59. A Stereospecific Synthesis of Vitamin A from 2,2,6-Trimethyl-cyclohexanone[1])

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Summary. An efficient synthesis of all-(*E*) vitamin A acetate from 2,2,6-trimethyl-cyclohexanone has been achieved *via* the intermediacy of 1-(9-acetoxy-3,7-dimethyl-nona-3,5,7-trien-1-ynyl)-2,2,6-trimethyl-cyclohexanol (**25**), readily prepared in high yield by allylic rearrangement of tertiary propenols with glacial acetic acid. The key step in the synthesis is the transformation of **25** to the unsaturated ketone **27** (9-acetoxy-3,7-dimethyl-1-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-3,5,7-trien-2-one) using a novel vanadium(V)-catalysed rearrangement reaction. The carbonyl in **27** affords the means for the essential isomerization of the adjacent double bond to the (*E*) isomer and the product is readily transformed into the polyene by reduction and elimination. An overall yield of 18–31% of vitamin A acetate from 2,2,6-trimethyl-cyclohexanone has been realized.

The synthesis of vitamin A (**1**) and its derivatives has been the subject of numerous investigations [1] since the structure elucidation of the vitamin by *Karrer* [2] in 1931. All of the synthetic routes which have achieved commercial prominence employ β-ionone as the common starting material, and there has been considerable recent effort at improved syntheses of β-ionone and its precursors [3]. Recent developments in the catalytic alkylation of phenols [4] and their conversion to cyclohexanones [5] encouraged us to investigate new routes to vitamin A utilizing 2,2,6-trimethyl-cyclohexanone (**2**) as a starting material. No study of this possibility has been published since the reports by *Heilbron et al.* [6] and *Attenburrow et al.* [7] in the 1950's.

In our approach (*Scheme 1*) it was considered to be essential to control the configuration about the 9,10 double bond (numbering of **1**) to produce the 9-(*E*) isomer and to effect any reductions with very high selectivity. We utilize a novel vanadium(V)-catalysed rearrangement of an ethynyl-substituted 2,2,6-trimethyl-cyclohexanol derivative (**3**) to produce an 8-oxo-compound (**4**). The carbonyl function is a convenient device for the important isomerization of the 9,10 double bond and is easily transformed into the polyene by reduction and dehydration. The rearrangement reaction, formally analogous to the *Meyer-Schuster* [8] reaction, is effected by tris(triarylsilyl)vanadate catalysts, discovered by *Pauling* [9] and improved by *Pauling et al.*

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[1]) Preliminary details presented at the 9th International Symposium on Chemistry of Natural Products, Ottawa, Canada, June 24–25, 1974.

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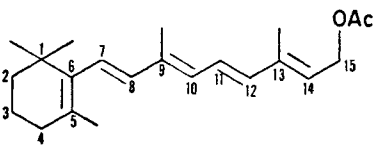
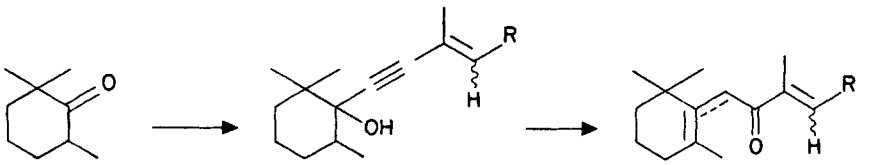
[10]. These catalysts were found to be particularly effective for the transformation of simple propynols into α,β-unsaturated carbonyl compounds in high yield [10] (*e.g.*

Scheme 1

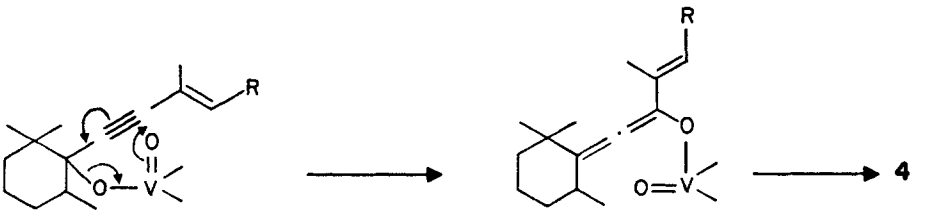


Vitamin A Acetate (**1**)



2 **3** **4**

dehydrolinalol → citral)[4]). We observed that the reaction of alkenyl, alkadienyl, and alkatrienyl substituted ethynyl-2,2,6-trimethyl-cyclohexanols (**3**) afforded good yields of the 8-oxo-compounds (numbering of **1**), primarily as the β,γ-unsaturated isomers **4**[5]). The reaction may be envisaged to proceed *via* a vanadate ester (**5**) which undergoes rearrangement to **6** and subsequent displacement-isomerization to afford the carbonyl compound.



5 **6**

At the outset it was established that the vanadate rearrangement[6]) afforded products not obtained under the usual *Meyer-Schuster* conditions [8] (formic acid). Thus reaction of 1-ethynyl-2,2,6-trimethyl-cyclohexanol (**7**) with formic acid af-

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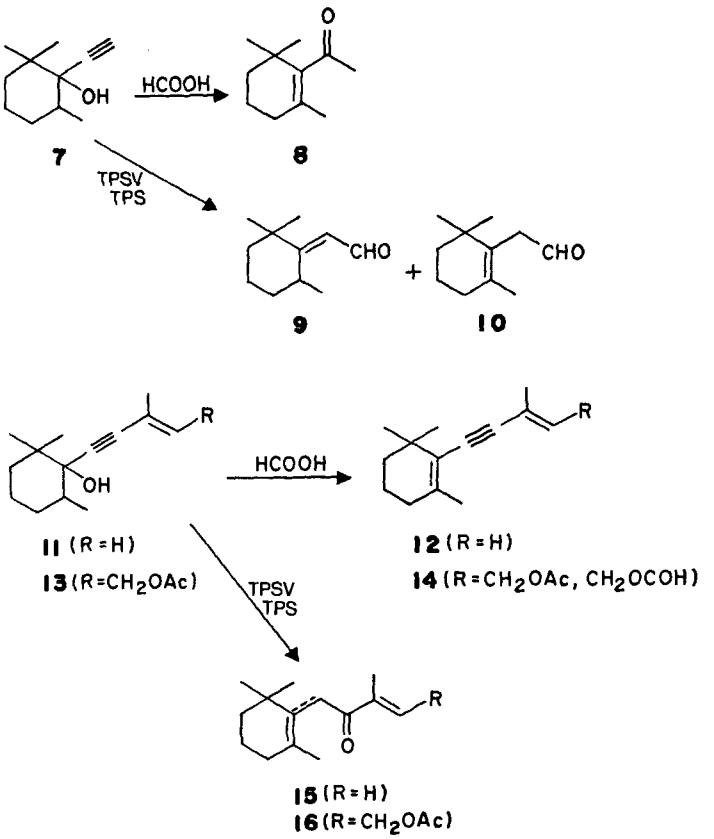
4) *Olson et al.* have studied this transformation in 17α-ethynyl-17β-hydroxy-steroids [11].

5) The conversion of dehydrolinalol to citral by trialkylorthovanadates has been reported [12]. These catalysts did not effect the desired transformations in the polyene systems, *e.g.* **3**, we studied.

6) The term vanadate rearrangement refers to the reaction of the propynol with a catalytic amount of a tris(triarylsilyl)vanadate generally in the presence of additional triarylsilanol as reported by *Pauling et al.* [10].

forded methyl 2,6,6-trimethyl-cyclohex-1-enyl ketone (**8**) [13] whereas **7** was converted to a mixture of the aldehydes **9** and **10** upon heating with tris(triphenylsilyl)vanadate/triphenylsilanol (TPSV/TPS) in mineral oil at 140° for 4 h. Treatment of the isopropenyl derivative **11** with formic acid (98–100%, two-phase system in hexane) gave no carbonyl products but afforded the dienyne **12** by dehydration in 76% yield (after distillation). Similarly its acetoxy derivative **13** was dehydrated smoothly to give **14** as a mixture of acetate and formate.

