Table II. Fractional Atomic Coordinates of the Non-Hydrogen Atoms of 7 with Standard Deviations in Parentheses[a]

	x	y	z	B_{eq}
Br	0.01648 (5)	1.15188 (3)	0.15281 (2)	2.55 (1)
O23	0.5000 (0)	1.0000 (0)	0.0000 (0)	15.7 (3)
N1	0.2719 (3)	0.9999 (2)	0.3199 (1)	2.35 (5)
N8	0.5292 (3)	0.6887 (2)	0.3003 (1)	2.19 (6)
N22	−0.1974 (5)	0.8905 (3)	0.1955 (2)	4.68 (8)
C2	0.3238 (4)	0.9019 (2)	0.3241 (1)	1.99 (6)
C3	0.1771 (4)	0.8292 (2)	0.2627 (1)	2.19 (6)
C4	0.2348 (4)	0.7981 (2)	0.2024 (1)	2.31 (6)
C5	0.1173 (5)	0.7044 (3)	0.1576 (1)	2.85 (8)
C6	0.1836 (5)	0.6146 (3)	0.2114 (2)	2.33 (7)
C7	0.4113 (5)	0.5984 (2)	0.2552 (2)	2.44 (8)
C9	0.5427 (4)	0.6984 (2)	0.3776 (2)	2.43 (7)
C10	0.6370 (5)	0.7936 (2)	0.4210 (1)	3.07 (7)
C11	0.5122 (4)	0.8861 (2)	0.3897 (1)	2.23 (6)
C12	0.5842 (4)	0.9788 (2)	0.4285 (1)	2.05 (7)
C13	0.7627 (5)	1.0090 (3)	0.4986 (1)	3.05 (8)
C14	0.7823 (5)	1.1063 (3)	0.5211 (2)	3.5 (1)
C15	0.6297 (6)	1.1733 (3)	0.4750 (2)	2.51 (9)
C16	0.4529 (5)	1.1456 (2)	0.4052 (2)	2.28 (8)
C17	0.4319 (4)	1.0487 (2)	0.3838 (1)	1.96 (6)
C18	0.4618 (4)	0.7754 (2)	0.2464 (1)	2.10 (7)
C19	0.1934 (7)	0.8858 (3)	0.1466 (2)	4.4 (1)
C20A	0.220 (1)	0.8801 (6)	0.0834 (4)	4.3 (1)
C20B	0.032 (1)	0.8845 (9)	0.0719 (6)	6.6 (2)
C21	−0.0343 (5)	0.8651 (2)	0.2231 (2)	3.01 (7)
C24	0.310 (2)	0.999 (1)	0.0023 (7)	8.8 (3)

[a] The given isotropic temperature parameters (B_{eq}) are one-third of the trace of the orthogonalized anisotropic B_{ij} tensor

min^{-1} in θ at which point any reflection with $I < \sigma(I)$ was coded as unobserved. Three standard reflections were monitored every hour and showed no significant (~1.8%) deviation. 3813 reflections were thus recorded, of which—after correction for Lorentz and polarization effects—3377 with $I > 0.3\sigma(I)$ were taken as observed. Although $\mu = 31.5$ cm^{-1}, no absorption correction was applied. The structure was solved by the MULTAN[12] program. The full-matrix least-squares refinement minimized $\sum w(\Delta F)^2$. 213 parameters were refined. In the course of the isotropic refinement (about $R = 0.15$) a difference Fourier synthesis revealed a conformational disorder around the terminal C20 atom of the 4-ethyl moiety; moreover, an additional methanol molecule was observed in a partly special position. Its oxygen atom is fixed in a center of symmetry at (0.5,1.0,0) while the methyl group occupies randomly (with 50–50% of probability) either of two center of symmetry related positions. Consequently, a half molecule of CH_3OH per each molecule of **7** had to be taken into account. The occupancy factors of the methanol C24 atom were fixed to 0.5 while those of C20 were allowed to vary. However, both remained in the vicinity of 0.5. The hydrogen positions were generated from assumed geometries and were only taken into account in the structure factor calculations with individual isotropic temperature factors (B_i of the corresponding heavy atom increased by 1 Å^2). No location of the randomly distributed H atoms belonging to the positionally disordered methanol molecule were attempted. The refinement was terminated at $R = 0.043$, $R_w = 0.068$, $S = 3.52$, $w = [\sigma^2(F_0) + 0.25(pF_0)^2]^{-1}$, where $p = 0.01$. Scattering factors were taken from ref 13. All calculations were performed on a PDP 11/34 minicomputer with the Enraf-Nonius SDP program package. The final positional and isotropic temperature factors of the non-hydrogen atoms are given in Table II.

Acknowledgment. We express our sincere thanks to Dr. Péter György, Dr. Gábor Czira, János Brlik, Anna Korcsog-Kassa, and Magdolna Tóth for their valuable help. The financial support of the Richter Gedeon Pharmaceutical Co. and the Hungarian Academy of Sciences is gratefully acknowledged.

Registry No. 1·$HClO_4$, 55390-29-9; (±)-**2a**, 64361-56-4; (±)-**2b**, 58451-77-7; (±)-**2c**, 97805-31-7; (±)-**2d**, 97720-67-7; (±)-**2e**, 56897-79-1; (±)-**3**, 97805-30-6; (±)-**4b**, 97720-56-4; (±)-**4c**, 97720-58-6; (±)-**4e**, 97720-54-2; (±)-**5a**, 58451-76-6; (±)-**5b**, 58451-77-7; (±)-**5c**, 58451-79-9; (±)-**5d**, 97720-59-7; (±)-**5e**, 56897-78-0; (±)-**5f**, 63038-13-1; (±)-**6** (X = CH_3SO_3), 97720-61-1; (±)-**7**, 97720-62-2; (±)-**8a**, 97805-35-1; (±)-**8b**, 2580-88-3; **9**, 97731-53-8; (±)-**10**, 97720-63-3; (±)-**11**, 97748-88-4; (±)-**12**, 97720-66-6; (±)-**13a**, 97731-48-1; (±)-**13b**, 97720-64-4; (±)-**13c**, 97720-70-2; (±)-**15**, 97720-69-9; (±)-**16a**, 97720-71-3; (±)-**16b**, 97720-72-4; (±)-**17a**, 97748-89-5; (±)-**17b**, 60384-17-0.

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Synthetic Studies Directed toward Cembranolides. Synthesis of the Basic Nucleus of Crassin Acetate

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Received January 17, 1985

A stereospecific synthesis of the basic crassin acetate nucleus, *erythro*-1-(hydroxymethyl)-14-hydroxy-4,8,12-trimethylcyclotetradeca-(*E*,*E*,*E*)-3,7,11-triene, has been achieved. Stereospecific syntheses of the two precursors to this ring system, (*E*,*E*)-3,7-dimethyl-9-(phenylthio)nona-3,7-dienal and (*E*)-2,8-bis(trimethylsiloxy)-2,7-dimethyloct-6-en-3-one, have been developed. These moieties were combined via an aldol condensation to yield *erythro*-9-hydroxy-10-[1-oxo-2-methyl-2-(trimethylsiloxy)propyl]-1-(phenylthio)-14-(trimethylsiloxy)-3,7,13-trimethyltetradeca-(*E*,*E*,*E*)-2,6,12-triene which, in a series of reactions, was cyclized to the titled 14-membered ring system.

In contrast to the mono- and sesquiterpenes, previous to 1962, the natural diterpene series contained no head-to-tail monocycles corresponding to the monoterpenes limonene and terpinolene and the sesquiterpenes germanacrene and humulene. In 1962, research in this laboratory provided the first example of such an analogous monocyclic structure derived from the diterpene geranylgeraniol, cembrene (1), a naturally occurring 14-carbon ring compound isolated from pine trees.[2] In the subsequent years

(1) Recipient of Feodor-Lynen Fellowship, Alexander von Humboldt Stiftung, 1983–1984.

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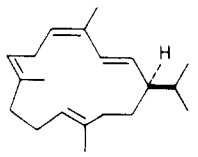

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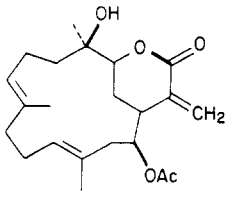
this 14-membered carbocyclic ring system has been found to be the most widely occurring diterpene nucleus in nature. It is found in a wide variety of conifers,[3] is known to occur in tobacco leaves[4] and to have plant growth inhibitor activity,[5] and has been isolated from African termites and shown to have protective activity.[6] However, in the past 10 years, the most widespread occurrence has been found in gorgonians and Pacific soft coral.[7] The structural diversity and the variety of biological activities found in the rapidly growing class of diterpenes has lead to our continued interest in the total synthesis of cembranoid systems.

