Total Synthesis of (±)-α-Cubebene and (±)-β-Cubebene

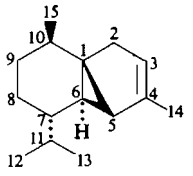
EDWARD PIERS,[1] RONALD W. BRITTON, AND WILLIAM DE WAAL
Department of Chemistry, University of British Columbia, Vancouver 8, British Columbia

Received August 10, 1970

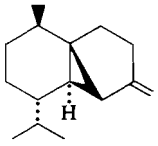
An efficient total synthesis of the racemic forms of the novel tricyclic sesquiterpenes α-cubebene (**1**) and β-cubebene (**2**) is described. The key step of this synthesis involved the cupric sulfate catalyzed intramolecular cyclization of the olefinic diazoketone **3**, which produced, in high yield, (±)-β-cubebene norketone (**24**) and (±)-1,6-epi-β-cubebene norketone (**25**), in a ratio of approximately 3:5, respectively.

Canadian Journal of Chemistry, 49, 12 (1971)

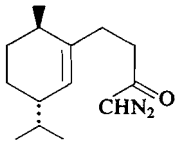
On the basis of spectral data, chemical degradation and correlation with known cadinane derivatives, Hirose *et al.* (1–3) have proposed that **1** and **2** correctly represent the structure and absolute stereochemistry of α-cubebene[2] and β-cubebene, respectively, two sesquiterpenes isolated from the commercial oil of cubeb (*Piper cubeba* L.). Structurally, these two natural products contain the bicyclo[3.1.0]hexane moiety and thus represent a novel and interesting variant of the more normal structures found within the cadinane class of sesquiterpenoids. We report in this paper the total synthesis of the cubebenes via a route which fully supports the structural and stereochemical assignments.[3]



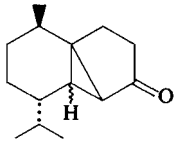
1



2



3

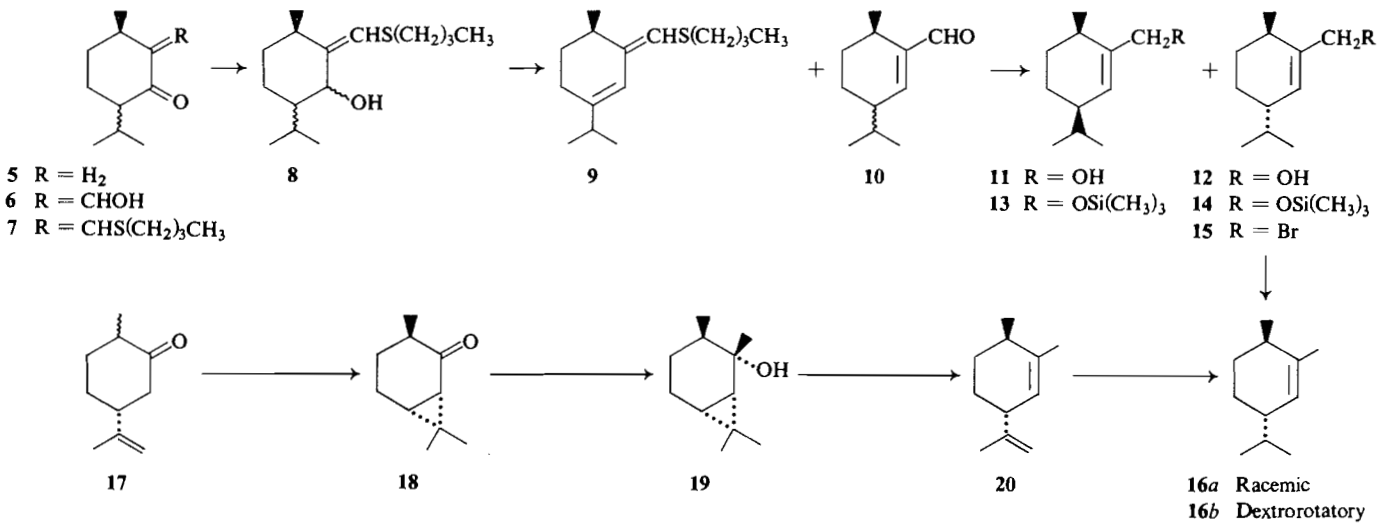


4

The key step of our envisaged synthesis involved the cupric sulfate catalyzed intramolecular cyclization of an appropriately substituted olefinic diazoketone.[4] In particular, it was proposed to prepare and attempt the cyclization of the olefinic diazoketone **3**. Obviously, success of the cyclization would lead to a synthetic intermediate **4** with functionality appropriate for further elaboration to α- (**1**) and β-cubebene (**2**).

Condensation of the commercially available mixture of (±)-menthone and (±)-isomenthone (**5**)[5] (see Scheme 1) with ethyl formate in the presence of sodium methoxide in benzene afforded, in 88% yield, the corresponding hydroxymethylene derivatives **6**. Treatment of the latter under the usual conditions (14) with *n*-butanethiol gave in 89% yield the corresponding *n*-butylthiomethylene derivatives **7**, which, upon reduction with a basic solution of methanolic sodium borohydride provided a quantitative yield of the crude β-hydroxythioenol ether **8**. This material was not purified further, but was immediately subjected to hydrolysis with 1% hydrochloric acid in aqueous acetone. Distillation of the resulting mixture of products produced two major fractions. The first fraction (40%, b.p. 66–68° at 0.35 mm) consisted of the desired α,β-unsaturated aldehydes **10**, while the second fraction (50%, b.p. 120–126° at 0.35 mm) was shown to be the thioenol ether **9**. Normally, the hydrolysis of β-hydroxythioenol ethers of structure similar to compound **8** affords, in good yield, the corresponding α,β-unsaturated aldehyde (15, 16). However, in the present case, although a variety of conditions were used, including the addition of mercuric salts, the isolated yield of the aldehydes **10** did not exceed 40%. Furthermore, various

