Synthesis of Compounds containing the Isoprene Unit. A New Stereoselective Synthesis of All-*trans* Vitamin A and of Methyl (2*E*,4*E*)-3,7,11-Trimethyldodeca-2,4-dienoate

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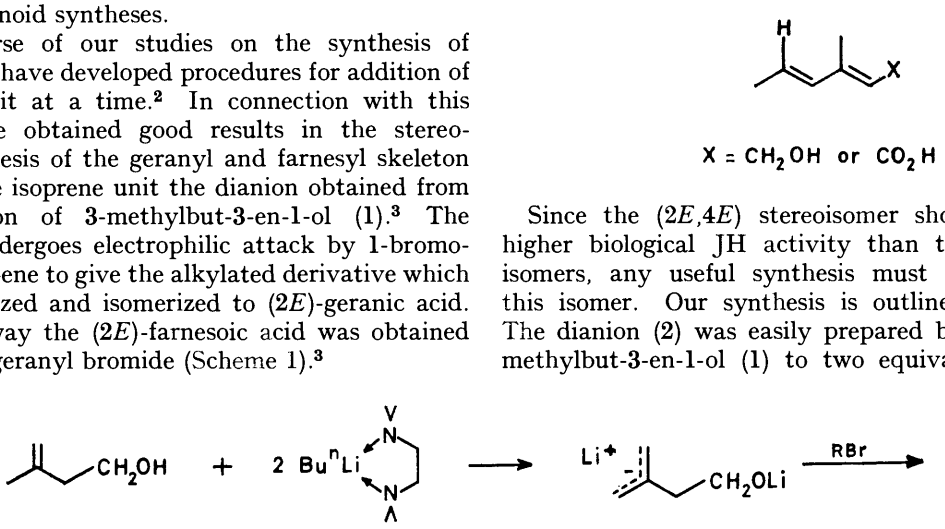
Methyl (2*E*,4*E*)-3,7,11-trimethyldodeca-2,4-dienoate (8b), a potent insect growth regulator, is synthesized from the dianion of 3-methylbut-3-en-1-ol (2) and tetrahydrocitral (3). Elimination of acetic acid to (8b) in (2*E*,4*E*) configuration is achieved by treatment of the intermediate acetoxy-ester (7b) with a base (NaH, KH, or Bu^{t}OK) in the presence of a catalytic amount of crown ether in hexane. Following the same scheme, a new synthesis of Vitamin A *via* all-*trans* retinal is achieved.

In recent years several new syntheses of all-*trans* vitamin A have been reported in the literature due to the nutritional and commercial importance of this substance.[1] On the other hand the use of insect growth regulators with JH activity has considerably stimulated the search for poly-isoprenoid syntheses.

In the course of our studies on the synthesis of terpenoids, we have developed procedures for addition of one prenyl unit at a time.[2] In connection with this work we have obtained good results in the stereoselective synthesis of the geranyl and farnesyl skeleton utilizing as the isoprene unit the dianion obtained from the metallation of 3-methylbut-3-en-1-ol (1).[3] The dianion (2) undergoes electrophilic attack by 1-bromo-3-methylbut-2-ene to give the alkylated derivative which has been oxidized and isomerized to (2*E*)-geranic acid. In the same way the (2*E*)-farnesoic acid was obtained starting from geranyl bromide (Scheme 1).[3]



SCHEME 1

We wish now to report the extension of this reaction to aldehydes with the aim of using our prenylating agent for a new stereoselective synthesis of all-*trans* vitamin A and of the powerful synthetic insect growth regulator Altozar.[4]

This new reaction allows the introduction, through a small number of facile steps, of a conjugate diene with a (2*E*,4*E*) configuration. This kind of sequence is present in ethyl (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienoate, a potent insect growth regulator, with juvenile hormone activity.

