panol under conditions described for the preparation of methoxyfulvene **13** gave an 89% yield of yellow isopropoxyfulvene **14**: mp 111–112°; ir ($CHCl_3$) 1740–1710, 1630, 1440 cm^{-1}; uv max (EtOH) 344 (ε 21,000) and 355 mμ (ε 21,200); nmr ($CDCl_3$) δ 1.35 (d, 6, J = 6.5 Hz), 3.9 (s, 3), 4.5 (m, 1, J = 6.5 Hz), 7.35 (AB, 2, J = 4 Hz), 8.2 (s, 1), and 8.3 (s, 1).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.14; H, 5.16.

Methyl 7-Chloromethylenecyclopenta[*c*]pyran-1(7H)-one-4-carboxylate (15). The hydroxyfulvene **12** (300 mg, 1.36 mmol) was stirred 12 hr at room temperature in a nitrogen atmosphere with 3 ml of oxalyl chloride. Excess oxalyl chloride was evaporated and the resulting solid was sublimed at 90° under vacuum giving 328 mg (94%) of the yellow chlorofulvene **15**: mp 126–127°; ir ($CHCl_3$) 1750–1710, 1610, 1600, 1440 cm^{-1}; uv max (pentane) 234 (ε 5010), 273 (ε 3640), 314 (ε 10,300), 327 (ε 9700) and 343 mμ (ε 5140); nmr ($CDCl_3$) δ 3.9 (s, 3), 7.3 (ABX, 2, J_{AB} = 6 Hz, J_{AX} = 2 Hz), 8.0 (d, 1, J = 2 Hz) and 8.3 (s, 1).

Anal. Calcd for $C_{11}H_7O_4Cl$: C, 55.36; H, 2.98. Found: C, 55.32; H, 3.37.

Methyl 7-Crotonylidenecyclopenta[*c*]pyran-1(7H)-one-4-carboxylate (1). To a solution of the chlorofulvene **15** (150 mg, 0.63 mmol) in dimethoxyethane (40 ml, distilled from $LiAlH_4$ in an argon atmosphere) maintained at −35°, was added an ethereal solution of lithium di(*trans*-1-propenyl)cuprate (**16**)[16] kept at −78° (0.73 mmol which was prepared from 1.47 mmol of *trans*-1-propenyllithium and 0.73 mmol of CuI). The dark red solution was stirred for 0.5 hr at −35°, then warmed to −5° and diluted with ether (150 ml). After extraction with dilute hydrochloric acid, washing with water, and drying (Na_2SO_4), the solvent was evaporated *in vacuo*. The residue was then dissolved in tetrahydrofuran (1 ml) and chromatographed over a column of zinc carbonate (7 g), supported on Celite (14 g), prepared in hexane suspension. Elution with ether gave 96 mg of product which was rechromatographed on a silicic acid (10 g)–Celite (10 g) column prepared in hexane and eluted with ether. Evaporation *in vacuo* and recrystallization from chloroform gave 40.5 mg (27%) of fulvoplumierin (**1**): mp 148–150° (lit.[3] mp 151–152°); ir ($CHCl_3$) 1730–1710, 1620, 1585, 1520, 1435 cm^{-1}; ir (Nujol) 1740, 1710, 1620, 1580, 1530 cm^{-1}; uv max (EtOH) 272 (ε 7000) and 365 mμ (ε 33,700); nmr (100 MHz) ($CDCl_3$) δ 2.05 (d, 3, J = 5.5 Hz), 3.95 (s, 3), 6.4–7.3 (ABX, 2, J_{AB} = 14, J_{AX} = 8 Hz), 7.3–7.6 (AB, 2, J_{AB} = 3 Hz), 7.9 (d, 1, J = 8 Hz), and 8.3 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 244 (100), 212 (55), 184 (24), 156 (37), 128 (81).

Acknowledgment. We are indebted to the National Institutes of Health for financial support and to Professor H. Schmid, University of Zürich, for having compared natural and synthetic fulvoplumierin.

The Synthesis of (−)-Aromadendrene and Related Sesquiterpenes

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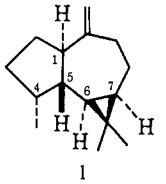
Received June 26, 1969

Abstract: Addition of hydrobromic acid to (−)-perillaldehyde (**3**) followed by base-induced elimination of hydrobromic acid gave the bicyclic aldehyde **4**. Wittig reaction, followed by Diels–Alder condensation with acrolein yielded the adduct **6**. Epimerization and reduction to the olefin **8**, followed by oxidation, furnished a mixture of diols containing mainly **9** and minor amounts of the diastereomer **10**. In two separate sequences of chemical operations the diols **9** and **10** were transformed to the epimeric olefins **13** and **16**. Neither proved to be the enantiomer of aromadendrene or alloaromadendrene. An analogous sequence of reactions again starting with the aldehyde **6** proceeding *via* the olefin **20**, the diol **21**, and the ketone **23** afforded (−)-aromadendrene (**24**) the enantiomer of naturally occurring (+)-aromadendrene (**1**). This finding requires revision of the previously postulated stereostructures of aromadendrene and a number of other related sesquiterpenes. Naturally occurring globulol, alloaromadendrene, ledol, and viridoflorol are now represented by structures **29**, **30**, **31**, and **32**, respectively. New evidence on the configuration of the crucial degradation product **27** shows that degradative and synthetic evidence concerning the stereochemistries of this group of sesquiterpenes is no longer in conflict.

Aromadendrene is a member of a group of naturally occurring sesquiterpenes structurally characterized by fusion of a cyclopropane ring to a hydroazulene skeleton. The currently accepted structure, exclusive of stereochemistry, was originally proposed in 1953.[2] Subsequent degradative work[3,4] eliminated an alternate structure proposed by the early workers. Studies on the stereochemistry of aromadendrene were pursued by two independent groups who both arrived at structure **2**.[3,4] The stereochemical arguments presented at that time seemed reasonable but supporting evidence was nevertheless needed. Synthetic work described in this paper provides unambiguous evidence that natural (+)-aromadendrene has in fact the relative and absolute stereochemistry indicated in structure **1**.[5]



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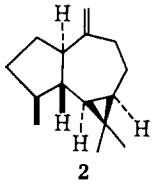


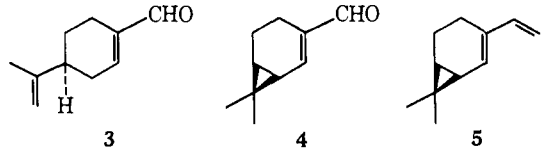
2

While considereing synthetic approaches to aromadendrene it was decided to construct the perhydroazulene portion of the molecule by skeletal rearrangement

(1) National Institutes of Health Postdoctoral Fellow, 1964–1966.
(2) A. J. Birch and F. N. Lahey, *Aust. J. Chem.*, **6**, 379 (1953).
(3) G. Buchi, S. W. Chow, T. Matsuura, T. L. Popper, H. H. Rennhard, and M. Schach v. Wittenau, *Tetrahedron Lett.*, 6, 14 (1959).
(4) L. Dolejs and F. Sorm, *ibid.*, **17**, 1 (1959); *Collect. Czech. Chem. Commun.*, **25**, 1837 (1960).
(5) A preliminary communication appeared in *J. Amer. Chem. Soc.*, **88**, 4113 (1966).

