Metal-Assisted Terpenoid Synthesis. V.[1] The Catalytic Trimerization of Isoprene to *trans*-β-Farnesene and Its Synthetic Applications for Terpenoids

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Isoprene oligomerization was effected with a catalyst system Ni(OR)(η^3-C_3H_5)PPh(NEt_2)$_2$ (R=*n*-$C_{11}H_{23}$, *n*-$C_{15}H_{31}$) to give a linear trimer fraction above 70% yield. The major component of the trimer fraction is (*E*)-7,11-dimethyl-3-methylene-1,6,10-dodecatriene (*trans*-β-farnesene) (**1**). The minor constituents of the fraction are (*E*)-2,6-dimethyl-10-methylene-1,6,11-dodecatriene. As slightly higher boiling point fractions, two cyclic trimers 1,5,9-trimethyl-1,5,9-cyclododecatriene and 1,5,10-trimethyl-1,5,9-cyclododecatriene were detected. Factors that influence the reaction path leading to **1** were discussed. Sesqui- and diterpenoids, including farnesyl acetate, farnesylacetone and isophytol were synthesised starting from **1**. A regioselective tail to tail coupling of **1** was achieved with a palladium catalyst to give the dimer $C_{30}H_{48}$ which, upon catalytic hydrogenation, gave perhydrosqualene in 85% yield.

The synthesis of natural terpenoids based on isoprene has attracted the interest of organic chemists,[2] extensive investigations being made to effect selective oligomerization of isoprene with transition metal catalysts.[3] Such attempts have been less rewarding than the case of 1,3-butadiene; only a few attempts were successful for the catalytic synthesis of natural terpenoids. Until recently only monoterpenoids, 2,6-dimethyl-1,3,6- and 1,3,7-octatriene, were obtained in reasonable yields.[4] The selective linear oligomerization of isoprene[5] to give higher terpenoids appears to be difficult.

Trans-β-farnesene (**1**) and its double bond isomer, (*E*)-2,6-dimethyl-10-metflylene-1,6,11-dodecatriene (**2**) can be produced catalytically.[6] Doubtless **1** is a useful intermediate for the synthesis of sesqui- and diterpenoids. For example, farnesyl acetate, farnesylacetone, isophytol and squalane could readily be derived in good yields from **1**. This paper describes the selective linear trimerization of isoprene and the synthetic applications of **1**.

Results and Discussion

Catalytic Oligomerization. The isoprene oligomerization was effected with a nickel alkoxide catalyst, Ni(OR)(η^3-C_3H_5)L [L=PPh(NEt_2)$_2$] (*vide infra*). Conversion reaches about 45% after 8 h at 70 °C. First, the catalyst was deactivated with methanol. A mixture of the dimers and trimers (79.5% based on reacted isoprene) was then isolated by vacuum distillation. As the results of analytical GLC show (Figure), the dimer fraction contains four components and the trimer fraction consists of six isomers in the ratio **1**/**2**/**3**/**4**/**5**/**6**= 87/4/3/2/1/3. Thus the linear oligomers constitute the major components. Under appropriate reaction conditions using a nickel complex as catalyst, it is possible to obtain **1** with a selectivity approaching as high as 87% of the trimer fraction (60% based on the total oligomers produced).

By the conventional fractional distillation, the crude products were separated into three fractions, *viz.*, the dimer, linear and cyclic trimers. Each fraction was then subjected to preparative GLC to isolate the isomers. All the dimer components (**a**—**d**) are readily identified by comparing the retention times with those of authentic samples.

The structural assignments of **1** and **2** have been reported.[6] Compounds **3** and **4** were identified on the basis of the catalytic hydrogenation and their spectro-