X = CH_2OH or CO_2H

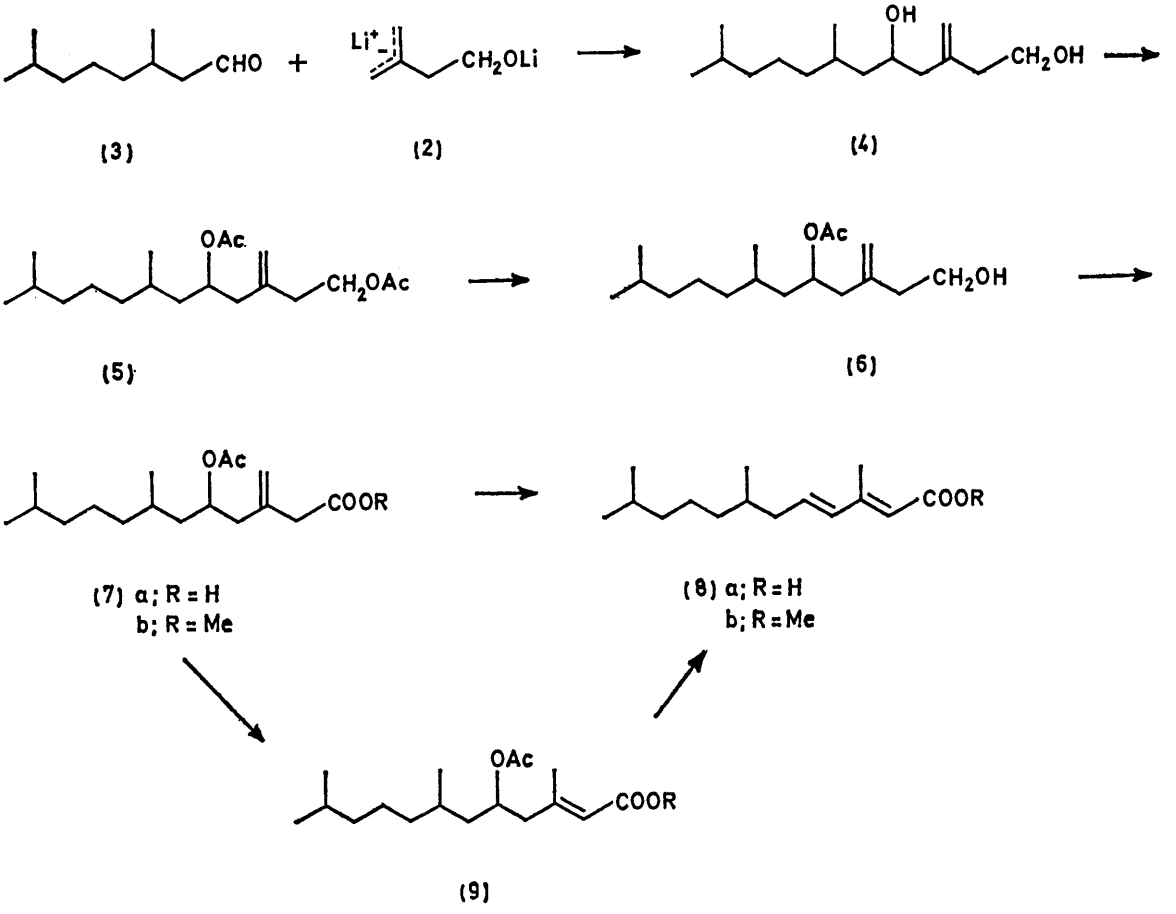
Since the (2*E*,4*E*) stereoisomer shows considerably higher biological JH activity than the other stereoisomers, any useful synthesis must form principally this isomer. Our synthesis is outlined in Scheme 2. The dianion (2) was easily prepared by addition of 3-methylbut-3-en-1-ol (1) to two equivalents of Bu^{n}Li–TMEDA complex in hexane at room temperature with stirring overnight. To the orange precipitate, a solution of tetrahydrocitral (3) in tetrahydrofuran was added dropwise over 2 h at −78 °C. The reaction mixture was then stirred overnight and warmed to 0 °C. After the usual work-up, the diol was obtained pure in 60%

yield by chromatography on SiO_2, after elution with hexane–ethyl acetate.

