Thujopsene Rearrangements. The Cyclopropylcarbinyl System[1-3]

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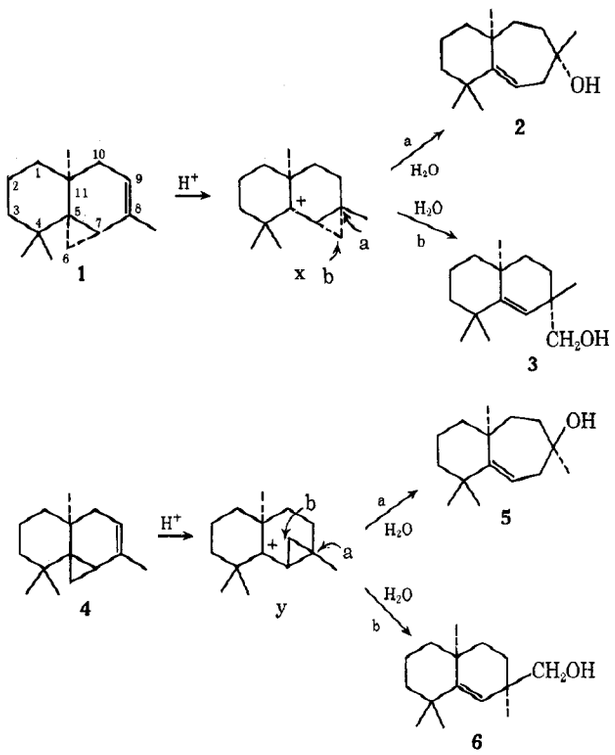
The earlier findings of the retention of the stereochemical integrity of the cyclopropylcarbinyl grouping in the isomeric *cis*- and *trans*-thujopsene in the early stages of the acid-catalyzed rearrangement of these sesquiterpenes have been extended. Upon longer reaction under mild acid conditions, *cis*-thujopsene (1) rearranged directly to **7** with concomitant ring enlargement and angular methyl group migration. The pathway for this conversion was established using 6,6-dideuterio-*cis*-thujopsene. In contrast to these results, *trans*-thujopsene (4) yielded the conjugated diene **8**, a compound resulting from ring enlargement but no angular methyl migration. The structures of these two rearrangement products were established by degradation and by synthesis. The mechanistic pathways for these conversions are discussed and it is shown that a combination of factors, all related to the steric configuration of the ring juncture, are responsible for the retention of the identity of the two initially formed stereoisomeric cyclopropylcarbinyl cations.

Part A

The development of organic chemical mechanistic theory and the development of the understanding of biosynthetic mechanisms have stimulated the postulation of biogenetic schemes for a variety of natural products. The sesquiterpenes have received much attention due to their wide occurrence and their variety of structures.[7] In turn, these biogenetic postulates have stimulated study of the transformation of one natural product to another using laboratory reagents. In recent years, the reactions of the tricyclic sesquiterpene thujopsene (1)[8] have attracted much interest since its postulated biogenesis involved a cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement.[9] This sesquiterpene, in addition to being a major constituent of cedar wood oil[10] and of Japanese Hibawood oil,[11] also occurs in the oils of practically all of the Cupressales.[12]

Thujopsene contains a cyclopropylcarbinyl grouping and it is this functionality which is mainly responsible for the complex chemical personality it possesses. For example, under mild acid conditions (0.02 *M* $HClO_4$ in 80% aqueous dioxane) this grouping rearranges to give two homoallylic alcohols, the naturally occurring widdrol (2) *via* path a and the *cis*-neopentyl-type alcohol **3** *via* path b.[2] Using thujopsene labeled with deuterium in the methylene position of the cyclopropane ring, it has been shown that the rearrangement goes through a cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement to give an intermediate, such as x,[2] and that such a rearrangement proceeds with retention of configuration. This result indicates that the interconversion must involve either a series of 1,2 shifts *via* a puckered cyclobutonium ion or direct bonding at the small lobe of the back bond of the cyclopropane ring and go in one step.[2]



In earlier work in this laboratory,[2,13] a sterospecific synthesis of the thujopsene nucleus had been developed and, thus, it was possible to prepare *trans*-thujopsene (4), the stereochemical designation referring to the ring juncture. When **4** was allowed to react under the above mild acid conditions, the major alcohols formed were *epi*-widdrol (5) and the *trans*-neopentyl-type alcohol 6. These materials can be derived from the *trans*-cyclopropylcarbinyl intermediate y in the same manner as discussed for the cis intermediate. In these two isomeric series there is a finite amount of leakage between the ions x and y but in the main series each stereoisomeric cation maintains its stereochemical integrity in this series of interconversions at this early stage of the rearrangement process.

(1) This work was partially supported by Grant No. GP-8700 from the National Science Foundation.

