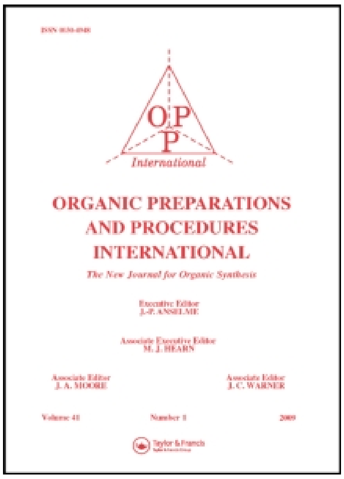

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A CONVENIENT SYNTHESIS OF ISOPHYTOL BY CROSS-COUPLING REACTION OF A GRIGNARD REAGENT AND A PROTECTED ALLYLIC CHLORIDE

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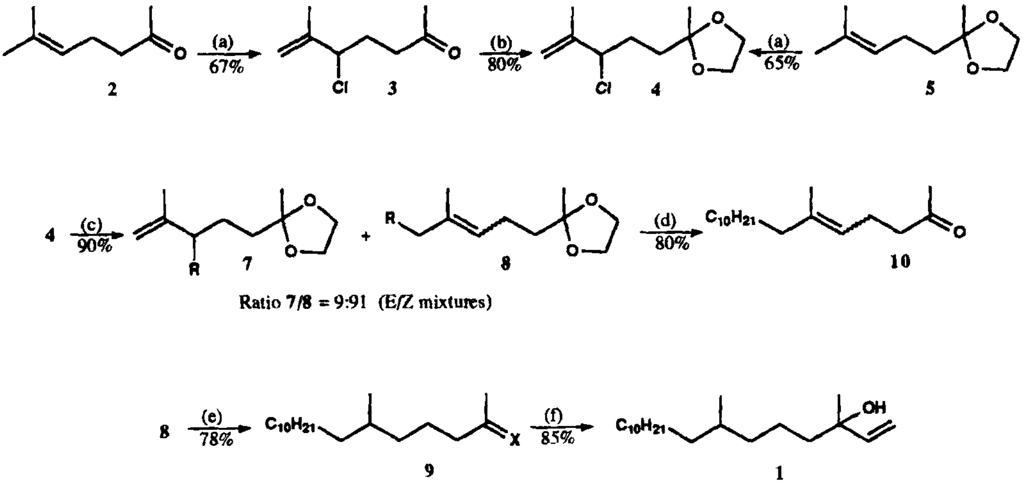
Naturally occurring isophytol (**1**)[1-4] is an important intermediate for the synthesis of vitamins E and K.[5-6] Much attention has been paid to the preparation of isophytol (**1**) in recent years.[7-18] A previous paper described the synthesis of terpenoids *via* the cross-coupling reaction of the allylic chloride derived from benzyl 3-methyl-2-butenyl ether with Grignard reagent of isopentyl bromide in the presence of copper(I) chloride catalyst.[19] We now report a synthesis of isophytol, which involves efficient construction of the isoprenoid skeleton and includes as a key step the cross-coupling reaction of protected allylic chloride (**4**). The synthetic pathway leading to isophytol (**1**) is outlined in the Scheme.



a) $Ca(OCl)_2$, H_3BO_4, CH_2Cl_2 b) $HOCH_2CH_2OH$, *p*-TosOH c) RMgX(**6**), MLX, THF
d) H^+ e) H_2, Pd/C, Then H_2SO_4, H_2O f) CH_2=CHMgCl, THF
6a R = $Me_2CHCH_2CH_2$ **9a** X = OCH_2CH_2O
6b R = $Me_2CH(CH_2)_3CH(CH_3)CH_2CH_2$ **9b** X = O
($C_{10}H_{21}$)