The mass spectrum of (4) shows *m/e* 242 (M^+) and in the i.r. spectrum there appears a signal at 900 cm^{-1}, typical of a terminal double bond; the n.m.r. data are consistent with the proposed structure. Acetylation of (4) with pyridine and acetyl chloride in dry benzene at 0 °C affords the diacetate (5) in almost quantitative yield. Partial hydrolysis of the diacetate with Na_2CO_3 in dry ethanol under controlled conditions (monitored by g.l.c.) leads to the secondary monoacetate (6).

G.l.c. of the crude product shows 88% of monoacetate (6), 8% of the diol (4), and 4% of the diacetate (5); (6) is obtained pure in 84% yield by chromatography on SiO_2 with hexane–ethyl acetate as eluant. Oxidation of (6) with Jones reagent [5] in acetone at 0 °C gives the acid (7a) in 82% yield. Esterification of the acetoxy-acid (7a) with diazomethane affords the corresponding acetoxy ester (7b). The i.r. spectrum shows signals at 1 720 (CO) and 900 cm^{-1} (=CH_2). It is interesting to note that no trace of αβ-unsaturated ester is present (t.l.c., g.l.c.).

Of decisive importance in this synthesis is the elimination procedure of (7b) which has to give (8b) in high yield with a high preponderance of the all-*trans* isomer. As shown in the Table, the best results were obtained with hexane as solvent, and NaH, KH, or Bu^{t}OK as base at low temperature in the presence of a catalytic amount of dicyclohexyl-18-crown-6. A high yield of (8b) (95%) with the best *E* : *Z* ratio (92 : 8), was obtained when (7b) was treated at 0 °C with 2 equivalents of NaH and crown ether in hexane.



SCHEME 2

In the absence of crown ether at 0 °C for 2 h, the con-

TABLE

Basic treatment of the acetoxy-ester (7b)

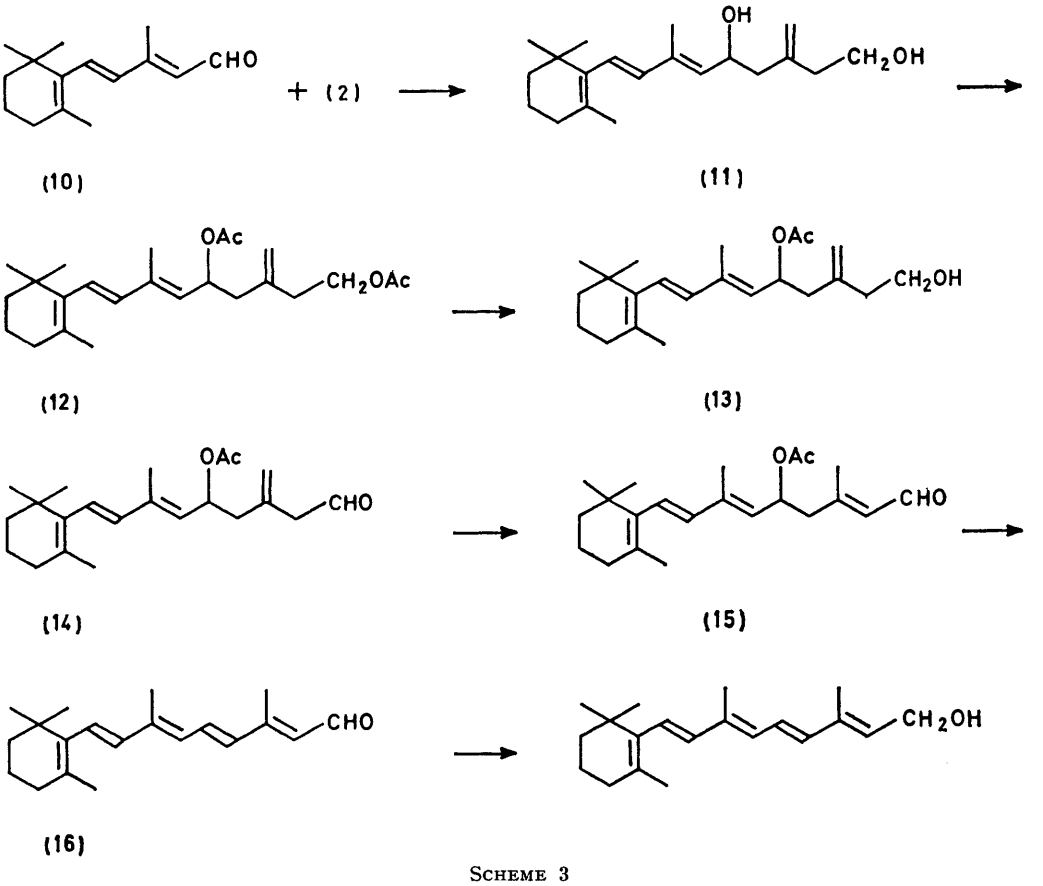
Base [a]	Solvent	*T* (°C)	Time/h	Ratio of isomers for (8b) (2*E*,4*E*) : (2*Z*,4*E*) [c]	Yield of (8b) (%) [d]	Yield of (9) (%)
NaH	THF	0	2			98
NaH	THF	25	7	60 : 40	95 [e]	
NaH [b]	Hexane	0	0.5	92 : 8	95	
KH [b]	Hexane	−20	2	87 : 13	96	
KH [b]	Hexane	0	0.25	81 : 19	96	
KH [b]	Hexane	25	0.1	70 : 30	96	
KH	Hexane	0	2			96
Bu^{t}OK	THF	0	2			98
Bu^{t}OK	THF	25	7	67 : 33	93 [e]	
Bu^{t}OK [b]	Hexane	0	0.5	92 : 8	86	

