Programme to the School of Chemistry) is gratefully acknowledged.

Registry No. 1c, 71980-98-8; 6, 18403-20-8; 7, 112348-33-1; 8, 112348-34-2; 9, 112348-35-3; 10, 112348-36-4; 11, 112348-37-5; 14, 112348-38-6; 15, 112348-39-7; 16, 112348-40-0; 17, 89824-53-3; α-20, 112348-41-1; β-20, 112348-42-2; 21α, 112348-43-3; 21β, 112348-44-4; H_2C=CHCN, 107-13-1; H_2C=CHCOOMe, 96-33-3; H_2C=$CHSO_2Ph$, 5535-48-8; Ph_3P=$CHCOCH_3$, 1439-36-7; D-xylose, 58-86-6.

Synthesis of Macrocyclic Terpenoids by Intramolecular Cyclization. 12.[1] Total Synthesis of Methyl Ceriferate I, a 14-Membered Ring Sesterterpene from Scale Insects

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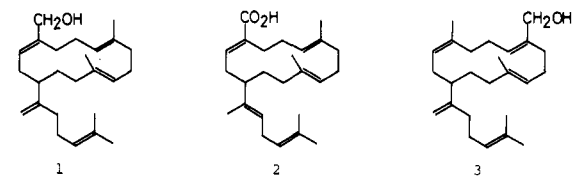
Total synthesis of (±)-methyl ceriferate I (6), the methyl ester of a cembrane-type sesterterpene isolated from the wax of scale insects, was achieved by means of Wadsworth–Emmons olefination as a key step. Three segments, 9, 10, and 11, were connected to yield, after some modifications, the allylic alcohol 22, which was converted into the phosphonoacetate 29 in nine steps including Claisen rearrangement of 22. Intramolecular Wadsworth–Emmons olefination of 29 afforded 6 and its geometrical isomer 30.

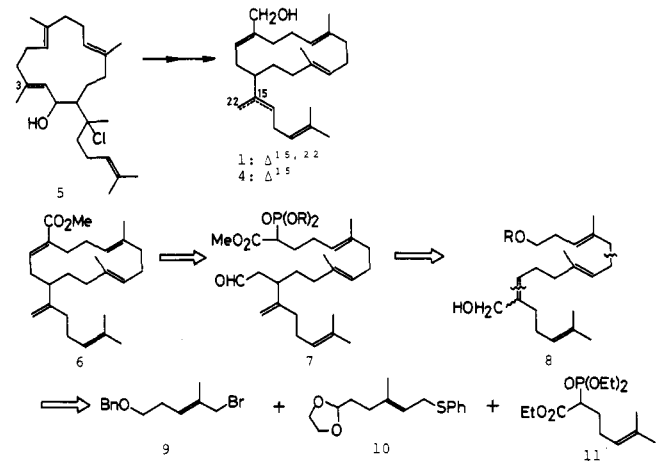
The wax secreted by the scale insect *Ceroplastes* sp. has been shown to contain various 14-membered ring sesterterpenes as exemplified by ceriferol I (1), ceriferic acid (2), and cericerol I (3).[2] To date 15 related substances have been isolated from the insect wax.[3]

Although the gross structure having a 14-membered ring with three annular double bonds (two trans and one cis) and an unsaturated side chain has been elucidated on the basis of spectroscopic analysis, the structural studies concerning the position of the annular cis double bond have been pursued with a somewhat complicated course. The common carbon framework with 2*Z*,6*E*,10*E* geometry was finally proposed by Naya et al.[3] on the basis of careful reexamination of NMR spectra and confirmed unequivocally by the synthesis of 1 and ceriferol (4).[4] In the first synthesis of cembrane sesterterpenes, namely 1 and 4, Kato et al.[4] employed a route involving functionalization of the C-3 methyl group of the preformed 14-membered ring compound 5. Considering the facts that one of the methyl groups on the ring is usually oxygenated into an allylic alcohol or unsaturated carboxylic acid in this class of sesterterpenes, intramolecular Wittig-type olefination should be a highly effective method since this route allows simultaneous construction of the macroring and an α,β-unsaturated ester moiety.[5] According to this methodology,

Chart I



Scheme I



we have recently achieved a total synthesis of (±)-methyl ceriferate I (6).[6] Our results demonstrate the usefulness