[1]Fellow of the Alfred P. Sloan Foundation, 1970–1972.
[2]The numbering scheme shown in structure **1** is that normally used for cadinane-type sesquiterpenoids.
[3]For a preliminary report regarding this work, see ref. 4. For another report concerning the synthesis of the cubebenes see ref. 5.
[4]For some previous applications of this type of reaction to terpenoid synthesis, see refs. 6–13, inclusive.
[5]Compounds **5**, **6**, **7**, and **10** represent racemic diastereomeric pairs. Analytical and spectral data of these mixtures were, in each case, in full accord with the structural assignments.



SCHEME 1

attempts to hydrolyze the thioenol ether **9** to the aldehydes **10** were also unsuccessful.

Reduction of the aldehydes **10** with sodium borohydride afforded, in 91% yield, the corresponding mixture of the alcohols **11** and **12**. To this stage in the synthesis, no attempt had been made to separate the diastereomeric pairs, since all of the intermediates which would have been amenable to separation contained an epimerizable isopropyl group. However, once the aldehyde functionality of **10** had been reduced with sodium borohydride, the possibility for epimerization had been removed. Therefore, attempts were made to separate the mixture of alcohols **11** and **12**.

Gas–liquid chromatographic analysis of this mixture on many different columns at various column temperatures and carrier-gas flow rates failed to reveal any appreciable separation of the two alcohols **11** and **12**. The corresponding acetate derivatives also proved to be extremely difficult to separate. However, the corresponding trimethylsilyl ether derivatives **13** and **14**, which were easily formed in virtually quantitative yield from the alcohols **11** and **12**, were found to separate reasonably well on a preparative Zonyl E-7 column.[6] Preparative g.l.c. thus provided a convenient method for obtaining a sufficient quantity of the pure trimethylsilyl ethers **13** and **14**.

It was important at this stage to ascertain the stereochemistry of the two trimethylsilyl ethers **13** and **14**. Since the ratio of the two compounds in the originally obtained mixture was approximately 1:1, it was impossible to assign the configurations in terms of conformational arguments. Therefore, a chemical proof regarding this point was sought, and the fact that the silyl ether of shorter g.l.c. retention time was indeed the desired *trans* compound **14** was shown as follows.

Hydrolysis of **14** in hot 2% aqueous ethanol gave in, 98% yield, the pure *trans* alcohol **12**, which, upon treatment with phosphorus tribromide in benzene–pyridine at 0° (17), afforded the allylic bromide **15**, in 77% yield. Lithium aluminum hydride reduction of **15** gave a virtually quantitative yield of racemic *trans*-2-methyl-*p*-mentha-2-ene (**16***a*). The spectral properties of this hydrocarbon were in complete accord with the assigned structure.

[6]We are very grateful to Mr. J. Booker, Varian-Aerograph, California, for his help in the selection of a g.l.c. column for this separation.

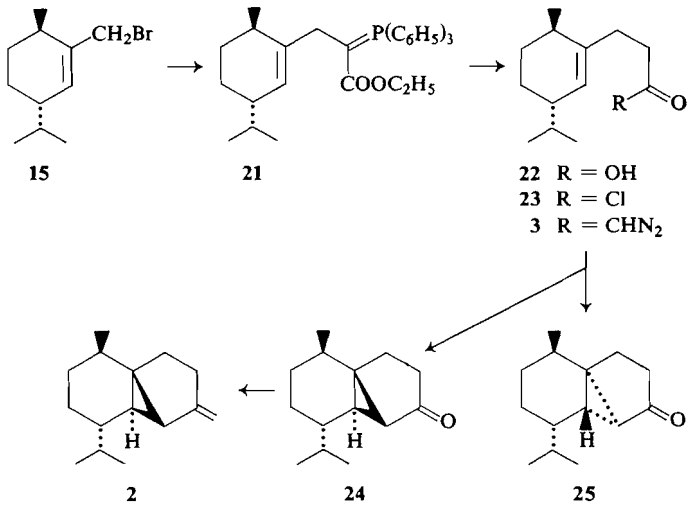
An unambiguous synthesis of (+)-*trans*-2-methyl-*p*-mentha-2-ene (**16***b*) was carried out as follows (see Scheme 1). The bicyclic ketone (−)-*trans*-caran-2-one (**18**) was prepared from (+)-dihydrocarvone (**17**) according to literature procedures (18, 19), and could be conveniently purified by recrystallization from *n*-hexane at −78°. A sample of **18** purified in this manner exhibited $[\alpha]_D^{22}$ − 181° [lit. $[\alpha]_D^{19}$ − 162.9° (19), − 153° (20)] and in the n.m.r. spectrum showed no signals due to olefinic protons.[7] Reaction of ketone **18** with ethereal methyllithium produced, in high yield, only one product, formulated as **19**. The stereochemistry of the latter was assigned on the basis of the reasonable assumption that the methyllithium would approach the carbonyl group of **18** from the less hindered side, opposite to the sterically bulky *gem*-dimethylcyclopropyl moiety (see ref. 21).

