mer), 32270-62-5; XIX (repeating unit), 32355-56-9; XX (polymer), 32270-63-6; XX (repeating unit), 32355-58-1; XXI (polymer), 32270-64-7; XXI (repeating unit), 32355-59-2.

Acknowledgment.—This work was supported by Grant No. G.M. 08795 from the National Institutes of Health, Public Health Service. We wish to thank Professor H. Horan for the infrared spectra.

Synthesis of *dl*-Hedycaryol[1]

P. S. WHARTON,*[2] C. E. SUNDIN, D. W. JOHNSON, AND H. C. KLUENDER

Departments of Chemistry, University of Wisconsin, Madison, Wisconsin 53706, and Wesleyan University, Middletown, Connecticut 06457

Received May 11, 1971

The synthesis of *dl*-hedycaryol (**5**) according to Scheme I is described. Dimethyl 4-hydroxyisophthalate (**1**) was hydrogenated over ruthenium dioxide and the resulting dimethyl hydroxycyclohexanedicarboxylate mixture **11** was acetylated. The acetate **12** was pyrolyzed at 260° in the presence of potassium acetate and the major product, dimethyl cyclohexene-2,4-dicarboxylate (**13**), was separated by distillation. Addition of methyllithium to **13** yielded the bis tertiary diol **15** which was selectively dehydrated to 2-(2-propenyl)-4-(2-hydroxy-2-propyl)-1-cyclohexene (**2**) by heating in dimethyl sulfoxide. Conversion of **2** to octalone **3** was effected by a previously established sequence: 1,4 cycloaddition of ethyl α-acetoxyacrylate, lithium aluminum hydride reduction, and sodium periodate oxidation. Direct angular methylation of **3** was effected by treatment with a mixture of sodium hydride and methyl iodide in dimethoxyethane (conditions corresponding to the reaction of kinetically generated enolates). The resulting octalone mixture **4** was correlated with γ-eudesmol (**41**) and epi-γ-eudesmol (**42**) by Wolff–Kishner reduction. From the reduction of the octalone mixture with lithium aluminum hydride a crystalline diol **43** was obtained which was converted to monotosylate **44** which yielded hedycaryol (**5**) upon treatment first with diborane and then with aqueous sodium hydroxide. The properties of synthetic *dl*-**5** match those reported for the natural *d* enantiomer.

Hedycaryol (**5**) is a biogenetically important sesquiterpene, isomeric with and derived from *trans,trans*-farnesol and the progenitor of a further set of sesquiterpene skeletal families, exemplified most directly by the eudesmols (hydronaphthalenes) and bulnesol and guaiol (hydroazulenes), related by acid-catalyzed cyclizations, and by elemol, related *via* the Cope rearrangement.[3]

Hedycaryol has a relatively recent history; although its biogenetic involvement as a 1,5-cyclodecadiene was appreciated in print in 1953,[4] the structure of the first sesquiterpene 1,5-cyclodecadiene was not established until 1959,[5] and hedycaryol itself was not isolated until 1968.[6] This article records the synthesis of *dl*-hedycaryol.

Synthetic Scheme.—The synthesis was planned and carried out according to the accompanying flow chart, in four main sections, A, B, C, and D (see Scheme I). This approach concedes to nature, at least temporarily, the exclusive ability to transform acyclic precursors directly to *trans,trans*-1,5-cyclodecadienes.[7] The present synthesis involves fragmentation of the appropriately functionalized and substituted hydronaphthalene precursor to the ten-membered ring of hedycaryol which is specifically a 1,5-dimethyl-*trans,trans*-1,5-cyclodecadiene bearing a 2-hydroxy-2-propyl chain at C-8. This was accomplished by Marshall's method:[8] hydroboration of octalyl tosylate **44** and subsequent generation of *dl*-hedycaryol at a relatively low temperature (65°) by fragmentation in the presence of base. Some care is necessary in planning and carrying out the synthesis because hedycaryol is relatively unstable thermally, rearranging to elemol (**6**) with a half-life of 3 hr at 100°,[6] and it is very susceptible to cyclization in the presence of acids.[9]

Sections B and C together exemplify the preparation of 9-methyl-$\Delta^{4(10)}$-1-octalones *via* 1,4 cycloaddition to a 1-isopropenylcyclohexene (B)[10] and subsequent angular methylation (C).[11] Section B involves the regiospecific but indirect 1,4-cycloaddition of ketene (which itself favors 1,2 cycloaddition).[12] This can be accomplished by the use of α-acetoxyacrylates and related substances.[10] Although the involvement of angular methylation as an essential part of the planned synthesis might be considered to be poor strategy, it may be noted that introduction of the angular methyl group by direct alkylation of $\Delta^{4(10)}$-1-octalones (β,γ-unsaturated) is a viable method, whereas direct angular methylation of 1-decalones is not. Moreover, prior incorporation of the methyl, using the same overall approach, can be summarily dismissed because of the failure of 1-methyl-2-isopropenylcyclohexenes to un-

(1) (a) The investigation was supported by Public Health Service Research Grants GM 09759, GM 14133, and GM 16338 from the Division of General Medical Sciences, U. S. Public Health Service. (b) The article is abstracted from the Ph.D. theses of C. E. S., University of Wisconsin, 1968, and H. C. K., Wesleyan University, 1971. The synthesis was first presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, Abstract P-2.