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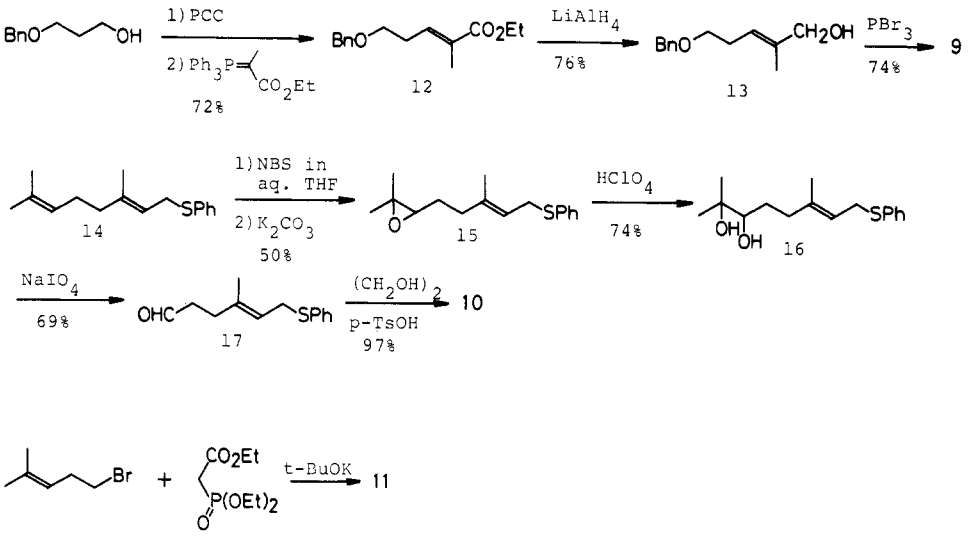
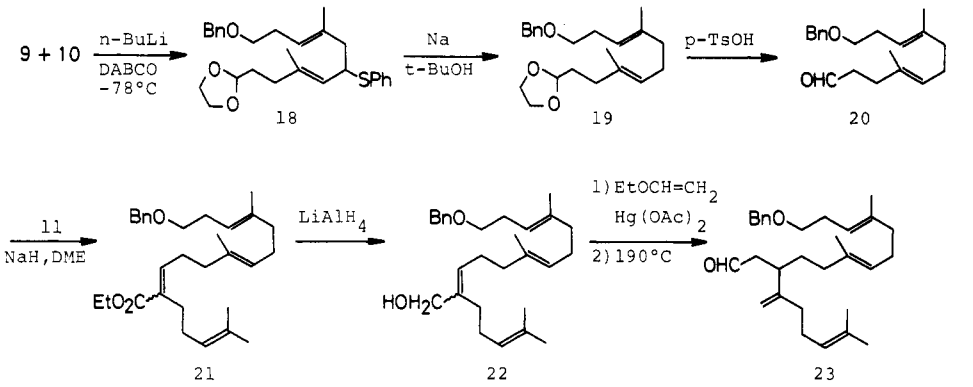
Scheme II



Scheme III



of this methodology toward the general synthesis of oxygenated macrocyclic terpenoids.[7] In this paper we disclose full details of our synthesis of **6**.

The retrosynthetic analysis of **6** is outlined in Scheme I. Thus, the immediate precursor to **6** is the phosphonoacetate **7**, which in turn should be accessible by the Claisen rearrangement of an allylic alcohol of type **8**. By employing this method the exocyclic double bond in the side chain would be introduced regioselectively. The intermediate **8** can be disconnected to three segments **9**, **10**, and **11** as shown in Scheme I.

Results

The synthesis was initiated starting from the preparation of three segments described above. Although the bromide **9** has been synthesized by Ziegler et al.,[8] we prepared it from 3-(benzyloxy)propanol via a modified route shown in Scheme II in 41% overall yield. For elaboration of the second segment **10**, the terminal double bond of geranyl phenyl sulfide[9] (**14**) was cleaved in four steps to yield the aldehyde **17** in 26% yield. The aldehyde group was then protected to give the second segment **10**. The third segment **11** can be prepared simply by the coupling of homoprenyl bromide[10] and triethyl phosphonoacetate (Scheme II).

In order to synthesize the subgoal **8**, three segments were combined as follows. The lithio anion of **10** was coupled with the bromide **9** in the presence of 1,4-diazabicyclo[2.2.2]octane (Dabco)[11] at −78 °C to furnish **18** in 72% yield (Scheme III). After reductive removal of the phenyl sulfide group with sodium in *tert*-butyl alcohol[12] to give **19** and subsequent hydrolysis of the acetal group, the aldehyde **20** was subjected to Wadsworth–Emmons olefination using the phosphonoacetate **11**. The unsaturated ester **21** obtained in 85% yield was an approximately 1:1 mixture of cis and trans isomers, which was then reduced with lithium aluminum hydride to give the allylic alcohol **22**. The Claisen rearrangement was performed by converting **22** into the vinyl ether by the reaction with ethyl