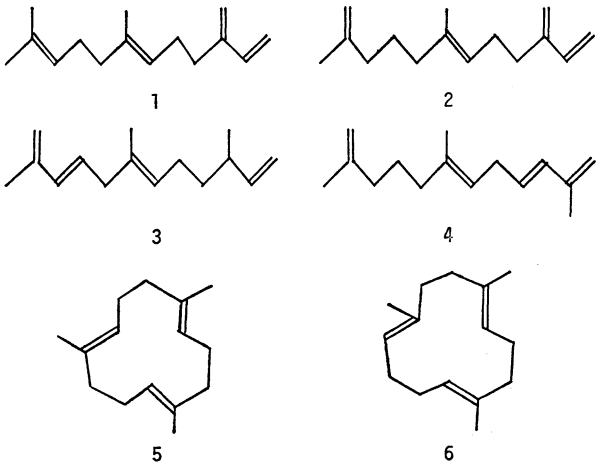
Table 1. Spectral data of linear trimers

Linear trimer	NMR[a] (δ)	IR[b] (cm^{-1})	UV[c] (nm)
1	1.59 (3H, s), 1.62—1.79 (6H, s), 1.90—2.18(8H, m), 4.60 (2H, s), 5.10 (4H, m), 6.27 (1H, t)	3080, 1772, 1601 908, 892	241 (ε 2.3×10^4)
2	1.50 (3H, m), 1.59 (3H, s), 1.68 (3H, s), 1.90 (4H, m), 2.18 (4H, m), 4.60 (2H, s), 4.92 (2H, s), 5.10 (3H, m), 6.26 (1H, t)	3082, 1770, 1604 906, 895	240 (ε 2.2×10^4)
3	1.15 (3H, d), 1.25 (3H, m), 1.59 (3H, s), 1.68 (3H, s), 2.15 (2H, q), 2.19 (2H, d), 4.60 (2H, s), 5.10 (3H, m), 5.60—7.01 (2H, m, J=16.0 Hz), 6.25 (1H, t)	3085, 1770, 1602 915, 892	232 (ε 2.0×10^4)
4	1.25 (2H, m), 1.59 (3H, s), 1.68 (6H, s), 2.15 (4H, t), 4.60 (4H, s), 5.10 (1H, t), 5.60—7.01 (2H, m, J=15.8 Hz)	3080, 1772, 1605 895	231 (ε 1.9×10^4)

a) 60 MHz, in CCl_4, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. b) Neat. c) Measured in ethanol.

scopic properties (Table 1). Upon catalytic hydrogenation, **3** and **4** absorbed 4 mol of hydrogen producing 2,6,10-trimethyldodecane and 2,6,11-trimethyldodecane, respectively. Their ^{1}H NMR and IR spectra are in line with the assignment of **3** as (3*E*)-2,6,10-trimethyl-1,3,6,11-dodecatetraene and of **4** as (3*E*)-2,7,11-trimethyl-1,3,6,11-dodecatetraene. Although the spectral data available do not allow unambiguous determination of the double bond geometries at C-6 in **3** and **4**, it is likely, in view of the established structures of **1** and **2**,[6] that these double bonds are of *E*-configuration. In line with this inference, the chemical shift (δ, 1.59 ppm) of the singlet signal of the inner allyl methyl protons of **3** and **4** coincides with that of the corresponding signal of **1** or **2**.

Cyclic trimers **5** and **6** can be further purified by crystallization from hexane. Isomer **5** forms less soluble crystals, mp 43.5 °C. Upon ozonization and subsequent treatment of the ozonide with dimethyl sulfide, **5** yield 4-ketopentanal as the sole product, while the mother liquid containing **5** and **6** (1/3) gives a mixture of 1,4-butanedial, 4-oxopentanal and acetonylacetone in a ratio 1/1.5/1. The structures of **5** and **6** are thus assigned as 1,5,9- and 1,5,10-trimethyl-1,5,9-cyclododecatriene, respectively. The full assignment of isoprene cyclotrimers, in spite of numerous studies on cyclotrimerizations of 1,3-butadiene, has not been established.[3c,5] Although the double bond geometries of these oligomers remain to be elucidated, the all trans configuration is tentatively assigned to isomer **5** of higher melting point.



