Addition of a Functionalized Isoprene Unit to an Allyl Alcohol. I. The Synthesis of β-Sinensal[1,2] and Related Topics

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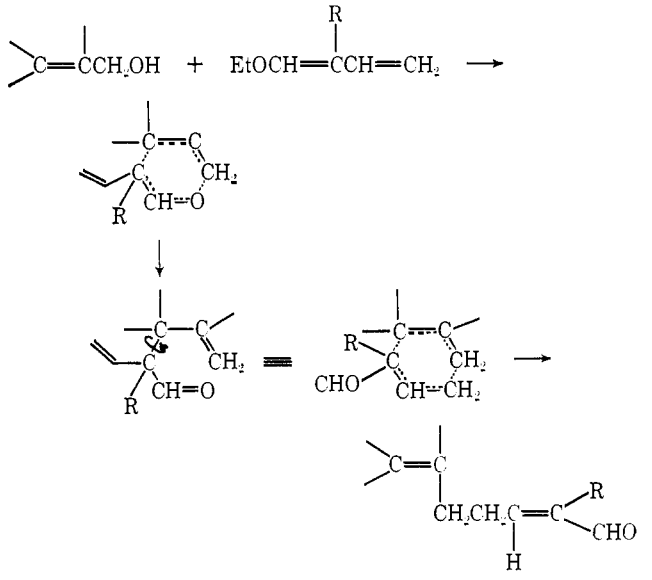
Abstract: Full details of the synthesis of β-sinensal (**16**) in one step from 2-methyl-6-methyleneocta-2,7-dienol (**12**) and 1-ethoxy-2-methylbuta-1,3-diene (**10**) are given. The reaction is a general one for allyl alcohols, and its stereochemistry has been examined using 2-methylbut-2-enol (**19**), nerol (**26**), and geraniol (**27**). The *cis* alcohol (nerol) leads to a *trans*-double bond in the product to the extent of about 70%, the *trans* alcohol leading mainly to a *cis* product. The double "Claisen–Cope" type rearrangement involved occurs to only a minor extent when 1-ethoxybuta-1,3-diene (**9**) is used, the intermediate formed after the first rearrangement of the enol ether being stabilized by hydrogen rearrangement to give an α,β-unsaturated aldehyde which cannot react further.

In preliminary communications, it was shown that an allyl alcohol will undergo *trans* etherification with a diene ether, the vinyl ether thus obtained undergoing a double rearrangement under mild conditions to yield an unsaturated aldehyde with the chain of the original allyl alcohol extended by the number of carbon atoms in the R group plus four, as in Scheme I.[1,3] The importance of this reaction arises from the fact that when R = CH_3, a means is available to add an isoprene unit functionalized at the end, thereby making it possible to synthesize a number of natural products by a very simple route, examples of which it is hoped to present in future publications.

Scheme I

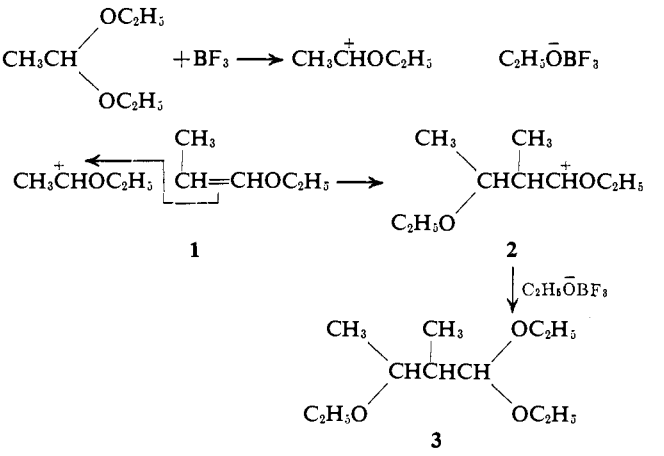


Such a reaction was recognized as a possibility by Julia, Julia, and Linarès[4] in 1962, but under their conditions they did not detect any of the chain-extended product, and as will be described below, when R = H, as in their example, the main product in any case possesses the carbon skeleton of the intermediate after the first rearrangement only.

Results and Discussion

Preparation of Diene Ethers. The method used to prepare both diene ethers **9** and **10** was the well-known one starting from acetaldehyde diethylacetal and 1-ethoxypropene (**1**)[5] reported to proceed by the mechanism shown in Scheme II.[6] It has now been found that when the reaction is carried out with *cis*-**1**, 80% of the product consisted of one stereoisomer (presumably *threo*-**3**), but that the *trans*-ether led to 86% of a different (*erythro*) product (**3**), signifying that the electrophilic attack of the carbonium ion on **1** must be subject to stereochemical control by the olefin.

Scheme II



The principal by-products of this reaction were the expected ones,[5] namely the acetals (**4a** and **4b**) resulting from attack of **2** on **1**, together with products arising from loss of ethanol from **4**, *i.e.*, a mixture of *threo*- and *erythro*-acetals (**5**).[7]

(1) Preliminary communication: A. F. Thomas, *Chem. Commun.*, 947 (1967).

(2) The nomenclature of the sinensals has recently been changed in order to relate them to α- and β-farnesene; see R. Teranishi, A. F. Thomas, P. Schudel, and G. Büchi, *ibid.*, 928 (1968).

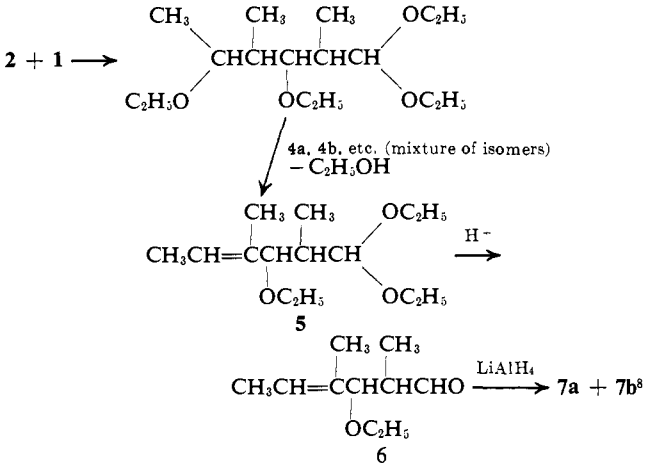
(3) A. F. Thomas, *Chimia*, 594 (1967).

(4) S. Julia, M. Julia, and H. Linarès, *Bull. Soc. Chim. France*, 1960 (1962).

(5) A review of this reaction has been published by L. S. Povarov, *Russ. Chem. Rev.*, 639 (1965).

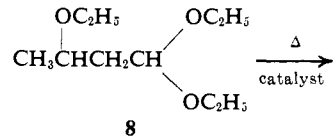
(6) R. J. Hoglin and D. H. Hirsh, *J. Am. Chem. Soc.*, 71, 3468 (1949).

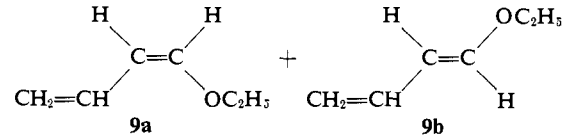
(7) The acetal mixture (**5**) was not resolvable, but the corresponding aldehydes (**6**) were readily separable by glpc, and converted to the alcohols (**7**). The ir spectra of these suggested the presence of an intramolecular hydrogen bond, stronger in one isomer than in the other. The stronger hydrogen bonds are generally formed by the *threo* isomer,[8,9] which in this case corresponded to the first peak eluted from a Carbowax glpc column, and to which the configuration **7b** is accordingly attributed.[10] The principal difference in the nmr spectra was that the chemical shift of the methyl group on the saturated carbon atom was at higher



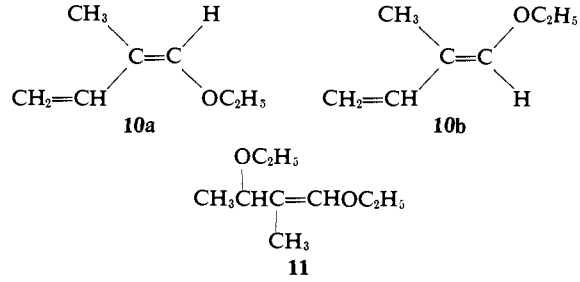
The pyrolysis of acetals has been studied many times, using ammonium dihydrogen phosphate,[11] *p*-toluenesulfonic acid in quinoline,[12] and many other catalysts,[13] but the stereochemistry of the products has been little discussed.[14] We have examined the effect of certain catalysts on the pyrolysis of propionaldehyde diethylacetal, and found that the quinoline–toluenesulfonic acid catalyst gave nearly equal amounts of *cis*- and *trans*-ethers (**1**) when fresh, the proportion of *cis*-ether rising with time. On a column of silica gel at 280°, we found 65% *cis*-ether and 35% *trans*. Extending these studies to the pyrolysis of 1,1,3-triethoxybutane (**8**), we found the ammonium hydrogen phosphate catalyst to produce almost exclusively *trans*-ethoxybutadiene (**9b**),[15] while the quinoline–toluenesulfonic acid catalyst gave a mixture (2:1) of *trans* (**9b**) to *cis* (**9a**).

