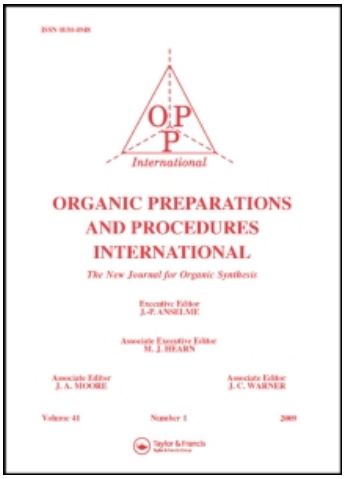

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FACILE CATALYTIC SYNTHESES OF SQUALANE

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FACILE CATALYTIC SYNTHESES OF SQUALANE

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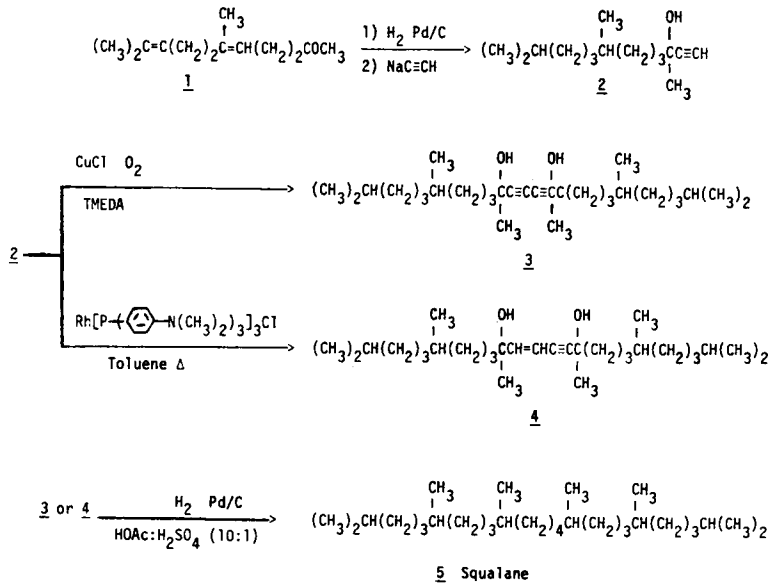
The triterpene hydrocarbon squalane (5) is widely used as a base for cosmetic formulations. The principal commercial source is hydrogenated squalene, which is obtained mainly from shark liver oil. This paper describes two syntheses of squalane from the readily available[1] isoprenoid synthon 1 (geranyl acetone).

Both syntheses of squalane begin with the known[2] two-step conversion of 1 to the acetylenic carbinol 2. In the first approach, oxidative dimerization of 2 gives 3 which is converted to squalane by hydrogenation-hydrogenolysis.[3] There was ample precedent[4,5] for the high yield oxidative dimerization of acetylenic carbinols such as 2. It was less clear[6-11] that reduction of diyndiol 3 to squalane could be effected cleanly and completely. The oxidative dimerization of 3,7,11-trimethyldodec-1-yn-3-ol (2) in the presence of 5 mole % each of cuprous chloride and N,N,N',N'-tetramethylenediamine[5] was rapid and clean. The diacetylenic diol 3 decomposed upon attempted distillation but column chromatography gave analytically pure material. In practice, no workup of the oxidation mixture other than solvent removal was required. Hydrogenation of crude 3 over 5% Pd/C in a 10:1 mixture of acetic and sulfuric acids led to uptake of ca. 5.1 equivalents of hydrogen (complete reduction would require 6.0 equivalents). Treatment of the crude product with conc. sulfuric acid

(to remove all materials that were not saturated hydrocarbons) and then distillation gave squalane of ≥ 97% gas chromatographic purity in an overall yield of 68-70%.

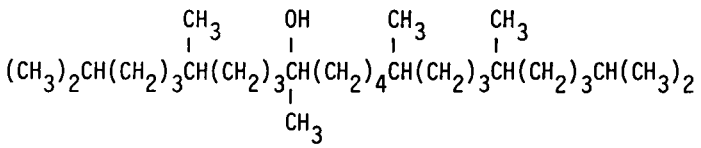
SCHEME 1



1 2 3 4 5 Squalane

In the second approach, dimerization of 2 to 4 was catalyzed by rhodium (I) phosphine complexes.[3,12] The use of ca. 1 wt.-% of bromo-tris-(triphenylphosphine)rhodium (I) gave a smooth conversion of 2 to 4, which could be isolated by chromatography in ca. 50% yield as a low melting solid. The ^1H nmr spectrum of 4 exhibited the characteristic AB pattern, confirming that 4 was the trans-isomer. Hydrogenation-hydrolysis of 4 under the same conditions used for 3 gave inferior results and mixtures of squalane and squalane alcohol, 6, were obtained in only modest yields, especially when it was attempted to use crude 4. Some improvement was possible by replacement of $[Rh(PPh_3)_3(Br)]$ by a rhodium (I) complex of tris-(4-dimethylaminophenyl)phosphine. After the initial condensation most of this catalyst was removed by washing with water. Hydrogenation-

hydrogenolysis over 10% Pd/C in 10:1 v:v acetic acid: sulfuric acid then gave an 8:1 mixture of 5 and 6 in 53% overall yield.