(2) Wesleyan University, Middletown, Conn.

(3) Sesquiterpene biogenetic relations are reviewed by W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev., Chem. Soc.*, **21**, 321 (1967).

(4) L. Ruzicka, A. Eschenmoser, and H. Heusser, *Experientia*, **9**, 357 (1953).

(5) J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959); V. Herout, M. Horak, B. Schneider, and F. Sorm, *Chem. Ind. (London)*, 1089 (1959).

(6) R. V. H. Jones and M. D. Sutherland, *Chem. Commun.*, 1229 (1968). Note the corrigendum, *ibid.*, 892 (1970).

(7) For an interesting, although unsuccessful, synthetic approach of this type see E. J. Corey and E. A. Broger, *Tetrahedron Lett.*, 1779 (1969).

(8) J. A. Marshall and G. L. Bundy, *Chem. Commun.*, 854 (1967).

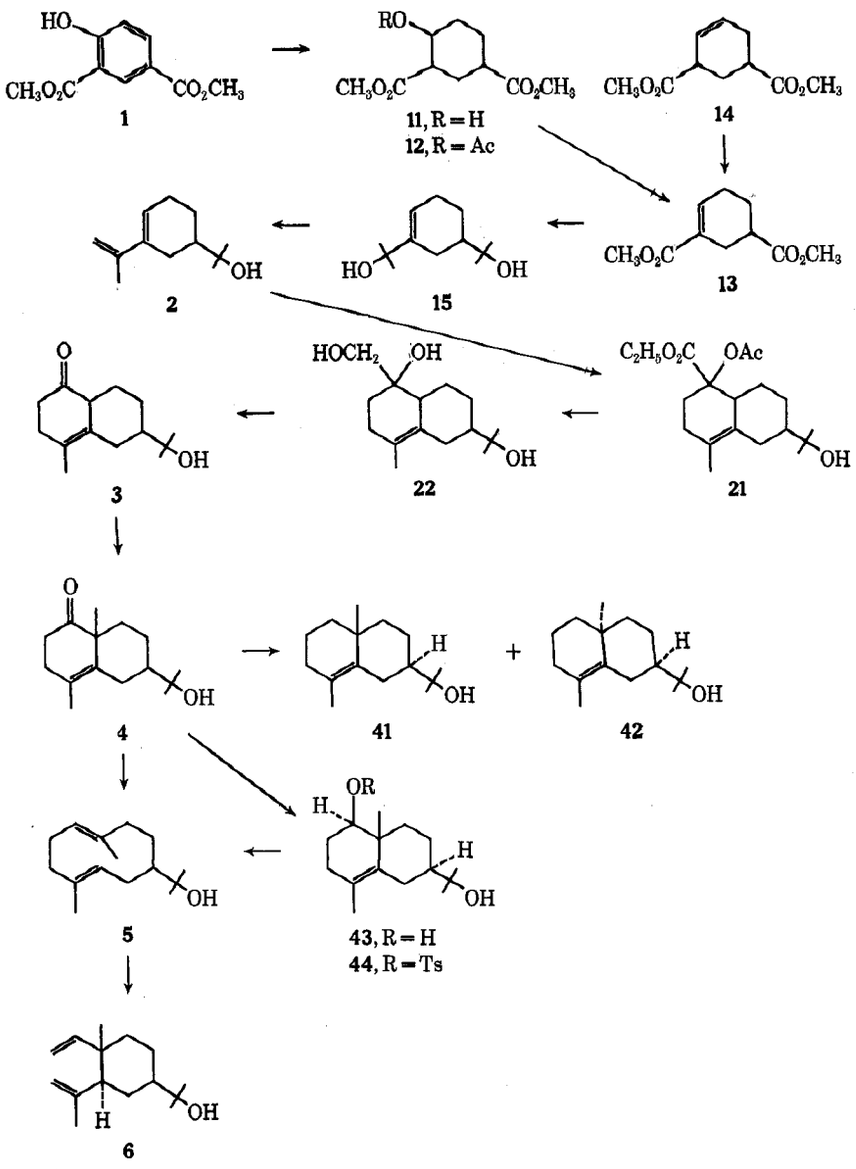
(9) The conversion of *d*-**5** to a mixture of eudesmols has been reported to occur upon refluxing a solution in ether containing 1% *p*-toluenesulfonic acid.[6] Our results provide an even more striking illustration of the sensitivity of **5** to acid, synthetic material suffering cyclization to the eudesmols in buffered acetic acid with a half-life of 15 min at 60°. The product of this reaction also consisted of a mixture of α-, β-, and γ-eudesmols; moreover, specific examination by glpc for the presence of bulnesol, which is biogenetically formed from **5** as are the eudesmols, by a simple acid-catalyzed cyclization (albeit anti-Markovnikov in the case of bulnesol), failed to detect any (<2%), and an intriguing problem of biogenetic simulation remains.

