^{1}H NMR δ 3.82 (s, 3, OMe), 6.3–7.2 (m, 5, aromatic and olefinic Hs); MS, *m/e* 324 (M^+, base), 309 (15%), 167 (38), 130 (66); exact mass, *m/e* 324.1468 (calcd for $C_{19}H_{20}O_3N_2$, *m/e* 324.1474).

20-Deethyl-2β,16α-dihydro-5-oxovincadifformine (9a). A mixture of 405 mg of ester **8** and 200 mg of 10% palladium–charcoal in 20 mL of methanol was hydrogenated at 50 psi for 6 h and then filtered through Celite. The filtrate was evaporated under vacuum. Crystallization of the residual solid from methanol yielded 387 mg (95%) of crystalline ester **9a**: mp 158–160 °C; IR (KBr) NH 3250 (m), C=O 1725 (s), 1660 (s), C=C 1600 (w) cm^{-1}; UV (EtOH) λ_{max} 249 nm (log ε 3.89), 302 (3.51); ^{1}H NMR δ 1.5–1.9 (m, 6, methylenes, methine), 2.18 (d, 1, *J* = 17 Hz, H-6), 2.2–2.8 (m, 2, methylene Hs), 2.87 (d, 1, *J* = 17 Hz, H-6), 3.51 (d, 1, *J* = 10 Hz, H-2), 3.76 (s, 3, OMe), 3.97 (d, 1, *J* = 3 Hz, H-21), 4.19 (d, 1, *J* = 13 Hz, H-3), 6.7–7.2 (m, 4, aromatic Hs); MS, *m/e* 326 (M^+, 94%), 240 (10), 180 (9), 157 (11), 131 (15), 130 (base); exact mass, *m/e* 326.1627 (calcd for $C_{19}H_{22}O_3N_2$, *m/e* 326.1630).

20-Deethyl-2β,16α-dihydrovincadifformine (9b). A 1 M tetrahydrofuran solution of diborane, 10 mL, was added dropwise to a solution of 326 mg of lactam **9a** in 30 mL of tetrahydrofuran at 0 °C over a 5 h period. Workup as in the preparation of ester **6** above, followed by chromatography on silica gel and elution with 1:1 cyclohexane–ethyl acetate yielded 228 mg (73%) of amorphous, solid ester **9b**: IR (film) NH 3380 (m), C=O 1735 (s), C=C 1610 (m) cm^{-1}; ^{1}H NMR δ 1.2–2.4 (m, 12, methylenes, methines), 2.50 (d, 1, *J* = 3 Hz, H-21), 3.0–3.2 (m, 2, 2 NCH), 3.62 (d, 1, *J* = 10 Hz, H-2), 3.73 (s, 3, OMe), 6.6–7.1 (m, 4, aromatic Hs); MS, *m/e* 312 (M^+, 21%), 311 (8), 226 (10), 97 (8), 96 (base); exact mass, *m/e* 312.1843 (calcd for $C_{19}H_{24}O_2N_2$, *m/e* 312.1838).

20-Deethyl-5-oxovincadifformine (5b). A mixture of 85 mg of ester **9a** and 65 mg of DDQ in 5 mL of freshly distilled dioxane was refluxed under nitrogen for 1.5 h and then poured into 5% sodium hydroxide solution. The mixture was extracted with methylene chloride. The extract was dried (Na_2SO_4) and evaporated under vacuum. The residue was chromatographed on silica gel and eluted with 2:1 cyclohexane–ether. Crystallization of the solid product, 48 mg (57%), from ether yielded lactam **5b**: mp 194–196 °C; IR (KBr) NH 3460 (m), C=O 1690 (s), 1660 (s), C=C 1610 (s) cm^{-1}; UV (EtOH) λ_{max} 230 nm (log ε 4.12), 302 (4.17), 333 (4.28); ^{1}H NMR δ 1.4–2.0 (m, 5, methylenes, methine), 2.21 (t, 1, *J* = 13 Hz, H-17), 2.48 (d, 1, *J* = 13 Hz, H-17), 2.61, 2.66, 2.75, 2.80 (AB, 2, 2 H-6), 2.85 (m, 1, H-3), 3.79 (s, 3, OMe) 4.15 (d, 1, *J* = 4 Hz, H-21), 4.35 (d, 1, *J* = 13 Hz, H-3), 6.8–7.3 (m, 4, aromatic Hs), 8.90 (s, 1, NH); MS, *m/e* 324 (M^+, base), 293 (28%), 292 (97), 265 (13), 263 (10), 215 (15), 214 (98), 182 (14), 180 (18), 167 (13), 155 (14), 154 (50), 127 (13); exact mass, *m/e* 324.1476 (calcd for $C_{19}H_{20}O_3N_2$, *m/e* 324.1474).

20-Deethylvincadifformine (5a). Lead tetraacetate, 28 mg, was added in small portions to a stirring solution of 20 mg of ester **9b** in 3 mL of dry methylene chloride under nitrogen at −15 °C over a 10 min period. Workup as in the above preparation of ester **5c**, alumina chromatography of the crude product and elution with 65:1 cyclohexane–ethyl acetate yielded 8 mg (40%) of amorphous, solid ester **5a**, spectrally identical with an authentic sample.[2c,8]

A mixture of 20 mg of lactam **5b** and 30 mg of lithium aluminum hydride in 10 mL of anhydrous ether was stirred under nitrogen at −5 to 0 °C for 4 h.[10] It then was poured slowly into 5% hydrochloric acid solution and a saturated sodium potassium tartrate solution was added. After the addition of a saturated sodium bicarbonate solution and methylene chloride the aqueous layer was extracted with more methylene chloride and the combined organic solutions dried (Na_2SO_4) and evaporated under vacuum. Chromatography of the crude product as above led to 5 mg (26%) of amorphous, solid ester **5a**, identical by IR, ^{1}H NMR spectra, and TLC with an authentic specimen.[2c,8]

Acknowledgment. E.W., K.O., and D.P.S. are grateful to the U.S. Public Health Service for the support of the work at Rice University and express their thanks to Dr. U. O. Cheriyan for the early experiments and to Professor M. E. Kuehne for a sample of deethylvincadifformine.

Registry No. 1 (R = CO_2Me), 54950-20-8; 2 (R = CO_2Me), 87495-03-2; 3 (R = CO_2Me), 87495-04-3; (±)-4 (R = CO_2Me), 87495-05-4; (±)-**5a**, 77080-74-1; (±)-**5b**, 87508-90-5; (±)-**5c**, 87508-87-0; (±)-**5d**, 87508-88-1; (±)-**6**, 87495-06-5; (±)-**7a**, 87495-08-7; (±)-**7b**, 87495-07-6; (±)-**8**, 87508-89-2; (±)-**9a**, 87495-09-8; (±)-**9b**, 87495-10-1; (±)-i, 87495-11-2; methyl nicotinate, 93-60-7; methyl acetate, 79-20-9; indoleacetic anhydride, 41547-05-1.

(10) Cf. Levy, J.; Laronze, J.-Y.; Laronze, J.; LeMen, J. *Tetrahedron Lett.* **1978**, 1579.

Synthesis of Two Macrolide Pheromones of the Rusty Grain Beetle, *Cryptolestes ferrugineus* (Stephens)[1]

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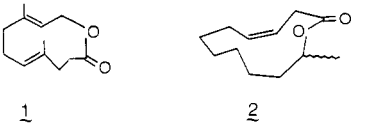
Two macrolide pheromones for *Cryptolestes ferrugineus* (Stephens), the rusty grain beetle, have been synthesized. Synthesis of 4,8-dimethyl-4(*E*),8(*E*)-decadienolide (**1**) was achieved by intramolecular alkylation of an ω-bromo (phenylthio)acetate derived from geraniol by reaction with (phenylthio)acetyl chloride and allylic functionalization of the 8(*E*)-methyl. Macrolide **1** was also synthesized by intramolecular esterification of an ω-hydroxy acid derived from geraniol by formal addition of acetate to tetrahydropyranyl-protected 8(*E*)-bromogeraniol. Synthesis of the second macrolide, 11-methyl-3(*Z*)-undecenolide (**2**), also involved intramolecular esterification of the appropriate hydroxy acid. The chiral center of **2** was introduced via chiral propylene oxides while the *Z* unsaturation was introduced by P-2 nickel reduction of the appropriate alkyne. Both chiral isomers of **2** were synthesized.

The rusty grain beetle, *Cryptolestes ferrugineus* (Stephens), is a widely distributed pest which primarily infests stored grain. Male beetles produce aggregation pheromones which are attractive to both sexes and probably function by promoting population buildup in suitable habitats.[2] Recently, we reported the isolation of two synergistic pheromones, ferrulactones I (**1**) and II (**2**), from



1 **2**

the volatile components of *C. ferrugineus* frass.[3] The

(1) Taken in part from the Ph.D. Thesis of J.W.W., Simon Fraser University, June 1982, and from the M.Sc. Thesis of V.G. V., Simon Fraser University, August 1980.

(2) J. H. Borden. M. G. Dolinski, L. Chong, V. Verigin, H. D. Pierce, Jr., and A. C. Oehlschlager, *Can. Entomol.*, 111, 681 (1979).