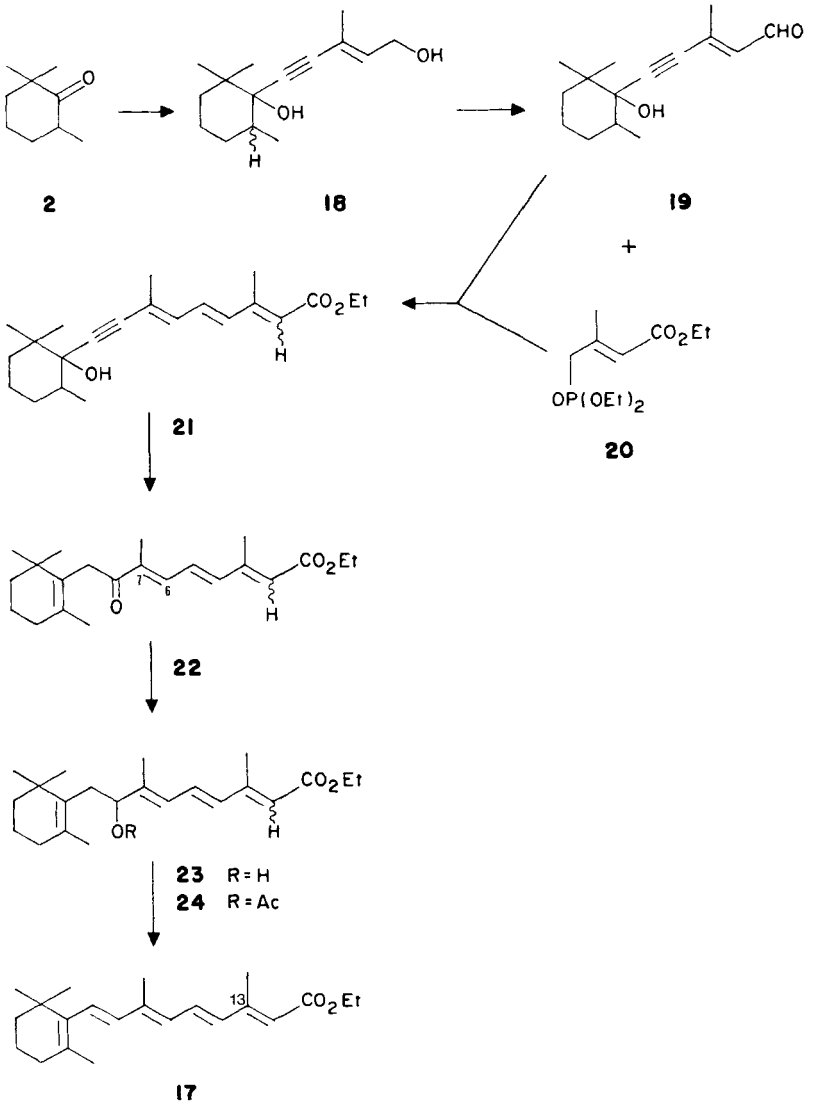
Reaction of alcohols **11** and **13** with TPSV/TPS in refluxing xylene afforded the ketones **15** and **16**, respectively, as mixtures of α,β- and β,γ-unsaturated isomers. By employing xylene instead of mineral oil [9] [10] these high-boiling products could be easily isolated by removal of the xylene and precipitation of the vanadate and silanol (suitable for re-use) upon dilution with hexane.



Synthesis of Vitamin A Acid Ethyl Ester. – The ethyl ester of vitamin A acid (**17**) was chosen for initial study because of its greater stability over vitamin A acetate. The synthesis of **17** is outlined in *Scheme 2*.

Addition of the *Grignard* reagent of (*E*)-3-methyl-pent-2-en-4-ynol [14] to 2,2,6-trimethyl-cyclohexanone[7]) (triMC), prepared from 2,6-dimethyl-phenol by reduction

Scheme 2



7) 2,2,6-Trimethyl-cyclohexanone (triMC) was prepared by the procedure of *Newman et al.* [15]. Thus alkylation of 2,6-dimethyl-cyclohexanone (diMC) with sodium amide and methyl iodide afforded a mixture of diMC (22%), triMC (66%) and 2,2,6,6-tetramethyl-cyclohexanone (tetraMC). The triMC was obtained in >98% purity by distillation at atmospheric pressure through a 1.2 m *Goodloe* column. The analogous reaction with methyl chloride afforded none of the tetraMC byproduct, but the conversion was only 11%. Further study of the alkylation with methyl chloride showed the expected increase in tetraMC as the conversion of diMC was increased.

and alkylation, afforded the diastereoisomeric diols **18** in 50% yield. The major, more polar isomer, m.p. 47–52°, was assigned the *cis*-configuration (equatorial C(6) methyl, equatorial OH) and the minor, less polar isomer, m.p. **53–57°**, the *trans*-configuration by analogy of their NMR. spectra to those of the major and minor 1-ethynyl-2,2,6-trimethyl-cyclohexanols[8]).

Oxidation of **18** with MnO_2 in methylene chloride afforded the (2*E*)-aldehyde **19** in 83–91% yield (crude) which was condensed with the senecioate **20** [18] (sodium hydride/THF) to afford the hydroxy ester **21** in 88% yield (chromatographed) from **18**. NMR. showed the product to be a mixture of all-(*E*) and (2*Z*,4*E*,6*E*) isomers. Vanadate rearrangement of **21** with TPSV/TPS in refluxing xylene for 3 h afforded ketoester **22** in 66% yield (chromatographed) as a mixture of all-(*E*) and (2*Z*,4*E*,6*E*) isomers. The NMR. spectrum of **22** exhibited a singlet for the C(9) methylene protons at 3.49 ppm which was characteristic (*vide infra*) of a (6*E*) configuration. Under these reaction conditions, none of the α,β-unsaturated ketone observed in the lower homologs **15** and **16** was detected.

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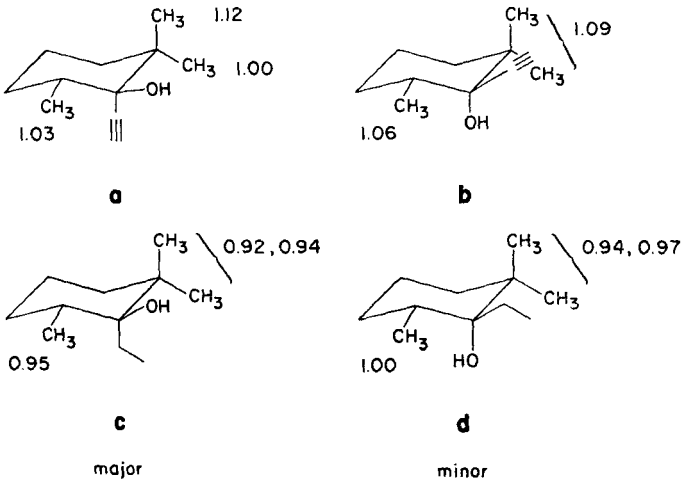
[8]) The NMR. assignments to the H-atoms of the major (85%), more polar, and minor (15%), less polar 1-ethynyl- and derived (H_2/Pd, EtOH) 1-ethyl-2,2,6-trimethyl-cyclohexanol are as shown.



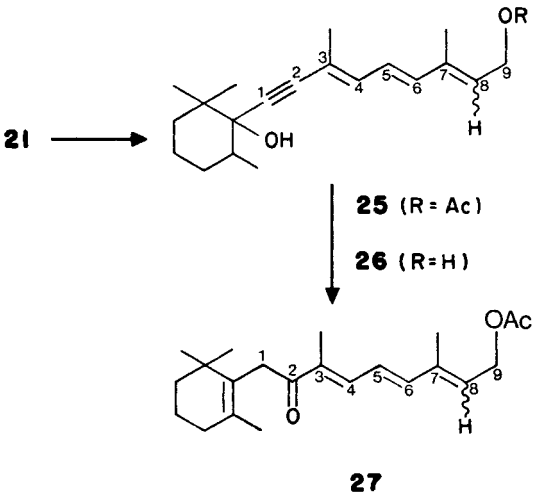
In **a** and **c** the C(1) hydroxyl, C(1) ethynyl, axial C(2) methyl and C(6) methyl groups bear a *gauche* relationship to one another and as expected the methyl groups have similar chemical shifts. In **b** and **d** the hydroxyl is seen to have a weak shielding effect on the axial C(2) methyl group. In the major ethynyl isomer **a** the axial C(2) methyl group is substantially deshielded relative to the equatorial methyl groups whereas in the minor ethynyl isomer **b** in which the ethynyl group bears a *gauche* relationship to both the C(2) methyl groups they have the same chemical shift. These data, together with the observations that acetylide generally prefers axial attack [16] on cyclohexanones and that the minor ethynyl isomer **b** dehydrates in high yield [17] whereas the mixture (80% **a**) dehydrates in low yield [7] support structure **a** with equatorial hydroxyl group for the major product.

In all of the addition reactions we examined, sodium, lithium, and *Grignard* salts of acetylenes were found to preferentially afford major, more polar, and minor, less polar ethynyl alcohols having the same stereochemical relationships as the isomers of 1-ethynyl-2,2,6-trimethyl-cyclohexanol.

Reduction of **22** with sodium borohydride in ethanol afforded hydroxyester **23** in 79% yield (crude) which was acetylated with acetyl chloride in pyridine/methylene chloride to give the acetoxyester **24**. Treatment of crude **24** with 62% aqueous HBr [19] gave crude vitamin A acid ethyl ester (**17**). Chromatography afforded pure **17** as a mixture of the all-(*E*) and (7*E*,9*E*,11*E*,13*Z*) isomers in 18% overall yield from ketoester **22**.

