for operation at much lower temperatures with these much more labile molecules. Measurements on cyclopropanone at −90° and at room temperature revealed no significant differences, and we conclude that no such rearrangements or tautomeric shifts occur. Although the present samples contained about 10% cyclobutanone, its presence did not interfere with the AP measurements on cyclopropanone since the AP of each ion was higher when produced from the heavier ketone.

The mass spectrum, the appearance temperature, I(70), and A(42) for our product *m/e* 70 at −90° and at room temperature agreed with similar data on an authentic sample of cyclobutanone (see Table I), and thus the four-membered ketone is formed at −145° by the insertion of a CH_2 group into the cyclopropanone ring by diazomethane.

The mass spectrum and critical potentials of cyclopropane and cyclopropene agreed well with previous data where available (see Table I). The abundant ring ions arise from the electronegative character of the ring and from the fact that the planar cyclopropenyl cation at *m/e* 39 is the simplest possible aromatic system ($4N + 2$ rule) resulting in electron delocalization stabilization of the ion.

The IP of cyclopropene of 9.7 eV is somewhat less than previous values (compare IP of propyne and allene at 10.54 eV[11] and 10.16 eV, respectively[12]), but the scatter in our data was not temperature correlatable, and we have found no evidence for rearrangement to a trimethylene structure or other isomerization that would influence the reactivity of cyclopropene. Cyclopropene reacts with itself in dilute solution at −25° to form a still very labile dimer.[13] The strain energy is about 54 kcal/mol, and the energy of isomerization to propyne is 22 kcal/mol. Although it is one of the most reactive known olefins, cyclopropene was much more stable and easier to handle than would be expected from the literature, and we certainly observed no explosive tendency.[13] Soaking experiments like those discussed with cyclopropanone revealed no volatile decomposition products and noticeable polymerization only at room temperature with some olefin remaining even after a week at room temperature. A dimer of undetermined structure was observed from this room temperature experiment, though it was presumably the "bow-tie" structure observed earlier.[13] The white, waxy polymer smeared upon contact, exhibited no gaseous evolution on heating to 300°, and was soluble in benzene but insoluble in acetone, methanol, and water at room temperature.

Detailed appearance potential studies of these two very interesting ketones and the corresponding cyclic hydrocarbons, including measurements of excess energy in the ion fragmentation processes, have been completed, and the resulting development of the molecular energetics of these molecules will appear elsewhere.

References and Notes

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A Synthesis of (±)-Cembrene, a Fourteen-Membered Ring Diterpene[1,2]

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Abstract: A convergent synthesis of cembrene (**1**), which employed a nickel carbonyl catalyzed coupling of a terminal allylic bromide as the key step, is described.

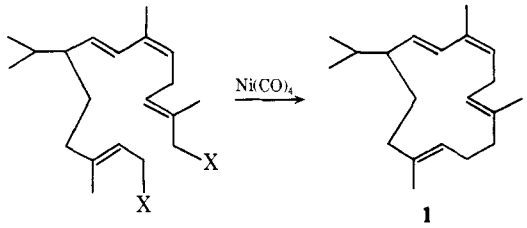
Cembrene [1-isopropyl-4,8,12-trimethylcyclotetradeca-2,4,7,11-tetraene (**1**)] is a crystalline, diterpene hydrocarbon first isolated from the Japanese black pine (*P. thunbergii*)[5] and subsequently from many species of pine,[6] in addition to several varieties of trees.[7] The 14-membered ring of cembrene was the first such structural unit encountered in nature[8] and represents an example of the simple biogenetic-like ring closure postulated to lead to many known compounds[9] (in this instance, compounds derived from geranylgeraniol).

Since the elucidation of the cembrene structure,[8] a rapidly expanding group of diterpenes which contain a 14-membered ring has emerged.[10] This group includes: the isomeric hydrocarbons isocembrene and neocembrene;[10b,11] several triene alcohols, the cembrols;[10b] the duvatriene diols and related compounds from tobacco smoke and tobacco products;[10a] incensol and isoincensol oxide from frankincense resin;[10c] and a group of highly oxygenated analogs from soft corals.[10d] Two of these compounds are of particular interest. Neocembrene,[11] the perfect biogenetic ring closed product of geranylgeraniol, has been found in the spruce and hinoki trees, commiphora mukul gum resin (Guggulu oil used in folk medicine) and, somewhat suprisingly, it was found to be the trail substance of the Australian termite. Further-

more, a recently discovered toxin, sarcophine, is believed to be a repellent protecting soft coral from the Red Sea against predators, in addition to some other interesting pharmacological properties.[10d]

Another group of compounds containing a varied sampling of bicyclic skeletons may have cembrene-like intermediates as biosynthetic precursors. These include verticillol from a conifer,[12] eunicellin from Atlantic coral,[13] and the diterpenes of the taxane type.[14]

The present approach to a synthesis of cembrene was based on two particular structural features of the molecule, the 14-membered ring and the 1,5-diene unit, in view of the findings of Corey that medium and large rings containing a 1,5-diene moiety can be prepared by nickel tetracarbonyl induced closure of terminal allylic bromides (eq 1).[15] Such

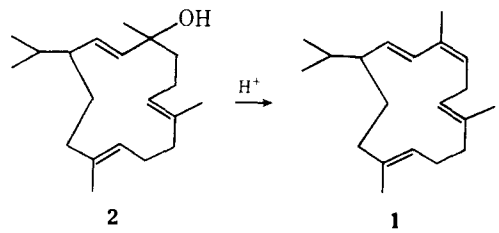


(1)

1

a synthetic sequence avoids the strong reducing conditions necessary for some more traditional methods of large ring synthesis, such as the acyloin reaction which has been utilized for the synthesis of cembrane, a fully hydrogenated cembrene.[16] The nickel tetracarbonyl coupling reaction, therefore, is compatible with the presence in the molecule of a different array of additional functional groups such as isolated double bonds and esters.

With this general synthetic approach in mind, consideration was next given to the stereochemistry of the four double bonds contained in the 14-membered ring of cembrene. The two trans trisubstituted double bonds which are part of the 1,5-diene moiety of cembrene would result from the nickel carbonyl catalyzed coupling reaction. This coupling reaction has been shown to give stereochemical mixtures of the double bonds regardless of the homogeneity of the precursors when trisubstituted double bonds were involved.[15,17] Therefore, the stereochemistry of these two double bonds in cembrene precursors was not an important consideration. The remaining two double bonds constitute the conjugated diene system of cembrene. Synthetically, the trans disubstituted double bond was envisioned as arising from the reaction of a stabilized ylide and an aldehyde. However, no similarly facile method for construction of the cis trisubstituted double bond presented itself. Furthermore, an intact conjugated diene could effectively compete for the nickel carbonyl or an organonickel intermediate during the proposed coupling reaction.[18] However, it has been shown that isocembrol (**2**) was transformed to cembrene upon mild acid treat-

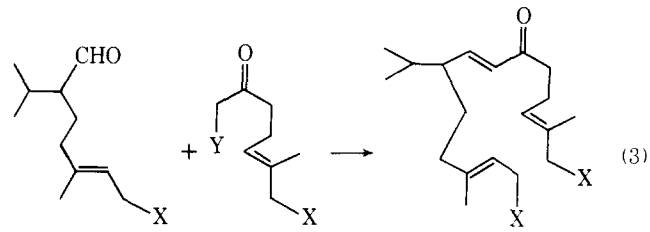


(2)

2 1

ment in nearly quantitative yield (eq 2).[10b,19] Thus a protected allylic oxygenated species could serve as a synthon for the conjugated diene of cembrene during the nickel promoted coupling reaction. Such a substitution pattern would circumvent some of the difficulties inherent in the conjugated diene of cembrene.