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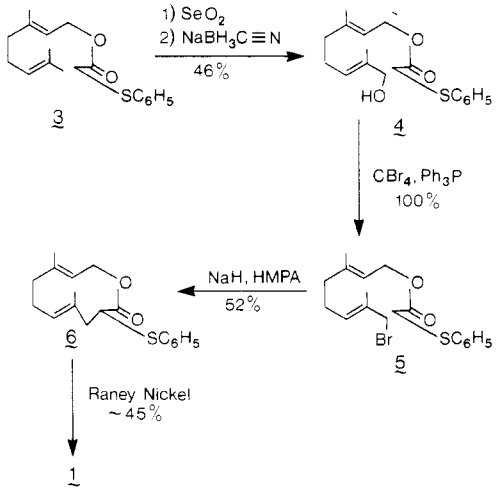
0022-3263/83/1948-5009$01.50/0

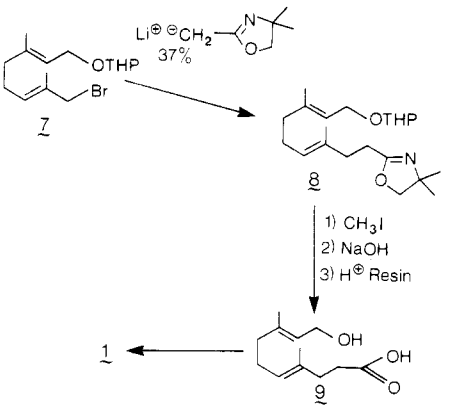
Table I. Intramolecular Alkylation of ω-Bromo (Phenylthio)acetate 5 to Phenylthio Lactone 6

entry	reagent (equiv)	solvent	[5], mM	reaction time	% yield of 6
1	NaH (1.25)	THF	50	24 h	0
2	NaH (1.25)	HMPA	50	6 h	21
3	NaH (1.25)	HMPA	12.5	24 h	37
4	NaH (3.5)	HMPA	2.0	5 min	52
5	NaHMDS (1.5)	THF	16	24 h	0

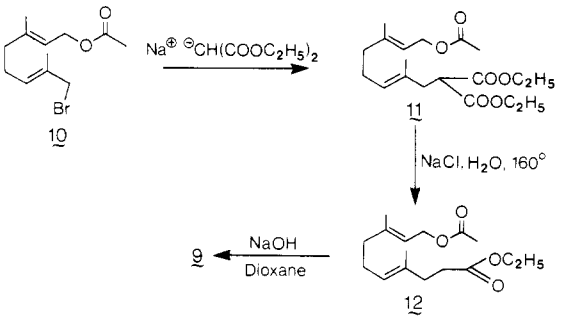
Scheme I



Scheme II



Scheme III



possibility that these pheromones could be utilized to increase the efficiency of detection traps[4] for *C. ferrugineus* in grain storage facilities[5] stimulated development of synthetic routes to **1** and **2**. We now report two stereospecific syntheses of **1** from geraniol and the stereospecific syntheses of racemic **2**, (*R*)-(−)-**2**, and (*S*)-(+)-**2**.

Retrosynthetic analysis of **1** revealed it to be a chain-extended, terminally bifunctional geraniol derivative. Construction of the 11-membered macrolide ring of **1** was attempted by the intramolecular alkylation of an ω-bromo (phenylthio)acetate (**5**, Scheme I).[6] (Phenylthio)acetate **3** was prepared from geraniol in 99% yield by reaction with (phenylthio)acetyl chloride and pyridine in methylene chloride. Allylic oxidation of **3** was best effected with selenium dioxide and pyridine in refluxing ethanol[7] and gave a mixture of the desired alcohol **4**, the corresponding aldehyde, and recovered starting material in a ratio of 1:1:1. Reduction of the crude product with sodium cyanoborohydride[8] followed by chromatography afforded **4** in 46% yield based on recovered starting material. Oxidation with selenium dioxide and *tert*-butyl hydroperoxide[9] failed to improve the yield of **4**. Bromination of alcohol **4** was carried out with 2 equiv of carbon tetrabromide and triphenylphosphine to give a quantitative yield of **5**.[10]

The cyclization of **5** was attempted via the method reported by Takahashi and others[6] under a variety of reaction conditions (Table I). Best results were obtained when **5** was added rapidly to 3.5 equiv of sodium hydride (NaH) in hot hexamethylphosphoramide (HMPA) under high-dilution conditions (Table I, entry 4). Lower yields resulted when less sodium hydride and higher concentrations of **5** were employed (Table I, entries 2 and 3). The use of sodium hydride or sodium–hexamethyldisilazane in THF (Table I, entries 1 and 5) failed to effect any cyclization, indicating the essential role of HMPA in the reaction.

Desulfurization of **6** was attempted with several reagents (zinc–trimethylchlorosilane[11], mercury–aluminum amalgam[12], lithium–ethylamine[13], Raney nickel[14]) of which only Raney nickel was effective. A 45% yield (determined by GLC) of **1** was obtained when **6** was treated with approximately 10 equiv (w/w) of W-2 Raney nickel in ethanol at 23 °C. Although the yield was poor, the reaction proceeded without isomerization of the unsaturated linkages and was therefore suitable for the preparation of **1**. Despite the successful preparation of **1** (as determined by GLC) by this short stereospecific synthesis, alternate routes were developed because the high-dilution conditions required for the preparation of **6** prevented scale-up.

Our second approach to the synthesis of **1** was by intramolecular esterification of ω-hydroxy acid **9**. Geraniol

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(8) Attempted reduction of the aldehyde with sodium borohydride resulted in virtually complete conversion of the ester moiety to an ether. Presumably, the proximity of the sulfur atom activated the ester carbonyl toward reduction.
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Table II. Lactonization of 9 by the Double Activation Method

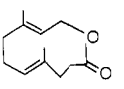
entry	reaction conditions: method[a]	addition time, h	temp, °C	$AgClO_4$, equiv	solvent (reflux time, h)	% yield[b]: 1	diolide
1	A	4	4		benzene (1)	23.3	0
2	A	4	4	1.1	benzene (1)	10.5	2.5
3	A	1	23		benzene (4)	11.5	3.6
4	B		4		benzene (5)	28.6	5.1
5	C		−10		toluene (0)	37.0	1.9
6	D		−10		toluene (5)	7.6	0

[a] Method A: the thio ester was prepared by stirring **9**, bis(4-*tert*-butyl-*N*-isopropylimidazol-2-yl) disulfide (1.5 equiv) and Ph_3P (1.5 equiv) in benzene at 4 °C for 18 h. The crude thioester was diluted with benzene and added dropwise to refluxing benzene. Method B: the thio ester was prepared as described for method A and then diluted all at once with benzene and refluxed. Method C: the procedure as described in method A was used except that the ingredients were mixed at −68 °C in toluene, allowed to warm to and held at −10 °C for 2.5 h, diluted with cold (−35 °C) toluene, and then heated to reflux for 2 h. Method D: the procedure as described in method C was used except that 2,2′-dipyridyl disulfide was used. [b] Reported yields were of isolated products after chromatography.

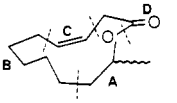
was utilized as the starting material for this route since it possessed the appropriate alkyl substitution pattern. Our plan called for protection of the alcohol and functionalization of the *E* terminal methyl followed by chain extention with an acetic acid moiety (Scheme II). Deprotection and ring closure would yield the desired lactone **1**. Bromide **7** was prepared in two steps from the tetrahydropyranyl ether of geraniol as described by Mori.[15] Alkylation of **7** with the lithium salt of 2,4,4-trimethyl-2-oxazoline[16] resulted in the 2-alkyloxazoline **8** which upon base hydrolysis, followed by acid resin treatment, afforded a 12% (overall from geraniol) yield of **9**. Because of the poor yield obtained via the oxazoline route, homologation was attempted by a malonic ester (Scheme III). Acetate was used to protect the alcohol because the poor yield in the oxazoline homologation was partially due to loss of the tetrahydropyranyl group. Bromide **10**, prepared in 95% yield by treatment of the alcohol with triphenylphosphine and carbon tetrabromide, was alkylated with diethyl sodiomalonate to give **11**. Thermal decarboxylation[17] of the crude product derived from this alkylation afforded a 58% yield of the acetoxy ester **12**. A 42% yield of **9** (from **10**) was realized after saponification of **12** with sodium hydroxide in dioxane and water.

The "double activation" method developed by Corey[18] for the lactonization of ω-hydroxy acids was used for the preparation of **1**. The results of a yield-optimization study on the lactonization of **9** with bis(4-*tert*-butyl-*N*-isopropylimidazol-2-yl) disulfide are summarized in Table II. Conditions which gave an 83% isolated yield of hexadecanolide[18] only gave a 23% yield of **1** (entry 1). When both the addition rate and temperature were increased (compare entry 1 to entry 3), a 50% reduction in the yield of **1** was observed. The results contained in entry 4 indicated that the addition temperature was the critical factor influencing yield since an increase was observed despite the immediate dilution of the thiol ester solution. The best yield was obtained when the thiol ester formation was conducted in cold toluene (entry 5). The lactonization of ω-hydroxy thiol esters at room temperature has been previously reported but only in the presence of silver ion.[21] Silver ion, which has been shown to promote lactonization in other ω-hydroxy thiol esters,[19,20] caused a large, and as yet unexplained, reduction in yield (entry 2). The lactonization of **9** via the 2-pyridyl thiol ester (entry 6), under the conditions described for entry 5, resulted in a poor yield of **1**. Formation of the unreactive *N*-acyl derivative of **9** in preference to the thiol ester derivative was the probable cause.[18] The synthetic lactone prepared by the malonic ester route was chromatographically and spectrally identical with the natural material.

The synthesis of **2** was also based on the intramolecular esterification of an ω-hydroxy acid (**24**). On the basis of functional groups and the chiral center, the structure of **2** can be divided into four segments (A–D). Synthesis of



1



2

2 from these segments could be accomplished in a linear (A + B + C + D) or convergent ((A + B) + (C + D)) manner. Initially, a synthesis was attempted in which the Grignard reagent of a protected 5-bromopentan-1-ol (B) was coupled to propylene oxide (A) via cuprous iodide catalysis. The secondary alcohol was then protected and the primary alcohol deprotected and converted to a primary bromide. Coupling of the bromide to the dilithium dianion of 3-butynoic acid (C + D) was attempted without success. This reaction failed presumably because treatment of 3-butynoic acid with *n*-butyllithium gave an allene due to the acidity of the C_2 protons. Since synthesis of **24** was not achieved with a free carboxyl group (D) and alkyne (C) joined, we developed a route in which the C–D unit was introduced as 3-butyn-1-ol which was subsequently oxidized to the requisite carboxylic acid. Thus our strategy for the construction of **24** involved the linkage of three segments: a protected 3-butyn-1-ol, 1,5-dihalopentane, and propylene oxide. The addition of HMPA to a mixture of **13** and the lithium salt of **14** resulted in a 62% yield of chloride **15** (Scheme IV). This method of addition was adopted since the standard procedure,[22] addition of the lithium salt of **14** to an HMPA–THF solution of **13**, only gave a 50% yield. Conversion (NaI in acetone) of the chloride to iodide **16** was required to facilitate the formation of the Grignard reagent. Initiation of Grignard formation for **16** was still difficult despite the use of various reagents (iodine, ethylene dibromide, and methylmagnesium bromide) and the application of heat. We

