Tetrahedron Vol. 34, pp. 2077–2081
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0040-4020/78/0715-2077/$02.00/0

THE BRASILENOLS, REARRANGED SESQUITERPENE ALCOHOLS ISOLATED FROM THE MARINE OPISTHOBRANCH *APLYSIA BRASILIANA*

MARTHA O. STALLARD and WILLIAM FENICAL*
Institute of Marine Resources, Scripps Institution of Oceanography, La Jolla, CA 92093, U.S.A.

and

J. S. KITTREDGE
Marine Biomedical Institute, University of Texas Medical Branch, Galveston, TX 77550, U.S.A.

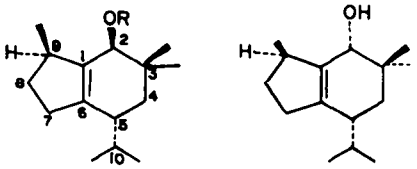
(*Received in USA* 6 *December* 1977; *Received in UK for publication* 6 *March* 1978)

Abstract—Two nonisoprenoid sesquiterpene alcohols, brasilenol and epibrasilenol, have been isolated, along with brasilenol acetate, from the digestive glands of the marine opisthobranch *Aplysia brasiliana*. The structures of these unusual sesquiterpenoids were determined by extensive spectral and chemical analysis and by their mutual conversion to the corresponding α,β-unsaturated ketone, brasilenone. The brasilenols are likely to have a dietary origin, since these compounds have also been observed as natural products of the red seaweed *Laurencia obtusa*.

Chemical studies of the marine molluscs known as sea hares (Opisthobranchia, Aplysidae) have revealed that the animals concentrate, in their digestive glands and to a lesser extent in the outer tissues, the secondary metabolites produced by various seaweeds which comprise their diets.[1] Feeding studies and field observations have further shown that the sea hares have distinct and specific preferences for the seaweeds *Laurencia*, *Plocamium*, *Dictyota* and *Lyngbya*, *inter alia*,[2] which produce large amounts of these metabolites in the form of terpenes, halogen-containing compounds, and products derived from acetate metabolism. These compounds, which appear to provide some selective advantage as feeding inhibitors for the seaweeds, are then sequestered by the sea hare, and it has been proposed that they function for the animal in a similar fashion.[3]

The Gulf of Mexico sea hare *Aplysia brasiliana* (Rang) is a prime example of this group for which there appear to be few predators.[4] Extracts of the digestive glands of *A. brasiliana* were recognized by tlc to contain several interesting secondary metabolites, and when a small amount of this extract was painted on the shell of a juvenile crab, *Callinectes sapidus*, this preferred prey became quite repulsive to an octopus, *Octopus vulgaris*. For these reasons, an extensive study of the digestive gland components was undertaken, and we wish to report here the isolation and structure elucidation of several new non-halogenated and nonisoprenoid sesquiterpene alcohols. Evidence has also been gathered that these metabolites originate in the red algae *Laurencia*.

A. brasiliana specimens collected along the Texas coast were immediately dissected, and the digestive glands were extracted with ethanol. After typical work-up, the ether-soluble portion was chromatographed on silica gel to yield numerous fractions, some of which were further purified by μ-porasil HPLC. Several typical *Laurencia* acetylenes were subsequently purified among them the previously described ether, dactylyne,[5] two new $C_{15}H_{20}OBrCl$ ethers and a new $C_{15}H_{20}OCl$ ether, the structures of which will be reported elsewhere. From several fractions we obtained three new sesquiterpenoids of unusual structures, for which we suggest the trivial names brasilenol, brasilenol acetate and epibrasilenol and propose structures 1–3.



1; R=H
2; R=Ac

3

Brasilenol (1) was isolated as a volatile solid, mp 55–6°, with a mild methol-like odor. High resolution mass spectrometry established a molecular composition of $C_{15}H_{26}O$, which requires three unsaturation equivalents. IR absorption at 3650 cm^{-1} established the alcohol functionality and the lack of CO absorptions confirmed that the unsaturation in brasilenol was from olefin and carbon ring components. The off-resonance ^{13}C NMR spectrum of brasilenol displayed two low field singlets at 142.1 and 138.7 ppm, which illustrated that 1 contains a single tetrasubstituted olefin. These combined data require that brasilenol possess a bicyclic carbon skeleton.