(2) For previous papers in this study, see W. G. Dauben and L. E. Friedrich, *Tetrahedron Lett.*, 2675 (1964); W. G. Dauben and L. E. Friedrich, *ibid.*, 1735 (1967); W. G. Dauben and E. I. Aoyagi, *Tetrahedron*, **26**, 1249 (1970).

(3) A portion of this work appeared in the Abstracts, IUPAC 5th International Symposium on the Chemistry of Natural Products, F-13, London, England, July 8–13, 1968, p 296.

(4) National Science Foundation Predoctoral Fellow.
(5) Roche Anniversary Foundation Postdoctoral Fellow.
(6) National Institutes of Health Predoctoral Fellow.

(7) J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959); W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev., Chem. Soc.*, **21**, 331 (1967).

(8) The projection represents the absolute configuration of *cis*-thujopsene.

(9) W. G. Dauben and P. Oberhänsli, *J. Org. Chem.*, **31**, 315 (1966).

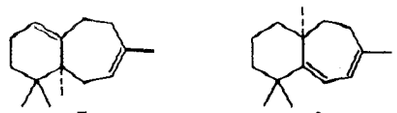
(10) J. Runeberg, *Acta Chem. Scand.*, **15**, 592 (1961).

(11) M. Yano, *J. Soc. Chem. Ind. Jap.*, **16**, 443 (1913); S. Uchida, *ibid.*, **31**, 501 (1928).

(12) H. Erdtman and T. Norin in "Progress in the Chemistry of Natural Products," Vol. 24, L. Zechmeister, Ed., Springer-Verlag, New York, N. Y., 1966, pp 206–287.

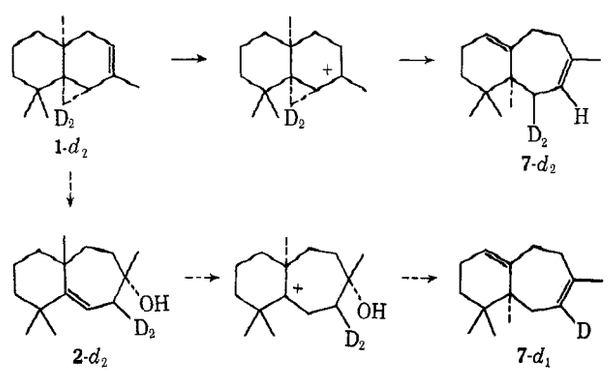
(13) W. G. Dauben and A. C. Ashcraft, *J. Amer. Chem. Soc.*, **85**, 3673 (1963).

When the acid-catalyzed reactions were allowed to proceed for an extended period, all of the products formed early in the reaction disappeared and *cis*-thujopsene yielded mainly hydrocarbon **7** and *trans*-thujopsene gave hydrocarbon **8**. Thus, it is found that the stereochemical difference of these two starting materials is still retained after destruction of the cyclopropylcarbinyl and related homoallyl systems. The retention of the stereochemical integrity of the two isomeric cyclopropylcarbinyl systems in *cis*- and *trans*-thujopsene is readily understood by evaluation of the changes in the geometry of the ring system required to bring about a stereochemical interconversion of the two isomeric cation systems. An understanding of the continued specificity found in this present investigation was gained by a study of the mechanism of formation of the rearranged hydrocarbon **7**.



7 **8**

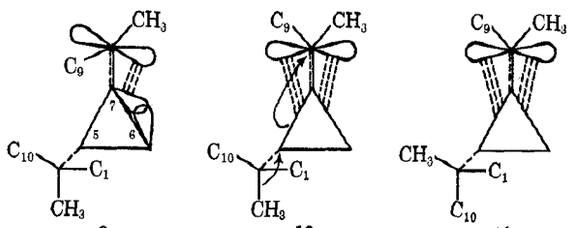
The presence of the bicyclo[5.4.0]undecane nucleus suggested that the rearranged diene **7** was derived from widdrol (**2**). However, it was possible that the methyl migration occurred concomitantly with the rearrangement of the cyclopropylcarbinyl cation to the homoallylic system (or possibly, a homoallylic cation was formed, followed by methyl migration). In order to establish the reaction pathway, *cis*-6,6-dideuteriothujopsene (**1**-d_2) was converted to the diene **7**. It was



1-d_2 **7**-d_2 **2**-d_2 **7**-d_1

found that the product retained both deuterium labels and both vinyl hydrogen atoms. Also, the allylic region of its nmr spectrum was reduced in intensity. Therefore, the diene must be **7**-d_2 as expected from the direct formation from thujopsene and not **7**-d_1 required if widdrol **2**-d_2 was the direct precursor.