Vitamin A Acetate. – *General Scheme.* Having demonstrated the viability of the synthetic route to vitamin A acid ester, our attention was focused on the acetoxy propynol **25** and its synthesis and conversion to vitamin A acetate. The vanadate rearrangement was first effected on **25** obtained by controlled reduction of the ethyl ester **21** (*Scheme 3*). Thus, **21** was reduced with lithium aluminium hydride at –70°

Scheme 3



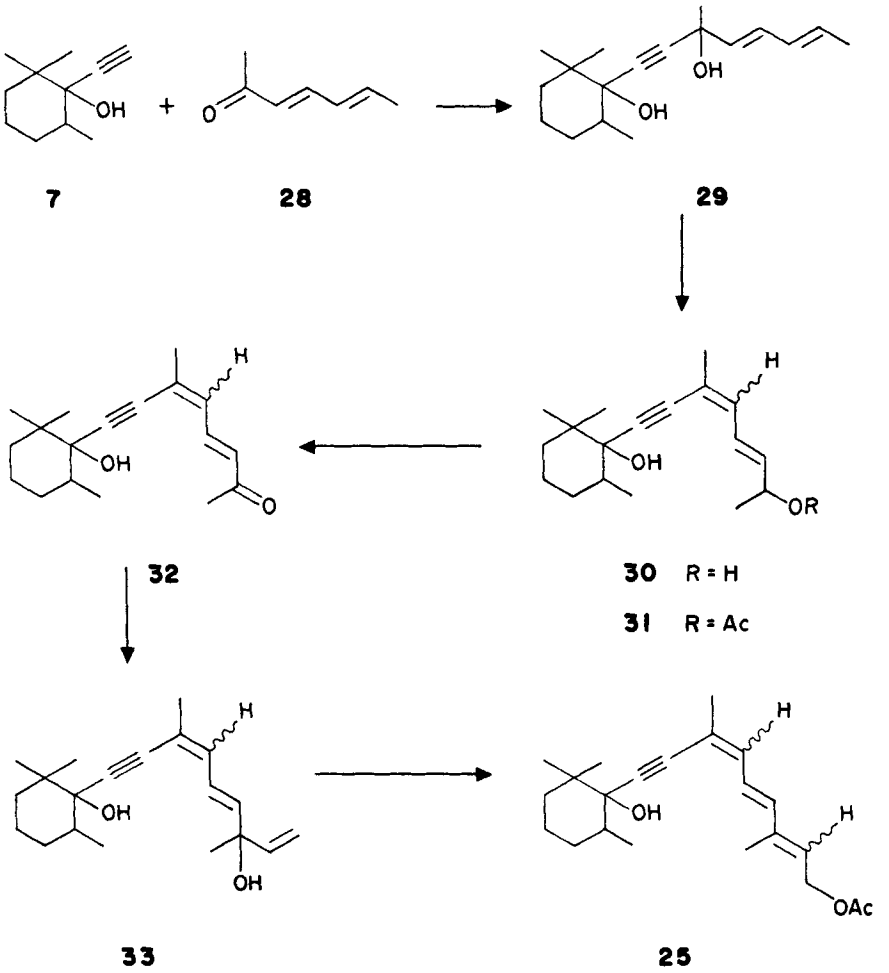
27

in ether (at 0 and 25° the 2,3 double bond was also reduced) to the crude diol **26** (87%). Acetylation afforded the all-(*E*) and (3*E*,5*E*,7*Z*) acetates **25** which could be purified (with some loss of the allylic acetate) on deactivated silica gel. The yield of pure **25** was 37% based on **21**. Vanadate rearrangement of this mixture gave acetoxyketone **27** in 96% yield (crude). Purification of **27** was accompanied by substantial decomposition, nevertheless it was isolated in 40% yield (UV. (2-propanol) λ_{max} = 313 nm (ε 26005)). In its NMR. spectrum, a two-proton singlet for the C(1) methylene protons was observed at 3.42 ppm.

Since our objective was to achieve a practical synthesis of vitamin A acetate using this novel rearrangement reaction, we directed our attention to considerations of the preparation of key intermediates and of yield improvements. Some of the chemistry of the *Heilbron* [6] and *Attenburrow* [7] groups was reinvestigated and led us to develop a highly efficient allylic rearrangement and to conclude that the *Heilbron-Attenburrow* approach afforded products having very high proportions of (9*Z*) isomers (numbering of **1**), a result which explains the low yields of all-(*E*) vitamin A obtained by these researchers.

Synthesis of Acetoxy Propynol **25**. Two basic schemes (*Schemes 4* and *5*) were investigated to prepare **25**. Addition of sodium acetylide to 2,2,6-trimethyl-cyclohexanone (**2**) afforded 1-ethynyl-2,2,6-trimethyl-cyclohexanol (**7**) in 98% yield and *Grignard* addition of **7** to hepta-3,5-dien-2-one (**28**) the known [7] diol **29** in 84–90% yield. Following the *Attenburrow* procedure, treatment of **29** with dilute aqueous hydrochloric acid in acetone gave the crude secondary alcohol **30** in 96% yield which was oxidized with MnO_2 to the crude hydroxyketone **32** in 95% yield. Reaction of **32** with vinylmagnesium chloride in THF afforded the diol **33** which was stable toward chromatography (Alumina III). Pure **33** was obtained in 49% overall yield from **7**. The reaction of diol **33** with glacial acetic acid in refluxing benzene effected a very clean (97% yield) allylic rearrangement to the acetoxy propynol **25** which was of suitable purity for further transformations without chromatography (the latter had been destructive in the preparation of the all-(*E*) and (3*E*,5*E*,7*Z*) acetates **25** by the ester route (*Scheme 3*).

Scheme 4



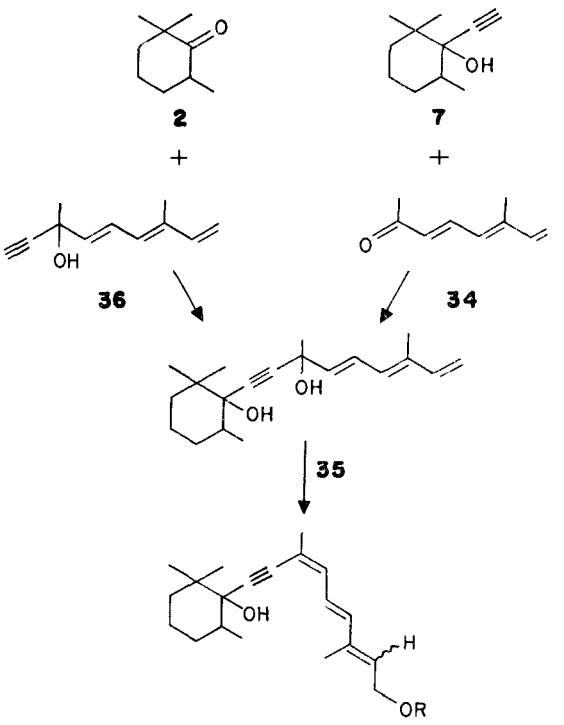
A second, highly efficient route (*Scheme 5*) was *via* the trienone **34**. *Grignard* addition of **7** to **34** afforded the known alka trienyl-diol **35** [7] in 97% yield after chromatography. Treatment of **35** with aqueous sulfuric acid by the *Attenburrow* procedure led to multiple allylic rearrangement to give the primary allylic alcohol **26** in 54–56% yield. Subsequent acetylation afforded 75–84% yields of crude acetate **25**. Reaction of **35** with glacial acetic acid in benzene directly afforded **25** in 81–91% yield and of better purity than the material prepared in the two step sequence.

Alternatively, ethynylmagnesium bromide was added to trienone **34** (53% yield) and the alcohol **36** was condensed with trimethyl-cyclohexanone to give diol **35** (75% yield).

For the three routes investigated to prepare the acetoxy propynol **25** the yields based on trimethyl-cyclohexanone were 49% (*Scheme 4*), 36% (*Scheme 5 via* **36**) and 87% (*Scheme 5 via* **34**).

Routes to Trienone **34**. The obvious advantage of the route based on the trienone **34** and 1-ethynyl-2,2,6-trimethyl-cyclohexanol (**7**) led us to re-examine the possible syntheses of **34**. One route developed by *Heilbron* [20] and *Cheeseman et al.* [6] was based on the *Oppenauer* oxidation of dienol **37** with aluminium-*t*-butoxide in acetone,

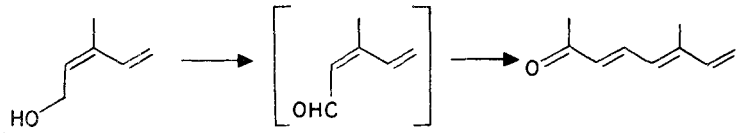
Scheme 5



25 R = Ac

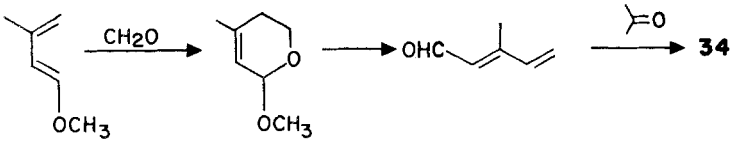
26 R = H

the intermediate aldehyde **38** condensing in an aldol reaction with acetone. The overall yield of trienone **34** based on dien-ol **37** was 30%.



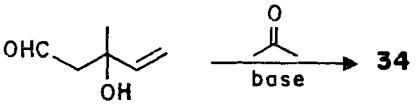
37 **38** **34**

An alternative synthesis of the unstable aldehyde **38** involves the acid-catalysed ring opening of the 2*H*-3,6-dihydropyran **39**, obtained by the *Diels-Alder* condensation of 1-methoxy-3-methyl-1,3-butadiene (**40**) with formaldehyde [21]. Thus **39** was treated with *p*-toluenesulfonic acid in benzene, and the solution of crude aldehyde **38** was added to acetone and sodium methoxide. Trienone **34** was obtained in 40% yield (chromatographed) based on **39**.



40 **39** **38**

Saito et al. [22] have reported in the patent literature a variation of the aldol condensation route in which the hydroxyaldehyde **41** (from the acetal of 3-oxo-butanal and vinylmagnesium bromide) is condensed with acetone and base to afford trienone **34** in high yield. This synthesis has not been checked by us.