Acetylation of brasilenol (Ac_2O/py/25°) gave brasilenol acetate (2), which was identical to an acetate isolated by HPLC from several original chromatography fractions. Comparisons of the ^1H NMR spectra of 1 and 2 showed that a one-proton band observed at δ 4.01 (dddd, J = 1,3,3,3) in 1 had moved to δ 5.36 (dddd, J = 1, 3,3,3) in the acetate. These data confirmed that brasilenol was a secondary alcohol and, based on the chemical shift of the alcohol methine proton, suggested that the OH was allylic.

Perhaps the most striking feature of the ^1H NMR spectrum of brasilenol was the existence of five high field Me signals, composed of two singlets at δ 0.82 and 1.02 and three doublets (J ≃ 7 Hz each) at δ 0.67, 0.87 and 1.10, rather than the more common four Me group composition of most sesquiterpenoids. The two Me singlets could be assigned to a gem-dimethyl constel-

lation, based upon the characteristic doublet IR absorptions at 1385 cm^{-1} and the existence in the off-resonance proton-decoupled ^{13}C NMR spectrum of a single high field tetrasubstituted C atom at 35.6 ppm.

Jones' oxidation of brasilenol gave the corresponding ketone, brasilenone (4) in only modest yield. The ketone showed CO and olefin absorptions at 1667 and 1626 cm^{-1} in the IR spectrum and UV absorption at 242 nm (ϵ = 10,000), both in good agreement with values for a 6-membered α,β-unsaturated homoannular ketone.[6] The mass spectrum of 4, as well as those obtained from 1 and 2, showed strong $M^+-C_3H_7$ fragments, which suggested that two of the three high field doublets observed in the ^1H NMR spectrum arose from an isopropyl group. Further, irradiation of one side of a complex two-proton multiplet ($\sim \delta$ 2.14) caused the two doublets at δ 0.98 and 0.74 (J = 6.7 Hz each) to collapse to singlets. From these and subsequent lanthanide shift experiments, the existence of an i-Pr group was securely established (Table 1).

The oxidation of 1 to 4 produced no new deshielded protons in the ^1H NMR spectrum of 4 at lower field than δ 1.6, as would be expected for a methylene or methine group alpha to a cyclohexyl ketone. Hence, the alpha

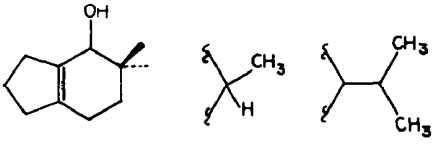
Table 1. 220 MHz ^1H NMR data for brasilenol and brasilenone

brasilenol		
Proton(s)	shift(s) ($CDCl_3$)	mult. (Hz)
2 α	4.01	dddd (3, 3, 3, 1)
3 α Me	0.82	s
3 β Me	1.02	s
4 α	~2.2*	dd (11, 3)
4 β	~2.2*	dd (11, 11)
5 β	~2.0*	dddd (11, 3.5, 3, 3)
7 α	~2.2*	dddd (15, 7, 2.6, 3)
7 β	~2.2*	dddd (15, 6.5, 6.5, 3)
8 α	1.41	dddd (10.5, 6.5, 2.6, 2.6)
8 β	2.0*	dddd (10.5, 7, 6.5, 6.5)
9 α	2.76	qddd (6.8, 6.5, 2.6, 1)
9 β Me	1.10	d (6.8)
10	~2.1*	qqd (6.7, 6.7, 3)
10 Me	0.87	d (6.7)
10 Me	0.67	d (6.7)
3 α Me	1.05	s
3 β Me	1.12	s
4 α	1.64	dd (J = 11, 3.5)
4 β	1.64	dd (J = 11, 11)
5 β	2.5*	ddd (J = 11, 3.5, 3)
7 α	2.5*	ddd (J = 15, 7, 2.6)
7 β	2.5*	ddd (J = 15, 6.5, 6.5)
8 α	1.50	dddd (J = 10.5, 6.5, 2.6, 2.6)
8 β	2.1*	dddd (J = 10.5, 7.0, 6.5, 6.5)
9 α	3.05	qdd (J = 6.8, 6.5, 2.8)
9 β Me	1.01	d (J = 6.8)
10	2.1*	qqd (J = 6.7, 6.7, 3)
10 Me	0.74	d (J = 6.7)
10 Me	0.98	d (J = 6.7)