The neutral auxiliary ligand (L) plays a role of paramount importance in the nickel mediated catalysis.[6] $[NiX(\eta^3\text{-}C_3H_5)]_2$ alone gave the linear trimers in a very low yield. The presence of electron-donating phosphines or arsine such as $PPh(NEt_2)_2$ or $As(i\text{-}C_3H_7)_3$ is necessary for efficient catalysis. Various catalysts or their precursors were prepared by use of the following mixture: (1) 1:1 $Ni(\eta^3\text{-}C_3H_5)_2$ and $PPh(NEt_2)_2$, (2) 1:1:3 $Ni(acac)_2$, $PPh(NEt_2)_2$, and $AlEt_3$, and (3) 1:1:1.2 $[NiX(\eta^3\text{-}C_3H_5)]_2$, $PPh(NEt_2)_2$ or $As(i\text{-}C_3H_7)_3$, and NaOR (R=long chain alkyl). Representative results obtained have been given.[6] Qualitatively the relative catalytic activities are (1)$\simeq$(3)$<$(2).

The anionic ligand also influences the catalysis.

Table 2. Trimerization of isoprene[a]

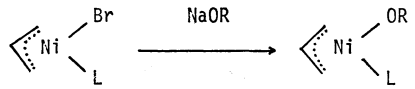
No.	Base[b]	Conversion (%)	Dimers (%)	Trimers (%)[c]	Highers (%)[d]	Content (%) of **1** in Trimers
1	—	0	—	—	—	—
2	MeONa	35.1	42.1	35.2	22.7	30.6
3	$n\text{-}C_4H_9ONa$	41.5	29.5	46.1	24.4	62.2
4	$n\text{-}C_{15}H_{31}ONa$	40.5	21.2	71.6	20.5	87.3
5	$n\text{-}C_{15}H_{31}ONa$[e]	30.7	30.5	51.0	18.5	71.0
6	$LiNEt_2$	15.6	75.2	3.5	11.3	0

a) The mol ratio of isoprene/$[NiBr(\eta^3\text{-}C_3H_5)L]$ (**7**) is 100/1, at 70 °C for 7 h. b) The ratio of **7**/base was 1.2 unless otherwise stated. c) Contains all trimers (**1**—**6**). d) Based on the reacted isoprene. e) The ratio of **7**/base was 1/2.4.

Mononuclear halide complexes, $[NiXL(\eta^3\text{-}C_3H_5)]_2$ (X= Cl, Br), were found ineffective. The halide ligand may be replaced by the diethylamino group. However, the trimer yield was much lower (Table 2). Use of acetate or thiolate anions for X completely killed the catalytic activity. When the halide X is replaced by an alkoxide, in particular by a long-chain alkoxide (recipe 3), the oligomerization occurs smoothly producing the two linear trimers (**1** and **2**) with high selectivities (>75%). Recipe (2) also gives a high selectivity for the trimers. A conspicuous difference between recipe (2) and (3) is the ratio **1**/**2**. The former gives **2** as the major trimer, the latter predominantly **1**.

The alkoxide catalyst (recipe 3) is the only nickel system so far which gives natural β-farnesene as the major product. The effect of the anionic ligand is therfore noteworthy. Both the selectivity for trimers (**1**+**2**) and the ratio **1**/**2** were found to increase in the order: $CH_3O < n\text{-}C_4H_9O < n\text{-}C_{15}H_{31}O$ (Table 2).

In view of the conspicuous tendency of related alkoxide nickel complexes $[Ni(OR)(\eta^3\text{-}C_3H_5)]_2$ to disproportionate into $Ni(\eta^3\text{-}C_3H_5)_2$ and "$Ni(OR)_2$"[7] and of the facile β-hydrogen elimination of alkoxide Pd(II) or Pt(II) compounds,[8] it is unlikely that compound **8** remains under the reaction conditions.



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It was difficult to follow **8** under the reaction conditions and attempts to identify the active catalyst species were unsuccessful. However, the marked controlling effect of the alkoxide anion suggests that the anion is involved in the active species producing the linear trimers.