In view of these considerations, the initial target of the synthesis was set as enone **5**, which was envisioned to arise from the reaction of an aldehyde with a stabilized ylide (eq 3).

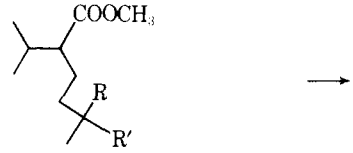


(3)

3 4 5

The synthesis of aldehyde **3** (X = OTHP) was achieved in seven steps from (±)-keto ester **6**, conveniently obtained by ozonolysis of piperitone and acid-catalyzed esterification.[9a] The selective addition of lithium acetaldehydecyclohexylimine[20] to the keto function of **6**, followed by two-phase hydrolysis[21] in benzene–1% oxalic acid of the resulting crude imine **7**, gave hydroxyaldehyde **8** in a 77% yield (Scheme I). Dehydration of **8** by heating in acetic acid[22]

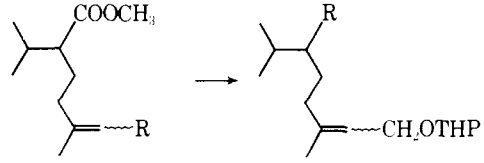
Scheme I



6, R = R′ = O

7, R = OH; R′ = $CH_2CH{=}N$–S

8, R = OH; R′ = CH_2CHO

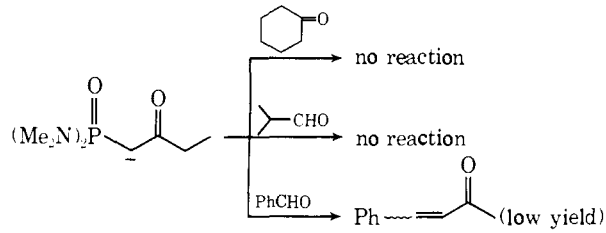


9, R = CHO
10, R = CH_2OH
11, R = CH_2OTHP

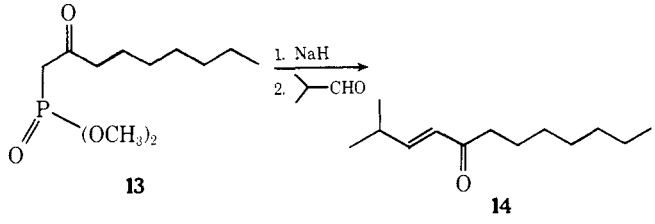
12, R = CH_2OH
3, R = CHO

gave only a low yield of the desired α,β-unsaturated aldehyde **9**, along with polymeric material. Standard procedures such as thionyl chloride in methylene chloride–pyridine at −70°, phosphorus oxychloride–pyridine, or stirring with aluminum oxide again gave only low yields. The optimum results were obtained when **8** was heated in Me_2SO at 160° for 1 hr.[23] This treatment resulted in a 57% yield of a mixture of aldehydes **9** after purification by silica gel chromatography. Also present in the reaction product was a 20% yield of keto ester **6**, presumably resulting from a retroaldol condensation of **8** under the reaction conditions. The aldehyde was selectively reduced with sodium borohydride in methanol to give an 80% yield[24] of alcohol **10**, which was converted in quantitative yield to its tetrahydropyranyl ether **11** upon treatment with dihydropyran in methylene chloride containing a trace of *p*-toluenesulfonic acid. Attempted direct conversion of ester **11** to aldehyde **3** (X = OTHP) with Dibal was unsuccessful, but the conversion could be facilely effected in two steps. The ester was reduced with lithium aluminum hydride in ether to give alcohol **12** in 80% yield which was oxidized with chromium trioxide–pyridine in methylene chloride[25] to give a 70% yield of pure aldehyde **3** (X = OTHP) after silica gel chromatography.

Before proceeding with a preparation of a stabilized ylide **4**, the nature of activating group Y had to be determined. The three possibilities investigated were the phosphonium salt (Y = Ph_3P^+, Br^-), the phosphonamide [Y = $PO(NMe_2)_2$], and the phosphonate [Y = $PO(OCH_3)_2$]. The phosphonium salt was immediately discarded because previous experience in this laboratory had shown that β-keto ylides derived from very similar phosphonium salts displayed rather low reactivity. Of the remaining two, preparation of the phosphonamide appeared to be more straightforward, and its reactions with aldehydes and ketones was investigated first. As a model for the condensation, a β-ketophosphonamide was prepared by acylation of α-lithiomethylphosphonic acid bis(dimethylamide) with ethyl proprionate, and the conjugate base of the β-ketophosphonamide was mixed with aldehydes and ketones. No reaction with cyclohexanone was observed after several hours in refluxing tetrahydrofuran. Similarly, isobutyraldehyde gave no reaction after 15 hr at room temperature. However, benzaldehyde did give a low yield of enone.

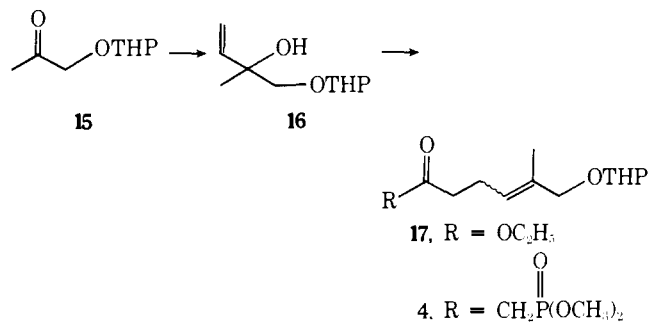


Since the results with the β-ketophosphonamide were unsatisfactory, attention was directed to ketophosphonates. Corey had reported the production of enones upon reaction of β-ketophosphonates and aldehydes.[26] Furthermore, although competing reactions were known to predominate during the preparation of β-ketophosphonates by the Arbuzov reaction,[27] it appeared that direct acylation of lithium dimethyl methylphosphonate could be a satisfactory alternative.[28] Indeed, acylation of lithium dimethyl methylphosphonate with methyl caprylate[29] gave β-ketophosphonate **13**. When the conjugate base of **13** was allowed to react with isobutyraldehyde, enone **14** was obtained in a 30% yield.

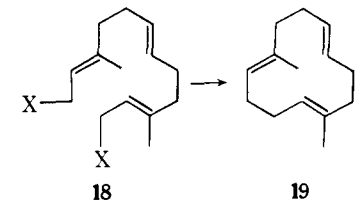


On the basis of these preliminary results, a synthesis of ketophosphonate **4** [Y = $(CH_3O)_2PO$; X = OTHP] was devised and carried out starting with acetol tetrahydropyranyl ether[30] (**15**) (Scheme II). Addition of vinyllithium to **15** afforded a 75% yield of allylic alcohol **16**. When **16** was heated at 160° with ethyl orthoacetate and a trace of propionic acid for several days,[31] ester **17**, the Claisen rearrangement product, was obtained in 76% yield following silica gel chromatography. This ester was easily transformed to the desired β-ketophosphonate **4** [X = OTHP; Y = $PO(OCH_3)_2$] in 95% yield by reaction with lithium dimethyl methylphosphonate at −70°. The reaction of the conjugate base of **4** [X = OTHP; Y = $PO(OCH_3)_2$] with aldehyde **3** (X = OTHP)[32] gave the desired enone **5** (X = OTHP) in 78% yield in which a new disubstituted double bond was formed with greater than 95% trans selectivity.[33] With the initial goal accomplished, attention was directed to the elaboration of **5** to cembrene.