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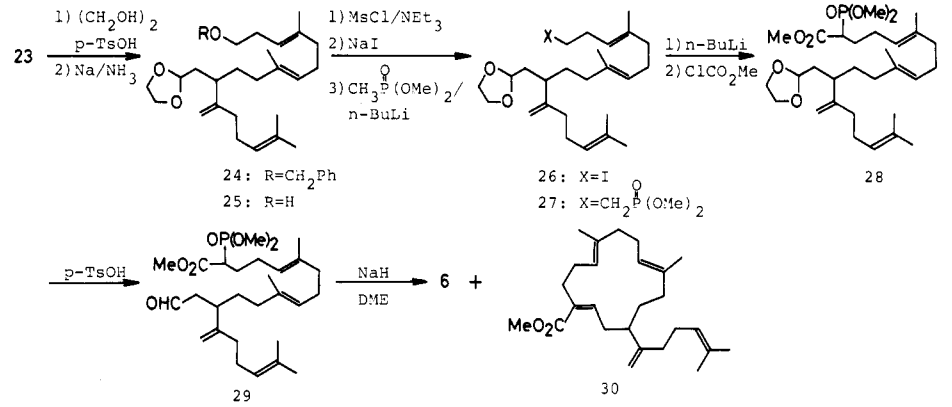
Scheme IV



vinyl ether in the presence of mercuric acetate followed by heating at 190 °C without solvent, thereby yielding aldehyde **23** as a single product in 35% overall yield. By utilizing this sequence, the $\Delta^{15,22}$-exo double bond in **6** was introduced regioselectively.

In order to allow the modification of the homoallyl alcohol moiety, the aldehyde group in **23** was first protected to afford **24** and then the benzyl ether was reductively removed to furnish **25** (Scheme IV). Some difficulties were encountered in the next step, i.e., transformation of **25** into the phosphonoacetate **28**. Thus, treatment of the iodide **26** prepared via the mesylate of **25** with trimethyl phosphonoacetate under various basic conditions gave rise to none of the desired alkylated product **28** and most of the starting material was recovered unchanged.[13] Prolonged reaction time caused the decomposition of the starting halide. This difficulty was overcome by employing a two-step sequence: (i) conversion of **26** into the phosphonate **27** by coupling with the lithio anion of dimethyl methylphosphonate and then (ii) trapping the lithio anion of **27** with ethyl chloroformate. With use of this method, the desired **28** was obtained in 49% yield. This two-step transformation would be generally applicable to the preparation of substituted phosphonoacetate that are difficult to prepare by the direct alkylation method. The acetal group in **28** was readily hydrolyzed to yield the immediate precursor **29**.

When the phosphonoacetate **29** was treated with sodium hydride in dry DME at 80 °C under high dilution conditions, formation of two products was observed. These were separated by medium-pressure liquid chromatography. The more polar product obtained in 24% yield was found to be identical with methyl ceriferate I by the comparison of ^{1}H NMR and ^{13}C NMR spectra with those of an authentic specimen. The spectra of the less polar product obtained in 52% yield were very similar to those of **6**, except for the upfield shift of the signal due to H-2 in the ^{1}H NMR spectrum and some changes in the chemical shifts of the methylene carbons in the ^{13}C NMR spectrum. These findings revealed that the less polar product was **30**, the geometrical isomer of methyl ceriferate I (**6**). Thus, the second synthesis of a naturally occurring cembrane-type sesterterpene was achieved via the intramolecular Wittig reaction approach. Although the stereoselectivity in the macroring formation was not high, the present work provided a methodology for the synthesis of functionalized macrocyclic terpenes. In contrast to our results, Tius has accomplished a completely selective olefination in the synthesis of (−)-asperdiol,[7o] although an *E,Z* mixture (2:1 ratio) was obtained in their synthesis of desepoxyasperdiol.[7k] These results suggest that the stereoselectivity in the intramolecular olefination is strongly affected by the neighboring circumstances of substrate and the reaction conditions employed.

(13) As the model experiment, homofarnesyl iodide was treated with sodio anion of triethyl phosphonoacetate. But essentially no alkylation took place although alkylation using homoprenyl bromide occurred in moderate yield.

Experimental Section

General. Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were reduced on a JEOL GX-400 instrument in $CDCl_3$ solution with Me_4Si as an internal standard. Infrared spectra (IR) were taken on a Shimadzu IR-27G spectrometer as a thin film (neat) on sodium chloride plates. Mass spectra (MS) were measured on a Shimadzu LKB-9000 spectrometer. High-resolution mass spectra (HRMS) were obtained on a JEOL HX-100 spectrometer.