We were particularly desirous of having both *cis*- and *trans*-1-ethoxy-2-methylbutadienes (**10a** and **10b**) in order to examine the stereochemistry of the double rearrangement described in the introductory section and it seemed likely that the quinoline–toluenesulfonic





acid method would give the larger amount of *cis* isomer (**10a**). In fact none of this isomer was ever detected using any of the catalysts (in contrast to a recent brief report[16]), and, moreover, there was no difference in the composition of the products obtained from the *threo*- or *erythro*-triethoxy compounds (**3**). The principal impurity identified was 1,3-diethoxy-2-methyl-1-butene (**11**) (the relevant spectra leading to the attribution of a structure are described in the Experimental Section).

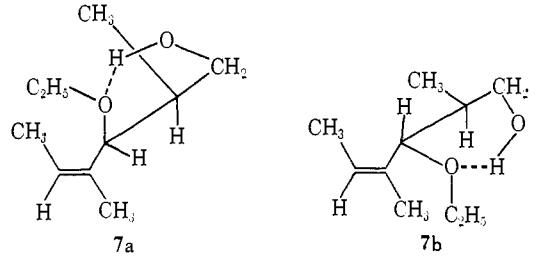


A few other minor impurities were present, including 2-methyl-2-butenal and its diethylacetal, but although a mass spectrum was taken of almost every other peak visible in the gas chromatogram, only one compound of molecular weight 112 was observed, namely **10b**.

The Synthesis of β-Sinensal (16)[17]

In the preliminary communication,[1] the preparation and stereochemistry of the alcohol component **12** were amply described, and these have since been confirmed by Büchi and Wüest.[18] Vinyl ether exchange of allyl alcohols has already been reported to yield the aldehyde resulting from a Claisen-type rearrangement,[20] *i.e.*, stage 1 of the rearrangement we are now discussing, and in our case, the aldehyde in question can exist in principle in two conformations, **13** with the large group, R, equatorial and the hydrogen axial, or **14**, with R axial and hydrogen equatorial. We suggested[1] that the large groups would be expected to prefer a pseudo-equatorial orientation in a chair-like intermediate, and evidence that this is indeed the case has been given by Viola, *et al.*,[21] and by Vitorelli, *et al.*[22] It is thus clear that the sinensal obtained from this reaction should have the double bond at C-6 in the *trans* configuration (**15** or **16** in Scheme III). Unfortunately we have little evidence so far about the configuration of the diene

field in the first isomer eluted; this isomer was therefore again given the configuration which, when the hydrogen bond was present, resulted in a conformation having this methyl further from the oxygen on the neighboring carbon (*i.e.*, **7b**, not **7a**).



(8) L. P. Kuhn and R. A. Wires, *J. Am. Chem. Soc.*, **86**, 2161 (1964).

(9) A. B. Foster, A. H. Haines, and M. Stacey, *Tetrahedron*, **16**, 177 (1961).

(10) See also B. Frémaux, M. Davidson, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. France*, 4243 (1967).

(11) I. N. Nazarov, S. M. Makin, and B. Kruptsov, *Dokl. Akad. Nauk SSSR*, 117, 823 (1957).

(12) B. M. Mikhailov and L. S. Povarov, *Zh. Obsch. Khim.*, **29**, 2079 (1959).

(13) W. Flaig, "Chemical Test No. 093," (PB 52020), Reichsamt Wirtschaftsausbau, 1942, p 1073; *Chem. Abstr.*, 6189 (1947).

(14) W. Kirmse and M. Buschhoff, *Chem. Ber.*, **100**, 1491 (1967), give spectral characteristics of the methyl ethers corresponding to **1**, making *cis* and *trans* isomers easily distinguishable.

(15) *cis*- and *trans*-diene ethers are readily distinguishable by the chemical shift of the vinyl C-3 hydrogen quadruplet, which is at higher field in *trans*-ethers (6.58 ppm in **9a**, 6.13 ppm in **9b**) or the C-1 hydrogen doublet (J = 6 cps in **9a**, 12.5 cps in **9b**) which is at higher field in the *cis*-ethers (5.85 ppm in **9a**, 6.47 ppm in **9b**). See also ref 16.

(16) G. J. Martin and J.-P. Guesnard, *Bull. Soc. Chim. France*, 2150 (1966).

(17) Two other syntheses of β-sinensal have been described.[18,19]

(18) G. Büchi and H. Wüest, *Helv. Chim. Acta*, **50**, 2440 (1967). We are very grateful to these authors for a sample of their β-sinensal.

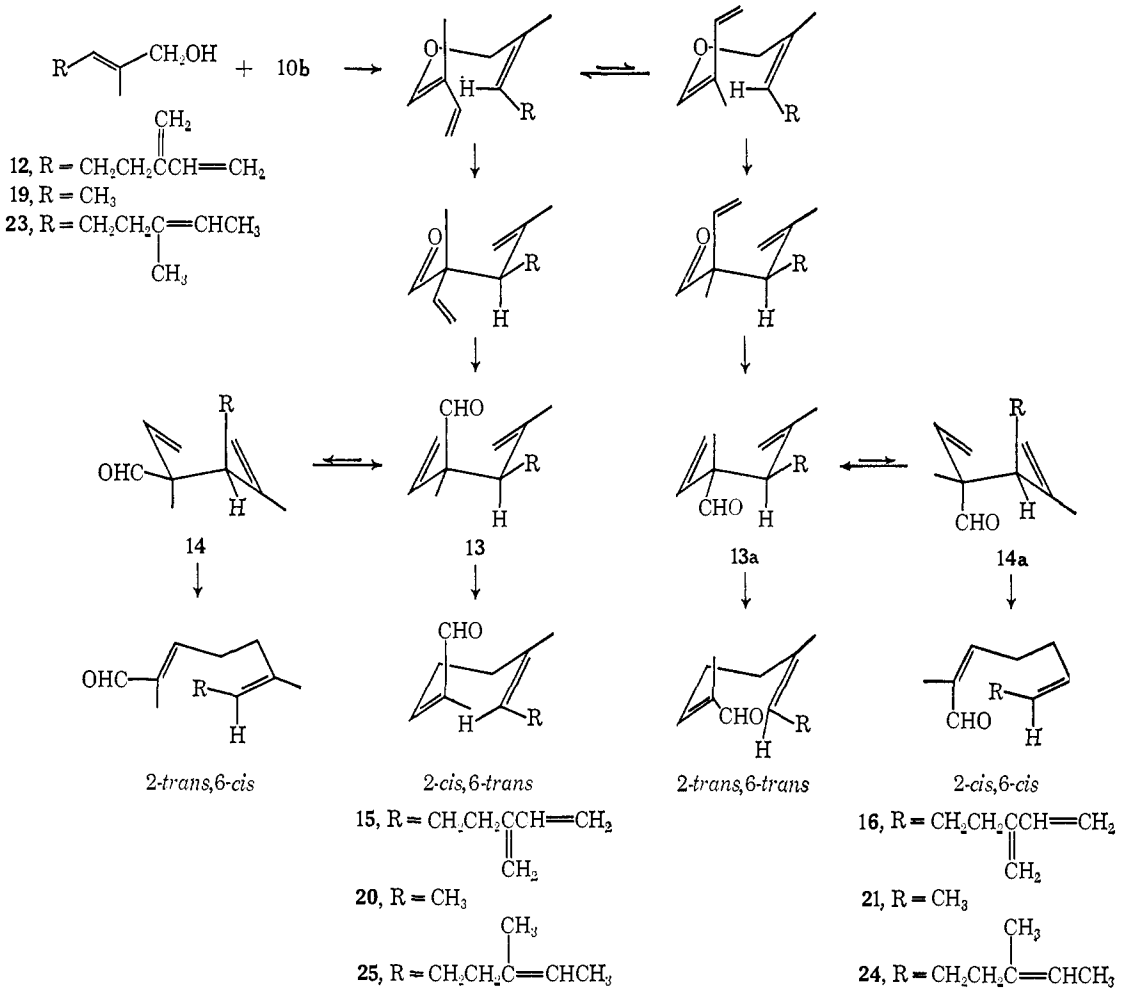
(19) E. Bertele and P. Schudel, *ibid.*, **50**, 2445 (1967).

(20) (a) R. Paul, G. Roy, M. Fluchaire, and G. Collardeau, *Bull. Soc. Chim. France*, 121 (1950); (b) S. F. Reed, *J. Org. Chem.*, **30**, 1663 (1965).

(21) A. Viola, E. J. Iorio, K. K. Chen, G. M. Glover, U. Nayak, and P. J. Kocienski, *J. Am. Chem. Soc.*, **89**, 3462 (1967).

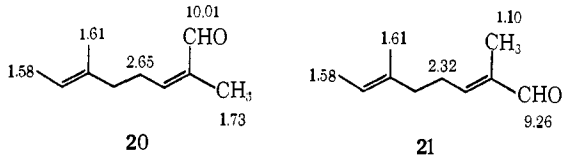
(22) P. Vitorelli, T. Winkler, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **51**, 1457 (1968).