The linear oligomerization is always accompanied to some extent by cyclo-oligomerization. This side reaction seems to occur with a "naked" Ni(0) or Ni(0)-L species containing no alkoxide anion, as established by Jolly and Wilke for the Ni(0)-catalyzed cyclooligomerization.[3c] The Ni(0) species could be produced directly from disproportionation[7] of **8** or from reductive elimination[8]

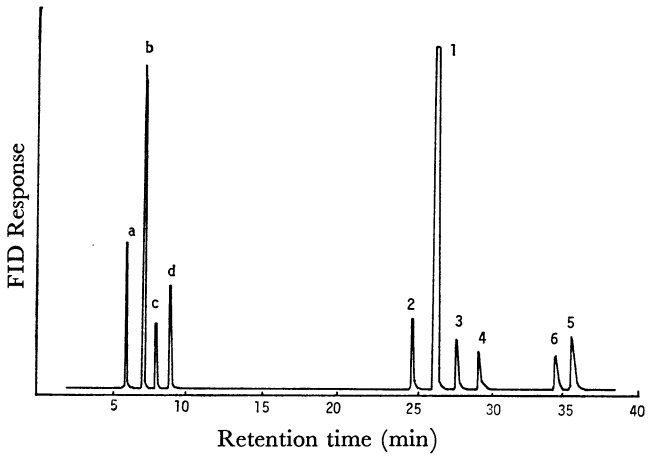
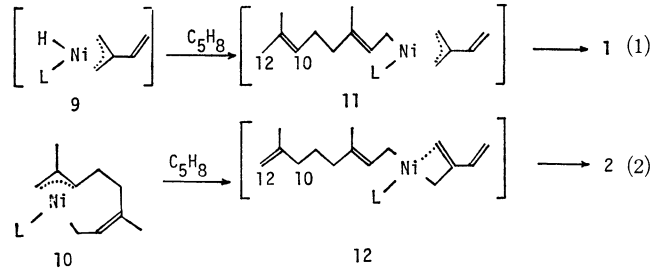


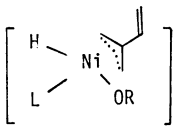
Fig. 1. Gas chromatogram[1] of the dimer and trimer fractions of the isoprene oligomerization.[2]
1) Column C, 130 °C; 2) Run 4 in Table 1 as representative example; **a**, 1,5-dimethyl-5-vinyl-1-cyclohexene; **b**, dipentene; **c**, 1,6-dimethyl-1,5-cyclooctadiene; **d**, 1,5-dimethyl-1,5-cyclooctadiene; **1**, *trans*-β-farnesene; **2**, (*E*)-2,6-dimethyl-10-methylene-1,6,11-dodecatriene; **3**, (3*E*)-2,6,10-trimethyl-1,3,6,11-undecateraene; **4**, (3*E*)-2,7,11-trimethyl-1,3,6,11-dodecateraene; **5**, 1,5,9-trimethyl-1,5,9-cyclododecatriene; **6**, 1,5,10-trimethyl-1,5,9-cyclododecatriene.

of **8**. It is inferred that although the major active species is the alkoxide-containing species (*vide infra*), the present catalyst systems also contains a minor amount of the "naked" Ni(0) species. The latter is responsible for the formation of the cyclotrimers.

A reaction scheme was proposed on the basis of a Ni(0)-L species.[6] Methyl hydrogen migration is assisted by an electron-donating ligand L. The hydrogen migration pathway was established by deuterium distribution studies on the trimer product **2** from 1,1,4,4-tetradeuterated isoprene. Key intermediates **9** and **10** were postulated to account for the formation of **1** and **2** (Eqs. 1 and 2).



The present catalyst systems are ineffective for the isomerization of **2** to **1** suggesting two separate routes leading to the double bond isomers **1** and **2**. Intermediate **10** would lead to **12** whose dimer ligand contains a terminal double bond, since a nucleophilic hydride attack would occur at the secondary carbon in the η^3-allyl part of **10** rather than at the terminal carbon which is more anionic. Since **10** is unlikely to be a precursor of **11**, the formation of **1** is best accounted for by isoprene insertion into a Ni–H bond in the postulated intermediate **9**. The marked effect of a long chain alkoxide ligand (Table 2) invokes an intermediacy of an alkoxide complex like **13** which can not be detected.