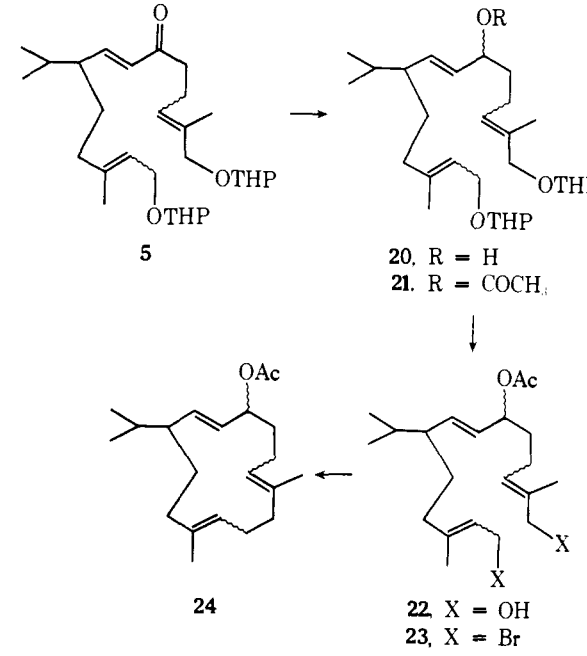
Scheme II



To be next determined was the nature of the allylic oxygenated species to serve as a synthon for the conjugated diene of cembrene. The enone of **5** proved to be an unsatisfactory grouping (see later discussion). A protected allylic alcohol was the next possibility investigated. Esters had been shown to be stable to the conditions employed during the nickel carbonyl coupling reactions.[15] However, Bauld had reported that allylic acetates couple as readily as bromides.[34] To investigate further the feasibility of an allylic acetate as a protecting group, diacetate **18** (X = OAc) was prepared from known diol **18** (X = OH).[35] Under conditions which induced a smooth coupling of dibromide **18** (X = Br) to cyclic triene **19**,[35] diacetate **18** (X = OAc) was recovered unchanged.

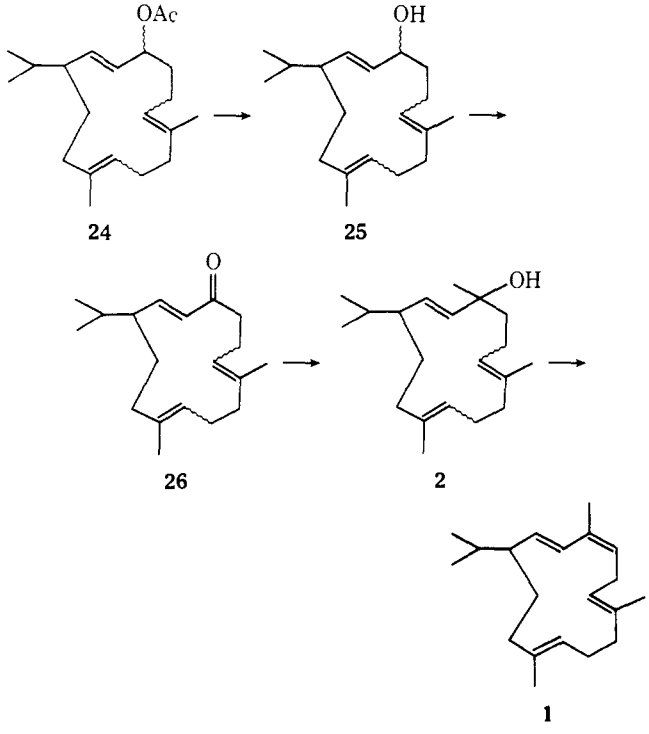


Therefore, an allylic acetate appeared to be an acceptable protecting group, and the synthesis was continued incorporating this grouping. Enone **5** (X = OTHP) was reduced with lithium aluminum hydride, and the resulting alcohol **20** was acetylated with acetic anhydride in pyridine in 91% overall yield. The tetrahydropyranyl ether blocking groups were selectively removed from **21** by heating in 95% ethanol containing a trace of *p*-toluenesulfonic acid in 90%



yield.[36] Labile dibromide **23** was best prepared by the action of phosphorus tribromide on diol **22**.[37] The crude dibromide (two closely running spots on TLC analysis) upon reaction with nickel carbonyl in *N*-methylpyrrolidone at 52° and under argon gave a 25% yield of monomeric products shown to be a mixture of isomeric trienes **24**. Also obtained from the reaction was a 21% yield of dimeric compounds largely resulting from involvement of the allylic acetate (see Experimental Section), which was apparently not completely inert to the conditions of the reaction.

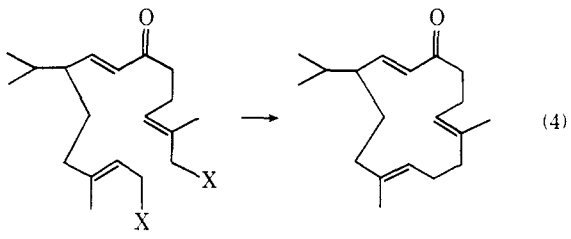
Elaboration of the mixture of triene acetates **24** to cembrene was accomplished beginning with treatment of **24**



24 **25** **26** **2** **1**

with lithium aluminum hydride to give alcohol **25** in 72% yield which, upon Jones oxidation, was transformed to enone **26** in 75% yield. Addition of methyllithium to **26** gave a mixture of alcohols **2** in 70% yield following purification by preparative layer chromatography. This material was chromatographically identical with and spectrally very similar to authentic isocembrol (isolated from *P. albicaulis*). The mixture of alcohols **2**, when treated with a trace of *p*-toluenesulfonic acid in benzene, gave a mixture of hydrocarbons which, although it showed a single spot on TLC analysis, proved to be a mixture of two major and several minor components upon VPC analysis. Of the major components, the compound that was eluted more rapidly (ca. 35% of the mixture) had, upon coinjection, a retention time identical with that of cembrene. This compound was separated from the other components in the mixture by preparative layer chromatography on silver nitrate impregnated silica gel plates to give a solid which was spectrally identical with authentic cembrene in every respect. The synthetic cembrene could be recrystallized to give short needles, mp 56–59°.

During the course of this investigation, a variety of related synthetic steps were studied, and the following two observations are worthy of mention. Enone **5** (X = OTHP) was converted to diol **5** (X = OH) (eq 4) by heating in 95% ethanol containing a trace of *p*-toluenesulfonic acid in essentially quantitative yield. The dibromide **5** (X = Br) was prepared in 80% yield with a modification of the method of Meyers[38] using mesyl bromide[39] and lithium bromide in di-

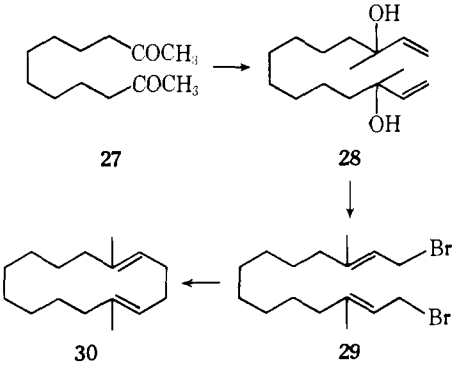


(4)

5 **26**

methylformamide–collidine. The dibromide upon treatment with nickel carbonyl under a variety of conditions did not give desired enone **26**. In all cases, a complex mixture of products was obtained, all of which had lost the enone functionality of **5**. Apparently, the initially formed π-allyl nickel complex added to the conjugate system, followed by further reaction; similar conjugative additions are known.[40]

The problems inherent in the enone system were overcome by modification of the oxygenated carbon to a sp^3-hybridized center. However, when the nickel catalyzed coupling reaction was carried out on allylic acetate **23** (X = Br), yields were still low. To some extent, the poor yield of this reaction could be accounted for in the reactivity of the allylic acetate moiety. Two additional structural features of dibromide **23** (X = Br) which could have influenced the reaction course were investigated. The 14-membered ring of product **24** containing two trisubstituted double bonds was unique as the product of a nickel-induced coupling reaction. Furthermore, the only previous example of a coupling reaction during which trisubstituted double bonds containing a similar substitution pattern were present also gave poor results.[15] Therefore, dibromide **29** was prepared as a model system for the reaction of **23** (X = Br).