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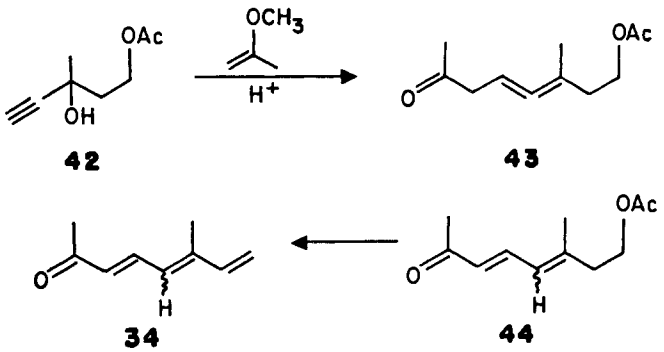
A third route (*Scheme 6*) was *via* the acetoxy propynol **42** (from 4-hydroxy-2-butanone and acetylide followed by acetylation). Thus reaction of **42** with 2-methoxypropene [21] afforded the acetoxy allenone **43** which was smoothly isomerized with triethylamine to the (5*Z*) acetoxydienone **44**. Treatment of the latter with *p*-toluenesulfonic acid in benzene gave the (5*E*) isomer. Reaction of **44** with tetraethylammonium acetate in refluxing acetone afforded trienone **34** in 55% yield from **44** and in 30% overall yield from **42** (chromatographed).

Vanadate Rearrangement. The acetoxy propynol **25** prepared by the routes outlined in *Schemes 4* and *5* was treated with TPSV/TPS in refluxing xylene in the same manner as was **25** prepared from the all-(*E*) ester route (*Scheme 3*). Surprisingly, the NMR. spectra revealed a significant difference between the products from **25** obtained by the routes involving allylic rearrangements (*Schemes 4* and *5*) and the products from **25** obtained by the ester route (*Scheme 3*). The vanadate rearrangement

Scheme 6

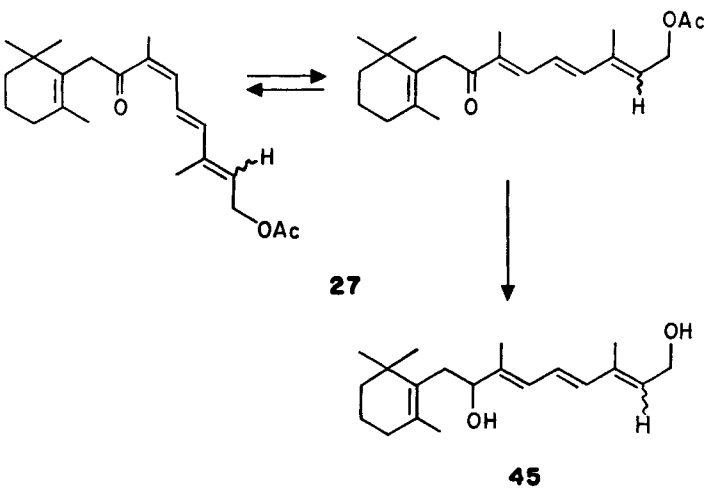


gave a ketone **27** which when derived from the diol **33** (*Scheme 4*) showed the C(1) methylene protons as two singlets at *ca.* 3.3 and 3.42 ppm in a 72:28 ratio and when derived from the diol **35** (*Scheme 5*) had the 3.3 ppm singlet prevailing to about 80%. The synthesis of **27** *via* the esters (*Scheme 3*) had been derived from a (3*E*)-precursor and had a singlet at 3.42 ppm. Thus the absorption at *ca.* 3.3 ppm is due to the (3*Z*) isomer.

Reaction of C_{18} ketone **32** with triethylphosphonoacetate afforded a C_{20} ethyl ester which upon vanadate rearrangement gave a ketoester. The resonances for its methylene protons were observed at *ca.* 3.30 (~76%) and *ca.* 3.46 ppm (~24%). Only the latter band had been observed in the rearrangement product **22** of the (6*E*) ester **21** (*Scheme 2*).

It was therefore evident that the allylic rearrangements outlined in *Scheme 4* and *5* had afforded predominantly (3*Z*) configurations of the acetoxy propynol **25**[9]).

Isomerization of (3Z) Acetoxyketone **27**. The carbonyl group at C(2) of **27** afforded the means for isomerization of the adjacent double bond. Basic and acidic treatments



[9]) In the publications by *Heilbron* [6] and *Attenburrow* [7] such rearrangements had been critical steps toward synthesizing vitamin A. It is therefore not surprising that low yields of all-(*E*) vitamin A were obtained in the early studies.

were examined, and the progress of the reactions was monitored by NMR. integration of the C(1) methylene protons. In pyridine, the thermodynamic equilibrium was found to be (3*E*):(3*Z*) = 7:3 using as starting material pure (3*E*) or mainly (3*Z*) acetoxyketone. The results of an isomerization study are given in Table 1.

Table 1. *Isomerization of Acetoxyketone* **27**

Catalyst	Solvent	Temperature	Time (h)	% (3*E*) Isomer[a]
None	–	–	–	28 (starting material)
Bu_4N^+OAc	Et_2CO	reflux	*20*	*33*
Dabco[b]	Et_2CO	reflux	5	33
Pyridine	–	reflux	96	68 (68 from (3*E*) starting material)
HOAc	HOAc	65°	21	64
Piperidine	Toluene	reflux	8	90
Piperidinium Acetate[c]	Toluene	reflux	9	95
Piperidinium Acetate[c]/ Piperidine 1:1	Toluene	reflux	8	95
Piperidinium Acetate[c]/ Acetic Acid 1:1	Toluene	reflux	8	70

[a] By NMR. integration of the C(1) methylene resonances at 3.28 (3*Z*) and 3.42 ppm (3*E*).
[b] 1,4-Diazabicyclo[2.2.2]octane.
[c] Five-fold molar excess.

The reaction of the (3*Z*)/(3*E*) mixtures with piperidinium acetate was remarkably non-destructive toward the acetoxyketone **27**. It resulted in a net increase in the UV. extinction (the (*E*) would be expected to have a greater ε_{max} than the (*Z*) isomer by analogy to vitamin A isomers). The product could not be easily purified at this stage, and was therefore reduced with sodium borohydride or lithium aluminum hydride to the more stable diol **45**. The yield of isolated **45** based on the pure diols **33** and **35** were found to correlate very well with the estimated UV. purity of the crude vanadate rearrangement products. With TPSV/TPS under the standard conditions developed for the model compounds, this yield was found to be 50–54%.

Vanadate Rearrangement with Substituted Silanols (*Scheme 7*). Study of the vanadate rearrangement reaction using modified conditions and modified catalysts was undertaken to attempt to find milder rearrangement conditions and to increase the yield. *Pauling* [9] [10] and *Andrews* [10] had shown that decreasing the amount of added silanol increased the reaction rate, but at the expense of the catalysts life time[10]). Additionally, silanols substituted with electron withdrawing and releasing substituents had been prepared and rate enhancements had been observed in the dehydrolinalol → citral case with tris(*p*-trifluoromethyl)phenyl silanol.

We prepared in addition nitro substituted silanols and vanadates and found them to be very active but considerably less stable than triphenylsilanol-based catalysts. The influence of the variation of conditions on the yield of the rearrangement of **25**

[10] In some cases the amounts of the catalysts were quite high, but they could be recovered in a state suitable for many reaction cycles. In the dehydrolinalol → citral conversion, for example [9] [10], the same catalyst was used for over one hundred cycles without a substantial yield decrease.

Table 2. *Vanadate Rearrangement Reactions of* **25** *with Substituted Silanols*[a])

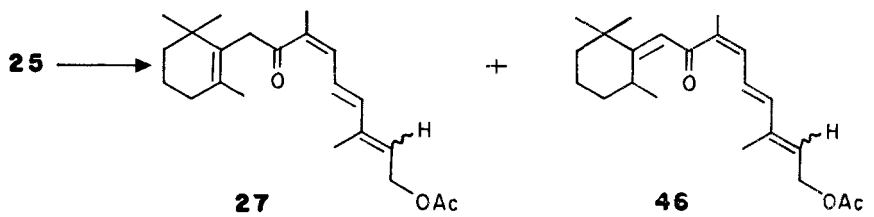
Silanol	Temp (°C)	Time (h)	UV. of Crude Product λ_{max} (nm)[b])	ε
Triphenyl	140	3.0	310	13,250
Tri-*p*-tolyl	140	2.75	311	12,630
Tri-*m*-tolyl	140	0.83	313–314	11,960
Tri-1-naphthyl	140	2.25	310	13,855
Trimethyl	140	3.0	314–318	low
Tricyclohexyl	140	13.0	313	8,900
Dicyclohexylmethyl	140	5.0	315–316	10,970
Diphenylmethyl	140	4.0	310	11,285
Tri-*p*-fluorophenyl	130	1.0	313	13,645
Tri-*p*-bromophenyl	110	0.58	317	14,730
Tri-*p*-chlorophenyl	110	0.67	317–318	13,080
Tris(*m*-trifluoromethyl)phenyl	100	0.58	317	13,120
Tris(*p*-trifluoromethyl)phenyl	100	0.58	317–318	13,562
Perfluorophenyl	80–100	1.0	307–315	11,770
Tris(3-nitrophenyl)	80	1.0	318–319	21,180
Tris(3,5-dinitrophenyl)	80–82	1.0	317	20,545

[a]) 1 mmol of propynol **25**, 0.18–0.2 mmol of substituted silanol, 0.05 mmol of tri-*n*-propyl vanadate.

[b]) Longer wavelength maxima are due to presence of α,β-unsaturated isomer **46**.