Scheme III



ether before the first Claisen-type rearrangement. In one case where we have been able to isolate this compound in a pure state (using 3-furfuryl alcohol[23]), there was clear nmr evidence that both *cis* and *trans* isomers were present, but in general these ethers are not sufficiently stable for satisfactory analyses to be carried out. Alternatively, they may result from an addition of the alcohol to the vinyl ether followed by loss of ethanol, in which case they might be expected to be mostly *trans* in analogy to the formation of **10b**. If both isomers are present the aldehyde resulting from the first step of the rearrangement will have another isomer, related to the first as a *threo* to an *erythro* compound (**13a** in Scheme III) which will give rise to a different isomer at C-2 (**16**). We had supposed originally that during the preparation of the sinensal, the presence of mercuric acetate and sodium acetate would cause this double bond to isomerize from *cis* to *trans*. While we have been able to show that this does occur (see below), it does not occur very rapidly, and, in addition to this isomerization during the reaction, isomerization during gas chromatography[24] and other purification techniques, there seems to be a direct path to the 2-*trans*,6-*trans* isomer **16**, which, we would suggest, is *via* the intermediate **13a**. There are few descriptions of 2-methyl-α,β-*cis*-unsaturated aldehydes in the literature, though Bertele and Schudel in a footnote[19] report a characteristic signal in the nmr spectrum of such substances at 10.02 ppm. The crude sinensal had such a signal in the nmr spectrum, but after purification it had disappeared, leaving only the *trans*-aldehyde proton signal at 9.20 ppm. In gas chromatograms of the β-sinensal prepared by both Büchi and Wüest and ourselves, a small amount of impurity was present with a shorter retention time on polar columns, but owing to the difficulty of chromatographing larger amounts of sinensal, we decided to examine the stereochemistry of the reaction using a simpler alcohol.

Reaction of *trans*-2-butenol (tiglic alcohol, **19** in Scheme III) with 1-ethoxy-2-methylbutadiene (**10b**) should occur stereochemically in the same way as the reaction with **12**. Gas chromatography of the resulting aldehyde showed that two isomers were present, which were ascribed the 2-*cis*,6-*trans*- (**20**) and 2-*trans*,6-*trans* (**21**) structures on the basis of the nmr signals shown on the formulas.[25]

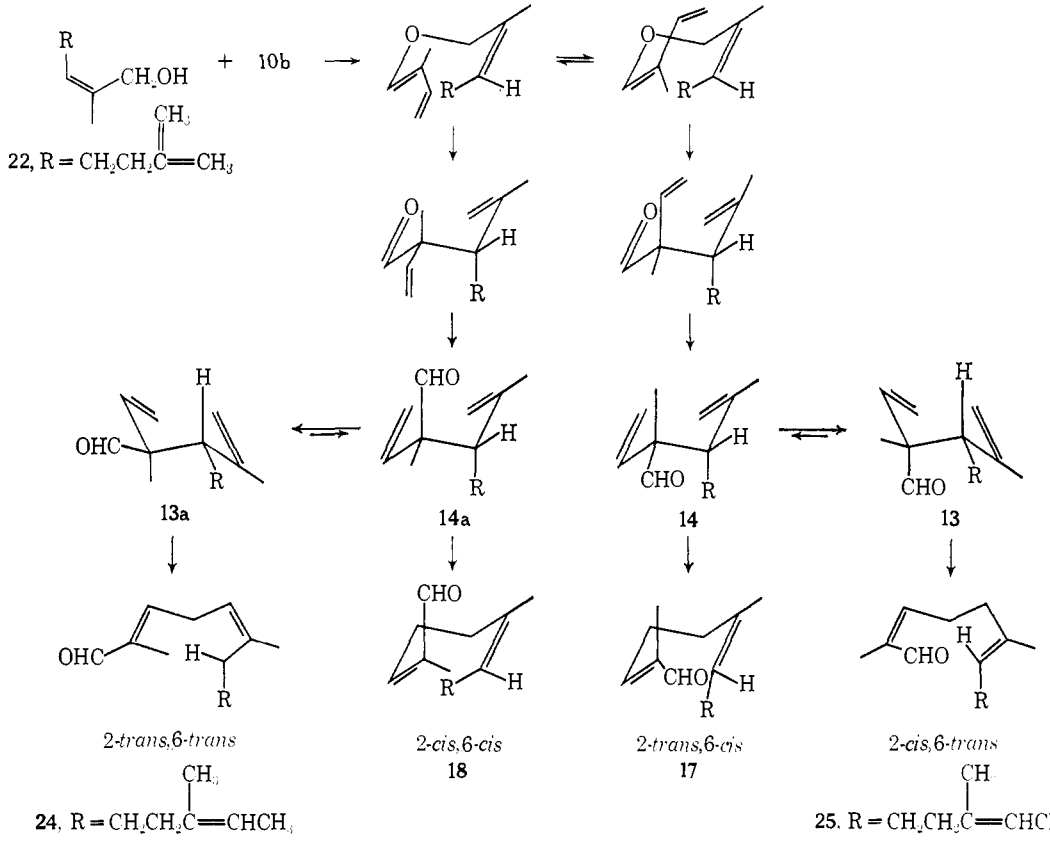


(23) A. F. Thomas *Chem. Commun.*, 1657 (1968).

(24) E. sz. Kovats, private communication, has found that geranial and neral rearrange on gas chromatography under even the most careful conditions.

(25) The nmr spectra of the two isomeric citrals show that the C-4 methylene group is markedly shielded when it is on the same side of the double bond as the carbonyl group, but is close to the C-5 methylene group signal when it is not (M. Ohtsuru, M. Teraoka, K. Tori, and K. Takeda, *J. Chem. Soc., B*, 1033 (1967)). A detailed discussion of *cis*- and *trans*-α,β-unsaturated aldehydes is given by K. C. Chan, R. A.

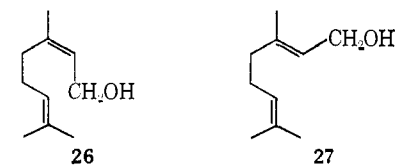
Scheme IV



Chromatography of the mixture on silica gel in a nylon column, and isolating the components by cutting up the column and washing the support[26] gave a fraction that could be concentrated by distillation to contain about 65% *cis*-aldehyde (**20**). From this fraction it was possible to prepare a pure semicarbazone by fractional crystallization which was different from the *trans*-aldehyde semicarbazone (melting point and nmr spectrum). Treatment of this fraction with mercuric acetate at 100° for 8 hr still left more than 50% *cis*-aldehyde in the mixture, although when sodium carbonate was added, the proportion of *cis*-aldehyde fell to 53% in 5 hr. Silica gel chromatography did not disturb the proportions.

Although preparative gas chromatography was not able to separate cleanly the *cis*- and *trans*-aldehydes, the corresponding alcohols, obtained after lithium aluminum hydride reduction of the aldehyde mixture, were readily separated. They were easily distinguished by the chemical shift of the 2-methyl group, that of the *cis*-alcohol being at lower field (1.73 ppm) than that of the *trans*-alcohol (~1.59 ppm). The reaction with **10b** and mercuric acetate was repeated on the individual isomers. Scheme IV illustrates what would be expected from the *cis*-alcohol (**22**), Scheme III remaining the same as before. In other words, provided both *cis*- and *trans*-diene ethers of **22** are present before rearrangement, and the rates from each are comparable in the first stage, the same proportion of products might be expected from both pure *cis*- and (**22**) and pure *trans*- (**23**) allyl alcohols. Two products of fairly similar retention times were obtained, the proportion being almost the same from both alcohols. It was only possible to purify the major product (about 75% of the mixture) by preparative gas chromatography, and this was found to be exclusively *trans* at C-2. The nmr signals in the methyl region are overlapping, but there is no signal between that of the methyl on C-2 at 1.72 ppm and one at 1.61 ppm which, if we are to believe Bates, *et al.*,[27] and some supporting evidence given below, is characteristic for a methyl on a *trans*-double bond in this type of sesquiterpene chain, but not on a *cis*-double bond. The main product is thus formulated as **24**, the minor one being presumably **25**.

The fact that we have observed exclusively C-6-*trans* configurations in the cases so far mentioned is thus readily explicable by Schemes III and IV, (in fact the four "key" conformations available are the same (**13**, **13a**, **14**, and **14a**) in both cases), but the products observed from the *cis*- and *trans*-allyl alcohols we had at our disposal (**22** and **23**) were not sufficiently clear to make a decision about the isomerization of the initially formed ethers. That this isomerization is not always complete was shown by the results obtained with the *cis*- and *trans*-alcohols nerol (**26**) and geraniol (**27**).



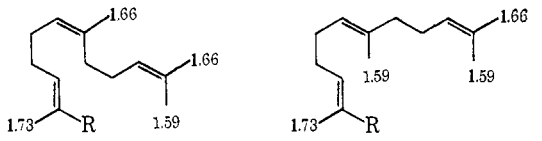
26 **27**

From geraniol, 70% of the aldehyde fraction was 2,7,11-trimethyldodeca-2-*trans*,6-*cis*,10-trienal (**28**), the re-

Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33**, 3382 (1968). See also A. F. Thomas and M. Ozainne *Chem. Commun.*, 46 (1969).

(26) B. Loev and M. M. Goodman, *Chem. Ind.* (London), 2026 (1967).

