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THE STRUCTURE OF ISOBARBATENE, THE STABLE TRICYCLIC END-POINT OF THE BAZZANENE-BARBATENE SESQUITERPENES

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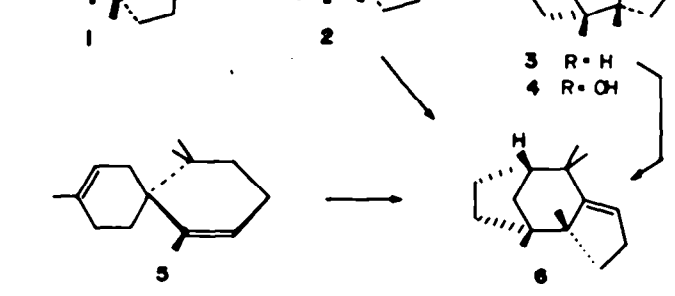
Abstract—The barbatenes (e.g. 3) and a number of other sesquiterpenes afford a novel rearrangement product on treatment with CF_3CO_2H. This substance, designated isobarbatene, is shown to have structure 6, the result of a bicyclo-[3.2.1]→[2.2.2]→[3.2.1] rearrangement followed by an exo Me shift and deprotonation. The structure assignment is based on spectral and chiroptical data for olefin 6 and its degradation products 8, 9 and 10.

Liverworts (Hepaticae) elaborate sesquiterpenes enantiomeric to those found in higher plants,[3-5] with three exceptions: (1) frullanolide occurs in both enantiomeric forms,[6] (2) (−)-caryophyllene is found in *Scapania undulata*,[3c] and (3) drimanes (bicyclofarnesanes) have been identical[4,7] to those previously isolated. In this respect the liverworts are like the fungi.[8] Among the major fungal metabolites are the trichothecanes[9] related to trichodiene (1),[10] and liverworts have been shown to elaborate closely allied substances: β-bazzanene (2),[3c,11a] -α- and β-barbatene (3)[3c,11] and gymnomitrol (4).[3c,12] Here however the stereochemical relationship is a diastereomeric one.

RESULTS AND DISCUSSION

Certain features of the isobarbatene structure were immediately apparent from the NMR and mass spectra: a tricyclic array bearing a single vinyl hydrogen (δ 5.26, –CH=C<, trip.) and four singlet Me groups (δ 1.17, 1.10, 1.03 and 0.96 ppm). Retention of chirality throughout the skeletal rearrangement was indicated by the distinct CD observed for the olefin bond: $\Delta\epsilon_{269} = -1.44$, $\Delta\epsilon_{193} = +10.1$.

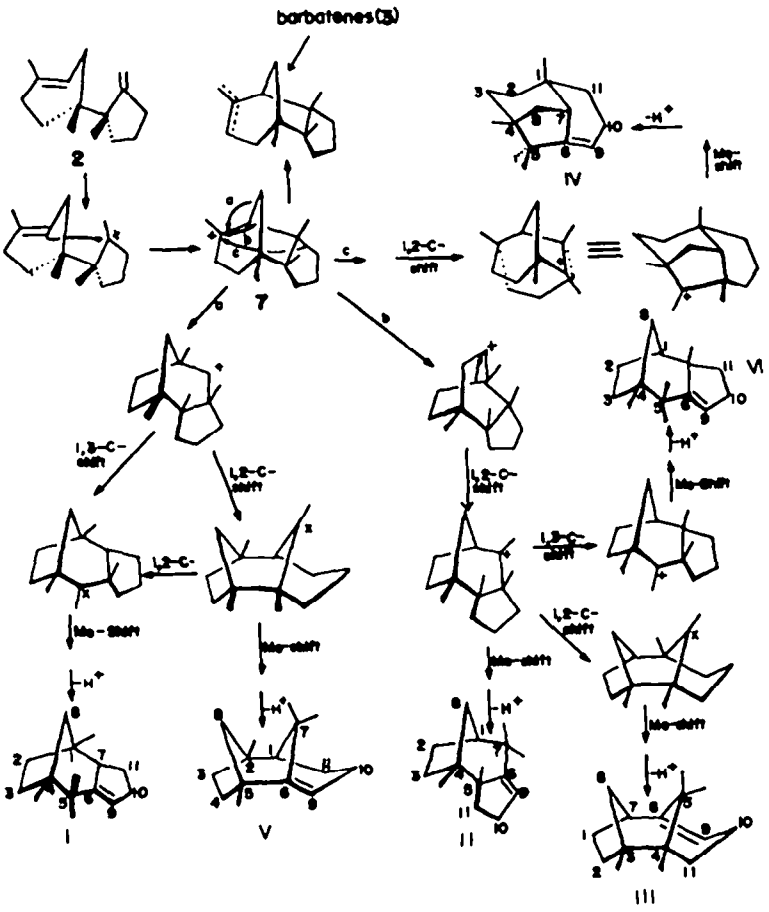
Although isobarbatene is most readily prepared by stirring a heptane solution of α-barbatene with an equal volume of CF_3CO_2H at 30–55° for a number of hours, it