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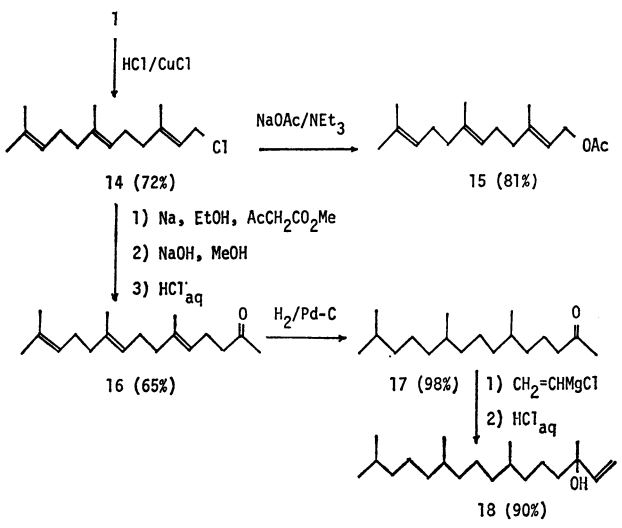
Recipe (2) might give predominantly **12**, which in turn is derived from the dimer complex **10**. Compound **10** has been isolated by Barnett *et al.*[9] The formation of **10** does not require the methyl hydrogen migration. It appears that one role of the alkoxide is to assist hydrogen abstraction to form a hydride species NiH(OR) involved in **13**. It is also possible that the large alkoxide group stabilizes the NiH(OR) species. The increased coordination number in **13** as compared to **9** is in line with the increased formal oxidation state. We tentatively postulate a reaction scheme essentially similar to the previous one for the formation of **1** and **2**. Regarding the minor isomeric products **3** and **4**, several routes involving the dimer intermediates **10** or its σ-π valence isomer are conceivable for the formation.

Derivative Chemistry. Purification of **1** can be achieved by repeated fractional distillation of the linear trimer fraction, but with a substantial loss due to polymerization. The crude product containing over 80% **1** was found to be satisfactory for most synthetic purposes. No further purification was necessary since many functionalization reactions occur preferentially at the 2-substituted 1,3-diene terminus of **1** and **2** rather than at the 1-substituted 1,3-diene part of **3** and **4**. The isolation of products, *e.g.* oxygen-containing terpenoids, is often achieved by distillation through a short fractionation column.

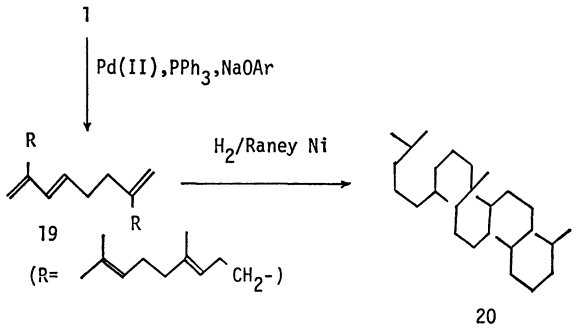
The high reactivity of the terminal group of **1** facilitates regio-selective introduction of a functional group useful for further extension of the carbon chain. Some representative examples are shown below.



These derivations[10] do not require further comment. Yield and selectivity for each process are satisfactory.

Since the starting material **1** is contaminated with a few percent of **2**, farnesyl chloride **14** or acetate **15** contains 1—3% of the corresponding double bond isomer (2,6,11-triene). Both *E* and *Z* geometries were found for the newly formed trisubstituted double bond at C-2. In the above scheme the *Z*-form is not shown for the sake of clarity.

It is known that a regioselective tail to tail coupling of isoprene molecules can be achieved by a palladium catalyst.[11] A modified palladium catalyst consisting of palladium nitrate, triphenylphosphine, and sodium *o*-methoxyphenolate (molar ratio; 1/2/4) was found to have much higher activity and excellent regioselectivity. More than one mol of **1** could be dimerized at the terminal carbon (**19**) by 1 m gram atom of palladium in 92% selectivity. Squalane (**20**) is obtained quantitatively from **19**.



Experimental

Nuclear magnetic resonance spectra were measured on a JEOL Model C-60HL (60 MHz), mass spectra on a Hitachi 6M-GC gas chromatogram-mass spectrometer, and infrared spectra on a JASCO-IRG. Analytical gaschromatograms were obtained with a Hitachi 063 instrument with a flame ionization detector using the following columns: A (20% Carbowax 20 M on Chromosorb W, 3 m×3 mm), B (7% SE-30 silicone rubber on Chromosorb W, 2 m×3 mm), C (Capillary, R-45, 45 m×0.5 mm), and D (Capillary, PEG 4000, 45 m×0.25 mm). Preparative separation was made on Shimadzu GC-1C gas chromatograph with a 2 m×1.5 cm column of 20% Carbowax 20 M on 60—80 Celite 545.