(27) R. B. Bates, D. M. Gale, and B. J. Gruner, *J. Org. Chem.*, **28**, 1086 (1963).



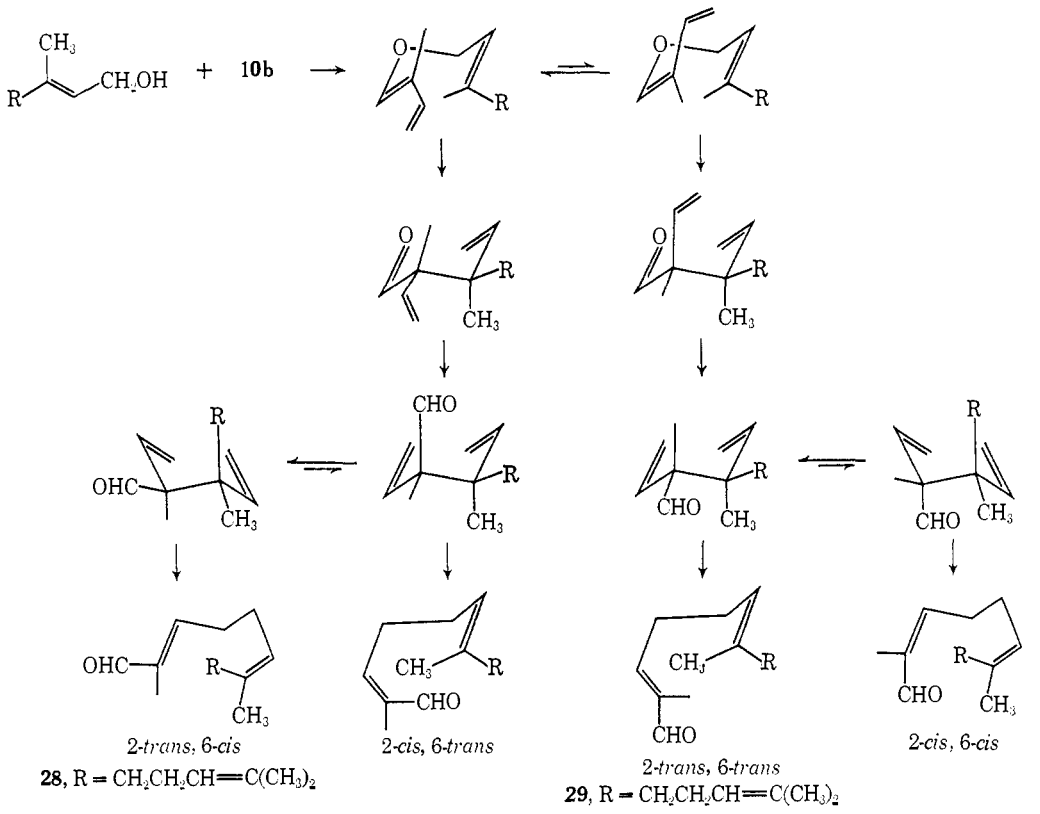
28, R = CHO
30, R = CH_2OH

29, R = CHO
31, R = CH_2OH

tions with a pseudo-equatorial formyl group rather than methyl are preferred. Evidently, too, the initial equilibrium between the diene ethers is, in this case, not 1:1, but in favor of the *trans*-ether. A similar scheme can be drawn for nerol.

If the formyl group is in fact decisive for the conformation of the intermediates, we could expect greater

Scheme V



28, R = $CH_2CH_2CH{=}C(CH_3)_2$

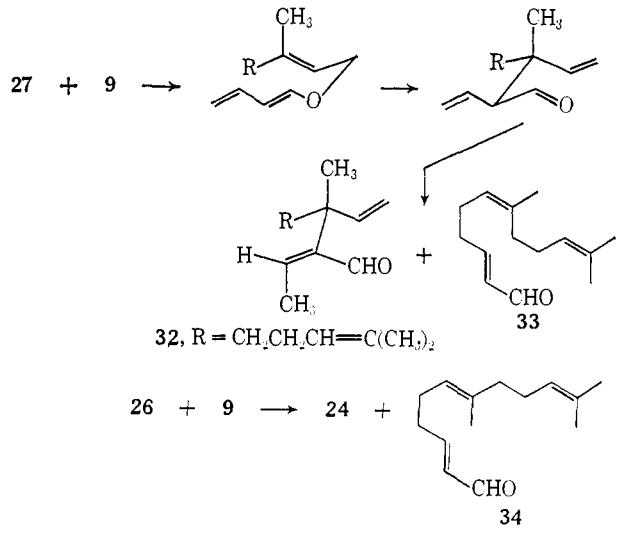
29, R = $CH_2CH_2CH{=}C(CH_3)_2$

mainder being the 2-*trans*,6-*trans* isomer (**29**), while from nerol 78% of the aldehyde fraction was 2,7,11-trimethyldodeca-2-*trans*,6-*trans*-10-trienal (**29**), the remainder being the isomer **28**. These compounds were purified by gas chromatography, and by fractional crystallization of the semicarbazones, and were identified by means of their 100 Mcps nmr spectra, the values found being shown on the formulas.[28] The integration clearly showed six hydrogens in the highest field signal at 1.59 ppm in the case of the 6-*trans* compound (**29**) with three hydrogens at 1.66 ppm, while in the *cis* isomer (**28**), three protons were in the signal at 1.59 ppm, while six were in the 1.66-ppm signal, in accord with Bates's results with the farnesols. Not only this, but the fact that the main compound (**29**) obtained from nerol could be reduced to the known alcohol (**31**) whose nmr spectrum was identical with that of the known compound,[29] and different from the 2-*trans*,6-*cis* isomer (**22**), constitutes proof that the structural attributions are correct. No 2-*cis* unsaturated aldehyde was detected in either case.

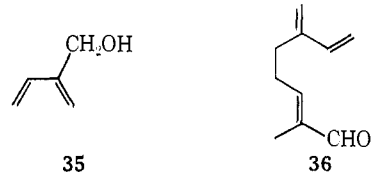
Scheme V illustrates the possibilities for geraniol, and the fact that only 2-*trans*-aldehydes were observed evidently means that in the intermediate, the conformaspecificity if the methyl group attached to the same carbon atom were absent. In order to examine this point, we studied the reaction between nerol or geraniol and ethoxy butadiene (**9**). No difference in the results was found using the *cis*- or the *trans*-ether, and in the case of both nerol and geraniol, the main product of the reaction (80%) was 2-ethylidene-3-vinyl-3,7-dimethyl-6-octenal (**32**), readily identified by its nmr spectrum, and the fact that the uv-absorption maximum was at 234 nm. The remaining 20% was different in each case. From geraniol, over 95% of this part was a single isomer, presumably *cis* at C-6 (**33**) (judging from the nmr spectrum and the shorter retention time on a Carbowax column, in agreement with all the other isomeric pairs so far mentioned), while from nerol, nearly 100% was 7,11-dimethyldodeca-2-*trans*-6-*trans*, 10-trienal (**34**), as expected from Scheme V, when the methyl group has been removed from the carbon carrying the formyl group and replaced with hydrogen. The formation of the main product (**32**) can be explained by a modification of Julia's original scheme,[4] whereby a competing reaction of the β,γ-unsaturated aldehyde intermediate is hydrogen rearrangement to the more stable α,β-unsaturated aldehyde, stable to further double bond reorganization. The double bond at C-2 in (**32**) is presumed to be largely *cis* on account of the aldehyde signal at 9.98 ppm (see Experimental Section).

(28) We are very grateful to Dr. U. Scheidegger (Varian AG., Zürich) for measuring the 100-Mcps nmr spectra.

(29) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 4245 (1967). Thanks are due to Professor Corey for a copy of the nmr spectrum of this alcohol.



The reaction described in this paper is clearly of wide applicability, but one limitation was shown by the fact that when it was carried out on 2-methylene-3-buten-1-ol (**35**), in the hope of preparing the aldehyde (**36**) corresponding to the alcohol (**12**) used in the sinensal synthesis, only traces of the aldehyde were visible in the gas chromatogram.



Further publications will deal with the application to the synthesis of heterocyclic compounds, and to a discussion of the stereochemistry when cyclic allyl alcohols are involved.

Experimental Section

Melting points were taken in capillaries and corrected. Infrared spectra were measured with a Perkin-Elmer Type 125 spectrophotometer. Ultraviolet spectra were obtained with an Optica type CF4 NI instrument. Nuclear magnetic resonance spectra were measured with a Varian A-60 HA-100 spectrometer. Mass spectra were obtained with the Atlas CH4 instrument, using an inlet temperature of about 150° and electrons of 70-eV energy. Gas chromatography (glpc) was carried out for analytical purposes on a Perkin-Elmer Type 226 or a Model 59T built by E. Palluy, Firmenich & Cie, and preparative chromatography was effected on a Carlo-Erba Fractovap Type P. In both cases, the stationary phase was Carbowax 20M on Chromosorb W.

The geraniol used was made by Firmenich & Cie, and contained 7% nerol and 5% citronellol as impurities, the nerol contained 10% geraniol. A correction in the figures of the yields has been made to take account of these impurities.