Chromatography. Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel $60F_{254}$ precoated silica gel plates and spots were visualized by irradiation with ultraviolet light (254 nm) and/or by spraying with anisaldehyde/sulfuric acid followed by warming to 120 °C. Column chromatography was performed on silica gel (Merck SG-60, 70–230 mesh) or neutral alumina (Merck Alminumoxide 90, activity grade II–III). High-pressure liquid chromatography (HPLC) was done on a Shimadzu LC 6A chromatograph. A Chemcosorb 5-SI column was used. Preparative medium pressure liquid chromatography was carried out on a Wako NQ-2 prepacked column (CQ-3 silica gel, 30–50 μM).

Anhydrous Solvents. Tetrahydrofuran (THF), ether, and 1,2-dimethoxyethane (DME) were distilled from lithium aluminum hydride ($LiAlH_4$) prior to use. Dimethylformamide (DMF) and pyridine were distilled from calcium hydride. Dichloromethane (CH_2Cl_2) was distilled from phosphorus pentoxide. Other solvents were dried over 4A molecular sieves.

Diethyl (1-Carbethoxy-5-methyl-4-hexenyl)phosphonate (11). To an ice-cooled solution of triethyl phosphonoacetate (4.60 g, 0.021 mol) and homoprenyl bromide (6.70 g, 0.041 mol) in 50 mL of dry DMF under argon was added potassium *tert*-butoxide (5.06 g, 0.045 mol) in one portion. The mixture was stirred at room temperature for 1 h and then poured into ice–water. After acidification with 2 N HCl (pH 4) the mixture was extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$), and concentration in vacuo. The residue was chromatographed on 90 g of silica gel (CH_2Cl_2) to afford **11** (5.20 g, 42%) as a colorless oil: IR (neat) 1738, 1250, 1045, 1015 cm^{-1}; ^{1}H NMR δ 1.26–1.38 (m, 9 H), 1.58 (s, 3 H), 1.68 (s, 3 H), 2.95 (ddd, J = 22.8, 11.0, 3.4 Hz, 1 H), 4.10–4.26 (m, 6 H), 5.06 (br t, J = 6.4 Hz, 1 H); MS, m/z 306 (M^+), 224 [base peak (b.p.)]; HRMS, calcd for $C_{14}H_{27}O_5P$ m/z 306.1597, found m/z 306.1584.

2-[(*E*,*E*)-10-(Benzyloxy)-3,7-dimethyl-5-(phenylthio)-3,7-decadienyl]-1,3-dioxolane (18). To a stirred solution of **10** (3.94 g, 0.015 mol) and 1,4-diazabicyclo[2.2.2]octane (Dabco, 2.52 g, 0.023 mol) in 70 mL of dry THF under argon in a dry-ice–acetone bath was added dropwise a hexane solution of *n*-BuLi (0.019 mol). The yellow solution was stirred for 1 h at −78 °C. A solution of **9** (6.05

g, 0.023 mol) in 10 mL of dry THF was added to the solution at −78 °C and stirring was continued overnight at room temperature. The reaction mixture was poured into water and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on 200 g of alumina (benzene–hexane, 1:2) to give **18** (4.85 g, 72%) as a colorless oil. An analytical sample was further purified by HPLC (hexane–ethyl acetate, 10:1): IR (neat) 1582, 730, 688 cm^{-1}; ^1H NMR δ 1.60 (s, 3 H), 1.61 (s, 3 H), 3.42 (t, J = 7.3 Hz, 2 H), 3.81 (m, 2 H), 3.83 (m, 2 H), 4.00 (ddd, J = 10.1, 9.3, 5.7 Hz, 1 H), 4.50 (s, 2 H), 4.73 (t, J = 4.9 Hz, 1 H), 5.01 (br d, J = 10.1 Hz, 1 H), 5.18 (br t, J = 7.3 Hz, 1 H), 7.22–7.40 (m, 10 H); MS, m/z 452 (M^+), 73 (b.p.). Anal. Calcd for $C_{28}H_{36}O_3S$: C, 74.34; H, 7.96. Found: C, 74.69; H, 7.96.