This stereochemical distinction appears to have some chemotaxonomic significance since β-barbatene has been found in virtually every liverwort of order *Jungermanniales*.[3c] The stereochemical features assigned to the barbatenes[11b] find additional support in the structure elucidation presented for gymnomitrol[12] and in an X-ray crystal structure.[13] Only one observation remains unexplained—the near quantitative conversion of the barbatenes to a novel crystalline tricyclic isomer, designated isobarbatene, on treatment with CF_3CO_2H.[11b] The observation has subsequently been a key to establishing the relationship between β-bazzanene and the barbatenes, and (+)-α-chamigrene (5) also affords this material under comparable conditions.[3c] We present here, the evidence that allows us to assign structure 6 to isobarbatene.

is also formed under the milder decane/HCO_2H conditions[18] at elevated temperatures. Under both conditions gc monitoring of the hydrocarbon layer fails to reveal any olefinic intermediates. Based on our previous work with these rearrangement conditions we could arrive at a set of structural possibilities for isobarbatene by detailing the rearrangement possibilities for cation 7 which can afford isomers in which all four methyls become non-equivalent singlets without the intervention of olefinic intermediates.[18b] The pathways we have considered are shown in Scheme 1.

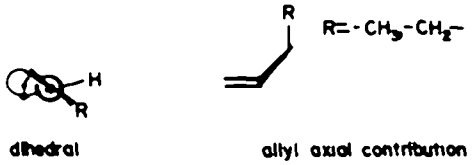
Thus I–VI are all candidate structures for isobarbatene. Of these six, only V has two Me groups (C_7-Me, C_5-Me) that become equivalent upon hydrogenation. Hydrogenation of isobarbatene affords primarily a single dihydro diastereomer which still displays four distinct



Scheme 1. Possible pathways for the formation of isobarbatene.

singlet Me resonances (δ 0.89, 0.91, 1.03 and 1.16 ppm) eliminating structure V from further consideration.

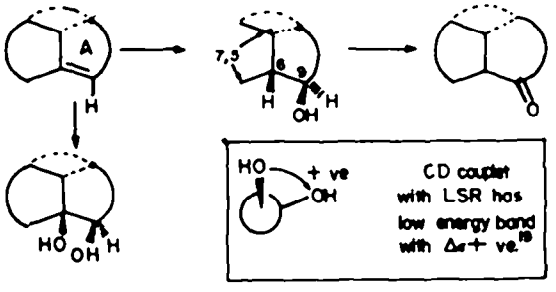
The distinct couplet olefin CD observed for isobarbatene also offered a basis for eliminating a candidate. Such CD couplets are characteristic of cyclic olefins which have a net torsion in the π-bond.[14,15] The torsion sense expected for each model can be assessed from molecular models and are collected in Table 1. The relationship between torsion sense and CD expectation is shown below:



− ve dihedral
+ ve λ_1 (205nm, $\pi_z \rightarrow \pi_z^*$?)
−ve λ_2 (190nm, $\pi_z \rightarrow \pi_y^*$?)

allyl axial contribution
- ve CD contribution
usually at λ_1[16]
+ ve λ_2 in some cases[17]

The chiral disposition of axial allyl groups also influences the olefin CD,[16] and in some of the candidates, predicts an opposite CD sense. On this basis, only structure VI can be excluded. Structure II seems the best fit since only in this case is a negative torsion couplet predicted. In light of the questions that remain concerning the interpretation of olefin CD[17] and the absence of close analogies in this case, we examined the model discrimination available in a simple set of olefin transformations: hydroboration–oxidation and glycol formation with OsO_4 (Table 1).