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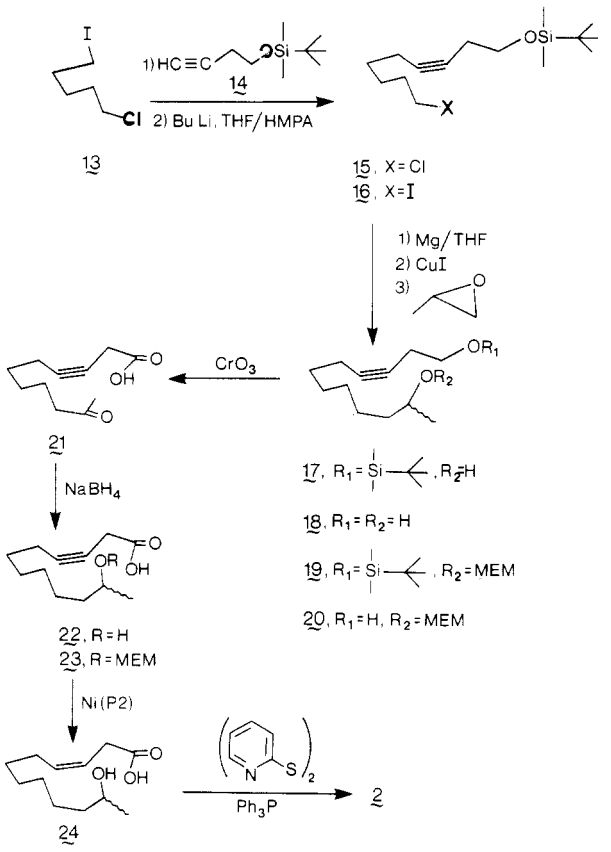
Scheme IV



eventually discovered that the addition of ethyl bromide to a refluxing mixture of **16** and magnesium in THF was required. Once Grignard formation was complete, coupling to methyloxirane was rapidly effected by the successive addition of cuprous iodide and methyloxirane to the ice-cold mixture.[23] Unfortunately, only a 45.9% yield of alcohol **17** was obtained despite numerous variations of solvent, temperature, and proportions of CuI.

Diol **18** obtained in quantitative yield upon removal of the *tert*-butyldimethylsilyl group was oxidized in acetone to **21** with $CrO_3 \cdot H_2SO_4$ by using the inverse addition procedure[24] to minimize formation of ester side products. Keto acid **21** was purified by crystallization and reduced to **22** in 67% yield from diol **18**. Reduction of the acetylene in **22** to the *Z* olefin **24** was stereospecific (376:1) with P-2 nickel.[25] Lactonization of **24** was initially attempted by using bis(4-*tert*-butyl-*N*-isopropylimidazol-2-yl) disulfide and conditions (A–D) developed for formation of **1**. Under these conditions no **2** was observed even when the reaction mixture was refluxed for several hours. The reaction was successfully conducted by using 2,2′-dipyridyl disulfide by adding the thiol ester dropwise to a refluxing xylene solution of silver perchlorate. Silver ion promoted formation of **2** whereas it decreased the yield of **1** under similar reaction conditions.

Although **2** contains a 12-membered ring and can be considered a large-ring macrolide, an examination of space-filling models reveals that it is much more rigid than **1**. The presence of the *Z* olefin in **2** appears to impart some measure of ring strain which we feel leads to the low cyclization yield (30–37%).[26] Recifeiolide, which is identical with **2**, except that the unsaturation is 5*E*, was prepared from the hydroxy acid in 75% yield under conditions[27] which were less severe (65 °C, $CH_3C{\equiv}N$) than those required for formation of **2**.

The enantiomers of **2** were synthesized by using the readily available chiral methyloxiranes (C)[23,28] for the formation of the enantiomers of **17**. The MEM ethers[29] of (*R*)- and (*S*)-**19** were formed prior to removal of the *tert*-butyldimethylsilyl group to yield (*R*)- and (*S*)-**20**. Oxidation of the enantiomers of **20** by using the inverse addition methodology[24] employed for the preparation of **21** gave a 54% yield of the enantiomers of the MEM acid **23**. Difficulty was encountered in the removal of the MEM group of **23**. When the reaction was carried out by Corey's procedure,[29] a complex mixture was produced. Reducing the reaction time to 5 min for (*R*)-**23** gave a 49% yield of (*R*)-**22**. Reduction of (*R*)-**22** and (*S*)-**22** to (*R*)-**24** and (*S*)-**24**, respectively, followed by cyclization of (*R*)-**24** and (*S*)-**24** gave the chiral isomers of **2**. The naturally occurring and biologically active enantiomer of **2** has the 11*S* configuration.[3]

Experimental Section

IR spectra were determined on a Perkin-Elmer 599B spectrophotometer. ^1H NMR spectra were determined on Varian EM-360 or XL-100 or on Bruker WM-400 instruments. ^{13}C NMR spectra were determined on the XL-100 instrument. Mass spectra (electron impact, EI, or chemical ionization, CI) were obtained at 70 eV on a HP 5985B GC/MS/DS. High-resolution mass spectra were obtained on a DS-50 instrument at the University of British Columbia. Microanalyses were performed by M. Yang (Department of Biological Science, Simon Fraser University) on a Perkin-Elmer Model 240 elemental analyzer. Optical rotations were measured with a Rudolph polarimeter (Model 70) on samples contained in a 1 dm × 2 mm i.d. cell (Zeiss, Germany). Concentrations (*c*) are reported as g/100 mL of solvent.

Thin-layer (0.25 mm) and preparative thick-layer (20 cm × 20 cm × 0.75 mm) plates were made from silica gel 60 GF_{254} (E. Merck, Darmstadt). All column chromatography was performed on silica gel 60 (40–63 μm, E. Merck, Darmstadt) as described by Still.[30] Tetrahydrofuran (THF) was distilled from lithium aluminum hydride ($LiAlH_4$). Dimethylformamide (DMF), benzene, and toluene were distilled from calcium hydride prior to use.

Analyses by GLC were carried out with HP5880A and 5830A gas chromatographs equipped with capillary inlet systems and flame-ionization detectors. The columns used in the 5880A were a 12 m × 0.2 mm i.d. fused silica column (A) coated with methylsilicone oil and a 31 m × 0.25 mm i.d. borosilicate glass column (B) coated with SP-2100. The polar column (C) operated in the 5830A instrument was a 33 m × 0.66 mm i.d. borosilicate glass column coated with SP-1000. Helium was the carrier gas. Injection port and detector temperatures were 260 and 275 °C, respectively.

Unless otherwise noted, the organic phase derived from product extraction was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure on a rotary evaporator.

Preparation of 3,7-Dimethyl-2(*E*),6-octadienyl (Phenylthio)acetate (3). (Phenylthio)acetyl chloride[31] (34.1 g, 183 mmol) was added dropwise over 1 h to an ice-cold solution of geraniol

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(25 g, 162 mmol) and pyridine (17 mL) in 25 mL of dichloromethane. The reaction mixture was stirred for 2 h and then poured into 150 mL of ice-cold 0.1 N HCl. The CH_2Cl_2 extract (3 × 100 mL) of the aqueous mixture was washed successively with 0.1 N HCl (2 × 100 mL), saturated aqueous $NaHCO_3$, and water. Product isolation resulted in a dark yellow liquid which was chromatographed on 275 g (30 cm × 4.5 cm I.D. column) of silica gel. Elution with 10% EtOAc in hexane gave 49.0 g (99.3%) of **3**. The light yellow liquid was homogeneous by TLC (50% EtOAc in hexane): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.56 (3 H, CH_3, s), 1.63 (6 H, *gem*-dimethyl, s), 2.03 (4 H, C_4, C_5, m), 3.58 (2 H, OCH_2, s), 4.58 (2 H, C_1, d, J = 7.2 Hz), 4.85–5.60 (2 H, C_2, C_6, m), 7.1–7.5 (5 H, phenyl, m); mass spectrum (EI), m/z (relative intensity) 304 (0.4), 168 (28), 136 (27), 123 (61), 121 (24), 93 (63), 81 (45), 69 (100). Anal. Calcd for $C_{18}H_{24}O_2S$: C, 71.01; H, 7.95. Found: C, 70.60; H, 8.07.

Preparation of 3,7-Dimethyl-8-hydroxy-2(*E*),6(*E*)-octadienyl (Phenylthio)acetate (4). Selenium dioxide (11.5 g, 103 mmol) was added to a solution of **3** (42.0 g, 138 mmol) and pyridine (25 mL) in 350 mL of 95% ethanol, and the mixture was refluxed for 4.5 h. The reaction mixture was filtered, and the filtrate concentrated in vacuo to give a crude product which was dissolved in THF (100 mL), acidified (pH 3) with HCl, cooled in an ice-bath, and treated with 3.3 g (53 mmol) of sodium cyanoborohydride. After 1 h at 0 °C the reaction mixture was stirred at 23 °C for 18 h. The reaction mixture was poured into water (200 mL) and extracted with diethyl ether (3 × 100 mL), and the ether extract was washed with saturated brine. Isolation yielded 48.5 g of crude product which was divided into eight portions and chromatographed on 180 g (20 cm × 4.5 cm i.d.) of silica gel. Regeneration of the silica gel by successive washing with EtOAc (500 mL) and the elution solvent (50% EtOAc in hexane, 500 mL) enabled each column to be used twice before the silica gel was discarded. Fractions (20 mL) containing alcohol **4** were pooled to give a yield of 17.07 g (45.9% based on recovered **3**) which gave one spot (R_f 0.48) when analyzed by TLC (50% EtOAc in hexane): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.62 (6 H, CH_3–C_3, CH_3–C_7, s), 2.08 (4 H, C_4, C_5, m), 3.60 (2 H, CO–CH_2, s), 3.95 (2 H, C_8, s), 4.60 (2 H, C_1, d, J = 7.2 Hz), 5.1–5.5 (2 H, C_2, C_6, m), 7.1–7.5 (5 H, phenyl, m); IR (film) 3400 (OH); mass spectrum (EI), m/z (relative intensity) 303 (2.3), 197 (6.9), 169 (7.6), 153 (18.8), 151 (13.6), 137 (29), 135 (100), 125 (17.5), 123 (27), 111 (56), 107 (25). Anal. Calcd for $C_{18}H_{24}O_3S$: C, 67.47; H, 7.55. Found: C, 67.46; H, 7.59.