Pyrolysis of the tertiary alcohol **19** in the presence of a small amount of pyridine in a sealed tube at 190–200° for 2 h (19) gave approximately 70% of (+)-*trans*-2-methyl-*p*-mentha-2,8-diene (**20**),[8] which was purified by preparative g.l.c. Hydrogenation of the latter in the presence of the homogeneous catalyst tris(triphenylphosphine)-chlororhodium (22, 23) stopped after the uptake of one equivalent of hydrogen. Isolation of the product afforded (+)-*trans*-2-methyl-*p*-mentha-2-ene (**16***b*), which exhibited i.r. and n.m.r. spectra and g.l.c. retention times identical with those obtained from the racemic compound **16***a*, prepared as described previously. This correlation provided unambiguous evidence for the stereochemistry of our synthetic intermediates **12** and **15** and allowed us to continue with the proposed synthesis of the cubebenes.

Treatment of the allylic bromide **15** (see Scheme 2) with two equivalents of carbethoxymethylenetriphenylphosphorane (24) in refluxing ethyl

[7]The n.m.r. spectrum of samples of **18** which had not been purified by recrystallization clearly showed the presence of small amounts of starting material, (+)-dihydrocarvone (**17**). Furthermore, purification of **18** by preparative g.l.c. or by distillation at temperatures greater than 100° was attended by partial isomerization to **17**. Presumably, these observations account for the fact that our specific rotation value for compound **18** was considerably higher than those previously reported.

[8]This material had to be purified and analyzed immediately, as it tended to autoxidize on standing for even short periods of time. This type of observation had been previously noted by Cocker *et al.* (19) in the case of the analogous compound, (+)-*trans*-*p*-mentha-2,8-diene.



SCHEME 2

acetate for 2.5 h (25) gave, in addition to the crystalline carbethoxymethyltriphenylphosphonium bromide, a virtually quantitative yield of the corresponding alkylated phosphorane **21** as a yellow oil. Hydrolysis of this crude material with 10% potassium hydroxide in refluxing aqueous methanol afforded, in 69% yield, the olefinic carboxylic acid **22**. The stage was now set for the rather simple sequence of reactions which would lead to the formation of the synthetically crucial diazoketone **3**. To this end, **22** was converted into its sodium salt, and the latter was reacted with oxalyl chloride in benzene at 0° to afford the crude acid chloride **23**. When this compound was treated with dry ethereal diazomethane, the corresponding diazoketone **3** was formed almost immediately. The spectral properties of the crude material were in full accord with the assigned structure and it was now possible to attempt the initially proposed cyclization.

When the diazoketone **3** was refluxed in cyclohexane in the presence of cupric sulfate (26) for 1.5 h, a remarkably clean and high-yielding intramolecular cyclization occurred, producing two isomeric ketones, (±)-β-cubebene norketone (**24**) and (±)-1,6-epi-β-cubebene norketone (**25**), in a ratio (g.l.c. analysis) of approximately 3:5, respectively. The minor isomer **24**, upon treatment with methylenetriphenylphosphorane in dimethyl sulfoxide (27), gave a quantitative yield of (±)-β-cubebene (**2**) as a clear, colorless oil. The spectral properties (i.r., n.m.r., u.v., and mass spectrum) of this material were identical with those of natural β-cubebene.[9] Furthermore, the two materials were indistinguishable by g.l.c. Since β-cubebene had already been converted into α-cubebene (1), the synthesis of (±)-β-cubebene (**2**), as described above, also represents a total synthesis of (±)-α-cubebene (**1**).

It should be noted that although the synthetic work described in this paper provides unambiguous evidence regarding the stereochemistry at C-7 and -10 of the two cubebenes **1** and **2**, the nature of the synthesis is such that it supplies no conclusive information concerning the stereochemistry at C-6 of these compounds. However, Hirose *et al.* (3) have presented excellent evidence regarding this point and it thus appears safe to assume that **1** and **2** correctly represent the structure and stereochemistry of α- and β-cubebene, respectively.

Experimental

Melting points, which were determined on a Kofler block, and boiling points are uncorrected. The u.v. spectra were, unless otherwise noted, measured in methanol solution on either a Cary, model 14, or a Unicam, model SP 800, spectrophotometer. Routine i.r. spectra were recorded on a Perkin–Elmer Infracord model 137 spectrophotometer, while all comparison spectra were re-

[9]Natural β-cubebene (**2**) was isolated from Oil of Cubeb, Extra, kindly supplied by Fritzsche Brothers, Inc., New York, N.Y. The i.r. and n.m.r. spectra of this material, isolated by preparative g.l.c., were identical with those kindly supplied by Professor Y. Hirose. In addition, upon ozonolysis, the β-cubebene which was isolated from Oil of Cubeb, Extra, gave the known β-cubebene norketone, m.p. 60–60.5° (lit. m.p. 58.5–59.5° (1)).

corded on a Perkin–Elmer model 421 spectrophotometer. The n.m.r. spectra were taken in deuteriochloroform solution on Varian Associates spectrometers, models T-60, A-60, and/or HA-100. Line positions are given in the Tiers τ scale, with tetramethylsilane as an internal standard; the multiplicity, integrated peak areas, and proton assignments are indicated in parentheses. Mass spectrometric measurements were recorded on an AEI, type MS-9, mass spectrometer. The g.l.c. was carried out on an Aerograph Autoprep, model 700. The following columns were employed, with the inert supporting material being 60/80 mesh Chromosorb W in each case: column A, (30 ft × 3/8 in.), 30% Zonyl E-7; column B (20 ft × 3/8 in.), 30% SE-30; column C (10 ft × 1/4 in.), 20% SE-30; column D (10 ft × 3/8 in.), 30% Apiezon J; column E (10 ft × 1/4 in.), 10% Apiezon J; column F (10 ft × 1/4 in.), 20% Carbowax 20 M. The specific column used, along with column temperature and carrier gas (helium) flow-rate (ml/min), are indicated in parentheses. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver, B.C.

