A Highly Stereoselective Synthesis of *trans*-Trisubstituted Olefinic Bonds

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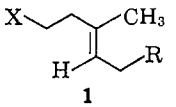
Abstract: The Julia olefin synthesis has been modified in such a way that homoallylic bromides containing *trans*-trisubstituted olefinic bonds are formed with high stereoselectivity. These substances are useful as intermediates in the preparation of polyolefinic isoprenoid types. The new scheme is illustrated by the synthesis of *trans*-1-bromo-3,7-dimethylocta-3,7-diene (**12**) (R = CH_3). Thus the known 1-acetyl-1-methylcyclopropane (**13**) (R = H) was converted, by condensation with diethyl carbonate, into the keto ester **13** (R = CO_2Et). The enolate anion of this keto ester was alkylated with methallyl chloride to give **14** (R = CH_3) which, on treatment with barium hydroxide followed by mineral acid, underwent hydrolysis and decarboxylation to give the unsaturated ketone **15** (R = CH_3). Lithium aluminum hydride reduction of this ketone afforded the carbinol **11** (R = CH_3), treatment of which with phosphorus tribromide and collidine effected its conversion into a mixture of bromides apparently containing substantial amounts of cyclopropylcarbinyl and cyclobutyl bromides. This mixture of bromides, on treatment at 0° with a suspension of anhydrous zinc bromide in ether, was smoothly isomerized to give a product which was mainly the *trans*-bromo diene **12** (R = CH_3). Only trace amounts of the *cis* isomer were formed. The over-all yield for the total process was good. The method has also been applied to the preparation of the lower homolog **12** (R = H).

The encouraging aspects[1-3] of our studies on polyolefinic cyclizations have stimulated a search for practical and efficient stereoselective syntheses of olefinic systems. In particular, attention has been focussed on the problem of generating substances with *trans*-trisubstituted olefinic bonds of the type represented by formula **1** (where R is an unsaturated hydrocarbon residue and X is a functional group) which can serve as intermediates for the production of polyolefinic substrates for cyclization studies. Herein we disclose a novel adaptation of the Julia olefin synthesis,[4] which has afforded several compounds of type **1** in good yield and with exceedingly high stereoselectivity. The method is applicable to systems containing highly acid-sensitive olefinic bonds.



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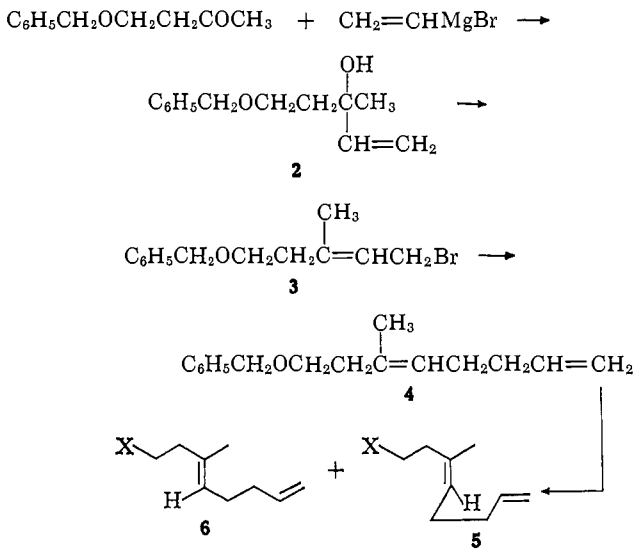
Of the various methods previously available for the synthesis of substances with trisubstituted olefinic bonds, we have found the method of Cornforth[5,6] particularly useful for producing the *trans* isomers. The stereoselectivity of the process is determined in the first step involving the formation of a chlorohydrin by addition of a Grignard reagent to an α-chloro ketone; one of the two possible diastereoisomeric chlorohydrins predominates in the reaction mixture.[7] Treatment with base transforms the chlorohydrin stereospecifically into the corresponding epoxide, which is then converted to the olefin by a two-step procedure that preserves the stereochemical integrity of the molecule. The efficacy of the method was dramatically demonstrated by the synthesis of all-*trans* squalene with greater than 70% stereoselectivity with respect to each of the double bonds.[6] In our own applications of the Cornforth scheme we have realized some improvement in the stereoselectivity simply by operating at lower temperatures in the first step. By this expedient, for example,[8] it was found that the proportion of *trans* isomer obtained at the end of the four-step sequence was increased from 75% when the reaction of 3-chloro-6-hepten-2-one with the Grignard reagent from 1-benzyloxy-4-chlorobutane was carried out at −70°, to over 90% when the reaction was performed at −90°. In another case the low-temperature modification gave a *trans*:*cis* ratio of 94:6. Such improvements have enabled us to secure samples of materials which were suitable for cyclization studies without the need for further purification.

In certain instances, however, the Cornforth method has proved inapplicable for our purposes. As a result we have sometimes had to rely on alternative syntheses that are considerably less stereoselective. In general the Wittig reaction[9] has served well when we have desired samples of both *cis* and *trans* forms,[3] but we were always faced with the often difficult problem of separating the isomers. Thus about equal amounts of *cis* and *trans* isomers are usually obtained when methyl ketones are allowed to react with alkylidenetriphenylphosphoranes by the procedure of Corey.[10] In a single attempt to apply the modification of Schlosser and Christmann,[11] whose report includes no example

(1) W. S. Johnson, N. P. Jensen, and J. Hooz, *J. Am. Chem. Soc.*, **88**, 3859 (1966).
(2) W. S. Johnson and R. B. Kinnel, *ibid.*, **88**, 3861 (1966).
(3) W. S. Johnson, A. van der Gen, and J. J. Swoboda, *ibid.*, **89**, 170 (1967).
(4) M. Julia, S. Julia, and R. Guégan, *Bull. Soc. Chim. France*, 1072 (1960).
(5) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959). The new method of E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 4245 (1967), provides another very highly stereoselective approach to these substances.
(6) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 2539 (1959).
(7) *Cf.* D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).
(8) F. E. Brot, Ph.D. Dissertation, Stanford University, 1966.
(9) (a) A. Maercker, *Org. Reactions*, **14**, 270 (1965); (b) S. Trippett, *Quart. Rev.* (London), **17**, 406 (1963); (c) W. Foerst, Ed., "Newer Methods of Preparative Organic Chemistry," Vol. III, Academic Press Inc., New York, N. Y., 1964, pp 111–150.
(10) *Cf.* R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

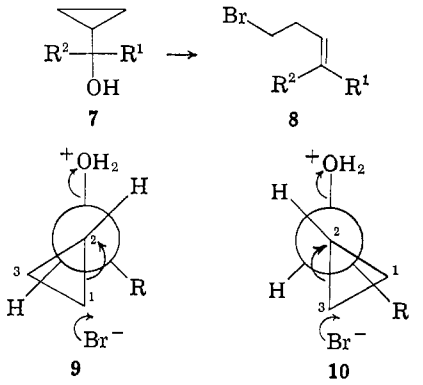
of reaction with an aliphatic methyl ketone, we noted no detectable increase in stereoselectivity.

