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New Industrial Synthesis of Squalane

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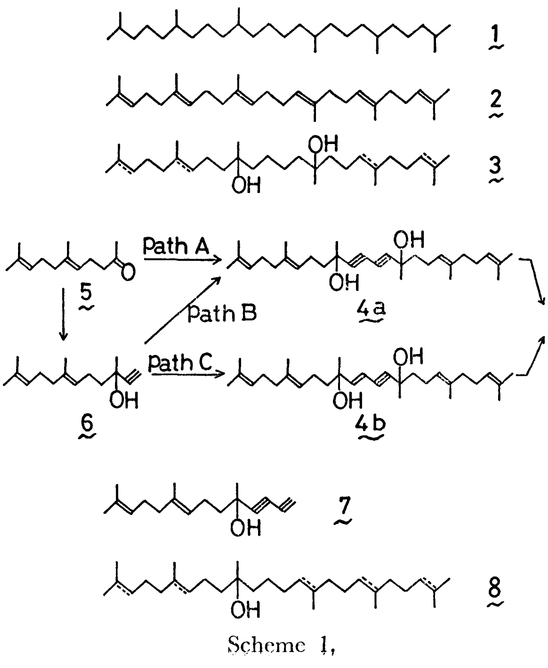
Squalane is synthesized by the ethynylation reaction of geranylacetone with a complex of 1,3-butadiyne : *N*-methylpyrrolidone (=1 : 1) in the presence of a KOH catalyst and by hydrogenation with a Raney nickel catalyst, followed by hydrogenation hydrogenolysis with a mixed catalyst of nickel/diatomaceous earth and silica-alumina. An alternative synthesis of squalane from dehydronerolidol is also achieved by oxidative coupling reaction with a copper(II) catalyst under a helium atmosphere.

Squalane (**1**), a useful base oil for cosmetic formulations, has been commercially produced in large quantities by the hydrogenation of squalene (**2**) obtained from shark liver oil.[1] In spite of numerous studies of the stereoselective synthesis of **2**,[2] there have been few investigations directed toward an efficient total synthesis of **1**.[3] Among the various possible key intermediates for constructing this symmetrical structure, attention was focused on diol (**3**), which could be synthesized by the Grignard reaction of 1,4-dibromobutane and geranylacetone (**5**).[4] Compound **5** is available as a precursor of isophytol on the scale of several thousand tons/year. Thus, we examined the ethynylation of **5**, using 1,3-butadiyne as a key building block, instead of the Grignard reaction of 1,4-dibromobutane to obtain an analogous diol (**4a**) [Path A]. The industrial synthesis of pure squalane is now achieved by the hydrogenation of the unsaturated bonds of **4a**, followed by hydrogenation hydrogenolysis. Then, two alternative methods for deriving **4a** and **4b** from dehydronerolidol (**6**) *via* an oxidative coupling reaction in the presence of a copper(II) ion catalyts [Path B] or via dimerization with a rhodium catalyst under a helium atmosphere [Path C] are also described.

1,3-Butadiyne, one of the major by products of acetylene synthesis by the cracking of natural gas, can be separated from a mixture of other acetylenic compounds (vinylacetylene, 1-propyne, *etc.*) as a complex of 1,3-butadiyne:*N*-methylpyrrolidone (NMP) (=1:1) by passing the mixed gas through a NMP solution.[5] 1,3-Butadiyne is liberated from the complex by heating at *ca.* 40 °C under reduced pressure.



Scheme 1.