Most of the materials isolated from the gorgonian and soft coral possess the α-methylene lactone structure and the groups are called cembranolides. In this series of lactones, a wide variety of biological activities have been found. One of the first cembranolides isolated, in 1960, from the Caribbean gorgonian, *Pseudoplexaura porosa*, was crassin acetate (**2**).[8] This material has also been found



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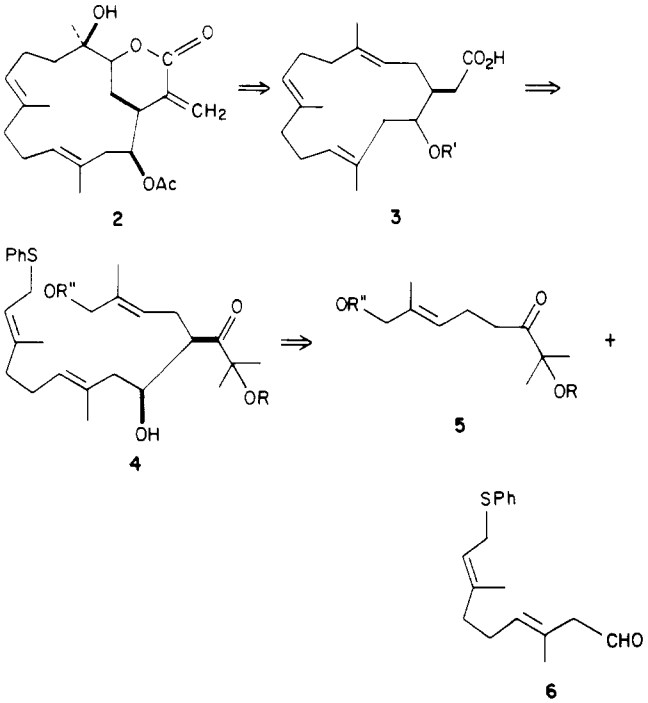
in other gorgonians of this species,[9] and its structure has been elucidated by chemical methods[7] and its absolute configuration by X-ray structural studies.[10] Crassin acetate has mild antibiotic activities[8] and its free alcohol (NSC No. 210236) possesses significant in vitro activity (1 μg/mL) against human epidermoid carcinoma of the nasopharynx (KB) but tests related to its in vivo activity yielded data which were inconclusive.[9] The related cinnamic esters (NSC No. 286161) showed good in vitro activity against leukemia.[9]

This cembranolide was prime choice as the target for the total synthesis of a lactone in this series. Synthetic studies directed toward the synthesis of crassin acetate have been reported by Marshall[11] and his synthetic plan was a convergent scheme where a diene unit would be coupled to an α,ω-difunctionalized triol acid with all the asymmetric centers fixed.

Our synthetic plan differed from the former in that previous studies of the chemistry of the 14-carbon ring system,[12] as well as molecular mechanics calculations,[13] had demonstrated that the ring system possessed a relatively high rigidity and its preferred conformations could be utilized to introduce stereospecifically the hydroxy lactone unit. The synthesis of the 14-membered ring can be achieved by a variety of methods,[3a,14,15] and, thus, the synthesis of the more highly oxygenated cembranoids can readily be approached once the carbocyclic ring system is intact.

The synthetic scheme to be followed is a convergent scheme in which the hydroxy lactone structure of **2** will



be introduced in a stereospecific manner from the acid **3** which, in turn, will be derived by a cyclization of the requisite acyclic precursor using the method of Ito and Kato[15,16] for the synthesis of 14-membered rings. This latter erythro structure will be obtained by the stereospecific aldol condensation between the smaller moieties **5** and **6**, thus fixing the stereochemistry of the hydroxyl grouping next to the lactonic ring.[17] In the synthesis of the antitumor cembranoid asperdiol, Still[18] used a diastereoselective macrocyclization, directed by a conformational bias, which also introduced two new asymmetric centers.

The syntheses of hindered ketone moieties related to **5** usually have been achieved by reaction of an acyl anion

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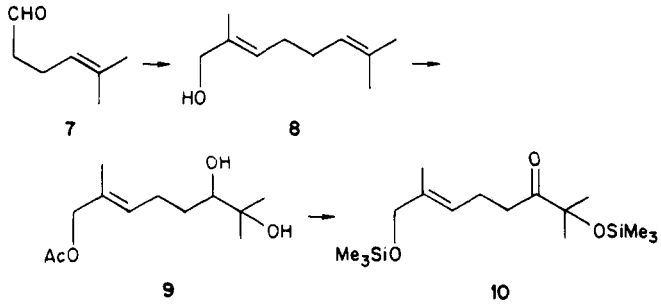
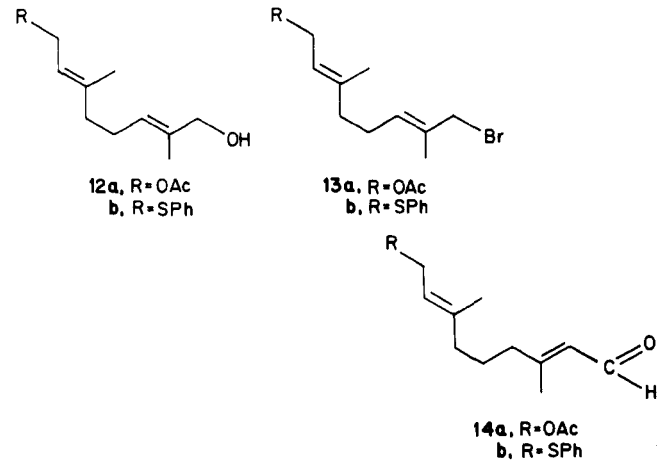
equivalent with acetone,[19] but due to the complex nature of the anion equivalent, a synthesis starting with so-called "isogeraniol" was developed. The readily available 5-methyl-4-hexenal (**7**)[20] upon reaction with sodium ethyl



7 8 9 10

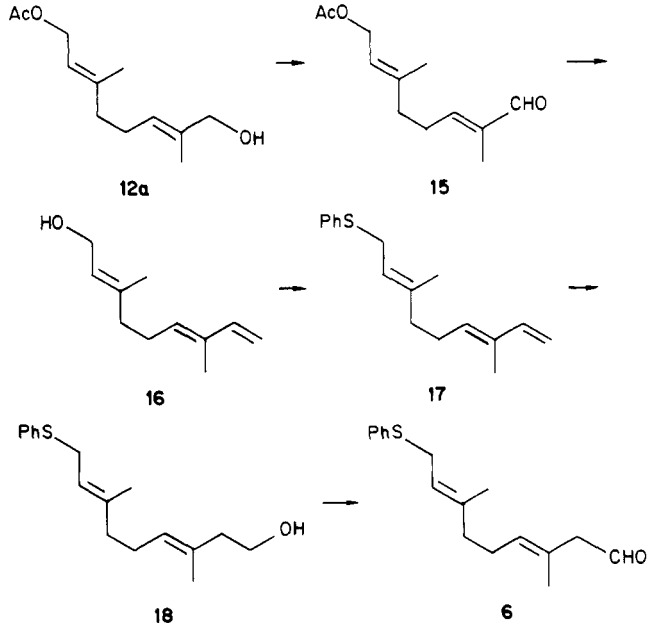
2-(diethylphosphono)propionate followed by LAH reduction gave the desired (*E*)-isogeraniol (**8**)[21] in 65% overall yield from **7**. The acetate derivative was selectively epoxidized on the dimethyl-substituted double bond using *m*-chloroperbenzoic acid in THF at 0 °C, and the resulting epoxide was hydrolyzed by aqueous THF containing a catalytic amount of perchloric acid to give diol acetate **9** in a 65% overall yield from alcohol **8**. The secondary alcohol was oxidized to a ketone, the acetate saponified, and the resulting diol silyated to give **10** in 40% overall yield from aldehyde **7**.