All of the structures in Scheme 1 have a distinct "sidedness" allowing a secure prediction of the stereochemistry of osmylation and hydroboration. Besides the opportunity to assess the size of ring A from $\nu_{C=O}$ for the ketone, other model discriminating features are the chirality of the glycol,[19] and the predicted $n \rightarrow \pi^*$ Cotton Effect of the ketone.† In addition the *cis* relationship between H-6 and C-9-OH in the hydroboration product assures the easy location of H-6 using lanthanide shift reagents (LSR). The coupling pattern for H-6 then reveals the substitution pattern for the adjacent centers

†The CO $n \rightarrow \pi$ CD predictions are based on the quadrant rule[20] with the emphasis on the contribution made by the primary zig-zag pathway and α- and β-axial alkyl groups.[21]

Table 1. Predictions based on the possible structures (I–IV, VI) of isobarbatene

Model	Isobarbatene CD torsion	Isobarbatene CD allyl-Me	6-ring conform.*	Alcohol $J_{H_6-H_9}$	Alcohol $J_{H_6-H_7}$	Alcohol $\nu_{C=O}$	Ketone CD(n-π*)	Diol chirality CD Sign
I	$+\lambda_1$	$-\lambda_1$†	CH	5-11	3-5	1745	-ve	0→+ve
	$-\lambda_2$	$+\lambda_2$†	HC	4-9	6-10	1745	-ve	±ve
			B	0-5	3-6	1745	+ve	-ve
II	$-\lambda_1$	$-\lambda_1$	CH	5-11	none	1745	+ve	-ve
	$+\lambda_2$	$+\lambda_2$†	HC	4-9	none	1745	+ve	+ve→-ve
			B	0-5	none	1745	-ve→+ve	0→+ve
III	$+\lambda_1$	$-\lambda_1$†	CH	~0	7-8	1715	+ve	+ve
	$-\lambda_2$		HC	~0	7-8	1715	+ve	+ve
			B	0-1	7-8	1715	+ve	+ve
IV	$+\lambda_1$	$-\lambda_1$†	CH	0-1	3	1715	-ve	-ve
	$-\lambda_2$		TB	7-8	5-6	1715	-ve	+ve
VI	$+\lambda_1$	$+\lambda_1$	CH	5-11	none	1745	-ve	+ve
	$-\lambda_2$	$(-\lambda_2)$	HC	4-10	none	1745	-ve	(+ve)
			B	0-5	none	1745	+ve→-ve	+ve→-ve

* CH = chair, HC = half-chair, B = boat, TB = twisted-boat. These terms refer to the relatively flexible cyclohexane rings of each structure in the case of alcohol or diol. For I, II, VI, designations refer to the cyclohexane ring ortho-fused to a cyclopentane ring. The cyclopentane ring is subject to more conformational mobility. For III and IV, designations refer to the cyclohexanol ring.

(indicated as C-7 and 5 in I–VI, Scheme 1). The combination of H_6-pattern and glycol chirality serve to distinguish between the possibilities. The full set of predictions appear in Table 1.

Osmylation of isobarbatene afforded after silica chromatography the major glycol (**8**) as white crystals, homogeneous by tlc. The NMR displayed a quartet (J = 6.7 Hz) for H-9 with one of the couplings associated with the C-9-OH. Addition of LSR to a CCl_4 solution of the glycol produced in all cases a couplet centered at *ca.* 300 nm with the lower energy band negative. We find, here as in other studies,[22] that the more electrophilic FOD-reagents give larger couplets, for Pr(FOD)$_3$ the couplet was, $\Delta\epsilon(\lambda, nm)$: −6.5(318), +3.3(285). The negative band eliminates structure III from consideration.

Hydroboration afforded primarily a single crystalline alcohol displaying an approximate quartet signal (J ≃ 9–10 Hz) for H-9. A Eu(FOD)$_3$ LIS study located additional signals including H-6, which appears as a sharp doublet (J = 10–11 Hz). Oxidation with H_2CrO_4 afforded the ketone. The observed C=O frequency, 1735 cm^{-1} (CCl_4) fits either for a cyclopentanone or possibly a strained cyclohexanone. The CD spectrum displayed an $n\rightarrow\sigma^*$ band (190 nm) of opposite sign to the $n\rightarrow\pi^*$ band ($\Delta\epsilon_{305} = +0.90$), a common feature of C_2-symmetry cyclopentanones.[22]

Referring back to Table 1, it is clear that model II (isobarbatene = **6**) provides the best fit, particularly assuming a chair to half chair conformation for ring *B* in the diol (**8**), alcohol (**9**), and ketone (**10**).

