Anal. Calcd. for $C_{19}H_{24}N_2O{\cdot}1/6\ H_2O$: C, 76.2; H, 8.18; N, 9.36; H_2O, 1.00. Found: C, 76.5; H, 8.36; N, 9.69; H_2O (K.F.), 1.00.

The crude hydroxy ester was chromatographed on Whatman #1 paper (impregnated with an ethanolic solution of formamide and ammonium formate) in the system chloroform:benzene (saturated with formamide).[4c] Ultraviolet absorbing spots were observed at R_f = 0.06, 0.32, 0.48, 0.65 and 0.80, corresponding to alloyohimban-17α-ol (R_f = 0.05), α-yohimbine (**10**) (R_f = 0.65) and alloyohimban-17-one (**9**) (R_f = 0.82).

Acknowledgment.—We wish to express our thanks to the following: Mr. L. Brancone and his staff for elemental analyses; Mr. W. Fulmor and Dr. J. Lancaster (Central Research Division) and their staffs for spectral determinations; Mr. W. Groth for the X-ray powder diffraction measurements; Professor E. L. Eliel (University of Notre Dame) for helpful discussions on the p.m.r. spectra.

Synthesis of Isophytol

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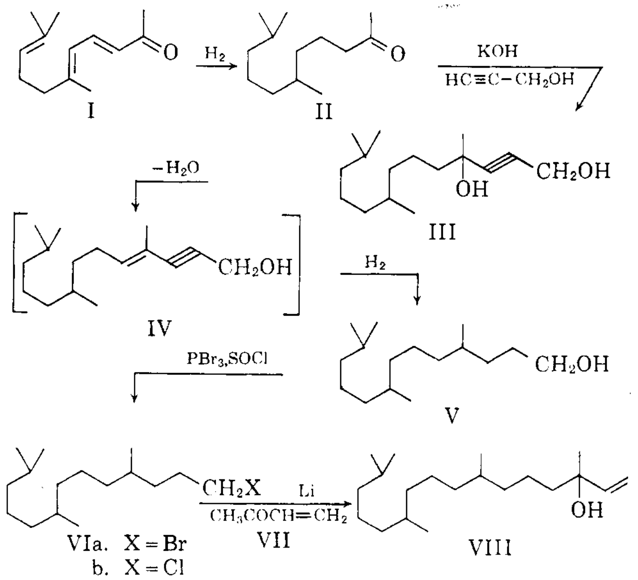
Isophytol was synthesized from pseudoionone and propargyl alcohol. The synthesis involved six steps, much fewer than the steps in other procedures. It was found in a model experiment that methyl vinyl ketone reacts with laurylmagnesium bromide to yield the 1,4-addition product, whereas the 1,2-addition product was obtained with lauryllithium. The specificity found for lauryllithium was applied for the synthesis of isophytol from 1-bromo-4,8,12-trimethyltridecane.

It has been known that tocopherols (vitamins E) are synthesized by condensation of hydroquinones with phytol[1] or its derivatives such as isophytol,[2] phytyl halides,[3,4] and phytadiene.[5] Isophytol (VIII) is a key material for the synthesis, since phytol, phytyl halides, and phytadiene can be easily derived from isophytol. A number of investigations of the synthesis of isophytol have been carried out with linalool or citral[6-14] as the starting material *via* pseudoionone. Recently, Nazarov[15] and Lukes[16] succeeded in the total synthesis of isophytol from acetylene and laevulic acid, respectively. However, these syntheses are awkward for a large scale operation, because of the many stages even from pseudoionone. A new synthesis of isophytol presented in this paper is comprised of six steps from pseudoionone (I) and propargyl alcohol. The process of the synthesis is as follows.