We have developed another approach to structures of type **1** based upon the known conversion of tertiary vinylcarbinols into primary allylic bromides.[12] Thus the alcohol **2**, produced from the addition of vinylmagnesium bromide to 1-benzyloxybutan-3-one, was converted by treatment with phosphorus tribromide into the olefinic bromide **3**. This unstable allylic bromide was immediately treated with a solution of allylmagnesium bromide in tetrahydrofuran to give the coupling product **4** (mixture of *cis* and *trans* isomers)



which was transformed, by the action of sodium in liquid ammonia, into a mixture of the *cis*- and *trans*-dienols **5** (X = OH) and **6** (X = OH). The vapor phase chromatogram of this product showed two overlapping peaks in a ratio of about 1:1.5. The composition of this mixture was more accurately ascertained by the nmr spectrum (see Experimental Section). In particular this spectrum exhibited a pair of "singlets" in the ratio of 1:1.8 at δ 1.71 and 1.63 ppm accounting for a total of three protons. These signals are due to the methyl groups in the *cis* and *trans* isomers, respectively.[13] The mixture of bromides **5** (X = Br) and **6** (X = Br) was obtained by conversion of the mixture of dienols to the corresponding mixture of tosylates which was treated with lithium bromide in acetone. The over-all yield from the carbinol **2** was 36%. Although this process is more stereoselective than the Wittig reaction, it is not sufficiently so to obviate the isomer separation problem.

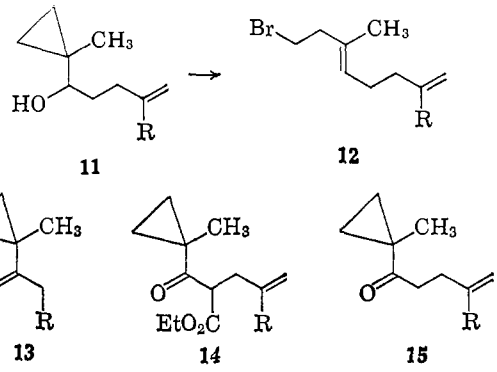
Julia[4,14] has developed a novel synthesis of homoallylic bromides by rearrangement of cyclopropylcarbinyl systems. Thus secondary cyclopropylcarbinols like **7** (R^1 = alkyl, R^2 = H), on treatment with 48% hydrobromic acid, have been converted into *trans*-bromo olefins, *i.e.*, **8** (R^1 = alkyl, R^2 = H), with 90–95% stereoselectivity.[14] It is to be noted that when the tertiary carbinol **7** (R^1 = alkyl, R^2 = CH_3)[4] is employed the process is less stereoselective. Thus in exploratory experiments carried out in our laboratory by B. B. Molloy, the Julia method was examined with the carbinol **7** (R^1 = *n*-C_4H_9, R^2 = CH_3) arising from addition of *n*-butylmagnesium bromide to cyclopropyl methyl ketone. Treatment of this carbinol with 48% hydrobromic acid gave a mixture of the bromide **8** (R^1 = *n*-C_4H_9, R^2 = CH_3) and its *cis* isomer in a ratio of about 3:1. Although the stereoselectivity was improved over the vinylcarbinol approach (see above), it was still not satisfactory. Moreover the method does not promise to be applicable to systems containing the acid-sensitive isopropenyl residue (see below).



The high stereoselectivity of the reaction with the aforementioned secondary carbinol can be rationalized[14] on the basis of transition states having geometry resembling that required for a concerted process as suggested by the Newman projection formulas **9** and **10** for the reactions to produce the *trans* and *cis* products, respectively. Models show that because of severe nonbonded interactions between hydrogen atoms on the cyclopropane ring at C-1 and on the R group the arrangement **10** is destabilized relative to **9**. Now if the hydrogen atom, which is located on the carbon holding the hydroxyl group, is replaced by a methyl group, the result would be to minimize this energy difference because of interactions between the hydrogen atoms at C-3 on the cyclopropane ring and on this methyl group in the form (**9**) leading to *trans* product. Thus it is entirely reasonable that the reaction of the tertiary carbinol **7** (R^1 = *n*-C_4H_9, R^2 = CH_3) is less stereoselective than that of the case where R^2 = H. On the other hand, it appeared from models that replacement of the hydrogen atom at C-2 on the cyclopropane ring by a methyl group would not appreciably alter the relative energies of **9** and **10** because this group interacts mainly with the hydroxyl in both cases. Therefore we were prompted to examine the rearrangement of carbinols of type **11** in the hope that high stereoselectivity would be realized to give the bromide **12**.[15]

The carbinols **11** were readily prepared from 1-methylcyclopropyl methyl ketone (**13**, R = H). Treatment with diethyl carbonate and sodium hydride[16]

(11) M. Schlosser and K. F. Christmann, *Angew. Chem. Intern. Ed. Engl.*, 7, 126 (1966).
(12) L. Ruzicka and G. Firmenich, *Helv. Chim. Acta*, **22**, 392 (1939).
(13) See ref 9, footnote 3.
(14) M. Julia, S. Julia, and S.-Y. Tchen, *Bull. Soc. Chim. France*, 1849 (1961).
(15) M. Julia, S. Julia, T. S. Yu, and C. Newville, *ibid.*, 1381 (1960), have prepared the ketone **13** (R = H) (see also M. Julia, *et al.*, *ibid.*, 1708 (1960)). They submitted this ketone to reduction and treated the resulting carbinol with hydrobromic acid. The bromide thus formed was reduced *via* the Grignard reagent to give a mixture containing several components. The principal component was shown to be *trans*-3-methyl-2-pentene; however, the degree of stereoselectivity of the synthesis was not ascertained. From the work described below in the present paper it seems probable that Julia's bromide was a complex mixture.
(16) *Cf.* S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963).



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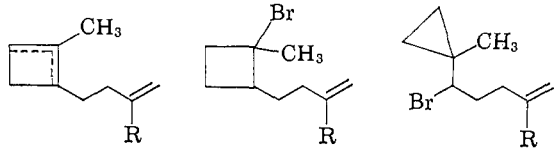
gave the keto ester **13** (R = CO_2Et). The sodio derivative, prepared by reaction of this keto ester with sodium hydride in tetrahydrofuran, was then treated with allyl bromide or with methallyl chloride to give the corresponding alkylation products **14** (R = H) and **14** (R = CH_3), which were decarbethoxylated by treatment with barium hydroxide.[4] Thus the ketones **15** (R = H) and **15** (R = CH_3) were produced in 84–86% over-all yields from the substance **13** (R = H). Each of these olefinic ketones was readily converted, by the action of lithium aluminum hydride in ether at 0°, into the corresponding carbinol **11** (R = H) or **11** (R = CH_3).



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Treatment of the carbinol **11** (R = H) with 48% hydrobromic acid at 0° for 1 hr afforded a mixture of at least four components. The nmr spectrum of this mixture showed singlet absorptions at δ 1.78, 1.62, 1.16, and 0.53 ppm in a ratio of about 50:10:25:15. The positions of these signals are in agreement with those expected for the methyl groups of the following substances, respectively: the cyclobutene **16** (R = H), the desired product **12** (R = H), the bromocyclobutane **17** (R = H), and the unrearranged bromide **18** (R = H) or the diene resulting from elimination of hydrogen bromide. Although these structural assignments are purely tentative, they conform to expectations based on the well-documented cationic interconversion of certain cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl systems.[17] Moreover, the apparent presence of a large proportion of the four-membered ring substances is in keeping with the expected substantial driving force for ring expansion resulting from formation of a tertiary (rather than secondary as in the case of the rearrangement of **7**, R^1 = H, R^2 = alkyl) methylcyclobutyl cation.