***cis*- and *trans*-Ethoxy-1-propenes.** A.[12] A mixture of 4 g of *p*-toluenesulfonic acid in 80 ml of quinoline was heated at 230° in a metal bath, and 1067 g of propionic aldehyde diethylacetal were introduced dropwise. The distillate (bp 55–80°) was collected directly in a 5% solution of sodium carbonate. The organic phase was separated, washed with water, dried over anhydrous potassium carbonate, and distilled, to obtain 461 g of the ethoxypropene mixture, bp 60–75°, and 218 g of recovered acetal.

B. The apparatus consisted of a flask heated to about 300° in a heating mantle, fitted to a column of silica gel granules heated to 280°, about 40 cm long, and surmounted by a conventional still head. The product was collected in sodium carbonate solution and worked up as in A.

For the relative amounts of *cis*- and *trans*-ethers see the theoretical section. The isomers were separated by distillation,[30] the *cis*-ether having bp 68° (730 mm), *trans*-ether, bp 71.5–72° (730 mm).

***threo*- and *erythro*-1,1,3-Triethoxy-2-methylbutane[31,32] (3).** *cis*-Ethoxy-1-propene (120 g, containing 12% *trans*-ether) was added dropwise to 300 g of acetaldehyde diethylacetal containing 1 ml of boron trifluoride etherate. The addition took 1 hr, during which time the temperature rose to 60° and the solution turned brown. The mixture was heated 0.5 hr to 65° then cooled and 50 g of anhydrous sodium carbonate added. After stirring for 2 hr, the mixture was filtered and distilled, collecting the fraction, bp 75–93° (10 mm), which consisted of 129 g of a mixture of two substances, 30% of which had a shorter retention time on glpc than the remaining 70%.

The corresponding *trans*-ether (58 g, containing 15% *cis*-ethoxy-1-propene), treated with 150 g of diethylacetal and boron trifluoride etherate under the same conditions, gave a product containing 73% of the substance with shorter retention time and 27% of the substance with longer retention time.

For analysis, the compounds were separated and purified by glpc. *threo*-**3**, the compound with the longer retention time from the *cis*-ether, had nmr spectrum (ppm) 4.32 (1 H, d, J = 5.5 Hz, CHC*H*(OEt)$_2$), 3.15–3.75 (7 H, m, three C*H*$_2$O plus one >C*H*O), 1.85 (1 H, m >CHCH(CH$_3$)–), and 0.7–1.3 (15 H, m, various C*H*$_3$ groups); mass spectrum, *m/e* (per cent relative abundance) 143 (8), 103 (100), 86 (21), 75 (52), 73 (99), 47 (61), 45 (77).

erythro-**3**, from the *trans*-ether had nmr 4.31 (1 H, d, J = 8 Hz, CHC*H*(OEt)$_2$), 3.1–3.8 (7 H, m), 1.55 (1 H, m), 0.8–1.3 (15 H, m); mass spectrum, 143 (7), 103 (100), 86 (18), 75 (50), 73 (87), 47 (56), 45 (64).

1,1,3,5-Tetraethoxy-2,4-dimethylhexane (4), and 1,1,3-Triethoxy-2,4-dimethyl-4-hexene (5). The end fraction of the preceding distillation (bp 94–115°) (10 mm) was redistilled, and found by glpc to consist principally of **5**, bp 112° (10 mm), n^{20}D 1.4345, d_4^{20} 0.9002; nmr 5.36 (1 H, q, J = 7 Hz, CH$_3$C*H*=), 4.59 (d, J = 2.5 Hz) and 4.17 (d, J = 7.5 Hz) (1 H together, HCC*H*(OEt)$_2$, two isomers), 3.0–3.75 (7 H, m, C*H*$_2$O and >C*H*O) 0.57–1.70 (19 H, m, C*H*$_3$ groups + 1 H); mass spectrum, 216 (<1), 199 (2) 183 (2), 113 (100), 103 (70), 85 (65), 75 (41), 47 (36).

Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.63; H, 11.55.

Two impurities were present in this fraction, the one with a longer retention time by glpc was identified as the diethoxyacetal (**4**), present as an isomeric mixture; nmr 4.52 (1 H, –C*H*(OEt)$_2$), 3.1–3.9 (10 H, C*H*$_2$O and C*H*O), 0.65–1.45 (23 H, C*H*$_3$, etc.); mass spectrum, 216 (<1), 199 (1), 183 (1), 159 (4.5), 143 (8), 129 (16), 113 (41), 103 (87), 86 (24), 85 (19), 75 (30), 73 (100), 45 (38).

Anal. Calcd for $C_{16}H_{34}O_4$: C, 66.16; H, 11.80. Found: C, 65.64; H, 11.15.

***threo*- and *erythro*-3-Ethoxy-2,4-dimethyl-4-hexenals.** The crude acetal (**5**) (50 g) was heated at reflux for 1 hr with 40 ml of 5% aqueous sulfuric acid in 20 ml of tetrahydrofuran and the product isolated in pentane. Washing, drying (MgSO$_4$), and distillation gave 21 g of a product, bp 101° (35 mm) consisting of three compounds that were separated by preparative glpc. The compound with the shortest retention time was not examined further after it was found to be a mixture of isomeric aldehydes from which the acetals (**4**) are derived. Its nmr spectrum had signals at 9.67 (1 H, d, J = 1.5 Hz, –C*H*O), 3.2–3.7 (6 H, m, C*H*$_2$OC and >C*H*OC), 2.2–2.7 (1 H, m, CHC*H*CH$_3$CHO), 0.8–1.6 (16 H, m, C*H*$_3$ etc.). Mass spectrum 170 (<1), 125 (13), 115 (13), 87 (54), 70 (23), 59 (100). The next compound eluted (50% of the total) was *erythro*-3-ethoxy-2,4-dimethyl-4-hexenal, closely followed by the *threo* isomer. The *threo* isomer had nmr 9.65 (1 H, d, J = 2 Hz, –C*H*=O), 5.54 (1 H, q+, J = 6.5 Hz, C=C*H*CH$_3$), 3.62 (1 H, d, J = 9.5 Hz, >CH—(O)C*H*C=), 3.21 (2 H, q+, J = 7 Hz, OC*H*$_2$CH$_3$), 2.45 (1 H, m, CHC*H*CH$_3$CHO), 1.67 (d, J = 6.5 Hz, C*H*$_3$CH=), superimposed on 1.56 (d, J = 1.5 Hz, C*H*$_3$C=CH–). 1.12 (3 H, t, J = 7 Hz, C*H*$_3$CH$_2$), 0.79 (3 H, d, J = 7 Hz, C*H*$_3$CH<),

Anal. Calcd for $C_{16}H_{22}N_4O_5$ [2,4-dinitrophenylhydrazone, mp 85–86° (EtOH)]: C, 54.84; H, 6.33; N, 15.99. Found: C, 55.04; H, 6.46; N, 15.91.

(30) M. Farina, M. Peraldo, and G. Bressan, *Chim. Ind.* (Milan), **42**, 967 (1960).

(31) I. N. Nazarov, S. M. Makin, and B. K. Kruptsov, *Dokl. Akad. Nauk SSSR*, **117**, 823 (1957).

(32) H. Normant and G. Martin, *Bull. Soc. Chim. France*, 1646 (1963).

The *erythro* isomer had nmr 9.67 (1 H, d, J = 2 Hz, -C*H*=O), 5.55 (1 H, q+, J = 6.5 Hz, C=C*H*CH_3), 3.75 (1 H, d, J = 6.5 Hz, >CH—(O)C*H*C=), 3.30 (2 H, CH_2(O)CH_3), 2.43 (1 H, m, CHC*H*CH_3CHO), 1.66 (d, J = 6.5 Hz, CH_3CH=) superimposed on 1.56 (d, J = 1.5 Hz, -(CH_3)C=C*H*-), 1.13 (3 H, t, J = 7 Hz, CH_3CH_2), 1.04 (3 H, d, J = 7 Hz, CH_3CH<).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 71.04; H, 10.76.

Anal. Calcd for $C_{16}H_{22}N_4O_5$ [2,4-dinitrophenylhydrazone, mp 138–139° (EtOH)]: C, 54.84; H, 6.33; N, 15.99. Found: C, 55.02; H, 6.50; N, 15.78.

The mass spectra of both isomers was practically the same, 170 (<1), 155 (1), 141 (1), 113 (93), 85 (100), 81 (13), 67 (10), 55 (16), 43 (37).

erythro-**3-Ethoxy-2,4-dimethyl-4-hexenol (7a).** Reduction of 0.5 g of the pure *erythro*-aldehyde in dry ether led to 0.45 g of the *erythro*-alcohol (**7a**), which had a longer retention time on glpc than the *threo*-alcohol (contrary to the aldehydes); ir spectrum (cm^{-1}, in CCl_4, 0.017 M), 3638 (free OH), 3520 (bonded OH), ratio of optical density free/bonded 1.4; nmr spectrum, 5.39 (1 H, q+, J = 7 Hz, C=C*H*CH_3), 3.0–3.6 (6 H, m, -OCH_2- and O*H*), 1.62 (3 H, broad d, J = 7 Hz, CH_3CH=) superimposed on 1.55 (3 H, broad s, CH_3C=), 1.13 (3 H, t, J = 7 Hz, CH_3CH_2), 0.90 (3 H, d, J = 6.5 Hz, CH_3CH).