Preparation of 3,7-Dimethyl-8-bromo-2(*E*),6(*E*)-octadienyl (Phenylthio)acetate (5). Because **5** was unstable, its preparation was carried out in small batches immediately before it was required. To an anhydrous ether (50 mL) solution of carbon tetrabromide (2.05 g, 6.24 mmol) and **4** (1.0 g, 3.12 mmol) was added triphenylphosphine (1.64 g, 6.24 mmol) at 23 °C. The reaction mixture was stirred for 20 h and then filtered to remove triphenylphosphine oxide. Removal of the ether in vacuo gave a residue which was chromatographed on 160 g (18 cm × 4.5 cm i.d.) of silica gel. Elution with 25% EtOAc in hexane afforded 1.19 g (99.8%) of **5**. Analysis of the product on TLC (25% EtOAc in hexane) revealed one spot (R_f 0.45): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.67 (3 H, CH_3–C_3, s), 1.72 (3 H, CH_3–C_7, s), 3.61 (2 H, CO–CH_2, s), 3.94 (2 H, C_8, s), 4.60 (2 H, C_1, d, 7.2 Hz), 5.1–5.7 (2 H, C_2, C_6, m), 7.1–7.75 (5 H, phenyl, m); mass spectrum (CI, CH_4), m/z (relative intensity) 413 (1.3), 411 (1.7), 385 (1.3), 383 (1.5), 303 (19), 217 (35), 215 (35), 169 (23), 151 (13), 135 (100), 123 (45), 107 (9), 93 (14), 81 (30).

Preparation of 2-(Phenylthio)-4,8-dimethyl-4(*E*),8(*E*)-decadienolide (6). To washed sodium hydride (35 mg of a 57% mineral oil dispersion, 0.83 mmol) in 40 mL of dry HMPA at 55 °C under dry nitrogen was added **5** (240 mg, 0.63 mmol) in 5 mL of dry THF over 30 min. The reaction mixture was maintained at 93 °C (bath temperature) for 23 h, after which it was poured into water (80 mL) and extracted with ether (3 × 50 mL) which was washed with brine (2 × 50 mL). The residue left after product isolation was applied onto a single preparative TLC plate and eluted with 25% EtOAc in hexane. The band at R_f 0.54 (UV visualization at 254 nm) was eluted with ether to give 70.2 mg (37%) of a colorless liquid (**6**), which was homogeneous by TLC analysis: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.66 (3 H, CH_3–C_4 or CH_3–C_8, s), 1.67 (3 H, CH_3–C_4 or CH_3–C_8, s), 2.0–2.6 (6 H, C_3, C_6, C_7, m), 3.92 (1 H, C_2, dd, J = 4.5 Hz, 12 Hz), 4.41 (1 H, C_{10a}, dd, J = 9.6 Hz, 11 Hz), 4.76 (1 H, C_{10b}, dd, J = 6 Hz, 11 Hz), 4.92 (1 H, C_5, br dd, J = 12 Hz, 2.5 Hz), 5.61 (1 H, C_9, br t, J = 6 Hz, 9.6 Hz), 7.36 (5 H, phenyl, m); mass spectrum (EI), m/z (relative intensity) 302 (14), 234 (26), 150 (14), 135 (22), 123 (17), 121 (21), 110 (19), 109 (14), 107 (18), 105 (16), 95 (11), 93 (29), 91 (19), 81 (100), 80 (54), 79 (48), 77 (25), 67 (17), 65 (16), 55 (16), 53 (20), 41 (17).

The result obtained in this reaction was not reproducible despite numerous attempts. The major product isolated from further unsuccessful attempts had an R_f (0.54, 25% EtOAc in hexane) which was identical with that of the phenylthio lactone **6**. This product was identified as 3,7-dimethyl-2(*E*),5(*E*),7-octatrienyl (phenylthio)acetate, the product of dehydrobromination of **6**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.66 (3 H, CH_3–C_3, s), 1.82 (3 H, CH_3–C_7, s), 2.77 (2 H, C_4, br d, J = 6.5 Hz), 3.58 (2 H, CO–CH_2, s), 4.60 (2 H, C_1, d, J = 7.0 Hz), 4.87 (2 H, *exo*-methylene, br s), 5.28 (1 H, C_2, t, J = 7.0 Hz), 5.60 (1 H, C_5, dd, J = 6.5 Hz, 15 Hz), 6.13 (1 H, C_6, d, J = 15 Hz); mass spectrum (EI), m/z (relative intensity) 302 (0.9), 218 (3), 168 (12), 134 (100), 123 (100), 119 (60), 107 (32), 105 (29), 93 (63), 91 (51), 81 (27), 79 (47), 77 (48), 69 (20), 65 (22), 55 (50), 45 (41), 41 (36); HRMS calcd for $C_{18}H_{22}O_2S$ m/z 302.4328, found m/z 302.1343.

Preparation of 1 via the Desulfurization of 6. Raney nickel[32] (450 mg, W-2) was added to a solution of **6** (45 mg, 0.15 mmol) in 9 mL of absolute ethanol. The suspension was stirred at room temperature and analyzed by GLC (columns A and C). Analysis of a sample (column A, 210 °C isothermal) removed after 1 h revealed that the reaction was 45% completed based on the consumption of **6**. Heating the reaction mixture to reflux did not increase the yield of product. The addition of a second portion of Raney nickel (450 mg) followed by 20 min of reflux resulted in the complete disappearance of both starting material (**6**) and product (**1**). Presumably, the organic material was irreversibly adsorbed onto the catalyst. No product was recovered from this reaction. An aliquot removed from the reaction prior to the second addition of Raney nickel was analyzed by GLC (column C) and contained material which coeluted with authentic **1**. No isomeric products were detected.

Preparation of 2-[9-[(Tetrahydropyranyl)oxy]-3,7-dimethyl-3(*E*),7(*E*)-nonadienyl]-4,4-dimethyl-2-oxazoline (8). To 2,4,4-trimethyl-2-oxazoline (0.8 g, 7.1 mmol) in 10 mL THF at −78 °C (dry ice–acetone bath) under N_2 was added 3.7 mL of 2.2 M (8.1 mmol) *n*-BuLi in hexane. The solution was stirred for 30 min, and 3.0 g (6.3 mmol) of bromide **7**[15] was added. The reaction was stirred for 30 min, warmed to room temperature, and poured into 50 mL of brine. Extraction with ether (3 × 50 mL) and the usual workup gave 2.1 g of crude product which was flash chromatographed (50% EtOAc in hexane) to give **8**: 0.85 g (37%); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.25 (6 H, C_4–CH_3, s) 1.63 (12 H, C_3 and C_7 CH_3's, br s, THP), 2.05 (4 H, C_5, C_6, s), 2.32 (4 H, C_1, C_2, s), 3.20–4.30 (6 H, CH_2–O, m), 4.63 (1 H, THP, br s), 5.00–5.50 (2 H, C_4, C_8, m); mass spectrum (EI), m/z (relative intensity) 349 (M^+, 0.8), 264 (63), 248 (59), 180 (100), 113 (75), 85 (79), 67 (40); HRMS calcd for $C_{21}H_{35}NO_3$ m/z 349.2616, found m/z 349.2612.

Preparation of 10-Hydroxy-4,8-dimethyl-4(*E*),8(*E*)-decadienoic Acid (9). Oxazoline **8** (.768 g, 2.20 mmol) was converted to the methiodide salt by reaction with excess methyl iodide overnight at room temperature. After the volatiles were evaporated in vacuo, the crude salt was added to 5 mL of 1 N NaOH and stirred for 20 h at room temperature. The solution was acidified to pH 2 with 10% HCl and extracted with ether (3 × 30 mL). The usual workup gave 0.564 g of crude product which was purified by preparative TLC (silica gel, 50% EtOAc in hexane with 1% acetic acid) to yield 0.498 g (76%) of the THP-protected acid: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.63 (12 H, C_3 and C_7 CH_3's, THP, br s), 2.05 (4 H, C_5, C_6, s), 2.35 (4 H, C_1, C_2, s), 3.30–4.30 (4 H, CH_2–O, m), 4.63 (1 H, THP, br s), 4.90–5.50 (2 H, C_3, C_7, m), 8.75 (1 H, D_2O exchangeable, s); IR 3000 (m), 2920 (s), 1700 (s), 1010 (m), 905 (m), 730 (s) cm^{-1}; mass spectrum (EI), m/z (relative intensity) 296 (M^+, 0.1), 154 (13), 127 (13), 101 (18), 85 (100), 68 (15), 67 (28); HRMS, calcd for $C_{17}H_{28}O_4$ m/z 296.1988, found m/z 296.1986.

(32) R. Monzingo, "Organic Syntheses", Collect. Vol. III, Wiley, New York, 1955, p 181.

This product was converted to 4,8-dimethyl-10-hydroxy-4-(*E*),8(*E*)-decadienoic acid (**9**) as follows. Dowex 50W-X8 resin was activated by washing with 6 N HCl. Excess acid was removed by washing with water until the washings showed no reaction with silver nitrate. The resin was then washed with methanol.

The tetrahydropyranyl-protected acid **9** (0.459 g, 1.55 mmol) was added to 5 mL of methanol containing 0.75 g of the activated resin. The heterogeneous mixture was stirred at room temperature for 1 h. The mixture was then filtered, added to 30 mL of distilled water, and extracted with ether (3 × 25 mL). The usual workup yielded **9** which was purified by preparative TLC (silica gel, 50% EtOAc in hexane, 1% acetic acid): 0.146 g (44%); mass spectrum (EI), *m/z* (relative intensity) 212 (M^+, 1), 194 (12), 109 (33), 99 (32), 85 (100), 81 (85), 68 (61), 67 (65), 55 (44), 43 (93), 41 (84); HRMS, calcd for $C_{12}H_{20}O_3$ *m/z* 212.1412, found *m/z* 212.1418.