Hexahydropseudoionone (II) prepared from pseudoionone by hydrogenation reacted smoothly with propargyl alcohol to give 4,8,12-trimethyltridec-2-yn-1,4-diol (III) in 84% yield. The condensation was carried out in the presence of finely powdered potassium hydroxide according to Chodkiewicz.[17] 4,8,12-Trimethyltridecan-1-ol (V) was obtained in 70–75% yield from this glycol (III), by dehydration of the tertiary hydroxy group of this glycol with fused potassium hydrogen sulfate and by subsequent hydrogenation. The dehydration reaction was vigorous and completed within about ten minutes at the boiling point of xylene. The intermediate, enyne alcohol (IV), if desired, could be isolated as a pale yellow oil which, upon exposure to air, slowly polymerized to a sticky dark red material. The alcohol was highly sensitive to heat and polymerized even by careful distillation. It is, therefore, recommended that, after treating with dehydrating agent and removing the solvent, the crude product, IV, be directly hydrogenated without isolation. The reduction was smooth and quantitative in the presence of Raney nickel catalyst in ethyl alcohol to 80° under a pressure of about 140 atmospheres of hydrogen. Compound V was a colorless, stable oil, and could be converted smoothly into its bromide (VIa) and chloride (VIb) by action of phosphorus tribromide and thionyl chloride, respectively.

The final product, isophytol, may be obtained by the reaction of a metallic compound of VI with methyl

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(1) P. Karrer, H. Salmon, and H. Fritzshe, *Helv. Chim. Acta.*, **21**, 309 (1938); Hoffmann–La Roche & Co., Swiss Patent 212,353 (1941); P. Karrer and O. Isler, U.S. Patent 2,411,968 (1946).

(2) P. Karrer and O. Isler, U.S. Patent 2,411,969 (1946); Hoffmann–La Roche & Co., Swiss Patent 208,446 (1940).

(3) P. Karrer, R. Escher, H. Fritzsche, H. Keller, B. Ringier, and H. Salmon, *Helv. Chim. Acta.*, **21**, 939 (1938).

(4) J. D. Surmatis and J. Weber, U.S. Patent 2,723,278 (1955); J. D. Surmatis and J. Weber, Can. Patent 530,254 (1956).

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(6) F. G. Fischer and K. Löwenberg, *Ann.*, **475**, 183 (1929).

(7) P. Karrer and B. H. Ringier, *Helv. Chim. Acta*, **22**, 610 (1939).

(8) P. Karrer, A. Geiger, H. Rentschler, E. Zbinder, and A. Kugler, *ibid.*, **26**, 1741 (1943).

(9) I. K. Sarycheva, G. A. Vorobova, N. A. Kuznetsova, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, **28**, 647 (1958).

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(11) J. Weicht and J. Hodrová, *Chem. Listy*, **51**, 568 (1957).

(12) L. I. Smith and G. Rouault, *J. Am. Chem. Soc.*, **65**, 745 (1943).

(13) J. W. K. Burrell, L. M. Jackmann, and B. C. L. Weedon, *Proc. Chem. Soc.*, 263 (1959).

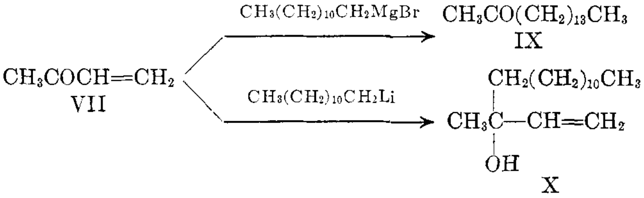
(14) V. I. Gunar and S. I. Zavyalov, *Dokl. Akad. Nauk SSSR*, **132**, 829 (1960).

(15) I. N. Nazarov, B. P. Gusev, and V. I. Gunar, *Zh. Obshch. Khim.*, **28**, 1444 (1958).

(16) R. Lukes and A. Zobácová, *Chem. Listy*, **51**, 330 (1957).