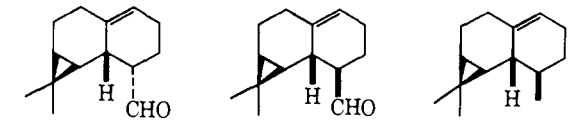
of a decalin[6] intermediate which we hoped to prepare by stereospecific processes.

For practical reasons we chose as starting material the commercially available (−)-perillaldehyde (**3**) rather than its rarer enantiomer.[7] Addition of hydrogen bromide in glacial acetic acid to **3** followed by treatment of the crude bromide with potassium *t*-butoxide yielded the bicyclic aldehyde **4**. The ultraviolet absorption spectrum of **4** is of some interest. It displays a maximum at 263 mμ[8] while the precursor **3** absorbs at 231 mμ. The bathochromic shift of 32 mμ observed seems too large to be attributed solely to cyclopropane conjugation and must be partly due to angle strain in the bicyclic aldehyde **4**. A modified Wittig reaction[9] served to transform the aldehyde **4** to the diene **5**.



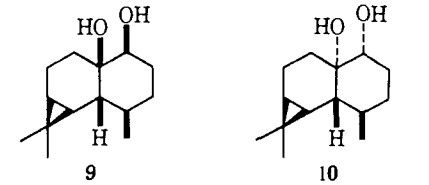
3 **4** **5**

Diels–Alder condensation of the diene **5** with acrolein in benzene solution at 100° furnished a mixture of adducts containing 75% of the tricyclic aldehyde **6** and 15% of its epimer **7**. The structures of the two adducts were assigned on the basis that stereomodels of the vinyl cyclohexene **5** show the bottom face of the diene to be more accessible than the top face. The principle of maximum accumulation of unsaturation in the transition state and the well-documented effect of substituents on the course of addition[10] allow the prediction that the kinetically formed adduct should have structure **6**.[11] If it is assumed that epimerization occurs to some extent under the conditions used, the minor product should be the epimer **7** and this was confirmed experimentally. Exposure of either aldehyde to potassium *t*-amylate in *t*-amyl alcohol led to an equilibrium mixture containing 83% of **7** and 17% of **6**. The thermodynamically more stable equatorial aldehyde **7** was now transformed to the tricyclic hydrocarbon **8** by consecutive treatments with lithium aluminum hydride, methanesulfonyl chloride and lithium aluminum hydride.

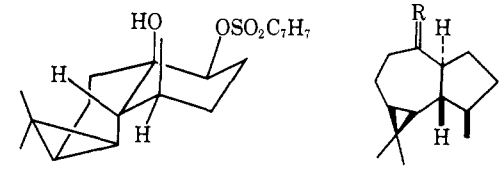


6 **7** **8**

Oxidation of the olefin **8** with osmium tetroxide afforded a mixture of diol **9** (84%) and the epimeric diol **10** (*ca.* 10%) which was not obtained in pure form. A Dreiding model of the tricyclic olefin **8** demonstrates that the electrophilic agent should attack the double bond mainly from the β side and the stereochemistries of the two *cis*-diols **9** and **10** were tentatively assigned on this basis. An argument to be described later verified this conclusion. *p*-Toluenesulfonic acid chloride was selective in the esterification of the diol **9** and the resulting monotosylate **11** on treatment with 1 equiv of potassium *t*-butoxide in *t*-amyl alcohol or on chromatography over alumina was smoothly transformed to a crystalline ketone, mp 64–65°. Models suggest that the preferred geometry of the tosylate is that shown in the conformational drawing **11** and this is exactly the geometry that permits rearrangements to the perhydrazulene ketone **12**.[12] The physical properties of this ketone **12** were distinctly different from those of apoaromadendrone, mp 82–83°,[2] and from those of its less stable C-1 epimer α-apoaromadendrone, mp 71–72°.[2] Similarly, the hydrocarbon **13** prepared from the ketone **12** by a Wittig reaction was not the enantiomer of aromadendrene nor its naturally occurring C-1 epimer alloaromadendrene.[13,14]



9 **10**

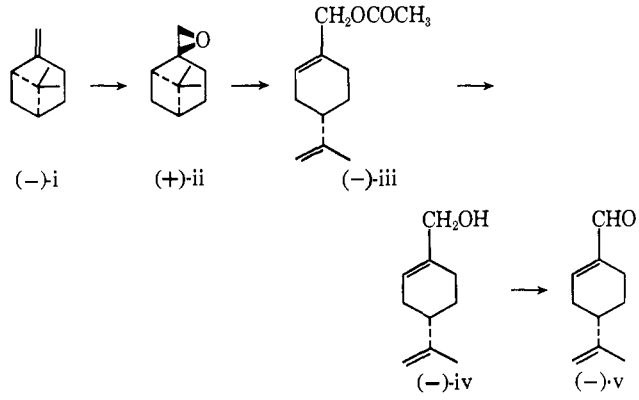


11 **12**, R = O; **13**, R = CH_2

At this point it became clear that the stereochemistries of either aromadendrene or the synthetic compounds already described needed revision. To clarify the situation we proceeded with the study of the minor diol **10** which we hoped to correlate with a tricyclic ole-

(6) A similar approach to guaiazulenic sesquiterpenes was subsequently explored by C. H. Heathcock and R. Ratcliffe (*Chem. Commun.*, 994 (1968)) and considered, but not tested experimentally, in the synthesis of bulnesol by J. A. Marshall and J. J. Partridge, *J. Amer. Chem. Soc.*, 90, 1090 (1968); *Tetrahedron*, 25, 2159 (1969).