The ethylnyation of ketones with 1,3-butadiyne on both terminal sides gives good yields when a stoichiometric amount of sodium amide[6] or the Grignard reagent[7] is used and also, more economically, by means of a semicatalytic reaction with potassium or sodium hydroxide.[8] In this report a 1,3-butadiyne: NMP complex in an NMP solution was employed instead of explosive 1,3-butadiyne, and the reaction was carried out in liquid ammonia at 15 °C in the presence of a potassium hydroxide catalyst (7 mol% *vs.* **5**) [Favorskii conditions].[8] As is shown in Fig. 1, the maximum yield of **4a** (80%) was obtained at the theoretical molar ratio of 1,3-butadiyne:**5** of 0.5:1. However, the undesired alcohol (**7**) was also generated in *ca.* a 10% yields, and the selectivity of **4a** (=yield of **4a**/conversion of **5**×100) is *ca.* 85% under these conditions. On the other hand, the optimum condition of industrial operation was a molar ratio of *ca.* 0.4:1 at which the selectivity of **4a** was 92%, with *ca.* a 75% conversion of **5**. It is better to use **5** in an excess for the complete consumption of 1,3-butadiyne, and the unreacted **5** can be recycled by distillation after the hydrogenation of the ethynylation mixture. The distillation of **5** directly from the ethynylation mixture is dangerous. It was confirmed by gel-permeation chromatography (GPC) that the yield of **7** was less than *ca.* 3% at this molar ratio.

The direct synthesis of squalane from **4a** via hydro-

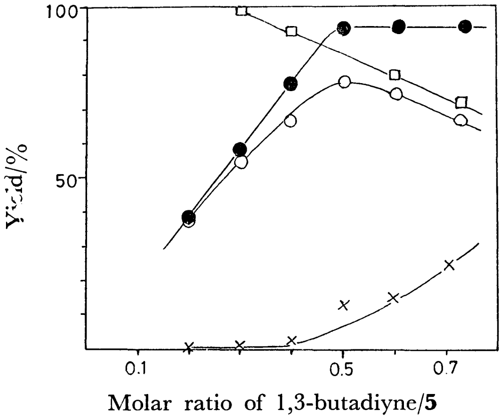


Fig. 1. Ethynylation of **5** with 1,3-butadiyne in ammonia (KOH 7 mol%; reac. temp, 15 °C; reac. time, 20 min). ●: Conversion of **5**; □: selectivity **4a**; ○: yield of **4a**; ×: yield of **7**.

TABLE 1. HYDROGENATION HYDROGENOLYSIS OF 4a1)

Expt No.	Catalyst (wt% *vs.* 4a)	Solvent	Reaction conditions Temp/°C	Time/h	H_2-Pressure kg cm^{-2}	Product ratio (%) 4a	3	8	1
1	5%-Pd/C (10)	Heptane	100	100 min	5	—	95	5	—
2	5%-Pd/C (10)	EtOAc	100	54 min	5	—	95.3	4.2	0.5
3	5%-Pd/C (10)	EtOH	100	210 min	5	—	84.9	14.6	0.5
4	5%-Pd/C (10)	$(CH_3)_2CHCO_2H$	100	12	5	—	56.1	30.3	13.6
5	5%-Pd/C (10)	CH_3CO_2H	100	12	5	—	9.3	30.9	57.8
6	5%-Pd/C (10)	CH_3CO_2H	150	12	5	—	—	7.0	93
7 2)	5%-Pd/C (10) +3 M-HCl (0.2 ml)	CH_3CO_2H	100	12	0	—	—	—	100
8 2)	Ni/Si-Al (4/4)	Hexane	230	2	110—112	—	—	—	100
9 2)	Ni/Si-Al (8/2)	Hexane	230	2	115—125	—	—	—	100
10 2)	Ni/Si-Al (8/1)	Hexane	230	2	100	—	—	10	90

1) A 10-g sample of **4a** in 100 ml of a solvent was treated under various conditions. 2) The GC analyses of **1** are exhibited in Fig. 2.

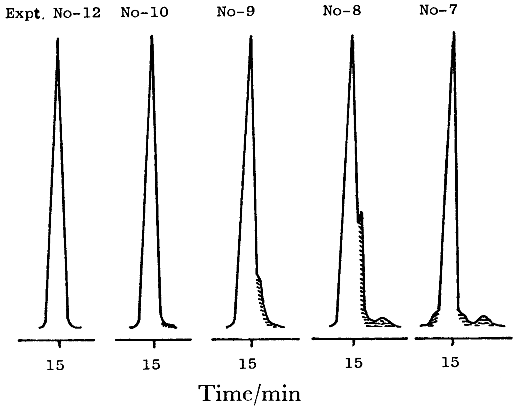


Fig. 2. GC-analyses of **1** prepared by hydrogenation hydrogenolysis of **4a** or **3**.
PEG-20M (2%), 2m, inject. temp, 350 °C, column temp. 150—240 °C (10 °C/min).