Preparation of Hydroxymethylene Derivatives **6**

To an ice-cooled, stirred suspension of powdered sodium methoxide (135 g, 2.46 moles) in 1500 ml of dry benzene, kept under an atmosphere of dry nitrogen, was added 154 g (1 mole) of a mixture of (±)-menthone and (±)-isomenthone (**5**). The resulting mixture was stirred for 10 min, and then 125 g (1.7 moles) of ethyl formate was added. The mixture was warmed to room temperature and allowed to stand overnight. Water was added, and the layers were separated. The organic layer was extracted with two portions of 10% aqueous sodium hydroxide. The combined aqueous layer and alkaline extracts were cooled, acidified with 6 *N* hydrochloric acid, and thoroughly extracted with ether. The combined extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual oil under reduced pressure, gave 171 g (94%) of the hydroxymethylene derivatives **6** as a pale yellow oil, b.p. 71–73° at 0.2 mm; n_D^{20} 1.4983; u.v. λ_{max} 294 mμ (ε = 7950), λ_{max} (NaOH added) 319 mμ (ε = 17 500); i.r. (film) λ_{max} 6.15, 6.35 μ.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.49; H, 10.06.

Preparation of n-Butylthiomethylene Derivatives **7**

A solution of the hydroxymethylene derivatives **6** (137.5 g, 0.755 mole), *n*-butanethiol (75 g, 0.825 mole), and *p*-toluenesulfonic acid (50 mg) in 500 ml of dry benzene was refluxed in a nitrogen atmosphere under a Dean–Stark water separator for 12 h at which time 13 ml of water had been collected. The cooled solution was washed with saturated aqueous sodium bicarbonate, then with water, and finally dried over anhydrous magnesium sulfate. Removal of the solvent gave an oil which, upon distillation under reduced pressure, afforded 170 g (89%) of the *n*-butylthiomethylene derivatives **7**, b.p. 130–136° at 0.35 mm; n_D^{20} 1.5292; u.v. λ_{max} 311 mμ (ε = 13 600); i.r. (film), λ_{max} 6.02, 6.50 μ.

Anal. Calcd. for $C_{15}H_{26}OS$: C, 70.83; H, 10.30; S, 12.61. Found: C, 71.09; H, 10.45; S, 12.30.

Preparation of Aldehydes **10**

To a solution of the *n*-butylthiomethylene derivatives **7** (140.7 g, 0.555 mole) in 1.8 l of methanol was added 21.25 g (0.555 mole) of sodium borohydride dissolved in 55.5 ml of 0.1 *N* sodium hydroxide. The mixture was stirred at room temperature for 2 h then a further 21.25 g (0.555 mole) of sodium borohydride dissolved in 55.5 ml of 0.1 *N* sodium hydroxide was added. After a further 2 h, the methanol was removed at aspirator pressure and the remaining aqueous layer was extracted three times with ether. The ether layers were washed with water then dried over anhydrous magnesium sulfate. Removal of the solvent gave 142 g (100%) of the β-hydroxythioenol ethers **8** as a pale yellow oil, i.r. (film) λ_{max} 3.00, 6.23 μ. This material was used without further purification in the hydrolysis step as described below.

To a solution of the crude alcohol **8** (25.6 g, 0.1 mole) in 500 ml of acetone was added 100 ml of 1% aqueous hydrochloric acid. The resulting mixture was heated on a steam bath for 20 min, then the acetone was removed at water aspirator pressure. The remaining aqueous layer was saturated with sodium chloride and extracted three times with ether. The combined ether layers were washed with water and dried over anhydrous magnesium sulfate Removal of the ether, followed by distillation of the resulting oil under reduced pressure (0.35 mm) gave two fractions: fraction 1, b.p. 66–68°, 6.65 g (40%) consisted of the desired α,β-unsaturated aldehydes **10** as a clear colorless oil, n_D^{20} 1.4878; u.v. λ_{max} 233.5 mμ (ε = 18 750); i.r. (film), λ_{max} 3.75, 5.95, 6.15 μ; n.m.r. τ 0.6 (singlet, 1H, *CH*O), 3.35 (multiplet, 1H, β-vinyl H), 8.82–9.16 (multiplet, 9H, secondary methyls).

Anal. Calcd. for $C_{11}H_{18}O$: C. 79.46; H, 10.91. Found: C, 79.64; H, 10.85.

Fraction 2, b.p. 120–126°, 11.9 g (50%), consisted of the pure thioenol ether **9** as a pale yellow oil, n_D^{20} 1.5363; u.v. λ_{max} 278 mμ (ε = 22 600), λ_{sh} 286 mμ (ε = 21 100); i.r. (film) λ_{max} 6.4, 11.4 μ; n.m.r. τ 4.08 (multiplet, 1H, vinyl H), 4.37 (singlet, 1H, vinyl H), 8.85–9.15 (multiplet, 12H, three secondary methyls and one primary methyl).

Anal. Calcd. for $C_{15}H_{26}S$: C, 75.56; H, 10.99. Found: C, 75.71; H, 11.10.

Preparation of the Mixture of Alcohols **11** *and* **12**

To a solution of sodium borohydride (4.5 g, 0.12 mole in 500 ml of methanol, cooled to 0° in an ice bath, was added a solution of the mixture of aldehydes **10** (20 g, 0.12 mole) in 100 ml of methanol. The reaction mixture was stirred under an atmosphere of nitrogen for 30 min and the methanol was removed at water aspirator pressure. Cold water (200 ml) was added and the aqueous layer was extracted three times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the ether was removed at water aspirator pressure. Distillation of the resulting oil under reduced pressure afforded 18.4 g (91%) of the mixture of alcohols **11** and **12**, b.p. 77–78° at 0.25 mm.