(7) Perillaldehyde is readily available from β-pinene: A. Kergomard, S. Philibert-Bigou, and M. T. Geneix, French Patent 1,813,849 (July 15, 1959); *Chem. Abstr.*, 55, 27404a (1961). No data regarding the optical activity of starting material and products were given. In subsequent work T. R. Keenan, B.S. Thesis, Massachusetts Institute of Technology, 1966, developed a process, based on the French synthesis, for the conversion of (−)-β-pinene (i) to (−)-perillaldehyde (v) using the sequence shown. As a result (+)-perillaldehyde should be available from (+)-β-pinene.



(−)-i (+)-ii (−)-iii (−)-iv (−)-v

(8) A transformation product of sirenin containing the same chromophore exhibits absorption at 260 mμ; W. H. Nutting, H. Rapoport, and L. Machlis, *J. Amer. Chem. Soc.*, 90, 6434 (1968).

(9) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, 28, 1128 (1963).

(10) J. Sauer, *Angew. Chem.*, 79, 76 (1967).

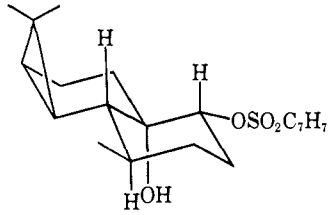
(11) *Cf.* the condensation of vinyl cyclohexene with methyl acrylate, I. N. Nazarov, V. F. Kutcherov, and G. M. Segal, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 559 (1956).

(12) N. L. Wendler, R. F. Hirschmann, H. L. Slates, and R. W. Walker, *J. Amer. Chem. Soc.*, 77, 1632 (1955); Y. Mazur and M. Nussim, *ibid.*, 83, 3911 (1961), and references cited.

(13) L. Dolejš and F. Šorm, *Tetrahedron Lett.*, 10, 1 (1959).

(14) A. J. Birch, J. Grimshaw, R. N. Speake, R. M. Gascoigne, and R. O. Hellyer, *ibid.*, 3, 15 (1959).

fin of known configuration previously encountered in the course of related work. The minor diol **10** and its monotosylate **14** have nmr absorptions at δ 0.89 and 0.88 caused by the secondary methyl groups. The methyl doublets are present at δ 1.18 in the major diol **9** and at δ 1.15 in the corresponding monotosylate **11**. The paramagnetic shift observed[15] in the latter two substances demands a 1,3-diaxal relationship between methyl and tertiary hydroxyl groups and this is only possible if the major glycol **9** and its derivative **11** are *cis*-decalins and the minor glycol **10** and its tosylate **14** are *trans*-decalins. Rearrangement of the tosylate **14** followed by immediate condensation of the resulting unstable ketone **15** with methylenetriphenylphosphorane gave a new hydrocarbon **16**.



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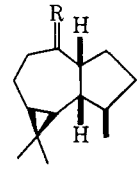
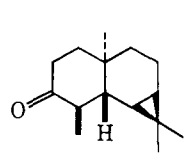


15, R = O
16, R = CH_2

We were able to ascertain that the olefin **16** in fact possesses the stereochemistry indicated by comparing it with a compound obtained in the following alternate synthesis. The tricyclic ketone **17**[16] in a few steps was transformed to the mesylate **18** which on exposure to potassium *t*-butoxide in hot *t*-butyl alcohol afforded a mixture of isomeric olefins from which 4-epialloaromadendrene (**19**) could be isolated by vpc.[17] The two enantiomers **19** and **16** had identical physical properties as judged by infrared and mass spectra and vapor chromatographic behavior.



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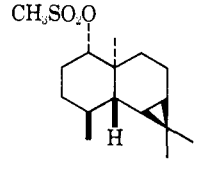

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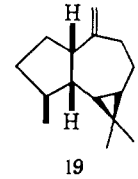
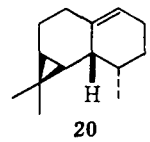


19

These findings left no doubt that the synthetic substances described had indeed the configuration already indicated and we proceeded with the synthesis of a tricyclic olefin epimeric at C-4 with those already described. The tricyclic aldehyde **6** was converted to the corresponding olefin **20** by the sequence of reactions previously used in the preparation of its epimer **8**. Oxidation with osmium tetroxide gave a single diol **21** which was esterified to the monotosylate **22**. The nmr spectra of both diol **21** and its derivative **22** reveal normally shielded secondary methyl groups (doublets at δ 0.87 and 0.83, respectively) demanding the presence of *cis*-decalins. Of the two possible conformations with chair cyclohexane rings, that shown in **22** is clearly preferred. It should allow facile rearrangement to the desired perhydroazulene ketone **23**. Indeed, when a solution of the tosylate **22** in chloroform remained in contact with activated alumina the ketone **23**, mp 82–83°, was formed quantitatively. When the rearrangement was performed in *t*-butyl alcohol-OD the resulting ketone contained only 8.5% of one deuterium atom. The configuration of the ketone is thus defined by that of its precursor. Infrared and mass spectra of the ketone **23** were identical with those of apoaromadendrone **25** derived from natural (+)-aromadendrene (**1**) and the two substances had opposite optical rotations. When condensed with methylenetriphenylphosphorane the ketone **23** yielded (−)-aromadendrene (**24**) $[\alpha]_D$ −11° (EtOH) identified by comparison of infrared and mass spectra as well as vapor chromatographic behavior with natural (+)-aromadendrene $[\alpha]_D$ +9° (EtOH). The stereoselective synthesis described leaves no doubt that natural aromadendrene has the relative and absolute configuration illustrated in structure **1**.



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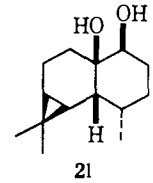

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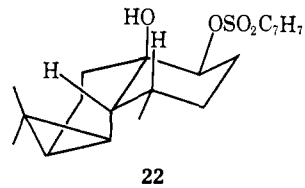

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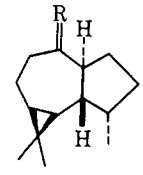
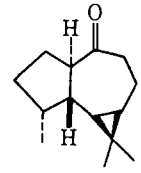


23, R = O
24, R = CH_2

The configuration at C-4 was originally assigned as follows.[2] Condensation of apoaromadendrone (**25**, without stereochemistry) with amyl nitrite in the presence of sodium ethoxide yielded an oximino ester transformed by base hydrolysis to the crystalline oximinocarboxylic acid **26** (without stereochemistry). Conversion to a liquid ketocarboxylic acid **27** (without stereochemistry) was brought about by mild hydrolysis with mineral acid. Condensation of the ketocarboxylic acid with hydroxylamine before and after treatment with alkali led to the original oximinocarboxylic acid and it was concluded that the ketocarboxylic acid already had the substituent next to the carbonyl group in the more stable orientation. Based on the not unreasonable assumptions that the oxime and its precursor **25** have the same configuration at C-5[18] and that the 2,3-disubstituted cyclopentanone should be more stable in the *trans* configuration[19] the relative configurations at C-4 and C-5 were postulated to be as shown in structure **2**.