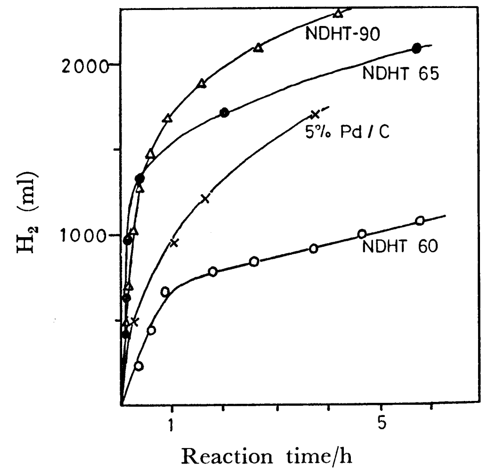


Fig. 3. Hydrogen absorption curve of **4a** with various Raney nickel or Pd/C catalyst. 10 g sample of **4a** in hexane (40 ml) at 100 °C; H_2 pressure 15—20 kg/cm^2; Raney nickel (5 wt%); Pd/C (2.5 wt%).

genation hydrogenolysis was carried out by using Pd/C or a mixed catalyst of Ni/diatomaceous earth and silica-alumina (Ni/Si–Al) under various conditions (Table 1). In the case of the Pd/C catalyst (Expt Nos. 1—7), the use of an acidic solvent such as acetic acid or isobutylic acid was indispensable to convert the diol (**3**) and monool (**8**) into **1** under a low hydrogen pressure and at a relatively low temperature. The addition of a catalytic amount of 3 M-hydrochloric acid (1 M=1 mol cm^{-3}) was effective in completing the conversion of **3** and **8**. The treatment of **4a** with a mixed catalyst of Ni/Si–Al under various conditions (high hydrogen pressure at high temperature) also yielded **1** almost quantitatively (Expt Nos. 8—10). In this reaction, the ratio of silica-alumina was critical to obtain **1** of a good quality. However, as is shown in Fig. 2, squalane synthesized by these procedures contained unknown impurities inseparable from **1** by rectification when **4a** was used as the starting material of the hydrogenation hydrogenolysis.

Consequently, as an industrial method we chose this three-step process: (i) the hydrogenation of the unsaturated triple (and partially some double) bonds of **4a** by means of a Raney nickel catalyst, (ii) the recovery of **5** by distillation, and (iii) the hydrogenation hydrogenolysis of the saturated diol (**3**) by means of a mixed catalyst of Ni/Si–Al. The hydrogenation of **4a** proceeded in the presence of *ca.* 5 wt% of the Raney Ni catalyst (NDH: trade name of Kawaken Fine Chem. Co.) in hexane at 100 °C, with a hydrogen-pressure range of 15—20 kg/cm^2 (Fig. 3).9)

After the separation of the catalyst, the unreacted **5** was recovered by distillation to obtain **3** as a residue. The results of the hydrogenation hydrogenolysis of **3** under various conditions are listed in Table 2. Expt Nos. 11—13 show the influence of the temperature, and Expt Nos. 14—17, the effect of the amount of the catalyst on the product distribution. Contrary to the previous direct synthesis of **1** from **4a**, good results were obtained in this case using much of the silica-alumina catalyst in order to complete the reaction without the formation of impurities (Fig. 2; Expt No. 12). This process is now employed for the industrial production of squalane in quantities amounting to several hundred tons a year.