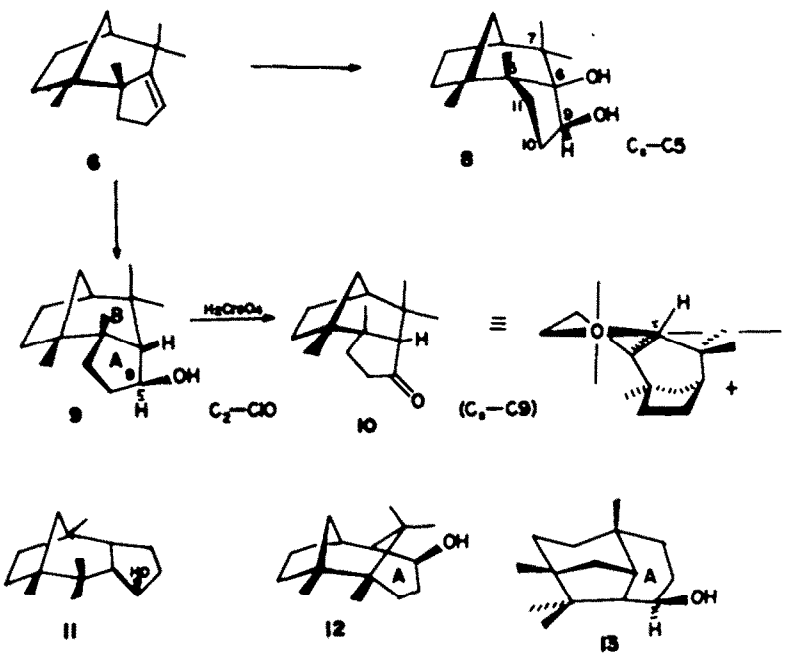
†A total of over 40 individual conformational models were considered when the pseudorotation of the cyclopentane ring is included.

As a confirmation of this assignment we prepared molecular models of the alcohols expected from hydroboration of each possible structure for measurements of proton to "Eu-complexing center" distances for a more detailed correlation of the LIS data with structure.† The complexing center is taken to be a point 1.65 Å from C-9 along the C–O bond axis. The fit is based on the relationship—$(LIS_{calc})_i = Ar_i^{-m}$—with expectation values of m ≃ 2.1, and judged based on the σ-values.[23]

Structure **9** for the alcohol gave, by far, the best fit to the LIS data. A comparison with the better fitting conformers of **11**, **12** and **13** (which would result from Structures I, III and IV, respectively) is given below:

Conformational model	σ(LIS) (ppm)
9 B-chair, A C_s-C5	0.6
9 B-chair, A C_2-C10	0.7
9 B-boat, A C_2-C10	0.8
9 B-boat, A C_s-C5	0.8 (best fit for Me signals)
11 B boat or chair, A various	1.4–1.6
12 A as half-chair	≥3.2
13 A, Twist-boat	≥2.3

Although the conformations of **9** in which ring B has a boat conformation give the better LIS fits for the Me signals, this model does not accord with the observed glycol chirality nor the coupling data for H-9: $J_{6,9} = 10.5$, $J_{9,10\alpha} \simeq J_{9,10\beta} = 8.3$–8.9 Hz. Those cyclopentane pseudorotamers of **9** (B-chair) which give the best overall LIS fit also fit the coupling data. It should be noted that these coupling constants remain unchanged (within experimental error, ±0.8 Hz) during the LIS experiment (Eu: **9** = 0.0–0.6).



CONCLUSIONS

The barbatenes (and a number of other bi- and tricyclic sesquiterpenes) afford a single, stable, tricyclic olefin (6) under moderately harsh acid rearrangement conditions. The rearrangement occurs via the *a priori* most facile [3.2.1]→[2.2.2]→[3.2.1]' sequence from the barbatene cation 7 followed by an exo methyl shift and deprotonation. In light of the ease and high yield of this chemical reaction we expect that it is only a matter of time before isobarbatene is found as a constituent of sesquiterpene-rich essential oils.