Preparation of 8-Acetoxy-2,6-dimethyl-2(*E*),6(*E*)-octadien-1-ol. Oxidation of geranyl acetate was carried out[9] by addition of *tert*-butyl hydroperoxide (28 mL, 90% solution, 242 mmol) to a suspension of selenium dioxide (7.1 g, 64 mmol) in dichloromethane (75 mL) and stirring for 30 min at 10 °C. Geranyl acetate [25 g, 128 mmol; bp 73–74 °C (0.65 mm); prepared by the treatment of geraniol with acetic anhydride and pyridine] was added at once to the selenium dioxide solution and stirred for 3 h (10 °C). Benzene (50 mL) was added to the reaction mixture and the dichloromethane removed in vacuo. The benzene solution was diluted with ether (100 mL) and washed with 10% aqueous potassium hydroxide (4 × 50 mL) and brine (2 × 50 mL). The residue which remained after product isolation contained aldehyde and was therefore subjected to reduction with sodium borohydride (1.9 g, 50 mmol; in 25 mL of absolute ethanol for 10 min). This reaction mixture was diluted with water (50 mL) and extracted with ether (3 × 50 mL), which was washed with brine (2 × 50 mL). Product isolation yielded the alcohol which was vacuum distilled: yield 15.4 g; bp 126–135 °C (0.9 mm). The distilled product contained the desired acetoxy alcohol (R_f 0.32; 50% EtOAc in hexane) and a contaminant (~20%, R_f 0.09) which was identified as 2,6-dimethyl-8-hydroxy-2(*E*),6(*E*)-octadien-1-ol: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.63 (6 H, C_2, C_6, s), 2.10 (4 H, C_4, C_5, m), 3.98 (2 H, C_1, s), 4.14 (2 H, C_8, d, *J* = 7.0 Hz), 5.43 (2 H, C_3, C_7, br t, *J* = 7.0 Hz). Separation of the desired acetoxy alcohol from the contaminant was achieved by chromatography on silica gel (200 g; 18 cm × 5 cm i.d. column). The sample was eluted with 50% EtOAc in hexane and 250 mL fractions were collected. Fractions 2–5 were combined to give 12.0 g (45%) of the pure acetoxy alcohol: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.64 (3 H, CH_3–C_6, s), 1.66 (3 H, CH_3–C_2, s), 2.00 (3 H, $COCH_3$, s), 2.05 (5 H, C_4, C_5, OH, m), 3.94 (2 H, C_1, s), 4.54 (2 H, C_8, d, *J* = 7.2 Hz), 5.30 (2 H, C_3, C_7, br t, *J* = 7.2 Hz); mass spectrum (EI), *m/z* (relative intensity) 134 (13), 121 (5), 119 (7), 93 (12), 84 (48), 68 (60), 67 (34), 55 (13), 43 (100), 41 (25); mass spectrum (CI, isobutane), *m/e* (relative intensity) 287 (3), 269 (1), 213 (15), 195 (12), 153 (18), 135 (100), 107 (10), 95 (8), 93 (12). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.10; H, 9.44.

Preparation of 8-Acetoxy-2,6-dimethyl-2(*E*),6(*E*)-octadienyl Bromide (10). To an ice-cold solution of the acetoxy alcohol prepared above (14.2 g, 67 mmol) and carbon tetrabromide (44.2 g, 133 mmol) in anhydrous ether (250 mL) was added 35.0 g (133 mmol) of triphenylphosphine.[10] The reaction mixture was then stirred at 4 °C for 24 h, after which it was filtered. The residue obtained after removal of the ether was diluted with 100 mL of ice-cold hexanes to precipitate the remainder of the triphenylphosphine oxide. Filtration of the hexane solution followed by evaporation of the filtrate gave a crude product which was chromatographed on 350 g (30 cm × 5 cm i.d. column) of silica gel (10% EtOAc in hexane, 20 mL fractions) to give 17.4 g (94.5%) of **10** which was homogeneous by TLC (R_f 0.59, 50% EtOAc in hexane): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.68 (3 H, CH_3–C_6, s), 1.72 (3 H, CH_3–C_2, s), 2.02 (3 H, $COCH_3$, s), 2.10 (4 H, C_4, C_5, m), 3.94 (2 H, C_1, s), 4.55 (2 H, C_8, d, *J* = 7.2 Hz), 5.15–5.70 (2 H, C_3, C_7, m); mass spectrum (CI, isobutane), *m/z* (relative intensity) 217 (48), 215 (50), 195 (19), 135 (100). Anal. Calcd for $C_{12}H_{19}O_2Br$: C, 52.38; H, 6.96. Found: C, 52.53; H, 6.97.

Preparation of Ethyl 10-Acetoxy-2-carbethoxy-4,8-dimethyl-4(*E*),8(*E*)-decadienoate (11). To washed sodium hydride (2.34 g of a 60% mineral oil dispersion, 59 mmol) in 180 mL of dry DMF under N_2 was added diethyl malonate (9.4 g, 59 mmol) over 20 min. The reaction mixture was stirred for 1 h. Then bromide **10** (14.6 g, 53 mmol) was added over 15 min to the solution of diethyl sodiomalonate. The reaction was heated to 60 °C for 4.5 h followed by 12 h at 23 °C. Workup of the reaction was carried out by dilution of the reaction mixture with water (250 mL) and extraction with ether (3 × 150 (87%)). Analysis by GLC on column A (200 °C) revealed two major products: **11** (77%) and diethyl malonate (11%). The diester **11** was subjected to decarboxylation without further purification. A small sample was purified by preparative TLC (R_f 0.27, 30% EtOAc in hexane) for analysis: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.24 (6 H, CH_3CH_2O, t, *J* = 7.0 Hz), 1.61 (3 H, CH_3–C_8, s) 1.68 (3 H, CH_3–C_4, s), 2.01 (3 H, $COCH_3$, s; 4 H, C_6, C_7, m), 2.57 (2 H, C_3, d, *J* = 7.6 Hz), 3.51 (1 H, C_2, t, *J* = 7.6 Hz), 4.17 (4 H, CH_3CH_2O, q, *J* = 7.0 Hz), 4.57 (2 H, C_{10}, d, *J* = 7.2 Hz), 5.0–5.5 (2 H, C_5, C_9, m); mass spectrum (CI, CH_4), *m/z* (relative intensity) 295 (100), 249 (23), 227 (34), 135 (30). Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.22; H, 8.64.

Preparation of Ethyl 10-Acetoxy-4,8-dimethyl-4(*E*),8-(*E*)-decadienoate (12). To a solution of partially purified **12** (15.5 g, ~42 mmol based on 77% purity) in Me_2SO (100 mL) were added 3.3 g (57 mmol) of sodium chloride and 2 mL of water.[17] The mixture was heated to 160 °C for 7 h and then stirred for 12 h at 23 °C. Analysis of an aliquot by GLC (column A, 210 °C) revealed that all of the starting material had been consumed. The mixture was poured into water (150 mL), extracted with ether (3 × 100 mL), and washed with brine (2 × 100 mL). Product isolation yielded 11.5 g which was chromatographed on 300 g (28 cm × 5 cm i.d. column) of silica gel (20% EtOAc in hexane): 8.3 g (58% yield from **10**; 91% pure by GLC, column C, 210 °C): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.25 (3 H, CH_3CH_2O, t, *J* = 7.2 Hz), 1.62 (3 H, CH_3–C_8, s), 1.71 (3 H, CH_3–C_4, s), 2.04 (3 H, $COCH_3$, s; 4 H, C_6, C_7, m), 2.34 (4 H, C_2, C_3, s), 4.13 (2 H, CH_3CH_2O, q, *J* = 7.2 Hz), 4.59 (2 H, C_{10}, d, *J* = 7.0 Hz), 4.95–5.50 (2 H, C_5, C_9, m); mass spectrum (CI, CH_4), *m/z* (relative intensity) 283 (8), 223 (100), 177 (7), 135 (31). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 67.75; H, 9.50.

Conversion of 12 to 4,8-Dimethyl-10-hydroxy-4(*E*),8-(*E*)-decadienoic Acid (9). To a solution of **12** (7.3 g, 26 mmol) in 50 mL of dioxane was added 4.1 g of sodium hydroxide in 15 mL of water. The mixture was refluxed for 2.5 h after which it was diluted with water (100 mL), acidified to pH 2 with concentrated HCl, extracted with ether (4 × 50 mL), and washed with brine (2 × 50 mL). Product isolation yielded crude **9** (4.2 g) which was chromatographed on 280 g (25 cm × 5 cm i.d. column) of silica gel (50% EtOAc in hexane with 1% acetic acid) to give 3.98 g (73%) of **9**. Analysis by TLC (solvent system used for column chromatography) revealed a major spot at R_f 0.25 (**9**) and minor impurities at R_f 0.19 and 0.39: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.61 (6 H, CH_3–C_4, CH_3–C_8, s), 2.07 (4 H, C_6, C_7, m), 2.37 (4 H, C_2, C_3, m), 4.16 (2 H, C_{10}, d, *J* = 7.0 Hz), 5.12 (1 H, C_5, m), 5.36 (1 H, C_9, br t, *J* = 7.0 Hz), 7.20 (2 H, OH, COOH, br s); IR (neat film) 3400, 1710 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.49. Found: C, 68.15, H, 9.59.

Preparation of 1 via the Intramolecular Esterification of 9. To 302 mg (1.43 mmol) of *9* and 856 mg (2.14 mmol) of bis(4-*tert*-butyl-*N*-isopropylimidazol-2-yl) disulfide in 20 mL of dry toluene at −68 °C under nitrogen was added triphenylphosphine (561 mg, 2.14 mmol). The mixture was allowed to reach −10 °C, stirred for 2.5 h, and then diluted with 300 mL of cold toluene (−35 °C). The cloudy reaction mixture was allowed to reach room temperature (23 °C) and then refluxed for 2 h. Samples removed from the reaction mixture (filtered through neutral alumina and eluted with dichloromethane) and analyzed by GLC (column C, 170 °C) revealed that the 2 h of reflux did not increase the yield of **1**. Most of the toluene was removed by distillation (10 mm Vigreux), and the remainder (~5 mL) was removed in vacuo. Chromatography of the residue on 150 g of silica gel (28 cm × 3.5 cm i.d. column; 7.5% EtOAc in hexane) gave 5.2 mg (1.9%) of a product at R_f 0.35 (7.5% EtOAc in hexane) and 102 mg (37%) of **1**. Analysis of **1** by TLC (R_f 0.50, 7.5% EtOAc in hexane) and GLC (column A, 210 °C) revealed a purity of greater than 99%: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.57 (3 H, CH_3–C_4, d, *J* = 0.9 Hz), 1.64 (3 H, CH_3–C_8, d, *J* = 1.2 Hz), 2.09 (4 H, C_6, C_7, br s), 2.32 (4 H, C_2, C_3, s), 4.56 (2 H, C_{10}, br d, *J* = 7.0 Hz), 4.82 (1 H, C_5, m), 5.54 (1 H, C_9, dt, $J_{10,9}$ = 7.0 Hz, $J_{7,9}$

= 1.5 Hz); ^{13}C NMR (25.2 MHz, $CDCl_3$) δ 14.7, 15.3, 24.9, 33.5, 38.5, 61.5, 122.3, 126.4, 132.8, 142.8, 174.2; mass spectrum (EI), *m/z* (relative intensity) 194 (1.8), 127 (31), 121 (5), 109 (8), 99 (37), 93 (7), 85 (11), 81 (20), 68 (100), 67 (62), 53 (15), 41 (17). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.48; H, 9.47.