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Table 2. Results of hydrogenation hydrogenolysis of 3[1)]

Expt No.	Ni/Si-Al (wt% *vs.* 3)	Reaction conditions Temp/°C	Time/h	H_2-Pressure kg cm^{-2}	Product ratio (%) 3	8	1
11	2/4	230	1	100—110	—	8.7	91.3
			2	100—110	—	0.4	99.6
12	2/4	260	0.5	105—112	—	3.9	96.1
			1	105—112	—	1.9	98.1
			2	105—112	—	—	100
13[2)]	2/4	290	1	110—115	—	—	100
14	2/6	290	1	100	—	1.1	98.9
15	1/6	230	1	100	—	1.6	98.4
16	0.6/6	230	1	100	—	9.0	91.0

1) A 10-g sample of 3 in 100 ml of hexane was treated under various conditions. 2) The GC analysis of 1 is exhibited in Fig. 2.

Table 3. Results of oxidative coupling reaction of 6

6 (mmol)	Cu-catalyst (mmol)	Pyridine (mmol)	Solvent (g)	Reaction conditions Temp/°C	Time/h	Conversion of 6/%[a)]	Yield of 4a/%[b)]
10	$CuCl_2$ (1.0)	136.4	Xylene (20)	65	2	21	0
10	CuCl (1.0)	136.4	Xylene (20)	65	3	93	[87]
10	$Cu(OAc)_2$ (1.0)	136.4	—	60	1	88	—
10	$Cu(OAc)_2$ (0.5)	136.4	—	40	1	64	—
10	$Cu(OAc)_2$ (0.3)	68.2	—	80	1	92	83
37.6	$Cu(OAc)_2 \cdot H_2O$ (1:2)	24.8	$C_{13}H_{28}$ (14)	72	0.5	44	—
					1	80	—
					3	94	85.6 [86.2]
1000	$Cu(OAc)_2$ (30)	600	Hexane	75	3	95	[87]

a) Determined by GC (PEG-20 M, 3 m, 190 °C), using eicosane as the internal standard. b) Determined by HPLC (butyl acetate/hexane=10/90), using solanesol as the internal standard; [ ]: isolated yield after silica gel column chromatography.

intermediate **4a** was also described in order to expand the production of squalane because of the limitation of the amount of 1,3-butadiyne obtained as a by product of the acetylene industry. The oxidative coupling reaction, which has been actively studied not only for its synthetic utility, but also for its mechanistic interest, seemed to be suitable for this purpose [Path B].[10)] The reaction, which has been thought to need an excess amount of a copper catalyst,[11—13)] was modified by Hay for practical usage as follows[14)]: oxygen (air) was bubbled into a mixture of **6** and the copper catalyst (3 mol% *vs.* **6**) in hexane/pyridine in the temperature range of *ca.* 40—80 °C for 3 h to afford **4a** in a high yield. It is recommended to dissolve the catalyst before the introduction of the oxygen. If the catalyst was not completely dissolved, the reaction usually stopped before completion, particularly when the reaction was carried out under a lower temperature (room temperature to *ca.* 60 °C). According to our reinvestigation of the copper catalyst, copper(I) chloride and copper(II) acetate gave good results. Copper (II) acetylacetonate, copper(II) chloride, copper(II) sulfate, *etc.* were ineffective. Pyridine, which has been known to be a good solvent (ligand) in this reaction, has a strong effect on the reaction rate and the conversion of **6**. A pyridine/copper catalyst molar ratio of at least 10, and better, 20—30, is required to complete the reaction (Table 3).

Kinetic studies of this reaction showed that the consumption rate of **6** was proportional to the amount of the pyridine and the copper catalyst, and the activation energy (E_a) was calculated to be approximately 10.8 kcal/mol (Fig. 4) in the presence of an excess amount of oxygen. The order of the reaction was estimated to be zero in the initial stage (0—60% conversion of **6**), first at a 60—90% conversion, and second in the final stage (90% conversion). The reaction usually stopped when the conversion of **6** reached *ca.* 94—97%. The reverse ethynylation of **6** and **4a**, which has never before been reported, was observed in a large-scale experiment: The purification of the reaction mixture by column chromatography (ethyl acetate/hexane=10/90—25/75) yielded **5** (*ca.* 2%) and **7** (*ca.* 3—4%), which might be derived from **6** (or **4a**) and **4a** respectively. Acetylene was also trapped as a white precipitate of silver acetylide by passing the outlet gas of the reaction into a silver nitrate/ethanol solution; the amount of silver acetylide increased when the supply of oxygen was decreased. The amount of the higher-boiling products was relatively small (*ca.* 3%),