EXPERIMENTAL

General methods. Those described in the accompanying article apply.[24] Mass spectral data is reported as follows: mass (% of base peak, formula, error in mmass). NMR data for $CDCl_3$ solns unless otherwise designated. The β-barbatene samples were obtained either from *Barbilophozia* sp. described in the accompanying article[24] or from *Scapania undulata*.[3c]

Isomerization of β-barbatene (3). β-Barbatene (94·% pure, 10 μl) in 100 μl n-decane was stirred with 100 μl of HCO_2H for 1 hr at 25–30°. GC analysis of the decane layer revealed rapid quantitative conversion to α-barbatene. An additional 2.5 hr period gave no further reaction. Upon warming to 90–100° (bath temp) a slow conversion (30% conversion in 19 hr) to 6 was detected by gc analysis on three columns with different stationary phases. Addition of 80 μl of CF_3CO_2H after 24 hr, led to complete (86·%) conversion to isobarbatene over a 1 hr period at 80–90°. The characteristic Kovats' indices[25] and R_f values ($AgNO_3/SiO_2$ plate, developed with 7:3 n-C_6H_{14}:PhH) for the barbatenes are given here:

	R_f($AgNO_3$)	KI (190°) Apiezon L	KI (170°) SF-96	KI (150°) C-20M
β-Barbatene	0.57	1536	1473	1690
α-Barbatene	0.82	1501	1440.5	1627.5
Isobarbatene	0.74	1515	1457.5	1645.2

Repeating the reaction of a 30-mg scale using heptane and HCO_2H afforded α-barbatene judged pure by NMR, gc, and CD comparison with the natural product.[11b]

Pure isobarbatene was prepared as follows: a soln of 45 mg of β-barbatene (97·% by gc) in 1.6 ml of n-heptane was treated with 0.6 ml HCO_2H with stirring for 12 hr. Addition of 0.8 ml CF_3CO_2H and 5 hr of stirring at 55° gave a heptane solution displaying a single peak by gc. Dilution with 60 ml of pentane, water washes, and evaporation afforded 40 mg of crystalline isobarbatene (6): IR (CCl_4) 3055, 1645 (>C=CH–), 1470, 1388, 1372, 1320, 1178, 1045, 1035, 1005, 845, 698 cm^{-1}; δ (CCl_4) 5.235 (1H, t), 1.95–2.4 (3H, m, allyl-H), 1.15, 1.08, 1.02 and 0.93 ppm (4Me, s); ms 204.1870 (26, $C_{15}H_{24}$ −0.6), 124.1236 (60, C_9H_{16} −1.4),[26] 123.1166 (100, C_9H_{15} −0.6), 96.0936 (25, C_7H_{12} −0.2),[26] 95.0872 (45, C_7H_{11} +1.2), 81.0696 (76, C_6H_9 −0.8), 55.0548 amu (75%, C_4H_7 +0.0 mass). Directly after preparative gc the pure substance displayed: m.p. 56°; $[\alpha]_D = +20°$, $[\alpha]_{589} = +197°$, $\Delta\epsilon_{289} = -1.44$, $\Delta\epsilon_{195} = +10.1$ (pentane).

For most preparative reactions, isobarbatene of 80–88% purity (GC) was employed. A typical synthesis being the reaction of 70–80% purity α- and/or β-barbatene. For example: a mixture of 290 mg (1.42 mmole) of β-barbatene (~70% pure) in 10 ml heptane and 4 ml HCO_2H was stirred at room temperature. After 24 hr, α-barbatene was formed as shown by tlc. To the same soln, 5 ml CF_3CO_2H was added and the mixture was stirred at 55° for 15 hr. The product was extracted into pentane, washed with water and said $NaHCO_3$ aq, and dried ($MgSO_4$). Upon evaporation of solvent, 269 mg of impure isobarbatene was obtained. Purification was effected by chromatography over a $AgNO_3/SiO_2$ column and then passage through basic Al_2O_3. The hexane fraction yielded 161 mg of isobarbatene (~84% pure, GC) which was crystalline at −10°.