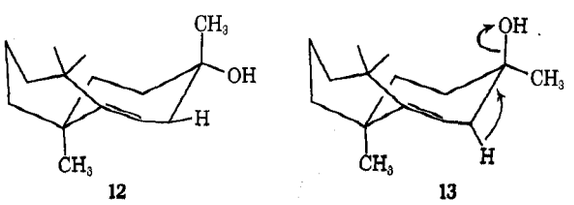
In *cis*-thujopsene (**1**), the unsymmetrical cyclopropylcarbinyl system **9** due to steric restraints within the molecule has the minimal energy and it is this cation which is involved in the cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement leading to widdrol (**2**) and its related neopentyl-type alcohol **3**. A similar series of rearrangements (not shown) exist for *trans*-thujopsene from an unsymmetrical cyclopropylcarbinyl cation leading to *epi*-widdrol (**5**) and the neopentyl-type alcohol **6**. These series of interconversions are reversible and with the continuous re-formation of a carbonium ion, the slightly more energetic bisected cyclopropylcarbinyl cations **10** and **11**, ions which are



9 **10** **11**

higher in energy in this series due to ring strain, not to lesser p–π overlap, may participate in the overall reaction. This bisected ion now makes the cleavage of the C-5–C-7 bond a competitive reaction. In the case of *cis*-thujopsene, the angular methyl group, as illustrated in **10**, is in the exact position for a trans coplanar transition state for migration of the methyl group leading to the rearranged diene **7**. As is seen in the bisected cation **11** from *trans*-thujopsene, the carbon best situated for migration is part of the left-hand ring and in rearranging would yield a spiran with a five-membered ring. This latter process must be sufficiently energy demanding so as not to compete with the other reactions.

These other reactions are related to widdrol and *epi*-widdrol. As seen in the projection **13**, the most stable



12 **13**

conformation of *epi*-widdrol places the tertiary hydroxyl group in an axial conformation. Such a conformational arrangement permits facile elimination to yield the conjugated diene **8**. That this reaction is more favored than the skeletal rearrangement to yield a spiran is quite understandable. The most stable conformation of widdrol is depicted as **12** and this conformation places the tertiary hydroxyl group in an equatorial conformation which is less prone to elimination. Thus a combination of factors, all related to the steric nature of the ring juncture, permits *cis*- and *trans*-thujopsene to retain their identity in all these rearrangement processes.

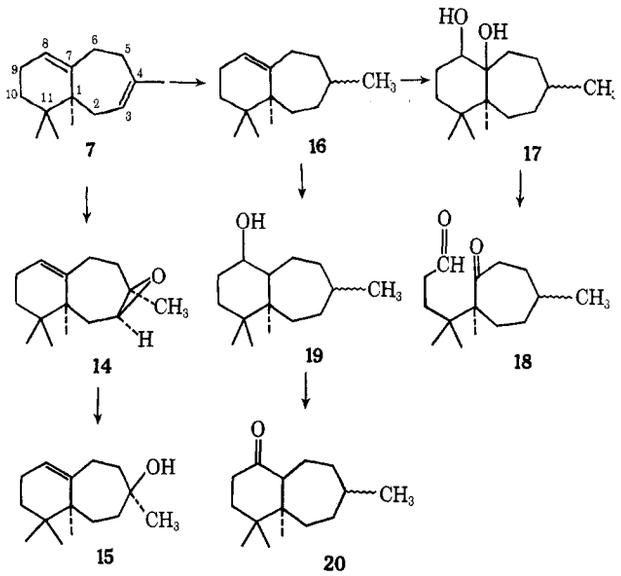
Part B

The hydrocarbon **7** was shown to have a molecular composition of $C_{15}H_{24}$, isomeric with *cis*-thujopsene, by the appearance of a molecular ion at *m/e* 204 in its mass spectrum. The nmr spectrum was extremely different from those of all previously reported compounds studied in that a multiplet at δ 1.8–2.5, corresponding to eight allylic methylene protons, was found. The additional resonances at δ 5.28 for two protons, a maximum in the ultraviolet spectrum at 192 nm (ϵ 13,900), and an infrared spectral absorption at 822 cm^{-1} indicated the presence of two nonconjugated, trisubstituted double bonds.[14] These features taken in conjunction with the molecular composition showed that **7** must be a bicyclic diene in which one of the double bonds was derived from one of the carbocyclic rings of thujopsene. The nmr spectrum of the diene also estab-

(14) R. A. Micheli and T. H. Applewhite, *J. Org. Chem.*, **27**, 345 (1962).

lished the presence of three quaternary methyl groups and a vinyl methyl group.