Commercially available 6-methyl-5-hepten-2-one (**2**) was chlorinated with hypochlorous acid, which was generated from commercially accessible calcium hypochlorite, as the chlorinating reagent, to give 3-chloro-2-methyl-1-hepten-6-one (**3**) in good yield (67%).[19-21] The allylic chloride (**3**) was converted to the ethylene ketal (**4**) by heating with ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid in 83% yield. Compound **4** was also prepared in the same procedure from 6,6-ethylenedioxy-2-methyl-2-heptene (**5**) by the ene-type chlorination with hypochlorous acid in 65% yield. The cross-coupling reaction of the protected allylic chloride **4** with 3,7-dimethyloctylmagnesium bromide (**6b**) (the bromide was prepared from tetrahydrogeraniol) in the presence of copper(I) chloride as catalyst in THF afforded mixtures consisting of the α-cross-coupling product (**7**), and an *E*/*Z* mixture of the γ-cross-coupling products (**8Z** and **8E**).[19] The γ-cross-coupling products (**8**) predominated in the reaction of protected allylic chloride **4** with compound **6b** (total yield: 90%, α:γ = 9:91, Z:E = 55:45). These cross-coupling products were isolated by HPLC (silica gel, hexane-EtOH).[19]

The use of nickel catalysts such as $Ni(Ph_2PCH_2CH_2PPh_2)Cl_2$ or $Ni(PPh_3)_2Cl_2$ instead of Cu(I) catalyst was effective in increasing the amount of E isomer (γ-attack) (total yield: 30-25%, ratio of α:γ = 12:88, Z:E = 2:8). Sugimura and Takei have recently studied the coupling reaction of 1,3-diethoxypropane with Grignard reagents in the presence of nickel-phosphine complex to give (E)-1-alkenyl ethers stereoselectively (yield: 36-59%, E:Z = 99:1).[22] The regioselectivity was explained by considering the conjugation between the alkoxy group and the π-electrons in the π-allyl nickel intermediate. We presume that similar π-allyl nickel complexes as reaction intermediates also affected the stereoselectivity in the reactions. Reaction of protected allylic chloride (**4**) with isopentylmagnesium bromide (**6a**) in the presence of catalytic amount of copper(I) chloride resulted in displacement of the chlorine group by the isopentyl group either in an S_N2 and S_N2' fashion (α- or γ-substitution). These results are summarized in Table 1.

TABLE 1. Transition Metal-Catalyzed Grignard Coupling of Allylic Chloride (4)

RMgBr R	Catalyst (1 mol%)	Solvent	Conditions (°C/hrs)	Yield (%)	Product Ratio 7:8	(Z/E)
C_5H_{11}	CuCl	THF	reflux/2	90	10:90	(51/49)
C_5H_{11}	CuCl	ether	reflux/2	72	12:88	(48/52)
$C_{10}H_{21}$	CuCl	THF	reflux/2	90	9:91	(55/45)
$C_{10}H_{21}$	CuCl	THF	r.t/4	88	8:92	(54/46)
$C_{10}H_{21}$	CuCl	ether	reflux/2	78	10:90	(47/53)
$C_{10}H_{21}$	$Ni(PPh_3)_2Cl_2$	THF	r.t./4	30	12:88	(20/80)
$C_{10}H_{21}$	$Ni(dppe)Cl_2$[a]	THF	r.t./4	25	11:89	(21/79)

a) dppe = 1,2-bis(diphenylphosphino)ethane

γ-Cross-coupling products (**8bE**) and (**8bZ**) were hydrogenated over Pd/C to give compound

9a in 92% yield. Removal of the ethylenedioxy group of compound **9a** by 5% aqueous H_2SO_4 in acetone afforded phytone (**9b**) in 85% yield. Alternatively, phytone (**9b**) was prepared in 80% yield from compound **10** by deprotection of γ-cross-coupling products (**8b**) (80% yield) followed by hydrogenation (90% yield). Isophytol (**1**) was prepared from phytone (**9b**) with vinylmagnesium chloride in THF in 85% yield. The physical and spectral data of isophytol (**1**) were identical with those reported in the literature.[7,10-12]

EXPERIMENTAL SECTION

IR spectra were recorded as liquid films on NaCl plates in a Shimadzu IR-435 spectrometer. ^1H NMR spectra were obtained on a Varian EM-390 spectrometer (90MHz) and JEOL GSX 270 (270MHz) with CCl_4 and $CDCl_3$ as solvent. Mass spectra were recorded on a JEOL-DX 300 mass spectrometer with EI ionization. Gas chromatography analyses were carried out on a Hewlett-Packard 5890A gas chromatograph equipped with a flame ionization detector on a fused-silica capillary column (silicon OV-1, 25 m X 0.32 mm I. D.). HPLC were performed on a Gilson liquid chromatography with silica gel column (Develosil 60, 5 μm, 1.8 mm I. D. X 25 cm). Thin layer chromatography was performed on silica gel with visualization by UV light and/or by iodine vapor. Flash column chromatography was performed with a glass column packed with Wako gel C-200 (200-400 mesh). Micro vacuum distillation was carried out on a Shibata GTO-250R Kugelrohr distilling apparatus.