Bis(diethylamino)phenylphosphine (bp 145 °C/2 Torr) was prepared by treating phenylphosphonous dichloride with an excess of diethylamine. η^3-Allylnickel bromide was prepared from nickel carbonyl and allyl bromide. Isoprene was distilled over calcium hydride under nitrogen. Solvents were distilled and kept over Molecular Sieves 5A. Other reagent-grade chemicals were used without further purification. Manipulation of organometallics was performed under nitrogen atmosphere.

Preparation of Bromo(η^3-allyl)[bis(diethylamino)phenylphosphine]-nickel(I) (7). To a benzene solution of bromo(η^3-allyl)-nickel(I) (5.1 g, 28.3 mmol) was added bis(diethylamino)-phenylphosphine (7.6 g, 30 mmol) at 10 °C. After being stirred at 20 °C for 10 h, the mixture was evaporated *in vacuo* to leave a black solid. Recrystallization from hexane gave 10.3 g of **7** as violet needles, mp 215 °C (dec), in 81.5% yield based on the nickel complex; NMR (C_6D_6) 0.48 (d, J=3, $\underline{CH_2}$=CH–), 0.57 (t, $\underline{CH_3}$–CH_2–), 1.67 (d, J=6, $\underline{CH_2}$=CH–), 2.80 (q, N–$\underline{CH_2}$–), 4.32 (m, CH_2=$\underline{CH}$–) and 6.58 (s, $\underline{C_6H_5}$–). Found: C, 47.1; H, 6.7; N, 6.8%; Ni, 12.9% (chelatometric titration). Calcd for $C_{17}H_{30}N_2PBrNi$: C, 47.3; H, 7.0; N, 6.5; Ni, 13.6%.

General Procedure for Isoprene Oligomerization. To an isoprene (50 mmol) suspension of a base (1.2 mmol) was added a benzene solution of **7** (1.0 mmol) at 0 °C. The brown solution was heated at 70 °C for 7 h. The reaction product, after deactivation with 1 ml of methanol, was distilled to give a mixture of dimers and trimers (bp 60 °C/30 Torr to 85 °C/3 Torr) and residues. The mixture of dimers and trimers was then analyzed by GLC on column C.

Preparation of Isoprene Trimers in Large Scale. Isoprene (1.36 kg, 20 mol), *n*-$C_{15}H_{31}ONa$ (120 g, 0.48 mol) and a benzene solution of **7** (96 g, 0.4 mol) were charged in this order in a 5-litre stainless steel autoclave. Autoclaving was carried out to let the temperature rise from 20 to 80 °C over a period of 5.5 h. After the autoclave had been cooled, 50 ml of methanol was added to deactivate the catalyst. The unreacted isoprene (740 g) was recovered by distilling directly from the autoclave to a trap chilled at −20 °C, leaving 835 g of crude products. The reaction products were poured into ice–water (1 litre), extracted with ether (3×1 litre), and the ether solution was washed with 1% hydrogen peroxide solution (2×100 ml), 2 M hydrochloric acid (2×100 ml), saturated sodium hydrogencarbonate solution (2×200 ml) and saturated brine. The solvent was evaporated *in vacuo*, the crude liquid products weighing 621 g. Fractional distillation of the liquid products with a 70 cm Widmer column gave the dimer fraction, 103 g (21.2% based on reacted isoprene), bp 70—95 °C/30 Torr, the linear trimer fraction, 349 g (71.6%), bp 97—105 °C/3 Torr, and the cyclic trimer fraction, 35 g (7.2%), bp 107—110 °C/3 Torr, leaving a residue, 125 g (20.5%). Each fraction was analyzed by GLC on column C.