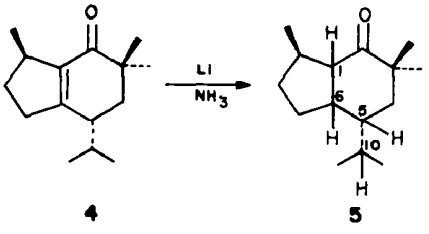
*estimated chemical shifts by extrapolation for the non-shifted spectrum. Coupling constants and assignments are derived from the shifted spectrum and decoupling experiments.

carbon must be disubstituted and the site for the gem-dimethyl substitution.

The aforementioned spectral features fixed brasilenol as a bicyclic sesquiterpene allylic alcohol with gem-dimethyl, secondary Me and i-Pr substituents. These substituents require six C atoms, hence nine remain for the construction of the bicyclic skeleton. Since brasilenone was shown to possess a cyclohexenone functionality and the single olefinic bond is tetra-substituted, these sesquiterpenoids must possess unusual bicyclo[4.3.0]nona-$\Delta^{1,6}$-ene skeletons. Any other bridged arrangement of atoms would render the olefin trisubstituted as well as violate Bredt's Rule. The locations of the secondary Me and i-Pr groups were not derivable from these data.



The final structure assignment for brasilenol was accomplished by extensive ^{1}H NMR experiments involving double-resonance techniques and the use of lanthanide shift reagent. With brasilenol, an apparent first-order spectrum with nine resolved one-proton bands and five three-proton Me groups was obtained at a concentration of 31.3 mg Eu(fod)$_3$ to 6.8 mg of **1** in $CDCl_3$. Sequential irradiation of each band allowed all signals to be interrelated. A one-proton multiplet, appearing under these conditions at δ 3.55, when irradiated collapsed two doublet Me's at δ 1.75 and 2.05, thus rigorously confirming the previously proposed i-Pr functionality. With brasilenol the accurate measurement of several coupling constants was difficult due to numerous small homoallylic couplings involving the C-2, C-5, C-7 and C-9 protons. Therefore, an analogous study was completed with brasilenone (**4**), which, by virtue of the C-2 CO functionality, provided for a more simplified spectrum. At concentrations of 11.4 mg Eu(fod)$_3$ to 3.3 mg of **4**, a completely resolved spectrum was obtained (Fig. 1). Sequential irradiation of each band allowed their mutual correlation and assigment. The double bond at the ring juncture separated brasilenone into two easily analyzed groups of protons. In the 5-membered ring, a single Me group was coupled to a methine proton, both of which were placed at C-9, since these groups were heavily shifted by the Eu(fod)$_3$ reagent and hence quite close to the CO group. The C-9 methine was coupled to an adjacent methylene pair ($8\alpha, 8\beta$)[7] which was itself coupled to another methylene pair ($7\alpha, 7\beta$). In the 6-membered ring, only two carbons are available as sites for the i-Pr substituent. This was substantiated by decoupling experiments, but, based on these data, the substituent could be placed at either C-4 or C-5. In the non-shifted spectrum of brazilenone only four protons were found in the allylic region, which suggested that C-5 bears i-Pr, rather than being unsubstituted. This assignment was confirmed after conversion of brasilenone to dihydrobrasilenone (**5**) by Li in ammonia reduction at