[a] 2 Equiv. of base per equiv. of (7b). [b] In the presence of crown ether. [c] Determined by g.l.c. [d] The remainder was (9) and starting material. [e] Yield determined after esterification with CH_2N_2 of the crude material due to the occurence of 30% hydrolysis.

jugated methyl ester (9) with 2*E* configuration was isolated. At higher temperatures and longer reaction times, elimination occurs to afford (8b) with partial isomerization of the αβ double bond.

The experience achieved in the synthesis of methyl (2*E*,4*E*)-3,7,11-trimethyldodeca-2,4-dienoate (8b), led us to a new synthesis of vitamin A (Scheme 3).

The β-ionylideneacetaldehyde (10) was obtained from β-ionone and cyanoacetic acid, followed by reduction of the corresponding β-ionylideneacetonitrile with di-isobutyl aluminium hydride at −78 °C in heptane.[6] To the dilithium salt (2) the aldehyde (10) was added at −78 °C and the mixture was stirred overnight, then warmed to room temperature. After work-up the product was chromatographed on SiO_2 (hexane–ethyl acetate as eluant) to give the diol (11) in 53% yield.



SCHEME 3

Under the same conditions as for the preparation of (5), the expected diacetate (12) was obtained in a virtually quantitative yield. The saponification of (12), performed in dry ethanol and Na_2CO_3, gives a 'retro product,' identified on the basis of its u.v. spectrum.[1d] Therefore the saponification was carried out under controlled conditions with an equivalent amount of *N*-benzyltrimethylammonium methoxide in methanol at 0 °C for 20 min.

The monoacetate (13) was recovered pure in 75% yield after chromatography on SiO_2 (hexane–ethyl acetate as eluant), the remainder being the diol (11). Treatment of (13) with CrO_3–pyridine complex[7] in methylene chloride at 0 °C affords the acetoxy-aldehyde (14) in very good yield, the i.r. [1 730 ($COCH_3$; CHO) and 900 cm^{-1} (=CH_2)] and n.m.r. [δ 5 (=CH_2)] data being in agreement with this structure. Treatment of (14) with Bu^tOK in THF at 0 °C for 10 min gave after preparative t.l.c. the αβ-unsaturated aldehyde (15) [$\nu_{max.}$ 1 730 ($COCH_3$) and 1 680 cm^{-1} (CHO)].