Desulfurization of the Sulfide 18. To a vigorously stirred solution of **18** (7.00 g, 15.5 mmol) in a mixture of dry THF (100 mL) and dry *tert*-butyl alcohol (20 mL) under argon was added sodium in small pieces at 30-min intervals (total 4 g, 0.17 mol) over 3 h at room temperature. Excess sodium was decomposed by addition of methanol (10 mL). The solution was concentrated in vacuo to one-third of its original volume. The residue was dissolved in water and extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on 100 g of silica gel (benzene–hexane, 1:1) to afford **19** (4.85 g, 91%) as a colorless oil: IR (neat) 730, 690 cm^{-1}; ^1H NMR δ 1.60 (s, 3 H), 1.62 (s, 3 H), 3.45 (t, J = 7.8 Hz, 2 H), 3.83 (m, 2 H), 3.95 (m, 2 H), 4.52 (s, 2 H), 4.84 (t, J = 5.2 Hz, 1 H), 5.12–5.20 (m, 2 H), 7.25–7.38 (m, 5 H); MS, m/z 344 (M^+), 91 (b.p.). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.74; H, 9.30. Found: C, 76.47; H, 9.26.

(*E*,*E*)-11-(Benzyloxy)-4,8-dimethyl-4,8-undecadien-1-al (20). The solution of **19** (4.85 g, 14.1 mmol) and *p*-TsOH (0.1 g) in 120 mL of aqueous acetone (6:1) was gently refluxed for 2 h. Most of acetone was evaporated in vacuo and the residue was extracted with ether. The combined ether solutions were washed with saturated $NaHCO_3$ solution and brine and then dried ($MgSO_4$). Evaporation of the solvent yielded **20** (4.00 g, 95%) as a colorless oil: IR (neat) 1725, 728, 690 cm^{-1}; ^1H NMR δ 1.61 (s, 6 H), 3.46 (t, J = 7.2 Hz, 2 H), 4.52 (s, 2 H), 5.10–5.20 (m, 2 H), 7.25–7.40 (m, 5 H), 9.73 (t, J = 2.1 Hz, 1 H); MS, m/z 300 (M^+), 91 (b.p.); HRMS, calcd for $C_{20}H_{28}O_2$ m/z 300.2089, found m/z 300.2115.

Wadsworth–Emmons Olefination of 20 and 11. To a suspension of sodium hydride (60% mineral oil dispersion, 156 mg, 3.9 mmol) in 10 mL of dry DME under argon was added **11** (398 mg, 3.9 mmol) in 5 mL of dry DME at room temperature, and the mixture was heated at 80 °C for 1 h with stirring. The aldehyde **20** (900 mg, 3.0 mmol) in 5 mL of dry DME was added to the hot solution dropwise and the temperature was maintained at 80 °C for 15 min. After cooling, the reaction mixture was poured into ice–water and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on 30 g of silica gel (benzene–hexane, 1:1) to afford **21** (1.15 g, 85%) as a colorless oil. This product was a ca. 1:1 mixture of cis/trans isomers: IR (neat) 1720, 1642, 725, 690 cm^{-1}; ^1H NMR δ 1.29 (t, J = 7.2 Hz, 3 H), 1.59 (s, 6 H), 1.62 (s, 3 H), 1.68 (s, 3 H), 3.45 (t, J = 7.4 Hz, 2 H), 4.18 (q, J = 7.2 Hz, 2 H), 4.52 (s, 2 H), 5.06–5.20 (m, 3 H), 5.82 and 6.73 (ca. 1:1) (each t, J = 7.4 Hz, total 1 H), 7.22–7.36 (m, 5 H); MS, m/z 452 (M^+), 91 (b.p.). Anal. Calcd for $C_{30}H_{44}O_3$: C, 79.64; H, 9.73. Found: C, 79.30; H, 9.83.

(2*E*/*Z*,6*E*,10*E*)-13-(Benzyloxy)-6,10-dimethyl-2-(4-methyl-3-pentenyl)-2,6,10-tridecatrien-1-ol (22). To an ice-cooled suspension of $LiAlH_4$ (77 mg, 2.03 mmol) in 25 mL of dry ether was added **21** (920 mg, 2.04 mmol) in 5 mL of dry ether over 15 min with stirring. The mixture was stirred at room temperature for 2 h. Excess reagent was decomposed by careful addition of water. The reaction mixture was acidified to pH 5 with 2 N HCl and extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on 30 g of silica gel (CH_2Cl_2) to give **22** (618 mg, 74%) as a colorless oil: IR (neat) 3350, 725, 688 cm^{-1}; ^1H NMR δ 1.60 (s, 6 H), 1.62 (s, 3 H), 1.68 (s, 3 H), 3.46 (t, J = 7.2 Hz, 2 H), 4.02 and 4.10 (ca. 1:1) (each br s, total 1 H), 4.52 (s, 2 H), 5.06–5.22 (m, 3 H), 5.30 and 5.40 (ca. 1:1) (each t, J = 7.4 Hz, total 1 H), 7.25–7.38 (m, 5 H); MS, m/z 410 (M^+), 91 (b.p.); HRMS, calcd for $C_{28}H_{42}O_2$ m/z 410.3158, found m/z 410.3174.