Table 4. Dimerization of **6** with Wilkinson catalyst

6 (mmol)	$RhX(PPh_3)_3$ (mmol)	Solvent (ml)	Reaction conditions Temp/°C	Time/h	Conversion of **6**/%[a)]	Yield of **4b**/% [isolated]
70	X=Cl (1)	Toluene (100)	110	8	96	[77]
50	X=Cl (1)	Benzene (100)	85	12	93	86
50	X=Cl (0.5)	Benzene (100)	85	12	84	72
50	X=Cl (0.3)	Toluene (100)	110	8	76	60
50	X=Cl (0.5)	Toluene (100)	110	8	97	83 [78]

a) Determined by GC (PEG-20 M, 3 m, 190 °C), using eicosane as the internal standard. b) Determined by HPLC (butyl acetate/hexane=10/90), using solanesol as the internal standard.

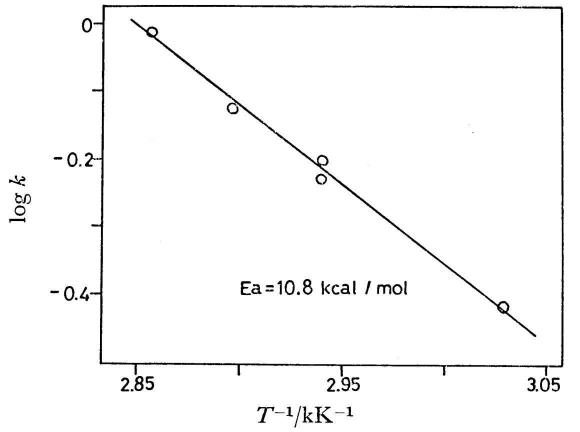

Fig. 4. Effect of temperature on rate constant (K) of disappearance of **6** in oxidative coupling reaction: **6** (37.6 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.2 mmol), pyridine (24.8 mmol) in $C_{13}H_{28}$ (14.0 g); air 5.5 l/h.

and the yield of **4a** was approximately 87%, with a 95% conversion of **6**.

The dimerization of **6** to **4b** with the Wilkinson catalyst (Path C)[15)] was also investigated. The treatment of **6** with $RhCl(PPh_3)_3$ (1—5 wt% *vs.* **6**) in dry benzene (toluene), sufficiently degassed with helium at 80—110 °C for 7 h, gave **4b** in a good yield (Table 4). If oxygen was contained in this reaction system, the reaction often stopped before completion and *ca.* 10% of the catalyst was required for completion. The almost pure product, **4b**, obtained by short-column chromatography on silica gel was converted to **1**, as has been mentioned in connection with the oxidative coupling process (total yield from **6**=77%). The disubstituted double bond of **4b** was identified as having an *E*-form. The economical recycling of this expensive catalyst, however, still remains open as a significant problem; it is now under investigation in our laboratories.[16)]

In conclusion, we first employed the 1,3-butadiyne process (Path A) as an industrial squalane synthesis and are now also investigating the oxidative coupling process (Path B) as an alternative. The dimerization process with the Wilkinson catalyst (Path C) can not now be employed as a practical method unless the economical recycling of the catalyst can be achieved.

Experimental

The boiling points are uncorrected. The IR spectra were recorded with a Digilab FTS-20 C/D spectrometer. The NMR spectra were taken with a Varian EM 390 apparatus (with hexamethyldisiloxane as an internal standard), and the mass spectra, with a Finnigan 9500 or JEOL JMS-D 300 instrument. GC analyses were made by means of a Shimadzu GC-7AG gas chromatograph using a 3 mm×200 cm column of 10% Silicone DC-550, 10% PEG-20M, or OV-1 on Celite 545 with He as the carrier gas, and HPLC analyses, with a Waters Associates liquid chromatograph using a μ-Porasil P/N 27477 S/N column.