If this basic treatment was prolonged for more than 10 min, aldehyde (14) gives the all-*trans* retinal (16), through isomerization of the external double bond and elimination of the acetoxy-group. The n.m.r. and u.v. spectra of (16) were identical with the data reported in the literature.[8] All-*trans* vitamin A was then obtained by reduction of the retinal with sodium borohydride in methanol and identified by comparison with authentic material.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 710B spectrometer, n.m.r. spectra on an R12B Perkin-Elmer instrument with Me_4Si as internal standard, and mass spectra on a Hitachi–Perkin-Elmer RMU6D (single focus) spectrometer at 60 eV. T.l.c. was performed on silica gel HF_{254} (Merck) and column chromatography on silica gel 0.05—0.20 mesh (Merck). Gas–liquid chromatographic analyses were performed on a model 5750 G Hewlett–

Packard instrument equipped with flame-ionization detectors.

THF was obtained dry and oxygen-free by distillation over sodium benzophenoneketyl under argon. TMEDA was distilled from calcium hydride and stored over molecular sieves. n-Butyl-lithium [Roth (Karlsruhe)] was a 2.2M-solution in n-heptane. Hexane was obtained dry and oxygen-free by distillation over sodium under argon.

Dilithium Salt of 3-*Methylbut*-3-*en*-1-*ol* (2).—To a solution of TMEDA (13.9 g, 120 mmol) and 2M-Bu^{n}Li (60 ml, 120 mmol) in hexane (30 ml), was added dropwise a solution of (1) (5.2 g, 60 mmol) in hexane (20 ml) at 0 °C and the mixture stirred overnight. The insoluble dianion was then ready for further reaction.

7,11-*Dimethyl*-3-*methylenedodecane*-1,5-*diol* (4).—To a suspension of the dianion (2) (60 mmol) was added at −78 °C, the tetrahydrocitral (3) (9.36 g, 60 mmol) in hexane–THF (2.5 : 1) (35 ml). The suspension was stirred for 3 h, warmed to room temperature, and stirred overnight. The mixture was then diluted with water, acidified with 2N-HCl, and extracted with ether. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on silica gel [hexane–ethyl acetate (6 : 4) as eluant] to yield the diol (4) (8.98 g, 62%) as an oil, $\nu_{max.}$ (neat) 3 420 (OH) and 900 cm^{-1} (=CH_2); δ($CDCl_3$) 0.9 (9 H, d, *J* 6 Hz, CH(CH_3)$_2$, 1—1.6 (CH_2), 2—2.5 (4 H, m, CH_2), 3.2 (2 × OH), 3.75 (2 H, t, *J* 7 Hz, CH_2OH; m, CHOH), and 5 (=CH_2); *m/e* 242 (M^+), 224, 157, and 139.

7,11-*Dimethyl* 3-*Methylenedodecane*-1,5-*diacetate* (5).—The diol (4) (2.4 g, 10 mmol) was dissolved in dry benzene–pyridine (1 : 1) (30 ml) and CH_3COCl (2.00 g, 25 mmol) in dry benzene (15 ml) was added at 0 °C with stirring. After 3 h the mixture was diluted with water, acidified with 2N-HCl, and extracted with ether. The organic layer was evaporated *in vacuo*, to give the diacetate (5) (3.1 g, 95%) as an oil, $\nu_{max.}$ (neat) 1 720 (C=O) and 900 cm^{-1} (=CH_2); δ($CDCl_3$) 0.9 (9 H, d, *J* 6 Hz), 1.1—1.7 (CH_2), 2 (s, CH_3CO), 2.2—2.5 (m, CH_2), 4.25 (t, *J* 7 Hz, CH_2O), 4.9 (=CH_2), and 5.15 (m, CHOAc); *m/e* 326 (M^+), 267, and 208.

5-*Acetoxy*-7,11-*dimethyl*-3-*methylenedodecan*-1-*ol* (6).—Na_2CO_3 (650 mg) was added to the diacetate (5) (1.9 g, 6 mmol) in dry ethanol (20 ml) and the mixture refluxed for 8 h under argon until reaction was complete (g.l.c.). The mixture was then poured into ice–water and extracted with ether. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. Pure monoacetate (6) (1.4 g, 82%) was obtained by chromatography of the residue on silica gel [hexane–ether (80 : 20) as eluant], $\nu_{max.}$ (neat) 3 450 (OH), 1 720 (C=O), and 900 cm^{-1} (=CH_2); δ($CDCl_3$) 0.9 (d, *J* 6 Hz, CH_3), 1—1.6 (CH_2), 2 (s, CH_3CO), 2—2.5 (4 H, m, CH_2), 3.1 (OH), 3.65 (t, *J* 7 Hz, CH_2OH), 4.85 (=CH_2), and 5.15 (m, CHOAc); *m/e* 284 (M^+).