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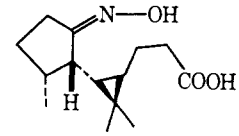
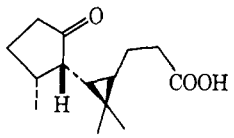


26

(15) R. F. Zurcher, *Helv. Chim. Acta*, **46**, 2054 (1963).
(16) R. B. Bates, G. Büchi, T. Matsuura, and R. R. Shaffer, *J. Amer. Chem. Soc.*, **82**, 2327 (1960).
(17) G. Büchi, J. Kagan, T. Mukai, and A. Zschocke, to be published.
(18) *Cf.* R. B. Woodward and W. v. E. Doering, *J. Amer. Chem. Soc.*, **67**, 860 (1945).
(19) The equilibrium mixture of 2-pentyl-3-methylcyclopentanone contains 92% of the *trans* isomer and 8% of the *cis* isomer: C. Ouannes Ph.D. Thesis, University of Paris, Paris, 1964, p 72; C. Ouannes and J. Jacques, *Bull. Soc. Chim. Fr.*, 3601 (1965).



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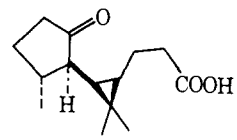
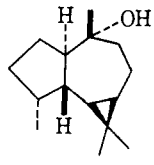


28

Since the completion of the synthesis of aromadendrene we have investigated the configuration of the crucial ketocarboxylic acid[20] and found that the *trans* acid **28** is indeed more stable but only slightly so. At equilibrium the mixture of epimers contains 56% of the *trans* isomer **28** and 44% of the *cis* epimer **27**. Much to our surprise only *cis* isomer **27** yielded an oxime identical with the original oxime **26** under conditions previously described[2] while the *trans* isomer **28** was recovered unchanged. Consequently the conclusions based on synthetic and degradative studies regarding the stereochemistry of aromadendrene are no longer contradictory.

The sesquiterpene alcohol globulol[21] has previously been prepared from natural aromadendrene[3,22] and is now assigned the new configuration **29**. Naturally occurring alloaromadendrene,[14,22] also available by partial synthesis[3] from aromadendrene, now has the configuration **30** and the two tertiary alcohols ledol and viridoflorol (identical with himbaccol[23]), previously prepared from the former olefin by partial synthesis,[3,22] have the structures **31** and **32**, respectively.



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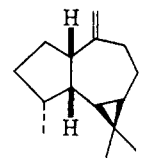

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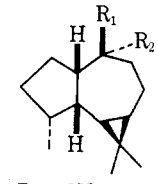

31, $R_1 = CH_3$; $R_2 = OH$
32, $R_1 = OH$; $R_2 = CH_3$

Experimental Section

Microanalyses were performed at the M.I.T. Microchemical Laboratory and Midwest Microlab., Inc., Indianapolis, Ind. Melting points and boiling points are uncorrected. Vapor phase chromatographic (glpc) analyses were performed on an F & M 720 instrument. The following spectrometers were used: nuclear magnetic resonance (nmr), Varian A-60 (peaks reported in ppm from TMS as internal standard); infrared (ir), Perkin-Elmer Model 237; ultraviolet (uv), Cary Model 14; optical rotation, Perkin-Elmer Model 141 polarimeter; and mass spectra, CEC-103 mass spectrometer (M^+ refers to molecular ion).

Bicyclic Aldehyde 4. A solution of dry hydrogen bromide (29.4 g, 0.36 mol) in glacial acetic acid (120 ml) was added to (−)-perillaldehyde (**3**)[24] (50.0 g, 0.33 mol) in 50 ml of glacial acetic acid at 0° during 1 hr. The mixture was allowed to warm to room temperature and after standing for 2 hr, ether (200 ml) was added and the solution poured onto ice and extracted with ether (three 200 ml portions). The combined ether extracts were washed with saturated NaCl, 10% sodium carbonate, saturated sodium bicarbonate, and saturated sodium chloride, dried ($MgSO_4$), and concentrated *in vacuo* below 25°. To a stirred solution of the crude bromide, under nitrogen, in *t*-amyl alcohol (400 ml) at 0° was added potassium *t*-butoxide (37.0 g, 0.33 mol) in *t*-amyl alcohol (400 ml) during 1.5 hr. After stirring for 1.5 hr at 0° and 2 hr at 25°, water (200 ml) and ether (600 ml) were added to the dark reaction mixture. Extraction with ether, washing of the combined ethereal extracts (saturated NaCl solution), drying ($MgSO_4$), and concentration *in vacuo* followed by distillation gave 20.4 g (41%) of the bicyclic aldehyde **4**: bp 63° (0.04 mm); uv max (95% C_2H_5OH) 263 mμ (ε 11,700); ir (film) 2715, 1670, 1630, 1190, 1172, 1130, 1060, 985, and 832 cm^{-1}; $[\alpha]D$ +107.8° (*c* 4.02, $CHCl_3$), $[\alpha]_{578}$ +115.2°, $[\alpha]_{546}$ +142.1°, $[\alpha]_{436}$ +405°, $[\alpha]_{365}$ +655°; nmr (CCl_4) δ 0.90 (s, 3), 1.19 (s, 3), 1.1–2.5 (m, 6), 6.93 (d, 1, J = 4.6 Hz), and 9.30 (s, 1).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.40. Found: C, 80.08; H, 9.11.