$-78°$. Extensive decoupling experiments with **5** illustrated that the isopropyl Me's were coupled (J = 6.7 Hz) to a C-10 methine, which was itself coupled to the C-5 methine (J = 3.5 Hz). The C-5 proton was further coupled to a C-6 methine (J = 10 Hz), which was coupled to the

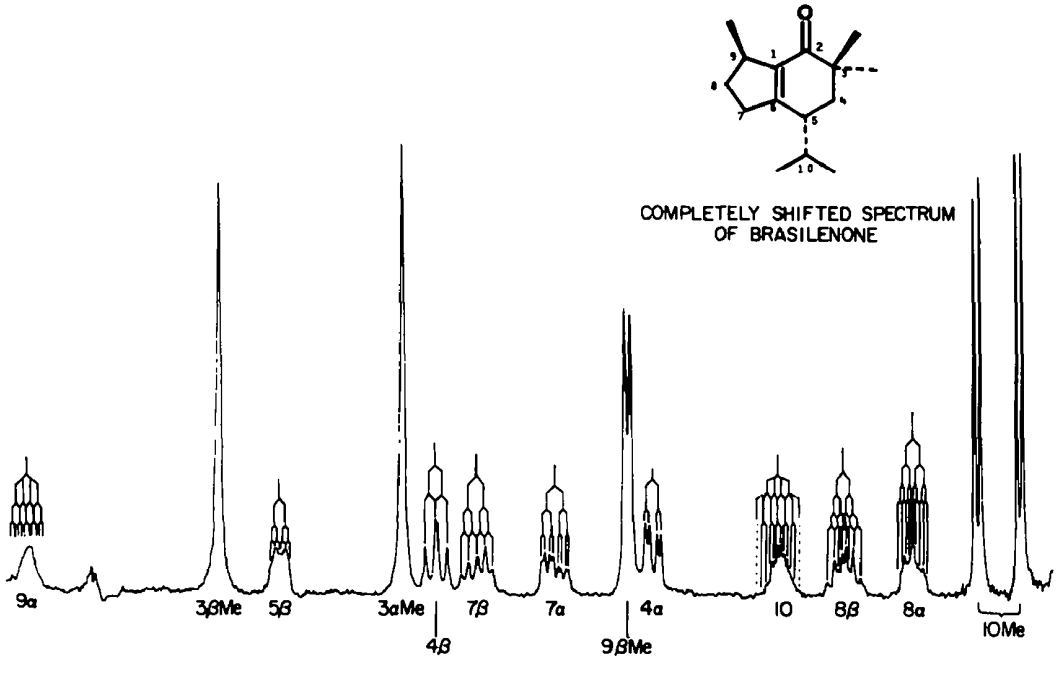


Fig. 1.

α-to-CO proton (C-1) observed at δ 2.82 (J = 10 Hz). Hence, via interrelating the protons at C-1, C-6 and C-5, the i-Pr substitution at C-5 was firmly established.

Chromatographic separation of the crude extract also yielded the C-2 epimer of brasilenol, epibrasilenol (3), as a mobile oil. Its epimeric relationship to 1 was illustrated, since 3 also gave brasilenone on Jones' oxidation. Epibrasilenol was also highly comparable spectrally, possessing all the ^{1}H and ^{13}C NMR characteristics of brasilenol.

Semiquantitative analysis of the lanthanide-induced proton shift NMR data for brasilenol and epibrasilenol confirmed the placement of substituents and provided convincing evidence to assign the relative stereochemistries of these alcohols (Table 2). The simplified relationship $\Delta\delta = -K/r^3$, which neglects angle considerations, was used to relate the magnitude of shift with the interatomic distances as measured using Drieding models.[8] $\Delta\delta$ values were calculated by least squares treatment of the linear portion of the plot of δ vs the [Eu(fod)$_3$]]/[terpene] ratio. For brasilenol the 4α proton was used to back-calculate K, which is a collection of constants which, *inter alia*, locates the position of the europium atom relative to the OH oxygen. With all protons, except the 3α Me group,[9] a close fit was obtained between calculated and observed interatomic distances. An alternative structure with the i-Pr group β and the C-9 Me α substituted was considered and eliminated since errors of between 10 and 24% were obtained with each affected proton or Me group. For epibrasilenol an equivalent good fit was obtained, except that in this case the 3β Me group is affected by the proximity of the europium atom.[9]