(17) W. Chodkiewicz, *Compt. rend.*, **240**, 1903 (1955).

vinyl ketone (VII). Smith and Sprung[10] examined the reaction of laurylmagnesium bromide with VII, and obtained no simple product owing to the polymerization of the ketone. Since no systematic study has been reported on the reaction of methyl vinyl ketone with organometallic compounds, a model experiment was carried out in the present study with laurylmagnesium bromide and lauryllithium in place of a metallic compound of VI. The reaction was conducted at low concentrations of the reactants and at the low temperature of −10° to suppress the polymerization reaction. In the reaction of methyl vinyl ketone (VII) with an organometallic compound, either 1,2- or 1,4-addition may take place and the tertiary carbinol or the saturated ketone may be obtained. 1,2-Addition is desirable for the preparation of isophytol. It was found that methyl vinyl ketone reacts with laurylmagnesium bromide to give the 1,4-addition product of hexadecan-2-one (IX) in 7.5% yield, whereas the 1,2-addition product of 3-methyl-pentadec-1-en-3-ol (X) was obtained in 13.5% yield with lauryllithium. These products were identified by microanalysis and infrared spectrum.



These results were successfully applied to the synthesis of isophytol (VIII) from 1-halo-4,8,12-trimethyltridecane (VI) as described below. The lithium reagent could not be obtained from lithium and the chloride (VIb) by a common procedure, probably because of the long aliphatic chain in the compound VI. The reaction of lithium with the bromide VIa was also extremely difficult to start. However, the reagent was obtained when the mixture was heated to 60–65° with stirring for thirty hours in the absence of solvent. To the lithium reagent thus obtained, was added slowly methyl vinyl ketone at −10°; isophytol (VIII) was obtained in 3.9% yield (based on VIa). Isophytol was identified from the data of microanalysis, specific density, refractive index,[9,15] and infrared spectrum. The spectrum indicated the presence of tertiary hydroxy and vinyl groups. By-products of $C_{16}H_{34}$ and $C_{32}H_{66}$ were formed in the reaction. The low yield of isophytol in this final stage of the reaction may arise from the formation of these by-products in the long period of heating for the preparation of the lithium reagent.

Experimental[18]

Hexahydropseudoionone (II).—A 100-g. sample of pseudoionone (b.p. 130–133° at 7 mm., a gift from Hasegawa Perfume Co.) in 100 ml. of ethanol was hydrogenated over 6 g. of palladium–calcium carbonate (1:12) with hydrogen at atmospheric pressure and room temperature. The theoretical amount of hydrogen was absorbed in about 10 hr.: b.p. 99–104° at 4 mm., yield 96 g. (93%), n^{20}_{D} 1.4359, d^{20}_{4} 0.8315, (lit.,[11] b.p. 121–122° at 12 mm., n^{20}_{D} 1.4360).

4,8,12-Trimethyltridec-2-yn-1,4-diol (III).—Finely powdered potassium hydroxide (200 g., 3.6 moles) was suspended in 500 ml. of anhydrous tetrahydrofuran in a 2.0-l. three-neck flask, fitted with a stirrer, a dropping funnel, and a reflux condenser. The mixture was heated to the boiling point and then 29.0 g. (0.51 mole) of propargyl alcohol[19] was added with stirring over a period of 0.5 hr. Stirring and refluxing were continued for 3 hr. after the addition and then 99.8 g. (0.51 mole) of II in 130 ml. of tetrahydrofuran was added dropwise over a period of 2 hr. at the boiling point. The reaction mixture was stirred and refluxed for 2 hr. It was then cooled to 0° and poured in portions into a well-stirred mixture of 800 ml. of ice–water and 360 g. of concentrated sulfuric acid. The aqueous layer was extracted three times with 80 ml. of ether, and the extracts were combined with the organic layer. The resultant solution was washed with water, 5% sodium bicarbonate solution, and finally with water, and dried over anhydrous magnesium sulfate. The ether in the solution was evaporated, and the residue was distilled *in vacuo*. The product distilled was a highly viscous oil; b.p. 161–164° at 2 mm., yield 97.2 g. (84%), n^{20}_{D} 1.4717, d^{20}_{4} 0.9449. The infrared spectrum showed the bands of tertiary and primary hydroxy groups at 1150 cm.$^{-1}$ and at 1050 cm.$^{-1}$, respectively.