Bicyclic Diene 5. Dry dimethyl sulfoxide (45 ml) was treated with sodium hydride (2.14 g, 0.089 mol) under nitrogen at 80° until hydrogen evolution ceased (45 min). After cooling to room temperature, methyltriphenylphosphonium bromide (31.7 g, 0.089 mol) in dimethyl sulfoxide (100 ml) was added to give a red-brown solution which was allowed to stir for 15 min prior to the addition of the bicyclic aldehyde **4** (10.0 g, 0.066 mol). A vigorous, exothermic reaction was observed during the addition (15 min). After 18 hr at room temperature, the reaction mixture was poured into water and extracted four times with pentane. The pentane extracts were washed with saturated sodium chloride, dried ($MgSO_4$) and eluted through 95 g of activity I alumina with hexane. Concentration of the hexane solution *in vacuo* gave 9.70 g (98%, 95% pure diene **5** by glpc) of the bicyclic diene **5**. A sample collected by glpc had the following physical properties: $[\alpha]D$ −57° (*c* 1.64, $CHCl_3$); uv max (95% C_2H_5OH) 245 mμ (ε 16,600); ir (film) 3090, 3010, 1632, 1602, 1375, 995, 895, 878, and 835 cm^{-1}; nmr (CCl_4) δ 0.88 (s, 3), 1.10 (s, 3), 0.8–2.4 (unresolved m, 6), 4.82 (broadened d, 1, J = 11 Hz), 4.95 (d of d, 1, J = 17.5, 2.0 Hz), 5.88 (d, 1, J = 4 Hz), and 6.30 (d of d, 1, J = 11, 17.5 Hz); mass spectrum *m/e* 148 (M^+), *m/e* 105 (base peak).[25]

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.14; H, 10.99.

Diels–Alder Condensation of the Diene 5 with Acrolein. A benzene solution (30 ml) of the bicyclic diene (7.0 g, 0.047 mol), acrolein containing 1% hydroquinone (5.2 g, 0.093 mol), and 30 mg of phenylnaphthylamine was sealed in a tube and heated at 100° for 28 hr. After cooling, the tube was opened and the solvent removed *in vacuo* to give 9.4 g (98%) of crude product. Gas–liquid chromatography indicated the presence of a trace of starting material and three products with relative retention volumes of 1.00:1.20:1.36 and relative areas 1.00:5.00:0.64. The major product, aldehyde **6**, was collected by glpc and had: ir (film) 2700, 1725, 1625, and 1375 cm^{-1}; and nmr (CCl_4) δ 0.3–0.6 (m, 2), 0.92 (s, 3), 1.02 (s, 3), 1.1–2.7 (complex m, 10), 5.30 (broad s, 1), and 9.66 (broadened s, 1). The aldehyde **6** was air sensitive and gave unsatisfactory analytical data.

Diels–Alder reaction at 180° (8 hr) gave a different product mixture in poorer over-all yield (59%). The four products had relative retention volumes of 0.85:1.00:1.20:1.36 with relative areas 0.09:1.00:0.22:0.08.

Treatment of aldehyde **6**, the major product of the low temperature Diels–Alder reaction, with sodium methoxide in refluxing methanol for 3 hr gave the epimeric aldehyde **7**. Aldehyde **7** was shown to be identical with the major product of the high temperature reaction by glpc. Isomerization of aldehyde **6** with potassium *t*-amylate in *t*-amyl alcohol at room temperature for 5 min or at 0° for 30 min proved a more efficient route to aldehyde **7**: nmr (CCl_4) δ 0.2–0.8 (m, 2), 1.02 (s, 3), 1.08 (s, 3), 1.2–2.7 (unresolved m, 10), 5.28 (broad s, 1), and 9.57 (d, 1, J = 2.0 Hz). Aldehyde **7** is rapidly oxidized by air and analytical results were erratic.

Confirmation of the epimeric nature of the two aldehydes was provided by the following equilibration studies. The aldehyde **6**, shown to be pure by glpc, gave on equilibration an 83:17 mixture of aldehydes **7** and **6**, respectively. The major isomer, aldehyde **7**, collected by glpc and shown to be pure by reinjection, gave an identical equilibration mixture (83:17).

Tricyclic Olefin 8. Dropwise addition of the tricyclic aldehyde **7** (1.02 g, 5.0 mmol, containing some epimer **6**) in 5 ml of ether to a suspension of lithium aluminum hydride (0.38 g, 10.0 mmol) in ether (10 ml) gave an immediate, vigorous reaction. After 3 hr at room temperature, 0.38 ml of water was added dropwise, followed by 15% sodium hydroxide solution (0.38 ml) and additional water

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(22) L. Dolejš, O. Motl, M. Soucek, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **25**, 1483 (1960).
(23) A. J. Birch and K. M. C. Mostyn, *Aust. J. Chem.*, **8**, 550 (1955).
(24) Perillaldehyde (**3**): $[\alpha]D$ −106° (*c* 3.554, $CHCl_3$) [lit. $[\alpha]D$ −146°; J. L. Simonsen, "The Terpenes," Vol. I, University Press, Cambridge, England, 1947, p 311].
(25) We thank Professor Biemann and his associates for the mass spectra.

(1.14 ml). The precipitate was filtered, washed with ether, and the ethereal solution dried ($MgSO_4$) and concentrated *in vacuo* to yield 1.02 g (99%) of a viscous oil: ir (CCl_4) 3620, 3400, 1650, 1375, 1060, and 1035 cm^{-1}; nmr (CCl_4) δ 0.3–0.8 (complex m, 2), 1.08 (s, 3), 1.13 (s, 3), 1.2–2.5 (complex m, 11), 3.97 (m, 2), and 5.72 (broad s, 1).

The crude alcohol (3.96 g, 19.2 mmol) was treated with methanesulfonyl chloride (3.32 g, 29.1 mmol) in pyridine (20 ml) and the mixture was allowed to stand for 12 hr at room temperature. Removal of the pyridine *in vacuo* and extraction of the residue with ether gave on concentration of the extracts 4.80 g (88%) of a clear oil: ir ($CHCl_3$) 1645, 1360, and 1180 cm^{-1}; nmr (CCl_4) δ 0.2–0.8 (m, 2), 0.97 (s, 3), 0.99 (s, 3), 1.1–2.2 (m, 10), 2.87 (s, 3), 4.08 (m, 2), and 5.32 (m, 1). The mesylate was used in the subsequent reaction without further purification. Dropwise addition of the tricyclic mesylate (4.80 g, 16.9 mmol) in 10 ml of ether to a suspension of lithium aluminum hydride (1.50 g, 40.0 mmol) in ether (50 ml) gave an immediate, vigorous reaction. After standing overnight, the reaction mixture was decomposed with water (1.50 ml) followed by 15% sodium hydroxide solution (1.50 ml), and water (4.50 ml). Filtration of the precipitate, washing with ether, and drying ($MgSO_4$) and concentration *in vacuo* of the combined washings gave 3.20 g of a mobile liquid. Gas–liquid chromatography indicated the presence of tricyclic olefin **8** (83%), a minor product (10%), and two additional impurities (7%). Short-path distillation yielded 2.97 g (93%) of hydrocarbons having the same composition. The major product was obtained pure by preparative glpc and on distillation gave tricyclic olefin **8**: bp 50° (0.05 mm); $[\alpha]_D$ −66° (*c* 0.771, $CHCl_3$), $[\alpha]_{578}$ −72°, $[\alpha]_{546}$ −80°, $[\alpha]_{436}$ −139°, $[\alpha]_{365}$ −227°; ir (film) 3030, 1660, 1375, 867, and 770 cm^{-1}; nmr (CCl_4) δ 0.2–0.9 (complex m, 2), *ca.* 1.0 (d, 3), 0.99 (s, 3), 1.02 (s, 3), 1.1–2.13 (complex m, 10), and 5.3 (broad m, 1); mass spectrum *m/e* 190 (M^+), *m/e* 147 (base peak).

Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.35; H, 11.65.

Oxidation of the Olefin 8 to the Diols 9 and 10. A solution of tricyclic olefin **8** (0.739 g, 3.90 mmol) in ether (3.0 ml) was treated dropwise with a solution of osmium tetroxide (1.0 g, 3.94 mmol) and pyridine (0.70 ml) in ether (15 ml). After standing for 17 hr at room temperature, the reaction was quenched by the addition of a 10% potassium hydroxide solution (20 ml) of mannitol (2.0 g). Evaporation of the ether at room temperature and sixfold extraction with methylene chloride gave, on drying ($MgSO_4$), and concentration *in vacuo*, 0.860 g (99%) of a crystalline colorless residue. Three components were identified by tlc on silica gel; starting olefin, the major product, diol **9**, and a minor product, diol **10**. Chromatography on alumina (Act. III) and recrystallization from hexane yielded 0.735 g (84%) of crystalline diol **9**: mp 132–133°; $[\alpha]_D$ +0.9° (*c* 1.12, $CHCl_3$), $[\alpha]_{578}$ +2.1°, $[\alpha]_{546}$ +2.7°, $[\alpha]_{436}$ +6.2°, $[\alpha]_{365}$ +11.3°; ir ($CHCl_3$) 3610, 3570, 3440, 1377, 1060, and 1040 cm^{-1}; nmr ($CDCl_3$) δ 0.25–0.60 (complex m, 2), 0.93 (s, 3), 0.96 (s, 3), 1.18 (d, 3, J = 6.0 Hz), 1.2–2.0 (broad m, 10), 2.31 (broad s, 2, OH), and 3.45–3.88 (broad m, 1).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.31; H, 10.63.

Impure diol **10** obtained from two reactions gave on chromatography (Act. III alumina, 250:1) 115 mg of *ca.* 90% pure minor diol **10**: nmr ($CDCl_3$) δ 0.3–0.8 (m, 2), 0.88 (d, 3, J = 5.5 Hz), 0.89 (s, 3), 1.04 (s, 3), 1.1–2.2 (m, 12), and 2.9–3.30 (m, 1). Diol **10** could not be recrystallized and was used in the preparation of tosylate **14** without further purification.

Tosylate 11. The glycol **9** (0.205 g, 0.913 mmol) in pyridine (1.5 ml) was treated with *p*-toluenesulfonyl chloride (0.190 g, 1.00 mmol). After 16 hr at room temperature the pyridine was removed *in vacuo*, and chromatography of the residue on alumina (Act. IV, 2 g, ether) gave on recrystallization from hexane 0.280 g (82%) of tosylate **11**: mp 130.5–131.5°; $[\alpha]_D$ −6.15° (*c* 1.918 $CHCl_3$), $[\alpha]_{578}$ −10.2°, $[\alpha]_{546}$ −11.1°, $[\alpha]_{436}$ −21.1°; ir ($CHCl_3$) 3580, 1360, 1190, 1180, 1100, 955, 940, 885, 845, and 820 cm^{-1}; nmr ($CDCl_3$) δ 0.2–0.6 (m, 2), 0.93 (s, 6), 1.15 (d, 3, J = 6 Hz), 1.1–2.1 (m, 11), 2.37 (s, 3), 4.68 (m, 1), and 7.50 (center of A_2B_2, 4).

Anal. Calcd for $C_{21}H_{30}O_4S$: C, 66.63; H, 7.99. Found: C, 66.67; H, 7.96.

Tosylate 14. A solution of glycol **10** (115 mg, 0.51 mmol) in pyridine (0.5 ml) was treated with *p*-toluenesulfonyl chloride (100 mg, 0.58 mmol) at room temperature for 14 hr. Chromatography on alumina (Act. IV, as previously described for the isomeric glycol) and two recrystallizations from hexane gave 79 mg (41%) of tosylate **14**: mp 135–136°; mixture melting point with isomeric tosylate **11** 124–128°; $[\alpha]_D$ −12.1° (*c* 1.216, $CHCl_3$), $[\alpha]_{578}$ −12.5°, $[\alpha]_{546}$ −13.7°, $[\alpha]_{436}$ −19.8°; ir ($CHCl_3$) 3580, 1370, 1190, 1180, 1100, 955, 930, 890, 880, 850, and 820 cm^{-1} (different from isomeric tosylate **11**); nmr ($CDCl_3$) δ 0.3–0.8 (m, 2), 0.88 (s, 3), 0.89 (d, 3, J = 5.8 Hz), 1.03 (s, 3), 1.2–2.3 (m, 11) 2.44 (s, 3), 4.25 (d of d, 1, J = 11, 5 Hz), and 7.55 (center of A_2B_2, 4).

Anal. Calcd for $C_{21}H_{30}O_4S$: C, 66.63; H, 7.99. Found: C, 66.37; H, 7.80.

Tricyclic Olefin 20. To a suspension of lithium aluminum hydride (2.8 g, 73.7 mmol) in ether (100 ml) was added a solution of tricyclic aldehyde **6** (9.0 g, 44.1 mmol) in ether (25 ml). After standing for 1.5 hr, the reaction was halted by the addition of water (2.8 ml), followed by 15% sodium hydroxide (2.8 ml) and water (8.4 ml). After filtration the ethereal solution was dried ($MgSO_4$) and concentrated *in vacuo* giving 8.45 g (94%) of a viscous oil: ir ($CHCl_3$) 3615, 3420, 1665, 1375, 1060, 1030, 1020, 965, 920, 897, 870, and 835 cm^{-1}; nmr (CCl_4) δ 0.3–0.7 (m, 2), 1.00 (s, 3), 1.05 (s, 3), 1.2–2.4 (m, 10), 2.90 (s, 1, OH), 3.55 (m, 2), and 5.30 (m, 1). This tricyclic alcohol was used in the next step without further purification.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.51; H, 10.73.