27 **28** **30** **29**

Sebacic acid on treatment with methyllithium in ether gave a low yield of known diketone **27** which with excess vinyllithium gave diol **28** in an 85% yield. On treatment with phosphorus tribromide in ether,[37] **28** yielded dibromide **29**, complete rearrangement being observed. When **29** was treated with nickel carbonyl in *N*-methylpyrrolidone, a mixture of 14-membered ring containing hydrocarbons **30** was obtained in 70% yield; a result very similar to the case in which only disubstituted double bonds were present.[15] Therefore, in this ring size, the trisubstituted double bonds do not appear to noticeably influence the reaction course.

Experimental Section

General. All melting and boiling points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60 instrument in CCl_4 with tetramethylsilane (Me_4Si) as an internal standard. Infrared (ir) spectra were taken on a Perkin-Elmer Model 137 (Infarcord) spectrophotometer and ultraviolet (uv) spectra on a Perkin-Elmer Model 202 spectrophotometer with 1-cm cells. Low resolution mass spectral (MS) data were collected at 70 eV on a AEI-MS 12 instrument. Microanalytical analyses were carried out by the University of California Microanalytical Laboratory.

Solvents. Tetrahydrofuran (THF) and ether were purified by distillation from Na metal directly into the reaction vessel employed. Pyridine, dimethyl sulfoxide (Me_2SO), dimethylformamide (DMF), and *N*-methylpyrrolidone were all distilled from CaH_2 onto activated Linde 4A molecular sieves. Methylene chloride was distilled from anhydrous potassium carbonate onto 4A sieves. Dimethoxyethane (DME, Ansul 121) was allowed to stand over CaH_2 for 1 week, decanted, and distilled from lithium aluminum hydride ($LiAlH_4$) onto 4A sieves.

Chromatography. Preparative vapor phase chromatography (VPC) was carried out on a 10 ft × 0.25 in. 5% SE-30 on 80–100 Chromosorb W (SE-30) column installed in an Aerograph A-90-P instrument using helium as a carrier. Analytical vapor phase chromatography was carried out utilizing three systems: a 500 ft × 0.003 in. OV-101 capillary column installed in a Teranishi custom-made chromatograph with a flame ionization detector and helium as a carrier; a 10 ft × ⅛ in. 3% SE-30 on 100–120 Chromosorb W column installed in an Aerograph Model 204/1B chromatograph and nitrogen as a carrier; and a 10 ft × ⅛ in. 10% Carbowax 20M, 10% KOH on 100–120 Chromosorb W column installed in the above Aerograph 204 apparatus. Column temperatures are noted throughout the text. Analytical thin layer chromatography (TLC) was done on microscope slides coated with silica gel PF 254, and preparative layer chromatography was carried out using 20 × 20 cm glass plates coated with a 1.25-mm thick layer of silica gel PF 254.

6-Carbomethoxy-3-hydroxy-3,7-dimethyloctan-1-al (8). To a solution of diisopropylamine (115 ml, 83 g, 0.82 mol) and 1 l. of dry ether under N_2 there was added, with cooling and mechanical stirring, an ethereal solution of methyllithium (410 ml, 0.82 mol) over a 1-hr period. A solution of *N*-ethylidenecyclohexylamine (96 g, 0.77 mol)[41] in 100 ml of ether was added, with stirring, over a 10-min period, and the stirring continued for 30 min. The resulting solution was cooled to −78°, and (±)-methyl 5-oxo-2-isopropylhexanoate[9a] (96 g, 0.53 mol) in 150 ml of ether was added during 25 min. The reaction was stirred for 25 hr at −78°, 50 ml of water added, and the mixture allowed to attain room temperature. An additional 1 l. of ether was added and the solution extracted with water (7 × 1000 ml). The aqueous layers were back extracted with ether (1500 ml), and this ether solution was again extracted with water. The combined ether layers were dried (Na_2SO_4) and concentrated to give 160 g (95%) of a yellow oil: ir 3400, 2940, 1745, and 1660 cm^{-1}; NMR δ 0.87 (d, 3, J = 7 Hz), 0.91 (d, 3, J = 7 Hz), 1.11 (s, 3), 2.26 (d, 2, J = 4 Hz), 1.0–2.2 (m, 17), 2.9 (m, 1), 3.58 (s, 3), 7.82 (t, 1, J = 4 Hz).

The crude imine adduct was dissolved in 6 l. of benzene, and the solution was added to 13 l. of 1% aqueous oxalic acid in a large vat equipped with a mechanical stirrer. The mixture was stirred for 40 hr, the layers were separated, and the aqueous layer was extracted with 1 l. of ether. The combined organic layers were washed with 1% oxalic acid (1 l.), water (1 l.), saturated $NaHCO_3$ (2 × 500 ml), and saturated NaCl (2 × 500 ml). The extract was dried (Na_2SO_4), the solvent rotary evaporated, the residual yellow oil (100 g) was filtered through 1000 g of silica gel with ether, and the ether rotary evaporated to give 88 g (77%) of pure hydroxyaldehyde: ir ($CHCl_3$) 3500, 2740, 1715 cm^{-1}; NMR δ 0.88 (d, 3), 0.92 (d, 3), 1.22 (s, 3), 1.1–2.2 (m, 6), 2.47 (d, 2, J = 2 Hz), 2.75 (m, 1), 3.60 (s, 3), 9.13 (t, 1, J = 2 Hz); MS *m/e* 212 ($-H_2O$).

Anal. ($C_{12}H_{22}O_4$) C, H.

6-Carbomethoxy-3,7-dimethyloct-3-en-1-al (9). A solution of **8** (88 g, 0.38 mol) in 900 ml of Me_2SO was heated at 175° for 1 hr under N_2. The cooled solution was added to 1.5 l. of water, and the mixture was extracted with hexane (4 × 600 ml). The hexane extracts were washed with water (2 × 1 l.), dried (Na_2SO_4), and concentrated to give 69 g of a deep brown oil. A portion of this material (7 g) was chromatographed on 250 g of basic Al_2O_3 to give 4.8 g (57%) of a 40:60 mixture of cis and trans isomers of the aldehyde: ir 2750, 1740, 1675, 1630 cm^{-1}; NMR δ 0.90 (d, 3), 1.2–3.0 (m, 6), 2.05 and 2.15 (2 s, 3), 3.62 (s, 3), 5.72 (d, 1, J = 7 Hz), 9.76 and 9.88 (2 d, 1, J = 7 Hz); MS *m/e* 212.

Anal. ($C_{12}H_{30}O_3$) C, H.