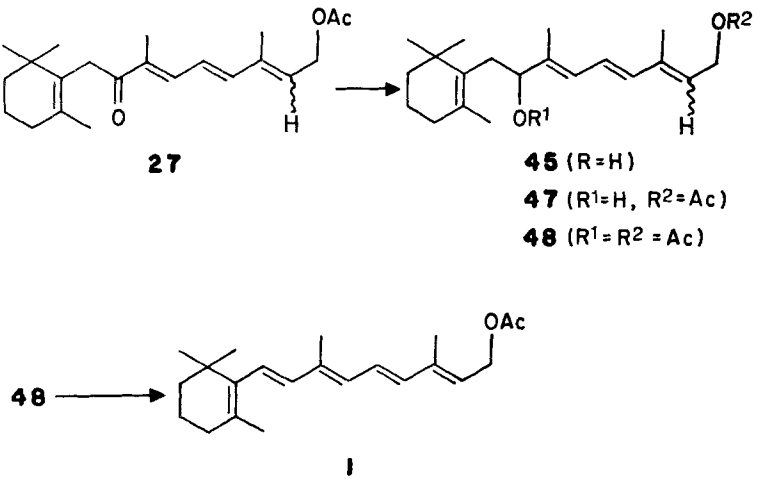
to **27** is summarized in Table 2. The yield of acetoxyketone **27** is estimated from the UV. extinction. As can be seen, the reaction with tris[tris(3-nitrophenyl)silyl]vanadate in refluxing benzene for 1 h affords the product with the highest extinction coefficient. Under these mild conditions, the α,β-unsaturated ketone **46** was also obtained as a mixture of isomers. Treatment of the mixture of **46** and **27** with piperidine acetate effected the (*Z*)/(*E*) isomerization of **27** but not the deconjugation of **46**. Conditions were not studied for the deconjugation but the results with the model compounds (formation of **10**, **15** and **16**) indicate that it should occur readily. In any case, the mixture could be reduced and dehydrated *via* the diacetate to afford vitamin A acetate (see below).

Scheme 7



Conversions to Vitamin A Acetate. The acetoxyketone **27** was converted to vitamin A acetate by the route shown in *Scheme 8*. Reduction of **27** gave the known [22] diol **45** with sodium borohydride in ethanol or with lithium aluminum hydride and gave the monoacetate **47** with sodium borohydride in aqueous tetrahydrofuran. The diol **45** was acetylated to afford the diacetate **48** which without purification was treated

Scheme 8



with 62% aqueous hydrobromic acid [17] to give crude vitamin A acetate still containing some (*Z*) isomers. Chromatography of the crude product afforded vitamin A acetate of > 80% purity (UV. estimation) in 44% yield from the diol **45**. Crystallization of a portion from hexane afforded light yellow crystals of all(*E*) vitamin A acetate (**1**) assaying for 99.8% purity.

The overall yield of chromatographed vitamin A acetate from 2,2,6-trimethylcyclohexanone *via* the trienone **34** and the TPSV/TPS rearrangement was 18% and *via* **34** and tris(tri-3-nitrophenyl)silyl vanadate 31%.

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Experimental Part

General. M.p. were determined on a *Kofler* hot stage microscope and are not corrected. Spectral measurements were performed using the following instruments: NMR.: *Varian* T-60, HA-100, and XL-100 spectrometers using tetramethylsilane as internal standard and deuteriochloroform as solvent; chemical shifts δ are given in ppm, coupling constants in Hz. – IR.: *Beckmann* IR 9 and *Perkin-Elmer* Model 621 and 237B spectrophotometers with chloroform as solvent or as a liquid film; absorptions in cm^{-1}. – UV.: *Cary* Model 14 and *Perkin-Elmer* Model 202 spectrophotometers with 2-propanol as solvent, unless otherwise specified; λ_{max} (ε) in nm. – GC., *Hewlett-Packard* Model 402B gas chromatograph. The phrase 'isolated as usual' indicates extraction or dilution with the indicated solvent, washing, where appropriate, with H_2O, 20% HCl, saturated $NaHCO_3$-solution, and/or saturated brine, drying ($MgSO_4$), and solvent removal on a rotary evaporator (RV.) at 30–50°. Chromatography was carried out on *Merck* 0.05–0.2 mm silica gel or *Woelm* Alumina, activity grade III, unless otherwise specified. Abbreviations: THF = tetrahydrofuran, BHT = 2,6-di-*t*-butyl-*p*-cresol, RT. = room temperature, RV. = rotatory evaporator.

Vanadate rearrangement of 1-ethynyl-2,2,6-trimethyl-cyclohexanol (**7**) *to give aldehydes* **9** *and* **10**. To a mixture of 180 ml of heavy mineral oil (Lubinol), 6.46 g (23.4 mmol) of triphenylsilanol

(*Arapahoe*), 150 mg of benzoic acid, and 14.4 g (86.6 mmol) of 1-ethynyl-2,2,6-trimethyl-cyclohexanol (**7**) (7:1 isomer mixture) were added 0.49 g (2.00 mmol) of tri-*n*-propyl vanadate[11]. The mixture was heated (becomes homogeneous) to 140° for 3.75 h, and then vacuum (0.10–0.05 Torr) was applied to remove the volatile products. Then a second portion, 19.30 g (116.1 mmol), of **7** was added, the mixture heated at 150° for 4 h and the product distilled out as before. The procedure was repeated a third time with 19.30 g of **7**. The first cycle yielded 63.0%, the second 77.5% and the third 94.6% of crude products. The third cycle product was distilled to afford a mixture of the known [25] aldehydes **9** and **10** in a ratio of 1:9 in 87% yield, b.p. 48–50°/0.4 Torr.

1-(3-Methyl-but-3-en-1-ynyl)-2,2,6-trimethyl-cyclohexanol (**11**). To a solution of ethylmagnesium bromide prepared from 5.28 g (0.217 g-atom) of magnesium and 24.0 g (0.220 mol) of ethyl bromide in 70 ml of dry THF were added 16.0 g (0.242 mol) of 2-methyl-1-buten-3-yne (*Air Products and Chemicals, Inc.*) in 100 ml of THF at 25°. The solution was warmed to 50° until no further gas was evolved, then cooled to 25°, and a solution of 28.0 g (0.200 mol) of 2,2,6-trimethyl-cyclohexanone[12] in 50 ml of THF was added over 15 min. The mixture was stirred for 30 min at RT. and for 15 min at 50°, and was then poured onto ice and ammonium chloride. Isolation of the product as usual with ether followed by distillation afforded 34.4 g of the diastereoisomeric alcohols **11** in 83% yield, b.p. 95–98°/5.0 Torr, as a colorless oil which solidified to a low m.p. solid upon standing in the freezer. Chromatography of the product from a similar experiment on Alumina III afforded the major, more polar isomer as a solid, m.p. 40–42° (55%), and the minor, less polar isomer (23%) as an oil.

$C_{14}H_{22}O$ (206.33) Calc. C 81.50 H 10.75% Found (major isomer) C 81.37 H 10.67%

1-(3-Methyl-but-3-en-1-ynyl)-2,6,6-trimethyl-cyclohexene (**12**). A mixture of 15.0 g (73 mmol) of alcohol **11** and 50 ml of 98–100% formic acid was stirred at 0° for 2.5 h. The product was isolated in the usual way with pentane to afford 13.4 g of crude oil which was distilled to give 8.75 g (64%) of hydrocarbon **12**, b.p. 63–66°/0.5 Torr. – NMR.: δ 1.16 (*s*, 6H, 2 *gem.* CH_3), 1.90 (*s*, 3H, vinylic CH_3), 1.93 (*s*, 3H, vinylic CH_3), 5.18 (*m*, 2H, $H_2C{=}C$).

3-Methyl-1-(2,6,6-trimethyl-cyclohex-1-enyl)-but-3-en-2-one (**15**). A mixture of 12.3 g (59.6 mmol) of alcohol **11**, 7.60 g (8.51 mmol) of tris(triphenylsilyl)vanadate[11], 1.92 g (6.95 mmol) of triphenylsilanol (*Arapahoe*), and 0.40 g of benzoic acid in 100 ml of xylene was heated under reflux for 1 h. The solution was stored in the freezer for several h, and the precipitated catalyst removed by filtration. Evaporation of the solvent and distillation of the residue afforded 10.1 g (82%) of the ketone **15**, b.p. 85–90°/ 0.6–0.7 Torr. – UV.: 203 (11620), 215 (infl., 11125). – IR.: 1685 (C=O). – NMR.: 0.88 (*s*, 6H, 2 *gem.* CH_3); 1.44 (*s*, 3H, H_3C-ring), 1.88 (*s*, 3H, $H_3C{-}C(3)$); 3.42 (*s*, 2H, $H_2C{-}CO$); 5.72 and 6.00 (2*s*, 2H, $H_2C{=}C$).