(10) P. S. Wharton and B. T. Aw, *J. Org. Chem.*, **31**, 3787 (1966).

(11) P. S. Wharton and C. E. Sundin, *ibid.*, **33**, 4255 (1968).

(12) See J. D. Roberts and C. M. Sharts, *Org. React.*, **12**, 1 (1962).

SCHEME I[a,b]



[a] The synthetic sequence is indicated by heavy arrows. [b] Relative stereochemistry is indicated only when dotted lines are present.

dergo synthetically useful 1,4-cycloaddition reactions.[13]

The four sections are considered in order A–D (Scheme I).

Section A (1 → 2) starts with an appropriately substituted compound, 4-hydroxyisophthalic acid, which is available as a by-product in the manufacture of salicylic acid. Hydrogenation of the dimethyl ester **1** at 100° in tetrahydrofuran over ruthenium dioxide yielded a mixture consisting of 35% of hydrogenolysis products, the isomeric dimethyl cyclohexane-1,3-dicarboxylates (**11**). On a large scale, separation of the products by distillation was accompanied by much lactonization, an unnecessary complication which was most efficiently avoided by acetylating the crude hydrogenation product prior to distillation. Furthermore, the acetate obtained in this way (**12**) could be converted directly to the conjugated diester, dimethyl cyclohexene-2,4-dicarboxylate (**13**), by heating to 260° in the presence of potassium acetate. The isomers of the unconjugated diester, dimethyl cyclohexene-3,5-dicarboxylate (**14**), were present in the neutral fraction of the pyrolysate but they comprised only 6% of the equilibrium mixture of unsaturated diesters at 200°, as shown in independent experiments, and they could be separated by fractional distillation, thus allowing the use of recycling procedures. Some acidic material was formed in the pyrolysis but this could also be recycled after esterification.

Conversion of the conjugated diester to a crystalline bis tertiary diol (**15**) was effected in high yield by treatment with methyllithium. Dehydration of the diol to isopropenylcyclohexene (**2**), an apparently simple transformation involving dehydration of the alcohol which is both tertiary and allylic but not of the simple tertiary alcohol, was accomplished with less ease than had been anticipated. Heating with pyridine-treated alumina[14] gave promising results which were, however, difficult to reproduce; and the desired product was always accompanied by varying amounts of isomeric diene, and trienes from bis dehydration, in addition to starting material. A simpler reproducible procedure consisted of heating the diol in dimethyl sulfoxide at

(13) See A. S. Onishschenko, "Diene Synthesis," Israel Program for Scientific Translation, Jerusalem, 1964, pp 418–419.

(14) E. von Rudloff, *Can. J. Chem.*, **39**, 1860 (1961).

130°.[15] The tertiary allylic alcohol suffered highly selective dehydration but the result was a mixture of dienes containing 80% of **2** and 20% of undesired isomeric diene. Attempts to reduce the amount of isomerization were to no avail. Furthermore, attempted separation of the mixture by distillation led to complete loss of **2** by isomerization, presumably induced by acidic impurities generated by dimethyl sulfoxide and retained in the product. In fact, contrary to report,[15] dehydration in dimethyl sulfoxide seemed to be acid-catalyzed because it was found that addition of 1,5-diazabicyclo[4.3.0]non-5-ene completely inhibited the reaction.

Sections B (2 → 3) and C (3 → 4).—By following procedures already described,[10,11] the mixture of dienes containing 80% of **2** was converted to **4**. A 1,4 cycloadduct **21** was first obtained by heating with ethyl α-acetoxyacrylate. Thereafter, excess acetoxyacrylate and most of the unreactive diene isomeric with **2** were removed *in vacuo* at 110° but it was not possible to distill the remaining glass because of accompanying dehydration. Direct reduction of the glass with lithium aluminum hydride in ether afforded, in 47% overall yield, a solid which must be predominantly one of the four possible diastereomeric *dl*-triols **22** and, in 40% yield, an oil consisting of an impure mixture of triol isomers. Careful oxidation of crystalline triol with sodium metaperiodate gave β,γ-unsaturated ketone **3**, which was immediately methylated with a mixture of 1.1 equiv of sodium hydride and excess methyl iodide in dimethoxyethane. (Some care is needed at this stage to obviate the disastrously irreversible isomerization of β,γ-unsaturated ketone **3** to the corresponding α,β-unsaturated ketone.) The crude product was chromatographed on alumina, a procedure which afforded, in 52% overall yield, a mixture consisting of diastereomers with the constitution of **4**. Wolff–Kishner reduction of crude ketonic product afforded a mixture of *dl*-γ-eudesmol (**41**, methyl cis to hydroxypropyl) and *dl*-epi-γ-eudesmol (**42**) in a ~80:20 ratio as determined by comparisons with authentic samples.[16]