Reaction of diene **7** with 0.9 equiv of *m*-chloroperbenzoic acid gave epoxide **14** whose nmr spectrum showed one vinyl hydrogen and four quaternary methyl absorptions. This result indicates that the methyl-substituted double bond in **7** is less hindered than the other trisubstituted double bond. It is of passing interest that the alcohol **15** formed by $LiAlH_4$ reduction of epoxide **14** was also isolated in 0.5% yield directly from the acid-catalyzed reaction mixture of thujopsene. Since in **15** the hydroxyl group and the angular methyl group must be trans to one another due to the stereochemistry of the epoxide, this alcohol must have resulted from hydration of the diene **7** rather than from a methyl migration in widdrol. Furthermore, in 1958,

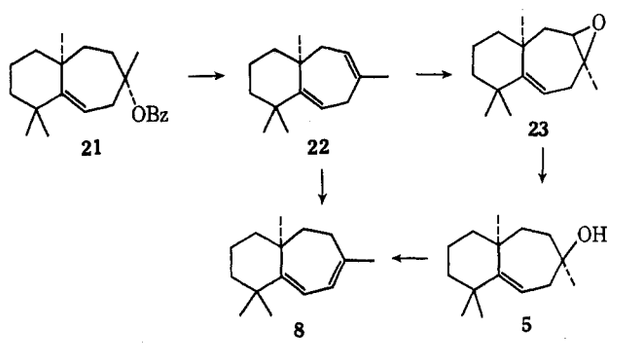


Tanaka and Yamashita[15] reported that a tertiary alcohol was formed from the reaction of *cis*-thujopsene with 50% sulfuric acid in acetic acid, followed by hydrolysis of the acetates. Since the physical constants of their alcohol were similar to those of **15**, it is most likely that the two alcohols are the same compound.

The bicyclo[5.4.0]undecane skeleton of **7** was established by the following series of reactions. The lesser hindered double bond of this diene was preferentially hydrogenated to yield a 6:1 mixture of dihydro and tetrahydro products. The dihydro product **16** was purified by preparative vpc and it was a mixture of the epimeric methyl compounds. The dihydro mixture reacted slowly with osmium tetroxide to yield diol **17**, the slow hydroxylation reaction confirming the hindered nature of the C-7–C-8 double bond. The diol was cleaved with lead tetraacetate to yield the keto aldehyde **18**. Its infrared spectrum (ir max at 2810, 2710, 1729, 1693 cm^{-1}) indicated the presence of an aldehyde and a ketone and the primary nature of the aldehyde was established by the presence of a one hydrogen triplet (J = 2 Hz) resonance at δ 9.41 in the nmr spectrum. The absorption at 1693 cm^{-1} is indicative of a seven-ring ketone.

The size of the other ring in diene **7** was determined by hydroboration and oxidation of the dihydro derivative **16** to yield alcohol **19** and ketone **20**, respectively. The 1706-cm^{-1} absorption of **20** is characteristic of a six-ring ketone. Thus, the foregoing data establish that diene **7** contains a bicyclo[5.4.0]undecadiene skeleton in which the more hindered double bond is situated endocyclic to the six-membered ring and exocyclic to the seven-membered ring. Taking into account the nmr data with regard to allylic methylene groups, the two double bonds must be placed as shown in **7**. The placement of the vinylic methyl group and the three quaternary methyl groups clearly follows from mechanistic considerations.

The structure of diene **8** derived from *trans*-thujopsene was established on the basis of the following information. Its mass spectrum (parent peak m/e 204) clearly established that the hydrocarbon was isomeric with starting *trans*-thujopsene. An absorption maximum at 262 nm established the presence of an *s-cis*-1,3-diene, the infrared spectrum indicated only trisubstituted double bonds (840 cm^{-1}), and the nmr spectrum established the presence of only one vinyl methyl group but two vinyl protons and three quaternary methyl groups. These data suggested the structure **8**, a diene formed directly from *epi*-widdrol **5**. This assignment was confirmed by the synthesis of **8** from widdrol benzoate (**21**). Pyrolysis of **21** in *N*,*N*-



dimethylaniline gave the nonconjugated diene **22**, the absence of skeletal rearrangement being shown by conversion to the epoxide **23** which, in turn, upon reduction with $LiAlH_4$ yielded *epi*-widdrol. The nonconjugated diene was converted to the conjugated diene **8** by treatment with potassium *tert*-butoxide in dimethyl sulfoxide.

Experimental Section

Melting points were taken with a Büchi Schmelzpunktbestimmungsapparatus or on a Fisher-Johns melting point apparatus and are uncorrected. Glpc were conducted either with Varian-Aerograph Models A-90-P, 600, or 204 B or with Hewlett-Packard Model 402. Nmr spectra were taken with Varian spectrograph Models A-60, T-60, or HR-100, using TMS as an internal standard. The mass spectra were obtained using a modified CRC Type 21-103C mass spectrometer, a Varian M-66 cycloidal mass spectrometer, or a Finnigan quadrupole mass spectrometer. Combustion analyses and high-resolution mass spectra were performed by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley, Calif.