Roberts and Mazur[18] reported that a 2:1 mixture of cyclopropylcarbinyl and cyclobutyl bromides was converted into allycarbinyl bromide upon treatment at 0° with a solution of zinc bromide in hydrobromic acid. Therefore we examined the effect of this reagent on the carbinol **11** (R = H). The nmr spectrum of the crude product, recovered in 86% yield, showed singlet absorptions at δ 1.77, 1.64, and 1.17 ppm in the ratio of about 20:70:10. Moreover, the remainder of the spectrum resembled that of the authentic mixture of bromides **6** (X = Br) and **5** (X = Br) (see above) except that the methyl signal at 1.71 ppm due to the *cis* isomer **5** (X = Br) was completely absent. Thus the zinc bromide–hydrobromic acid treatment produced material containing a large proportion of the desired *trans* homoallylic bromide **12** (R = H) to the virtual exclusion of the *cis* isomer. When this method was applied to the homologous carbinol **11** (R = CH_3), we were disappointed to discover that the infrared spectrum of the product showed only a trace of absorption due to the terminal methylene group. Thus the acidic reaction conditions had effected isomerization of the isopropenyl into the more stable isopropylidene residue. In the hope of circumventing this undesired side reaction, we explored a variety of modified reaction conditions. It was discovered that the use of hydrobromic acid could be eliminated altogether by conducting the reaction in two stages. First the carbinol **11** (R = H) was treated at 0° in ether with phosphorus tribromide in the presence of collidine[19] and lithium bromide to give what was assumed, by analogy to the case of the higher homolog (see below), to be mainly a mixture of the bromides **17** (R = H) and **18** (R = H). Treatment of this mixture with a 1:4 molar ratio of zinc bromide in water at 0° gave a product, the infrared spectrum of which was practically identical with that of the aforementioned product from the zinc bromide–hydrobromic acid treatment.

When the phosphorus tribromide treatment was applied to the acid-sensitive homolog **11** (R = CH_3), the nmr spectrum of the product showed singlet absorption at δ 0.53, 1.09, and 1.17 ppm in a ratio of about 6:7:7. These values are consistent with those expected for the nonvinylic methyl signals of the following substances: **18** (R = CH_3), **17** (R = CH_3), and an epimeric form of **17** (R = CH_3). Since the spectrum showed absorption for two protons at 4.71 (terminal methylene) there was no appreciable double-bond migration. The aqueous zinc bromide treatment (see above) of this mixture gave a rearranged product which appeared, from the nmr spectrum, to contain about 60% of the desired *trans*-dienic bromide **12** (R = CH_3). In another rearrangement experiment in which the zinc bromide–water molar ratio was changed from 1:4 to 1:6, the terminal methylene group underwent extensive migration. Since the presence of water appeared to be deleterious, we tried effecting the rearrangement of the bromide mixture in ether solution by stirring with anhydrous zinc bromide at 0°. The product, obtained in 85–90% over-all yield from the carbinol **11** (R = CH_3), proved (see below) to be almost entirely the desired *trans*-dienic bromide **12** (R = CH_3). The nmr spectrum (see Experimental Section) was consistent with this structure, showing in particular a two-proton "singlet" at δ 4.68 ppm (terminal methylene) and two three-proton singlets at 1.65 (C-3 methyl, *trans* C=C) and 1.71 ppm (C-7 methyl).

Similarly the mixture of bromides obtained from the carbinol **11** (R = H) by the phosphorus tribromide reaction was converted, on treatment with anhydrous

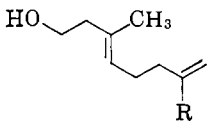
(17) R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Am. Chem. Soc.*, **81**, 4390 (1959). A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 138–140.

(18) J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951).

(19) *Cf.* C. G. Bergstrom and S. Siegel, *ibid.*, **74**, 145, 254 (1952).

zinc bromide, into the desired *trans*-dienic bromide **12** (R = H) in 71% over-all yield. The nmr spectrum of this product showed a three-proton singlet at δ 1.64 ppm (C-3 methyl, *trans* C=C) and only a trace signal at 1.73 ppm corresponding to the *cis* isomer.

Both bromides **12** (R = H and R = CH_3) appeared to be essentially homogeneous on thin layer chromatography. However they were relatively unstable substances, decomposing slightly on short-path distillation and extensively on prolonged storage at room temperature. Therefore it was found desirable to use the crude products as soon as possible after preparation.



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Confirmation of the structure and configuration of the aforementioned dienic bromides was obtained by conversion, upon treatment with potassium acetate in dimethylformamide followed by cleavage of the resulting acetates with lithium aluminum hydride, into the corresponding dienols **19** (R = H and R = CH_3). The spectral properties (see Experimental Section) of these products were in full accord with the assigned formulas. Vapor phase chromatographic analysis of the lower homolog **19** (R = H) indicated that it was 96% pure and was contaminated with only 3% of the *cis* isomer. The retention times of these isomers were identical with those observed for the mixture of dienols **5** (X = OH) and **6** (X = OH) prepared by independent synthesis (see above). Similar analysis of the dienol **19** (R = CH_3) indicated a purity of 97% with about 2% of the *cis* isomer as an impurity.

The high stereoselectivity of these zinc bromide catalyzed rearrangements is consistent with a concerted process involving attack of bromide on the cyclopropylcarbinyl system (see above). A consistent picture is also obtained if the transition state is envisaged as resembling a *folded* bicyclobutonium cation; however the stereoselectivity would be lost if a flat bicyclobutonium cation-like geometry were involved. Similarly, a transition state resembling a symmetrical tricyclobutonium cation is precluded. Since the composition of the mixture of bromides **5** (X = Br) and **6** (X = Br) remained unchanged on treatment in ether with anhydrous zinc bromide, it is clear that the rearrangement in question is a kinetically controlled process and does not involve an equilibration of the *cis* and *trans* isomers.

Experimental Section

General Considerations. All asymmetric substances described herein are racemic compounds; the prefix *dl* is omitted. Melting points were determined on a Kofler hot-stage microscope calibrated against totally immersed Anschutz thermometers. Vapor phase chromatographic analyses were performed on Wilkins Aerograph Hy-Fi vapor phase chromatographs (Models A-600 and A-600C) equipped with hydrogen flame ionization detectors. Nitrogen was used as carrier gas at a flow rate of approximately 25 cc/min. Relative peak areas were determined with a disk chart integrator, and values for peak areas of 10% or greater were usually accurate to ±5%. Nuclear magnetic resonance (nmr) spectra were determined under the supervision of Dr. L. J. Durham, Department of Chemistry, Stanford University, on either a Varian Associates A-60 or HA-100 spectrometer. Unless otherwise stated, carbon tetrachloride was employed as the solvent, with tetramethylsilane as the internal reference. The chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane = 0. Thin layer chromatographic (tlc) experiments were performed according to Stahl (E. Stahl, "Dünnschicht-Chromatographie Ein Laboratoriumshandbuch," Springer-Verlag, Berlin, 1962). Silica gel G (E. Merck AG) was employed as the adsorbent. The spots were detected either by the use of iodine or by spraying the plate with a 2% solution of ceric sulfate in 2 *N* sulfuric acid, followed by a heating period of 10 min at 150°. Unless otherwise stated, the elution order used in column chromatography was pentane, pentane–ether mixtures, and pure ether.

5-Benzyloxy-3-methylpent-1-en-3-ol (2). Vinylmagnesium bromide was prepared[20] from 28.5 g of magnesium and 126 g of vinyl bromide[21] in a total of 620 ml of tetrahydrofuran (0.5 ml of methyl iodide was used to initiate the reaction). Titration indicated that the solution contained 0.89 mol of the Grignard reagent. This reagent was cooled in an ice bath while a solution of 129 g of 4-benzyloxybutan-2-one,[22] bp 67–72° (0.15 mm), n^{23}D 1.498, in 200 ml of anhydrous ether and 100 ml of tetrahydrofuran was added with stirring over a period of 1.75 hr. Stirring was continued for 2 hr at 0° and then for 10 hr at ambient temperature. The mixture was cooled in an ice bath, and the excess vinylmagnesium bromide was decomposed by the slow addition of a saturated solution of 53.5 g of ammonium chloride in water which was made basic with ammonium hydroxide. The organic layer was decanted, and the residue was diluted with water and extracted with ether. The combined organic layers were dried over anhydrous magnesium sulfate. The orange oily residue obtained on removal of the solvent at reduced pressure was distilled through a 2-ft spinning-band column to give 117 g (78% yield) of colorless product, bp 80–82° (3 μ), λ_{max}^{film} 2.80 (OH), 6.08 and 10.95 (vinyl), and 9.10 μ (benzyl ether). The nmr spectrum showed absorption for 3 protons as a singlet at δ 1.18 ppm (CH_3), 2 protons as a multiplet between 1.55 and 2.01 (C-4 methylene), 2 protons as a triplet (J = 6.5 cps) centered at 3.54 (C-5 methylene), 2 protons as a singlet at 4.37 (benzyl methylene), 3 protons as a multiplet between 4.76 and 6.09 (vinyl protons), and 5 protons as a singlet at 7.20 (aromatic protons). A sample was submitted to short-path distillation at 80–82° (4 μ), n^{24}D 1.508.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 76.0; H, 8.7.