Methyl 7-Hydroxy-2-isopropyl-5-methyl-5-heptenoate (10). To a stirred solution of $NaBH_4$ (15 g, 0.4 mol) in 500 ml of anhydrous methanol at 0° under N_2 was added a solution of crude **9** (62 g, 0.29 mol) in 100 ml of methanol over a 25-min period. The solution was stirred for 1 hr, poured into 1500 ml of H_2O, and extracted with ether (5 × 500 ml). The combined ether extracts were washed with water (2 × 500 ml), dried ($MgSO_4$–Na_2SO_4), and evaporated to leave 56 g of a dark oil. A portion of this material (4 g) was chromatographed on 200 g of Al_2O_3 (activity III) to give 3.5 g (80%) of pure hydroxy ester: ir 3400, 1740 cm^{-1}; NMR δ 0.88 (d, 3, J = 7 Hz), 0.92 (d, 3, J = 7 Hz) 1.2–1.4 (m, 6), 1.6 (m, 1), 1.66 (b s, 3), 3.62 (s, 3), 3.95 (2 d, 2, J = 7 Hz), 5.35 (t, 1, J = 7 Hz); MS *m/e* 214, 196.

Anal. ($C_{12}H_{22}O_3$) C, H.

Methyl 2-Isopropyl-5-methyl-7-(2′-tetrahydropyranyloxy)-5-heptenoate (11). To a stirred solution of alcohol **10** (2.3 g, 10.5 mol) and dihydropyran (1.1 g, 13 mmol) in 30 ml of dichloromethane under N_2 at 0° was added 50 mg of *p*-toluenesulfonic acid monohydrate. The solution was stirred at 0° for 5 min and at room temperature for 10 min, and 300 mg of anhydrous $NaHCO_3$ was added. The mixture was filtered, and the solvent was rotary evaporated to yield 3.2 g (100%) of a pale yellow oil which by NMR and TLC analysis was pure ester **11.** An analytical sample was obtained by preparative layer chromatography on silica gel and bulb-to-bulb distillation: ir 1745 cm^{-1}; NMR δ 0.93 (d, 3), 0.97 (d, 3), 1.2–2.3 (m, 12), 1.67 (b s, 3), 3.3–4.2 (m, 4), 3.62 (s, 3), 4.57 (b s, 1), 5.30 (t, 1, J = 7 Hz); MS *m/e* 214 (M − 84).

Anal. ($C_{17}H_{30}O_4$) C, H.

2-Isopropyl-5-methyl-7-(2′-tetrahydropyranyloxy)-5-hepten-1-ol (12). In a dry 1-l. flask equipped with a reflux condenser, a magnetic stirrer, and an addition funnel were mixed, under N_2, 200 ml of anhydrous ether and $LiAlH_4$ (4.6 g, 0.12 mol). The mixture was refluxed for 0.5 hr, and a solution of tetrahydropyranyl ester **11** (30.0 g, 0.1 mol) in 50 ml of ether was added over 20 min at room temperature. The resulting mixture was refluxed for 30 min and cooled, and 250 ml of H_2O-saturated ether followed by 15 ml of water was slowly added. The mixture was stirred until a white precipitate was obtained. The precipitate was filtered, and the ether solution was dried ($MgSO_4$–Na_2SO_4) and concentrated to give 25 g of crude alcohol which was chromatographed over 500 g of silica gel to give 22 g (80%) of pure **12:** NMR δ 0.88 (d, 6, J = 7 Hz), 1.1–2.1 (m, 15), 2.2 (b, 1, OH), 3.46 (d, 2, J = 5 Hz), 3.8–4.2 (m, 4), 4.53 (b s, 1), 5.27 (t, 1, J = 7 Hz); MS *m/e* 186 (M − 84). Anal. ($C_{16}H_{30}O_3$) C, H.

2-Isopropyl-5-methyl-7-(2′-tetrahydropyranyloxy)-5-hepten-1-al (3). To a cooled, mechanically stirred solution of pyridine (95 g, 1.2 mol) in 1500 ml of dry CH_2Cl_2 in an ice bath and under N_2, there was added dry chromium trioxide (60 g, 0.6 mol). The ice bath was removed, the stirring was continued for 15 min, and alcohol **12** (19.0 g, 70 mmol) in 50 ml of CH_2Cl_2 was added. The resultant mixture was stirred at room temperature for 1.5 hr, at which time the solution was decanted from the dark gum. The gum was washed well with ether (4 × 200 ml), and the combined organic layers were evaporated to dryness. The concentrate was washed well with ether (1 × 500 ml, then 3 × 100 ml), and the combined ether layers were washed with saturated $NaHCO_3$ (2 × 300 ml) and water (5 × 100 ml). The ether extracts were dried (Na_2SO_4) and concentrated to give 16 g of crude aldehyde which was chromatographed over 400 g of silica gel, giving 13.4 g (70%) of pure aldehyde **13:** ir 2780, 1720 cm^{-1}; NMR δ 1.0 (d, 6, J = 7 Hz), 1.0–2.4 (m, 12), 3.3–4.2 (m, 4), 4.6 (b s, 1), 5.35 (t, 1, J = 7 Hz), 9.68 (s, 1).

3-Methyl-4-(2′-tetrahydropyranyloxy)-1-buten-3-ol (16). To a solution of acetol tetrahydropyranyl ether (62.3 g, 0.39 mmol)[30] in 200 ml of absolute ether under N_2 and in a Dry Ice–acetone bath was added 150 ml of vinyllithium solution (0.43 mol, 2.9 *M* in THF) at such a rate that the reaction temperature never exceeded −60° (ca. 25 min). The reaction mixture was stirred at −78° for 30 min and was allowed to slowly attain room temperature, and 150 ml of wet ether was slowly added. The ethereal solution was washed with water until neutral, dried (Na_2SO_4), and rotary evaporated. The residue was distilled, bp 55–59° (0.05 mm), to yield 54 g (75%) of allylic alcohol **16.** An analytical sample was obtained by preparative VPC (SE-30, 140°): ir 3440, 1642 cm^{-1}; NMR δ 1.17 (s, 3), 1.63 (m, 6), 2.20 (m, 1), 3.2–4.0 (m, 4), 4.52 (b s, 1), 4.9–6.1 (m, 3, CH=CH_2); MS *m/e* 185 (M − H).[42]

Anal. ($C_{10}H_{18}O_3$) C, H.

Ethyl 5-Methyl-6-(2′-tetrahydropyranyloxy)-4-hexenoate (17). In a dry 1-l. flask, equipped with a magnetic stirrer and a short-path still, allylic alcohol **16** (30.8 g, 0.165 mol), triethyl orthoacetate (220 g, 1.35 mol), and propionic acid (1 g, 15 mmol) were heated

until a very slow, steady distillation was obtained (pot temp ca. 150–155°). The distillation was continued until, in an aliquot of the reaction mixture, and the ABX pattern for the vinylic protons of the allylic alcohol in the ^1H NMR spectrum (between δ 4.9 and 6.2 in the crude reaction mixture) had completely disappeared (ca. 3 days), Periodically 1-g portions of propionic acid were added. The reaction mixture was rotary evaporated to give 38 g of a yellow oil which was chromatographed over 600 g of silica gel to give 30.5 g (76%) of pure ester **17**: ir 1745 cm^{-1}; NMR δ 1.22 (t, 3, J = 7 Hz), 1.63 (m, 9), 2.27 (m, 4), 3.2–4.0 (m, 4), 4.08 (q, 2, J = 7 Hz), 4.53 (b s, 1), 5.33 (m, 1); MS m/e 172 (M − 84).

Anal. ($C_{14}H_{24}O_4$) C, H.