Isomerization of *cis*-Thujopsene to Diene 7.—A solution of 150 g of *cis*-thujopsene, 300 ml of 0.1 *M* aqueous perchloric acid, and 1200 ml of dioxane was heated under reflux for 27 hr. The cooled solution was neutralized with aqueous sodium carbonate, most of the dioxane removed under reduced pressure, and the residual mixture extracted with petroleum ether. The organic extract was washed with aqueous potassium bicarbonate and with water and dried, and the solvent removed under reduced

(15) J. Tanaka and I. Yamashita, *Bull. Osaka Ind. Res. Inst.*, **9**, 5 (1958).

pressure. A pentane solution of the residual oil was filtered through 150 g of Woelm neutral alumina (activity I) to yield after removal of the solvent 130 g of a brown oil, glpc analysis (DEGS, 128°) of which indicated that diene **7** comprised 54% of the mixture.

The oil was distilled through a 24-in. spinning-band column and the central fraction, 42 g, bp 149–150° (9.5 mm), containing 71% of **7** was further purified by preparative glpc (20% NPGS, Chromosorb P-HMDS, 20 ft × 3/8 in., 168°) to yield material of 97% purity. The absence of α-chamigrene was confirmed by coinjection and by quantitative analysis of the nmr spectrum: $[\alpha]^{23}D$ +65.3° (*c* 0.209, $CHCl_3$); uv max (hexane) 192 nm (ε 13,900); ir max (neat) 822 cm^{-1}; nmr (CCl_4) δ 5.28 (2 H, m), 1.8–2.5 (8 H, m), 1.60 (3 H, sharp m), 0.94 (3 H, s), 0.87 (6 H, s).

Anal. Calcd for $C_{15}H_{24}$ (204.36): C, 88.16; H, 11.84. Found: C, 88.48; H, 11.62; *m/e* 204.

Epoxidation of Diene 7.—A solution of 100 mg (0.5 mmol) of 85% *m*-chloroperbenzoic acid in 2.5 ml of chloroform was added, dropwise, over a period of 5 min to a cooled solution (0°) of 204 mg (1.0 mmol) of diene **7** in 2.0 ml of chloroform. The solution was allowed to stand at 3° for 30 hr; a starch–iodide test indicated the absence of peracid but glpc analysis indicated 50% of starting material. An additional 80 mg (0.4 mmol) of *m*-chloroperbenzoic acid was added to the solution and allowed to react for an additional 2.5 hr. The solution was diluted with ether, washed with aqueous ferrous sulfate, potassium bicarbonate, and water, and dried, and the solvent was removed to yield 190 mg of an oil. Glpc analysis (10% SE-30, 160°) indicated the presence of four products in 10, 60, 20, and 10%, respectively, in order of elution.

The major material **14** was purified by preparative glpc (10% SE-30, Chromosorb P, HMDS, 162°, 5 ft × 0.75 in.). Reinjection of the collected product indicated a purity of greater than 95%: nmr (CCl_4) δ 5.23 (1 H, m), 2.60 (1 H, t, J = 5.5 Hz), 1.12 (3 H, s), 0.92 (3 H, s), 0.88 (3 H, 2), 0.87 (3 H, s); *m/e* 220.

$LiAlH_4$ Reduction of Epoxide 14.—A mixture of 13 mg of **14** and 37 mg of $LiAlH_4$ in 20 ml of glyme was heated under reflux for 9 hr and the mixture worked up in the usual fashion. The crude white solid alcohol was recrystallized from hexane: mp 118–121°; $[\alpha]^{23}D$ +106° (*c* 0.1118, $CHCl_3$); nmr (CCl_4) δ 5.28 (1 H, broad s), 1.12 (3 H, s), 0.97 (3 H, s), 0.92 (3 H, s), 0.88 (3 H, s).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.12; H, 11.79. Found: C, 81.17; H, 11.70.

Hydrogenation of Diene 7.—A mixture of 100 mg (0.49 mmol) of diene **7**, 20 mg of 20% palladium on charcoal, 5 ml of ethanol, and 2 ml of ethyl acetate was shaken under 1 atm of hydrogen at room temperature for 18 hr. Glpc analysis (DEGS, 102°) indicated an 86% yield of dihydro products **16** and 14% yield of a tetrahydro material; no starting diene remained. The dihydro products appeared to be an equal mixture of two isomers (at the methyl group) and they were collected together by preparative glpc (DEGS, 102°): nmr (CCl_4) δ 5.28 (1 H, m), 2.0 (4 H, m), 0.92 (6 H, s), 0.84 (6 H, s).

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.28; H, 12.72.