3-Chloro-2-methyl-1-hepten-6-one (3).- To a stirred mixture of freshly distilled 6-methyl-5-hepten-2-one **2** (2.0 g, 15.9 mmol) at 0°, calcium hypochlorite (active chlorine 60%, 1.95 g, 8.0 mmol), boric acid (1.8 g, 29 mmol) and dichloromethane (30 mL), was added water (10 mL, 0.56 mol). The reaction mixture was stirred for 2 hrs below 15°. The reaction mixture was filtered, and the residue washed with dichloromethane. The combined organic layer was washed with sodium bicarbonate solution and brine, then dried over magnesium sulfate overnight. Filtration and removal of the solvents at 40° *in vacuo* gave an oil. The crude product was purified by column chromatography using hexane-ethyl acetate (95:5) to give 1.7 g (67%) of allylic chloride **3**, R_f = 0.27 (hexane-ethyl acetate, 95:5), IR (neat): 3100, 1715, 1640, 1465, 1160, 905 cm^{-1}; ^1H NMR (90MHz, TMS/CCl_4): δ 1.75 (s, 3H, CH_3C=C), 1.90-2.20 (m, 2H, CH_2), 2.00 (s, 3H, CH_3CO), 2.50 (t, *J* = 7Hz, 2H, CH_2CO), 4.30 (t, *J* = 7Hz, 1H, CHCl), 4.83 (s, lH, CH=C), 4. 97 (s, 1H, CH=C); EI-MS (70eV): m/z (rel. int., %) 162 (M^+, 8), 160 (M^+, 26), 125 (13), 109 (8), 92 (11), 90 (33), 83 (100), 81 (17), 71 (62), 67 (16), 58 (18). *Anal.* Calcd. for $C_8H_{13}ClO$: C, 59.81; H, 8.16. Found: C, 59.78; H, 8.10

3-Chloro-6,6-ethylenedioxy-2-methyl-l-heptene (4).- Ethylene glycol (0.97 g, 15.6 mmol), compound **3** (1.5 g, 9.3 mmol), benzene (30 mL) and *p*-toluenesulfonic acid (20 mg) were placed in a flask fitted with a Dean-Stark trap, and the mixture was heated to reflux for 6 hrs. The reaction mixture was then neuralized by the use of a dilute sodium hydrogen carbonate solution and extracted with benzene. The extract was washed with water, dried over sodium sulfate, and concentrated to give the protected allylic chloride **4** (1.59 g, 83% yield) after purification by column chromatography over silica gel with hexane-ethyl acetate (95:5), R_f = 0.30 (hexane-ethyl acetate, 95:5), IR (neat): 3100, 1640, 1445, 1380, 1130, 1060, 945, 900, 860 cm^{-1}; ^1H NMR (90MHz, CCl_4): δ 1.20 (s, 3H,

CH_3), 1.40-2.10 (m, 4H, CH_2), 1.70 (s, 3H, $CH_3C=C$), 3.80 (br.s, 4H, OCH_2CH_2O), 4.23 (t, J = 7Hz, 1H, CHCl), 4.82 (s, 1H, CH=C), 4.95 (s, lH, CH=C); EI-MS (70eV): m/z (rel. int., %) 189 (M^+-CH_3, 3), 125 (4), 115 (7), 109 (4), 99 (11), 87 (100), 71 (26), 58 (12).

Anal. Calcd. for $C_{10}H_{17}ClO_2$: C, 58.68; H, 8.37. Found: C, 58.59; H, 8.49

Cross-coupling Reaction.- A Grignard reagent was obtained from 3,7-dimethyloctyl bromide (**6b**) (2.8 g, 12.7 mmol), prepared from tetrahydrogeraniol, and magnesium turnings (0.3 g, 12.5 mmol) in THF (5 mL) with a small amount of I_2 at 50-60° under dry nitrogen. To this Grignard solution, a solution of a mixture of compound **4** (1.3 g, 6.4 mmol) and CuCl (10 mg, 0.1 mmol) in THF (5 mL) was added at 0° over 10 min. The mixture was stirred for 2 hrs at reflux temperature. Then the ice-cooled reaction mixture was carefully added dropwise to a cold saturated NH_4Cl solution. The THF layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with water, dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed on a silica gel column to give the cross-coupled products, 1.77 g (90% yield); (**7b**):(**8b**) = 9:91, (**8bZ**):(**6bE**) = 55:45. The cross-coupled products were then separated by HPLC using hexane:ether (95:5), as eluent.