Section D (4 → 5).—Reduction of the mixture of diastereomeric octalones (**4**) was carried out after analyzing reduction of the octalone similarly constituted but lacking the hydroxypropyl side chain;[17] in this case, lithium aluminum hydride in ether gave a mixture of major and minor alcohols (85:15) which were separated by preparative glpc and characterized by their nmr spectra, which showed signals at δ 3.35 and 3.33 ppm as broadened triplets with $W_{1/2}$ of 17 and 10 Hz, illustrative of the difference in cyclohexane systems expected for hydrogens on carbon bearing equatorial and axial oxygen, respectively.[18] Various other hydride–solvent systems were examined but they afforded almost no variation in the product ratio.

Subsequent reduction of **4** (87% *cis* diastereomer) with lithium aluminum hydride in dimethoxyethane at −15° gave a mixture of diols from which the expected major product (**43**) was obtained crystalline in 29% yield. Oxidation of this diol with chromic acid and subsequent Wolff–Kishner reduction yielded *dl*-γ-eudesmol only, the absence of *dl*-epi-γ-eudesmol showing that crystalline diol is stereochemically homogeneous at C-6 and C-9. The stereochemistry of the hydroxyl group at C-1 is equatorial according to the nmr signal at δ 3.47 ($W_{1/2}$ = 17 Hz).

Crystalline diol was converted to the corresponding monotosylate **44** in high yield and fragmentation of the tosylate to *dl*-hedycaryol (**5**) was then examined. After initial experiments with an old bottle of commercial diborane in tetrahydrofuran had afforded variable results, reproducibility was achieved with a previously unopened batch of the same reagent, a cautionary note perhaps worthy of comment although the nature of the problem was not determined.

Fragmentation of the boron-containing compounds was carried out with aqueous sodium hydroxide for 13 hr at 65°. The nmr spectrum of the resulting oil showed the presence of ~20% residual tosylate (which was inert to prolonged fragmentation conditions) and a yield of *dl*-hedycaryol, based on the unique absorption at δ 4.92 ppm, of 60%. Nmr and ir data showed that only a small amount of *dl*-elemol (**6**) had been formed, consistent with the established preference for an internal rather than peripheral mode of fragmentation.[8]

dl-Hedycaryol was isolated in 50% yield from the crude product *via* extraction of the oil with aqueous silver nitrate without addition of an organic solvent. Samples of *dl*-**5** isolated in this way could be distilled *in vacuo* over solid sodium hydroxide but no further purification was apparent; in both cases only small amounts (2–4%) of *dl*-**6** could be detected by nmr spectroscopy. It was not possible to assay the overall purity of synthetic *dl*-**5** directly by glpc because of the occurrence of thermal or acid-catalyzed rearrangements on all columns tested, but use was made of the thermal rearrangement in an indirect determination. After heating in cyclohexane at 130° for 16 hr, a sample of *dl*-**5** gave, with no material loss, *dl*-**6** of >96% purity as established by glpc. Spectroscopic data afforded by samples of synthetic *dl*-**5** match those reported for the natural *d* enantiomer.[19]

Experimental Section

Physical Data.—Melting points were determined using a Thomas Unimelt capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were obtained using a Perkin-Elmer Model 137 spectrophotometer. Nmr spectra were recorded using a Varian A-60A spectrometer employing tetramethylsilane as an internal reference. Spinning band distillations were performed using a 24-in. Nester–Faust NFT-50 Teflon spinning band column fitted with an automatic reflux ratio control. Gas–liquid phase chromatography (glpc) was performed on Varian Aerograph, Model A-90-P, and Perkin-Elmer, Model F-11, units, using packed and capillary stainless steel columns, respectively. Peak areas were calculated using a Disc chart integrator. The various columns used for glpc were: 5 ft × 0.25 in. 5% Carbowax 20M on Teflon 6 (1); 5% Carbowax 20M on 40–60 Chromosorb T (2); and 150 ft × 0.01 in. SF-96 (3).

Materials.—All solvents were dried and/or distilled before use with the exception of Mallinckrodt anhydrous ether. Magnesium sulfate was used as a drying agent. *n*-Butyllithium in

(15) V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962); *ibid.*, **29**, 123 (1964).

(16) Authentic samples were generously supplied by Dr. J. A. Marshall, Northwestern University.

(17) Y. C. Poon, Ph.D. Thesis, Wesleyan University, 1971.

(18) See N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 49–53.

(19) Copies of the ir and nmr spectra of hedycaryol-*d* were generously supplied by Dr. M. D. Sutherland.

hexane (Alpha) was titrated and found to be 2.54 *M* in total base and 2.44 *M* in butyllithium.