***cis*- and *trans*-3-Methylocta-3,7-dien-1-ol Benzyl Ether (4).** The tertiary alcohol **2** was converted into the allylic bromide **3** by an adaptation of a published procedure.[23] Thus a solution of 24.5 ml of phosphorus tribromide in 70 ml of petroleum ether (bp 68–70°) was added with stirring over a period of 1 hr to a cold (Dry Ice–2-propanol bath) solution of 110 g of the aforementioned carbinol **2** in 150 ml of anhydrous petroleum ether containing 13.5 ml of pyridine. The temperature of the reaction mixture was maintained between −15 and −5° during the addition and for an additional 2 hr afterwards. Then 30 ml of ice-cold saturated sodium bicarbonate solution was slowly added. The mixture was diluted with petroleum ether and ether, and the aqueous phase was extracted with ether. The combined organic layers were washed thoroughly with saturated sodium bicarbonate solution, then with water followed by saturated brine, and finally were dried over anhydrous magnesium sulfate. The residue obtained on removal of the solvent at reduced pressure was used immediately in the coupling reaction with allylmagnesium bromide.

A 500-ml portion of a concentrated solution of allylmagnesium bromide[24] in ether, containing (as shown by titration) 1.92 mol of Grignard reagent, was diluted with 780 ml of anhydrous tetrahydrofuran. This solution was stirred while a solution of the aforementioned crude 5-benzyloxy-3-methylpent-2-enyl bromide in 200 ml of tetrahydrofuran was added under nitrogen at such a rate that steady reflux was maintained. After the addition was complete (75 min), the mixture was heated at reflux for 1 hr and was then stirred at ambient temperature for 8 hr. The mixture was cooled (ice bath) while a saturated solution of 106 g of ammonium chloride in water made basic with ammonium hydroxide was added slowly with stirring. The organic layer was decanted and the residue washed with

(20) H. Normant, *Advan. Org. Chem.*, **2**, 37 (1960).
(21) P. N. Kogerman, *J. Am. Chem. Soc.*, **52**, 5060 (1930).
(22) This substance was prepared by a published procedure, (Ciba Ltd., British Patent 888,923 (Feb 7, 1962); *Chem. Abstr.*, **57**, 3290 (1962)) except that in the work-up the reaction mixture was diluted with ether and washed repeatedly with saturated sodium bicarbonate solution.
(23) J. W. Cornforth, R. H. Cornforth, G. Popják, and I. Y. Gore, *Biochem. J.*, **69**, 146 (1958).
(24) O. Grumitt, E. P. Budewitz, and C. C. Chudd, *Org. Syn.*, **36**, 60 (1956).

ether. The combined organic solutions were dried over anhydrous magnesium sulfate. The solvent was removed by distillation through a 2-ft, spinning-band column at atmospheric pressure; then the pressure was reduced to 0.5 mm and the distillation continued. The main fraction amounted to 86 g (70% yield) of a colorless liquid, bp 95–97° (0.5 mm), n^{23}D 1.506, λ_{max}^{film} 6.08, 10.05, and 10.95 (vinyl) and 9.10 μ (benzyl ether).

Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.6; H, 9.7.

The vapor phase chromatogram of this material at 185° on a 7.5-ft, 15% neutral Carbowax column showed two incompletely resolved peaks at retention times of 11.5 and 13 min in a ratio of about 1:1.8. A sample of the higher retention time material was separated by preparative vapor phase chromatography at 215° on a 20 ft × 0.375 in. Carbowax column. The nmr spectrum of this component (in $CDCl_3$) showed absorption for 3 protons as a singlet at δ 1.63 ppm (CH_3, *trans* C=C), 4 protons as a multiplet centered at 2.09 (C-5 and -6 methylenes), 2 protons as a triplet (J = 7 cps) at 2.30 (C-2 methylene), 2 protons as a triplet (J = 7 cps) at 3.55 (C-1 methylene), 2 protons as a singlet at 4.50 (benzylic methylene), 3 protons as a multiplet at 4.8–5.3 (C-4 and -8 vinyl protons), 1 proton as a multiplet at 5.5–6.1 (C-7 H), and 5 protons as a singlet at 7.30 (aromatic protons). This material therefore corresponded to the pure *trans* isomer.

***cis*- and *trans*-3-Methylocta-3,7-dien-1-ol (5, X = OH, and 6, X = OH).** To a solution of 6.5 g of the aforementioned mixture of *cis*- and *trans*-dienic benzyl ethers **4** in 150 ml of liquid ammonia and 50 ml of anhydrous ether was added slowly a total of 1.2 g of sodium in small pieces. When the last portion of sodium was added and the blue color persisted for about 30 min, solid ammonium chloride was added to decompose the excess sodium; then 200 ml of ether was added and the ammonia allowed to evaporate. The ether solution was washed well with water and with saturated brine and dried over anhydrous magnesium sulfate. The pale yellow liquid residue obtained on removal of the solvent by distillation through a 15-in. Podbielniak-type column was submitted to short-path distillation at 130° (22 mm) to give 3.7 g (93% yield) of colorless oil, n^{25}D 1.465, λ_{max}^{film} 2.85 (OH), 6.09, 10.05, and 10.95 μ (vinyl). A comparable specimen from another run was analyzed.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.9; H, 11.3.

The vapor phase chromatogram of this material at 130° on a 7.5-ft, 15% neutral Carbowax column showed two overlapping peaks at retention times of 17.3 and 19 min in a ratio of approximately 1.5:1. The nmr spectrum of this material (in $CDCl_3$) showed absorption for 3 protons as a pair of singlets in the ratio of about 1.8:1 at δ 1.63 and 1.72 ppm (CH_3 on *trans* and *cis* C=C, respectively), 6 protons as a multiplet at 2.0–2.43 (C-2, -5, and -6 methylenes), 2 protons as a triplet (J = 6 cps) at 3.63 (C-1 methylene), 3 protons as a multiplet at 4.8–5.4 (C-4 and C-8 vinyl protons), and 1 proton as a multiplet at 5.5–6.2 (C-7 H).