8,12-Dimethyl-2,2-ethylenedioxyl-5-isopropenyltridecane (7b).- R_f = 0.24 (hexane-ethyl acetate, 97:3); IR (neat): 3100, 1640, 1460, 1380, 1060, 940, 885, 860 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$): δ 0.90 (d, J = 7Hz, 9H, CH_3), 1.00-1.70 (m, 16H, CH_2 and CH), 1.30 (s, 3H, CH_3), 1.56 (s, 3H, $CH_3C=C$), 1.80-2.10 (m, lH, CH), 3.90 (m, 4H, OCH_2CH_2O), 4.65 (s, lH, CH=C), 4.74 (s, lH, CH=C); EI-MS (70eV), m/z (rel. int., %), 310 (M^+, 0.5), 295 (1), 248 (5), 135 (2), 123(12), 107(13), 99(10), 87(100), 53(100).

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.36; H, 12.34. Found: C, 77.25; H, 12.13

(Z)-2,2-Ethylenedioxy-6,10,14-trimethyl-5-pentadecene (8bZ).- R_f = 0.29 (hexane-ethyl acetate, 97:3); IR (neat): 3100, 1460, 1380, 1320, 1135, 1060, 940, 860 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$): δ 0. 90 (d, J = 7Hz, 9H, CH_3), 1.00-1.70 (m, 14H, CH_2 and CH), 1.30 (s, 3H, CH_3), 1.65 (s, 3H, $CH_3C=C$), 1.80-2.20 (m, 4H, CH_2), 3.90 (m, 4H, OCH_2CH_2O), 5.11 (t, J = 7Hz, 1H, CH=C, 11% NOE enhancement, irradiated at 1.65 ppm); EI-MS (70eV): m/z (rel. int., %) 310 (M^+, 2), 248 (2), 208 (2), 179 (2), 155 (10), 139 (6), 108 (7), 87 (100), 71 (11), 56 (25).

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.36; H, 12.34. Found: C, 77.18; H, 12.15

(E)-2,2-Ethylenedioxy-6,10,14-trimethyl-5-pentadecene (8bE).- R_f = 0.27 (hexane-ethyl acetate, 97:3); IR (neat):3100, 1460, 1380, 1320, 1135, 1060, 940, 860 cm^{-1}; ^1H NMR (270MHz,$CDCl_3$): δ 0.90 (d, J = 7Hz, 9H, CH_3), 1.00-1.70 (m, 14H, CH_2 and CH), 1.30 (s, 3H, CH_3), 1.59 (s, 3H, $CH_3C=C$), 1.80-2.20 (m, 4H, $CH_2C=C$), 3.90 (m, 4H, OCH_2CH_2O), 5.11 (t, J = 7Hz, 1H, CH=C, 0% NOE, irradiated at 1.59 ppm); EI-MS (70eV): m/z (rel. int., %) 310 (M^+, 7), 295 (11), 248 (8), 208 (2), 163 (5), 155 (42), 138 (6), 123 (17), 111 (20), 95(33), 87 (100), 81 (38), 69 (38), 56 (45).

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.36; H, 12.34. Found: C, 77.30; H, 12.07

Similar treatment of allylic chloride **4** with isopentylmagnesium bromide (**6a**) in the presence of copper(I) chloride in THF gave α-(**7a**) and γ-cross-coupling products (**8a**) in 90% yield. This isomer mixture is separated by HPLC to give the α-(**7a**), (Z) -γ-(**8aZ**) and (E) -γ-(**8aE**) isomers in ratio of α:γ = 10:90 and E/Z = 51/49, respectively.