Treatment of the tricyclic alcohol (2.33 g, 11.3 mmol) in pyridine (10 ml) with methanesulfonyl chloride (1.60 g, 13.9 mmol) after standing 3 hr at room temperature gave on removal of the pyridine, extraction of the residue with ether, and concentration of the extract, the corresponding mesylate: ir (film) 1645, 1360, 1180, 980, 960, 850, 830, and 755 cm^{-1}. This mesylate was not purified further and was used directly in the subsequent reaction. An ethereal solution of the crude mesylate (3.16 g, 11.1 mmol) was added to a suspension of lithium aluminum hydride (0.70 g, 18.4 mmol) in ether (30 ml). After 1.5 hr the reaction was quenched with water (0.7 ml), followed by 15% sodium hydroxide solution (0.7 ml) and water (2.1 ml). The entire reaction mixture was chromatographed on alumina (Act. I) column and eluted with ether (100 ml). Removal of the ether *in vacuo* and distillation (bp 45°, 0.05 mm) gave 1.765 g (84%) of a mixture containing 85% of the desired olefin **20** as determined by glpc. The major component was collected by preparative glpc (Carbowax 20M) and distilled, yielding 1.075 g of olefin **20** (>97% pure): $[\alpha]_D$ −188° (*c* 2.32, $CHCl_3$); ir (film) 3025, 1660, 1460, 1440, 1375, 1125, 995, 910, 870, 830, 815, and 775 cm^{-1}; nmr (CCl_4) δ 0.3–0.6 (m, 2), 0.96 (d, 3, J = 7 Hz), 1.00 (s, 3), 1.02 (s, 3), 1.2–2.2 (m, 10), and 5.26 (m, 1); mass spectrum *m/e* 190 (M^+), *m/e* 147 (base peak).

Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.08; H, 11.53.

Diol 21. Tricyclic olefin **20** (0.715 g, 3.76 mmol) in ether (5 ml) was treated with an ethereal (20 ml) solution of osmium tetroxide (1.00 g, 3.94 mmol) and pyridine (0.7 ml). After standing for 15 hr at room temperature, the reaction was quenched by the addition of 10% potassium hydroxide solution (25 ml) containing mannitol (2.5 g). Evaporation of the ether at room temperature and sixfold extraction with methylene chloride gave, on drying ($MgSO_4$) and concentration *in vacuo*, a colorless solid. Thin layer chromatography of the product prior to or after recrystallization showed a barely detectable impurity of higher R_f. The product sublimed readily (90–100°, 0.05 mm) and on recrystallization from methanol–water gave 0.724 g (86%) of diol **21**: mp 124.5–125.5°; $[\alpha]_D$ −8.6° (*c* 1.67, $CHCl_3$), $[\alpha]_{578}$ −8.8°, $[\alpha]_{546}$ −9.9°, $[\alpha]_{436}$ −17.6°, $[\alpha]_{365}$ −26.0°; ir ($CHCl_3$) 3590, 3560, 3440, 1460, 1375, 1095, 1045, 1020, 990, 955, 928, and 890 cm^{-1}; nmr ($CDCl_3$) δ 0.3–0.6 (m, 2), 0.87 (d, 3, J = 6.7 Hz), 0.98 (s, 3), 1.00 (s, 3), 1.1–2.2 (m, 10), 2.30 (s, 2, OH), and 3.70 (m, 1).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.62; H, 11.03.

Tosylate 22. A solution of diol **21** (0.203 g, 1.00 mmol) and *p*-toluenesulfonyl chloride (0.195 g, 1.03 mmol) in pyridine (1.5 ml) was allowed to stand for 18 hr at room temperature. The pyridine was removed *in vacuo* and the residue was chromatographed on an alumina column (Act. IV, ether). Evaporation gave 0.310 g (89%) of colorless crystalline tosylate **22**: mp 129.5–130.5° (hexane); $[\alpha]_D$ −20.6° (*c* 1.64, $CHCl_3$), $[\alpha]_{578}$ −21.4°, $[\alpha]_{546}$ −24.4°, $[\alpha]_{436}$ −42.2°, $[\alpha]_{365}$ −68°; ir ($CHCl_3$) 3580, 1375, 1360, 1190, 1180, 1100, 955, 940, 925 (s), 895, 875, and 848 cm^{-1}; nmr ($CDCl_3$) δ 0.3–0.6 (m 2), 0.83 (d, 3, J = 7.0 Hz), 0.93 (s, 3), 1.00 (s, 3), 1.2–1.9 (m, 10), 1.97 (s, 1, OH), 2.45 (s, 3), 4.79 (d of d, 1, J = 10, 6 Hz), and 7.55 (center of A_2B_2, 4).

Anal. Calcd for $C_{21}H_{30}O_4S$: C, 66.63; H, 7.99; S, 8.47. Found: C, 66.98; H, 7.98; S, 8.46.

(+)-Apoaromadendrone (23). Tosylate **22** (0.304 g, 0.785 mmol) was chromatographed on an alumina column (Act. I, 5 g, $CHCl_3$).

The first 30 ml of eluent contained 0.142 g of rearranged material which crystallized on concentration of the solvent *in vacuo*. Sublimation (50°, 0.05 mm) gave a crystalline material with glpc retention times, mass spectra, and ir spectra identical with those of "natural" apoaromadendrone (**25**). The product had: ir ($CHCl_3$) 1693, 1460, 1380, 1170, and 1145 cm^{-1}; $[\alpha]D$ +4.0° (*c* 1.53, $CHCl_3$), $[\alpha]_{578}$ +4.4°, $[\alpha]_{546}$ +6.0°, $[\alpha]_{436}$ +22.4°, $[\alpha]_{365}$ +83°. A sample of "natural" apoaromadendrone has $[\alpha]D$ −3.5° (*c* 2.70, $CHCl_3$).