Methyl 5-*Acetoxy*-7,11-*dimethyl*-3-*methylendodecanoate* (7b).—To a solution of (6) (2.8 g, 10 mmol) in acetone (40 ml) distilled over potassium permanganate, Jones reagent [5] was added dropwise until an orange-brown colour persisted. After the usual work-up, the monoacetate (7a) (2.4 g, 85%) was recovered and esterified with diazomethane to give the *diester* (7b) in quantitative yield, $\nu_{max.}$ (neat) 1 720 (CO) and 900 cm^{-1} (=CH_2); δ(CCl_4) 0.9 (d, *J* 6 Hz, CH_3), 1—1.6 (m, CH_2), 2 (CH_3CO), 2.3 (2 H), 3.05 (s, $CH_2CO_2CH_3$), 3.65 (3 H, s, OCH_3), 4.95 (CH_2=), 5.15 (m, AcOCH) (Found: C, 69.2; H, 10.2. $C_{18}H_{32}O_4$ requires C, 69.2; H, 10.3%).

Methyl (2E,4E)-3,7,11-*Trimethyldodeca*-2,4-*dienoate* (8b).—To a suspension of NaH (or KH, Bu^{t}OK) (60 mg; 80% dispersion in oil; 2 mmol) and dicyclohexyl-18-crown-6 (60 mg, 0.16 mmol) in hexane (7 ml), the diester (7b) (326 mg, 1 mmol) in hexane (4 ml) was added at 0 °C and stirred for 30 min. The mixture was then poured into ice–water and acidified with 2N-HCl. After extraction with ether the organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*, $\nu_{max.}$ (neat) 1 720 (C=O) and 1 640 cm^{-1} (C=C); δ(CCl_4) 0.9 (d, CH_3), 1—1.5 (CH_2), 2.26 (s, CH_3C=, *E*-isomer), 3.67 (s, OCH_3), 5.68 (1 H, s), 6.1 (2 H, br m) (Found: C, 76.2; H, 11.2. $C_{16}H_{28}O_2$ requires C, 76.1; H, 11.2%). Yields are reported in the Table.

Methyl (2Z,4E)-3,7,11-*Trimethyldodeca*-2 4-*dienoate*.—Following the preparation of (8b) but in the absence of crown ether at 25° for 7 h, a mixture of 2*E*- and 2*Z*-isomers was obtained. The 2*Z*-isomer was isolated by preparative t.l.c. (see Table), δ($CDCl_3$) 0.9 (d, CH_3), 2.03 (CH_3C=, *Z*-isomer), 3.73 (OCH_3), 5.63 (1 H, s), 6.17 (d of t, *J* 7, 16 Hz), 7.55 (d, *J* 16 Hz).

Methyl (2E)-3,7,11-*Trimethyl*-5-*acetoxydodec*-2-*enoate* (9).—To a suspension of NaH (60 mg; 80% dispersion in oil, 2 mmol), in dry THF (7 ml), the diester (7b) (326 mg, 1 mmol) in THF (4 ml), was added and stirred for 2 h at 0 °C. After the usual work-up, the ester (9) was obtained practically pure in 98% yield, $\nu_{max.}$ (neat) 1 730 ($OCOCH_3$), 1 720 (CO_2CH_3), and 1 640 cm^{-1} (C=C); δ($CDCl_3$) 0.9 (d, *J* 6 Hz, 3 × CH_3), 1—1.15 (CH_2), 2 (−$OCOCH_3$), 2.2 (s, CH_3-C=, 2*E*-isomer), 3.67 (s, OCH_3), 5.2 (m, CHOAc), and 5.66 (br s, =$CHCO_2CH_3$).