The strong resemblance of the aldehyde **6** to the known ω-hydroxygeraniol (**11**)[22] clearly indicated that utility of **6** as a starting material, especially in view of its facile preparation from geranyl acetate using the Sharpless[23] selenium dioxide catalyzed *tert*-butyl hydroperoxide oxidation. Such an intermediate as **12a** has the advantage



of possessing the 1,5-diene arrangement with the correct regio- and stereochemistry and distinguishable primary hydroxy functions on each end of the chain. Attention was first given to the introduction of an acyl anion equivalent that is transformable under mild conditions to an aldehyde function. The alcohol **12a** was cleanly converted to the bromide **13a** by using *N*-bromosuccinimide–dimethyl sulfide reagent.[24] Using (diethylamino)acetonitrile as the acyl anion equivalent was unsuccessful since the anion attacks the acetoxy group faster than the bromide function. Using the thiophenyl ether **13b**, the displacement went well, but it was found that under mild conditions using 1:1 aqueous 30% oxalic acid only the isomerized α,β-unsaturated aldehyde **14b** was obtained. It was shown that the substitution pattern on the double bond was responsible for this isomerization since under the same condition geraniol (β-methyl-α,β-unsaturated alcohol) was transformed to the β,γ-unsaturated aldehyde but isogeraniol (α-methyl-α,β-unsaturated alcohol) gave an α,β-unsaturated aldehyde. Of a wide variety of other 1-carbon equivalents studied, only 2-lithio-1,3-dithiane functioned well, but the overall yield was low.

The reagent of choice was the methylene Wittig reagent as the one carbon source. Hydroxygeranyl acetate (**12a**)



12a 15 16 17 18 6

was oxidized with the Swern reagent,[25] and the resulting aldehyde **15** converted to the triene acetate by using methylenetriphenylphosphorane. The acetate was saponified and the resulting alcohol **16** converted to the phenylthio ether **17**. The diene was selectively hydroborated with diisoamylborane and the resulting alcohol **18** oxidized directly with Swern's reagent to the desired aldehyde **6** in an overall yield of 25% from **12a**.

With the successful preparation of the enolate precursor **5** and the β,γ-unsaturated aldehyde acceptor **6**, the coupling of the two moieties was accomplished by using the now standard aldol condensation condition employing an *E*-enolate.[18] The best results were obtained when the enolate was formed at −78 °C by addition of the ketone to LDA in THF and the mixture was stirred for 1 h at this temperature. The neat aldehyde was added with efficient stirring at −78 °C, and the reaction was allowed to continue for 30 s and quenched to give the erythro product **19** in 58% yield (Scheme I). The ketone of **19** was reduced with LAH, and the silyl ethers were removed by using aqueous methanolic sodium hydroxide to give the triol **20** in 61% yield. The oxidative cleavage of the 1,2-diol proved to be difficult due to the presence of the easily oxidizable thiophenyl group. It was found that lead tetraacetate in pyridine[26] was the reagent of choice, the crude aldehyde upon LAH reduction giving the triol **21** in 66% yield, which, in turn, was converted to the acetonide **22** in 58%

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yield. The primary alcohol **22** was converted into a 3:1 mixture of the tosylate and chloride and the mixture used directly for the ring closure since separate studies showed that each leaving group functioned equally in the closure reaction. The crude tosylate mixture was ring closed by using LDA at −78 °C to yield **23** in 32% yield from **22** as a diastereomeric mixture. The product was reduced by using lithium in ethylamine[27] to afford the desired substituted ring system in 68% yield.

The ring closure of **19** was studied under many conditions and at various stages of modification of the substituents but it was found that the procedure presented above was the cleanest and the most efficient. With **24** in hand, the addition of the lactone ring is now being studied.

Experimental Section[28]

Ethyl 2,7-Dimethyl-(*E*)-2,6-octadienoate.[21] To a suspension of 25.0 g (0.52 mol) of a 50% dispersion of NaH in mineral oil (washed with pentane) in 800 mL of dry glyme at 0 °C was slowly added 125.0 g (0.52 mol) of ethyl 2-(diethylphosphono)propionate, and the suspension was stirred for 3 h. Over a 10–15-min period, with external ice cooling, there was added 62.0 g (0.50 mol) of 5-methyl-4-hexenal (**7**),[20] the mixture was stirred for 18 h and poured into water, and the organic material was extracted with hexane (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated on a rotary evaporator. The crude product was distilled under reduced pressure to give 68.9 g (70%) of a colorless oil: bp 70–75 °C (1 torr); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.28 (t, 3, J = 7 Hz), 1.62 (s, 3), 1.69 (s, 3), 1.82 (s, 3), 2.15 (m, 4), 4.18 (q, 2, J = 7 Hz), 5.11 (m, 1), 6.75 (m, 1).

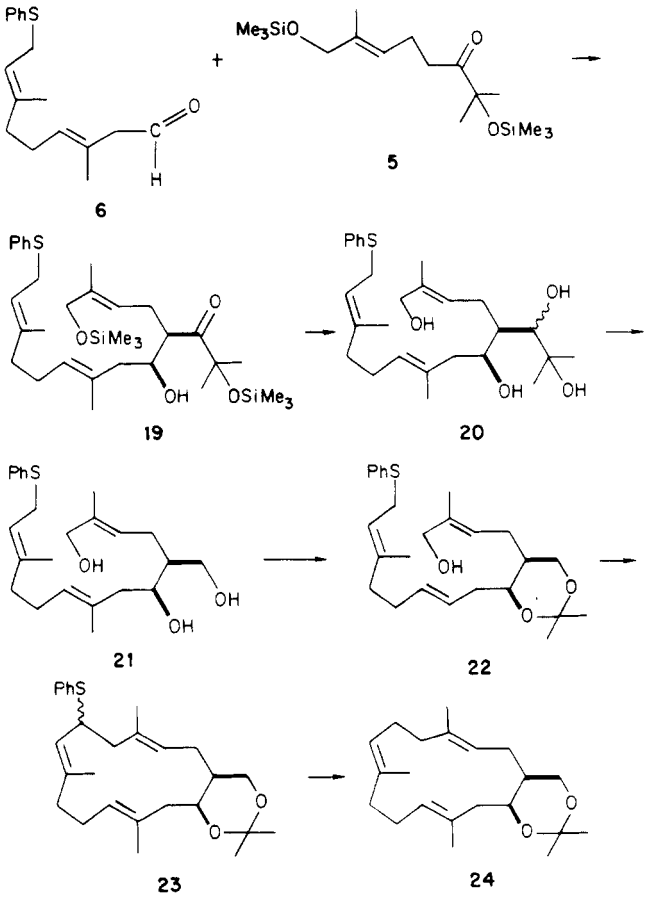
(*E*)-2,7-Dimethyl-2,6-octadienol (8).[21,29] To 78.5 g (0.396 mol) of ethyl 2,7-dimethyl-(*E*)-2,6-octadienoate in 500 mL of dry ether at 0 °C was added 9.2 g (0.240 mol) of LAH, with cooling. The resulting suspension was stirred at room temperature for 20 h and cooled to 0 °C, and a saturated aqueous solution of sodium sulfate was added until the precipitate was granular. The suspension was filtered, the filtrate was dried ($MgSO_4$), and the solvent was removed on a rotary evaporator to give 62 g of crude product. The material was distilled under reduced pressure to yield 58.0 g (94%) of a colorless oil: bp 105–112 °C (10 torr); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.60 (s, 3), 1.66 (s, 3), 1.68 (s, 3), 2.04 (br s, 4), 3.99 (s, 2), 5.12 (m, 1), 5.41 (m, 1).

(*E*)-1-Acetoxy-2,7-dimethylocta-2,6-diene. To 20.3 g (0.132 mol) of alcohol **8** in 165 mL of pyridine at room temperature was added 25.8 g (0.250 mol) of acetic anhydride. The solution was stirred for 24 h and poured into water/hexane (1:1). The layers were separated, and the aqueous layer was reextracted with hexane. The combined organic layers were washed with water (3×), 10% HCl (3×), and brine (3×) and dried over $MgSO_4$. The solvent was removed on a rotary evaporator, and the residue was distilled under reduced pressure to give 23.6 g (91%) of colorless oil: bp 80 °C (1 torr); IR (thin film) 2910, 1730, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.59 (s, 3), 1.64 (s, 3), 1.67 (s, 3), 2.06 (m, 7), 4.44 (s, 2), 5.10 (m, 1), 5.46 (m, 1); mass spectrum (70 eV), m/e (relative intensity) 196 (M^+, 1), 154 (6), 136 (34), 93 (55), 69 (100). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.26.