Dimethyl 6-Methyl-2-oxo-7-(2′-tetrahydropyranyloxy)-5-heptenylphosphonate (4). To a stirred solution of dimethyl methylphosphonate (24.8 g, 0.200 mol) in 300 ml of dry THF under N_2 in a Dry Ice–acetone bath was added a hexane solution of n-butyllithium (0.18 mol, 2 M in hexane) over a 4-min period. The resultant solution was allowed to cool to −78°, and ester **17** (22 g, 91 mmol) in 50 ml of THF was added at such a rate that the temperature never exceeded −70°. The mixture was stirred for 30 min, and 50 ml of water was added. The mixture was warmed to room temperature and poured into 1.5 l. of ether, and the ether layer was extracted with 5% NH_4Cl (2 × 250 ml) and water (2 × 250 ml). The aqueous layer was acidified to pH 3 with concentrated HCl and extracted with ether (2 × 500 ml). This ether solution was back extracted with pH 3 water (200 ml), and the combined organic layers were dried ($MgSO_4$–Na_2SO_4) and concentrated to give 32 g of a yellow oil which was chromatographed on silica gel to yield 28.3 g (95%) of nearly pure phosphonate. An analytical sample was obtained by bulb-to-bulb distillation: ir 2450, 1720, 1650 cm^{-1}; NMR δ 1.66 (m, 9), 2.1–2.8 (m, 4), 2.98 (d, 2, J = 23 Hz), 3.3–4.1 (m, 4), 3.68 (d, 6, J = 11 Hz), 4.52 (b s, 1), 5.33 (m, 1); MS m/e 250 (M − 84), 232.

Anal. ($C_{15}H_{27}O_6P$) C, H, P.

2,12-Dimethyl-9-isopropyl-1,14-bis(2′-tetrahydropyranyloxy)tetradeca-2,7,12-trien-6-one (5, X = OTHP). Into a dry, 100-ml flask equipped with a magnetic stirrer and an N_2 inlet was weighed 360 mg of a mineral oil suspension of NaH (57% NaH, 9.5 mmol) which was washed with dry DME (3 × 5 ml). The NaH was covered with 20 ml of dry DME, and a solution of oxophosphonate **4** (2.7 g, 8.2 mmol) in 3 ml of DME was added. The resulting clear yellow solution was stirred for 1 hr at room temperature, and a solution of aldehyde **13** (1.83 g, 6.8 mmol) in 4 ml of DME was added. The reaction mixture was stirred for 20 hr, 50 ml of water was added, and the resultant solution was extracted with ether (4 × 75 ml). The combined ether layers were back extracted with 75 ml of water and 50 ml of saturated NaCl, dried (Na_2SO_4–$MgSO_4$), and concentrated to give 3.65 g of a nearly colorless oil which was chromatographed on 350 g of silica gel to give 2.51 g (78%) of pure **5** (X = OTHP): ir 1680, 1635 cm^{-1}; NMR δ 0.85 (d, 3, J = 7 Hz), 0.90 (d, 3, J = 7 Hz), 1.2–2.6 (m, 28), 3.2–4.2 (m, 8), 4.55 (b s, 2), 5.28 (t, 2), 6.05 and 6.55 (AB, 2, J_{AB} = 17 Hz); MS m/e 386, 290, 205; $[\alpha]_{546}$ 0°.

Anal. ($C_{29}H_{48}O_5$) C, H.

2,12-Dimethyl-9-isopropyl-1,14-(2′-tetrahydropyranyloxy)tetradeca-2,7,12-trien-6-ol (20). To a mixture of $LiAlH_4$ (360 mg, 9.5 mmol) and 50 ml of ether under N_2 was added enone **5** (X = OTHP) (2.51 g, 5.3 mmol) in 10 ml of dry ether. This mixture was refluxed for 30 min, and 40 ml of wet ether and 2 ml of water were added. The precipitate was filtered and was washed with fresh ether. The combined ether solutions were dried (Na_2SO_4) and were concentrated to yield 2.54 g (100%) of a colorless oil which showed a single spot on TLC analysis: ir 3440 cm^{-1}; NMR δ 0.82 (d, 3, J = 7 Hz), 0.86 (d, 3, J = 7 Hz), 1.2–2.4 (m, 29), 3.3–4.2 (m, 9), 4.52 (b s, 2), 5.33 (m, 4).

The crude alcohol was used in the next reaction without further purification.

6-Acetoxy-2,12-dimethyl-1,4-bis(2′-tetrahydropyranyloxy)-9-isopropyltetradeca-2,7,12-triene (21). A solution of alcohol **20** (2.5 g, 5.2 mmol), pyridine (7 ml, 90 mmol), and acetic anhydride (2.5 ml, 25 mmol) was heated under N_2 (bath temp 77–79°) for 80 min. The excess Ac_2O and pyridine were removed under high vacuum at room temperature, and the residue was taken up in 100 ml of ether. The solution was washed with saturated $NaHCO_3$ (2 × 50 ml), with water (2 × 50 ml), and with saturated NaCl (50 ml), dried ($NaSO_4$), and concentrated to give 2.6 g of a light yellow oil which was chromatographed over silica gel to give 2.48 g (91%) of pure **21**: ir (neat) 1740, 1665 cm^{-1}; NMR δ 0.82 (d, 3, J = 6 Hz), 0.89 (d, 3, J = 6 Hz), 1.3–2.2 (m, 29), 1.95 (s, 3), 3.3–4.2 (m, 9), 4.52 (b s, 2), 5.28 (m, 4).

Anal. ($C_{31}H_{52}O_6$) C, H.

6-Acetoxy-2,12-dimethyl-9-isopropyltetradeca-2,7,12-triene-1,14-diol (22). A solution of bis(tetrahydropyranyl) ether **21** (2.24 g, 4.3 mmol), p-toluenesulfonic acid monohydrate (100 mg, 0.5 mmol), and 95% ethanol (125 ml) was heated (bath temp 66–69°) under N_2 for 2.5 hr. Water (200 ml) and excess $NaHCO_3$ were added, and the mixture was extracted with ether (5 × 150 ml). The extract was dried (Na_2SO_4–$MgSO_4$) and concentrated to give 1.55 g of crude diol which was chromatographed on 80 g of silica gel to give 1.35 g (90%) of pure diol **22**: ir 3380, 1745, 1660 cm^{-1}; NMR δ 0.81 (d, 3, J = 6 Hz), 0.87 (d, 3, J = 6 Hz), 1.2–2.4 (m, 16), 1.95 (s, 3), 2.80 (b s, 2), 3.91 (m, 5), 5.23 (m, 4).

Anal. ($C_{21}H_{36}O_4$) C, H.

6-Acetoxy-1,14-dibromo-2,12-dimethyl-9-isopropyltetradeca-2,7,12-triene (23). To a solution of acetoxydiol **22** (502 mg, 1.43 mmol) in 10 ml of dry ether, under N_2, and in the dark was added PBr_3 (190 μl, 1.2 mmol) over 15 min. The reaction mixture was refluxed for 1 hr and was poured with stirring into 25 ml of ice-water, and the layers were separated. The aqueous layer was extracted with ether (3 × 10 ml), and the combined ether extracts were washed with 20 ml each of saturated $NaHCO_3$ and of water. The organic layer was dried ($MgSO_4$–Na_2SO_4) and was concentrated to the dibromide **23** that was unstable to purification. The crude material exhibited two closely moving spots on TLC analysis but gave spectra totally consistent with the proposed structure: ir (neat) 1735, 1660 cm^{-1}; NMR δ 0.82 (d, 3, J = 6 Hz), 0.88 (d, 3, J = 6 Hz), 1.3–2.4 (m, 16), 1.98 (s, 3), 4.87 (m, 4), 4.8–5.8 (m, 5).