7-*Methyl*-3-*methylene*-9-(2,6,6-*trimethylcyclohex*-1-*en*-1-*yl*)-*nona*-(6E,8E)-*diene*-1,5-*diol* (11).—To the dianion (2) (15 mmol) was added (10) (15 mmol, 3.2 g), dissolved in dry THF (20 ml) at −78 °C. The mixture was stirred overnight, then poured into ice–water, acidified with 2N-HCl, and extracted with ether. The organic layer was dried and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel [hexane–ethyl acetate (70 : 30) as eluant] to afford the diol (11) (2.5 g, 55%), $\nu_{max.}$ (neat) 3 420 (OH) and 900 cm^{-1} (=CH_2); δ($CDCl_3$) 1 (d, 2 × CH_3), 1.5 (4 H, m, CH_3), 1.7 (s, CH_3), 1.9 (s, CH_3), 2.35 (4 H, d, t, CH_2C=), 2.7 (OH), 3.8 (t, CH_2OH), 4.8 (m, CHOH), 5 (=CH_2), 5.5 (CH=), and 6.1 (2 H, m).

7-*Methyl*-3-*methylene*-9-(2,6,6-*trimethylcyclohex*-1-*en*-1-*yl*)-*nona*-(6E,8E)-*diene* 1,5-*Diacetate* (12).—To a solution of (12) (3.04 g, 10 mmol) in benzene–pyridine (1 : 1; 34 ml), was added dropwise at 0 °C acetyl chloride (2 ml) in dry benzene (17 ml) and the mixture stirred for 3 h. The *diacetate*, obtained in quantitative yield, was purified by chromatography on silica gel [hexane–ether (90 : 10) as eluant], $\nu_{max.}$ (neat) 1 740 (C=O) and 900 cm^{-1} (=CH_2); δ(CCl_4) 1 (s, 2 × CH_3), 1.5 (m, CH_2), 1.7 (s, CH_3), 1.9 (s, CH_3), 2 (s, CH_3–CO), 2.4 (4 H, d, t, CH_2), 4.2 (t, *J* 7 Hz, CH_2OAc), 4.9 (s, =CH_2), 5.35 (d, CH=), 5.8 (m, CHOAc), 6.1 (2 H); *m/e* 388 (M^+), 374, 359, and 339 (Found: C, 74.5; H, 9.1. $C_{24}H_{36}O_4$ requires C, 74.2; H, 9.31%).

5-*Acetoxy*-7-*methyl*-3-*methylene*-9-(2,6,6-*trimethylcyclohex*-1-*en*-1-*yl*)*nona*-(6E,8E)-*dien*-1-*ol* (13).—To a solution of (12) (1.5 g, 3.86 mmol) in methanol was added dropwise a equimolar amount of benzyltrimethylammonium methoxide at 0 °C over 30 min. The mixture was diluted with water, extracted with ether, and the organic layer dried and evaporated *in vacuo*. The residue was chromatographed on silica gel [hexane–ethyl acetate (8 : 2) as eluant]. The monoacetate, obtained in 80% yield along with 20% of diol (11), showed $\nu_{max.}$ (neat) 3 450 (OH), 1 730 (C=O), and 900 cm^{-1} (=CH_2); δ($CDCl_3$) 1 (s, 2 × CH_3), 1.5 (m, CH_2),

1.7 (s, CH_3), 1.9 (s, CH_3) 2 (s, $OCOCH_3$), 2.3 (d t, CH_2C=), 2.7 (OH), 3.7 (t, *J* 7 Hz, CH_2OH), 4.9 (=CH_2), 5.35 (d, =*CH*-CHOAc), 5.8 (m, *CH*OAc), and 6.1 (2 H, m, CH=CH); *m/e* 346 (M^+), 286, and 271.