$C_{14}H_{22}O$ (206.33) Calc. C 81.50 H 10.75% Found C 81.27 H 10.99%

(2E)-*3-Methyl-5-(1-hydroxy-2,2,6-trimethyl-cyclohexyl)-pent-2-en-4-ynol* (**18**) *and its acetate* **13**. To a stirred solution of 9.5 ml of 3 M ethereal ethylmagnesium bromide (28.0 mmol) in 20 ml of dry THF at 0° was added a solution of 1.44 g (15.0 mmol) of (*E*)-3-methyl-pent-2-en-4-ynol [14] in 5.0 ml of THF. The solution was stirred for 30 min at 25° and then heated under reflux for 15 min and cooled to 25°. A solution of 1.40 g (10 mmol) of 2,2,6-trimethyl-cyclohexanone (**2**) in 5 ml of THF was added and the mixture heated under reflux for 3 h. Isolation of the product in the usual manner afforded 2.4 g of crude material which was chromatographed on Alumina III to afford two fractions: a minor, less polar of 0.35 g (14.8%), and a major, more polar of 0.80 g (34.0%). Recrystallization of the crude solids (ether/hexane) gave pure compounds. Major diastereomer, m.p. 47–52°. – UV.: 228 (14250). – IR. (KBr): 3350 (OH). – NMR.: 1.05 (*d*, J = 6, 3H, H_3C-ring); 1.07 and 1.10 (2*s*, 6H, 2 *gem.* CH_3); 1.83 (*s*, 3H, vinylic CH_3); 4.23 (*t*, J = 6.5, 2H, H_2COH); 6.00 (*t*, J = 6.5, 1H, vinylic H).

$C_{15}H_{24}O_2$ (236.36) Calc. C 76.22 H 10.24% Found C 76.12 H 10.41%

Minor diastereomer, m.p. 53–57°. – UV.: 228 (15220). – IR. (KBr): 3350 (OH). – NMR.: 1.04 (*d*, J = 6, 3H, H_3C-ring); 1.07 (*s*, 6H, 2 *gem.* CH_3); 1.83 (*s*, 3H, vinylic CH_3); 4.25 (*t*, J = 7, 2H, H_2COH); 6.01 (*t*, J = 7, 1H, vinylic H).

$C_{15}H_{24}O_2$ (236.36) Found C 76.01 H 10.62%

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[11] Prepared by Dr. *D. Andrews, Hoffmann-La Roche*, following the procedure outlined in [10].

[12] Prepared by the procedure of *Newman et al.* [15] as described above[7]).

The monoacetate **13** of the diastereomeric diols **18** was prepared by warming a solution of 3.2 g of **18** (13.5 mmol) in 10 ml of pyridine with 1.5 g of acetic anhydride for 3 h at 45–50°. Isolation of the product in the usual way followed by chromatography on Alumina III gave 2.8 g (74.5%) of acetate **13**. Evaporative distillation gave pure **13**, b.p. 124°/0.15 Torr. – IR.: 1740, 1250.

$C_{17}H_{26}O_3$ (278.38) Calc. C 73.35 H 9.41% Found C 73.28 H 9.49%

Dehydration of monoacetate **13** *with formic acid.* To a solution of 220 mg (0.79 mmol) of acetate **13** in 5 ml of hexane were added 0.4 ml of 98–100% formic acid. The mixture was vigorously stirred at 25° overnight. Isolation of the product in the usual way gave the dehydration product **14** as a mixture of acetate and formate. – IR.: 2180 (C≡C), 1730 (C=O), 1225 (acetate C–O), 1150 (formate C–O). – NMR.: 1.10 (*s*, 6H, 2 *gem.* CH_3); 1.87 (*s*, 3H, vinylic H_3C-ring); 1.93 (br. *s*, coupled to vinylic H, 3H, H_3C–C(3)); 2.00 (*s*, 1.3H, H_3C–COO); 4.88 (*d*, J = 6, 2H, H_2C–O–CO); 5.75 (*t*, J = 7, 1H, vinylic H); 8.07 (*s*, 0.6H, H–COO).

*(3*E*)-5-Acetoxy-3-methyl-1-(2,6,6-trimethyl-cyclohex-1-enyl)-pent-3-en-2-one* (**16**). A solution of 1.40 g (5.0 mmol) of monoacetate **13**, 0.21 g (0.76 mmol) of triphenylsilanol, 0.046 g (0.05 mmol) of tri-*n*-propyl vanadate[11]), and 0.01 g of benzoic acid in 10 ml of xylene was heated under reflux for 2 h. Isolation of the product in the usual manner followed by chromatography on Alumina III afforded 0.70 g (50%) of ketone **16**. – UV. (MeOH): 224–225 (8400). – IR.: 1745 (ester C=O), 1683 (ketone C=O), 1250 (acetate). – NMR.: 0.90 (*s*, 6H, 2 *gem.* CH_3); 1.46 (*s*, 3H, vinylic H_3C-ring); 1.84 (*s*, 3H, H_3C–C(3)); 2.15 (*s*, 3H, H_3C–COO); 3.47 (*s*, 2H, H_2C–CO); 4.90 (*d*, J = 7.5, 2H, H_2C–O); 6.71 (*t*, J = 7.5, 1H, vinylic H). – MS.: *m/e* 278 (M^+), 219 (M^+ – OAc), 99 (base peak).

*Ethyl (4*E*,6*E*)-3,7-dimethyl-9-(1-hydroxy-2,2,6-trimethyl-cyclohexyl)-nona-2,4,6-trien-8-ynoate* (**21**). A solution of 6.0 g (25.4 mmol) of diol **18** in 400 ml of dichloromethane was stirred with 30 g of activated manganese dioxide (*Winthrop*) for 1.5 h. Filtration and evaporation of the solvent afforded 5.3 g (89%) of crude aldehyde **19**. – UV.: 277 (21500). – IR.: 3460 (OH), 2200 (C≡C), 1660. – NMR.: 1.06–1.10 (*m*, 9H, 3 H_3C-ring); 1.55 (*s*, 3H, vinylic CH_3); 6.25 (*d*, J = 8, 1H, vinylic H); 9.68 (*d*, J = 8, 1H, H–CO).

A solution of 7.45 g (28.2 mmol) of the phosphono-senecioate **20** [18] in 30 ml of THF was added to a suspension of 1.26 g (31.0 mmol, 59% NaH) of sodium hydride in 60 ml of THF at 0°. The mixture was then stirred for 1 h at 25°, cooled to 0° and a solution of the freshly prepared aldehyde **19** (5.3 g, 22.6 mmol) in 30 ml of THF was added at 0°. The mixture was stirred for 2 h at 25° and was poured onto ice water. Isolation of the product in the usual manner afforded 8.8 g of crude ester **21**. Chromatography of a 1.0 g portion on Alumina III afforded pure ester **21**. – UV.: 332 (40820). – IR.: 3500 (OH), 2710 (C=O). – NMR.: 1.09 (*d*, J = 6, 3H, H_3C-ring); 1.06 and 1.16 (2*s*, 6H, 2 *gem.* CH_3); 2.06 (*s*, 3H, H_3C–C(7)); 2.37 (*s*, 3H, H_3C–C(3)); 4.28 (*q*, J = 7, 2H, $CO_2CH_2CH_3$); 5.85–6.90 (*m*, 4H, 4 vinylic H).

*Ethyl (4*E*,6*E*)-3,7-dimethyl-8-oxo-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6-trienoate* (**22**). A mixture of 1.0 g (2.90 mmol) of the hydroxyester **21**, 0.36 g (0.40 mmol) of tris(triphenylsilyl)-vanadate[11]), 0.09 g (0.33 mmol) of triphenylsilanol (*Arapahoe*), and 0.02 g of benzoic acid was heated under reflux in 12 ml of xylene for 3 h. The product was isolated in the usual manner after cooling, dilution with hexane, and removal of the vanadate catalyst by filtration to afford 0.99 g of crude oil. Chromatography on Alumina III afforded 0.39 g of pure ketoester **22**. An analytical sample was obtained by evaporative distillation, b.p. 170–180°/0.1 Torr. – UV.: 318–319 (39765). – IR.: 1715 (ester C=O), 1675 (ketone C=O), 1615 (C=C). – NMR.: 0.90 (*s*, 6H, *gem.* CH_3); 1.30 (*t*, J = 7, 3H, $CO_2CH_2CH_3$); 1.46 (*s*, 3H, vinylic H_3C-ring); 2.02 (*s*, 3H, H_3C–C(7)); 2.12 and 2.38 (2*s*, 3H, H_3C–C(3)); 3.49 (*s*, 2H, 2 H–C(9)); 4.25 (*q*, J = 7, 2H, $CO_2CH_2CH_3$); 5.70–7.44 (*m*, 4H, 4 vinylic H).

$C_{22}H_{32}O_3$ (344.50) Calc. C 76.71 H 9.36% Found C 77.14 H 9.56%

Vitamin A acid ethyl ester (**17**) via *ethyl (4*E*,6*E*)-8-hydroxy-3,7-dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6-trienoate* (**23**) *and its 8-acetoxy derivative* **24**. A solution of the ketoester **22** (2.2 g, 6.39 mmol) in 100 ml of ethanol was stirred for 72 h with 0.6 g (15.9 mmol) of sodium borohydride at 25°. Isolation of the product in the usual manner gave 1.75 g of crude hydroxyester **23**. – UV.: 312–313 (26500). – IR. (film): 3450 (OH), 1700 (C=O), 1600 (C=C).

To a solution of 0.35 g (1.00 mmol) of the crude hydroxyester **23** in 1.0 ml of dichloromethane at –5° were added 0.16 ml of pyridine and 0.1 g of acetyl chloride in 1 ml of dichloromethane. After

stirring for 30 min at $-5°$, the mixture was poured onto ice water, the product isolated in the usual manner, and retreated under the same conditions to effect complete acetylation. The acetoxyester **24** was used immediately in the deacetylation. – IR.: 1735 (acetate C=O), 1701 (ester C=O), 1601 (C=C), 1240 (acetate C–O).