In another experiment tosylate **22** (45 mg, 0.116 mmol) in *t*-amyl alcohol (2 ml) was treated with a solution of *t*-amyl alcohol containing potassium *t*-butoxide (13 mg, 0.116 mmol). A precipitate began to form immediately and in 2 min the solution was neutral to litmus. After standing for an additional 3 min the reaction was quenched by pouring into water (neutral solution) and the water was extracted with ether. The ethereal extracts were dried ($MgSO_4$), evaporated *in vacuo*, and the residue was sublimed at 55° (0.05 mm) to give 21 mg (88%) of material, mp 82.5–83.5°, identical with the material prepared by rearrangement on alumina.

The rearrangement of the tosylate was repeated in *t*-butyl alcohol-OD. The reaction mixture was worked up with deuterated water and the product was sublimed. Comparison of mass spectra showed that no more than 8.5% D was incorporated, indicating that the product formed was in fact the kinetic rather than the equilibrium product.

(−)-Aromadendrene (24). Methylenetriphenylphosphorane was prepared from methyltriphenylphosphonium bromide (433 mg, 1.20 mmol) in dimethyl sulfoxide (2.5 ml) as previously described. (+)-Apoaromadendrone (**23**) (118 mg, 0.572 mmol) was added at room temperature and the reaction was allowed to stand at ambient temperature for 18 hr before being poured into water, extracted with hexane four times, and concentrated *in vacuo* to give an oil. The oil was filtered through an alumina column. (Act I, 5 g, hexane), the hexane removed *in vacuo*, and the residue distilled yielding 63 mg (53%) of aromadendrene. The infrared, nmr, and mass spectra of natural and synthetic aromadendrene were superimposable. The rotations, however, were of opposite sign. The synthetic compound had: $[\alpha]D$ −6.0° (*c* 0.738, $CHCl_3$) and $[\alpha]D$ −10.5° (*c* 0.677, C_2H_5OH) (lit. value for natural aromadendrene: $[\alpha]D$ +13.9° (*c* 1.58, C_2H_5OH)); ir (film) 3080, 1635, 1460, 1377, and 895 cm^{-1}; nmr (CCl_4) δ 0.3–0.9 (m, 2), 0.96 (d, 3, J = 6 Hz), 0.98 (s, 3), 1.03 (s, 3) 1.1–2.5 (m, 11), and 4.53 (broadened s, 2); mass spectrum *m/e* 204 (M^+), *m/e* 41 (base peak).

4-Epiapoaromadendrone (12). Tosylate **11** (37 mg, 0.095 mmol) in *t*-butyl alcohol (1 ml) was treated with a solution of potassium *t*-butoxide (10.0 mg, 0.090 mmol) in *t*-amyl alcohol. After 5 min the reaction mixture was poured into water, extracted with ether, dried ($MgSO_4$), evaporated *in vacuo*, and the resulting solid sublimed to give crystalline 4-epiapoaromadendrone (**12**), 18 mg (85%, >98% pure **12**): mp 64–65°; ir ($CHCl_3$) 1989, 1460, 1379, 1352, 1170, 1140, 1135, 1074, and 1010 cm^{-1}; $[\alpha]D$ −21.0° (*c* 0.654, $CHCl_3$); $[\alpha]_{578}$ −29.8°, $[\alpha]_{546}$ −31.9°, and $[\alpha]_{436}$ −43.2°. The infrared spectrum of **12** and its glpc retention time were different from those of apoaromadendrone and α-apoaromadendrone. Rearrangement of tosylate **9** on alumina gave the same ketone indicating that 4-epiapoaromadendrone (**12**) is more stable than its C-1 epimer **15**.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.52; H, 10.66.

4-Epiaromadendrene (13). To a suspension of methyltriphenylphosphonium bromide (284 mg, 0.793 mmol) in dry ether (8 ml) was added a solution of *n*-butyllithium in hexane (0.44 ml, 1.75 *M*). After stirring for 30 min at room temperature, a solution of ketone **12** (93 mg, 0.451 mmol) in ether (5 ml) was added. After 8 hr the ether was evaporated by a stream of nitrogen, hexane was added, and the precipitate was removed by filtration. The residue was washed, the hexane solution concentrated *in vacuo*, and the residue was chromatographed on alumina (Act I, 2 g, hexane). The hexane was removed *in vacuo* to give 73 mg (79%) of 4-epiaromadendrene (**13**) which was 99% pure by glpc and had different retention volumes from those of aromadendrene and alloaromadendrene. It had: $[\alpha]D$ −31.4° (*c* 0.881, $CHCl_3$), $[\alpha]_{578}$ −32.1°, $[\alpha]_{546}$ −33.6°, $[\alpha]_{436}$ −56°, $[\alpha]_{365}$ −91°; ir (film) 3080, 1635, 1460, 1390, 1375, 1135, and 895 cm^{-1} (different from aromadendrene and alloaromadendrene); nmr (CCl_4) δ 0.2–0.8 (m, 2), 0.90 (d, 3, J = 5.9 Hz), 0.92 (s, 3), 0.99 (s, 3), 1.1–2.5 (m, 11), 4.53 (finely split m, 2); mass spectrum *m/e* 204 (M^+), *m/e* 41 (base peak).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.02; H, 11.73.

4-Epialloaromadendrene (16). The tosylate **14** (68 mg, 0.176 mmol) in 2 ml of *t*-amyl alcohol was treated with 20 mg (0.175 mmol) of potassium *t*-butoxide in 5 ml of *t*-amyl alcohol. After 5 min the reaction was worked up as previously described. The crude ketone was added to freshly prepared Wittig reagent prepared from 210 mg (0.59 mmol) of methyltriphenylphosphonium bromide in 5 ml of ether and 0.33 ml of 1.64 *M* *n*-butyl lithium in hexane. After 5 hr the ether was removed by a stream of nitrogen and hexane was added. The solid was removed by filtration and was carefully washed with hexane. The concentrated filtrate was passed through an alumina column (Act I, 1 g) and the hexane was removed *in vacuo* yielding 18 mg of a hydrocarbon: ir (film) 3080, 1680, 1460, 1375, 1130, and 885 cm^{-1} (different from those of aromadendrene, alloaromadendrene, and 4-epiaromadendrene). The mass spectrum indicated that the compound was very similar to the three aromadendrene isomers mentioned above, *m/e* 204 (M^+), *m/e* 41 (base peak). The sample had $[\alpha]D$ −40.2° (*c* 0.747, $CHCl_3$), $[\alpha]_{578}$ −42.3°, $[\alpha]_{546}$ −48.8°, $[\alpha]_{436}$ −88°, $[\alpha]_{365}$ −148°.

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