Spectroscopic analysis of the crystalline minor product (R_f 0.35) showed that it was the diolide of **1**: ^1H NMR (60 MHz, $CDCl_3$) δ 1.60 (6 H, CH_3–C_4, s), 1.67 (6 H, CH_3–C_8, s), 2.05 (8 H, C_6, C_7, m), 2.33 (8 H, C_2, C_3, br s), 4.57 (4 H, C_{10}, d, J = 7.0 Hz), 4.8–5.3 (4 H, C_5, C_9, m); mass spectrum (EI), *m/z* (relative intensity), 195 (26), 194 (43), 193 (29), 177 (10), 175 (13), 127 (85), 121 (52), 109 (26), 99 (42), 93 (77), 81 (76), 68 (100), 67 (98), 55 (20), 53 (18).

Preparation of 1-(*tert*-Butyldimethylsiloxy)-3-butyne (14). To an ice-cold solution of 3-butyn-1-ol (35 g, 0.5 mol) and imidazole (85 g, 1.25 mol) in 150 mL of dry DMF was added 90.3 g (0.6 mol) of *tert*-butyldimethylchlorosilane. The ice-bath was removed after 30 min and the reaction mixture stirred for 4 h at 23 °C. The reaction mixture was then poured into water (300 mL), extracted with pentane (4 × 150 mL), and washed with brine (3 × 100 mL). The isolated product was distilled (Vigreux 10 mm) to give **14**: 90.2 g (98%); bp 82–89 °C (10–15 mm); analysis by GLC on column A (130 °C) revealed a purity of 95%; ^1H NMR (60 MHz, $CDCl_3$) δ 0.12 (6 H, CH_3Si, s), 0.92 (9 H, *t*-BuSi, s), 1.96 (1 H, C_4, t, J = 3.0 Hz), 2.42 (2 H, C_2, dt, $J_{1,2}$ = 7.2 Hz, $J_{4,2}$ = 3.0 Hz), 3.75 (2 H, C_1, t, J = 7.2 Hz).

Preparation of 1-(*tert*-Butyldimethylsiloxy)-9-chloro-3-nonyne (15). To **14** (18.4 g, 100 mmol) in 50 mL of dry THF under nitrogen was added *n*-butyllithium (66 mL, 1.6 M, 105 mmol) over 20 min. After *n*-butyllithium addition, 23.3 g (100 mmol) of **13**[33] and 40 mL of dry THF were added. Dry HMPA (50 mL) was then added dropwise to the mixture, resulting in a slightly exothermic reaction. The ice bath was removed, and the reaction mixture was stirred at 23 °C for 30 min. The reaction mixture was diluted with water (250 mL) and extracted with ether (4 × 75 mL) followed by a brine wash (2 × 150 mL). The crude products from this reaction and a second reaction performed under identical conditions (on 165 mmol of **14**) were combined and distilled (Vigreux): bp 95–112 °C (0.05 mm); 47.5 g (62.2%); purity of 76.4% based on GLC analysis (column A, 120–250 °C at 10 °C/min). This product was suitable for iodination without further purification. A small sample was purified by redistillation [Vigreux, bp 110–118 °C (0.2 mm)] for analysis: GLC analysis on column A (120–250 °C at 10 °C/min) revealed a purity of 93%; ^1H NMR (60 MHz, $CDCl_3$) δ 0.12 (6 H, CH_3Si, s), 0.92 (9 H, *t*-BuSi, s), 1.34–1.94 (6 H, C_6, C_7, C_8, br m), 2.0–2.63 (4 H, C_2, C_5, br m), 3.56 (2 H, C_9, t, J = 6.0 Hz), 3.72 (2 H, C_1, t, J = 7.0 Hz); mass spectrum (EI), *m/z* (relative intensity) 273 (0.1), 233 (3), 231 (9), 123 (69), 105 (16), 95 (57), 93 (100), 89 (43), 79 (87), 75 (40, 73 (81), 67 (20), 59 (16), 55 (28). Anal. Calcd for $C_{15}H_{29}OSiCl$: C, 62.36; H, 10.12. Found: C, 62.64; H, 10.01.

Preparation of 1-(*tert*-Butyldimethylsiloxy)-9-iodo-3-nonyne (16). To 7.9 g (27 mmol) of **15** was added 100 mL of acetone containing 8.2 g (55 mmol) of sodium iodide. The resultant solution was refluxed for 65 h, concentrated in vacuo, diluted with water (150 mL), and extracted with ether (3 × 75 mL). The ether extract was washed with aqueous sodium thiosulfate (2 × 75 mL) and brine (2 × 75 mL). Distillation (Vigreux) gave **16**: 10.0 g (96%); purity of 94% by GLC (column A, 120–240 °C at 10 °C/min); bp 120–122 °C (0.1 mm); ^1H NMR (60 MHz, $CDCl_3$) δ 0.12 (6 H, CH_3Si, s), 0.92 (9 H, *t*-BuSi, s), 1.27–2.07 (6 H, C_6, C_6, C_8, br m), 2.07–2.64 (4 H, C_2, C_5, br m), 3.25 (2 H, C_9, t, J = 6.8 Hz), 3.74 (2 H, C_1, t, J = 6.8 Hz).

Preparation of 1-(*tert*-Butyldimethylsiloxy)-11-hydroxy-3-dodecyne (17). To magnesium powder (830 mg, 35 mmol) and **16** (8.7 g, 23 mmol) in 40 mL of dry THF under nitrogen was added ethyl bromide (0.1 mL, ~1.3 mmol). Grignard formation was maintained by refluxing for 3 h. The formation of the Grignard reagents was monitored by GLC. Aliquots taken from the reaction were quenched by addition into saturated aqueous ammonium chloride, extracted with ether, dried over anhydrous magnesium sulfate, and analyzed on column A (160–250 °C) at 10 °C/min). After iodide **16** was consumed, 2.2 g (11.5 mmol) of cuprous iodide was added. The mixture was cooled in an ice bath and stirred for 30 min. Propylene oxide (2.7 q, 46 mmol) diluted in 10 mL of dry THF was added dropwise. The reaction mixture was stirred for 30 min at 23 °C and quenched with saturated aqueous ammonium chloride (100 mL). The ether extract (3 × 75 mL) of the aqueous mixture washed with brine (3 × 75 mL). The isolated product was purified by chromatography (20 cm × 4.5 cm i.d. column) on 180 g of silica gel (20% EtOAc in hexane) to give **17**: 3.3 g (46%); >99% pure by GLC on column A (180–250 °C at 10 °C/min); ^1H NMR (60 MHz, $CDCl_3$) δ 0.08 (6 H, CH_3Si, s), 0.89 (9 H, *t*-BuSi, s), 1.19 (3 H, C_{12}, d, J = 6.0 Hz), 1.36 (10 H, C_6–C_{10}, br s), 1.77 (1 H, OH, s), 2.00–2.57 (4 H, C_2, C_5, br m), 3.70 (3 H, C_1, t, J = 7.0 Hz), 3.50–3.90 (1 H, C_{11}, br m); mass spectrum (EI), *m/z* (relative intensity) 255 (1.2), 237 (1.6), 121 (18), 107 (25), 105 (50), 95 (23), 93 (33), 89 (27), 81 (30), 79 (24), 75 (100), 73 (44), 67 (20), 59 (10), 55 (19), 45 (15).

Preparation of 1,11-Dihydroxy-3-dodecyne (18). To a solution of **17** (2.9 g, 9.4 mmol) in THF (15 mL) was added 19 mL of *tertra-n*-butylammonium fluoride (19 mmol, 1 M solution in THF). The reaction mixture was stirred for 1 h at 23 °C and then diluted with 75 mL of water. The aqueous mixture was extracted with ether (3 × 50 mL) and the ether extract washes with brine (2 × 50 mL). Product isolation yielded 1.86 g (100%) of the diol **18** which TLC analysis (25% EtOAc in hexane) revealed to contain one impurity (R_f 0.37) less polar than **18** (R_f 0.29). No further purification was carried out on **18**: ^1H NMR (60 MHz, $CDCl_3$) δ 1.14 (3 H, C_{12}, d, J = 6.0 Hz), 1.34 (10 H, C_6–C_{10}, br s), 1.94–2.57 (4 H, C_2, C_5, br m), 2.85 (2 H, OH, br s), 3.63 (2 H, C_1, t, J = 6.3 Hz), 3.38–3.83 (1 H, C_{11}, br m); HRMS, calcd for $C_{12}H_{22}O_2$ *m/z* 198.1619, found *m/z* 198.1624.

Preparation of 11-Hydroxy-3-dodecynoic Acid (22). To a vigorously stirred, ice-cold solution of chromic trioxide (5.4 g, 54 mmol) in 50 mL of 6 N sulfuric acid was added dropwise over 3 h 1.76 g (8.9 mmol) of **18** in 50 mL of acetone.[23] The reaction mixture was kept in an ice bath for 30 min and then warmed to 23 °C before the workup. Water (200 mL) was added and the reaction mixture extracted with ether (4 × 75 mL). The ether extract was washed with brine (3 × 50 mL). Product isolation yielded crude 11-oxo-3-dodecynoic acid (**21**) which was purified by crystallization from 10% ether in hexane to yield 1.28 g (68%) of **21** with a melting point of 49–51 °C. Analysis of the methyl ester of the crystalline 11-oxo-3-dodecynoic acid (prepared by treatment of the keto acid with an excess of ethereal diazomethane) by GLC on column A (180–250 °C at 10 °C/min) revealed that it was 90% pure: ^1H NMR (60 MHz, $CDCl_3$) δ 1.08–1.77 (8 H, C_6–C_9, br m), 2.10 (3 H, C_{12}, s), 1.95–2.60 (4 H, C_5, C_{10}, br m), 3.27 (2 H, C_2, t, J = 2.2 Hz), 10.3 (1 H, COOH, br s).