Osmylation of Dihydro Product 16.—A mixture of 204 mg (1.0 mmol) of dihydro product **16**, 270 mg (1.1 mmol) of osmium tetroxide, 250 μl of dry pyridine, and 30 ml of dry ether was allowed to stand at room temperature for 11 days. To the brown mixture was added several milliliters of 50% aqueous methanol which was saturated with sodium sulfide, the black precipitate filtered, and the filtrate diluted with ether. The ethereal solution was washed with aqueous sodium sulfide and water and dried, and the solvent was removed under reduced pressure to yield 175 mg of an oil which was chromatographed on 10 g of Woelm neutral alumina (activity II). Elution with 30 ml of petroleum ether and evaporation of the solvent yielded 99 mg (49%) of starting olefin **16**. Elution with 100 ml of diethyl ether afforded 44 mg of semicrystalline diol **17**: ir max (CCl_4) 3635, 3600, 3460 cm^{-1}; nmr (CCl_4) δ 3.68 (1 H, m). The crude material was used directly in the following experiment.

Cleavage of Diol 19.—A mixture of 44 mg (0.18 mmol) of crude diol **19**, 200 mg (0.45 mmol) of lead tetraacetate, and 10 ml of acetic acid was allowed to react at room temperature for 5 days. The mixture was poured onto crushed ice, extracted with petroleum ether, and processed in the usual manner to yield 37 mg of an oil. Glpc analysis (10% SE-30, 180°) of the crude material indicated that the major product comprised 75% of the mixture: ir max (CCl_4) 2810, 2710, 1729, 1693 cm^{-1}; nmr (CCl_4) δ 9.41 (1 H, t, J = 2 Hz). The keto aldehyde **18** was purified by preparative glpc (10% SE-30, 190°).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.85; H, 10.98.

Hydroboration of Dihydro Product 16.—Diborane generated from 156 mg (4.12 mmol) of sodium borohydride and 0.85 ml of boron trifluoride–etherate in diethylene glycol was passed into a solution of 200 mg (0.97 mmol) of monoolefin **16** in 12 ml of tetrahydrofuran at 0° with a nitrogen sweep. The solution was allowed to stand at room temperature for 3 hr, and 0.5 ml of water was added slowly, followed by 1 ml of 3 *M* aqueous sodium hydroxide and 0.1 ml of 30% aqueous hydrogen peroxide. After 1 hr, an additional 0.5 ml of 3 *M* sodium hydroxide was added and the mixture allowed to stand for 30 min. The solvent was partially rotary evaporated, the remaining mixture extracted with ether, and the ethereal extract processed in the usual fashion to yield 160 mg of an oil. The crude product was chromatographed on 10 g of Woelm neutral alumina (activity II); elution with 25 ml of petroleum ether yielded 73 mg (37%) of starting material and elution with 50 ml of ether produced 70 mg (32%) of crystalline alcohol **19**: ir max (CCl_4) 3620, 3380 cm^{-1}; nmr (CCl_4) δ 3.66 (1 H, broad multiplet).

Anal. Calcd for $C_{15}H_{26}O$: C, 80.29; H, 12.58. Found: C, 82.20; H, 12.20.

Oxidation of Alcohol 19.—A solution of 65 mg (0.29 mmol) of alcohol **19** was oxidized at 0° with 0.2 ml of Jones reagent in the usual fashion. After 5 min, the mixture was processed to yield 65 mg of an oil which by glpc analysis (DEGS, 160°) indicated the major product comprised 80% of the mixture. The ketone **20** was purified by preparative glpc (DEGS, 161°): ir max (CCl_4) 1706 cm^{-1}; nmr (CCl_4) δ 2.1 (3 H, m).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.80; H, 11.68.

Rearrangement of *cis*-6,6-Dideuteriothujopsene to Diene 7.—A solution of 0.95 g (4.9 mmol) of *cis*-6,6-dideuterothujopsene (1-d_2) in 9.6 ml of 80% aqueous dioxane–perchloric acid (prepared from 6.18 g of water, 24.72 g of dioxane, and 76 mg of 70% aqueous perchloric acid) was heated under reflux for 175 min under an atmosphere of nitrogen. The reaction mixture was worked up in the standard fashion and the 1.0 g of residual solid was chromatographed on 30 g of Woelm neutral alumina (activity II). Elution with 150 ml of hexane yielded 0.565 g of hydrocarbon fraction and elution with benzene yielded the alcohol fraction.

The hydrocarbon fraction was analyzed by glpc (10% KOH, 10% Carbowax, 163°, 5 ft × 3/8 in.) and found to contain 38% unreacted dideuteriothujopsene and 43% of diene **7**-d_2. The diene was purified by preparative glpc; its ir spectrum was practically identical with that of undeuterated **7** and its nmr spectrum was identical with the spectrum of the undeuterated diene except for several prominent absorptions in the allylic region, δ 1.8–2.5, which were reduced in intensity. The mass spectrum of the product indicated that the material was 87% dideuterated, as was the starting material.