The crude acetoxyester **24** in 3 ml of dichloromethane was cooled to $-50°$, and 0.17 ml of 62% aqueous hydrobromic acid (precooled to $-20°$) were added. The mixture was stirred for 15 min at $-50°$. Ice water and sodium hydrogencarbonate were added to neutralize the mixture. Isolation of the product as usual afforded 0.18 g of crude vitamin A acid ethyl ester (**17**) (UV.: 352). Chromatography on Alumina III gave 0.073 g of pure ester **17** as a 6:1 mixture of all-(*E*) and (7*E*,9*E*,11*E*,13*Z*) isomers. – UV.: 354 (34710). – NMR.: 5.66 (*s*, 0.17H, H–C(14) of (13*Z*) isomer); 5.80 (*s*, 0.83H, H–C(14) of (13*E*) isomer).

3,7-Dimethyl-9-(1-hydroxy-2,2,6-trimethyl-cyclohexyl)-nona-1,4,6-trien-8-yn-3-ol (**33**). To a solution of 780 ml of 2.85 M vinylmagnesium chloride in THF (2.23 mol) in 3.620 l additional THF were added over 1.8 h at 10–15° 253.5 g (0.92 mol) of the crude hydroxyketone **32**[13]. The mixture was warmed to 35° over 20 min, maintained at 35° for 2.6 h, and poured onto an equal volume of ice and water. The organic phase was washed with brine, concentrated to 500 ml and diluted with 1 l of ether. This solution was washed with saturated ammonium chloride and combined with the organic phase obtained by extracting the initial aqueous phase with three 1 l portions of ether added by 350 ml, 100 ml, and 100 ml of methanol, respectively, to break up the emulsions and washing these combined extracts with saturated ammonium chloride. The combined solution was washed with brine, dried ($MgSO_4$) and concentrated on a RV. to give 279.75 g of crude diol **33** which was chromatographed in two portions on Alumina III. The fractions were combined with fractions of a chromatography of 274.2 g of crude **33** from another experiment to afford a total of 337.95 g (61%) of pure diol **33** as an oil. (Overall yield of pure **33** from pure **7** = 49%.) – UV.: 270 (26190). – IR. (film): 3440 (OH). – NMR.: 1.08–1.21 (*m*, 9H, 3 H_3C-ring); 1.45 (*s*, 3H, H_3C–C(3)); 1.99 (*s*, 3H, vinylic CH_3); 5.09 ($d \times d$, $J_{1,1'} = 1.5$, $J_{1,2} = 10.5$, 1H, H–C(1)); 5.30 ($d \times d$, $J_{1,1'} = 1.5$, $J_{1,2} = 17.5$, 1H, H–C(1)); 5.89 (*d*, $J_{4,5} = 15.5$, 1H, H–C(4)); 6.04 ($d \times d$, $J_{1,2} = 10.5$, $J_{1',2} = 17.5$, 1H, H–C(2); 6.27 (*d*, $J = 11$, 0.7H, H–C(6) of (6*Z*) isomer); 6.39 (*d*, $J = 11$, 0.3H, H–C(6) of (6*E*) isomer); 6.78 ($d \times d$, $J_{5,6} = 11$, $J_{4,5} = 15.5$; 0.3H, H–C(5) of (6*E*) isomer); 6.80 ($d \times d$, $J_{5,6} = 11$, $J_{4,5} = 15.5$, 0.7H, H–C(5) of (6*Z*) isomer).

$C_{20}H_{30}O_2$ (302.46) Calc. C 79.42 H 10.00% Found C 79.50 H 9.76%

1-(9-Acetoxy-3,7-dimethyl-nona-3,5,7-trien-1-ynyl)-2,2,6-trimethyl-cyclohexanol (**25**). a) *Preparation of the (3E) isomer by reduction-acetylation of ethyl ester* **21**. To a suspension of 5.0 g (130 mmol) of lithium aluminium hydride in 250 ml of ether at $-70°$ were added 3.6 g (10.5 mmol) of ethyl ester **21** in 25 ml of ether. The mixture was stirred at $-70°$ for 2 h and 15 ml of ethyl acetate were added at $-70°$ followed by saturated sodium sulfate solution at 0°. Isolation of the product as usual afforded 2.75 g (87%) of crude diol **26**. – UV. (EtOH): 290 (sh, 26225), 313 (36535), 316 (32305). – IR. (film): 3400 (OH).

Acetic anhydride (0.08 ml) was added to a solution of 0.15 g of crude diol **26** in 2 ml of pyridine. The solution was warmed to 50–60° for 1.5 h. Isolation of the product as usual afforded 0.14 g of acetate **25**. – IR.: 3500 (OH), 1735 (acetate C=O), 1275 (acetate C–O). – UV.: 305. Chromatography of a sample of the crude acetate on silica gel deactivated with 10% of water afforded two diastereoisomeric acetates each as a (7*Z*)/(7*E*) mixture. – NMR. (major diastereomer): 1.03 and 1.14 (2*s*, 6H, 2 *gem.* CH_3); 1.04 (*d*, $J = 6$, 3H, H_3C-ring); 1.87 (*s*, 3H, vinylic CH_3); 1.96 (*s*, 3H, vinylic CH_3); 2.07 (*s*, 3H, H_3C–COO); 4.71 (*d*, $J = 7.5$, H_2C–O–CO); 5.60 (*t*, $J = 7.5$, 1H, H–C(8)); 6.25–6.93 (*m*, 3H, 3 vinylic H).

b) *Preparation of (3Z)/(3E) isomer mixture by allylic rearrangement of diol* **33**. To a solution of 131.5 g (0.44 mol) of the pure diol **33** (UV.: 270 (25850)) in 825 ml of benzene were added 131.5 g of glacial acetic acid and 260 mg of BHT. The solution was heated under reflux for 3.5 h, cooled, washed with water, hydrogencarbonate, and brine and dried ($MgSO_4$). Evaporation of the solvent afforded 138.0 g (93%) of crude acetate **25**. – UV.: 291–292 (sh, 27050), 303 (34573), 316 (28365).

$C_{22}H_{32}O_3$ (344.50) Calc. C 76.71 H 9.36% Found C 76.53 H 9.38%

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[13]) Obtained following the general procedure of *Attenburrow et al.* [7] in 80.6% overall yield (crude) from 1-ethynyl-2,2,6-trimethyl-cyclohexanol (**7**) without purification of any intermediates.

c) *Preparation of (3Z)/(3E)isomer mixture by allylic rearrangement of diol* **35**. **35** was prepared following the *Attenburrow et al.* [7] procedure from 8.28 g (50.0 mmol) of propynol **7** and 6.8 g (50.0 mmol) of trienone **34** in 97% yield after chromatography on Alumina III. Alternatively, **35** was prepared from 1.12 g (8.05 mmol) of 2,2,6-trimethyl-cyclohexanone (**2**) and 1.0 g (6.2 mmol) of the propynol **36** in 75% yield after chromatography.

A solution of diol **35** (11.78 g, 39.0 mmol) in 33 ml of glacial acetic acid was stirred at 25° for 1 h and at 40° for 1.1 h. The solution was poured onto ice water and the product isolated as usual to afford 10.98 g (82%) of crude acetate. UV.: 302 (33685).

Following the published procedure [7] for the allylic rearrangement using aqueous sulfuric acid 4.8 g (15.9 mmol) of diol **35** afforded 2.71 g (56%, chromatographed) of the known 9-hydroxy compound [7] which was acetylated to afford crude **25** in 82% yield. Chromatography of a sample of this product on silica gel deactivated by the addition of 10% of water afforded two diastereoisomeric acetates. – NMR. (minor isomer): 1.13 (*s*, 6H, 2 *gem.* CH_3). – NMR. (major isomer, 220 MHz): 1.07 and 1.18 (2*s*, 6H, 2 *gem.* CH_3); 1.11 (*d*, J = 6.5, 3H, H_3C-ring); 1.87 (*s*, 3H, H_3C–C(3)); 1.97 (*s*, 3H, H_3C–C(7)); 2.07 (*s*, 3H, H_3C–COO); 4.75 (*d*, J = 7, 2H, H_2C–O–CO); 5.67 (*t*, J = 7, 1H, vinylic H–C(8)); 6.19 (*d*, J = 16, 1H, vinylic H–C(6)); 6.29 (*d*, J = 11, 1H, vinylic H–C(4)); 6.79 (*AB*, $J_{5,6}$=16, $J_{4,5}$ = 11, 1H, vinylic H–C(5)).

8-Acetoxy-6-methyl-octa-3,5-dien-2-one (**44**). To a solution of 19.87 g (0.127 mol) of 5-acetoxy-3-methyl-pent-1-yn-3-ol, 27.5 g (0.381 mol) of 2-methoxypropene (*Fluka*), and 85 ml of toluene were added 30.5 mg of *p*-toluenesulfonic acid. The brown solution was heated under reflux from 50° to 100°, gradually increasing the temperature over a 4.5 h period, and then heated at 100° for 10 h. To the mixture were added 20 ml of triethylamine and the solution was heated at 100° for 2.5 h. Removal of the solvent and fractional distillation of the residue afforded 13.62 g (55%) of acetoxy dienone **44**, b.p. 77–83°/0.05 Torr.

6-Methyl-octa-3,5,7-trien-2-one (**34**). A mixture of 13.40 g (68.3 mmol) of acetoxy dienone **44** and 21.23 g of tetraethylammonium acetate tetrahydrate (*Eastman*) in 165 ml of acetone was heated under reflux for 5.5 h. After cooling the suspension was filtered, the filtrate was evaporated, and the residue dissolved in ether. After washing with water, hydrogencarbonate and brine, the solution was concentrated and chromatographed on Alumina III to afford 5.12 g of pure trienone **34** (55%).