A comparison of the relative shifts of the C-9 β-Me group and the C-10 isopropyl Me's clearly established the alcohol stereochemistries in 1 and 3. For brazilenol the C-2 OH eclipses the C-9 Me inducing a large shift with a $\Delta\delta$ value of 4.56. Since the OH is *trans* to the i-Pr substituent, the C-10 Me's experience only slight shifts of 1.14 and 1.23. For epibrasilenol, the C-9 Me is no longer eclipsed and shows a lesser $\Delta\delta$ value of 3.44. The i-Pr, now *cis* oriented to the OH group, shows C-10 Me shifts of 2.15 and 3.17. The C-9 α proton shows inverted behavior with a $\Delta\delta$ value of 7.18 in the eclipsed epibrasilenol and only 5.21 in brasilenol.

Table 2. Semiquantitive lanthanide shift data analysis for brasilenol and epibrasilenol

Brasilenol

Proton(s)	Induced shift ($\Delta\delta$)	r(meas)A°	r(calc)A°	%error
9 α	5.21	6.0	6.4	6.2
3 β Me	6.90	6.0	5.8	3.4
3 α Me	6.50	5.2	5.9	11.8
9 β Me	4.56	6.5	6.6	1.5
5 β	2.68	8.0	8.0	0
4 α	3.48	7.3	*	-
7 β	2.29	8.5	8.4	1.2
4 β	2.63	7.6	8.0	5.0
7 α	1.80	9.3	9.1	2.2
10	1.62	9.8	9.5	3.2
8 β	1.64	8.6	9.4	8.5
8 α	1.62	9.0	9.4	4.3
10 Me	1.23	10.1	10.3	1.9
10 Me	1.14	10.3	10.6	2.8

Epibrasilenol

Proton(s)	Induced Shift ($\Delta\delta$)	r(meas)A°	r(calc)A°	%error
3 α Me	11.4	4.6	4.6	0
4 α	11.0	4.7	4.6	2.2
9 α	7.18	5.4	5.3	1.9
4 β	5.23	5.9	*	-
3 β Me	4.80	6.8	6.1	11.4
9 β Me	3.44	7.2	6.8	5.9
10 Me	3.17	7.3	7.0	4.3
10 Me	2.15	7.5	7.9	5.1

* protons used to calculate K in the relationship $\Delta\delta = -K/r^3$.

At the beginning of this work, the potential dietary sources for the brasilenols were unknown since non-halogenated sesquiterpenoids of this type had not been isolated from marine algae. We have, however, subsequently isolated both 1 and 3, of identical absolute stereochemistry, from the Mediterranean alga *Laurencia obtusa*. While not totally conclusive, this strongly suggests that the brasilenols isolated here are produced by one of several Texas coast *Laurencia* species.

EXPERIMENTAL

IR spectra were recorded on Perkin–Elmer models 137 or 521 spectrophotometers, and UV spectra on a Perkin–Elmer Coleman model 124 spectrophotometer. Mass spectra were obtained using a Hewlett Packard model 5930A mass spectrometer or were obtained through the Department of Chemistry at UCLA. Proton NMR spectra and FT dcoupling experiments were completed using a Varian HR-220 spectrometer interfaced with a Nicolet computer. Carbon NMR spectra were obtained with a Varian CFT-20 spectrometer. Melting points were obtained using a Fisher-Johns apparatus and are uncorrected.

Extraction and purification. Approximately 20 specimens of *Aplysia brasiliana* were collected near the southern tip of Padre Island in Southern Texas, 1975. The digestive glands (620 g) were homogenized in warm EtOH and the concentrated EtOH extract was partitioned between water and diethyl ether. The ether phase was dried over $MgSO_4$ and concentrated *in vacuo* to yield 25.5 g of a mobile oil. A portion of the oil (20 g) was chromatographed on a column (150 g) of Biosil A (100–200 mesh), eluting with various proportions of $CHCl_3$ in petroleum ether.