6

EXPERIMENTAL

(6RS,10RS,15RS,19RS)-2,6,10,15,19,23-Hexamethyltetracosane (Squalane, 5) by Oxidative Dimerization. - A mixture of 4.48 g (20 mmol) of (3RS,7RS)-3,7,11-trimethyldodec-1-yn-3-ol (2),[2] 99 mg (1.0 mmol) of cuprous chloride, 116 mg (1.0 mmol) of N,N,N',N'-tetramethylethylenediamine and 12.5 ml of acetone was rapidly stirred in an oil bath at 31-32° under a slight positive pressure of oxygen maintained by a pressure equalizing gas manometer.[13] The mixture gradually changed from light green to dark blue-grey as oxygen uptake (129 ml; complete after 2.5 hr) proceeded. The mixture was concentrated, finally at 50°/0.1 mm, to give diacetylenic diol 4 as a viscous green oil. A similarly prepared sample was chromatographed on 0.063-0.2 mm silica gel (E. Merck) with 95:5 and 90:10 benzene-ethyl acetate mixtures to give analytically pure (6RS,10RS,15RS,19RS)-2,6,10,15,19,23-hexamethyltetracos-11,13-diyne-10,15-diol (3) as a very slightly yellow resin; UV max (C_2H_5OH): 228 nm (ε 410), 241 (ε 410) and 255 (ε 215); MS m/e: 446 (M^+), 431 (M^+-CH_3), 428 (M^+-H_2O), 403 ($M^+-C_3H_7$) and 291 ($M^+-C_{11}H_{23}$); nmr ($CDCL_3$): δ 0.88 (d, 18, J = 6Hz, 6 CH_3CH), 1.50 (s, 6, 2 CH_3COH) and 2.17 ppm (s, 2, 2 OH).

Anal. Calcd. for $C_{30}H_{54}O_2$: C, 80.65; H, 12.18. Found: C, 80.73; H, 12.24.

To a suspension of the crude diol 3 in 44 ml of 10:1 acetic acid-sulfuric acid was added 2.0 g of 10% Pd/C catalyst and the mixture was hydrogenated at atmospheric pressure and room temperature until uptake (1280 ml) of hydrogen had ceased (4.5 hr). The mixture was diluted with hexane and filtered. The filtrate was washed with H_2O, conc. H_2SO_4 (4x) and water and dried over Na_2SO_4. Solvent removal followed by Kugelrohr distillation at 170°/0.01 mm gave 2.90 g (68.8%) of squalane as a clear, colorless oil. The material had a gc purity of 97.8% and was identical in all respects with a sample prepared by hydrogenation of squalene.

(6RS,10RS,15RS,19RS)-2,6,10,15,19,23-Hexamethyltetracosan-11(E)-en-13-yn-10,15-diol (4).-(3RS,7RS)-3,7,11-Trimethyldodec-1-yn-3-ol[2] (11.7 g) and 114 mg of bromo-tris-(triphenylphosphine)rhodium (I) were heated for 24 hours at reflux in 45 ml of toluene under argon. The resulting deep red reaction mixture was concentrated on the rotary evaporator to give 11.8 g of residue. Column chromatography on silica gel of a 2.2 g portion of the residue gave 0.6 g of starting material and 1.22 g of (6RS,10RS, 15RS,19RS)-2,6,10,15,19,23-hexamethyltetracos-11(E)-en-13-yn-10,15-diol (4) as an off-white, low melting solid.

Anal. Calcd. for $C_{30}H_{56}O_2$: C, 80.29; H, 12.57. Found: C, 80.15; H, 12.73. The characteristic AB pattern for trans- -CH=CH- is observed in the nmr ($CDCl_3$) at 5.75 and 6.19 δ (J = 16HZ); CH_3-C-O at δ 1.30, 1.51.

Squalane from 2 by Non-oxidative Dimerization.-(3RS,7RS)-3,7,11-Trimethyldodec-1-yn-3-ol[2] (10.0 g) in 70 ml of deaerated toluene was added to a solution prepared from 24 mg of μ,μ'-dichloro-bis-[bis-(cycloctene)-rhodium] and 76.2 mg of tris-[4-(dimethylamino)phenyl]phosphine in 10 ml of deaerated toluene. The resulting solution was heated for 16 hours at 115-120°, then allowed to cool to room temperature. The reaction mixture was washed with 2x100 ml of H_2O, dried ($MgSO_4$), filtered and concentrated (rotary evaporator) to yield 10.1 g of orange oil. The oil (4.2 g) was hydrogen-

ated over 2.0 g of 10% Pd/C in 40 ml of 10:1 acetic acid-sulfuric acid at 40 psi H_2 and 25°. The reduction mixture was worked up as in the preceding procedure, without the H_2SO_4 wash, to yield 2.0 g of an 8:1 mixture of squalane and squalane alcohol.

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