The keto acid was converted quantitatively to **22** by reduction with sodium borohydride. To an ice-cold solution of the keto acid (676 mg, 3.2 mmol) in 10 mL of absolute ethanol was added 244 mg (6.4 mmol) of sodium borohydride. After 5 min the reaction mixture was warmed to 23 °C, diluted with cold 5% HCl (30 mL), and extracted with ether. Product isolation yielded 680 mg (99%) of **22** which was 97% pure by GLC analysis (of methyl ester) on column A (180–250 °C at 10 °C/min): ^1H NMR (60 MHz, $CDCl_3$) δ 1.17 (3 H, C_{12}, d, J = 6.0 Hz), 1.35 (10 H, C_6–C_{10}, br s), 2.0–2.4 (2 H, C_5, br m), 3.26 (2 H, C_2, t, J = 2.2 Hz), 3.6–4.0 (1 H, C_{11}, br m), 6.77 (2 H, COOH, OH, br s); HRMS, calcd for $C_{12}H_{18}O_3$ *m/z* 210.1256, found *m/z* 210.1261.

Preparation of 11-Hydroxy-3(*Z*)-dodecenoic Acid (24). To a vigorously stirred mixture of nickel acetate (1 g) and absolute ethanol (25 mL, saturated with hydrogen) was added 5 mL of the filtrate from a solution of sodium borohydride (500 mg) in ethanol (12 mL) and 2 N aqueous sodium hydroxide (0.63 mL). After hydrogen evolution had ceased, the black suspension was treated with 0.7 mL of ethylenediamine.[25] Alkyne **22** (643 mg, 3.0 mmol) was added and the reaction mixture stirred for 1 h at 23 °C. The reaction mixture was diluted with brine (100 mL), acidified with 5% HCl, and extracted with ether (4 × 50 mL): HRMS, calcd for $C_{12}H_{20}O_3$ *m/z* 212.1413, found *m/z* 212.1419. The ether extract was washed with brine (2 × 50 mL). Product isolation gave 620 mg (96%) of **24** which was 96% pure by GLC analysis of the methyl ester on column A (180–250 °C at 10 °C/min): ^1H NMR (60 MHz, $CDCl_3$) δ 1.20 (3 H, C_{12}, d, J = 6.0 Hz), 1.34 (10 H, C_6–C_{10}, br s), 1.87–2.20 (2 H, C_5, br m), 3.12 (2 H, C_2, d, J = 5.4

(33) W. R. Taylor and F. M. Strong, *J. Am. Chem. Soc.*, **72**, 4263 (1950).

Hz), 3.5–4.0 (1 H, C_{11}, br m), 5.4–5.7 (2 H, C_3, C_4, m), 7.15 (2 H, COOH, OH, br s).

Preparation of (*R*,*S*)-11-Methyl-3(*Z*)-undecenolide ((*R*,*S*)-2). Triphenylphosphine (196 mg, 0.75 mmol) was added to a solution of 2,2′-dipyridyl disulfide (165 mg, 0.75 mmol) and **24** (80 mg, 0.37 mmol) in 4 mL of dry acetonitrile and stirred for 1.5 h at 23 °C under argon. The yellow solution was then diluted with 26 mL of dry xylenes and added dropwise over 4 h to a refluxing solution of silver perchlorate (387 mg, 1.9 mmol) in xylenes (50 mL, under nitrogen). The reaction mixture was refluxed for 6 h after the addition of the thio ester and then filtered. The filtrate was diluted with 160 mL of hexane and chromatographed on 80 g (20 cm × 3 cm i.d. column) of silica gel in hexane. The column was washed free of xylenes with hexanes (200 mL) and then eluted with 5% EtOAc in hexane to yield lactone (*R*,*S*)-**2**, 61 mg [78% pure by GLC analysis on column A (150–250 °C at 10 °C/min)]. Kugelrohr distillation yielded (*R*,*S*)-**2**: 22 mg (30%); bp 60–70 °C (0.1 mm); 97% pure by GLC analysis. Spectroscopic data obtained for the synthetic product were identical with those obtained for the isolated natural product.[3] GLC analysis of the distilled material on column C [70 °C (2 min) and then 4 °C/min to 200 °C (hold 20 min)] revealed the presence of 11-methyl-3(*Z*)-undecenolide, the *E* isomer, and 11-methylundecanolide in a ratio of 376:18:1.

Preparation of (*R*)- and (*S*)-1-(*tert*-Butyldimethylsilyoxy)-11-hydroxy-3-dodecyne [(*R*)-17 and (*S*)-17]. The Grignard reagent of **16** (4.0 g, 10.5 mmol) was coupled with (*S*)-propylene oxide[29] (1.2 g, 21 mmol; $[\alpha]^{24}_D$ −12.8° (neat)), via the procedure described for the preparation of (*R*,*S*)-**17**, to give (*S*)-**17**: 1.65 g (42%); $[\alpha]^{22}_{obsd}$ +4.0° (neat). Analysis by GLC (column A, 180–250 °C at 10 °C/min) revealed a purity of 81%.

(*R*)-**17** was prepared from **16** (19.0 g, 50 mmol) and (*R*)-propylene oxide[23a] (3.5 g, 60 mmol; $[\alpha]^{24}_D$ +13.9° (neat)) by following the procedure described above. After the workup and column chromatography, (*R*)-**17** was obtained: 4.9 g (31%); $[\alpha]^{22}_{Obsd}$ −3.0° (neat); purity of 88% determined by GLC on column A (180–250 °C at 10 °C/min.); HRMS, calcd for $C_{12}H_{20}O_2$ *m*/*z* 196.2908, found *m*/*z* 196.1463. The ^{1}H NMR spectra of (*R*)- and (*S*)-**17** (60 MHz, $CDCl_3$) were identical with the spectrum of (*R*,*S*)-**17**.

Preparation of (*R*)- and (*S*)-11-[(β-Methoxyethoxy)-methoxy]-3-dodecyn-1-ol [(*R*)-20 and (*S*)-20]. To an ice-cold mixture of (*S*)-**17** (1.2 g, 3.8 mmol) and diisopropylethylamine (0.74 g, 5.7 mmol) in dry dichloromethane (4 mL) was added 0.71 g (5.7 mmol) of (β-methoxyethoxy)methyl chloride. After 30 min the reaction was warmed to 23 °C and stirred for 5 h. The reaction mixture was then diluted with water (15 mL), extracted with dichloromethane (3 × 25 mL), and washed with brine (2 × 25 mL). Product isolation yielded 1.60 g of the MEM ether (S)-**19** which was 92% pure by GLC analysis on a column A (180–250 °C at 10 °C/min): ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.08 (6 H, CH_3Si, s), 0.90 (9 H, *t*-BuSi, s), 0.90 (9 H, *t*-BuSi, s), 1.16 (3 H, C_{12}, d, *J* = 6.4 Hz), 1.28–1.60 (10 H, C_6–C_{10}, m), 1.96–2.57 (4 H, C_2, C_5, br m), 3.42 (3 H, CH_3O, s), 3.53–3.83 (7 H, OCH_2CH_2O, C_1, C_{11}, br m), 4.72 (2 H, OCH_2O, s). The MEM ether was stirred for 5 h in a mixture of AcOH/THF/water (3:1:1 v/v/v) at 23 °C. Water (50 mL) was then added to the reaction mixture, and the resultant aqueous mixture was extracted with ether (3 × 50 mL) and washed with brine (2 × 50 mL). Chromatography of the isolated product on silica gel (60 g; 15 cm × 3 cm i.d. column; 75% EtOAc in hexane) gave (*S*)-**20**: 0.78 g (72% yield); 98% pure by GLC (column A, 180–250 °C at 10 °C/min); $[\alpha]^{22}_{obsd}$ +10.8° (neat); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.14 (3 H, C_{12}, d, *J* = 6.0 Hz), 1.32 (10 H, C_6–C_{10}, br s), 1.89–2.64 (5 H, C_2, C_5, OH, br m), 3.34 (3 H, CH_3O, s), 3.47–3.83 (7 H, OCH_2CH_2O, C_1, C_{11}, br m), 4.69 (2 H, OCH_2O, s).

(*R*)-**20** was prepared from 4.5 g (14.4 mmol) of (*R*)-**17** by the procedure described above except that the *tert*-butyldimethylsilyl ether was cleaved with *tetra*-*n*-butylammonium fluoride instead of the AcOH/THF/water mixture. Chromatography yielded (*R*)-**20**: 62% yield (from (*R*)-**17**); 99% pure by GLC (column B, 180–250 °C at 10 °C/min); $[\alpha]^{22}_{obsd}$ −10.7° (neat).

Preparation of (*R*)- and (*S*)-11-[(2-Methoxyethoxy)-methoxy]-3-dodecynoic Acid [(*R*)-23 and (*S*)-23]. To an ice-cold solution of chromium trioxide (1.1 g, 11 mmol) in 2 N sulfuric acid (15 mL) was added dropwise 0.78 g (2.7 mmol) of (*S*)-**20** dissolved in 30 mL of acetone. After the addition was completed (2 h), the reaction mixture was warmed to 23 °C and stirred for 3 h. The acetone was removed in vacuo, leaving a residue which was diluted with water (50 mL) and extracted with ether (3 × 50 mL). The ether extract was washed with brine (3 × 50 mL) and then subjected to product isolation which gave 0.72 g of crude product. Analysis of the crude product by GLC (column A, 180–250 °C at 10 °C/min) after treatment with diazomethane revealed a purity of 50%. This material was utilized for the next step without further purification.