Brasilenol (1). The fractions from Biosil A chromatography eluted with 50% $CHCl_3$ in petroleum ether (2.79 g) were rechromatographed on Davison grade 62 silica gel, eluting with increasing portions of CH_2Cl_2 in petroleum ether. Fractions eluted with 20% CH_2Cl_2 were combined and the major component was further purified by HPLC on 2 ft. μ-porasil eluting with CH_2Cl_2. After several collections of the second peak eluted, the solvent was removed to yield crystals of brasilenol (0.4 g); m.p. 55–6°; $[\alpha]_D^{21} = 33.4°$ (*c* 1.58, $CHCl_3$); IR (CCl_4): 3650, 1385 cm^{-1}, MS: M^+ measured 222.1981, calculated for $C_{15}H_{26}O$ 222.1984, *m/e* 207 (M^+–CH_3), 204 (M^+–H_2O), 179 (M^+–C_3H_7), 166 (M^+–C_4H_8); ^{13}C NMR ($CDCl_3$): 142.1 (s), 138.7 (s), 77.7 (d), 40.5 (d), 39.3 (d), 36.3 (t), 35.6 (s), 33.4 (t), 30.8 (t), 28.8 (d), 28.0 (q), 21.3 (q), 20.2 (q), 18.8 (q), 16.4 (q); ^1H NMR (C_6D_6): δ 3.86 (1H, dddd, J = 1, 3, 3, 3 Hz), 2.79 (1 H, m), 2.13 – 1.88 (5 H, m), 1.47 (1 H, m), 1.24 (3 H, d, J = 6.8), 1.2 (2 H, m), 0.97 (3 H, s), 0.88 (3 H, s), 0.84 (3 H, d, J = 6.7 Hz), 0.68 (3 H, d, J = 6.7 Hz).

Brasilenol Acetate (2). The fractions from Biosil A chromatography eluted with 10% $CHCl_3$ in petroleum ether (4.52 g) were rechromatographed on a Davison grade 62 silica gel column (2 × 100 cm) eluting with CH_2Cl_2 in petroleum ether. The fraction obtained with 30% CH_2Cl_2 in petroleum ether was further purified by reverse-phase HPLC using a 2 ft μ-bondapak C_{18} column with acetonitrile. The major component, brasilenol acetate (2), was obtained as a mobile oil; IR (CCl_4): 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.36 (1 H, dddd, J = 1, 3, 3, 3 Hz), 2.57 (1 H, m), 2.3 – 1.9 (5H, m), 2.08 (3 H, s), 1.44 (1 H, m), 1.33 (2 H, m), 0.95 (3 H, d, J = 6.8 Hz), 0.91 (3 H, s), 0.88 (3 H, d, J = 6.8), 0.87 (3 H, s), 0.68 (3 H, d, J = 6.8). Brasilenol acetate, identical in all respects to the natural product, was obtained in high yield upon treatment of brasilenol (12 mg) with Ac_2O (1.5 ml) and pyridine (2.0 ml) for 15 hr at 40°.

Epibrasilenol (3). The same column chromatography fractions which yielded brasilenol also gave a minor peak on μ-porasil HPLC (CH_2Cl_2) which yielded epibrasilenol, 210 mg, as a mobile oil, $[\alpha]_D^{21} = 96°$ (*c* 1.05, $CHCl_3$); IR (CCl_4): 3660, 1390, 1375 cm^{-1}; MS: $M^+ = 222$; ^{13}C NMR ($CDCl_3$): 141.8 (s), 140.6 (s), 70.8 (d), 39.7, 39.4, 34.4 (s), 31.8, 31.7, 29.2, 28.7, 27.0, 24.1, 20.1, 20.4, 18.9, 16.6; ^1H NMR ($CDCl_3$): δ 3.47 (1 H, s), 2.86 (1 H, m), 2.28–1.97 (5 H), 1.5 – 1.0 (4 H), 1.04 (3 H, s), 0.97 (3 H, d, J = 6.8 Hz), 0.93 (3 H, d, J = 6.7 Hz), 0.76 (3 H, s), 0.70 (3 H, d, J = 6.7 Hz).