Dimethyl 4-hydroxyisophthalate (1) was prepared from the "brown dust" by-product of salicyclic acid production, generously supplied by the Hilton–Davis Chemical Co. In portions, *ca.* 4000 g of "brown dust" was extracted and then esterified and afforded, after work-up, 1716 g of brown crystals of 1, mp 96–98° (lit.[20] mp 97.5°). Crystallization from hexane failed to raise the melting point.

Dimethyl 4-Acetoxycyclohexane-1,3-dicarboxylate (12).—Into a 1400-ml capacity hydrogenation bomb was placed 300.5 g of crystalline dimethyl 4-hydroxyisophthalate, mp 96–98°, 16.5 g of ruthenium dioxide (62.5%, Engelhard), and enough tetrahydrofuran to half fill the bomb. The bomb was flushed with nitrogen, filled with hydrogen to a pressure of 1590 psi, and slowly heated, with shaking. The temperature was finally maintained at 100°. The bomb was refilled with hydrogen after 2 hr and again after 24 hr. After a total of 46 hr hydrogen uptake had become slow and the bomb was allowed to cool. Work-up gave 297.4 g of a light brown oil to which was added 320 g of pyridine and 277 g of acetic anhydride. After 10 days at room temperature work-up yielded 317 g of a light brown oil which was subjected to a spinning band distillation to remove 75.6 g of lower boiling components, bp to 85° (0.3 mm). The remaining oil was then subjected to a simple distillation which afforded 224.2 g of acetate (61% based on dimethyl 4-hydroxyisophthalate), bp 143° (0.4 mm).

Dimethyl Cyclohexene-2,4-dicarboxylate (13).—A mixture of 162.6 g of dimethyl 4-acetoxycyclohexane-1,3-dicarboxylate and 15.1 g of fused potassium acetate was heated at 260–265° under nitrogen in a round-bottom flask fitted with a distillation head. Over a period of 15 min 45.7 g of distillate was collected (theoretical yield of acetic acid, 37.8 g). After 17 min of heating a large amount of solid suddenly separated in the reaction flask. The flask was cooled, and the reaction mixture was worked up, affording 94.3 g (76%) of dark oil as the neutral fraction.

Combination of similar material from various runs gave a total of 270 g which was first simply distilled, affording 251.4 g of light yellow oil, bp 100–110° (0.9 mm). The distillate was subjected to spinning band distillation with the reflux ratio set at 100:1, giving 59.4 g up to a recorded head temperature of 67° (0.2 mm) before glpc analysis of the distillate showed that little or no dimethyl cyclohexene-3,5-dicarboxylate (14) remained in the pot. The remaining oil, from which 53.2 g had been removed, was subjected to a simple distillation, yielding 132.5 g of 13 (52% overall from starting acetate): bp 115–118° (0.2 mm); homogeneous by glpc analysis on column 2 at 223°; nmr (CCl_4) δ 6.92 (broad s, 1), 3.67 and 3.69 (two sharp s, 6), and 1.35–2.85 ppm (complex, 7).

2,4-Di(2-hydroxy-2-propyl)cyclohexene (15).—To a stirred solution of 4 mol of 2.16 *M* methyllithium in ether (Alpha) was added dropwise, over 1 hr, under nitrogen, and with cooling in an ice–water bath, a solution of 117.5 g (0.593 mol) of dimethyl cyclohexene-2,4-dicarboxylate, obtained as described above, in 320 ml of anhydrous ether. During the addition a fine white precipitate formed. After the addition was complete the ice bath was removed and the mixture was allowed to stir at room temperature for 7 hr. To the reaction mixture was then added dropwise over 20 min, with stirring and cooling in an ice–water bath, 100 ml of water. Further work-up yielded 117.6 g (97%) of a white powder: mp 114–121°; nmr (CCl_4) δ 5.7 (broad, 1.0) and 0.9–2.4 ppm (complex, showing equal intensity peaks at 1.20 and 1.30 ppm, 23.1).

Recrystallization from acetone raised the melting point to 121–122° and afforded an analytical sample.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.76; H, 11.41.

2-(2-Propenyl)-4-(2-hydroxy-2-propyl)-1-cyclohexene (2).—To 15.1 g of alumina (Woelm neutral, activity I) was added, with thorough mixing, first 1 ml of pyridine and then 49.2 g of 2,4-di(2-hydroxy-2-propyl)-1-cyclohexene, obtained as described above, mp 120–122°. The mixture was stirred for 3 hr at 170° and then cooled and repeatedly extracted with ether. Work-up and subsequent distillation at 0.2 mm yielded 3.24 g, bp 75–81°; 1.43 g, bp 82–83°; 11.79 g (49% based on unrecovered diol), bp 84–85°; and 2.44 g, bp 86–105°; with 13 g undistilled. The third fraction was shown to consist of 98% one component by glpc on column 1 at 190°: ir (film) 2.97, 6.11, 6.21 μ; uv max (EtOH) 234 nm (ϵ 16,400); nmr ($CDCl_3$) δ 5.89 (m, 1), 4.99 (m, 1), 4.85 (m, 1), 1.92 (s, 3), and 1.23 (s, 6). Preparative glpc on column 1 at 160° afforded an analytical sample.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.78; H, 11.33.