Preparation of Trimethylsilyl Ethers **13** *and* **14**

To a solution of the mixture of alcohols **11** and **12** (9 g, 0.053 mole) in 150 ml of dry pyridine was added 30 ml of hexamethyldisilazane and 15 ml of trimethylsilyl chloride.

The mixture was stirred under an atmosphere of nitrogen for 10 min, then the mixture was filtered and the excess reagents and pyridine were removed at water aspirator pressure. The crude product was distilled under reduced pressure to give 12.2 g (95%) of the mixture of trimethylsilyl ether derivatives **13** and **14**, b.p. 62–63° at 0.35 mm. Analysis of this mixture by g.l.c. (column A, 150°, 200) revealed that the two isomers were present in a ratio of approximately 1:1. Purification of the two isomers was achieved by preparative g.l.c. (column A, 140°, 240). The pure *trans*-isomer **14**, of shorter retention time, was a clear colorless oil and exhibited n_D^{20} 1.4544; i.r. (film) λ_{max} 8.00, 9.4, 11.4, 11.9 μ; n.m.r. τ 4.43 (broad singlet, 1H, vinyl H, $w_{\frac{1}{2}}$ = 4 Hz), 5.92 (unresolved multiplet, 2H, —CH_2—OTMS), 8.99, 9.09, 9.13 (doublets, 9H, secondary methyls, J = 7 Hz), 9.87 (singlet, 9H, Si(CH_3)$_3$).

Mol. Wt. Calcd. for $C_{14}H_{28}OSi$: 240.191. Found (high resolution mass spectrometry): 240.190.

The pure *cis*-isomer **13**, of longer retention time, was a clear colorless oil and exhibited n_D^{20} 1.4540; i.r. (film), λ_{max} 8.03, 9.45, 11.4, 11.9 μ; n.m.r., τ 4.43 (broad singlet, 1H, vinyl H, $w_{\frac{1}{2}}$ = 4 Hz), 5.92 (unresolved multiplet, 2H, —CH_2—OTMS), 8.98, 9.08, 9.13 (doublets, 9H, secondary methyls, J = 7 Hz), 9.87 (singlet, 9H, Si(CH_3)$_3$).

Mol. Wt. Calcd. for $C_{14}H_{28}OSi$: 240.191. Found (high resolution mass spectrometry): 240.191.

Preparation of Alcohol ***12***

The pure *trans*-trimethylsilyl ether **14** (600 mg. 2.5 mmoles) was refluxed in 6 ml of ethanol containing 0.2 ml of water for 2 h. The solvents were removed at water aspirator pressure and the resulting oil was distilled under reduced pressure to afford 413 mg (98%) of the alcohol **12** as a clear colorless oil, b.p. 80° (hot-box) at 0.15 mm; n_D^{20} 1.4825; i.r. (film) λ_{max} 3.0, 6.02, 9.9 μ; n.m.r. τ 4.39 (broad singlet, 1H, vinyl H, $w_{\frac{1}{2}}$ = 5 Hz), 5.92 (unresolved multiplet, 2H, CH_2O—H), 8.22 (singlet, 1H, exchangeable, CH_2OH), 8.98, 9.10, 9.14 (doublets, 9H, secondary methyls, J = 6.8, 6.4, and 6.4 Hz respectively).

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.76; H, 12.03.

Preparation of Bromide ***15***

A solution of the alcohol **12** (400 mg, 2.38 mmoles) in 10 ml of benzene containing 0.08 ml of dry pyridine was cooled to 0° in an ice-bath. To this cold stirred solution was added, from a dropping funnel, 312 mg (1.15 mmoles) of phosphorous tribromide in 1.1 ml of dry benzene. The reaction mixture was stirred for 30 min and then diluted with 5 ml of cold dilute aqueous sodium bicarbonate solution. The mixture was extracted with ether and the combined organic layers were dried over anhydrous magnesium sulfate. The solvents were removed at aspirator pressure and the resulting crude product was distilled under reduced pressure to afford 425 mg (77%) of the bromide **15**, b.p. 75° at 0.2 mm; n_D^{20} 1.5027; i.r. (film) λ_{max} 6.08, 8.30 μ; n.m.r. τ 4.30 (broad singlet, 1H, vinyl H, $w_{\frac{1}{2}}$ = 5 Hz), 6.03 (quartet, 2H, $-CH_2Br$, J_{AB} = 10 Hz), 8.95, 9.09, 9.12 (doublets, 9H, secondary methyls, J = 7 Hz).

Anal. Calcd. for $C_{11}H_{19}Br$: C, 57.15; H, 8.28. Found: C, 57.25; H, 8.27.