(*E*)-1-Acetoxy-6,7-dihydroxy-2,7-dimethyloct-2-ene (9). To 20.0 g (0.102 mol) of (*E*)-1-acetoxy-2,7-dimethylocta-2,6-diene in 120 mL of THF at 0 °C was added, with vigorous stirring, 17.6 g (0.102 mol) of *m*-chloroperoxybenzoic acid (80–85%) in 25 mL of THF. The mixture was stirred for 30 min, and the cooling bath was removed. The solution was stirred for 15 min, and an additional 2.64 g (0.015 mol) of *m*-chloroperoxybenzoic acid in 5 mL of THF was added. The mixture was stirred for 15 min, and 23 mL of water was added, followed by 1.2 mL of aqueous 60% perchloric acid. The mixture was stirred for 45 min, and 4.0 mL of saturated aqueous $NaHCO_3$ was added. The solvent was removed on a rotary evaporator, and the residue was poured into water. The aqueous layer was extracted with ether (5×) and chloroform. The combined organic extracts were dried ($MgSO_4$), and the solvents were removed on a rotary evaporator to give 21.9 g of crude product which was chromatographed (silica gel, 60:40 ethyl acetate/hexane) to yield 16.7 g (71%) of colorless oil: IR (thin film) 3440, 2980, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.15 (s, 3), 1.20 (s, 3), 1.35–1.6 (m, 2), 1.68 (s, 3), 2.08 (s, 3), 2.1–2.4 (m, 2), 3.36 (m, 1), 4.46 (s, 2), 5.48 (t, 1, J = 7 Hz); mass spectrum (70 eV), m/e (relative intensity) 170 ($M^+ - CH_3CO_2H$, 46), 155 (46), 119 (57), 94 (77), 55 (100). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.42; H, 9.58.

(*E*)-1-Acetoxy-7-hydroxy-2,7-dimethyloct-2-en-6-one. To a solution of 28.0 mL (40.7 g, 0.321 mol) of oxalyl chloride in 400 mL of dichloromethane at −60 °C was added 46 mL (50.6 g, 0.64

Scheme I



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(28) Ether, 1,2-dimethoxyethane (glyme), and tetrahydrofuran (THF) were distilled from sodium benzophenone immediately prior to use. Triethylamine and diisopropylamine were distilled from calcium hydride. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere with oven-dried glassware. The solution of butyllithium in hexane was titrated with diphenylacetic acid in THF at −78 °C. Most reactions were followed by analytical thin layer chromatography (TLC) using precoated Analtech Uniplates (250μM thick) and appropriate mixtures of ethyl acetate and hexane as solvents. Compounds were visualized by iodine vapor or ethanolic phosphomolybdic acid spray. Flash chromatography was performed according to the method of Still[30] using 400–230-mesh silica gel. IR spectra were recorded on a Perkin-Elmer Model 281 infrared spectrophotometer. ^1H NMR spectra were determined on the UCB 250 and UCB 300 spectrometer (superconducting FT instruments operating at 250-MHz and 300-MHz, respectively). ^{13}C NMR spectra were measured at 63 MHz and 75 MHz on the UCB 250 and UCB 300 spectrometers, respectively. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. The ^1H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; mc, multiplet center), number of protons, coupling constant in hertz. Mass spectra were obtained with AEI MS-12, Kratos MS-50, and Consolidated 12-110 B mass spectrometers. Mass spectral data are tabulated as m/e (intensity expressed as percent of base peak). Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, CA.

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mol) of dimethyl sulfoxide in 45 mL of dichloromethane over a period of 30 min. The mixture was stirred for 5 min, and 35.0 g (0.152 mol) of diol acetate **9** in 40 mL of dichloromethane was slowly added. The mixture was stirred for 30 min, and 106 mL (77 g, 0.76 mol) of triethylamine was added. The cooling bath was removed, and the mixture was allowed to warm to room temperature and stirred for 3.5 h. The solution was poured into 1 L of water, the layers were separated, and the aqueous layer was reextracted with CH_2Cl_2. The combined organic layers were washed with aqueous 10% HCl, saturated aqueous $NaHCO_3$, and brine and dried ($MgSO_4$). The solvent was removed on a rotary evaporator, and the residue was purified by flash chromatography (silica gel, 10% to 75% ethyl acetate/hexane) to yield 25.2 g (73%) of yellow oil: IR (thin film) 3460, 2960, 1735, 1710, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.35 (s, 6), 1.66 (s, 3), 2.05 (s, 3), 2.36 (m, 2), 2.61 (t, 2, J = 7 Hz), 4.42 (s, 2), 5.38 (t, 1, J = 7 Hz); mass spectrum (70 eV), m/e (relative intensity) 169 (M^+ – CH_3CO_2, 13), 125 (48), 110 (56), 82 (86), 59 (93), 43 (100). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.69; H, 8.68.

(*E*)-2,8-Dihydroxy-2,7-dimethyloct-6-en-3-one. A mixture of 7.37 g (43.1 mmol) of barium hydroxide and 70 mL of methanol was filtered into a solution of 18.0 g (78.9 mmol) of acetate **9** in 30 mL of methanol. The mixture was stirred for 10 min and 5.2 mL (5.5 g, 91.0 mmol) of acetic acid was added. The mixture was stirred for 5 min, and the solvent was removed on a rotary evaporator. The residue was swirled with 300 mL of ether, and the mixture was filtered through Celite. The solvent was evaporated, and the crude product was chromatographed (silica gel, 40:60 ethyl acetate/hexane) to give 12.3 g (84%) of light yellow oil: IR (thin film) 3400, 2970, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.36 (s, 6), 1.66 (s, 3), 2.33 (q, 2, J = 7 HZ), 2.60 (t, 2, J = 7 Hz), 3.95 (s, 2), 5.35 (t, 1, J = 7 Hz); mass spectrum (70 eV), m/e (relative intensity) 186 (M^+, 1), 140 (31), 110 (64), 82 (86), 59 (100); exact mass calcd for $C_{10}H_{18}O_3$ 186.1256, found 186.1259.

2,8-Bis(trimethylsiloxy)-2,7-dimethyloct-6-en-3-one (10). To a solution of 2.34 g (19.2 mmol) of 4-(dimethylamino)pyridine and 17.8 mL (12.9 g, 127.7 mmol) of triethylamine in 50 mL of dichloromethane at room temperature was added, in one portion, 16.3 mL (13.92 g, 129.0 mmol) of chlorotrimethylsilane. The mixture was placed in an ice bath and stirred for 5 min, and 10.8 g (58.1 mmol) of the diol from the above reaction in 20 mL of dichloromethane was added. A precipitate formed upon addition. A 100-mL volume of dichloromethane was added, and the cooling bath was removed. The mixture was stirred for 10 min and poured into water. The organic layer was washed with brine and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed (silica gel, 5:95 ethyl acetate/hexane) to afford 16.3 g (85%) of ketone **10**: IR (thin film) 2950, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.11 (s, 9), 0.14 (s, 9), 1.32 (s, 6), 1.63 (s, 3), 2.25 (m, 2), 2.69 (t, 2, J = 7.5 Hz), 3.97 (s, 2), 5.35 (t, 1, J = 7 Hz); mass spectrum (70 eV), m/e (relative intensity) 330 (M^+, 2), 131 (91), 73 (100); exact mass calcd for $C_{16}H_{34}O_3Si_2$ 330.2037, found 330.2036.

1-Acetoxy-3,7-dimethylocta-2,6-dien-8-ol (12a). To 1.11 g (0.01 mol) of selenium dioxide, 6.1 g (0.05 mol) of benzoic acid, and 100 mL of methylene chloride in a flask in a room temperature water bath was added 100 mL of a methylene chloride extract of 162 g (1.8 mol) of 70% *tert*-butyl hydroperoxide. The mixture was stirred for 5 min and 98.0 g (0.5 mol) of geranyl acetate was added. The mixture was stirred for 26 h, 113.5 mL of dimethyl sulfide was added, and a reflux condenser was attached to the reaction flask. The mixture was stirred for 6 h and poured into 10% aqueous potassium hydroxide. The organic layer was washed with brine and dried ($MgSO_4$), and the solvent was removed on a rotary evaporator. The resulting light green oil was distilled to give 51.86 g (48.9%) of a light green oil: bp 105–127 °C (0.1 torr); R_f 0.44 (benzene/ether, 2:1) [lit.[22] R_f 0.44 (benzene/ether, 2:1)].