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.53: H, 11.89. Found: C, 74.97: H, 11.71.

4,8,12-Trimethyltridec-2-yn-4-en-1-ol (IV).—A 500-ml. flask fitted with a stirrer, a dropping funnel, a thermometer, and a condenser was charged with 12 g. of fused potassium hydrogen sulfate and 150 ml. of anhydrous xylene. The bottom of the condenser was connected to a trap to collect the water formed in such a way as used in esterification. The mixture was heated to the boiling point of xylene. A solution of 25.4 g. (0.1 mole) of glycol III in 50 ml. of xylene was added to the mixture all at once with stirring. After the initial vigorous reaction had subsided, stirring was continued for 10 min. at the boiling point of xylene. The reaction mixture was then cooled with an ice bath, poured into water, and extracted with three portions, each 50 ml. of ether. The ether extract was washed with water and with 5% sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The crude product was obtained as the residue after removal of a trace of solvent under reduced pressure. The sample for analysis was distilled as a pale yellow oil at 132–135° (3 mm.), n^{20}_{D} 1.4757, d^{20}_{4} 0.8474.

Anal. Calcd. for $C_{16}H_{28}O$: C, 81.29: H, 11.94. Found: C, 81.03: H, 11.62.

4,8,12-Trimethyltridecan-1-ol (V).—A 13-g. sample of the crude product of IV in 40 ml. of ethanol was hydrogenated in an autoclave with 4 g. of Raney nickel catalyst under 140 atm. and 80°. Reduction was completed in 5 hr. The catalyst was separated by filtration and the saturated alcohol was distilled at 119–122° (2 mm.), yield, quantitative. Over-all yield from III to V was 70–75%, n^{20}_{D} 1.4537, d^{20}_{4} 0.8416.

Anal. Calcd. for $C_{16}H_{34}O$: C, 79.26: H, 14.14. Found: C, 79.00: H, 13.81.

1-Chloro-4,8,12-trimethyltridecane (VIb).—A 12.0-g. sample (0.11 mole) of thionyl chloride was added to 20 g. (0.08 mole) of V over a period of 20 min. keeping the temperature below 5°. The mixture was allowed to stand overnight at room temperature, warmed to 70–80° for 3.5 hr., poured into water, and extracted with ether. The ether extract was washed with water and 5% sodium bicarbonate solution and finally with water, and dried over calcium chloride. The product was distilled at 119–123° (1.5 mm.), yield 18.2 g. (87%), n^{20}_{D} 1.4528, d^{20}_{4} 0.8674.

Anal. Calcd. for $C_{16}H_{33}Cl$: C, 73.65: H, 12.75. Found: C, 73.08: H, 12.29.

1-Bromo-4,8,12-trimethyltridecane (VIa).—This substance was prepared by the method reported by Fischer[20] for the preparation of farnesyl bromide. The bromide (29.2 g.) was obtained as a pale yellowish oil from 37.3 g. (0.16 mole) of V and 40 g. (0.15 mole) of phosphorus tribromide: b.p. 130–133° at 2 mm., n^{20}_{D} 1.4620, d^{20}_{4} 0.9910. The infrared spectrum indicated the absence of hydroxy group.

Anal. Calcd. for $C_{16}H_{33}Br$: C, 62.88: H, 10.89. Found: C, 62.72: H, 10.72. (lit.,[10] b.p. 140–145° at 3.5 mm., n^{25}_{D} 1.4600. Found: C, 63.04: H, 11.17).

Model Experiment. (a) The Reaction of Methyl Vinyl Ketone (VII) with Laurylmagnesium Bromide.—Methyl vinyl ketone was prepared from γ-ketobutanol (78–80° at 18 mm., prepared

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[18] Boiling points and melting points are uncorrected. Infrared spectra were recorded with a Shimadzu Model AR 275 spectrophotometer.

[19] Purchased from Union Carbide Co., after drying over calcium carbide, distilled; b.p. 111–113°.