6-Methyl-octa-3,5,7-trien-2-one (**34**) *from 2-methoxy-4-methyl-5,6-dihydro-2H-pyran* (**39**). A solution of 0.6 g (4.7 mmol) of **39** [21] in 12 ml of benzene was refluxed for 3 h with a crystal of *p*-toluenesulfonic acid. A 10 ml portion of the mixture (*ca.* 3.9 mmol) was added over 30 min at 0° to a solution of 0.42 g of sodium methoxide in 10 ml of acetone and stirred for 1 h at 0°. The mixture was poured onto ice water and the product was isolated as usual with ether and chromatographed on Alumina III to afford 0.21 g (40%) of trienone **34**.

Preparation of acetoxyketone **27** *by vanadate rearrangement of acetoxy propynol* **25**. *General procedure.* A solution of **25** in xylene was heated under reflux for 1–5 h (until the starting material had disappeared on TLC.) with *ca.* 20 mol-% of the vanadate and *ca.* 5 mol-% of excess silanol. The reaction mixture was cooled and diluted with hexane to precipitate the vanadate and silanol which was removed by filtration, and the filtrate was washed with hydrogencarbonate and brine and dried ($MgSO_4$). The solvent was evaporated on the RV. at 25–35° and then at 35–45°/0.1 Torr before measurement of the UV. and NMR. spectra. Results for substituted silanols are given in Table 2. The following procedures using tris(triphenylsilyl)vanadate/triphenylsilanol (TPSV/TPS) are typical:

a) *From the (3E) compound derived from ethyl ester* **21**: Rearrangement of 1.30 g (3.77 mmol) of **25** with 0.47 g (0.5 mmol) of TPSV and 0.12 g (0.43 mmol) of TPS afforded 1.25 g of crude **27** which was chromatographed to give 0.113 g of pure (3*E*)-ketone **27**. – UV.: 313 (26005). – IR.: 1740 (acetate C=O), 1670 (ketone C=O), 1260 (acetate C–O). – NMR.: 0.86 (*s*, 6H, 2 *gem.* CH_3); 1.89 and 1.93 (2*s*, 6H, 2 vinylic CH_3); 2.04 (*s*, 3H, H_3C–COO); 3.42 (*s*, 2H, 2 H–C(1)); 4.75 (*d*, J = 7, 2H, H_2C–O–CO); 5.77 (*t*, J = 7, H–C(8)); 6.5–7.3 (*m*, 3H, 3 vinylic H).

$C_{22}H_{32}O_3$ (344.50) Calc. C 76.71 H 9.36% Found C 76.99 H 9.58%

b) *From isomer mixture derived from diol* **35**: Rearrangement of 11.4 g (33.1 mmol) of **25** with 3.59 g (4.0 mmol) of TPSV and 0.925 g (3.3 mmol) of TPS in 200 ml of xylene for 3 h afforded 13.6 g of crude **27**. Chromatography of a 10.6 g portion on silica gel deactivated with 10% of water

gave 3.30 g (37%) of pure ketone **27**, mainly as the (3*Z*) isomer. – UV.: 310 (24160). – IR.: 1735 (acetate C=O), 1670 (ketone C=O), 1250 (acetate C–O). – NMR.: 3.32 (*s*, 0.8H, H_2C–C=O of (3*Z*) isomer); 3.42 (*s*, 0.2H, H_2C–C=O of (3*E*) isomer).

c) *From isomer mixture derived from diol* **33**: Rearrangement of 55.8 g (0.162 mol) of **25** with 20.0 g (0.022 mol) of TPSV and 5.0 g (0.018 mol) of TPS in 550 ml of xylene containing 1.08 g of benzoic acid and 100 mg of hydroquinone afforded 62.0 g of crude **27** and 19.8 g of recovered TPSV/TPS catalyst. – UV.: 308 (14060). – NMR.: 3.28 (*s*, 0.7H, H_2C–C=O of (3*Z*) isomer); 3.42 (*s*, 0.3H, H_2C–C=O of (3*E*) isomer).

A portion of the recovered catalyst, 11.0 g, was used to rearrange 23.4 g of **25** (same isomer mixture as above) to afford 24.1 g of crude **27**. – UV.: 311 (13150).

*Isomerization of (3*Z*)/(3*E*)acetoxyketone* **27** *to the (3*E*) isomer.* A solution of 25.1 g (0.073 mol) of crude **27** (from c)) in 250 ml of toluene was added at 25° to a 1:1 mixture of piperidine and piperidinium acetate in 750 ml of toluene (prepared by the dropwise addition of 32.5 g (0.54 mol) of glacial acetic acid to a solution of 91.5 g (1.08 mol) of piperidine at 0° followed by stirring 0.5 h at 25°). The mixture was heated under reflux for 8 h. It was then washed with 10% hydrochloric acid, hydrogencarbonate and brine. Drying (Na_2SO_4) and removal of the solvent as usual afforded 24.6 g (98%) of crude isomerized acetoxyketone. – UV.: 313 (19180). – NMR.: 3.42 (*s*, >1.90H, H_2C–C=O of (3*E*) isomer).

Repetition of the isomerization on a 30.0 g scale afforded 30.0 g (100%) of crude isomerized acetoxyketone. – UV.: 312 (21990). – NMR.: 3.42 (*s*, >1.90H, H_2C–C=O of (3*E*) isomer).

Other isomerization reactions are summarized in Table 1, the percentage of the (3*Z*)/(3*E*) isomers being determined by NMR. analysis of the ratio of the absorbances for the (3*Z*) and (3*E*) isomers at 3.28 and 3.42 ppm, respectively.

*(4*E*,6*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6-trien-1,8-diol* (**45**). To a 0° suspension of 5.85 g (0.15 mol) of lithium aluminum hydride in 1 l of ether was added dropwise a solution of 35 g (0.10 mol) of isomerized (to (3*E*)) acetoxyketone **27**. Isolation of the product as usual (EtOAc/Na_2SO_4 quench) afforded 31.8 g of crude diol (100%) (UV.: 279–280 (14260)). Chromatography of all crude material on Alumina III afforded 14.2 g of pure diol **45** (46% overall yield from pure diol **33**[14]). – UV.: 280–281 (23340).

Vitamin A acetate (**1**). To a solution of 12.0 g (39.5 mmol) of the diol **45** in 230 ml of pyridine at 0° was added over 30 min a solution of 8.65 g (110.2 mmol) of acetyl chloride in 115 ml of dichloromethane. The mixture was stirred for 2.5 h at 0°, poured into ice water and the product was isolated with ether, washing the combined extracts with hydrogencarbonate, saturated cupric sulfate solution (to remove pyridine), and brine. Evaporation of the solvent gave 12.9 g of crude diacetate **48**. – UV.: 225 (22610).

The diacetate **48** was immediately dissolved in 310 ml of dicbloromethane, and to the solution, cooled to −55° in a dry ice/2-propanol bath, 60 mg of cetyltrimethylammonium bromide, and with vigorous stirring, 28.5 ml of precooled (−25°) 62% aqueous hydrobromic acid were added over 20 sec. The cooling bath was removed and the mixture vigorously stirred for 6 min at −30 to −35°. Then a solution of 70 g of sodium carbonate in 300 ml of water was added as rapidly as foaming would allow. The light yellow mixture was cooled in an ice/water bath and was stirred for 5 h at 0°. The mixture was diluted with water, and 0.6 ml of a solution prepared from 1.0 g of BHT, 2.0 ml of pyridine and 10 ml of dichloromethane were added. The layers were separated and the aqueous phase extracted with two portions of dichloromethane. The combined organic solutions were washed with hydrogencarbonate and, before evaporation, 2.85 ml of a solution prepared from 2 ml of pyridine, 5 ml of 5% hydrogencarbonate solution, and 50 ml of ethanol were added. Evaporation of the solvent gave 13.0 of crude vitamin A acetate. Chromatography of a 10.4 g portion on 280 g of silica gel containing 10% (by weight) of water and 15% (by weight) of sodium acetate afforded 3.8 g of vitamin A acetate. – UV.: 327 (40000).

Crystallization of a 2.4 g fraction of the chromatographed product from an equal volume of hexane at −20° afforded 1.0 g of light yellow crystals of all-(*E*) vitamin A acetate, of 99.8% assay by UV. ($E_1^{1\%}$ = 1585.5 at 325 nm). The chromatographed material was seen by NMR. to contain <2% of isomers other than the all-(*E*).

[14]) Diol **33**, probably as the (4*Z*) stereoisomer has been prepared by a different route [26].

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60. Radiolabelled Peptide Ergot Alkaloids

83. Mitteilung über Mutterkornalkaloide [1]

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(18. XII. 75)

Summary. Paspalic acid (**11**), labelled at different positions with ^{3}H or ^{14}C and at specific activities up to 1 Ci/mmol (^{3}H) and 2 mCi/mmol (^{14}C), has been prepared biosynthetically in a scale of 2–5 mmol in submerged cultures of a selected strain of *Claviceps paspali* by incorporation of DL-[5-^{3}H]-tryptophan, DL-[6-^{3}H]-tryptophan, DL-[alanine-2,3-^{3}H]-tryptophan, or DL-[alanine-3-^{14}C]-tryptophan. Radioactive lysergic acid (**12**) was obtained from paspalic acid by base catalysed rearrangement.