Brasilenone (4). Brasilenol (118 mg) in acetone at 0° was treated with Jones' reagent ($CrO_3/H_2SO_4/H_2O$) by dropwise addition until an orange soln persisted. A few drops MeOH were added to destroy excess reagent and the mixture was partitioned between ether and water. The ether phase was washed with water, satd $NaHCO_3$ and finally dried over $MgSO_4$. Removal of solvent *in vacuo* gave an inpure oil (97 mg) which was further purified by PLC on a 20 × 20 × 0.15 cm silica gel plate (Analtech GF precoated), developing with CH_2Cl_2. Removal and extraction of the one major band at R_f 0.5 gave pure brasilenone (4, 50 mg) as a mobile oil; $[\alpha]_D^{21} = 40.9°$ (*c* 0.95, $CHCl_3$); IR (film): 1667, 1626 cm^{-1}; UV (Et_2O): 242 nm (ϵ = 10,500). In a separate reaction, epibrasilenol was treated under similar conditions to give brasilenone, however, the yield with this epimer was very low (~ 10%). Epibrasilenol, however, when treated with pyridinium chlorochromate in NaOAc buffered CH_2Cl_2 gave brasilenone in 50% yield. Brasilenone, from 3, showed $[\alpha]_D^{21} = 30.5°$ (*c* 0.5, $CHCl_3$).

Dihydrobrasilenone (5). Brasilenone (96 mg in 2 ml Et_2O) was added all at once to a Li in liquid ammonia soln at −78° (1 g Li in 25 ml NH_3). After 1 hr, solid NH_4Cl was cautiously added and the soln was allowed to come to room temp. The contents of the flask were partitioned between ether and water and the ether phase was dried ($MgSO_4$) and concentrated *in vacuo* to yield an impure product. HPLC on μ-porasil (CH_2Cl_2) gave the desired compound, 5 as a light oil (56 mg): IR (CCl_4): 1710 cm^{-1}; MS: $M^+ = 224$; ^{13}C NMR ($CDCl_3$): 220.3, 52.9, 45.3, 44.2, 43.8, 39.7, 37.0, 32.4, 31.4, 29.6, 27.9, 24.2, 21.1, 16.9, 16.2; ^1H NMR ($CDCl_3$): δ 2.82 (1 H, dd, J = 10, 6 Hz), 2.26 (2 H, m), 1.91 (1 H, m), 1.75 (1 H, qd, J = 6.7, 3.5 Hz), 1.6 – 1.3 (5 H, m), 1.16 (1 H, ddd, J = 10, 5, 3.5 Hz), 1.09 (3 H, s), 1.01 (3 H, s), 1.00 (3 H, d, J = 6.8 Hz), 0.92 (3 H, d, J = 6.7 Hz), 0.81 (3 H, d, J = 6.7 Hz).

Acknowledgements—This research was supported by a National Institute of Health postdoctoral fellowship to MOS and by NOAA, Office of Sea Grant, Department of Commerce, under Grant No. 04-6-158-44110, R/MP-7. The U.S. Government is authorized to produce and distribute reprints for governmental purposes, notwithstanding any copyright notation that may appear hereon. We are grateful for the use of the NMR facility of the chemistry department, U.C. San Diego, supported under an NIH Grant, No. RR-708. We thank Mr. Bruce Howard for providing samples of the brasilenols from *Laurencia obtusa*.

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[7]The α and β denotations applied herein are used to assign groups or hydrogens below and above the plane of the brasilenol ring as drawn in 1, analogous to nomenclature in the steroids.

[8]A. F. Cockerill, G. L. O. Davies, R. C. Harden and D. M. Rackham, *Chem. Rev.* **73**, 553 (1973).

[9]The C-3 substituted Me groups in both 1 and 3 (for 1 the 3α-Me, and for 3 the 3β-Me) are apparently too close to the europium atom, or disposed near a node, such that they show unpredictable behavior.