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.85; H, 11.48.

threo-**3-Ethoxy-2,4-dimethyl-4-hexenol (7b).** Reduction of 0.5 g of the pure *threo*-aldehyde led to the *threo*-alcohol (0.46 g), with a shorter retention time on glpc than **7a**; ir spectrum (0.017 M), 3638 (free OH), 3518 (bonded OH), ratio of optical density free/bonded 0.15. At higher concentrations (up to 5%), the bonded OH band in the *threo*-alcohol remains fairly sharp compared with the *erythro*-alcohol, when the intermolecular bonding is apparent at 2% concentration; nmr spectrum, 5.39 (1 H, q, 6.5 Hz, C=C*H*CH_3), 3.0–3.6 (6 H, m, -OCH_2- and O*H*), 1.62 (3 H, d, J = 6.5 Hz, CH_3CH=) superimposed on 1.54 (3 H, d, J = 1 Hz, -(CH_3)C=), 1.15 (3 H, t, J = 7 Hz, CH_3CH_2), 0.66 (3 H, d, J = 6.5 Hz, CH_3CH<); mass spectrum (same for both isomers), 172 (<1), 113 (100), 85 (95), 67 (6), 55 (10), 43 (21).

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.67; H, 11.35.

1-Ethoxy-1,3-butadiene. In addition to the methods A and B described above for the preparation of ethyl propenyl ether, Nazarov's method[11] was employed. 1,1,3-Triethoxybutane (250 g) was heated with 10 g of ammonium dihydrogen phosphate in a distillation apparatus with a column surmounted by a total condensation take-off head. The distillate (bp 120–130°) was collected in 5% sodium carbonate solution, washed, dried, and refractionated to obtain 42 g of crude diene ether, together with 43 g of recovered acetal (40% yield based on converted material). By glpc, this product was found to be 98% *trans*-diene.[15]

1-Ethoxy-2-methyl-1,3-butadiene. This was prepared by methods A, B, and the ammonium phosphate method[11] just described. Apart from the starting materials, the principal impurity in the *trans*-diene ether (5–10% of the desired product) was **1,3-diethoxy-2-methyl-1-butene (11)**, with a retention time somewhat longer than the diene ether on glpc. **11** had the following spectral properties: nmr 5.72 (1 H, s, >C=C*H*O), 4.39 (1 H, q, J = 6.5 Hz, -(O)C*H*-CH_3), 3.64 (2 H, q, J = 7 Hz, CH_3CH_2O-), 1.40 (<3H, d, J 1.5 Hz, CH_3CH=, a weaker signal at 1.55 implying the presence of another isomer), 0.95–1.35 (9 H, m, CH_3); mass spectrum, 158 (26), 143 (100), 129 (3), 115 (35), 113 (74), 103 (12), 87 (100), 85 (96), metastables at m/e 65.8 (115 → 87), 63.9 (113 → 85).

β-Sinensal (16). A mixture of 1.5 g of 2-methyl-6-methyleneocta-2-*trans*,7-dienol,[1,18,33] 4.5 g of 1-ethoxy-2-methyl-1,3-butadiene, 1.0 g of mercuric acetate, and 0.4 g of sodium acetate (anhydrous) was heated at 100° for 48 hr, then filtered and distilled. A fraction weighing 2.4 g had bp 60–100° (0.02 mm), and after redistillation, 1.6 g of a mixture, bp 75–80° (0.02 mm), was obtained, consisting (glpc) mainly of β-sinensal. For analysis the substance was chromatographed on silica gel, 0.75 g of pure β-sinensal being eluted with benzene. The spectra (nmr, ir, and mass[34]) were identical with those of authentic β-sinensal.[35]

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.40; H, 10.35.

2,4-Dinitrophenylhydrazine, mp 80–81°, undepressed on mixing with authentic β-sinensal 2,4-dinitrophenylhydrazone.[35]

2,6-Dimethylocta-2-*cis*,6-*trans*-dienal (20) and 2,6-Dimethylocta-2-*trans*,6-*trans*-dienal (21). A mixture of 50 g of 2-methyl-2-butenol, 125 g of 1-ethoxy-2-methyl-1,3-butadiene, 15 g of mercuric acetate, and 5 g of anhydrous sodium acetate was heated at 100° for 15 hr in an argon atmosphere. Filtration and distillation gave 62.6 g of a fraction bp 62–96° (10 mm). This was purified by chromatography in the following way.[36] A 2-m length of nylon tubing (diameter 2 in.)[16] was sealed at one end, and filled with a slurry of silica gel[37] in petroleum ether (bp 80–100°) for 1.5 m of its length. Several small holes were made in the bottom of the nylon tube, then the crude aldehyde carefully added at the top. When this had fully been absorbed into the silica gel, 1000 ml of petroleum ether was added. At this stage, samples were taken with a hyperdermic syringe from various points along the column, the solutions obtained being tested by thin layer chromatography,[38] and in the regions where single spots were obtained, the nylon column was cut, and the products were washed out of the silica gel with ether. A fraction of 21.3 g was obtained, most of which distilled at bp 96–97° (10 mm), and consisted of about 85% (by glpc) of one isomer. For analysis, this was purified by glpc, its retention time being somewhat longer than its isomer. This compound, 2,6-dimethylocta-2-*trans*,6-*trans*-dienal (**21**), has nmr spectrum, 9.26 (1 H, s, -C*H*=O), 6.35 (1 H, t, J = 7 Hz, >C=C*H*CH_2-), the remaining signals are given in the theoretical part; mass spectrum, 152 (7), 137 (41), 123 (3), 109 (4), 84 (28), 69 (89), 55 (11), 53 (10), 41 (100).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.98; H, 10.66.

Anal. Calcd for $C_{11}H_{19}N_3O$ [semicarbazone, mp 175–176° (MeOH), nmr 7.43 (s, -C*H*=N-)]: C, 63.12; H, 9.15; N, 20.08. Found: C, 63.12; H, 9.36; N, 19.97.

Anal. Calcd for $C_{16}H_{20}N_4O_4$ [2,4-dinitrophenylhydrazone, mp 155–156° (EtOH)]: N, 16.86. Found: N, 16.87.

From a section of the silica gel chromatogram that was adjacent to that described previously (above), 9.5 g of a product were obtained that were distilled on a spinning-band column. The first fractions (bp 94–95° (10 mm)) contained (by glpc) 65% of a compound with slightly shorter retention time than the *trans,trans* isomer that could be purified by glpc for analysis, and which was identified as 2,6-dimethylocta-2-*cis*,6-*trans*-dienal (**20**); nmr spectrum 10.01 (1 H, s, -C*H*=O), 6.37 (1 H, t, J = 7.5 Hz, C=C*H*CH_2-), the remaining signals are given in the theoretical part.

From the fraction obtained from the spinning-band column, 1 g was converted to a mixture of the semicarbazones, and after several recrystallizations, a fraction, mp 121–123°, was isolated from the more soluble part, and which appeared to be pure by nmr (in CCl_4–$CDCl_3$), having a signal at 7.87 (s, -C*H*=H-).

Anal. Calcd for $C_{11}H_{19}N_3O$: N, 20.08. Found: N, 19.89.

2,6-Dimethylocta-2-*trans*,6-*trans*-dienol and 2,6-Dimethylocta-2-*cis*,6-*trans*-dienol. The aldehyde mixture described above was reduced with lithium aluminum hydride in dry ether, and after conventional work-up, the title compounds were separated by preparative glpc; boiling point of mixture 104–106° (10 mm).

The *trans,trans*-dienol was the major product (80%), and had nmr spectrum, 5.0–5.4 (2 H, broad, -CH=C<), 3.84 (2 H, s, -CH_2O), 2.0 (4 H, broad, =CCH_2CH_2C=), 1.59 (6 H, s, CH_3C=) superimposed on 1.54 (3 H, d, J = 6.5 Hz, CH_3CH=); mass spectrum, 154 (<1), 136 (27), 123 (15), 121 (19), 107 (6), 95 (10), 84 (20), 69, (55), 55 (26), 43 (100), 41 (82).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.98; H, 11.88.

The *cis,trans*-dienol had nmr spectrum, 5.0–5.4 (2 H, broad, -C*H*=C<), 3.98 (2 H, s, -CH_2O), 2.0 (4 H, broad, =CCH_2-CH_2C=), 1.73 (3 H, s, -(CH_3)C=), 1.59 (s) superimposed on 1.54 (d, J = 6.5 Hz, 6 H in both, -(CH_3)-C= and CH_3CH=). The mass spectrum was practically identical with that of the other isomer.

2,6,10-Trimethyldodeca-2,6,10-trienal (*all-trans*) (**24**). A mixture of 3.3 g of *all-trans*-2,6-dimethylocta-2,6-dienol (containing 2%

(33) R. Delaby and E. Dupin, *Bull. Soc. Chim. France*, **5**, 931 (1938).

(34) A. F. Thomas, B. Willhalm, and R. Müller, *Org. Mass Spectry.*, **2**, 223 (1969).