1-Acetoxy-8-bromo-3,7-dimethylocta-2,6-diene (13a). To a magnetically stirred suspension of 2.16 g (12 mmol) of *N*-bromosuccinimide in 40 mL of methylene chloride, under nitrogen, was added, dropwise at 0 °C, 0.88 g (14.4 mol) of dimethyl sulfide over a period of a few minutes. The solution was allowed to stir 15 min and cooled to –20 °C, and 1.66 g (8 mmol) of alcohol **12a** in 4 mL of methylene chloride was added, dropwise, over a 5-min period. The solution was warmed to 0 °C, stirred for 3 h, diluted with 60 mL of cold pentane, and poured into 30 mL of ice water. The organic phase was washed with cold brine (2 × 40 mL), filtered through 2 g of silica gel, and concentrated on a rotary evaporator to yield 1.76 g (80%) of bromide **13a**: IR (thin film) 2950, 1740, 1300 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 3.90 (s, 2), 5.23 (t, 1, J = 6 Hz), 5.41 (m, 1) [lit.[22] R_f 0.75 (benzene/ether, 4:1)].

8-Hydroxy-3,7-dimethyl-2,6-octadiene Phenyl Sulfide (12b). To 0.11 g (1 mmol) of selenium dioxide in 2 mL of methylene chloride in a flask in a room-temperature water bath was added 2 mL of the methylene chloride extract of 2.3 g (18.0 mmol) of 70% *tert*-butyl hydroperoxide. The suspension was stirred for 5 min and 1.21 g (5.0 mmol) of geranyl phenyl sulfide was added. The solution was stirred for 20 h and poured into 10 mL of 10% aqueous potassium hydroxide. The organic layer was separated, washed with brine (10 mL), dried ($MgSO_4$), and concentrated on a rotary evaporator to give 1.5 g of crude product. The crude product was dissolved in 100 mL of ether, the solution was cooled in an ice bath, and, with good stirring, 1.0 g of lithium aluminum hydride was added. The suspension was stirred for 4 h at 0 °C and 3 mL of 10% aqueous potassium hydroxide solution was slowly added. The resulting slurry was filtered, the filter cake washed with ether, the organic solution was dried ($MgSO_4$), and the solvent was removed on a rotary evaporator to give 1.2 g of a viscous yellow oil. The oil was chromatographed (silica gel, 15:85 ethyl acetate/hexane) to give 0.5 g (38%) of pure **12b**: IR (thin film) 3360, 2930, 1580, 1440, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.59 (s, 3), 1.65 (s, 3), 2.06 (m, 4), 3.54 (d, 2, J = 7.7 Hz), 3.96 (s, 2), 5.31 (m, 2), 7.26 (m, 5); mass spectrum (70 eV), m/e (relative intensity) 262 (M^+, 0.45), 57 (3.8); exact mass calcd for $C_{16}H_{22}SO$ 262.1393, found 262.1382.

8-Bromo-1-(phenylthio)-3,7-dimethyl-2,6-octadiene (13b). To 0.59 g (3.3 mmol) of *N*-bromosuccinimide in 9 mL of methylene chloride, at 0 °C, was added 8.29 mL (3.9 mmol) of dimethyl sulfide. The solution was stirred for 5 min at –20 °C and 0.57 g (2.2 mmol) of hydroxy sulfide **12b** was added. The suspension was allowed to warm to room temperature, stirred for 3 h, and poured into 10 mL of cold pentane. The organic layer was separated, washed with ice water (2 × 25 mL) and brine (2 × 25 mL), and dried ($MgSO_4$). The solution was filtered through 1.0 g of silica gel and concentrated on a rotary evaporator to give 0.56 g (80%) of a clear oil: IR (thin film) 2930, 1592, 1440, 1220, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.46 (s, 3), 1.71 (s, 3), 7.0 (m, 4), 3.22 (d, 2, J = 8 Hz), 5.16 (m, 2), 7.08 (m, 5); mass spectrum (70 eV), m/e (relative intensity) 324 (M^+, 1.92), 245 (17.9), 135 (50.9), 67 (base); exact mass calcd for $C_{16}H_{21}BrS$ 324.0548, found 324.0547.

9-(Diethylamino)-9-cyano-1-(phenylthio)-3,7-dimethylnona-2,6-diene. To 1 equiv of lithium diethylamide in 50 mL of tetrahydrofuran, containing 1 equiv of hexamethylphosphorus triamide, at –78 °C was added 0.25 g (2.3 mmol) of (diethylamino)acetonitrile. The solution was stirred for 10 min and 0.57 g (1.76 mmol) of bromide **13b** in 3 mL of tetrahydrofuran was added. The solution was stirred for 2 h at –78 °C and 55 h at 25 °C. The solution was poured into an equal volume of pentane and the pentane layer washed with water (3 × 100 mL), dried ($MgSO_4$), and concentrated on a rotary evaporator to give 0.7 g of crude product. The material was chromatographed on silica gel (10:90 EtOAc/hexane) to give 0.45 g (75%) of material giving a single spot on TLC analysis: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.0 (t, 6, J = 9 Hz), 1.5 (s, 3), 1.56 (s, 3), 1.98 (s, 4), 2.4 (m, 6), 3.37 (d, 2, J = 7 Hz), 3.5 (t, 1, J = 7 Hz), 5.16 (br t, 2, J = 6 Hz), 7.1 (m, 5).

3,7-Dimethyl-9-(phenylthio)nona-2,6-dienal (14b). A 220-mg portion of the above (diethylamino)nitrile derivative was refluxed for 20 min in an equal volume of 30% aqueous oxalic acid and tetrahydrofuran and poured into an equal volume of ice water and chloroform. The organic layer was separated, dried ($MgSO_4$), and concentrated on a rotary evaporator to yield 120 mg of liquid which gave mainly one spot on TLC analysis. The NMR spectrum was practically identical with that reported for compound **6** except conjugated protons appear at δ 5.7.

(*E*,*E*)-8-Acetoxy-2,6-dimethylocta-2,6-dienal (15). To 35.0 mL (50.1 g, 0.39 mol) of oxalyl chloride in 750 mL of dichloromethane at –70 °C was added 60 mL (66.1 g, 0.85 mol) of dimethyl sulfoxide in 175 mL of dichloromethane within 0.5 h. The alcohol **12a** (74.0 g, 0.35 mol)[23] was added over a period of 2 h. The

mixture was stirred for 1 h, and 250 mL (181.5 g, 1.79 mol) of triethylamine was added. The cooling bath was removed, and the mixture was allowed to warm to room temperature and stirred overnight. The mixture was poured into water, the layers were separated, and the aqueous layer was reextracted with dichloromethane. The combined organic layers were concentrated on a rotary evaporator to a total volume of about 700 mL. Hexane was added, and the solution was washed with water, aqueous 5% HCl, aqueous 5% sodium hydrogen carbonate, and water. The organic extract was dried ($MgSO_4$), and the solvents were removed on a rotary evaporator. The crude product was distilled under reduced pressure to yield 59.6 g (81%) of light yellow oil: bp 110–125 °C (1 torr); IR (thin film) 2950, 2740, 1740, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.75 (s, 6), 2.05 (s, 3), 2.24 (t, 2, J = 7 Hz), 2.50 ("q", 2, J = 7 Hz), 4.60 (d, 2, J = 7 Hz), 5.39 (t, 1, J = 7 Hz), 6.45 (t, 1, J = 7 Hz), 9.39 (s, 1).

(*E,E*)-1-Acetoxy-3,7-dimethylnona-2,6,8-triene. To a suspension of 23.1 g (57.14 mmol) of methyltriphenylphosphonium iodide in 130 mL of dry THF at 0 °C was added 30.3 mL (50.00 mmol) of a 1.65 M solution of butyllithium in hexane. The mixture was stirred for 10 min, and 20 mL of dry HMPA was added. The cooling bath was removed, and the stirring was continued for 45 min. The mixture was cooled to −60 °C, and 10.0 g (47.62 mmol) of (*E,E*)-8-acetoxy-2,6-dimethylocta-2,6-dienal (**15**) in 40 mL of dry THF was slowly added. The mixture was allowed to warm to room temperature over a period of 3 h, filtered through silica gel (70–230 mesh), diluted with some ether, and poured into water. The organic layer was washed with aqueous Na_2SO_3 and brine and dried ($MgSO_4$). The solvents were removed on a rotary evaporator to give 7.22 g of crude material. The residue was purified by flash chromatography (120 g silica gel, 0% to 10% ethyl acetate/hexane) and yielded 6.91 g (70%) of triene: IR (thin film) 2930, 1740, 1240, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.69 (s, 3), 1.71 (s, 3), 2.03 (s, 3), 2.10 (mc, 2), 2.25 (mc, 2), 4.57 (d, 2, J = 7 Hz), 4.91 (d, 1, J = 11 Hz), 5.06 (d, 1, J = 17 Hz), 5.34 (t, 1, J = 4 Hz), 5.43 (t, 1, J = 7 Hz), 6.33 (dd, 1, J = 11 Hz, J = 17 Hz); mass spectrum (70 eV), m/e (relative intensity) 208 (M^+, 4), 148 (62), 133 (67), 119 (51), 105 (55), 93 (59), 81 (88), 79 (80), 77 (100); exact mass calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1469.