Isomerization of *trans*-Thujopsene to Diene 8.—A solution of 260 mg (1.28 mmol) of *trans*-thujopsene in 2.6 ml of 80% aqueous dioxane was brought to reflux and 4.4 μl of 70% perchloric acid was added. The reaction solution was heated under reflux for 20 hr, cooled, neutralized, and extracted with hexane. The hexane solution was rotary evaporated, and the residue chromatographed on 5 g of neutral Woelm alumina (activity II) to give 170 mg of hydrocarbon mixture and 70 mg of *trans*-neopentyl type alcohol **6**. Glpc analysis of the hydrocarbon fraction showed the presence of three materials in a ratio of 3:1:1; the major material was purified by preparative glpc (10% TCNE, 120°) and was obtained in 85% purity: uv max (cyclohexane) 262 nm (ε 7500) with shoulders at 254 and 273 nm; nmr (CCl_4) δ 5.6 (2 H, distorted AB quartet), 1.78 (3 H, d), 1.13 (6 H, 2), 1.03 (3 H, s); mass spectrum *m/e* 204, 121, 119 (base peak), 105.

Widdrol Benzoate (21).—A solution of 5.5 g (24.8 mmol) of widdrol and 12.4 ml of benzoyl chloride in 120 ml of pyridine was heated on a steam bath for 4 hr, cooled, and diluted with 740 ml of 1 *N* hydrochloric acid. The mixture was extracted twice with hexane, and the hexane solution was washed with 100 ml of 2 *N* hydrochloric acid and 50 ml of aqueous sodium bicarbonate solution and dried. The solvent was rotary evaporated and the residual oil chromatographed on Woelm neutral alumina (activity II). Elution with hexane yielded 6.4 g of product which slowly solidified: ir max (CCl_4) 1712 cm^{-1};

nmr (CCl_4) δ 7.45–7.87 (3 H, m), 7.20–7.27 (2 H, m), 5.43 (2 H, q, J = 8 and 6 Hz), 2.53–2.78 (2 H, m), 1.57 (3 H, s), 1.20 (3 H, s), 1.09 (6 H, s).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.22; H, 9.01.

1,4,8,8-Tetramethyl[5.4.0]undeca-3,6-diene (22)—A mixture of 3.8 g of widdrol benzoate and 100 ml of freshly distilled *N,N*-dimethylaniline was heated under reflux for 40 hr, diluted with 500 ml of 2 *N* aqueous hydrochloric acid, and extracted three times with hexane. The hexane extract was washed with saturated aqueous sodium bicarbonate solution and dried, and the solvent was rotary evaporated to give 3.1 g of oily material. Glpc analysis (20% DEGS, Chromosorb P, HMDS, 130°, 5 ft × 0.25 in.) indicated three hydrocarbons in a ratio of 70, 25, and 5% yields. This crude material after filtration through Woelm neutral alumina (activity II) was used directly in the next experiment.

A 250-mg portion was chromatographed on 20 g of silica gel impregnated with 22% silver nitrate. Elution with 72 ml of hexane–benzene (9:1) afforded a total of 185 mg of the diene **22** in six fractions. The major product from the middle chromatography fraction was still impure as indicated by a low residual uv absorption in the 255–273-nm region. No further purification was attempted and the purified diene had the following properties: uv max (cyclohexane) 185 nm (ϵ 17,400), 254 (1120), 263 (1240), 273 (860); nmr (CCl_4) δ 5.17–5.83 (2 H, poorly formed quartet, J = 7 and 3 Hz), 3.17 (1 H, d, J = 20 Hz), 1.72 (3 H, narrow multiplet), 1.10 (3 H, s), 1.08 (3 H, s), 1.09 (3 H, s).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.20; H, 11.67.

1,4,8,8-Tetramethyl[5.4.0]undeca-4,6-diene (8).—To a solution of 2.0 g (72% pure) of diene **22** in 2 ml of dry benzene and 100 ml of dry dimethyl sulfoxide (distilled from calcium hydride) was added 3.1 g of potassium *tert*-butoxide. The dark red solution was stirred at room temperature for 6 hr, poured into water, and processed in the usual fashion. The crude product was chromatographed on 20 g of Woelm neutral alumina (activity II) to give 1.7 g (85%) of hydrocarbon mixture which upon glpc analysis showed two peaks (78 and 22%). The minor product has a retention time identical with starting diene **22**. The dominant reaction product was purified by preparative glpc; the retention time and all spectra were identical with those of diene **8** prepared from *trans*-thujopsene.

3β,4β-Oxa-1α,4α,8,8-tetramethylbicyclo[5.4.0]undec-6-ene (23).—A solution of 469 mg (2.24 mmol) of 82.5% *m*-chloroperbenzoic acid in 7 ml of chloroform was slowly added to a solution of 551 mg (2.70 mmol) of diene **22** (70% purity) in 5 ml of chloroform at 0°. The reaction was allowed to proceed for 3.5 hr at 0°, diluted with pentane, and worked up in the standard fashion. The crude product was chromatographed on 25 g of Woelm neutral alumina (activity II). Elution with 32 ml of hexane gave 100 mg of unreacted hydrocarbon; elution with hexane–ether (increasingly greater amounts of ether) gave two products. The first product was 70 mg (14%) of impure isomeric 6,7-oxa-3-ene: nmr (CCl_4) δ 5.13 (1 H, d, J = 8 Hz), 2.83 (1 H, t, J = 3 Hz), 2.43–2.75 (2 H, m), 2.00–2.38 (2 H, broad multiplet), 1.63 (3 H, narrow multiplet), 1.11 (6 H, s), 0.76 (3 H, s).