(35) K. L. Stevens, R. E. Lundin, and R. Teranishi, *J. Org. Chem.*, **30**, 1690 (1965). Dr. Teranishi was most helpful in helping us to establish the identity of our synthetic sinensal with the natural product.

(36) Obtained from Walter Coles & Co., Ltd., Backhouse Works, Surrey square, Walworth, London, S.E., England.

(37) Kieselgel 0.05–0.2 mm (70–325 mesh ASTM), Merck AG, Darmstadt, Germany.

(38) Finished silica gel plates for thin layer chromatography, 20 × 20 cm, obtained from Merck AG, Darmstadt, Germany.

2-*cis*,6-*trans* isomer), 5 g of 1-ethoxy-2-methylbutadiene, 0.5 g of mercuric acetate, and 0.5 g of sodium acetate was heated at 100° for 18 hr, then distilled, collecting the fraction bp 100° (0.01 mm). Glpc indicated that the C_{15} fraction of the product contained 27% of a substance with shorter retention time (presumably 2,6,10-trimethyldodeca-2-*cis*,6-*trans*,10-trienal) and 73% of the principal substance, identified after collection and analysis, as the title compound; nmr spectrum, 9.23 (1 H, $-CH{=}O$), 6.35 (1 H, t, J = 7.5 Hz, $-CH_2CH{=}CC{=}O$), 4.9–5.3 (2 H, $-CH{=}C$), 1.95–2.6 (8 H, m, $-CH_2CH_2-$), 1.72 (3 H, broad s, $CH_3C(CHO){=}$), 1.61 (s) superimposed on 1.59 (s) and 1.54 (d, J = 6.5 Hz); mass spectrum, 220 (1), 205 (2), 203 (1), 137 (59), 136 (18), 123 (20), 107 (13), 95 (53), 93 (72), 84 (58), 81 (85), 69 (100), 55 (91), 41 (100).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 82.10; H, 11.01.

When the experiment was repeated in exactly the same way with 2 g of 2,6-dimethylocta-2-*cis*,6-*trans*-dienol containing 25% of the *all-trans* isomer, glpc indicated the presence of 25% of the substance of shorter retention time, and 75% of the product with longer retention time. The latter was collected, and had identical ir, nmr, and mass spectra with *all-trans* compound described above.

2,7,11-Trimethyldodeca-2-*trans*,6-*cis*,10-trienal (28). A mixture of 10 g of geraniol, 25 g of 1-ethoxy-2-methylbutadiene, 6.6 g of mercuric acetate, and 2.7 g of anhydrous sodium acetate was heated for 18 hr at 100° under an argon atmosphere. After distillation, the fraction (9.3 g) with bp 105–120° (0.01 mm) contained (glpc) at least 70% of the aldehyde fraction as an isomer of shorter retention time than the remaining 30%. The composition was not greatly changed after purification of this fraction by chromatography in benzene on a column of silica gel. Collected by glpc, this main fraction was identified as the title compound, with the following spectra: nmr, at 100 Mcps in $CDCl_3$, 9.38 (1 H, s, $-CH{=}O$), 6.47 (1 H, t, J = 6.5 Hz, $-CH{=}C(CHO)-$), 5.1 (2 H, appears as three superimposed signls, $-CH{=}C<$), 2.0–2.5 (8 H, m, characterized by two sharp signals at 2.02 and 2.05, $=CCH_2CH_2C{=}$), 1.73 (3 H, s, $CH_3C(CHO){=}$), 1.66 (6 H, s, $-(CH_3)C{=}$) 1.59 (3 4, s, $-(CH_3)C{=}$); mass spectrum, 220 (1), 205, 187, 177, 162 (all about 1), 149 (2), 137 (8), 123 (3), 109 (2), 95 (8), 84 (24), 81 (24), 69 (100), 55 (10), 41 (38).

Anal. Calcd for $C_{15}H_{24}O$: C, 81,76; H, 10.98. Found: C, 81.39; H, 10.86.

The aldehyde was also purified through the **semicarbazone.** The crude semicarbazone from the reaction mixture (mp 108.5–111°) was recrystallized seven times from methanol, when the melting point was 121–122.5°. Further recrystallization did not raise the melting point.

Anal. Calcd for $C_{16}H_{27}N_3O$: C, 69.27; H, 9.81; N, 15.15, Found: C, 69.58; H, 10.26; N, 15.51.

The **2,4-dinitrophenylhydrazone** was prepared from the semicarbazone in alcohol (20 ml) containing 1 ml of concentrated HCl, mp 85°.

Anal. Calcd for $C_{21}H_{28}N_4O_4$: N, 13.99. Found: N, 14.16.

When 1 g of the semicarbazone was heated at reflux with 1 g of oxalic acid in 20 ml of water, then steam distilled, 0.3 g of recovered aldehyde (pure) was obtained, which was used to make the corresponding alcohol.

2,7,11-Trimethyldodeca-2-*trans*,6-*trans*,10-trienal (29). This was made from nerol in exactly the same way as described above for the *trans*,*cis* isomer. Purification was either by preparative glpc, or by fractional crystallization of the **semicarbazone.** The latter, after eight recrystallizations from methanol had mp 137–138°.

Anal. Calcd for $C_{16}H_{27}N_3O$: N, 15.15. Found: N, 15.38.

The **2,4-dinitrophenylhydrazone** was prepared from the semicarbazone in alcohol (20 ml) containing 1 ml of concentrated HCl, mp 106–107°.

Anal. Calcd for $C_{21}H_{28}N_4O_4$: N, 13.99. Found: N, 14.35.

The free aldehyde (**29**) had the following spectra: nmr, at 100 Mcps in $CDCl_3$, 9.38 (1 H, s, $-CH{=}O$), 6.47 (1 H, t, J = 6.5 Hz, $-CH{=}C(CHO)-$), 5.1 (2 H, appears as four superimposed signals, $-CH{=}C<$), 2.0–2.5 (8 H, m, characterized by a single signal at 2.01, $=CCH_2CH_2C{=}$), 1.73 (3 H, s, $CH_3C(CHO){=}$), 1.66 (3 H, s, $-(CH_3)C{=}$), 1.59 (6 H, s, $-(CH_3)C{=}$); mass spectrum 220, 205, 177 (all about 1), 149 (2), 137 (8), 123 (5), 109 (2), 95 (7), 84 (26), 81 (20), 69 (100), 55 (11), 41 (35).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.39; H, 10.86.

2,7,11-Trimethyldodeca-2-*trans*,6-*cis*,10-trienol (30). This was prepared by reducing the aldehyde (**28**) with lithium aluminum hydride in dry ether. After work-up, the product was distilled, bp 93° (0.001 mm), when it had the following spectra: nmr (different from the corresponding *all-trans*-alcohol (below)), 2.02 and 1.97 (the two maxima in the CH_2CH_2 multiplet region are of equal intensity), 1.66 (6 H, two maxima just visible, $-(CH_3)C{=}CR$ (*cis*)[39]), 1.60 and 1.61 (6 H, two maxima visible, $-(CH_3)C{=}C-$ (*trans*)[39]); mass spectrum, 222, 204, 191 (<1), 179 (2), 137 (12), 123 (5), 109 (3), 95 (18), 93 (10), 81 (59), 69 (100), 55 (9), 43 (24), 41 (42).

2,7,11-Trimethyldodeca-2-*trans*,6-*trans*,10-trienol. This was prepared in a similar manner from the *all-trans*-aldehyde **(29)**, and after distillation, bp 101° (0.01 mm), had nmr spectrum identical in all respects with that of the substance described by Corey, *et al.*,[29] in particular the $-CH_2CH_2-$ region has three maxima, at 2.09, 2.02, and 1.99 (intensity increasing in that order), and the CH_3 region has two maxima only at 1.66 and 1.60; mass spectrum, almost identical with the *trans*,*cis* isomer.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.74; H, 11.52.

Reaction of Geraniol with 1-Ethoxybuta-1,3-diene. A mixture of 20 g of geraniol, 50 g of ethoxybutadiene, 6.6 g of mercuric acetate, and 2.7 g of sodium acetate was heated in an argon atmosphere for 18 hr at 98°. After removing the excess diene at 100° (10 mm), the residue was chromatographed on a column of silica gel. The first compound eluted with benzene was distilled, bp 94–96° (0.1 mm), giving 6.3 g of **2-ethylidene-3-vinyl-3,7-dimethyl-6-octenal (32)**, that was shown (glpc) to be about 92% of one isomer; nmr spectrum, 9.98 (1 H, s, CH_3C = CCHO (*cis*)), trace at 9.22 (CH_3C = CCHO (*trans*)), 6.36 (1 H, q, J = 7.5 Hz, CH_3CH = C<), 5.7–6.2 (1 H, m, $-CH{=}CH_2$), 4.7–5.2 (3 H, m, $-CH{=}CH_2$ + $-CH{=}C<$), 2.08 (3 H, d, J = 7.5 Hz, $CH_3CH{=}$), 1.35–1.9 (10 H, $CH_3C{=}$ and CH_2CH_2), 1.23 (3 H, s, $CH_3C<$); mass spectrum, 206 (2), 191 (15), 173 (12), 163 (17), 138 (30), 123 (38), 110 (35), 109 (42), 95 (41), 83 (35), 69 (56), 55 (100), 41 (90) (a complex spectrum; only the most important fragments in each group are given); uv spectrum, λ_{max} 234 nm (ϵ_{max} 8502).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.28; H, 10.78.