(*E,E*)-3,7-Dimethylnona-2,6,8-trien-1-ol (16). A mixture of 9.7 g (46.6 mmol) of (*E,E*)-1-acetoxy-3,7-dimethylnona-2,6,8-triene, 40 mL of methanol, and 35 mL of a 1 M solution of sodium hydroxide in 50% aqueous methanol was stirred for 3 h at room temperature. The mixture was poured into water and extracted with hexane (2×) and ether (1×). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvents were evaporated to yield 7.5 g (97%) of slightly yellow oil which was used without further purification: IR (thin film) 3330, 2920, 1600, 1440, 990, 890 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.70 (s, 3), 1.75 (s, 3), 2.10 (m, 2), 2.28 (m, 2), 4.16 (d, 2, J = 7 Hz), 4.94 (d, 1, J = 11 Hz), 5.09 (d, 1, J = 17 Hz), 5.45 (m, 2), 6.37 (dd, 1, J = 11 Hz, J = 17 Hz); mass spectrum (70 eV), m/e (relative intensity) 166 (M^+, 5), 133 (25), 105 (24), 93 (72), 91 (35), 81 (100), 80 (74), 79 (69); exact mass calcd for $C_{11}H_{18}O$ 166.1357, found 166.1352.

(*E,E*)-3,7-Dimethyl-1-(phenylthio)nona-2,6,8-triene (17). To a solution of 7.5 g (45.2 mmol) of (*E,E*)-3,7-dimethylnona-2,6,8-trien-1-ol (**16**) and some crystals of 2,2′-bipyridine in 110 mL of dry THF at −60 °C was added a 1.6 M solution of butyllithium in hexane until the indicator changed color (about 28 mL). The solution was stirred for some minutes, 9.5 g (49.7 mmol) of tosyl chloride in 35 mL of dry THF was added, the cooling bath was removed, and the solution was allowed to warm to room temperature. The tosylate was formed as a white precipitate. The reaction mixture was allowed to stand for 2.5 h, and a solution of lithium thiophenoxide in THF was added at room temperature. This latter solution had been prepared in a separate flask by adding a 1.6 M solution of butyllithium in hexane to the solution of 7.5 g (68.2 mmol) of thiophenol and some crystals of 2,2′-bipyridine in 30 mL of dry THF at −60 °C until the indicator turned red (about 41 mL).

The mixture of thiophenoxide and the tosylate was stirred for 2.5 h and was poured into water. The aqueous layer was extracted 3 times with ether/hexane. The combined organic layers were washed with aqueous potassium hydroxide (10%) and brine and dried ($MgSO_4$). The solvents were removed on a rotary evaporator to give 14.0 g of crude product. The material was purified by flash chromatography (140 g of silica gel, 0% to 15% ethyl acetate/hexane); 10.4 g (89%) of **17** was isolated: IR (thin film) 2920, 1480, 1440, 890, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.58 (s, 3), 1.72 (s, 3), 2.07 (m, 2), 2.19 (m, 2), 3.54 (d, 2, J = 7.6 Hz), 4.92 (d, 1, J = 11 Hz), 5.07 (d, 1, J = 17 Hz), 5.32 (m, 1), 5.42 (m, 1), 6.33 (dd, 1, J = 11 Hz, J = 17 Hz), 7.20–7.36 (m, 5); mass spectrum (70 eV), m/e (relative intensity) 258 (5), 149 (32), 135 (34), 109 (33), 93 (40), 81 (100). Anal. Calcd for $C_{17}H_{22}S$: C, 79.01; H, 8.58; S, 12.40. Found: C, 78.67; H, 8.48; S, 12.32.

(*E,E*)-3,7-Dimethyl-9-(phenylthio)nona-3,7-dienol (18). To 46.05 mL (46.05 mmol) of a 1 M solution of a borane–tetrahydrofuran complex in THF at 0 °C was added 10.9 mL (7.22 g, 102.9 mmol) of 2-methyl-2-butene. The mixture was stirred at 0 °C for 2.5 h and added to a precooled solution of 10.8 g (41.9 mmol) of (*E,E*)-3,7-dimethyl-1-(phenylthio)nona-2,6,8-triene (**17**) in 40 mL of THF. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was cooled to −10 °C, and 15 mL of a 3 M solution of aqueous sodium hydroxide and 15 mL of 30% hydrogen peroxide were added very slowly such that the temperature never exceeded −5 °C. The mixture was allowed to warm to room temperature and stir for 3 h and was poured into water, and the aqueous layer was extracted several times with ether. The combined organic layers were washed with brine and dried, and the solvent was removed on a rotary evaporator. The crude product was purified by flash chromatography (200 g of silica gel, 0% to 50% ethyl acetate/hexane) to afford 8.3 g (72%) of alcohol **18**: IR (thin film) 3360, 2920, 1430 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.58 (s, 3), 1.61 (s, 3), 2.06 (m, 4), 2.22 (t, 2, J = 6 Hz), 3.54 (d, 2, J = 8 Hz), 3.63 (t, 2, J = 6 Hz), 5.17 (m, 1), 5.30 (t, 1, J = 8 Hz), 7.17–7.35 (m, 5); mass spectrum (70 eV), m/e (relative intensity) 276 (M^+, 3), 149 (15), 110 (51), 81 (100).

(*E,E*)-3,7-Dimethyl-9-(phenylthio)nona-3,7-dienal (6). To a solution of 0.83 mL (1.20 g, 9.47 mmol) of oxalyl chloride in 25 mL of dichloromethane at −60 °C in a 100-mL, three-necked flask equipped with a mechanical stirrer was added slowly 1.46 mL (1.61 g, 20.66 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane. The mixture was stirred for some minutes at −60 °C and warmed to −15 °C to −10 °C, and 1.19 g (4.30 mmol) of (*E,E*)-3,7-dimethyl-9-(phenylthio)nona-3,7-dienol (**18**) in 5 mL of dichloromethane was slowly added via syringe within 5–10 min. The mixture was stirred for 15 min, 3.0 mL (2.17 g, 21.52 mmol) of triethylamine was added, and the solution was stirred an additional 15 min at −10 °C. The mixture was allowed to warm to room temperature and poured into water. The layers were separated, and the aqueous layer was reextracted with dichloromethane. The combined organic layers were concentrated on a rotary evaporator to a total volume of about 20–30 mL. Hexane was added, and the solution was washed with aqueous 5% HCl (2×), aqueous 5% Na_2CO_3 (2×), and brine and dried ($MgSO_4$). The solvents were removed on a rotary evaporator to give 1.09 g of crude material which was purified by flash chromatography (silica gel, 5:95 ethyl acetate/hexane) to yield 0.85 g (72%) of aldehyde **6**: IR (thin film) 2930, 1730, 1440, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.59 (s, 3), 1.64 (s, 3), 2.07 (m, 4), 3.00 (d, 2, J = 2 Hz), 3.54 (d, 2, J = 8 Hz), 5.23 (t, 1, J = 6 Hz), 5.31 (t, 1, J = 8 Hz), 7.16–7.40 (m, 5), 9.56 (t, 1, J = 2 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 16.75, 16.82, 26.24, 31.80, 38.92, 54.00, 119.57, 125.79, 126.48, 128.52 (double intensity), 129.51, 129.88, 136.50, 138.96, 200.29; mass spectrum (70 eV), m/e (relative intensity) 274 (M^+, 16), 147 (29), 121 (76), 110 (86), 105 (42), 95 (61), 81 (79), 69 (100). Anal. Calcd for $C_{17}H_{22}OS$: C, 74.41; H, 8.08; S, 11.68. Found: C, 74.18; H, 8.05; S, 11.53.