***cis*- and *trans*-1-Bromo-3-methylocta-3,7-diene (5, X = Br, and 6, X = Br).** A cold solution of 12.1 g of *p*-toluenesulfonyl chloride in 50 ml of anhydrous pyridine was added with stirring over a 1-hr period to a solution of 3.2 g of the aforementioned mixture of dienols **5** (X = OH) and **6** (X = OH) in 50 ml of pyridine. The mixture was kept at 5° for 48 hr, then 2 ml of water was added slowly with cooling, the resulting mixture was poured into 100 ml of ice-cold 20% hydrochloric acid and 200 ml of ether, and the aqueous phase was extracted with ether. The combined organic layers were washed with cold 10% hydrochloric acid and saturated sodium bicarbonate solution, followed by saturated brine, and finally dried over anhydrous magnesium sulfate. The crude yellow oily tosylate (4.2 g) obtained on evaporation of the solvent at reduced pressure was dissolved in 20 ml of acetone; then 2.6 g of lithium bromide (dried at 100° (0.1 mm) for 10 hr) was added. The mixture was stirred in the dark at ambient temperature under nitrogen for 48 hr. Most of the acetone was evaporated at reduced pressure; water and ether were added, and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated brine and dried over anhydrous magnesium sulfate. The yellow oily residue remaining after removal of the solvent by distillation through a 15-in. Podbielniak-type column was washed with pentane through a column of 30 g of Woelm basic alumina, activity II. Short-path distillation of the eluate at 100–110° (14 mm) gave 2.6 g (56% yield) of colorless oil, n^{20}D 1.494, λ_{max}^{film} 6.09, 10.03, and 10.95 μ (vinyl).

In another comparable run the crude product was chromatographed on Merck acid-washed alumina and submitted to short-path distillation at 40–45° (0.15 mm); then the product was purified by preparative vapor phase chromatography on a 20-ft Carbowax column at 135°. The major fraction was distilled as described above, n^{20}D 1.490.

Anal. Calcd for $C_9H_{15}Br$: C, 53.22; H, 7.45; Br, 39.34. Found: C, 53.0; H, 7.45; Br, 39.5.

The nmr spectrum of this material showed absorption for three protons as a pair of singlets in the ratio of about 1.9:1 at δ 1.63 and 1.72 ppm (CH_3 on *trans* and *cis* C=C, respectively), 3.9 protons as a multiplet centered at 2.11 (C-5 and -6 methylenes), 2.1 protons as a multiplet at 2.33–2.74 (C-2 methylene), 2 protons as a triplet (J = 7.5 cps) at 3.37 (C-1 methylene), 3 protons as a multiplet at 4.8–5.4 (C-4 and C-8 vinyl protons), and 1 proton as a multiplet at 5.5–6.2 (C-7 H).

1-Methylcyclopropyl Carbethoxymethyl Ketone (13, R = CO_2Et). The following is an adaptation of a published procedure.[16] A 1.85-g sample of a 54.7% dispersion of sodium hydride in mineral oil (Metal Hydrides, Inc.) was washed with three 10-ml portions of anhydrous pentane under nitrogen. Then 40 ml of anhydrous diethyl carbonate was added. This suspension was stirred while a solution of 2.00 g of 1-acetyl-1-methylcyclopropane,[15] bp 127–129° (760 mm), in 7 ml of diethyl carbonate containing four drops of absolute ethanol was added. After the addition was complete, the mixture was stirred for 15 min at 25°, then heated on the steam bath until reaction commenced as indicated by the steady evolution of hydrogen. Gentle heating was continued until gas evolution had ceased (about 1 hr). The mixture was cooled in an ice bath, and a solution of 2.4 ml of glacial acetic acid in 20 ml of ether was added. Water was then added, and the aqueous phase was extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution, followed by saturated brine, and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent at reduced pressure was distilled through a 2-ft spinning-band column to remove the excess diethyl carbonate, bp 35–37° (17 mm). The yellow oily residue was used without purification in the alkylation reaction described below.

A sample of the crude keto ester from another run was purified by chromatography on Merck acid-washed alumina. The fraction eluted with 20% ether in pentane was submitted to short-path distillation at 118–119° (15 mm) to give a colorless liquid, n^{22}D 1.4522, λ_{max}^{film} 5.75 (ester C=O), 5.92 (ketone C=O), and 6.18 μ (enol C=C).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.2; H, 8.2.

1-Methylcyclopropyl 1-Carbethoxy-3-butenyl Ketone (14, R = H). A 0.90-g sample of a 54.7% dispersion of sodium hydride in mineral oil was washed with three 5-ml portions of anhydrous pentane under nitrogen; then 20 ml of anhydrous tetrahydrofuran was added. The suspension was cooled to 0° and stirred while a solution of the aforementioned crude keto ester **13** (R = CO_2Et) in 5 ml of tetrahydrofuran was added over a period of 40 min. The mixture was stirred for 15 min at 20–25°; then a solution of 2.37 g of allyl bromide in 10 ml of tetrahydrofuran was added gradually over a period of 20 min. Toward the end of the addition a white precipitate began to form. The mixture was stirred at 20–25° for 10 hr, then heated at reflux for 1 hr, cooled in an ice bath, and treated with 5 ml of water, and the aqueous layer was extracted with ether. The combined organic layers were washed thoroughly with brine and dried over anhydrous magnesium sulfate. The pale orange liquid residue obtained on removal of the solvent at reduced pressure was employed, without further purification, in the decarboxylation step described below. A sample of comparable material from another run was submitted to short-path distillation at 75–80° (0.10 mm) to give a colorless liquid, $n^{24.5}$D 1.4579, λ_{max}^{film} 5.74 (ester C=O), 5.92 (ketone C=O), and 3.24, 6.08, and 10.84 μ (vinyl).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.5; H, 8.65.

1-Methylcyclopropyl 3-Butenyl Ketone (15, R = H). The following is an adaptation of a published procedure.[4] A mixture of the crude alkylated keto ester described in the preceding section, 15 ml of 95% ethanol, 40 ml of water, and 12.7 g of barium hydroxide octahydrate was heated at reflux for 19 hr in an atmosphere of nitrogen. The mixture was cooled and poured into 100 ml of water containing 25 ml of 10% hydrochloric acid overlaid with 100 ml of ether, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and saturated sodium bicarbonate solution, followed by saturated brine, and finally dried over anhydrous magnesium sulfate. The oily residue obtained on evaporation of the solvent at reduced pressure was submitted to short-path distillation at 80–90° (18 mm) to give 2.43 g (86% over-all yield from the ketone **13**, R = H) of a colorless

liquid, $n^{24}D$ 1.4543, λ_{max}^{film} 5.91 (C=O), 3.25, 6.07, 10.0, and 10.90 (vinyl), and 9.7 μ (cyclopropyl).

Anal. Calcd for $C_{19}H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.4; H, 10.3.

The vapor phase chromatogram on a 7.5-ft Carbowax column at 115° showed a single symmetrical peak, retention time 8.7 min. The nmr spectrum showed absorption for 4 protons as a pair of complex multiplets centered at δ 0.62 and 1.13 ppm (cyclopropyl protons), 3 protons as a singlet at 1.34 (CH_3), 4 protons as a triplet centered at 2.38 (methylenes α and β to carbonyl), 2 protons as a multiplet at 4.81–5.08 (vinyl methylene), and 1 proton as a multiplet at 5.4–6.0 (vinyl H).

1-Methylcyclopropyl-3-butenylcarbinol (11, R = H). A solution of 0.276 g of the aforementioned 1-methylcyclopropyl 3-butenyl ketone, $n^{24}D$ 1.4543, in 5 ml of anhydrous ether was added over a period of 20 min to a stirred mixture of 0.076 g of lithium aluminum hydride and 10 ml of ether. The temperature of the reaction mixture was maintained at 0° during the addition and for another hour afterwards. Saturated sodium sulfate solution (0.25 ml) was added, and the mixture was stirred for 15 min at 15–20°. This mixture was allowed to stand over anhydrous sodium sulfate for 30 min and filtered; the solvent was removed under reduced pressure to give 0.270 g of colorless liquid, λ_{max}^{film} 2.95 (OH) and 9.78 μ (cyclopropyl), which was suitable for use in subsequent steps.

A sample of the crude carbinol prepared as described above from 1.9 g of ketone was submitted to short-path distillation at 110–120° (18 mm) to give 1.86 g (96% yield) of a colorless liquid, $n^{23}D$ 1.4552.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.25; H, 11.5.