*(±)-trans-2-Methyl-p-mentha-2-ene (**16a**)*

To a solution of lithium aluminum hydride (50 mg, 1.3 mmoles) in 6 ml of dry tetrahydrofuran was added 300 mg (1.3 mmoles) of the allylic bromide **15**. The mixture was refluxed under an atmosphere of nitrogen for 1.5 h, then cooled to 0°. Water (1 ml) was cautiously added, and the resulting mixture was extracted with ether. The combined ether layers were dried over anhydrous magnesium sulfate and the solvent was removed at water aspirator pressure. Distillation of the resulting oil under reduced pressure gave 188 mg (95%) of (±)-2-methyl-*p*-mentha-2-ene (**16a**) as a clear colorless oil, b.p. 80° (hot-box) at 10 mm; n_D^{20} 1.4602; i.r. (film) λ_{max} 6.93, 7.23, 7.32, 11.5, 11.9 μ; n.m.r. τ 4.87 (broad singlet, 1H, vinyl H, $w_{\frac{1}{2}}$ = 5 Hz), 8.37 (singlet, 3H, vinyl CH_3), 9.05, 9.15, 9.18 (doublets, 9H, secondary methyls, J = 6.6 Hz). This material exhibited spectra (i.r., n.m.r.) identical with those obtained from an authentic sample of (+)-*trans*-2-methyl-*p*-mentha-2-ene (**16b**), the synthesis of which is described below.

Mol. Wt. Calcd. for $C_{11}H_{20}$: 152.156. Found (high resolution mass spectrometry): 152.156.

*(−)-trans-Caran-2-one(**18**)*

A solution of (+)-dihydrocarvone (**17**) (15.2 g, 0.1 mole) in 130 g of 9.4% hydrogen bromide in glacial acetic acid was stirred at room temperature for 15 min, then poured onto 500 g of crushed ice. The resulting mixture was extracted three times with ether and the combined ether extracts were washed with dilute aqueous sodium bicarbonate and water until all of the acetic acid had been removed. The ether layer was dried over anhydrous magnesium sulfate and the ether was removed at water aspirator pressure to afford 23.3 g (100%) of the crude (+)-dihydrocarvone hydrobromide.

To a solution of potassium hydroxide (5.9 g, 0.105 mole) in 250 ml of ethanol at 0° was added the crude hydrobromide (23.3 g, 0.1 mole), and the resulting mixture was stirred for 2 h at 0°. The precipitated potassium bromide was filtered off and the ethanol was removed from the filtrate at water aspirator pressure. Distillation of the resulting oil under reduced pressure gave 12.18 g (80%) of (−)-*trans*-caran-2-one (**18**), b.p. 38–40° at 0.15 mm [lit. b.p. 60° at 1 mm (19)]. This material was crystallized by dissolving it in hexane and cooling the resulting solution to −78° (acetone – Dry Ice). The mother liquors were removed with a pipet and the crystals were warmed to room temperature to give a clear colorless oil. The resulting material was recrystallized under the same conditions and any excess hexane was removed under reduced pressure (vacuum pump, 0.1 mm). A sample of material purified in this way exhibited n_D^{20} 1.4773; $[\alpha]_D^{22}$ −181° (*c*, 1.2 in methanol) [lit. $[\alpha]_D^{19}$ −162.9° (19), −153° (*c*, 5.0) (20)]; i.r. (film) λ_{max} 5.96 μ; n.m.r. τ 8.81, 8.96 (singlets, 6H, tertiary methyls, ), 8.98 (doublet, 3H, secondary methyl, J = 6.3 Hz).

Preparation of Alcohol ***19***

To a solution of (−)-*trans*-caran-2-one (**18**) (1.52 g, 0.01 mole) in 50 ml of dry ether was added 15 ml of 2.13

M ethereal methyllithium (0.032 mole), and the resulting mixture was stirred for 3 days. The excess methyllithium was destroyed by the cautious addition of 2 ml of water, and the ether layer was dried over anhydrous magnesium sulfate. Removal of the ether at water aspirator pressure gave 2.1 g of a pale yellow oil. This material was purified by column chromatography on 60 g of florisil. The fractions eluted with 1:9 ether–hexane and 1:4 ether–hexane were combined to give 1.65 g (98%) of the alcohol **19**, n_D^{20} 1.4800; $[\alpha]_D^{21}$ −9.4° (*c*, 1.0 in methanol); i.r. (film) λ_{max} 2.95, 9.15, 10.95 μ; n.m.r. τ 8.3 (singlet, 1H, exchangeable, O—*H*), 8.74, 8.75, 8.95 (singlets, 9H, tertiary methyls), 9.09 (doublet, 3H, secondary methyl, J = 6.5 Hz).

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.63; H, 11.80.

(+)-trans-2-Methyl-p-mentha-2,8-diene (20)

A mixture of the alcohol **19** (836 mg, 5 mmoles) and 0.17 ml of pyridine was placed in a pyrolysis tube and sealed under an atmosphere of nitrogen. The tube was heated in an oil bath at 190° for 2 h after which time it was cooled and carefully opened. The mixture was diluted with ether and dried over anhydrous magnesium sulfate. Removal of the solvents at water aspirator pressure afforded 730 mg of colorless oil. Analysis of this mixture by g.l.c. (column B, 155°, 200) revealed that it consisted of a mixture of 70% (+)-*trans*-2-methyl-*p*-mentha-2,8-diene (**20**) and several minor unidentified components. A sample of **20** purified by preparative g.l.c. (column B, 155°, 200) exhibited n_D^{20} 1.4736; $[\alpha]_D^{20}$ +139.3° (*c*, 3.7 in methanol); i.r. (film) λ_{max} 3.25, 6.08, 11.28 μ; n.m.r. τ 4.72 (broad singlet, 1H, C_3 vinyl H, $w_{\frac{1}{2}}$ = 5 Hz), 5.27 (broad singlet), 2H, CH_3—C=C*H*$_2$, $w_{\frac{1}{2}}$ = 3 Hz), 8.27 (singlet, 6H, vinyl methyls), 8.99 (doublet, 3H, secondary methyl, J = 6.4 Hz).

Anal. Calcd. for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 88.20; H, 11.85.