[20] F. G. Fischer, *Ann.*, **464**, 69 (1928).

from acetone and formalin[21]) by dehydration with oxalic acid according to the method of Murata,[22] b.p. 80–82°. Laurylmagnesium bromide was prepared from 102.3 g. (0.41 mole) of lauryl bromide[23] and 9.9 g. (0.41 g.-atom) of magnesium in 500 ml. of anhydrous ether in a 1.0-l. three-neck flask equipped with a condenser, a stirrer, a dropping funnel, and a nitrogen inlet tube. To the solution, 19.7 g. (0.28 mole) of freshly distilled methyl vinyl ketone in 200 ml. of anhydrous ether was added under nitrogen stream with such a rate that temperature was maintained at −10°. The reaction mixture was allowed to stand overnight at room temperature. The complex was decomposed with 15% ice-cooled dilute acetic acid, and was extracted with ether. The ether extract was washed with water, saturated sodium bicarbonate solution, and water. The solvent was removed, after drying over anhydrous magnesium sulfate. The material was fractionally distilled at 4 mm. Fraction I boiled at 60–70°, fraction II at 100–108°, and fraction III at 110–120°. The residue solidified upon cooling, and crystallized from ethanol to yield 12.0 g. of tetracosan: m.p. 50.5° (lit.,[24] m.p. 51.5°).

Anal. Calcd. for $C_{24}H_{50}$: C, 85.12: H, 14.88. Found: C, 85.17: H, 14.04.

Fractions I, II, and III were redistilled. Fraction I gave 17.0 g. of *n*-dodecane boiling at 62.5–63.0° (2 mm.), n^{20}D 1.4233 (lit.,[25] n^{20}D 1.4209).

Anal. Calcd. for $C_{12}H_{26}$: C, 84.61: H, 15.39. Found: C, 84.85: H, 14.97.

Fraction II gave 1.5 g. of lauryl alcohol boiling at 105–107° (3 mm.) The infrared spectrum showed a band of a primary hydroxy group at 1060 cm.$^{-1}$, n^{20}D 1.4405.

Anal. Calcd. for $C_{12}H_{25}O$: C, 77.35: H, 14.07. Found: C, 77.77: H, 13.82.

Fraction III, upon redistillation, gave 7.3 g. (7.5% based on lauryl bromide) of *n*-hexadecane-2-one boiling at 121–126° (4 mm.), m.p. 41° (lit., b.p. 165° at 12 mm.,[26] m.p. 43°[27]). The infrared spectrum showed a carbonyl band at 1710 cm.$^{-1}$. and the absence of hydroxy and vinyl groups.

Anal. Calcd. for $C_{16}H_3 O$: C, 79.93: H, 13.42. Found: C, 79.90: H, 13.49. Semicarbazone, m.p. 124° (lit.,[26] m.p. 120°).

Anal. Calcd. for $C_{17}H_{35}ON_3$: N, 14.13. Found: N, 14.03.

(b) **The Reaction of Methyl Vinyl Ketone (VII) with Lauryllithium.**—Lauryllithium was prepared from 1.5 g. (0.21 g.-atom) of lithium and 20.5 g. (0.1 mole) of lauryl chloride (b.p. 100–101.5° at 3 mm., n^{20}D 1.4428) by the same method as for the preparation of butyllithium.[28] Methyl vinyl ketone (7.0 g., 0.1 mole) in 70 ml. of anhydrous ether was added to the solution in the same way as in the reaction of laurylmagnesium bromide. The reaction mixture was decomposed with 15% dilute acetic acid and worked up in a usual way. The product thus obtained was distilled fractionally at 4 mm. The distillation afforded 6.5 g. of *n*-dodecane, b.p. 70–72°, n^{20}D 1.4225, and 3.2 g. of 3-methylpentadec-1-en-3-ol, b.p. 127–129° in 13.5% yield (based on lauryl chloride), n^{20}D 1.4521, d^{20}_4 0.8431. The infrared spectrum showed a band of tertiary hydroxy group at 1150 cm.$^{-1}$ and three bands of $CH{=}CH_2$ at 1650, 995, and 910 cm.$^{-1}$, respectively.