The vapor phase chromatogram of this material on a 7.5-ft Carbowax column at 120° showed a single symmetrical peak, retention time 13.5 min. The nmr spectrum showed absorption for 4 protons as a pair of broad singlets at δ 0.26 and 0.35 ppm (cyclopropyl protons), 3 protons as a singlet at 0.98 (CH_3), 4 protons as a pair of multiplets centered at 1.6 and 2.1 (methylenes α and β to carbinol), 1 proton as a triplet (J = 6.5 cps) centered at 2.78 (H on carbon holding OH), 2 protons as a multiplet at 4.83–5.10 (vinyl methylene), and 1 proton as a multiplet at 5.5–6.1 (vinyl H).

Transformations of 1-Methylcyclopropyl-3-butenylcarbinol. a. On Treatment with Hydrobromic Acid. The following is a modified adaptation of a published procedure.[14] A 0.140-g sample of the aforementioned crude 1-methylcyclopropyl-3-butenylcarbinol was added over a period of 5 min to 0.4 ml of vigorously stirred 48% hydrobromic acid at 0°. After addition was complete the mixture was stirred at −5 to 0° for 1 hr, 1 ml of pentane was added, and the resulting mixture was poured into 10 ml of ice-cold water overlaid with 20 ml of pentane. The organic layer was washed with saturated sodium bicarbonate solution, followed by saturated brine, and dried over anhydrous magnesium sulfate. The colorless oily residue obtained on removal of the solvent at reduced pressure amounted to 0.170 g. The nmr spectrum was complex but exhibited sharp singlet absorption at δ 1.78, 1.62, 1.16, and 0.53 ppm in the ratio of about 50:10:25:15. These signals are regarded as corresponding to the assignments made in the Discussion section. The spectrum also showed the same strong absorption in the 4.8–6.0 region that was present in the starting alcohol and is attributable to the vinyl group, which therefore appeared to survive the conditions of the reaction. The infrared spectrum, λ_{max}^{film} 6.08 and 10.9 μ, confirmed the survival of the vinyl group. This complex mixture was not examined further.

b. On Treatment with Zinc Bromide–Hydrobromic Acid. The following is a modified adaptation of a published procedure.[18] A 0.118-g sample of the aforementioned crude 1-methylcyclopropyl-2-butenylcarbinol was added over a period of 5 min to a vigorously stirred 0.655-g portion of a solution of 6.75 g of anhydrous zinc bromide in 5 ml of 48% hydrobromic acid. The temperature of the mixture was maintained at −20° during the addition and then at 0° for an additional hour thereafter. The product was isolated as described in the preceding experiment and amounted to 0.148 g of colorless oil, λ_{max}^{film} 6.09, 10.01, and 10.92 (vinyl) and 6.00 μ (C=CH). The infrared spectrum was also similar in the fingerprint region to that of the mixture of *cis*- and *trans*-bromides prepared by the vinylcarbinol method (see above). The nmr spectrum exhibited the features described in the Discussion section.

c. On Treatment with Phosphorus Tribromide Followed by Zinc Bromide. Preparation of *trans*-1-Bromo-3-methylocta-3,7-diene (12, R = H). The following is a description of a run carried out by K. E. Harding. A mixture of 2.66 g of the aforementioned 1-methylcyclopropyl-3-butenylcarbinol, 1.85 g of anhydrous collidine, and 3.32 g of anhydrous lithium bromide in 40 ml of anhydrous ether was cooled to −40° and vigorously stirred while 1.20 ml of phosphorus tribromide was added over a period of a few minutes. The mixture was allowed to warm to 0°, stirring was continued for 1.5 hr, and 2 ml of collidine was then added, followed by water to destroy the excess phosphorus tribromide. The resulting mixture was poured into water overlaid with pentane, and the aqueous layer was extracted with pentane. The combined organic solutions were washed with water, saturated sodium bicarbonate solution, and brine and were finally dried over anhydrous magnesium sulfate. The residue (3.2 g) obtained on evaporation of the solvent at reduced pressure was added slowly with stirring to a cooled (−40°) suspension of 3.75 g of anhydrous zinc bromide in 7 ml of anhydrous ether. A total of 2.4 ml of ether was used to aid in the transfer. The reaction mixture was then allowed to warm to 0°, stirring was continued for 1.5 hr, then pentane and 50% saturated brine were added. The aqueous layer was extracted with pentane, and the combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The pale yellow liquid residue (3 g) obtained on evaporation of the solvent at reduced pressure was washed through 150 g of Merck acid-washed alumina with 500 ml of pentane to give 2.77 g of a colorless liquid, $n^{25}D$ 1.4870. The infrared spectrum of this material was very similar to that of the authentic mixture of dienic bromides prepared by the vinylcarbinol method (see above). This product was used in subsequent transformations (see below) without further purification.

Anal. Calcd for $C_9H_{15}Br$: C, 53.20; H, 7.45; Br, 39.37. Found: C, 53.6; H, 7.3; Br, 39.1.

The high degree of stereoisomeric purity of this material was indicated by the nmr spectrum which showed absorption for 3 protons as a singlet at δ 1.64 ppm (CH_3, *trans* C=C), 4 protons as a triplet (J = 3 cps) centered at 2.10 (C-5 and -6 methylenes), 2 protons as a triplet (J = 7 cps) centered at 2.51 (C-2 methylene), 2 protons as a triplet (J = 7 cps) centered at 3.37 (C-1 methylene), 3 protons as a set of broad multiplets at 4.75–5.42 (C-4 and -8 vinyl protons), and 1 proton as a multiplet at 5.4–6.1 (C-7 H). There was only trace absorption at 1.73 for the methyl group of the *cis* isomer **5** (X = Br). A weak absorption at 1.26 ppm was also noted as being identical with a band exhibited by the spectrum of the hydrocarbon fraction produced as a by-product (elimination) in the preparation of the alcohol **19** (R = H) described below.

***trans*-3-Methylocta-3,7-dien-1-ol (19, R = H).** This run was also performed by K. E. Harding. A mixture of 1.18 g of the *trans*-dienic bromide **12** (R = H) prepared as described under section c directly above and 2.3 g of anhydrous potassium acetate in 30 ml of anhydrous dimethylformamide was stirred under nitrogen at 100° for 22 hr. The mixture was cooled; water and pentane were added, and the aqueous layer was extracted with pentane. The combined organic layers were washed with water followed by saturated brine and dried over anhydrous sodium sulfate. Most of the solvent was removed by distillation through a 15-in. Podbielniak-type column. The residue was diluted with 5–10 ml of anhydrous ether, and 0.27 g of lithium aluminium hydride was then added. The mixture was heated at reflux for 30 min, cooled to 25°, treated with 0.27 ml of water followed by 0.27 ml of 15% sodium hydroxide, then with an additional 0.8 ml of water. The resulting mixture was stirred for 10 min, dried over anhydrous magnesium sulfate, and filtered. The residue obtained on evaporation of the solvent from the combined filtrate and washings amounted to 0.71 g of a colorless liquid, λ_{max}^{film} 3.00 μ (OH), which was chromatographed on 35 g of Merck acid-washed alumina. The fraction eluted with 50% ether in pentane was submitted to short-path distillation at 125° (26 mm) to give 0.555 g (68% yield) of colorless sweet-smelling liquid, λ_{max}^{film} 3.00 (OH), 6.00 and 12.1 (C=CH), 6.11, 10.0, and 10.93 (vinyl), and 9.6 μ (CO).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.2; H, 11.6.