Geranylacetone (**5**) and dehydronerolidol (**6**), commercially available from the Kuraray Co., Ltd., NIC-division, are used as (*Z*)- and (*E*)-forms or as *Z*/*E*=4/6 mixture.

*2,6,10,15,19,23-Hexamethyl-2,6,18,22-tetracosatetraene-11,13-diyne-10,15-diol (**4a**). Ethynylation of Geranylacetone (**5**) with 1,3-Butadiyne*: In a 500-ml autoclave was placed a *Z*/*E*=4/6 mixture of 6,10-dimethyl-5,9-undecadien-2-one (**5**) [38.8 g; 0.2 mol], 40 g of a 10% solution of 1,3-butadiyne (0.08 mol) in NMP, and 3.92 g of a 20 wt% aqueous KOH catalyst in 200 ml of liquid ammonia to react at 15—20 °C for 3 h. The autoclave was then cooled to *ca.* −35 °C, and the reaction mixture was neutralized with ammonium chloride. After the ammonia had then been purged, 200 ml of hexane was added to the residue and the mixture was washed with water and dried over magnesium sulfate. The evaporation of hexane afforded crude **4a** (42.1 g), which was then analyzed by means of HPLC (butyl acetate/hexane=1/9; solanesol as the internal standard) and found to contain **5** (24%), **4a** (70%), and **7** (3%). **4a** was composed of three stereoisomers of (6*Z*,18*Z*)[HPLC retention time 14.2 min], (6*Z*,18*E*) [15.9 min], and (6*E*,18*E*) [18.0 min] in a ratio of *ca.* 1:3:2. The analytical sample of **4a** was purified by means of silica gel column chromatography (ethyl acetate/hexane=10/90—25/75): IR (neat) 3360, 2962, 2920, 2850, 1446, 1375, 1118 cm^{-1}. NMR ($CDCl_3$) δ=1.46 (s, 6H, CH_3COH), 1.57, 1.63, 1.64 (each s, 18H, CH_3), 2.23 (s, 2H, OH), 5.07 5.10 (each t, 4H, =CH, J=7.5 Hz). Found: C, 81.86; H; 10.33, O; 7.58. Calcd for $C_{30}H_{46}O_2$: C; 82.14, H; 10.57, O; 7.29.

Compound **7** was confirmed by the following data: GC-mass (OV-1, 2 m, 100—290 °C) m/e=229 (M^+-CH_3), 142, 127, 69. The hydrogenation of the ethynylation mixture with Pd/C afforded 5,9,13-trimethyl-5-tetradecanol, whose GC retention time agreed completely with that of the authentic sample prepared by the Grignard reaction of 1-bromobutane and 6,9-dimethyl-2-undecanone.

*Oxidative Coupling of Dehydronerolidol (**6**).* In a fournecked flask fitted with a thermometer, a gas-inlet tube, and a condenser (−20 °C) was placed 400 ml of hexane, pyridine (95 g; 1.2 mol), and copper(II) acetate (5.45 g; 0.03 mol) to dissolve at room temp. After the addition of **6** (220 g; 1 mol), the reaction temp was elevated to 70 °C by introducing air at the rate of 5.5 l/h for 3 h. The reaction mixture was then successively washed with water (100 ml × 3), 5% sulfuric acid (100 ml × 3), and 5% sodium hydroxide (50 ml)/15% sodium sulfate (100 ml). Quantitative analyses of the product with HPLC showed that the conversion of **6** was 94% and that the yield of **4a** was 85.6%, containing 4% of **7**. The subsequent purification of the product by means of silica gel column chromatography gave 188.8 g of **4a** (yield, 86.2%).

A kinetic study of this reaction was carried out at various temperature ranges by using 8.27 g (37.6 mmol) of **6**, 0.12 g (0.6 mmol)—0.36 g (1.8 mmol) of copper(II) acetate monohydrate, 0.5—4 ml of pyridine, and 2.0 g of elicosane as an internal standard in 14.0 g of a tridecane solvent by bubbling an air at the rate of 5.5 l/h. The rate of the disappearance of **6** was monitored by means of GC (PEG-20 M, 3 m, 190 °C).