Repeated extraction with hot acetone of both the alumina and the magnesium sulfate (used as a drying agent) afforded 19.9 g of a sticky solid which was combined with the distillation residue and crystallized from acetone; a total of 22.6 g (46%) of starting diol was recovered with mp above 115°.

***cis,cis*-1-Hydroxy-6-(2-hydroxy-2-propyl)-4,9-dimethyl-$\Delta^{4(10)}$-octalin** (43).—A solution of 49.6 g (0.250 mol) of 2,4-di-(2-hydroxy-2-propyl)cyclohexene (mp 115–120°) in 250 g of dimethyl sulfoxide (Aldrich) was heated under nitrogen at 130° for 1.5 hr. The resulting light yellow oil was successively cooled in an ice–water bath, poured into 1500 ml of water, and extracted three times with a total of 1000 ml of pentane. The combined pentane extracts were washed five times with water and once with brine. After drying, evaporation yielded 42.6 g (96.7%) of a yellow, viscous oil: nmr (CCl_4) δ 6.38 (broadened d, 0.17, J = 10 Hz), 5.6 and 5.8 (broad, total integration 1.21), 4.93 (broad, 1.00), 4.78 (broad, 1.0), 4.33 (broad, 0.09), and 0.8–2.9 (complex, with spikes at 1.17 and 1.86 ppm, 28.2).

A mixture of 74.6 g of material similarly obtained, 80.6 g (0.510 mol) of ethyl α-acetoxyacrylate,[21] and 1.4 g of 3,5-di-*tert*-butylcatechol (Aldrich) was heated at 110° under nitrogen for 38 hr, at which time the ir spectrum of the reaction mixture showed little further change. Heating of the crude product in a bath at 110° starting at 5 mm and ending at 0.2 mm yielded first 39.9 g of recovered ethyl α-acetoxyacrylate, bp to 76° (5 mm), and then 9.5 g, bp to 90° (1 mm). Undistilled was 111.4 g of a yellow glass showing weak nmr signals at δ 6.45 (broad), 6.28 (broad), 5.5 (very broad) and 4.72 ppm, consistent with the presence of ~11 mol % of isomerized diene and ~4 mol % of dehydrated adduct.

To a stirred mixture of 25.6 g (0.674 mol) of lithium aluminum hydride and 1100 ml of anhydrous ether was added dropwise a solution of the 111.4 g of yellow glass in 880 ml of anhydrous ether. After 6 hr of stirring at room temperature, 5.2 g (0.137 mol) of additional lithium aluminum hydride was added. After a total of 14 hr at room temperature, 100 ml of saturated aqueous magnesium sulfate was added dropwise with stirring, followed by 50 ml of water. After 1 hr 150 g of anhydrous magnesium sulfate was added. The mixture was filtered and the solid was washed with ether. The combined filtrates were dried and evaporated, yielding 34 g of a viscous, yellow oil. The solid salt mixture was then extracted several times with methanol and the methanol extracts were dried and evaporated. The resulting white solid was washed with water and then dried at reduced pressure, affording 35.3 g of triol 22. This was combined with similar material from another run, and the total of 49.6 g was recrystallized from 150 ml of methanol, yielding 22.9 g, mp 162–170°, of a first crop, and 7.2 g, mp 155–167°, of a second crop of white crystals.

To a stirred suspension of 21.4 g (84.3 mmol) of crystalline triol in 300 ml of methanol was added a solution of 20.0 g (93.5 mmol) of sodium metaperiodate in 100 ml of water. The mixture warmed slightly on mixing and a voluminous white precipitate rapidly formed, requiring the addition of another 100 ml of methanol to facilitate stirring. After 1 hr the mixture was poured into 800 ml of brine containing 6.3 g of dissolved sodium thiosulfate. The mixture was extracted with ether and the ether extracts were evaporated. In order to remove residual methanol the residual oil was twice treated with 50-ml portions of benzene and the solvent was removed both times, yielding a yellow oil: ir (film) 2.94, 5.87 (β,γ-unsaturated ketone) with a very small shoulder at 6.0 μ (α,β-unsaturated ketone).

To a mixture of sodium hydride (86 mmol from pentane washing of 3.912 g of sodium hydride dispersion, 50–55% in mineral oil), 20 ml of methyl iodide, and 20 ml of dimethoxyethane, stirred under nitrogen and cooled in an ice–water bath, was added, over 5 min, a solution of 18.73 g of yellow oil, obtained as described above (84 mmol based on 3) in 40 ml of dimethoxyethane. The ice bath was removed and the mixture was allowed to warm to room temperature and then remain for a total of 16 hr. Volatile compounds were then removed by evaporation and the residue

(20) A. S. Lindsey, *J. Chem. Soc.*, 3222 (1958).