The vapor phase chromatogram (7.5-ft Carbowax column at 133°) of comparable material, $n^{25}D$ 1.4647, from another run showed a major peak (96% of total area) at retention time 17.5 min and a small peak (3%) at 19 min. These peaks were enhanced by co-injection with the mixture of *trans*- and *cis*-dienols prepared as described above by the vinylcarbinol method. The nmr spectrum at 100 Mc showed absorption for 3 protons as a singlet at δ 1.63 ppm (CH_3, *trans* C=C), 6 protons as a pair of triplets (J = 4 and 7 cps) centered at 2.09 and 2.17 (C-2, -5, and -6 methylenes), 1 proton as a singlet at 3.29 (OH), 2 protons as a triplet (J = 7.0 cps) at 3.55 (C-1 methylene), 3 protons as a multiplet at 4.88–5.19 (C-4 and -8 vinyl protons), and 1 proton as a multiplet at 5.5–6.0 (C-7 H). In addition there was a very faint signal at 1.70 (CH_3,

cis C=C) accounting for about 3% of the total intensity of the methyl signals.

1-Methylcyclopropyl 1-Carbethoxy-3-methyl-3-butenyl Ketone (14, R = CH_3). The procedure described for the alkylation of 1-methylcyclopropyl carbethoxymethyl ketone was modified. The crude keto ester obtained from 2.03 g of 1-methylcyclopropyl methyl ketone as described above was converted to the sodium enolate with sodium hydride prepared (see above) from 0.92 g of the 54.7% dispersion. A total of 30 ml of tetrahydrofuran was used, and after the addition (30 min) the solution was stirred for 3 hr at 25°. A solution of 2 g of methallyl chloride in 5 ml of tetrahydrofuran was added, and the mixture was heated at reflux for 35 hr. At the end of this period a precipitate had formed but the solution was still basic. Therefore, 0.4 g of anhydrous sodium iodide was added and refluxing continued for an additional 6 hr.[25] The mixture was cooled, water was added, and the aqueous layer was extracted with ether. The combined organic solutions were washed well with brine and dried over anhydrous magnesium sulfate. The pale orange liquid residue obtained on evaporation of the solvent under reduced pressure was used in the next stage of the synthesis without purification. A sample of comparable material from another run was chromatographed on Merck acid-washed alumina. The fraction eluted with pentane to 1% ether in pentane was submitted to short-path distillation at 80–85° (0.1 mm) to give a colorless liquid, $n^{22}D$ 1.4604, λ_{max}^{film} 5.74 (ester C=O), 5.92 (ketone C=O), and 3.24, 6.06, and 11.13 μ (C=CH_2).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.85; H, 8.9.

1-Methylcyclopropyl 3-Methyl-3-butenyl Ketone (15, R = CH_3). The crude keto ester of the preceding experiment was saponified and decarboxylated according to the procedure described above for the lower homolog. Short-path distillation of the product at 105–110° (17 mm) gave 2.78 g (88% yield over-all from ketone **13**, R = H) of colorless liquid, $n^{22}D$ 1.4604, λ_{max}^{film} 3.25, 6.06, and 11.21 (C=CH_2) and 5.91 μ (C=O). The vapor phase chromatogram on a 7.5-ft Carbowax column at 120° showed two peaks at retention times of 14.4 and 15.2 min with a peak area ratio of 19:1. These peaks comprised 97.3% of the total area. In an attempt to further purify this material, a sample was chromatographed on Merck acid-washed alumina. The fraction eluted with pentane to 2% ether in pentane gave on short-path distillation at 105° (17 mm) a colorless liquid, $n^{22}D$ 1.4604. The vapor phase chromatogram of this material was essentially the same as that of the unchromatographed product. The nmr spectrum showed absorption for 4 protons as a pair of complex multiplets centered at δ 0.63 and 1.15 ppm (cyclopropyl protons), 3 protons as a singlet at 1.35 (angular CH_3), 3 protons as a broad "singlet" at 1.73 (vinyl CH_3), 4 protons as a complex multiplet at 2.0–2.6 (methylenes α and β to carbonyl), and 2 protons as a broad "singlet" at 4.65 (vinyl methylene). The spectrum also exhibited a spurious weak signal at 3.48 possibly due to the unidentified impurity observed in the vapor phase chromatogram.[25]

An analytical specimen was secured by preparative vapor phase chromatography on a 20 ft × 0.375 in. 20% Carbowax column at 130°. The major component had a retention time of about 57 min and was readily separated from the minor contaminant.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.0; H, 10.5.

1-Methylcyclopropyl-3-methyl-3-butenylcarbinol (11, R = CH_3). A 2.59-g specimen of the distilled ketone described in the preceding preparation, $n^{22}D$ 1.4604, was reduced with lithium aluminum hydride according to the procedure described above for the lower homolog. Short-path distillation of the product at 115–120° (17 mm) afforded 2.54 g (97% yield) of a colorless liquid, $n^{21}D$ 1.4606, λ_{max}^{film} 2.97 (OH) and 3.26, 6.07, and 11.25 μ (C=CH_2). The vapor phase chromatogram on a 7.5-ft Carbowax column at 122° showed a major peak at retention time 19.0 min comprising 96.5% of the total area. Two minor peaks at 13.1 min (2.1%) and 3.3 min (1.4%) were noted. The nmr spectrum was in accord with the indicated formulation except for a very weak signal at δ 3.47 ppm which was probably due to the unidentified impurity present also in the starting ketone (see above).[25]

An analytical specimen was prepared by preparative vapor phase chromatography as described in the preceding experiment. The retention time of the major component was about 57 min.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.8; H, 11.75.

***trans*-1-Bromo-3,7-dimethylocta-3,7-diene (12, R = CH_3).** A mixture of 0.306 g of the aforementioned 1-methylcyclopropyl-3-methyl-3-butenylcarbinol, $n^{21}D$ 1.4606, 0.2 g of collidine, 0.59 g of lithium bromide, and 3 ml of ether was treated with 0.13 ml of phosphorus tribromide as described above for the lower homolog. The excess phosphorus tribromide was destroyed by the addition of 0.52 ml of collidine and 0.5 ml of water, and the product was isolated as described above to give 0.394 g of a colorless liquid, λ_{max}^{film} 3.25, 6.06, and 11.21 μ (C=CH_2). The nmr data and the tentative assignments of the constituents of this mixture of bromides are given in the Discussion section.

A 0.106-g sample of the crude mixture of bromides obtained from the phosphorus tribromide treatment described directly above was treated with a suspension of 0.124 g of anhydrous zinc bromide in 0.3 ml of ether as described above for the lower homolog. The crude product amounted to 0.101 g of a colorless liquid, λ_{max}^{film} 3.25, 6.06, and 11.22 μ (C=CH_2). The nmr spectrum at 100 Mc showed absorption for 3 protons as a singlet at δ 1.65 ppm (CH_3 at C-3), 3 protons as a singlet at 1.71 (CH_3 at C-7), 4 protons as a sharp multiplet centered at 2.01 (C-5 and -6 methylenes), 2-protons as a triplet (J = 7.0 cps) centered at 2.50 (C-2 methylene), 2 protons as a triplet (J = 7.0 cps) centered at 3.37 (C-1 methylene), 2 protons as a broad "singlet" at 4.68 (C-8 methylene), and 1 proton as a broad triplet (J = 6.0 cps) centered at 5.25 (C-4 H). The intensity of the signal at 1.71 was about 3% greater than that of the signal at 1.65 indicating the presence of about 3% of the *cis* isomer. The spurious weak signal at 3.49 (see above)[25] was still present as well as faint signals at 1.09 and 1.04.