***erythro*-9-Hydroxy-10-[1-oxo-2-methyl-2-(trimethylsiloxy)propyl]-1-(phenylthio)-14-(trimethylsiloxy)-3,7,13-trimethyltetradeca-(*E,E,E*)-2,6,12-triene (19).** To 32.5 mL (16.25 mmol) of a 0.50 M solution of lithium diisopropylamide (LDA) in THF/hexane at −78 °C in a 100-mL, three-necked flask equipped with a mechanical stirrer was added 5.0 g (15.15 mmol) of ketone **5** over a period of 5–10 min. The solution was stirred for 1.0 h at −78 °C, and then, with vigorous stirring, 3.77 g (13.77 mmol) of aldehyde **6** was added, neat, in one portion. The mixture was stirred 30 s, 15 mL of saturated ammonium chloride was added, and the cooling bath was removed. The mixture was stirred until both layers were liquid, and the aqueous layer was separated

and extracted with hexane. The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was removed on a rotary evaporator. The crude material was purified by flash chromatography (silica gel, 0% to 10% ethyl acetate/hexane) to give 5.11 g (58.3%) of **19** as a light yellow oil: IR (thin film) 3500, 2950, 1700, 1245, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.10 (s, 9), 0.18 (s, 9), 1.27 (s, 3), 1.34 (s, 3), 1.57 (s, 3), 1.60 (s, 3), 1.62 (s, 3), 2.06 (m, 5), 2.2–2.4 (m, 4), 3.50 (m, 1), 3.53 (d, 2, J = 7.6 Hz), 3.92 (s, 2), 5.18 (m, 1), 5.30 (m, 2), 7.31 (m, 5); mass spectrum (70 eV), m/e (relative intensity) 605 (M^+ + 1, 2) 604 (M^+, 1), 405 (23), 315 (22), 269 (88), 131 (100). Anal. Calcd for $C_{33}H_{56}O_4SSi_2$: C, 65.51; H, 9.33; S, 5.30. Found: C, 65.58; H, 9.16; S, 5.29.

***erythro*-9,14-Dihydroxy-10-(1,2-dihydroxy-2-methylpropyl)-1-(phenylthio)-3,7,13-trimethyltetradeca-(*E*,*E*,*E*)-2,6,12-triene (20).** To 3.00 g (5.05 mmol) of aldol product **19** in 55 mL of dry ether at −20 °C was added 200 mg (5.26 mmol) of LAH. The mixture was stirred for 2 h, and a saturated aqueous solution of sodium sulfate was added until a granular precipitate developed. The suspension was filtered, the filtrate was dried ($MgSO_4$), and the solvent was removed on a rotary evaporator. The resulting oil was dissolved in 30 mL of methanol, and 10 mL of a 1 M solution of sodium hydroxide in methanol/water (1:1) was added. The solution was stirred for 2.75 h at room temperature. The solution was poured into water and extracted 3 times with ethyl acetate. The combined organic layers were dried ($MgSO_4$), and the solvent was removed on a rotary evaporator to give 2.22 g of crude product. The material was purified by flash chromatography (60 g of silica gel, 20% to 100% ethyl acetate/hexane) to yield 1.43 g (61%) of tetrol **20**: IR (thin film) 3380, 2970, 2920, 1735, 1440, 1375 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MZ) δ 1.22 (s, 3), 1.24 (s, 3), 1.57 (s, 3), 1.60 (s, 3), 1.68 (s, 3), 2.0–2.5 (m, 9), 3.53 (d, 2, J = 8 Hz), 3.63 (m, 1), 3.83 (m, 1), 3.97 (br s, 2), 5.16 (m, 1), 5.29 (t, 1, J = 7.5 Hz), 5.45 (m, 1), 7.15–7.35 (m, 5); mass spectrum (70 eV), m/e (relative intensity) 462 (M^+, 0.2), 444 ($M^+ - H_2O$, 6), 110 (42), 81 (50), 71 (100); exact mass calcd for $C_{27}H_{42}SO_4$ 462.2803, found 462.2798.

***erythro*-9,14-Dihydroxy-10-(hydroxymethyl)-1-(phenylthio)-3,7,13-trimethyltetradeca-(*E*,*E*,*E*)-2,6,12-triene (21).** To a solution of 268 mg (0.581 mmol) of tetrol **20** in 10 mL of pyridine at room temperature was added 257 mg (0.580 mmol) of lead tetraacetate, and the mixture was stirred for 2.5 h. Some ether and some water were added, the layers were separated, and the organic layer was washed with dilute aqueous copper sulfate (4×) and brine (2×) and dried ($MgSO_4$). The solvent was removed in a rotary evaporator to give 287 mg of crude aldehyde as a yellow oil. For recording spectroscopic data, a sample was purified by flash chromatography (0% to 50% ethyl acetate/hexane): IR ($CDCl_3$) 3500, 2970, 2940, 1720, 1590, 1440, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.59 (s, 3), 1.63 (s, 3), 1.71 (s, 3), 2.0–2.6 (m, 9), 3.56 (d, 2, J = 8 Hz), 4.00 (s, 2), 4.10 (m, 1), 5.21 (m, 1), 5.32 (m, 1), 5.43 (m, 1), 7.15–7.38 (m, 5), 9.78 (s, 1).

The 287 mg of crude aldehyde was dissolved in 20 mL of dry ether, the solution was cooled to 0 °C, and 22.1 mg (0.581 mmol) of LAH was added. The mixture was stirred for 1 h and a saturated aqueous solution of sodium sulfate was added until a granular precipitate developed. The suspension was filtered, the filtrate was dried ($MgSO_4$), and the solvent was removed on a rotary evaporator. The residue was purified by flash chromatography (6 g of silica gel, 10% to 80% ethyl acetate/hexane) to give 155.3 mg (66%) of triol **21**: IR (thin film) 3390, 2930, 1450, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.58 (s, 3), 1.62 (s, 3), 1.68 (s, 3), 2.05–2.18 (m, 9), 3.54 (d, 2, J = 8 Hz), 3.64–3.75 (m, 2), 3.95 (m, 1), 3.99 (s, 2), 5.20 (mc, 1), 5.30 (mc, 1), 5.45 (mc, 1), 7.18–7.36 (m, 5); mass spectrum (70 eV), m/e (relative intensity) 404 (M^+, 1), 386 ($M^+ - H_2O$, 4), 177 (11), 141 (91), 81 (78), 69 (84), 43 (100); exact mass calcd for $C_{24}H_{36}O_3S$ 404.2385, found 404.2377.

***erythro*-9,15-*O*-Isopropylidene-9,14-dihydroxy-10-(hydroxymethyl)-1-(phenylthio)-3,7,13-trimethyltetradeca-(*E*,*E*,*E*)-2,6,12-triene (22).** To 438 mg (1.084 mmol) of triol **21** was added, at room temperature, 8.0 mL (6.8 g, 65.1 mmol) of 2,2-dimethoxypropane in 20 mg of tosic acid. The mixture was stirred for 0.5 h at room temperature, poured into water, and extracted with ether. The combined organic layers were dried ($MgSO_4$), and the solvent was removed on a rotary evaportor to give 510 mg of crude material which was chromatographed (20 g silica gel, 0% to 30% ethyl acetate/hexane) to yield 281 mg (58%) of **22**: IR (thin film) 3420, 2920, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.41 (s, 3), 1.46 (s, 3), 1.60 (s, 3), 1.64 (s, 3), 1.73 (s, 3), 2.00–2.35 (m, 8), 2.58 (m, 1), 3.56 (d, 2, J = 8 Hz), 3.71 (d, 1, J = 12 Hz), 3.92 (d, 1, J = 12 Hz), 4.03 (br s, 2), 4.16 (dt, 1, J = 2 Hz, J = 7 Hz), 5.19 (m, 1), 5.32 (m, 1), 5.40 (m, 1), 7.21–7.37 (m, 5); mass spectrum (70 eV), m/e (relative intensity) 444 (M^+, 0.3), 199 (42), 95 (51), 59 (62); exact mass calcd for $C_{27}H_{40}O_3S$ 444.2698, found 444.2714.

***erythro*-14,15-*O*-Isopropylidene-1-(hydroxymethyl)-14-hydroxy-6-(phenylthio)-4,8,12-trimethylcyclotetradeca-(*E*,*E*,*E*)-3,7,11-triene (23).** To 255 mg (0.574 mmol) of hydroxy acetonide **22** in 8 mL of dichloromethane at 0 °C was added 120 mg (0.631 mmol) of tosyl chloride and 115 mg (0.943 mmol) of 4-(dimethylamino)pyridine. The solution was stirred at this temperature for 3 h and allowed to stand at 0 °C (refrigerator) overnight. Some more dichloromethane was added, and the mixture was poured into ice water. The organic layer was washed with aqueous 3 HCl, saturated aqueous $NaHCO_3$, and ice water and dried ($MgSO_4$). As soon as the solvent had been removed on a rotary evaporator, the crude tosylate–chloride mixture (3:1) started to crystallize.