A second compound was eluted from the silica gel column later, after distillation, bp 110–113° (0.01 mm), 2.1 g of nearly pure (glpc) **7,11-dimethyldodeca-2-*trans*,6-*cis*,11-trienal (33)** with the following spectra: nmr, 9.38 (1 H, d, J = 7.5 Hz, $=CHCH{=}O$) 6.75 (1 H, d of t, J = 15.5 and 6 Hz, $-CH_2CH{=}CH-$ (*trans*)), 5.98 (1 H, d of d, J = 7.5 and 15.5 Hz, $-CH{=}CHCHO$), 4.8–5.3 (2 H, $-CH_2CH{=}$), 1.9–2.5 (8 H, $-CH_2CH_2-$), 1.67 (6 H, $CH_3C{=}CH$) (*cis*)), 1.59 (3 H, $CH_3C{=}CH$ (*trans*)); mass spectrum, 206, 191, 173 (all about 1), 163 (2), 136 (5), 123 (4), 109 (3), 93 (8), 81 (11), 70 (23), 69 (100), 41 (45); uv, λ_{max} 218 nm (ϵ_{max} 19,950).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.96; H, 10.74.

Anal. Calcd for $C_{20}H_{26}N_4O_4$ [2,4-dinitrophenylhydrazone, mp 94–95° (EtOH)]: N, 14.50. Found: N, 14.91.

Reaction of Nerol with 1-Ethoxybuta-1,3-diene. The reaction was carried out with the same quantities and by the same technique as in the case of geraniol. The products were purified as before, and the first compound eluted from the silica gel column was identical in ir, nmr, mass, and uv spectra with **32** described above. The second compound eluted was different from the second compound described above, and was **7,11-dimethyldodeca-2-*trans*,6-*trans*,11-trienal**, having a longer retention time on glpc than the *trans*,*cis* isomer, and with the following spectra: nmr, very similar to the previous isomer, but with 1.66 (3 H, s, $CH_3C{=}C$) and 1.59 (6 H, broad s, $CH_3C{=}C$ (*trans*)). The mass spectrum was practically identical with the other isomer.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.60; H, 10.72.

Anal. Calcd for $C_{20}H_{26}N_4O_4$ [2,4-dinitrophenylhydrazone, mp 91° (EtOH)]: N, 14.50. Found: N, 13.86.

Anal. Calcd for $C_{15}H_{25}N_3O$ [semicarbazone, mp 113–114° (MeOH)]: C, 68.40; H, 9.57; N, 15.96. Found: C, 68.10; H, 9.95; N, 15.33.

1-Hydroxy-2-methylene-3-butene (35). A sample was prepared by reduction (lithium aluminum hydride) of dimethyl itaconate, and pyrolysis of the resulting acetate,[40] but the following procedure was preferred for larger amounts.

1,1-Dioxy-3-bromomethyl-1,5-dihydrothiophene (50 g, made by brominating the sulfur dioxide adduct of isoprene with N-bromo-

(39) Refers to the double-bond configuration, not to the side on which the methyl is placed.

(40) W. J. Bailey, W. G. Carpenter, and M. E. Hermes, *J. Org. Chem.*, 27, 1975 (1962).

succinimide[41]) was heated at 160–165° (10 mm), collecting the distillate in, first, a trap at 0°, then a second trap cooled in liquid nitrogen. There were 20 g of 1-bromo-2-methylene-3-butene obtained by this technique,[42] of bp 25° (10 mm), sufficiently pure for the next step. After purification by glpc on a silicone column, the compound had nmr, 4.05 (2 H, s, CH_2Br), 5.0–5.6 (4 H, m, $C{=}CH_2$), 6.33 (1 H, d of d, J = 10.5 and 17 Hz, $-CH{=}C$); mass spectrum 146/148 (28), 67 (100), 41 (51).

Anal. Calcd for C_5H_7Br: Br, 54.37. Found: Br, 53.19.

This compound was heated at reflux for 18 hr in 10 ml of ethanol with 1.64 g of anhydrous sodium acetate, then distilled. Redistillation gave 0.8 g of pure 1-acetoxy-2-methylene-3-butene, bp 72° (45 mm), of identical ir, nmr, and mass spectra with that obtained from dimethyl itaconate.[40] When the acetate was reduced with lithium alumin hydride in ether, a product (**35**) of identical properties with that described by Bailey, *et al.*,[40] was obtained.

When this compound was treated under the usual conditions with 1-ethoxy-2-methyl-1,3-butadiene, only traces (glpc) of the aldehyde **36** were obtained.

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(41) R. C. Krug and T. F. Yen, *J. Org. Chem.*, **21**, 1082, 1441 (1956).
(42) G. B. Butler and R. M. Ottenbrite, *Tetrahedron Letters*, 4873 (1967), report a similar preparation of 1,4-dibromo-2,3-dimethylenebutane.

A Novel Synthesis of Substituted Allenes[1]

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Contribution from the Research Laboratories, Syntex, S.A., Mexico, D. F., Mexico. *Received December 21, 1968*

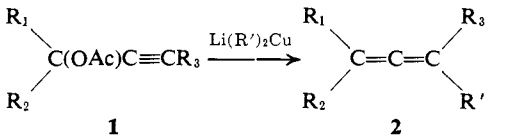
Abstract: Alkyl allenes were obtained by the reaction of 1-ethynylcycloalkanol acetates with the organocopper reagents, $LiMe_2Cu$ and $Li\text{-}n\text{-}Bu_2Cu$. Reactions of steroidal ethynylcarbinol acetates show that the reaction is not stereoselective. The functional group specificity of the organocopper reagents and the scope of the reaction are outlined.

Although allenes were characterized long ago as a distinct class of organic compounds, they have received only limited attention from organic chemists.[3] Even at the present time, the more common synthetic methods for the preparation of alkylallenes present a number of inherent difficulties when applied to complicated polyfunctional molecules.

In connection with some studies with the organocopper(I) reagent[4,5] we observed the ready transformation of ethynylcarbinol acetates to alkyl allenes.

In this paper we wish to report full details of our novel allene synthesis,[6] as well as additional findings obtained recently.

The general applicability of the organocopper(I) reagents for the synthesis of alkylallenes **2**, from substituted ethynylcarbinol acetates **1** was tested by the transformations listed in Table I.



1 **2**

These results (Table I) show that secondary, tertiary, and quaternary nonterminal allenes are obtained in fair to high yields by this method. No allenic product could be isolated from the reaction of 1-ethynylcyclohexanol acetate (**5**), with methyllithium alone, thus the reaction is not effected by the latter reagent. As expected, allenic material was not isolated from the reaction of 1-hexyne with $LiMe_2Cu$, indicating that an appropriate leaving group is necessary for the formation of the allene system. That the structure of the leaving group is of considerable importance is indicated by the absence of allenic material in the product of reaction 1-ethynylcyclohexanol (**9**) and lithium dimethylcopper(I).

The organocopper(I) compounds reported in organic synthesis (excluding reactions of organomagnesium halides with catalytic amounts of copper compounds present), to our knowledge, are the methyl, ethyl, and butyl derivatives.[4,7–9]

Our findings suggest that the lithium di-*n*-butylcopper(I) ($Li\text{-}n\text{-}Bu_2Cu$) compound behaves in a manner analogous to the $LiMe_2Cu$ reagent. Thus the compound obtained from the reaction of equimolar amounts of *n*-butyllithium and copper(I) iodide did not react with 1-ethynylcyclohexanol acetate (**5**), whereas the product of the reaction of 2 mol equiv of *n*-butyllithium with 1 mol equiv of copper(I) iodide reacted with the substituted ethynylcarbinol acetates **5** and **11** to produce allenes (Table I).

(1) Publication No. 354 from the Syntex Institute of Steroid Chemistry. For No. 353, see: P. Rona, L. Tökes, J. Tremble, and P. Crabbé, *Chem. Commun.*, 43 (1969).
(2) Syntex Postdoctoral Research Fellow, 1967–1968.
(3) (a) D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967), and references cited therein; (b) K. Griesbaum, *Angew. Chem. Int. Ed. Engl.*, **5**, 933 (1966); (c) M. V. Mavrov and V. F. Kucherov, *Russ. Chem. Rev.*, **36**, 233 (1967); (d) M. Bertrand, *Bull. Soc. Chim. Fr.*, 3044 (1968); (e) See also: H. Fischer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter 13.
(4) This study was stimulated by the reported exchange of halogen by alkyl with this reagent, see: E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967); **90**, 5615 (1968).
(5) P. Rona, L. Tökes, J. Tremble, and P. Crabbé, *Chem. Commun.*, 43 (1969).
(6) For a preliminary communication, see: P. Rona and P. Crabbé, *J. Amer. Chem. Soc.*, **90**, 4733 (1968).
(7) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966), and references therein.
(8) J. A. Marshall and H. Roebke, *ibid.*, **33**, 840 (1968).
(9) H. O. House and W. F. Fisher, Jr., *ibid.*, **33**, 949 (1968).