The *R* enantiomer of **23** was prepared from 2.12 g (7.41 mmol) of (*R*)-**20**. To a solution of chromium trioxide (2.97 g, 30 mmol) in 2 N sulfuric acid (42 mL) maintained at 10 °C was added (*R*)-**20** (in 85 mL acetone) over 30 min. The reaction mixture was then stirred for 3 h at 23 °C and worked up by the method described above. Partial purification of the crude product was achieved by chromatography on 170 g (15 cm × 5 cm i.d. column) of silica gel (EtOAc/hexane/AcOH, 49.5:49.5:1.0) to yield (*R*)-**23**: 0.87 g (39%); purity of 77% by GLC analysis of the methyl ester (column B, 180–250 °C at 20 °C/min); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.14 (3 H, C_{12}, d, *J* = 6.0 Hz), 1.36 (10 H, C_6–C_{10}, br s), 1.95–2.60 (1 H, C_5, br m), 3.27 (2 H, C_2, t, *J* = 1.8 Hz), 3.38 (3 H, CH_3O, s), 3.48–3.88 (5 H, OCH_2CH_2O, C_{11}, m), 4.73 (2 H, OCH_2O, s), 10.25 (1 H, COOH, br s).

Preparation of (*R*)- and (*S*)-11-Hydroxy-3-dodecynoic Acid [(*R*)-22 and (*S*)-22]. To an ice-cold solution of (*S*)-**23** in 35 mL of dry dichloromethane (under nitrogen) was added 13.5 g (60 mmol) of anhydrous zinc bromide (dried under vacuum at 100 °C for 24 h). The resultant supension was stirred for 2 h, after which it was filtered, evaporated to dryness, and dissolved in ether (50 mL) which was washed with brine (2 × 50 mL). Chromatography of the crude product on 60 g (15 cm × 3 cm i.d. column) of silica gel (EtOAc/hexane/AcOH, 49.5:49.5:1 v/v/v) gave 71.6 mg of (*S*)-**22** (12.5% yield) which was 84% pure by GLC analysis of the methyl ester (column A, 180–250 °C at 10 °C/min).

A modification of the procedure described above was used for the cleavage of the MEM ether of (*R*)-**23**. To a solution of (*R*)-**23** (720 mg, 1.8 mmol) in 20 mL of dry dichloromethane was added 10.7 g (47 mmol) of anhydrous zinc bromide. The suspension was shaken vigorously for exactly 5 min at 23 °C and then diluted with 50 mL of brine. The aqueous mixture was acidified (pH 2) with 2 N sulfuric acid, extracted with dichloromethane (3 × 40 mL), and washed with brine (2 × 50 mL). Product isolation was followed by chromatography on 90 g (23 cm × 3 cm i.d. column) of silica gel to yield 190 mg (49%) of (*R*)-**22** with a purity of 80% by GLC analysis of methyl ester on column B (180–250 °C at 10 °C/min).

Preparation of (*R*)-24 and (*S*)-24. (*S*)-**22** (71.6 mg, 0.34 mmol) was hydrogenated in 83% yield with P-2 nickel catalyst by the procedure described for the racemic material. The (*S*)-**24** was 90% pure by a GLC analysis of the methyl ester (column C, 180–250 °C at 10 °C/min).

(*R*)-**24** (153 mg, 84% pure by GLC analysis) was prepared in 84% yield by the same procedure.

Preparation of (*R*)-(−)-2 and (*S*)-(+)-2. The lactonization of (*R*)-**24** and (*S*)-**24** was carried out by the procedure described for (*R*,*S*)-**24**. Lactonization of 60.3 mg (0.28 mmol) of (*S*)-**24** gave 15.6 mg (28%) of (*S*)-**2** after chromatography and Kugelrohr distillation; $[\alpha]^{22.5}_D$ +70.5° (*c* 0.96, $CHCl_3$).

The lactonization of 128 mg (0.6 mmol) of (*R*)-**24** gave 43 mg (37%) of (*R*)-**2** after chromatography and distillation; $[\alpha]^{22.5}_D$ −78° (*c* 16.4, $CHCl_3$). Spectroscopic data for (*R*)- and (*S*)-**2** were identical with those obtained for (*R*,*S*)-**2**.

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Registry No. **1**, 86578-98-5; 1 diolide, 87532-00-1; (*R*,*S*)-**2**, 87583-37-7; (*S*)-**2**, 86578-99-6; (*R*)-**2**, 87583-38-8; **3**, 87519-21-9; **4**, 87519-22-0; **5**, 87519-23-1; **6**, 87519-24-2; **7**, 38290-55-0; **8**,

87519-25-3; **8** methiodide, 87519-26-4; **9**, 38609-44-8; **9** THP ether, 87519-27-5; **10**, 37905-04-7; **11**, 87519-28-6; **12**, 87519-29-7; **13**, 60274-60-4; **14**, 78592-82-2; **15**, 87519-30-0; **16**, 87519-31-1; (*R,S*)-**17**, 87519-32-2; (*S*)-**17**, 87583-39-9; (*R*)-**17**, 87583-40-2; (*R,S*)-**18**, 87519-33-3; (*S*)-**19**, 87519-34-4; (*S*)-**20**, 87519-35-5; (*R*)-**20**, 87519-36-6; **21**, 87519-37-7; **21** methyl ester, 87519-38-8; (*R,S*)-**22**, 87519-39-9; (*S*)-**22**, 87583-41-3; (*R*)-**22**, 87583-42-4; (*R*)-**22** methyl ester, 87519-40-2; (*S*)-**23**, 87519-41-3; (*R*)-**23**, 87519-42-4; (*R*)-**23** methyl ester, 87519-43-5; (*R,S*)-**24**, 87519-44-6; (*R,S*)-**24** methyl ester, 87519-45-7; (*S*)-**24**, 87583-43-5; (*S*)-**24** methyl ester, 87583-44-6; (*R*)-**24**, 87583-45-7; (phenylthio)acetyl chloride, 7031-27-8; geraniol, 106-24-1; 3,7-dimethyl-2(*E*),5(*E*),7-octatrienyl (phenylthio)acetate, 87519-46-8; 2,4,4-trimethyl-2-oxazoline, 1772-43-6; geranyl acetate, 105-87-3; 2,6-dimethyl-8-hydroxy-2-(*E*),6(*E*)-octadien-1-ol, 26488-97-1; 8-acetoxy-2,6-dimethyl-2-(*E*),6(*E*)-octadien-1-ol, 37905-03-6; diethyl malonate, 105-53-3; 3-butyn-1-ol, 927-74-2; (*R,S*)-propylene oxide, 16033-71-9; (*S*)-propylene oxide, 16088-62-3; (*R*)-propylene oxide, 15448-47-2.

Studies on the Nactins: Total Synthesis of (±)-*tert*-Butyl 8-*O*-(*tert*-Butyldimethylsilyl)nonactate

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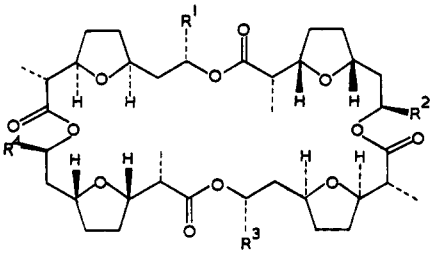
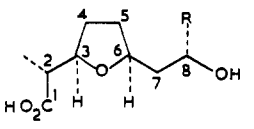
The title nonactic acid derivative (**32**) was prepared in racemic form from 2,3,5-tri-*O*-acetyl-γ-D-ribonolactone (**17**). Lactone **17** reacted with DBU to give 3-acetoxy-5-methylene-2,5-dihydrofuran-2-one (**18**), which on hydrogenation over $Pd/CaCO_3$ stereoselectively (>97:3) gave 3[*R*(*S*)]-acetoxy-5[*S*(*R*)]-methyltetrahydrofuran-2-one (**16a**). Reaction of this with diisobutylaluminum hydride, $EtO_2CCH{=}PPh_3$, hydrogen over Rh/Al_2O_3, CF_3CO_2H, and *t*-$BuMe_2SiCl$ in sequence gave 5*S*(*R*)-[2[*S*(*R*)]-[(*tert*-butyldimethylsilyl)oxy]propyl]tetrahydrofuran-2-one (**30b**). Subsequent condensation with *tert*-butyl 2-lithiopropanoate gave, on acidification and hydrogenation over Rh/Al_2O_3, **32**, which was formed with an 85:15 diastereoselectivity. Alternative but less concise routes to **16a** were explored. In addition, unsuccessful attempts to prepare nonactic acid (**2a**) from *threo*-pentanetriol (**21a**) were examined.

The nactins **1** are a group of macrotetrolide antibiotics produced by *Streptomyces* sp.[2] These are neutral ionophores noted for the ability to mediate cation transport. In particular, nonactin (**1a**) is especially effective in con-



1 a $R^1=R^2=R^3=R^4=Me$
b $R^1=Et$, $R^2=R^3=R^4=Me$
c $R^1=R^3=Et$, $R^2=R^4=Me$
d $R^1=R^2=R^3=Et$, $R^4=Me$
e $R^1=R^2=R^3=R^4=Et$



2 a R = Me
b R = Et

trolling mitochondrial potassium ion flux. All the nactins **1** consist of four hydroxy acids, either nonactic acid **2a** or **2b**, linked to produce a 32-membered tetralactone ring. Nonactin (**1a**) is a meso compound since the alternating hydroxy acid subunits (**2a**) are of opposite absolute stereochemistry. Thus, hydrolysis of **1a** produces racemic **2a**.[2,3] Monactin (**1b**), dinactin (**1c**), trinactin (**1d**), and tetranactin (**1e**) are homologues of **1a** containing an increasing ratio of **2b**:**2a**. Clearly the nactins **1** are both stereochemically and biosynthetically[4] intriguing.

Nonactic acid (**2a**) has been the subject of extensive synthetic studies. Introduction of the cis stereochemistry at the tetrahydrofuran ring (C-3 and C-6) is easiest to achieve. Thus, either catalytic hydrogenation[5] of, or oxyallyl cycloaddition to,[6] suitably functionalized furans has been widely exploited in nonactic acid (**2a**) synthesis. Alternative approaches by Ireland[7] and Fraser-Reid[8] have used carbohydrates as precursors to both antipodes of **2a**. Both Gerlach[9] and Bartlett[10] have prepared racemic **2a** from acyclic precursors, namely, 7-octene-2,4-dione and 1,7-octadien-4-ol, respectively. With the sole exception of Bartlett's elegant studies,[10] all total syntheses of **2a** have not adequately controlled the stereochemistry at both the extracyclic centers (C-2 and C-8). Bartlett employed both phosphate extension methodology, converting **3** to **4**, and steric approach directed hydrogenation, in transforming **5** into **6**, in the synthesis of (±)-**2a**. Herein we report

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