5-Acetoxy-1,11-dimethyl-8-isopropylcyclotetradeca-1,6,11-triene (24). A dry, three-necked flask equipped with a magnetic stirrer, a Dry Ice condenser (topped with a three-way stopcock attached to an argon-filled balloon and a bubbler), a stopper, and a rubber serum cap was thoroughly degassed with argon by alternately pumping (0.05 mm) and filling with argon from the balloon. Using a dry argon flushed syringe, 20 ml of N-methylpyrrolidone was transferred to the flask, and the degassing procedure was repeated. At this time, the apparatus was transferred to a high velocity hood and the stopper replaced with an argon source. The flow was adjusted such that a very slow purge was routed through the entire apparatus and exited through the bubbler to a trap containing concentrated HNO_3. The condenser was filled with an ice-salt mixture, $Ni(CO)_4$ (0.93 ml, 7.2 mmol) was added, and the mixture was heated to 52°. The crude product from the preparation of dibromoacetate **23** (685 mg, 1.43 mmol theoretical) dissolved in 4.5 ml of N-methylpyrrolidone was added by motor-driven syringe over a 5.5-hr period. The faintly yellow solution of $Ni(CO)_4$ became a light rusty brown during the early stages of addition, acquired an olive color after 1 hr, and eventually assumed a deep blue-green color upon completion of the addition. The solution was cooled, the excess $Ni(CO)_4$ removed by rotary evaporation (Hood), and the reaction mixture was poured into 50 ml of 1 N HCl. The resultant mixture was extracted with hexane–ether (1:1, 4 × 50 ml), the combined extracts were washed with water (3 × 50 ml), saturated NaCl (50 ml), and dried (Na_2SO_4). The solvents were rotary evaporated to yield 300 mg of a viscous yellow oil which showed four spots on TLC analysis (silica gel, benzene). This material was resolved by chromatography on 40 g of silica gel using benzene as an eluent to give a fraction (110 mg, 25%) of monomeric acetates [MS m/e 318 (M^+), 258 (M − HOAc)] and three fractions (total 94 mg, 21%) containing dimeric materials.[43] Thus, a total of 68% of the crude product may be accounted for as monomeric or dimeric materials, and the remainder was presumed to be higher order analogs. The spectral and analytical data for the monomeric fraction **24** were: ir 1730, 1680 cm^{-1}; NMR δ 0.86 (m, 6), 1.3–2.4 (m, 20), 1.94 (s, 3), 4.6–6.2 (m, 5); MS low resolution m/e 318 (M^+), 258 (M − HOAc); high resolution (for M^+ calcd, 318.256) 318.255.

Anal. ($C_{21}H_{34}O_2$) C, H.

1,11-Dimethyl-8-isopropylcyclotetradeca-1,6,11-trien-5-ol (25). To a stirred mixture of $LiAlH_4$ (100 mg, 2.6 mmol) and 15 ml of ether was added acetate **24** (240 mg, 0.75 mmol) in 3 ml of ether, and this mixture was refluxed for 30 min. To the cooled mixture was added 15 ml of wet ether followed by 1 ml of water. The pre-

cipitate was filtered, washed with ether, and the ether solution was dried (Na_2SO_4-$MgSO_4$). The solvent was rotary evaporated to give 228 mg of crude alcohol which was purified by preparative layer chromatography on silica gel (2 plates 20 × 20 × 0.125 cm, 3% EtOAc-C_6H_6). The fraction R_f 0.18-0.37 yielded 150 mg (72%) of pure **25**: ir 3400, 1660, 1630 cm^{-1}; NMR δ 0.87 (m, 6), 1.2-1.8 (m, 9), 1.8-2.5 (m, 12), 4.00 (m, 1), 4.6-5.7 (m, 4); MS low resolution *m/e* 276 (M^+), 258 ($M - H_2O$); high resolution (for M^+ calcd, 276.246) 276.245.

1,11-Dimethyl-8-isopropylcyclotetradeca-1,6,11-trien-5-one (26). To a solution of allylic alcohol **25** (140 mg, 0.51 mmol) in 10 ml of acetone cooled in an ice bath, there was added Jones reagent[44] dropwise, until the color persisted. The solution was stirred for an additional 5 min, 3 drops of isopropyl alcohol was added, and the mixture was poured into 30 ml of 5% $NaHCO_3$. The aqueous mixture was extracted with ether–hexane (1:1, 3 × 35 ml), the extract dried (Na_2SO_4), and the solvent removed to give 128 mg of crude enone which was purified by preparative layer chromatography on silica gel (two plates, 20 × 20 × 0.125 cm, 1% EtOAc-C_6H_6). The fraction R_f 0.19-0.48 gave 105 mg (75%) of nearly pure enones; an analytical sample was collected by preparative VPC (SE-30, 210°): ir 1695, 1675, 1635 cm^{-1}; NMR δ 0.88 (d, 3, J = 6 Hz), 0.92 (d, 3, J = 6 Hz), 1.3-1.75 (m, 10), 1.75-2.10 (m, 6), 2.10-2.65 (m, 4), 5.07 (m, 2), 6.09 and 6.41 (AB, 2, J_{AB} = 16 Hz); MS *m/e* 274 (M^+), 259 ($M - CH_3$).

Anal. ($C_{19}H_{30}O$) C, H.

8-Isopropyl-1,5,11-trimethylcyclotetradeca-1,6,11-trien-5-ol (2). A solution of ketone **26** (105 mg, 0.37 mmol) in 5 ml of dry ether, under N_2, and cooled in a Dry Ice–acetone bath was treated with 0.4 ml of methyllithium solution (0.7 mmol, 1.7 *M* in ether). The cooling bath was removed, the solution allowed to attain room temperature, and several drops of water were added. The solution was dried (Na_2SO_4-$MgSO_4$) and was concentrated to give 101 mg (90%) of crude alcohols that on TLC showed a single spot of approximately the same R_f as natural isocembrol. The material was dissolved in benzene, the solution filtered through silica gel, and the benzene rotary evaporated to give 78 mg (70%) of a mixture of alcohols, spectrally very similar to natural isocembrol: ir 3420 cm^{-1}; NMR δ 0.83 (d, 3, J = 6 Hz), 0.89 (d, 3, J = 6 Hz), 1.26 (s, 3), 1.3-1.83 (m, 12), 1.85-2.6 (m, 9), 5.09 (m, 3), 5.43 (AB, J_{AB} = 16 Hz); MS *m/e* 290 (M^+), 275 ($M - CH_3$), 272 ($M - H_2O$).

8-Isopropyl-1,5,11-trimethylcyclotetradeca-1,4,6,11-tetraene [(±)-Cembrene]. A solution of alcohol **2** (78 mg, 0.27 mmol), 11 mg of *p*-toluenesulfonic acid monohydrate, and 4 ml of dry benzene was stirred under N_2 for 60 min, saturated $NaHCO_3$ (1 ml) added, and the layers were separated. The benzene layer was dried (Na_2SO_4), the solvent was evaporated, the residual 68 mg of material dissolved in a minimal volume of benzene was filtered through silica gel, and the solvent removed to give 62 mg of crude hydrocarbons. This material showed a single spot on TLC analysis (silica gel) but contained six components by VPC (500 ft × 0.003 in.) OV-101 at 150°), two of which comprised ca. 80% of the mixture and were present in about equal amounts. The more rapidly eluted of these components (R_t 31 min) was shown by coinjection to correspond to natural cembrene and comprised 40-45% of the crude hydrocarbon product. TLC analysis on 20% $AgNO_3$-impregnated silica gel separated the hydrocarbon mixture into seven distinguishable spots with R_f's ranging from 0.1 to 0.95 (1:1 benzene-hexane). The mixture was separated by preparative layer chromatography on one 20 × 20 × 0.125 cm plate using the same absorbant and solvent; the band with R_f 0.59-0.71 was removed and the absorbant extracted to yield 21 mg (29%) of a solid that was chromatographically and spectrally identical in every respect with an authentic sample of cembrene. This material could be recrystallized with difficulty from MeOH-CH_2Cl_2 to give short white needles (2 mg), mp 56-59°.