2,2-Ethylenedioxy-5-isopropenyl-8-methylnonane (7a).- R_f = 0.31 (hexane-ethyl acetate, 95:5); IR (neat): 3100, 1646 1460, 1380, 1060, 940, 885, 860 cm^{-1}; ^{1}H NMR (270MHz, $CDCl_3$): δ 0.90 (d, *J* = 7Hz, 6H, CH_3), 1.00-1.70 (m, 9H, CH_2 and CH), 1.30 (s, 3H, CH_3), 1.58 (s, 3H, CH_3C=C), 1.80-2.10 (m, 1H, CH), 3.90 (m, 4H, OCH_2CH_2O), 4.65 (s, lH, CH=C), 4.74 (s, lH, CH=C); EI-MS (70eV): m/z (rel. int., %) 240 (M^+,l), 225 (21), 197 (3), 178 (28), 163 (7), 155 (7), 135 (5), 122 (33), 115 (20), 107 (42), 99 (97), 93 (27), 87 (100), 69 (52), 58 (32).

Anal. Calcd. for $C_{15}H_{28}O_2$: C,74.95; H, 11.74. Found: C, 74.88; H, 11.57

(Z)-5,10-Dimethyl-2,2-ethylenedioxy-5-undecene (8aZ).- R_f = 0.35 (hexane-ethyl acetate, 95:5); IR (neat): 3100, 1465, 1380, 1320, 1135, 1060, 940, 860 cm^{-1}; ^{1}H NMR (270MHz, $CDCl_3$): δ 0.90 (d, *J* = 7Hz ,6H, CH_3), 1.00-1.70 (m, 7H, CH_2 and CH), 1.30 (s, 3H, CH_3C=C), 1.67 (s, 3H, CH_3C=C), 1.80-2.20 (m, 4H, CH_2C=CCH_2), 3.90 (m, 4H, OCH_2CH_2O), 5.11 (t, *J* = 7Hz, 1H, CH=C. 9.8% NOE enhancement, irradiated at 1.67 ppm); EI-MS (70eV): m/z (rel. int.,%) 240 (M^+, 1), 225 (3), 205 (4), 178 (6), 163 (4), 155 (10), 138 (6), 123 (9), 109 (39), 95 (31), 87 (100), 82 (27), 69 (37), 54 (43).

Anal. Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.73; H, 11.52

(E)-5,10-Dimethyl-2,2-ethylenedioxy-5-undecene (8aE).- R_f = 0.32 (hexane-ethyl acetaide, 95:5); IR (neat): 3100, 1465, 1386 1320, 1135, 1060, 940, 860 cm^{-1}; ^{1}H NMR (270MHz, $CDCl_3$): δ 0.90 (d, *J* = 7Hz, 6H, CH_3), 1.00-1.70 (m, 7H, CH_2 and CH), 1.30 (s, 3H, CH_3C=C), 1.59 (s, 3H, CH_3C=C), 1.80-2.20 (m, 4H, CH_2C=CCH_2), 3.90 (m, 4H, OCH_2CH_2O), 5.11 (t, *J* = 7Hz, lH, CH=C, NOE 0.1%, irradiated at 1.59 ppm); EI-MS (70eV): m/z (rel. int., %) 240 (M^+, l), 225 (3), 205 (4), 178 (6), 163 (4), 155 (10), 138 (6), 123 (9), 109 (39), 95 (31), 87 (100), 82 (27), 69 (37), 54 (43).

Anal. Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.80; H, 11.49

2,2-Ethylenedioxy-6,10,14-trimethylpentadecane (9a).- A mixture of compounds (**8b**) (0.37 g, 1.2 mmol) in ethyl acetate (20 mL), and in the presence of 5% Pd/C 50 mg was hydrogenated under atmospheric pressure of hydrogen at room temperature for 5 hrs. After filtration of the catalyst through celite and evaporation of solvent, a crude product was obtained. The product was chromatographed on silica gel with hexane-ethyl acetate (97:3) to gave compound (**9a**) as a colorless oil 0.34 g (92% yield), bp. 152-154°/16 Torr, R_f = 0.27 (hexane-ethyl acetate 97:3); IR (neat): 1460, 1380, 1260, 1220, 1070, 940 cm^{-1}; ^{1}H NMR (90MHz, CCl_4): δ 0.9 (d, *J* = 7Hz, 9H, CH_3), 1.0-1.7 (m, 14H, CH_2 and CH), 1.3 (s, 3H, CH_3), 3.8 (br.s, 4H, OCH_2CH_2O); EI-MS (70eV): m/z (rel. int., %) 297 (M^+-CH_3, 100), 198 (2), 180 (5), 165 (5), 115 (5), 109 (22), 99 (21), 87 (100), 83 (42), 69 (38), 56 (36), 51 (67).