Separation of Cyclic Trimer. A hexane solution of the cyclic trimer fraction (25 g) was cooled at −30 °C and kept at this temperature overnight. The resulting crystals were rapidly filtered at this temperature and washed with chilled hexane (3×5 ml); needle (10.7 g), mp 43.5 °C. The GLC analysis on column C exhibits one peak, the retention time of which coincides with that of **5**. NMR ($CDCl_3$), 1.91 (s, $\underline{CH_3}$–C=), 2.29 (m, –$\underline{CH_2}$–C=) and 5.45 (t, J=16.0, C=$\underline{CH}$–); mass, *m/e* 204 (3.5%, M^+).

Ozonolysis of Cyclic trimers. A stream of ozone-containing (3.2%) oxygen was introduced into a solution of **5** (7.5 g) in dichloromethane (150 ml) at −10 °C for 5 h. The ozonide was decomposed by adding dimethyl sulfide (20 ml) at −15 °C and subsequent heating at 50 °C for 4 h. The mixture was then poured into ice–water (100 ml), extracted with dichloromethane (3×50 ml). The usual work-up gave a yellow oil (6.2 g), bp 72 °C/12 Torr. The oil was homogeneous on GLC (column D) and identical with an authentic sample of 4-oxopentanal in IR and NMR.

The ozonolysis of a mixture of cyclic trimers 5.5 g (the mother liquid, a 1/3 mixture of **5** and **6**) was carried out similarly to give a mixture of 1,4-butanedial (28.6%), 4-oxopentanal (42.8%) and 2,5-hexanedione (26.1%).

Attempted Isomerization of Linear Trimers. A 71.5/28.5 mixture of **1** and **2** (3.5 g) was heated in the presence of **7** (0.96 g) and *n*-$C_{15}H_{31}ONa$ (1.2 g) at 80 °C for 7 h. After adding methanol (1 ml), the mixture was worked up as usual to give 2.1 g of a mixture of **1** and **2**, bp 101 °C/3 Torr and a polymeric residue (1.4 g). The ratio of recovered **1** and **2** was the same as that of starting material.

Hydrogenation of Linear Trimers. A mixture of linear trimers (2.0 g) was hydrogenated (Pd–C, 0.1 g, H_2, 10 kg/cm² at 25 °C) to give two saturated hydrocarbons in the ratio 93.7/6.3. The abundant isomer was identical with an authentic sample of 2,6,10-trimethyldodecane in the retention time

of GLC (column C) and mass spectra. The other isomer was identified as 2,6,11-trimethyldodecane, which was prepared by reaction of 3,7-dimethyloctylmagnesium chloride with 3-methylbutanal and subsequent dehydration and hydrogenation.

Hydrochlorination of Linear Trimers. Hydrogen chloride was introduced to a solution of linear trimers (300 g) in dichloromethane (300 ml) containing a catalytic amount of copper(I) chloride (3 g) at 0 °C for 5 h (weight increase, 45 g). The mixture was neutralized with 10% aqueous sodium carbonate, the organic layer being extracted with dichloromethane (2× 200 ml). The combined extracts were washed with saturated salt solution and evaporated *in vacuo* to give **14** (341 g) as a light yellow oil; NMR ($CDCl_3$), 3.46 (d, J=8.0, $-\underline{CH_2}Cl$). Found: Cl, 12.1% (titration method) Calcd for 87.3% content of $C_{15}H_{25}Cl$: Cl, 12.9%.

Synthesis of Farnesyl Acetate (15). A mixture of **14** (137 g, 0.5 mol), anhydrous sodium acetate (49.2 g, 0.6 mol) and triethylamine (6 ml) was stirred at 60 °C for 5 h. The reaction mixture was poured into ice–water (200 ml), extracted with ether (3× 150 ml), and the ether solution was washed with 2 M hydrochloric acid (2× 30 ml), 5% aqueous sodium hydrogen carbonate (3× 50 ml) and saturated brine, dried and evaporated to give a slightly yellow oil (135 g). The fractional distillation of the crude products with a 20 cmWidmer column gave a mixture of **3** and **4** (17.8 g), bp 91 °C/2 Torr and a mixture of stereoisomers of **15** (112 g), bp 105—107 °C/2 Torr (58.9% yield based on **1**). The ratio of stereoisomers was 65/35 for (2*E*,6*E*)- and (2*Z*,6*E*)-farnesyl acetate. The products were identified by comparison with authentic samples as regards retention times of GLC and mass spectra.