The white solid was dissolved in 100 mL of dry THF. The solution was cooled to −78 °C, and 12.4 mL (5.83 mmol) of a 0.47 M solution of lithium diisopropylamide (LDA) in THF/hexane was slowly added. The solution was stirred for 2 h at −78 °C, 8 mL of methanol was added, and the cooling bath was removed. The solution was warmed to room temperature, and 5 mL of water was added. Most of the solvent was removed on a rotary evaporator. The residue was taken up in ether, washed with water, and dried ($MgSO_4$). The solvent was evaporated to give a dark yellow oil which was purified by flash chromatography (silica gel, 10:90 ethyl acetate/hexane) to afford 79 mg (32%) of ring closure product **23** as a white solid: IR (thin film) 2920, 2850, 1375, 1190, 905, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.20–1.64 (m, 15), 1.80–2.60 (m, 10), 3.65–3.95 (m, 2), 4.00 & 4.04 (2 br s, 3), 4.82–5.12 (m, 3), 7.28 (br s, 3), 7.47 (br s, 2); mass spectrum (70 eV), m/e (relative intensity) 426 (M^+, 19), 411 (18), 317 (79), 259 (90), 107 (72), 93 (81), 81 (100); exact mass calcd for $C_{27}H_{38}O_2S$ 426.2592, found 426.2599.

***erythro*-14,15-*O*-Isopropylidene-1-(hydroxymethyl)-14-hydroxy-4,8,12-trimethylcyclotetradeca-(*E*,*E*,*E*)-3,7,11-triene (24).** Thioether **23** (66.6 mg, 0.156 mmol) in 1 mL of dry THF was added at −78 °C to the solution of 120 mg (17.1 mmol) of lithium wire dissolved in 10 mL of dry ethylamine (dried over sodium). The mixture was stirred for 3.5 h at −78 °C, and some solid ammonium chloride and some methanol were added. The solution was allowed to warm to room temperature and poured into ether/water. The layers were separated, and the aqueous layer was extracted twice with ether. The combined organic layers were washed with water and dried over $MgSO_4$. The solvent was removed on a rotary evaporator to give 46.5 mg (94%) of crude material which was purified by flash chromatography (silica gel, 5:95 ethyl acetate/hexane) to afford 33.7 mg (68%) of **24** as a colorless oil: IR ($CDCl_3$) 2920, 1390, 1270, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 3), 1.47 (s, 3), 1.55 (s, 3), 1.56 (s, 3), 1.63 (s, 3), 1.85–2.45 (m, 13), 3.75 (m, 1), 4.03 (m, 2), 4.90 (m, 1), 5.06 (mc, 2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.0, 15.2, 16.7, 19.1, 23.4, 24.4, 24.6, 29.9, 37.3, 38.8, 39.1, 42.5, 66.8, 70.2, 98.8, 125.8, 126.1, 127.1, 129.4, 132.6, 133.4; mass spectrum (70 eV), m/e (relative intensity) 318 (M^+, 4), 303 (8), 260 (36), 243 (7), 242 (7), 121 (56), 93 (93), 81 (94), 68 (100); exact mass calcd for $C_{21}H_{34}O_2$ 318.2559, found 318.2547.

Acknowledgment. This work was supported by Grant No. GM 27320, National Institute of General Medical Sciences. We thank Molecular Design Limited for their cooperation in the molecular mechanics calculations.

Registry No. **2**, 28028-68-4; **5** (R′ = H, R″ = Ac), 97634-52-1; **5** (R′ = R″ = H), 97634-56-5; **6**, 97634-53-2; **7**, 764-32-9; **8**, 32663-38-0; **8** (acetate), 97634-51-0; **9**, 97634-54-3; **10**, 97634-55-4; **12a**, 37905-03-6; **12b**, 97634-65-6; **13a**, 37905-04-7; **13b**, 97634-66-7; **14b**, 97634-67-8; **15**, 37905-02-5; **16**, 97634-57-6; **16** (acetate), 97634-69-0; **16** (tosylate), 97634-70-3; **17**, 97634-58-7; **18**, 97634-59-8; **19**, 97644-30-9; **20**, 97634-60-1; **21**, 97634-61-2; **21** (aldehyde),

97634-72-5; **22**, 97634-62-3; **22** (tosylate), 97634-71-4; **22** (chloride), 97644-31-0; **23** (isomer 1), 97634-63-4; **23** (isomer 2), 97673-13-7; **24**, 97634-64-5; $(EtO)_2P(O)CH(CH_3)CO_2Et$, 3699-66-9; $Ph_3PMe^+I^-$, 2065-66-9; PhSLi, 2973-86-6; ethyl 2,7-dimethyl-(*E*)-2,6-octadienoate, 73658-21-6; geranyl phenyl sulfide, 35162-74-4; 9-(diethylamino)-9-cyano-1-(phenylthio)-3,7-dimethylnona-2,6-diene, 97634-68-9; (diethylamino)acetonitrile, 3010-02-4; geranyl acetate, 105-87-3.

Efficient Total Syntheses of the Oligopeptide Antibiotics Netropsin and Distamycin

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Received March 19, 1985

New and efficient total syntheses of the natural oligopeptide antiviral antibiotics netropsin and distamycin are described. These procedures feature a different strategy of introduction of the terminal groups from that used hitherto, high yield coupling steps, improvements in the Pinner reaction for introducing the amidine moiety, and the novel use of *N*-formylimidazole for introduction of the formyl moiety in distamycin. The methods also avoid column chromatography with the attendant contamination of the oligopeptide hydrochlorides with inorganic salts eluted from adsorbents. The synthetic procedures are general and may be adapted to the synthesis of related oligopeptide structures.

The family of naturally occurring oligopeptides includes netropsin,[1] distamycin,[2,3] anthelvencin,[4] kikumycin B,[5] amidinomycin,[6] and norformycin.[7] They have attracted considerable attention on the part of synthetic chemists and pharmacists because some representatives exhibit antiviral, antibacterial, and anticancer activities.[3,8,9] The first two agents are also of interest in molecular biology because their biological properties appear to arise, in part, from the unique XTTT and XTTTT sequence preferential and minor groove selective binding to DNA of netropsin and distamycin, respectively.[3,10,11] Our interest in molecular recognition has led us to explore the synthesis of related "lexitropsins" based on the oligopeptide structures but designed to recognize and bind to alternative and unique sequences in the minor groove of duplex DNA.[12] The consequent requirement for an adaptable and general synthesis of such oligopeptides directed our attention to existing synthetic procedures of some of the natural lead antibiotics. We report efficient and general total syntheses of netropsin and distamycin. The methods developed offer several advantages of yield and purity on individual steps over reported procedures and avoid the chromatographic separations generally used hitherto.

Synthetic Strategy. A number of elegant total syntheses of natural oligopeptide antibiotics have been reported.[2,13–16] All except one[16] have been based essentially on the method introduced by Julia and Préau-Joseph. The latter consists of introducing the amidino group early, carrying forward the nitro heterocyclic intermediate which is then reduced catalytically prior to coupling of the guanidino group.[13] The one exception to this general plan, due to Grehn and Ragnarrson[16] cannot be evaluated from the viewpoint of efficiency because all the yields are given on crude products. The synthesis of distamycin starting from *N*-methyl-4-nitropyrrole-2-carboxylic acid requires twelve steps in this procedure. This approach also used uncommon reagents like (*tert*-butyloxy)carbonyl fluoride and formic anhydride.

Thus the existing methods[2,13–16] do not lend themselves to the development of an adaptable general synthetic procedure and suffer from several disadvantages including the following: (i) The coupling reactions employ unsatisfactory methods, e.g., the reaction of an amine with an acyl chloride in the presence of aqueous sodium bicarbonate or triethylamine in ethanol gives unsatisfactory yields in our hands; one procedure also uses uncommon protecting groups for coupling.[16] (ii) Existing methods of introduction of the formyl group in distamycin[14–16] are unsatisfacotry with regard to yield and the required purification. (iii) The sequence of attachment of the end groups is inconvenient in that the products require column chromatography, which is also undesirable because of contamination with inorganic salts (from the adsorbents) of the final oligopeptides that are customarily isolated as hydrochloride salts. (iv) The reaction conditions for the Pinner reaction were not optimized.

Thus our objectives were to try to improve existing methods in not only increasing the yields but also to avoid chromatographic methods of separation.

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