(±)-trans-2-Methyl-p-mentha-2-ene (16b)

The hydrogenation of the diene **20** was carried out in benzene at room temperature and atmospheric pressure using tris(triphenylphosphine)chlororhodium (22, 23) as the catalyst. The reaction solution was filtered through a small column of activity II alumina. From 240 mg of **20** there was obtained 225 mg of a clear colorless oil. Analysis of this material by g.l.c. (column C, 110°, 100) showed that it consisted of 80% (+)-*trans*-2-methyl-*p*-mentha-2-ene (**16*b***) and several other minor, unidentified components. A sample of compound **16*b*** obtained by preparative g.l.c. (column D, 145°, 200) exhibited n_D^{20} 1.4602; $[\alpha]_D^{22}$ +25.4° (*c*, 0.6 in methanol). This material displayed i.r. and n.m.r. spectra and g.l.c. retention times identical with those obtained from compound **16*a***, prepared as described previously.

Mol. Wt. Calcd. for $C_{11}H_{20}$: 152.156. Found (high resolution mass spectrometry): 152.156.

Preparation of Carboxylic Acid 22

To a hot solution of carbethoxymethylenetriphenylphosphorane (24) (1.28 g, 3.7 mmoles) in 10 ml of ethyl acetate was added 425 mg of the allylic bromide **15** (1.84 mmoles). The resulting mixture was refluxed for 5 h, then cooled and the precipitated carbethoxymethyltriphenylphosphonium bromide (575 mg, 73%) was filtered off. The solvent was removed at water aspirator pressure, and the remaining crude product (**21**) was dissolved in 12 ml of 10% potassium hydroxide in 1:1 methanol–water, and the resulting solution was refluxed for 1 h. The reaction mixture was cooled and the methanol removed at water aspirator pressure. The basic aqueous layer was extracted with ether and then neutralized with 6 *N* hydrochloric acid. The resulting mixture was extracted with ether and the ether extract was dried over anhydrous magnesium sulfate. Removal of the ether followed by distillation of the oily residue under reduced pressure afforded 270 mg (69%) of the carboxylic acid **22** b.p. 120° (hot-box) at 0.15 mm; n_D^{20} 1.4818; i.r. (film) λ_{max} 3.1–3.9, 5.85 μ; n.m.r. τ 4.69 (broad singlet, 1H, vinyl H, $w_{\frac{1}{2}}$ = 4 Hz), 7.40 (singlet, 4H, —C*H*$_2$C*H*$_2$-CO_2H), 9.00, 9.13, 9.17 (doublets, 9H, secondary methyls).

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.22; H, 10.53.

(±)-β-Cubebene Norketone (24) and (±)-1,6-Epi-β-cubebene Norketone (25)

The carboxylic acid **22** (242 mg, 1.15 mmoles) was dissolved in aqueous sodium hydroxide (1.32 mmoles), the water was evaporated under reduced pressure, and the residue was dried in a vacuum oven at 70°. A stirred suspension of the resulting dry sodium salt in 20 ml of dry benzene containing 0.02 ml of pyridine was cooled to 0° and 1.5 g (12 mmoles) of oxalyl chloride was added. The reaction mixture was stirred at 0° for 15 min, filtered, and evaporated under reduced pressure (vacuum pump). The solution was kept at 0° during this process. The crude acid chloride **23** (i.r. (film) λ_{max} 5.58 μ; n.m.r. very similar to that of the carboxylic acid **22** except at τ 7.00 (complex multiplet, 4H, —C*H*$_2$C*H*$_2$COCl)) thus obtained was taken up in 15 ml of dry ether and the resulting solution was added to excess alcohol free ethereal diazomethane which had been dried over potassium hydroxide. The solution was stirred for 15 min and evaporated under reduced pressure affording the crude diazoketone **3**, i.r. (film) λ_{max} 3.27, 4.78, 6.10 μ; n.m.r. τ 4.75 (broad singlet, 2H, vinyl H and COC*H*N_2, $w_{\frac{1}{2}}$ = 4 Hz), 7.64 (singlet, 4H, —C*H*$_2$C*H*$_2$COCHN_2). The crude diazoketone **3** was dissolved in 30 ml of cyclohexane and cupric sulfate (750 mg) was added. The resulting suspension was refluxed with stirring for 1.5 h after which time the i.r. absorption at 4.78 μ due to the diazoketone **3** had disappeared. The cooled mixture was filtered and the cyclohexane was removed at water aspirator pressure. Distillation of the oily residue under reduced pressure gave 185 mg (78%) of a pale yellow oil, b.p. 100–103° (hot-box) at 0.2 mm. This material was shown by g.l.c. analysis (column E, 190°, 90) to consist of approximately 36% of (±)-β-cubebene norketone (**24**) and 64% (±)-1,6-epi-β-cubebene norketone (**25**). Preparative g.l.c. (column D, 235°, 135) provided pure samples of **24** and **25**. Pure (±)-β-cubebene norketone (**24**) thus obtained exhibited n_D^{20} 1.4940; u.v. λ_{max} 206 mμ (ε = 6150); i.r. (film) λ_{max} 5.85 μ; n.m.r. τ 9.00, 9.05, 9.07 (doublets, 9H, secondary methyls, J = 6.5 Hz).

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.49; H, 10.74. Found: 81.79; H, 10.59.

Pure (±)-1,6-epi-β-cubebene norketone (**25**) obtained in the same manner exhibited n_D^{20} 1.4984; u.v. λ_{max} 205 mμ (ε = 6280); i.r. (film) λ_{max} 5.82 μ; n.m.r. τ 7.95 (broadened singlet, 4H $w_{\frac{1}{2}}$ = 2 Hz), 8.91 (doublet, 3H, secondary methyl, J = 7 Hz), 8.98 (poorly resolved multiplet, 6H, $CH(CH_3)_2$).