Hydrogenation of isobarbatene. To a solution of isobarbatene (23 mg, 96·% pure, 0.11 mmole) in 3 ml HOAc, 3 mg of PtO_2 was added. Before the reaction flask was sealed with a hydrogen balloon, the flask was flushed thoroughly with H_2 gas. The soln was stirred at room temp. for 20 hr. Work-up was accomplished by partitioning between water and hexane. The hexane layer was washed with H_2O, $NaHCO_3$, and dried over $MgSO_4$. The hexane soln showed two peaks on gc: $I_A^{190} = \sim 1573$, ~85%; $I_A^{190} = 1606$, 15%. Pure isobarbatane (6 mg) was obtained from preparative gc collections of the crude product: δ (CCl_4) 0.89, 0.91, 1.03 and 1.16 ppm for the four Me singlets; ms 206.2022 (26, $C_{15}H_{26}$ − 1.0), 125.1324 (37, C_9H_{17} −0.4), 123.1164 (32, C_9H_{15} −0.9), 96.0928 (33, C_7H_{12} −1.0),[26] 95.0864 (36, C_7H_{11} +0.4), 85.07 (100), 83.0866 (33,

C_6H_{11} +0.6), and 81.0708 amu (81%, C_6H_9 +0.4 mmass). A comparison of 60 and 80 MHz NMR confirmed the Me resonance assignments.

Osmylation of isobarbatene. A soln of OsO_4 (33 mg, 0.13 mmole) in 0.4 ml benzene was added to 0.5 ml of dry pyridine containing isobarbatene (26 mg, 0.128 mmole, 84% purity). The dark soln was stirred at room temp. for 42 hr, then 100 mg $NaHSO_3$, 0.8 ml H_2O and 0.8 ml pyridine were added to the mixture. The dark soln turned to a reddish color immediately. The soln was stirred for an additional hr. Extraction with methylene chloride (3 times) and washing with satd $CuSO_4$ aq and water gave a dark colored soln. Removal of solvent afforded 61 mg of brownish oil (largely a single spot on tlc) which was chromatographed on a small SiO_2 (6 g, neutral) column. Elution with 5% EtOAc/PhH gave, as the center-cut, 7.1 mg of crystalline diol 8: R_f (5% EtOAc/PhH) = 0.168; δ 4.2 (1H, OH, H-bonded), 3.47 (1H, CHOH, q, 6.7 Hz), 2.5 (1H, OH), 1.18 (Me, s), 1.01 (2Me, s) and 0.985 ppm (Me, s); ms 238.1926 (very weak, $C_{15}H_{26}O_2$ −0.4), intense peaks at 220.1824 ($C_{15}H_{24}O$ −0.2), 149.1302 ($C_{11}H_{17}$ −2.6), 141.1214 ($C_9H_{17}O$ −6.4), 139.1106 ($C_9H_{15}O$ −1.6), 124.1224 (C_9H_{16} −2.6),[26] 123.1098 (C_9H_{15} −7.4), 122.1100 (C_9H_{14} +0.6), 114.0652 ($C_6H_{10}O_2$ −2.8), 113.0606 ($C_6H_9O_2$ +0.4), 109.0998 (C_8H_{13} −1.8), 107.0854 (C_8H_{11} −0.6), 96.0564 (C_6H_8O −1.2),[26] 95.0866 (C_7H_{11} +0.6), and 81.0662 amu (C_6H_9 −4.2 mmass).

To a 3.36×10^{-4} M soln of diol 8 in anhyd CCl_4 (filtered through Al_2O_3, Woelm I) was added Pr(FOD)$_3$ sufficient to produce a diol:Pr molar ration of 0.67. The CD spectra (l = 1 mm) was scanned (370–250 nm) repeatedly. After 30 min a relatively constant spectrum was obtained: $\Delta\epsilon_{318} = -6.48$, $\Delta\epsilon_{301} = 0$, $\Delta\epsilon_{285} = +3.3$.† Similar, but weaker couplets were observed with Pr(DPM)$_3$ and Eu(DPM)$_3$.