5-*Acetoxy*-7-*methyl*-3-*methylene*-9-(2,6,6-*trimethylcyclohex*-1-*en*-1-*yl*)*nona*-(6E,8E)-*dien*-1-*al* (14).—Chromium trioxide (1 g) was added to pyridine (1.5 ml) in CH_2Cl_2 (20 ml), and the mixture stirred for 20 min. To this mixture, (13) (600 mg, 1.7 mmol) in CH_2Cl_2 (5 ml) was added at room temperature. The reaction was stopped after 10 min. After usual work-up, the aldehyde (14) was recovered pure in 90% yield, $\nu_{max.}$ (neat) 1 730 (C=O) and 900 cm^{-1} (=CH_2); $\delta(CCl_4)$ 1 (s, 2 × CH_3), 1.5 (6 H, m, CH_2), 1.7 (s, CH_3), 1.9 (s, CH_3), 2 (s, $OCOCH_3$), 2.35 (d, $AcOCHCH_2C$=), 3.1 (m, =$CHCH_2$-CHO), 5 (br d, =CH_2), 5.35 (br d, =CH), 5.8 (m, *CH*OAc), 6.1 (m, CH=CH), and 9.7 (m, CHO); *m/e* 344 (M^+) and 284.

5-*Acetoxy*-3,7-*dimethyl*-9-(2,6,6-*trimethylcyclohex*-1-*en*-1-*yl*)*nona*-(2E,6E,8E)-*trien*-1-*al* (15).—To a solution of (15) (0.5 g) in THF (10 ml) was added with stirring at 0 °C a small amount of Bu^tOK (0.05 g). The mixture was diluted with water, extracted with ether, and the extract dried (Na_2SO_4). After evaporation, the residue was purified by preparative t.l.c. [hexane–ether (50 : 50) as eluant] to yield the aldehyde (15) (400 mg, 80%), $\nu_{max.}$ (neat) 1 730 ($COCH_3$) and 1 680 cm^{-1} (CHO); $\delta(CDCl_3)$ 1 (s, 2 × CH_3), 1.5 (6 H, CH_2), 1.7 (s, CH_3), 1.9 (s, CH_3), 2 (s, $OCOCH_3$), 2.2 (d, *J* 1 Hz, CH_3C=), 5.35 (br d, =*CH*CHOAc), 5.9 (m, *CH*OAc), 5.85 (d, *CH*CHO), 6.1 (2 H, br m, CH=CH), and 9.95 (m, CHO).

All-trans *Retinal* (16).—To a solution of (15) (1.03 g, 3 mmol) in THF (10 ml) under argon, was added at 0 °C Bu^tOK (3 mmol). The mixture was stirred until no starting material remained (*ca.* 30 min; t.l.c.). The mixture was diluted with water and extracted with ether. After evaporation, the residue was purified with preparative t.l.c. [hexane–ether (50 : 50) as eluant] to yield all-*trans* retinal (16) (720 mg, 84%), $\nu_{max.}$ (neat) 1 675 (CHO) and 1 630 cm^{-1} (C=C); $\delta(CCl_4)$ 1 (s, 2 × CH_3), 1.5 (m, 2 × CH_2), 1.7 (s, CH_3), 2 (s, CH_3), 2.31 (d, *J* 1 Hz, CH_3), 5.86 (d, *J* 7 Hz, =*CH*CHO), 6.62 (m, CH=), 6.25 (m, CH=CH), 6.25—6.5 (m, CH=), 6.83, 7.02, 7.07, and 7.26 (m, C*H*=), and 10.02 (d, *J* 7.5 Hz, CHO); $\lambda_{max.}$ (EtOH) 381 nm.

All-trans *Vitamin A*.—A solution of all-*trans* retinal (16) (570 mg, 2 mmol) in methanol (20 ml), was treated with $NaBH_4$ (200 mg) at 0 °C for 20 min. After the usual work-up, the residue was purified by preparative t.l.c. [hexane–ether (50 : 50) as eluant] to yield all-*trans* vitamin A alcohol (475 mg 80%), identified by comparison with an authentic sample, $\delta(CCl_4)$ 1 (s, 2 × CH_3), 1.5 (6 H, m, CH_2), 1.7 (s, CH_3), 1.85 (s, CH_3), 1.94 (s, CH_3), 4.20 (d, *J* 7 Hz, CH_2OH), 5.6 (t, *J* 6.5 Hz, $CHCH_2$), 5.9—6.07 (m, CH), 6.05—6.3 (m, CH), 6.07 (s, CH=CH), and 6.4—6.8 (m, CH); $\lambda_{max.}$ (EtOH) 325 nm (ε 45 000); *m/e* 286 (M^+), 268, 255, and 199.

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