Anal. Calcd. for $C_{16}H_{32}O$: C, 79.93; H, 13.42. Found: C, 80.08; H, 13.58.

From the residue, 0.8 g. of tetracosan was obtained; m.p. 50°.

3,7,11,15-Tetramethylhexadec-2-en-3-ol (VIII) Isophytol.—No reaction occurs between the chloride, VIb, and lithium even in the absence of solvent and at 50°. A 29.0-g. sample (0.095 mole) of the bromide (VIa) and 1.5 g. (0.21 g.-atom) of lithium was heated to 60–65° in a stream of nitrogen for 30 hr. The reaction was extremely difficult to start and proceeded very slowly. An appreciable amount of lithium dissolved. After cooling and dilution with 25 ml. of anhydrous tetrahydrofuran, 13.6 g. (0.19 mole) of VII in 25 ml. of anhydrous tetrahydrofuran was slowly added to the lithium reagent with stirring so as to keep the temperature below −10°. The cooling bath was removed, and the stirring was continued until the temperature of the mixture rose to room temperature. The complex left standing overnight was decomposed with dilute acetic acid (15%) and extracted with ether. The ether extract was washed with water and dilute sodium bicarbonate solution, and again with water. After drying over anhydrous magnesium sulfate and removing the solvent, the residual oil was fractionated by distillation into three fractions Fraction I (5.9 g.) was *n*-hexadecane, boiling at 87–90° (1.5 mm.), n^{20}D 1.4356, d^{20}_4 0.7757. (lit.,[29] d^{18}_4 0.7754).

Anal. Calcd. for $C_{16}H_{34}$: C, 84.86: H, 15.14. Found: C, 84.48: H, 15.04.

Fraction II (1.1 g., 3.9% based on VIa) was isophytol and boiled at 107–110° (0.01 mm.,) n^{20}D 1.4571, d^{20}_4 0.8519 (lit.,[15] b.p. 125–128° at 0.06 mm., n^{20}D 1.4546, d^{20}_4 0.8459). The infrared spectrum showed a band of a tertiary hydroxy group at 1150 cm.$^{-1}$ and three bands of $-CH{=}CH_2$ at 1640, 995, and 915 cm.$^{-1}$, respectively.

Anal. Calcd. for $C_{20}H_{40}O$: C, 81.00: H, 13.60. Found: C, 81.67: H, 13.39.

Fraction III (7.2 g.) was a hydrocarbon and boiled at 180–190° (0.2 mm.), n^{20}D 1.4560, d^{20}_4 0.8196.

Anal. Calcd. for $C_{32}H_{66}$: C, 85.24: H, 14.76. Found: C, 84.91: H, 14.59.

Acknowledgment.—The authors wish to express their gratitude to Hasegawa Perfume Co. for a generous gift of pseudoionone and also to Dr. Kuroiwa and the staffs of Tekkosha Co. for the measurements of infrared spectra. The authors also are grateful to Mr. T. Oonuma and Mr. T. Nakano in our laboratory for their great help in carrying out the study presented in this report.

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[21] J. Murata "Synthetic Methods of Monomers," Vol. 9, Kyōritsu Publishing Co., Tokyo, 1957, p. 183.

[22] See ref. 21, p. 186.

[23] Commercial lauryl bromide was treated with concentrated sulfuric acid and distilled; b.p. 102–104° at 4 mm., n^{20}D 1.4580.

[24] F. Krafft, *Ber.*, **15**, 1718 (1882).

[25] F. Krafft, *ibid.*, **15**, 1698 (1882).

[26] L. Ruzicka, H. Schinz, and M. Pfeiffer, *Helv. Chim. Acta.*, **11**, 686 (1928).

[27] F. Krafft, *Ber.*, **15**, 1705 (1882).

[28] H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, **54**, 1957 (1932).

[29] F. Krafft, *Ber.*, **15**, 1702 (1882).