Claisen Rearrangement of 22 to 23. A mixture of **22** (430 mg, 1.05 mmol), ethyl vinyl ether (10 mL), mercuric acetate (200 mg, 0.63 mmol), and sodium acetate (100 mg, 1.22 mmol) was stirred at room temperature overnight. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on 20 g of alumina (benzene–hexane, 1:1) to afford a vinyl ether (356 mg, 78%) as a colorless oil.

A neat liquid of the vinyl ether (356 mg) was heated at 190 °C for 20 min. The reaction mixture was chromatographed on 12 g of silica gel (benzene–hexane, 1:1) to yield **23** (250 mg, 70%) as a colorless oil: IR (neat) 1728, 1640, 888 cm^{-1}; ^1H NMR δ 1.58 (s, 3 H), 1.61 (s, 6 H), 1.69 (s, 3 H), 3.45 (t, J = 7.3 Hz, 2 H), 4.52 (s, 2 H), 4.82 (br s, 1 H), 4.86 (br s, 1 H), 5.06–5.18 (m, 3 H), 7.26–7.36 (m, 5 H), 9.65 (t, J = 2.5 Hz, 1 H); MS, m/z 436 (M^+), 91 (b.p.); HRMS, calcd for $C_{30}H_{44}O_2$ m/z 436.3342, found m/z 436.3315.

Acetal 24. The aldehyde **23** (730 mg) was converted into the acetal **24** (780 mg, 97%) by the same manner as described in the preparation of **10**. **24**: colorless oil; IR (neat) 1640, 882, 726, 688 cm^{-1}; ^1H NMR δ 1.57 (s, 3 H), 1.62 (s, 6 H), 1.68 (s, 3 H), 3.45 (t, J = 7.8 Hz, 2 H), 3.80 (m, 2 H), 3.95 (m, 2 H), 4.52 (s, 1 H), 4.75–4.84 (m, 3 H), 5.04–5.20 (m, 3 H), 7.25–7.38 (m, 5 H); MS, m/z 480 (M^+), 73 (b.p.); HRMS, calcd for $C_{32}H_{48}O_3$ m/z 480.3604, found m/z 480.3611.

(*E*,*E*)-11-[(1,3-Dioxolan-2-yl)methyl]-12-methylene-4,8,16-trimethyl-3,7,15-heptadecatrien-1-ol (25). To a solution of **24** (780 mg, 1.63 mmol) in a mixture of absolute ethanol (15 mL), dry ether (70 mL), and liquid ammonia (ca. 300 mL) was added sodium (79 mg, 3.43 mmol) in small pieces under argon at −78 °C. After stirring for 1 h, ammonia was allowed to evaporate at room temperature. The residue was dissolved in water and extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on 20 g of silica gel (CH_2Cl_2) to give **25** (580 mg, 92%) as a colorless oil: IR (neat) 3400, 1638, 882 cm^{-1}; ^1H NMR δ 1.62 (s, 6 H), 1.64 (s, 3 H), 1.69 (s, 3 H), 3.61 (t, J = 6.6 Hz, 2 H), 3.82 (m, 2 H), 3.95 (m, 2 H), 4.78–4.88 (m, 3 H), 5.05–5.18 (m, 3 H); MS, m/z 390 (M^+), 73 (b.p.). Anal. Calcd for $C_{25}H_{42}O_3$: C, 76.92; H, 10.77. Found: C, 76.71; H, 10.86.

Iodide 26. To an ice-cooled solution of **25** (200 mg, 0.51 mmol) and triethylamine (0.62 mL, 4.46 mmol) in 15 mL of dry CH_2Cl_2 was added methanesulfonyl chloride (0.27 mL, 1.6 mmol) under argon, and the mixture was stirred for 30 min. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed successively with 2 N HCl and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in 10 mL of dry DMF under argon and sodium iodide (115 mg, 0.77 mmol) was added. The mixture was heated at 80 °C for 2 h with stirring and was poured into ice–water. The product was extracted with ether. The ether layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by chromatography on 10 g of silica gel (benzene–hexane, 1:1) furnished **26** (165 mg, 64%) as a colorless oil: IR (neat) 1640, 882 cm^{-1}; ^1H NMR δ 1.57 (s, 3 H), 1.60 (s, 3 H), 1.62 (s, 3 H), 1.69 (s, 3 H), 3.11 (t, J = 7.8 Hz, 2 H), 3.82 (m, 2 H), 3.95 (m, 2 H), 4.76–4.86 (m, 3 H), 5.05–5.16 (m, 3 H); MS, m/z 500 (M^+), 73 (b.p.); HRMS, calcd for $C_{25}H_{41}O_2I$ m/z 500.2152, found m/z 500.2131.