*2,6,10,15,19,23-Hexamethyl-2,6,11,18,22-tetracosapentaen-13-yne-10,15-diol (**4b**).* *Dimerization of **6** with Rhodium Catalyst*: A mixture of a chlorotris(triphenylphosphine)rhodium catalyst (0.925 g; 1 mmol) in dry toluene (100 ml) was sufficiently degassed under a helium atmosphere to make possible the addition of **6** (15.4 g; 70 mmol) in one portion. A reaction at 110 °C for 8 h, the evaporation of the solvent, and the purification of the residue by means of silica-gel column chromatography (ethyl acetate/hexane = 10/90—25/75) afforded **4b** (11.8 g; 77%) as a dark red oil: IR (neat) 3380, 2960, 2920, 2850, 1450, 1375, 1105, 960 cm^{-1}. NMR (CDCl$_3$) δ = 1.23, 1.45 (s, 6H, CH$_3$COH), 1.58, 1.66 (s, 18H, CH$_3$), *ca.* 5.10 (m, 4H, =CH), 5.72 (d, 1H, =CH, J = 16 Hz), 6.15 (d, 1H, =CH, J = 16 Hz). Found: C, 81.58, H; 10.62, O; 7.07. Calcd for C$_{30}$H$_{48}$O$_2$: C, 81.76, 10.98, O; 7.26.

*2,6,10,15,19,23-Hexamethyltetracosane (**1**).* *Direct Synthesis from **4a** with Pd/C catalyst*: Hydrogen was bubbled vigorously into a mixture of **4a** (10 g; 22.8 mmol), 3 M-hydrochloric acid (0.2 ml), and 5% Pd/C (1 g) in acetic acid (100 ml) at 100 °C for 12 h. After the filtration of the catalyst, the filtrate was poured into water and extracted with hexane. The organic layer was washed with 5% sodium carbonate and dried over magnesium sulfate. The evaporation of the solvent and subsequent distillation of the residue afforded **1** (9.04 g; 94%): bp 202—208 °C/0.3—0.4 mmHg.[†] The analyses of **1** by means of ^{13}C-NMR, IR, mass, and GC-retention time agreed with those of an authentic sample prepared by the hydrogenation of squalene.

*Direct Synthesis from **4a** with Mixed Catalyst of Nickel/Diatomaceous Earth and Silica-alumina.* In a 300-ml stainless steel autoclave was placed **4a** (10 g; 22.8 mmol), nickel/diatomaceous earth (0.4 g), and a silica-alumina (0.4 g) catalyst in hexane (100 ml). After the atmosphere had been sufficiently replaced with hydrogen, further hydrogen was introduced into the system until a pressure of *ca.* 30 kg/cm^2 was reached. The reaction temperature was then rapidly elevated to 230 °C, while carefully controlling the pressure range of 110—112 kg/cm^2; stirring was then continued for 2 h. The subsequent filtration of the catalyst, evaporation of solvent, and distillation of the residue afforded **1** in a 95% yield.

*Step-by-step Synthesis from **4a** via **3**.* In a 300-ml autoclave, 50 g (114 mmol) of **4a**, 3.6 ml of Raney nickel (about 2.5 g), and 100 ml of hexane were placed, after which the mixture was hydrogenated at 100 °C under a hydrogen pressure of 15—20 kg/cm^2 for 6 h. After the reaction, the catalyst was filtered off and the hexane was removed under reduced pressure to give 49.5 g of a viscous brown liquid, **3**. Investigation by means of the ^{13}C-NMR spectra confirmed qualitatively that this liquid has no triple bond and that some parts of the double bonds were hydrogenated, but a considerable amount of the double bonds remained. The liquid in hexane (500 ml) with the nickel/diatomaceous earth (1 g)/silica-alumina (2 g) catalyst was reacted in an autoclave at 260 °C for 2 h under a hydrogen pressure of 105—115 kg/cm^2 to obtain 41.6 g of **1** (total yield from **4a** after distillation, 86%).

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[†] 1 mmHg ≈ 133.322 Pa.

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