Anal. Calcd. for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90. Found: C, 76.72; H, 12.71

6,10,14-Trimethyl-2-pentadecanone (phytone) (9b).- Compound (**9a**) (0.30 g, 0.96 mmol) was added to 5% H_2SO_4 (10 mL) and the mixture was stirred in acetone (10 mL) for 10 hrs at room temperature. The mixture was extracted with methylene dichloride. The extract was washed with water, dried (K_2CO_3), and concentrated to give compound (**9b**) in 0.22 g (85% yield). The compound

(**9b**) was purified by column chromatography on silica gel. bp. 151-153°/3 Torr (Lit.[7] bp. 150-152°/3 Torr), R_f = 0.26 (hexane-ethyl acetate, 97:3). IR and ^{1}H NMR spectroscopic data were identical with those of the reported ones.[15]

(Z)- and (E)-6,10,14-Trimethyl-5-pentadecen-2-one (**10**) were obtained from compounds (**8**) with 5% H_2SO_4 in the same procedure in 80% yield, bp. 183-187°/16 Torr. A GLC analysis with capillary column (OV-1, 25 m) showed two peaks in the ratio of 9/91 corresponding to Z and E isomer, respectively. The product is purified by HPLC using hexane-EtOAc (20:1) as eluent to give compounds (**10Z**) and (**10E**), respectively.

Anal. Calcd. for $C_{18}H_{34}O$: C,81.13; H, 12.86. Found: C, 81.02; H, 12.95

(Z)-6,10,14-Trimethyl-5-pentadecen-2-one (10Z).- IR (neat): 1730, 1460, 1380, 1170 cm^{-1}; ^{1}H NMR (270MHz, $CDCl_3$): δ 0.90 (d, *J* = 7Hz, 9H, CH_3), 1.00-1.70 (m, 12H, CH_2 and CH), 1.66 (s, 3H, Z-$\underline{CH_3}$C=CCH), 1.80-2.20 (m, 4H, CH_2C=C), 2.10 (s, 3H, CH_3CO), 2.40 (t, *J* = 7Hz, 2H, CH_2CO), 5.05 (t, *J* = 7Hz, lH, CH=C); EI-MS (70eV) : m/z (rel. int., %) 266 (M^+, 16), 284 (8), 208 (8), 153 (17), 138 (19), 123 (58), 111 (57), 95 (86), 69 (83), 56 (87), 51 (100).

(E)-6,10,14-Trimethyl-5-pentadecen-2-one (10E).- IR (neat): 1730, 1460, 1380, 1170 cm^{-1}; ^{1}H NMR (270MHz, $CDCl_3$): δ 0.90 (d, *J* = 7Hz, 9H, CH_3), 1.00-1.70 (m, 12H, CH_2 and CH), 1.59 (s, 3H, E-$\underline{CH_3}$C=CCH), 1.80-2.20 (m, 4H, CH_2C=C), 2.10 (s, 3H, CH_3CO), 2.40 (t, *J* = 7Hz, 2H, CH_2CO), 5.05 (t, *J* = 7Hz, lH ,CH=C); EI-MS (70eV) : m/z (rel. int., %) 266 (M^+, 12), 284 (6), 153 (16), 138 (18), 123 (64), 111 (64), 95 (83), 69 (82), 56 (83), 51 (100).

The ketones (**10**) were hydrogenated over Pd/C at hydrogen to give practically pure compound **9b** in 90% yield. The IR and NMR spectra of (**9b**) were in agreement with those of the reported values.[15]

3,7,11,15-Tetramethyl-l-hexadecen-3-ol (Isophytol) (1).- The ketone (**9b**) (1.0 g,18 mmol) was alkylated with vinylmagnesium chloride (20 mmol) in THF and hydrolyzed with NH_4Cl aq. solution. Isophytol (**1**) was obtained in 85% yield, bp. 179-180°/3 Torr, lit.[13] bp. 178-180°/7-8 Torr. The spectral data[13,15] were fully consistent with those of the authentic samples.

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