Dodeca-2,11-dione (25). To a solution of sebacic acid (50 g, 0.25 mol) and 500 ml of THF-DME (4:1) in a dry flask equipped with a mechanical stirrer, an addition funnel, and a reflux condenser, under N_2, and cooled in an ice bath, there was added 300 ml of methyllithium (0.7 mol, 2.3 *M* in ether) over a 2-hr period. The ether was distilled (total of 450 ml of distillate collected), the reaction mixture refluxed for 3 days, and 800 ml of 3% HCl was added with cooling. The aqueous layer was adjusted to pH 2 with concentrated HCl, 600 ml of ether added, the mixture shaken, and the layers were separated. The organic extracts were washed with saturated $NaHCO_3$ (2 × 500 ml) and dried (Na_2SO_4-$MgSO_4$). The solvent was rotary evaporated to give 13 g of an impure oil which was chromatographed on silica gel to give 3.6 g (19%)[45] of crystalline **25**, mp 63.0-65.5° (lit.[46] 67.0-67.5°) which was analytically pure: NMR δ 1.29 (m, 12), 2.04 (s, 6), 2.32 (b t, 4, J = 6 Hz).

Anal. ($C_{12}H_{22}O_2$) C, H.

3,12-Dimethyltetradeca-1,13-diene-3,12-diol (28). To a solution of diketone **25** (1.98 g, 10 mmol) in 75 ml of dry ether under N_2, cooled in a Dry Ice–acetone bath, was added vinyllithium (12 ml, 35 mmol, 2.9 *M* in THF) with a dry N_2-flushed syringe over 15 min. The resultant yellow solution was allowed to warm to room temperature, and 50 ml of wet ether was added cautiously. This solution was washed with water (3 × 50 ml), dried (Na_2SO_4-$MgSO_4$), and concentrated to give 4 g of a yellow oil which was chromatographed on silica gel to yield 2.19 g (85%) of a colorless oil which gave a low melting solid on standing: ir 3610, 3450, 1650 cm^{-1}; NMR δ 1.20 (s, 6), 1.29 (m, 16), 2.14 (b s, 2), 4.8-5.3 (m, 2, CH=CH_2), 5.6-6.1 (m, 1, CH=CH_2).

Anal. ($C_{16}H_{30}O_2$) C, H.

1,14-Dibromo-3,12-dimethyltetradeca-2,12-diene (29). To a stirred solution of diol **27** (500 mg, 1.97 mmol) in 10 ml of dry ether, under N_2, was added, in the dark, 260 μl of PBr_3 (0.45 g, 1.6 mmol) over a 10-min period. The resultant solution was refluxed for 1 hr, poured into 25 ml of ice-water, and the layers were separated. The aqueous layer was extracted with ether (3 × 10 ml), and the combined ether extracts were washed with 20-ml aliquots of both saturated $NaHCO_3$ and water. The ether layer was dried (Na_2SO_4-$MgSO_4$) and concentrated to give crude dibromide **29** that showed a single spot on TLC analysis and which decomposed on attempted purification. The NMR spectrum of this material indicated complete rearrangement: ir 1665 cm^{-1}; NMR δ 1.26 (m, 12), 1.73 (s, 6), 2.04 (m, 4), 3.92 (d, 4, J = 8 Hz), 5.50 (b t, 2, J = 8 Hz).

1,6-Dimethylcyclotetradeca-1,5-diene (30). The procedure was exactly that used to prepare cyclic acetate **24** from dibromide **23**, and 750 mg (1.97 mmol) of dibromide **29** and 1.17 ml (1.55 g, 9 mmol) of $Ni(CO)_4$ were utilized. Following the normal work-up, solvent removal yielded 331 mg (76% based on diol **28**) of a colorless oil which exhibited a single spot on TLC analysis and two closely eluting peaks on VPC analysis (5% SE-30, 170°, presumably double bond isomers). A benzene solution of the crude product was filtered through 30 g of silica gel and the solvent removed to give 220 mg (50%) of analytically pure **30**: ir 1660 cm^{-1}; NMR 1.28 (m, 12), 1.55 and 1.66 (2 s, 6), 1.96 (m, 8), 5.05 (m, 2); MS *m/e* 220 (M^+), 205 ($M - CH_3$).

Anal. ($C_{16}H_{28}$) C, H.

References and Notes

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Studies on Vitamin D and Its Analogs. VII. Solution Conformations of Vitamin D_3 and 1α,25-Dihydroxyvitamin D_3 by High-Resolution Proton Magnetic Resonance Spectroscopy[1]

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Abstract: The conformations of the A and seco-B rings of vitamin D_3 have been studied by two ^1H NMR methods: correlation of the observed coupling constants with the Karplus equation; and computer analysis of the 300-MHz tris(dipivalomethanato)europium(III) [Eu(dpm)$_3$] shifted spectra. Both methods show that the A ring of vitamin D_3 exists as an approximate equimolar mixture of rapidly equilibrating chair conformers. The torsion angle about the C_6–C_7 bond is essentially the same in solution as previously determined by X-ray diffraction studies. Comparison of the spectra of side chain modified analogs (20,21,22,23,24,25,26,27-octanorvitamin D_3 and vitamin D_2) with that of vitamin D_3 establish that A and seco-B ring conformations are independent of the nature of the side chain. Analysis of the ^1H NMR spectra obtained for 1α,25-dihydroxyvitamin D_3 (the natural hormone) and 1α-hydroxyvitamin D_3 shows that the A-ring conformational populations are identical with one another and similar to that observed for D_3. Observed coupling constants of D_3 in the presence of 0.55 molar equivalents of La(dpm)$_3$ (a diamagnetic analog of the europium shift reagent used in these studies) are smaller than those observed for D_3. This implies that the shift reagent detectably affects conformational populations. An estimate of the relative association constants for axial vs. equatorial hydroxyl groups (K_a/K_e = 1.29) was determined by a competitive titration of *cis*- and *trans*-4-*tert*-butylcyclohexanol with Eu(dpm)$_3$ and is in agreement with the observed perturbation of the chair–chair equilibrium of D_3 by La(dpm)$_3$.

Vitamin D_3 (**1**, D_3) is metabolized in the liver[4] to 25-hydroxyvitamin D_3 (**2**, 25-OH-D_3), which is then further hydroxylated in the kidney[5] to give 1α,25-dihydroxyvitamin D_3 (**3**, 1α,25-(OH)$_2$-D_3). The renal metabolite [1α,25-(OH)$_2$-D_3] has been shown to produce all of the known physiological responses attributable to vitamin D_3 including stimulation of intestinal calcium transport and bone calcium mobilization.[6] From all indications, 1α,25-(OH)$_2$-D_3 appears to be the active form of vitamin D_3[6] and behaves in a manner characteristic of classical steroid hormones.[6,7]