Mol. Wt. Calcd. for $C_{14}H_{22}O$: 206.166. Found (high resolution mass spectrometry): 206.167.

(±)-β-Cubebene (2)

A stirred suspension of sodium hydride (300 mg, 12.5 mmoles) in dry dimethyl sulfoxide (14 ml) was slowly heated under an atmosphere of nitrogen to 75° and kept at this temperature until frothing had ceased (approximately 30 min). The solution was cooled to room temperature and a solution of methyltriphenylphosphonium bromide (5.32 g, 14.8 mmoles) in 8 ml of dimethyl sulfoxide was added. The solution was stirred for 10 min and then a solution of (±)-β-cubebene norketone (**24**) (515 mg, 2.5 mmoles) in 15 ml of dimethyl sulfoxide was added. The reaction mixture was heated to 50° for 6 h, cooled, diluted with water, and then thoroughly extracted with hexane. The combined extracts were washed with water and brine, then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual oil under reduced pressure afforded 506 mg (99%) of **2** as a clear colorless oil, b.p. 80–82° (hot-box) at 0.2 mm. Analysis of this material by g.l.c. (column F, 170°, 90) revealed that it was only one component and it exhibited n_D^{20} 1.4975; u.v. λ_{max} 208 mμ (ε = 9850); i.r. (film) λ_{max} 3.26, 6.10, 11.72 μ; n.m.r. τ 5.28, 5.47 (unresolved multiplets, 2H, $\diagdown C{=}CH_2$), 9.04, 9.06, 9.10 (doublets, 9H, secondary methyl groups, J = 6.0, 6.5, 6.5 Hz respectively). This material exhibited spectra (u.v., i.r., n.m.r.) and g.l.c. retention times identical with those obtained from authentic β-cubebene, isolated from Oil of Cubeb, Extra (see footnote 9).

Mol. Wt. Calcd. for $C_{15}H_{24}$: 204.187. Found (high resolution mass spectrometry): 204.186.

We thank the National Research Council of Canada and the University of British Columbia Committee on Research for financial support. A National Research Council of Canada Studentship (to W. de W.) and a H. R. MacMillan Family Fellowship (to R.W.B.) are gratefully acknowledged.

1. Y. Ohta, T. Sakai, and Y. Hirose. Tetrahedron Lett. 6365 (1966).
2. Y. Ohta and Y. Hirose. Tetrahedron Lett. 2073 (1967).
3. Y. Ohta, K. Ohara, and Y. Hirose. Tetrahedron Lett. 4181 (1968).
4. E. Piers, R. W. Britton, and W. de Waal. Tetrahedron Lett. 1251 (1969).
5. A. Tanaka, H. Uda, and A. Yoshikoshi. Chem. Commun. 308 (1969).
6. E. Piers, W. de Waal, and R. W. Britton. Chem. Commun. 188 (1968); Can. J. Chem. **47**, 4299 (1969).
7. E. Piers, R. W. Britton, and W. de Waal. Can. J. Chem. **47**, 831 (1969).
8. E. J. Corey and K. Achiwa. Tetrahedron Lett. 1837 (1969).
9. E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen. J. Amer. Chem. Soc. **91**, 4318 (1969).
10. R. M. Coates and R. M. Freidinger. Chem. Commun. 871 (1969).
11. K. Mori and M. Matsui. Tetrahedron Lett. 2729 (1969); Tetrahedron Lett. 4435 (1969).
12. J. J. Plattner, U. T. Bhalerao, and H. Rapoport. J. Amer. Chem. Soc. **91**, 4933 (1969); J. Amer. Chem. Soc. **92**, 3429 (1970).
13. P. A. Grieco. J. Amer. Chem. Soc. **91**, 5660 (1969).
14. R. E. Ireland and J. A. Marshall. J. Org. Chem. **27**, 1615 (1962).
15. R. F. Church, R. E. Ireland, and J. A. Marshall. J. Org. Chem. **27**, 1118 (1962), and references therein.
16. R. E. Ireland and J. A. Marshall. J. Org. Chem. **27**, 1620 (1962), and references therein.
17. W. C. Young and J. F. Lane. J. Amer. Chem. Soc. **59**, 2051 (1937).
18. A. Baeyer. Chem. Ber. **27**, 1915 (1894).
19. W. Cocker, D. P. Hanna, and P. V. R. Shannon. J. Chem. Soc. C, 489 (1968).
20. W. Cocker, P. V. R. Shannon, and P. A. Staniland. J. Chem. Soc. C, 485 (1967).
21. J. W. Daly, F. C. Green, and R. H. Eastman. J. Amer. Chem. Soc. **80**, 6330 (1958).
22. F. A. Jardine and G. Wilkinson. J. Chem. Soc. C, 270 (1967).
23. J. F. Biellmann. Bull. Soc. Chim. Fr. 3055 (1968).
24. O. Isler, H. Gutmann, M. Montavon, R. Ruegg, G. Ryser and P. Zeller. Helv. Chim. Acta, **40**, 1242 (1957).
25. H. J. Bestmann and H. Schulz. Chem. Ber. **95**, 2921 (1962).
26. M. M. Fawzi and C. D. Gutsche. J. Org. Chem. **31**, 1390 (1966), and references therein.
27. E. J. Corey and M. Chaykovsky. J. Amer. Chem. Soc. **87**, 1345 (1965), and references therein.