In a larger scale preparation, carried out by Charles A. Harbert, a 22.2-g specimen of the carbinol gave, upon treatment with phosphorus tribromide, 28.5 g (91% yield) of the bromide mixture. An 11.6-g sample of this bromide mixture, upon treatment with zinc bromide in ether, gave 10.8 g (93% yield) of the *trans*-bromo diene, the nmr spectrum of which was essentially identical with that of the product described above, except that the spurious signal at 3.49 ppm[25] was absent. The zinc bromide catalyzed reaction was repeated twice on approximately the same scale and afforded 94 and 100% yields of crude products with infrared spectra nearly identical with that of the product described above. These specimens of crude bromide **19** (R = CH_3) have been used to alkylate sodio diethyl malonate. The monoester (from decarbethoxylation) proved to be easily analyzed by vapor phase chromatography. The results of this analysis indicated that the bromo diene was contaminated with about 1% of the *cis* isomer (separated by vpc and identified by nmr spectroscopy) and 5% of the bond-migrated isomer.

The crude bromide tends to decompose on standing. When purified as follows, it is considerably more stable. A portion of the crude bromide was dissolved in pentane and filtered through a column of Merck acid-washed alumina. The yellow oily residue obtained on evaporation of the filtrate was submitted to vapor phase chromatographic analysis on a 15% Carbowax on 60–80 Chromosorb W column at 120°. The major peak amounted to 80% of the total area with retention time 18.5 min; the major residual peaks were of shorter retention time and possibly corresponded to hydrocarbons resulting from elimination of hydrobromic acid. This oil was submitted to preparative vapor phase chromatography on a $^3/_8$ in. × 20 ft 20% Carbowax on 45–60 Chromosorb W column at 145°. The main fraction was submitted to short-path distillation at 35–40° (0.05 mm) to give a colorless liquid, $n^{20}D$ 1.4940, which was estimated to be at least 90% pure by vapor phase chromatographic analysis under the conditions described above. The low retention time impurities (about 5%) presumably arose from decomposition of the bromide during the analysis. The remaining impurities were probably the bond-migrated isomer and a trace of the *cis* isomer (see above).

Anal. Calcd for $C_{10}H_{17}Br$: C, 55.32; H, 7.88; Br, 36.80. Found: C, 55.5; H, 7.85; Br, 36.6.

***trans*-3,7-Dimethylocta-3,7-dienol (19, R = CH_3).** A solution of 0.705 g of the bromo diene **12** (R = CH_3) described in the preceding section in 16.6 ml of dimethylformamide was treated with 1.33 g of potassium acetate just as described above for the lower homolog. The crude acetate, which amounted to 0.576 g of a pale yellow oil, λ_{max}^{film} 5.74 μ (acetate C=O), was dissolved in 60 ml of anhydrous methanol, 2.16 g of anhydrous potassium carbonate was added, and the mixture was stirred for 1.5 hr at 25°. Most of the methanol was evaporated under reduced pressure; water was added to the

(25) In a subsequent larger scale preparation it was found that when the step involving the alkylation of the β-keto ester was carried out by heating at reflux for a total of 65 hr, the reaction was complete and the addition of sodium iodide was not necessary. In this case the small amount of spurious by-product, responsible for the weak nmr absorption at 3.47–3.49 ppm (see below), was absent.

residue, and the mixture was extracted with ether. The combined organic solutions were washed with water followed by saturated brine and were dried over anhydrous magnesium sulfate. The crude pale yellow oil obtained on evaporation of the solvent at reduced pressure was chromatographed on 29 g of Merck acid-washed alumina. The fraction eluted with 50% ether in pentane was submitted to short-path distillation at 122–123° (17 mm) to give 0.334 g (67% over-all yield from the bromo diene) of a colorless liquid, n^{25}D 1.4680, λ_{max}^{film} 3.00 (OH), 3.25, 6.07, and 11.22 (C=CH$_2$), 12.2 (C=CH), and 9.55 μ (CO). The vapor phase chromatogram on a 7.5-ft Carbowax column at 140° showed a major component comprising 94% of the total area at retention time 20.3 min. A shoulder on this peak with retention time 21.7 min amounted to about 2% of the area and is tentatively considered to correspond to the *cis* isomer. Small "impurity" peaks were found with retention times of 11.6 and 15–19 min. The nmr spectrum showed absorption for 3 protons as a singlet at δ 1.64 ppm (CH$_3$ at C-3), 3 protons as a singlet at 1.71 (CH$_3$ at C-7), 7 protons appearing as a "singlet" at 2.06 and a multiplet centered at 2.17 (C-2, -5, and -6 methylenes and OH), 2 protons as a triplet (J = 6.5 cps) centered at 3.55 (C-1 methylene), 2 protons as a "singlet" at 4.65 (C-8 methylene), and 1 proton as a broad triplet (J = 6 cps) centered at 5.18 (C-4 proton).

An analytical specimen was secured by preparative vapor phase chromatography as described above at 150°. The major component, retention time of about 70 min, was obtained as a colorless liquid, n^{24}D 1.4685.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 78.0; H, 11.8.

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A Stereoselective Synthesis of Racemic Andrographolide Lactone

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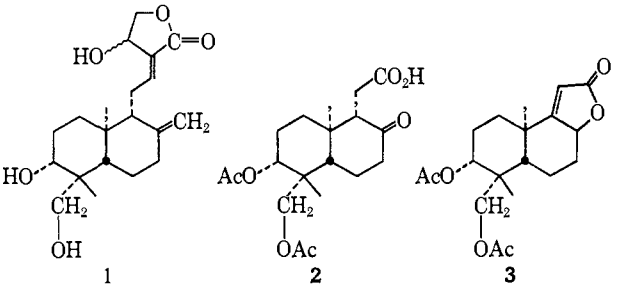
Abstract: This paper reports a ten-step stereoselective synthesis of the racemic α,β-unsaturated lactone **3**, which has been obtained previously in optically active form by degradation of triacetylandrographolide. The stereochemistry of ring fusion and the relative configurations of the substituents at C-4 in the crucial bicyclic intermediate **22** were established by chemical reactions and analysis of the nmr spectra of compounds **18b** and **19**. Methylation of **15** obtained by selective ketalization of **6** afforded **16** in 63% yield. Reduction of the latter with $NaBH_4$ afforded **17** which was reduced with $LiAlH_4$ to the diol **28**. Acetylation of **28** followed by deketalization gave the keto diacetate **30** which on hydrogenation and subsequent oxidation afforded the *trans*-decalin **22**. The same compound was obtained by the sequence **17** → **19** → **22**. Treatment of **22** with lithium ethoxyacetylide gave an ethynylcarbinol **32** which was rearranged in acid to the α,β-unsaturated ester **33**. Oxidation of **33** with selenium dioxide in acetic acid gave lactone **34**.

Andrographolide, the main bitter principle of *Andrographis paniculata* Nees (rice bitters), was first isolated by Gorter[1] and characterized as a trihydroxy lactone. Subsequent work,[2–8] particularly by Cava and his collaborators,[6,8] established the structure and stereochemistry of this interesting molecule as **1**. As a possible intermediate for the total synthesis of andrographolide we set out to synthesize the racemic α,β-unsaturated lactone **3** which has been obtained in the optically active form by ozonolysis of triacetylandrographolide to the diacetoxyketo acid **2** followed by refluxing with acetyl chloride.[8] The stereospecific synthesis of this degradation product confirms not only the structure of the α,β-unsaturated lactone **3** but also the structure and relative stereochemistry of rings A and B of andrographolide (**1**).



5-Carbomethoxy-9α-methyl-1,6'-dioxo-$\Delta^{5(10)}$-octalin (**6**) was used as a convenient source of the bicyclic ring system. The condensation of carbomethoxymethyl vinyl ketone[9–11] (**4**) with 2-methylcyclohexane-1,3-dione[12] (**5**) in the presence of anhydrous potassium fluoride[13–15] in dry methanol gave the ketone **6** in one step in 30–50% yield. When benzene or toluene[13] was

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