Hydroboration-oxidation of isobarbatene. A soln of 1 M BH_3·THF (3 ml, 3 mmole) was added slowly to a soln of isobarbatene (72 mg, 0.35 mmole, 84% pure) in anhyd THF and the mixture stirred at room temp. for 5 hr. Excess hydride was cautiously decomposed with water. 3N NaOH (1 ml) was added, followed by 30% H_2O_2 (1 ml). The mixture was stirred at room temp. overnight. The product was extracted into ether which was then washed with brine and dried ($MgSO_4$). Removal of solvent gave 100 mg of oily product displaying eight components by tlc (SiO_2, 5% EtOAc/PhH) and seven alcohol products by gc. The major spot (R_f = 0.232), and gc peak‡ (RR_C^{200} = 1.66, 37%, 46% based on recovered 6) corresponded to the major product (80+%) of a small scale hydroboration of 96+% pure isobarbatene. Repeated preparative tlc (8% EtOAc/PhH) of the crude product afforded 6.7 mg of 9 (R_f = 0.232, RR^{200}_{acetyl} = 1.66): m.p. 100–102.5°, IR ($CHCl_3$) 3640 and 3600 (sharp), 3500–3200 cm^{-1} (broad band); δ (60 MHz) 4.22 (1H, CHOH, q, J = 8–10, LIS = 1684),§ 1.27 (1H, d, J = 10.5, H-6, LIS = 1086), 1.27, 1.13, 1.09, and 0.91 ppm (Me each, s, LIS = 304.1, 680.2, 321.8 and 162.3 Hz, respectively for the 7β-, 7α-, 5- and 4-Me).¶ The LIS studies were with Eu(FOD)$_3$ and shifts are expressed as Hz/eq.Eu. The LIS studies also revealed the initial positions of the hydrogens at C-10: H-10β (~1.5, ~1150) and H-10α ($\delta \sim 2.1$ ppm, LIS = 800 Hz). LIS structure correlation employed the values for all Me signals and the hydrogens at C-6, 9, and 10. The molecular formula was established by mass spectroscopy: 222.1936 (18, $C_{15}H_{26}O$ −4.6), 178.1716 (7, $C_{13}H_{22}$ −0.4), 165.1630 (11, $C_{12}H_{21}$ −1.2), 141.1248 (10, $C_9H_{17}O$ −3.0), 124.1184 (39, C_9H_{16} −6.6),[26] 123.1122 (100, C_9H_{15} −5.0), 97.0644 (15, C_6H_9O −1.0), 96.0936 (13, C_7H_{12} −0.2),[26] 95.0862 (9, C_7H_{11} +0.2), 81.0664 (80, C_6H_9 −4.0), and 80.0596 amu (70% C_5H_8 −3.0 mmass).

7 mg (0.032 mmole) of isobarbatene alcohol in 50 μl of distilled diethyl ether was chilled in ice bath for 30 min. An aqueous chromic acid soln (30 μl, 8N),[27] was also cooled in an ice bath for 30 min. The chilled chromic acid soln was added dropwise to the stirred alcohol soln. After addition, the soln was allowed to stand in an ice bath with vigorous stirring for an additional 10 min. The mixture was diluted with ether, washed with satd $NaHCO_3$ aq and water, and dried ($MgSO_4$). TLC showed one major spot with R_f (5% EtOAc/PhH) = 0.56. GC (Carbowax) indicated 87% of a new peak at RR_C^{200} = 1.246 besides the unreacted alcohol at RR = 1.644. Removal of solvent gave 2.7 mg of crystalline product (ketone 10): IR (CCl_4) 1735 cm^{-1} (1725 cm^{-1} in $CHCl_3$); δ 1.33, 1.25, 1.08 and 1.03 ppm for four methyl singlets; CD (n-C_5H_{12}), $\Delta\epsilon_{325} = +0.37$, $\Delta\epsilon_{315} = +0.88$, $\Delta\epsilon_{305} = +0.90$, $\Delta\epsilon_{290} = -0.86$!; ms 220.1822 (38, $C_{15}H_{24}O$ −0.4), 187.1472 (13, $C_{14}H_{19}$ −1.4), 124.1236 (12, C_9H_{16} −1.4),[26] 123.1166 (100, C_9H_{15} −0.6), 107.0852 (61, C_8H_{11} −0.8), 97.1012 (14, C_7H_{13} −0.4), 95.0858 (54, C_7H_{11} −0.2), 81.0692 amu (90%, C_6H_9 −1.2 mmass).

†The $\Delta\epsilon$ values are based on the original concentration of diol and assume a stoichiometric formation of a 1:1 bidentate complex.[19,22]

‡The next largest component was 7% of the total alcohols.

§The LIS experiment was done at 60 MHz and the couplings of H-9, H-6 and H-10 were confirmed by double resonance experiments. At 100 MHz and higher resolution, the H-9 pattern implies: $J_{6,9} = 10.5$, $J_{9,10\alpha} \simeq J_{9,10\beta} = 8.3$–8.9 Hz.

¶The Me assignment is based on structure 9 with ring B in the chair conformation and the cyclopentane ring in the C_8-C5 conformation or the related C_7-C9 or C_7-C10 forms.

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