The second product was 248 mg (51%) of pure epoxide **23**: $[\alpha]D$ +67° (*c* 16.9, $CHCl_3$); ir max (CCl_4) 1650, 840 cm^{-1}; nmr (CCl_4) δ 5.52 (1 H, q, J = 7, 4 Hz), 2.79 (1 H, q, J = 8, 7 Hz), 2.25–2.50 (1 H, m), 1.29 (6 H, s), 1.13 (3 H, s), 1.05 (3 H, s).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.87; H, 10.77.

***epi*-Widdrol (5).**—A mixture of 1.44 g (6.54 mmol) of epoxide **23**, 1.17 g (31 mmol) of $LiAlH_4$, and 125 ml of glyme was heated under reflux in a nitrogen atmosphere for 16 hr. The cooled mixture was diluted with ether and water carefully added until a clear organic layer was obtained. The organic layer was decanted and processed in the usual manner. The 1.47 g of crude product was 95% pure *epi*-widdrol (glpc, 10% KOH, 10% Carbowax 6000, 185°). A portion of the crude product (365 mg) was chromatographed on Woelm neutral alumina to yield *epi*-widdrol: mp 54–56°; $[\alpha]D$ +132° (*c* 5.81, $CHCl_3$).

Registry No.—**1,** 32435-95-3; **4,** 32436-14-9; **5,** 25490-91-9; **7,** 32436-16-1; **8,** 32436-17-2; **14,** 32436-18-3; **15,** 32436-19-4; **16,** 32436-20-7; **17,** 32436-21-8; **18,** 32436-22-9; **19,** 32436-23-0; **20,** 32436-24-1; **21,** 32436-25-2; **22,** 32436-26-3; **23,** 32436-27-4; **23** 6,7-oxa-3-ene isomer, 32436-28-5.

A Stereoselective Nonannelation Synthesis of Eudalene Sesquiterpenes[1]

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A new stereoselective synthetic approach to the eudalene sesquiterpenes has been devised which does not utilize the Robinson annelation sequence. Clemmensen reduction of 5-methoxy-1-tetralonecarboxylic acid (**4**) gives 8-methoxytetralin-2-carboxylic acid (**5**), which on Birch reduction affords 3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one-7-carboxylic acid (**3**) as the major product. Conjugate addition of lithium dimethyl cuprate to **3** gives a mixture of three stereoisomeric 4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1(2*H*)-one-7-carboxylic acids (**9**, **10**, and **11**). Treatment of the mixture of acids with methylenetriphenylphosphorane, followed by esterification, equilibration, and hydrolysis affords 4aβ-methyl-8-methylene-1,2,3,4,4a,5,6,7,8aα-decahydronaphthalene-2β-carboxylic acid (**12**), a compound which has previously been converted to β-eudesmol (**1**).

Although several syntheses of eudalene-type sesquiterpenes have been reported,[2] every successful synthetic approach has utilized the Robinson annelation sequence to construct the bicyclic skeleton characteristic of this group of natural products. Unfortunately, owing to the steric course of the annelation reaction, this approach necessitates multistep synthetic schemes with the stepwise introduction of the various substituents on the perhydronaphthalene ring system.[3]

In order to circumvent these problems, we attempted to design a new, general synthesis of these sesquiterpenes which did not utilize the annelation reaction and which would permit stereochemical control at each step. Examination of the structure of β-eudesmol (**1**) reveals that this molecule is basically a 9-methyl-*trans*-decalin with an equatorial substituent

(1) (a) A preliminary communication describing a portion of this work appeared in *Tetrahedron Lett.*, 501 (1971). (b) Abstracted in part from the Ph.D. dissertation of M. L. Mole, Clemson University, May 1971. (c) Supported in part by Career Development Award GM-5433 from the National Institutes of Health.

(2) Earlier synthetic approaches to these sesquiterpenes are described: (a) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 1801 (1968); (b) J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966); (c) J. A. Marshall and M. T. Pike, *ibid.*, **33**, 435 (1968); (d) D. C. Humber, A. R. Pinder, and R. A. Williams, *ibid.*, **32**, 2335 (1967); (e) J. M. Mellor and S. Munavelli, *Quart. Rev., Chem. Soc.*, **18**, 270 (1964).

(3) The details of these stereochemical problems are particularly apparent in the syntheses described in ref 2a, b, and d.