Phosphonate 27. To a stirred solution of dimethyl methylphosphonate (92 mg, 0.74 mmol) in 9 mL of dry THF was added a hexane solution of *n*-BuLi (0.74 mmol) under argon at −78 °C. After stirring for 15 min, a solution of **26** (185 mg, 0.37 mmol) in 1 mL of dry THF was added at −78 °C. After 30 min, water (30 mL) was added and the mixture was extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on 10 g of silica gel. Elution with benzene–hexane (1:1) afforded recovered **26** (130 mg). Further elution with CH_2Cl_2 yielded **27** (35 mg, 64% based on the consumed **26**) as a colorless oil: IR (neat) 1640, 1235, 1050, 1025 cm^{-1}; ^1H NMR δ 1.55 (s, 3 H), 1.58 (s, 3 H), 1.60 (s, 3 H), 1.67 (s, 3 H), 3.72 (d, J = 11.0 Hz, 6 H), 3.80 (m, 2 H), 3.93 (m, 2 H), 4.78–4.84 (m, 3 H), 5.05–5.16 (m, 3 H); MS, m/z 496 (M^+), 73 (b.p.); HRMS, calcd for $C_{28}H_{49}O_5P$

m/z 496.3318, found m/z 496.3304.

Phosphonoacetate 28. To a solution of **27** (87 mg, 0.175 mmol) in 4.5 mL of dry THF was added a hexane solution of *n*-BuLi (0.52 mmol) under argon at −78 °C. After stirring for 20 min, a solution of methyl chloroformate (50 mg, 0.52 mmol) in 1.5 mL of dry THF was added at −78 °C. After 30 min, water (30 mL) was added and the mixture was extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$), and then concentrated in vacuo. The residue was chromatographed on 10 g of silica gel (CH_2Cl_2) to afford **28** (75 mg, 77%) as a colorless oil: IR (neat) 1740, 1640, 1256, 1050, 1030, 882 cm^{-1}; ^1H NMR δ 1.57 (s, 6 H), 1.62 (s, 3 H), 1.69 (s, 3 H), 3.01 (m, 1 H), 3.76 (s, 3 H), 3.78 (d, J = 10.7 Hz, 3 H), 3.80 (d, J = 10.7 Hz, 3 H), 3.82 (m, 2 H), 3.95 (m, 2 H), 4.76–4.85 (m, 3 H), 5.02–5.18 (m, 3 H); MS, m/z 554(M^+), 73 (b.p.). Anal. Calcd for $C_{30}H_{51}O_7P$: C, 64.94; H, 9.27. Found: C, 64.64; H, 9.12.

Hydrolysis of 28 to 29. The acetal **28** (70 mg) was converted into the aldehyde **29** (59 mg, 91%) by the same manner as described in the preparation of **20**. **29**: colorless oil: IR (neat) 1740, 1728, 1642, 1256, 1050, 1025, 885 cm^{-1}; ^1H NMR δ 1.58 (s, 3 H), 1.60 (s, 3 H), 1.62 (s, 3 H), 1.69 (s, 3 H), 3.00 (m, 1 H), 3.76 (s, 3 H), 3.78 (d, J = 11.0 Hz, 3 H), 3.79 (d, J = 11.0 Hz, 3 H), 4.83 (br s, 1 H), 4.87 (br s, 1 H), 5.02–5.15 (m, 3 H), 9.66 (t, J = 2.4 Hz, 1 H); MS, m/z 510 (M^+), 182 (b.p.); HRMS, calcd for $C_{28}H_{47}O_6P$ m/z 510.3110, found m/z 510.3110.