Synthesis of Farnesylacetone (16). To a solution of sodium ethoxide prepared by dissolving 2.5 g (0.11 g atom) of sodium in ethanol (100 ml) was added methyl acetoacetate (12.8 g, 0.11 mol) and **14** (27.4 g, 0.1 mol). After being refluxed for 5 h with stirring, the mixture was poured into ice–water (100 ml) and extracted with ether and worked up as usual to give an oil (39.1 g). A methanol solution of 1 M sodium hydroxide (120 ml) was added to the oil and the mixture was heated at 50 °C for 3 h. After the solvent had been evaporated, the whole mixture was poured into ice–water (100 ml) and acidified with 1 M hydrochloric acid and extracted with ether (3× 100 ml). The ether solution was worked up as usual to give an oil (29.3 g). The fractional distillation of the oil with a 20 cm Widmer column gave a mixture of **3** and **4** (3.6 g), bp 90 °C/2 Torr and a mixture of stereoisomers of farnesylacetone (**16**) (19.8 g), bp 105—107 °C/2 Torr, in 47.1% yield based on **1**. The ratio of stereoisomers, (5*E*,9*E*)- and (5*Z*,9*E*)-farnesylacetone, was 72/28. They were identified by comparison with authentic samples as regards retention times of GLC (column A) and in mass spectra.

Synthesis of Isophytol (18). A sample (15 g) of **16** was hydrogenated (Pd–C, 1.0 g in 30 ml 2-propanol, H_2, 70 kg/cm² at 100 °C for 3 h) to give **17** (14.9 g), bp 103 °C/1 Torr, semicarbazone, mp 85.1 °C (lit, 85.1 °C).

To a THF solution of vinylmagnesium chloride (12 ml, 0.012 mol), prepared from magnesium and vinyl chloride in THF, was added a THF (10 ml) solution of **17** (2.72 g, 0.01 mol) at 5 °C. After being stirred for 5 h at 25 °C, the mixture was poured into ice–water (50 ml) and acidified with 1 M hydrochloric acid and extracted with ether (3× 50 ml). The ether solution was worked up as usual to give **18** (2.85 g), bp 115 °C/1 Torr in 87.7% yield based on **17**. The GLC analysis (column A) of **17** and **18** showed a 95.2 and 94.1%, respectively, purity.

Dimerization of trans-*β-Farnesene.* A mixture of palladium nitrate (0.14 g, 1.0 mmol), triphenylphosphine (0.52 g, 2.0 mmol) and sodium *o*-methoxyphenolate (0.58 g, 4.0 mmol) and the linear trimers (102 g, 0.5 mol) in 2-propanol (100 ml) was heated at 60 °C for 12 h with stirring. After 2-propanol had been distilled off *in vacuo*, the residual mixture was extracted with ether (3× 100 ml). The usual work up of the extract gave an oil (101 g) which was distilled to give a mixture of **3** and **4** (13.2 g), bp 90 °C/3 Torr, and farnesene dimer (**19**), 80.1 g, bp 95 °C/0.005 Torr (90.5% based on **1**). For 19: IR, 1800, 1640, 973, 890, and 835 (cm^{-1}); NMR (CCl_4), 1.18 (s, $\underline{CH_3}$–C=), 1.50 (m, $-CH_2-$), 2.18 (m, =C–$\underline{CH_2}-$), 4.60 (s, $-\underline{CH_2}$=C), 5.15 (t, J=7, $-\underline{CH}$=C) and 5.52 (m, $-\underline{CH}$=C); *m/e* 408 (2.5%, M^+).

Synthesis of Perhydrosqualene (squalane) (20). The hydrogenation of **19** (20 g) in the presence of Raney nickel (W-4, 1.0 g) under H_2 (80 kg/cm² at 100 °C) gave **20** (20.1 g) quantitatively, bp 102 °C/0.01 Torr; *m/e* 422 (15.2%, M^+). The GLC analysis on column B showed a main peak (91%) retention time of which was identical with that of an authentic sample of squalane.

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