(21) The ethyl ester was prepared by the procedure described for the methyl ester by J. Wolinsky, R. Novak, and R. Vasileff, *J. Org. Chem.*, **29**, 3596 (1964).

was dissolved in 20 ml of 80:20 ethanol–water, 2 *N* in potassium hydroxide, and the mixture was stirred at room temperature for 9 hr. Work-up yielded 19.9 g of a brown oil (100% based on monomethylation); glpc on column 2 at 200° showed three sets of components with retention times of <7 min (6%, dehydrated products), 7–14.5 min (75%, β,γ-unsaturated ketones), and 14.5–25 min (19%, α,β-unsaturated ketones). This oil was combined with material similarly obtained and the total, 29.1 g, was chromatographed on 1670 g of silica gel (Grace 60/200 mesh) in a 60 × 7 cm column. The oil was transferred to the column with a total of 100 ml of carbon tetrachloride (50 + 25 + 25 ml), and development and elution were effected in 22 fractions, 1–20 consisting of 1000-ml portions of 2:3 ether–hexane, yielding 21.7 g of recovered material, 21 of 4000 ml of the same solvent, yielding 0.59 g, and 22 of 4000 ml of ether, yielding 4.0 g. The total material recovery was 90%.

Fraction 13 yielded the following data: ir (film) 5.87 (strong) with 6.04 μ (very weak, α,β-unsaturated ketone contaminant); nmr (CCl_4) δ 0.9–2.9 (complex, with spikes at 1.16 and 1.18, and a broadened singlet at 1.71 ppm); glpc on column 2 at 190° one major peak at 8.3 min with a shoulder at 7.5 min (total 96%). Fractions 11–14 (totalling 13.7 g) were analyzed by glpc and were all found to consist of the same "peak plus shoulder" with no marked change in relative amounts of the two components which together accounted for no less than 95% of discernible peaks in all fractions. The major and minor components in fractions 11–14 corresponded to *dl*-1-oxo-γ-eudesmol and *dl*-1-oxo-epi-γ-eudesmol, respectively, in a combined yield of 44%.

From 410 mg of material similar to that of fraction 13 there was obtained 408 mg (93%) of crude oxime, mp 145–152°, which afforded an analytical sample after crystallization from ethanol–water and sublimation; mp 153–155°; nmr ($CDCl_3$) δ 1.68 (s, 3), 1.30 (s, 3), 1.30 (s, 3), and 1.23 (s, 6).

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.68; H, 10.14; N, 5.57.

To a mixture of 0.837 g (22.1 mmol) of lithium aluminum hydride and 75 ml of dry dimethoxyethane, stirred under nitrogen with cooling in an ice–brine bath at −20 to −25°, was added dropwise over 45 min a solution of 4.88 g of fraction 13 obtained as described above in 60 ml of dimethoxyethane. The mixture was allowed to come to room temperature over 4 hr. After 14 hr at room temperature 0.231 g (6.08 mmol) of additional lithium aluminum hydride was added. After another 3 hr, work-up (using saturated magnesium sulfate solution) yielded 4.79 g (97.4%) of a gummy white solid which was crystallized from 25 ml of ether at −8°. The resulting white solid was recrystallized from cyclohexane and yielded 1.45 g (29%) of **43** as white plates: mp 124–125°; nmr ($CDCl_3$) δ 3.47 (broadened triplet, 1, J = 7.5 Hz) and 0.8–2.9 (complex, with spikes at 1.01 and 1.21 and broadened singlet at 1.60 ppm, total integration 25).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.48; H, 10.84.

Wolff–Kishner Reductions.—To a solution of 15.6 mg (0.656 mmol) of *cis,cis*-1-hydroxy-6-(2-hydroxy-2-propyl)-4,9-dimethyl-$\Delta^{4(10)}$-octalin (**43**), mp 121.5–124°, in 1 ml of acetone was added, *via* syringe, 18 μl of 8 *N* chromium trioxide in aqueous sulfuric acid.[22] The final traces of oxidant yielded a persistent orange color. Work-up yielded 14.6 mg (94%) of a light yellow oil.

A.—The 14.6 mg obtained as described above was mixed in a tube with 0.5 ml of triethylene glycol (Aldrich), 5 μl of acetic acid, and 20 μl of hydrazine hydrate. The mixture was heated under nitrogen at 75° for 21 hr. The tube was then cooled and 27.2 mg of potassium hydroxide was added. The tube was then bent and sealed and one end was immersed in a bath at 200° for 6.5 hr so that distillate collected in the other end. Work-up yielded 8.5 mg (62%) of an oil which, by glpc analysis on column 2 at 140°, consisted solely of *dl*-γ-eudesmol (**41**), retention time 16.8 min.

B.—In the same manner 89.0 mg of chromatography fraction 13, obtained as described above, yielded 65.4 mg (78%) of an oil consisting of 87% *dl*-γ-eudesmol (**41**) and 13% *dl*-epi-γ-eudesmol (**42**) by glpc analysis.[16]

C.—In the same manner 71.0 mg of the total crude reaction product, obtained in the methylation described above, yielded 57.6 mg (86%) of an oil. Glpc analysis of the ratio of *dl*-γ- to *dl*-epi-γ-eudesmol was rendered difficult by broadening and overlapping of peaks caused by the presence of other components, but a rough estimate of 15% *dl*-epi-γ-eudesmol in the mixture was made.