Intramolecular Wadsworth–Emmons Olefination of 29. A solution of **29** (30 mg, 0.059 mmol) in 30 mL of dry DME was heated at 80 °C under argon, and sodium hydride (60% mineral oil dispersion, 12 mg, 0.3 mmol) was added with stirring. After being stirred at 80 °C for 30 min, the reaction mixture was poured into ice–water and extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The product showed mainly two spots on TLC. These were separated by medium-pressure liquid chromatography. Elution with benzene–hexane (1:2) gave **30** (11.8 mg, 52%) as a colorless oil. Further elution with benzene–hexane (1:1) afforded **6** (5.5 mg, 24%) whose ^1H and ^{13}C NMR spectra were identical with those of the methyl ester of natural ceriferic acid I (**30**): IR (neat) 1720, 1640, 880 cm^{-1}; ^1H NMR δ 1.53 (s, 3 H), 1.57 (s, 3 H), 1.61 (s, 3 H), 1.69 (s, 3 H), 3.73 (s, 3 H), 4.77 (br s, 1 H), 4.79 (br s, 1H), 4.98 (br t, J = 7.2 Hz, 1 H), 5.05 (br t, J = 6.3 Hz, 1 H), 5.12 (br t, J = 7.2 Hz, 1 H), 5.85 (t, J = 7.7 Hz, 1 H); ^{13}C NMR δ 15.1 (q), 17.7 (q × 2), 23.7 (t), 25.6 (t), 25.7 (q), 26.7 (t), 29.0 (t), 34.0 (t × 2), 34.2 (t × 2), 39.4 (t), 44.2 (d), 51.0 (q), 108.7 (t), 122.3 (d), 124.3 (d), 125.1 (d), 130.9 (s), 131.5 (s), 133.7 (s), 134.6 (s), 141.3 (d), 152.8 (s), 168.5 (s); MS, m/z 384 (M^+), 135 (b.p.); HRMS, calcd for $C_{26}H_{40}O_2$ m/z 384.3028, found m/z 384.3033.

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Registry No. (±)-**6**, 107655-35-6; **9**, 95531-81-0; **10**, 81027-74-9; (±)-**11**, 113219-29-7; **12**, 113219-30-0; **13**, 95531-99-0; **14**, 35162-74-4; (±)-**14** (bromohydrin), 113219-35-5; (±)-**15**, 113219-31-1; (±)-**16**, 113219-32-2; **17**, 113219-33-3; (±)-**18**, 113219-34-4; **19**, 107553-96-8; **20**, 107554-01-8; (*E*)-**21**, 107554-03-0; (*Z*)-**21**, 107553-97-9; (*E*)-**22**, 107553-98-0; (*Z*)-**22**, 107554-12-1; (*E*)-**22** (vinyl ether), 107554-04-1; (*Z*)-**22** (vinyl ether), 107553-99-1; (±)-**23**, 107554-05-2; (±)-**24**, 107574-35-6; (±)-**25**, 107554-06-3; (±)-**25** (R = Ms), 107554-11-0; (±)-**26**, 107554-08-5; (±)-**27**, 107554-09-6; **28**, 107554-10-9; **29**, 107569-40-4; (±)-**30**, 107655-36-7; $BnO(CH_2)_3OH$, 4799-68-2; $BnO(CH_2)_2CHO$, 19790-60-4; $Ph_3P{=}C(CH_3)CO_2Et$, 5717-37-3; $(CH_3)_2C{=}CH(CH_2)_2Br$, 2270-59-9; $(EtO)_2P(O)CH_2CO_2Et$, 867-13-0; $CH_3P(O)(OMe)_2$, 756-79-6; homofurnesyl iodide, 113219-28-6.

Supplementary Material Available: Experimental procedures for the preparation of compounds **9**, **10**, **12**, **13**, **15**, **16**, and **17** (5 pages). Ordering information is given on any current masthead page.

(+)-Pleuromutilin Synthetic Studies. Degradative and de Novo Acquisition of a Levorotatory Tricyclic Lactone Subunit

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The diterpene antibiotics pleuromutilin and tiamulin have been degraded to the common levorotatory lactone **3** in four steps. This important intermediate has been constructed in optically active condition from simple starting materials. The key elements of this synthesis were (i) stereoselective introduction of the second methyl group in **8** and regiospecific cyclopentenone annulation of this oxocyclohexanecarboxylate ester, (ii) stereocontrolled attachment of the lactone ring to give **20**, and (iii) proper introduction of the methyl and vinyl substituents α to the lactone carbonyl functionality in **20**. This and other synthetic methodologies have been utilized to prepare stereoisomers of **3** that could potentially lead to unnatural pleuromutilins by reconstruction of the cyclooctane ring.

Pleuromutilin (**1a**) was isolated in the early 1950's by Kavanagh and co-workers from several species of basidiomycetes including *Pleurotus mutilus*, *Pleurotus passeckerianus*, and *Drosophilia substrata*.[3] From the outset, the colorless crystalline substance attracted considerable attention as a consequence of its significant in vitro antibiotic activity against gram-positive bacteria and its low animal toxicity. In the intervening years, several additional pleuromutilins have been uncovered. The majority possess a structurally modified glycolic ester subunit that has either been esterified with a fatty acid[4] or involved in a glycosidic linkage with α-D-xylose.[5] Other congeners possess one or more additional hydroxyl groups.[5,6]

The clinical efficacy of **1a** has prompted a great deal of effort toward understanding its mechanism of action and improving its potency.[7] As a consequence of a systematic

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