1.30–2.35 (8 H, multiplet), 1.51 (3 H, singlet), 3.21 (1 H, doublet, J = 3.3 Hz), 3.53 (1 H, doublet of doublet of doublet, J = 3.3, 9.0, 10.8 Hz), 3.69 (1 H, multiplet), 3.80 (1 H, doublet, J = 10.8 Hz), 3.85 (3 H, singlet), and 4.76 (1 H, doublet of doublet of doublet, J = 7.2, 9.0, 10.8 Hz); chemical ionization mass spectrum *m/e* 359, 361.

Anal. ($C_{15}H_{19}BrO_5$) C, H.

Preparation of 2,3,3aβ,4,6,7,8,8a,9,9aβ-Decahydro-4α-hydroxy-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (79). The zinc–silver couple was prepared by the method of Corey.[74] To a solution of silver acetate (16 mg) in acetic acid (15 mL) at 70 °C under nitrogen was added zinc dust (165 mg, 2.5 mmol). After stirring for 30 s, the mixture was decanted (under nitrogen with a syringe) and washed with dry THF (3 × 10 mL). To the zinc–silver couple was added THF (4 mL) followed by a solution of bromo epoxide **79** (91.5 mg, 0.25 mmol) in THF (3 mL) containing acetic acid (0.15 mL, 2.54 mmol) and the resulting mixture stirred at room temperature for 6 h, after which the mixture was filtered. The filtrate was diluted with chloroform and the resulting solution washed with 1 N sodium bicarbonate and brine. After the solution was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give **79** as a colorless, crystalline solid (71 mg, 99%). Recrystallization from ethyl acetate–hexane gave an analytical sample: mp 148–150 °C; IR ($CHCl_3$) 2.90, 5.62, and 5.76 μ; ^1H NMR δ ($CDCl_3$) 1.09 (3 H, singlet), 1.33–2.33 (9 H, multiplet), 3.56 (2 H, multiplet), 3.82 (3 H, singlet), 4.68 (1 H, multiplet), 4.91 (1 H, multiplet), and 5.86 (1 H, multiplet).

Anal. ($C_{15}H_{20}O_5$) C, H.

Preparation of 2,3,3aβ,4,6,7,8,8a,9,9aβ-Decahydro-8aβ-methyl-2-oxo-4β-(phenylthio)naphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (80a). To a solution of vinylcyclopropane **60** (50 mg, 0.19 mmol) in benzenethiol (20 μL, 0.20 mmol) in dry benzene (3 mL) at room temperature under nitrogen was added 1,5-diazabicyclo[4.3.0]non-5-ene (9.5 μL, 0.4 equiv). After stirring for 20 h, the mixture was diluted with ether and the resulting solution washed with 1 N hydrochloric acid and brine. After the solution was dried over anhydrous magnesium sulfate, the solvent and removed at reduced pressure to give **80a** as a light yellow oil in nearly quantitative yield: IR ($CHCl_3$) 5.62 and 5.75 μ; ^1H NMR δ ($CDCl_3$) 1.10–2.43 (8 H, multiplet), 1.36 (3 H, singlet), 3.33 (2 H, multiplet), 3.60 (3 H, singlet), 3.90 (1 H, singlet), 5.09 (1 H, multiplet), 5.69 (1 H, triplet, J = 3.6 Hz), and 7.20–7.62 (5 H, multiplet).

Preparation of 5β-Acetoxy-2,3,3aβ,5,6,7,8,8a,9,9aβ-decahydro-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (81b). To a cold (−78 °C) solution of allylic sulfide **80a** (71 mg, 0.19 mmol) in dry methylene chloride (2.5 mL) under nitrogen was added a solution of 85% *m*-chloroperbenzoic acid (58 mg, 1.5 equiv) in methylene chloride (1.2 mL) over 2 min. After the solution was stirred for 5 min, a solution of trimethyl phosphite (0.22 mL, 10 equiv) in dry methanol (4 mL) was added and the resulting mixture was heated at 50 °C for 9 h. Ether was added and the resulting solution was washed with 1 N sodium bicarbonate, water, and brine. After the solution was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give allylic alcohol **81a.**

The crude mixture containing **81a** was treated with acetic anhydride (1 mL) in pyridine solution (4 mL) at room temperature under nitrogen for 20 h. After the mixture was cooled to 0 °C, water (3 mL) was added and the resulting mixture was stirred at room temperature for 30 min and then extracted with ether. The combined ether fractions were washed with 1 N sodium bicarbonate, 1 N hydrochloric acid, and brine. After the solution was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed (silica gel, chloroform–ethyl acetate, 95:5) to give allylic acetate **81b** as a colorless oil (41 mg, 67% overall yield from vinylcyclopropane **60**): IR ($CHCl_3$) 5.62 and 5.76 μ; ^1H NMR δ ($CDCl_3$) 1.23 (3 H, singlet), 1.27–2.10 (8 H, multiplet), 2.00 (3 H, singlet), 3.33 (1 H, doublet, J = 12 Hz), 3.58 (1 H, doublet of doublet of doublet, J = 3.9, 7.5, 12 Hz), 3.83 (3 H, singlet), 4.86 (1 H, doublet of doublet of doublet, J = 5.1, 7.5, 12.7 Hz), 5.36 (1 H, multiplet), and 5.77 (1 H, doublet, J = 3.9 Hz).

Preparation of 2,3,3aβ,5,6,7,8,8a,9,9aβ-Decahydro-8aβ-methyl-2-oxo-5β-(phenylthio)naphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (82a). A solution of vinylcyclopropane **60** (50 mg, 0.19 mmol) and benzenethiol (20 μL, 0.20 mmol) in dry benzene (3 mL) containing a trace of 2,2′-azobisisobutyronitrile under nitrogen was heated at 60 °C for 20 h and cooled. The mixture was diluted with ether and the resulting solution was washed with water and brine. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give **82a** as a light yellow oil in nearly quantitative yield: IR ($CHCl_3$) 5.62 and 5.75 μ; ^1H NMR δ ($CDCl_3$) 1.10–2.30 (8 H, multiplet), 1.42 (3 H, singlet), 3.33 (2 H, multiplet), 3.80 (3 H, singlet), 3.93 (1 H, multiplet), 4.86 (1 H, multiplet, 5.21 (1 H, broadened doublet, J = 4 Hz), and 7.16–7.59 (5 H, multiplet).

Preparation of 4β-Acetoxy-2,3,3aβ,4,6,7,8,8a,9,9aβ-decahydro-8aβ-methyl-2-oxonaphtho[2,3-*b*]furan-3-carboxylic Acid Methyl Ester (83b). Allylic acetate **83b** was prepared from allylic sulfide **82a** (50% overall yield from vinylcyclopropane **60**) in the manner described for the preparation of allylic acetate **81b:** IR ($CHCl_3$) 5.61 and 5.76 μ; ^1H NMR δ ($CDCl_3$) 1.20 (3 H, singlet), 1.31–2.26 (8 H, multiplet), 2.03 (3 H, singlet), 3.28 (2 H, multiplet), 3.83 (3 H, singlet), 5.00 (1 H, multiplet), 5.26 (1 H, singlet), and 5.98 (1 H, triplet, J = 2.8 Hz).

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studies presented in this report continue in the laboratory of A.G.S. at Rensselaer Polytechnic Institute.

References and Notes

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