Tosylate of *cis,cis*-1-Hydroxy-6-(2-hydroxy-2-propyl)-4,9-dimethyl-$\Delta^{4,(10)}$-octalin (44).—To a solution of 2.343 g (9.85 mmol) of diol **43** in 5 ml of pyridine, cooled in an ice bath, was added 2.348 g (12.33 mmol) of *p*-toluenesulfonyl chloride. The mixture was warmed momentarily to room temperature to yield a clear solution which was then stored at 5° for 28 hr. Ten drops of water were then added and the mixture was shaken intermittently for 1 hr at room temperature. Work-up yielded 3.14 g (97%) of a white foam which gave 2.76 g (81%), mp 62–68°, from 10 ml of ether at −8°. Material with this melting point was suitable for subsequent reactions; it could be recrystallized from ether and an analytical sample of **44** was thereby obtained: mp 67–70°; nmr (CCl_4) δ 4.35 ppm (broadened t, 1, J = 7.9 Hz).

Anal. Calcd for $C_{22}H_{32}O_4S$: C, 67.31; H, 8.22; S, 8.17. Found: C, 67.22; H, 8.38; S, 8.11.

***dl*-Hedycaryol (5).**—To 5 ml (5 mmol) of a solution of diborane in tetrahydrofuran (Alpha), stirred under nitrogen and cooled in an ice–water bath, was added dropwise over 12 min a solution of 204.8 mg (0.522 mmol) of tosylate **44**, mp 62–68°, in 9 ml of tetrahydrofuran. After 1.5 hr the ice bath was removed, and the solution was allowed to stand at room temperature for 7 hr; 0.24 ml of water was added dropwise and then 10 ml of 5 *N* aqueous sodium hydroxide. The resulting two-phase mixture was heated at 65° for 13 hr, with stirring under nitrogen. Work up (no acid washes) yielded 127.6 mg (theoretical 116.2 mg) of a clear oil: nmr (CCl_4) δ 7–8 (AB, residual tosylate, 1.12), 4.93 (broad, characteristic of hedycaryol, normalized to 2.0), and 0.6–2.9 (complex, with spikes at 1.17, 1.48, and 2.44 ppm, total integration 38.6). The oil was stirred with and then separated from several portions of 20% aqueous silver nitrate solution (total 9 ml). The residual oil was taken up in 5 ml of ether and extracted with 2 ml of silver nitrate solution as the ether was gently evaporated under a stream of nitrogen. This procedure was repeated on the remaining gummy material. The combined aqueous silver nitrate extracts were washed once with ether before 20 ml of concentrated aqueous ammonia was added. The resulting milky suspension was extracted several times with ether and the combined ether extracts, after further work-up, afforded 59.8 mg (51%) of *dl*-hedycaryol: nmr (CCl_4) δ 4.93 (broad, 2) and 0.8–2.6 (complex, with a sharp signal at 1.17, less sharp signals at 1.48 and 1.57, total integration, theoretically 24, 25.7). A weak signal at 0.97 ppm revealed the presence of no more than 4% of *dl*-elemol. In the presence of a pellet of sodium hydroxide, a 47.6-mg sample of similar material obtained from another run was subjected to short-path distillation at 0.2 mm from an oil bath at 90–95°: 33.3 mg of distillate was collected; ir (film) and nmr (CCl_4) spectra matched those of the natural isomer.[19]

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.18; H, 11.65.

A solution of 52 mg of *dl*-hedycaryol (distilled) in 1 ml of cyclohexane was heated at 130° for 16 hr in a sealed tube which had been subjected to a pretreatment involving an ammonia rinse. Evaporation of solvent gave a quantitative recovery of material with an ir matching that obtained from an authentic sample of *l*-elemol;[23] nmr (CCl_4) δ 5.79 (A of AMX, 1.00, J_{AM} = 10.1, J_{AX} = 18.0 Hz), 4.5–5.1 (complex, 3.83), and 0.85–2.5 (complex, with sharp signals at 1.70, 1.15, and 0.97 ppm, total integration 21.7); glpc analysis on column 2 at 137° revealed a major component (>95.6%) at 17.9 min with minor components at 15.5 (<0.4%) and 23.0 and 25.5 min (total <4%).

Registry No.—**2**, 32319-37-2; **4** oxime, 32319-38-3; **5**, 32319-39-4; **12**, 32319-40-7; **13**, 32319-41-8; **15**, 32319-42-9; **22**, 32319-43-0; **43**, 32319-44-1; **44**, 32319-45-2.

(22) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).

(23) An ir spectrum of *l*-elemol was generously supplied by Dr. T. G. Halsall, Oxford University.