A Selective Synthesis of Brasilenol, a Novel Sesquiterpene from the Sea Hare *Aplysia brasiliana* and the Red Alga *Laurencia obtusa*

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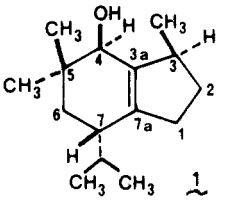
Brasilenol, a metabolite isolated from both *Aplysia brasiliana* and *Laurencia obtusa*, has been synthesized in racemic form. The selective synthesis, which requires 13 steps from 4-isopropylphenol and proceeds in about 5% overall yield, confirms both the novel structure and the stereochemistry of the natural product.

The herbivorous swimming sea hare *Aplysia brasiliana*, an opisthobranch mollusc, is known to graze on the red algae of the genus *Laurencia* and to concentrate in its digestive gland and then slowly release a number of secondary metabolites from these seaweeds.[1] Stallard, Fenical, and Krittredge[2] in 1978 reported the isolation from both *Aplysia brasiliana* and *Laurencia obtusa* of brasilenol, most probably one such metabolite,[1-3] and principally on the basis of NMR studies proposed the structure and relative stereochemistry that are indicated in formula 1. In this paper we report the first synthesis of brasilenol, which confirms the novel nonisoprenoid bicyclo[4.3.0]nonane skeleton and the relative stereochemistry of the natural product.



Brasilenol

In our planning, enone **6** (Scheme I) was viewed as a potentially useful intermediate for selectively securing the stereochemistry found at the C-3, C-4, and C-7 allylic centers of brasilenol. It seemed likely that the cis isomer **6b** would readily lend itself to equilibration and thus, assuming a separation of the cis and trans isomers could be performed, an otherwise most likely difficult "selective" generation of the C-3,C-7 trans isomer, brasilenone, would be possible. Furthermore, in that an examination of molecular models indicated the face opposite to that of the C-3 and axial C-5 methyl groups in **6a** to be by far the less sterically shielded of the two, the subsequent C-4 reduction of enone **6a** was confidently expected to occur highly stereoselectively to yield the natural product. The realization of the synthesis of racemic brasilenol according to this approach is described below.

4-Isopropylphenol (**2**) was converted in high yield to the anisole **3** by Claisen rearrangement[4] of the derived crotyl ether followed by methylation. Standard hydroboration–oxidation of this olefin then provided a carboxylic acid, which on heating at 60 °C in neat polyphosphoric acid smoothly cyclized to give the crystalline indanone **4a**. Not surprisingly, however, the Birch reduction of indanone **4a** and of the corresponding indane **4b**, obtained in nearly quantitative yield from **4a** by stepwise reduction, proved very troublesome.[5a] Numerous attempts that involved various solvents, cosolvents, and metals at different temperatures and for varying reaction times resulted in either complete recovery of the starting compound or conversion to mainly over-reduced material. Fortunately, reasonable success in this reduction could eventually be achieved by modifying slightly a procedure recently described by Hendrickson and DeCapite.[5b] Thus, by treating a solution of the indanone or the indane in methylamine–*tert*-butyl alcohol–tetrahydrofuran at −40 °C with a large excess of lithium for 15–30 min, an easily separable ca. 1:2 mixture of the enones **5a** and **5b** could be obtained in 43–58% yield after hydrolysis. In that the reduction of the indane was both more efficient and decidedly more reproducible than that of the indanone, it was preferred for the synthesis of these enones.

The target enone **6** could readily be secured from **5a** by geminal dimethylation[6] and from **5b** by the same conversion followed by rhodium chloride catalyzed isomerization[7] of the double bond from the Δ^6 to the Δ^{3a} position. While this isomerization could also be carried out before dimethylation (i.e., **5b** → **5a**), predictably, a much cleaner transformation resulted when the $\Delta^6 \rightarrow \Delta^5$ option was first removed. Conveniently, the stereoisomers **6a** and **6b** just yielded to separation by preparative thick-layer chromatography (ΔR_f 0.05, three developments). These enones, as had been expected, also displayed very similar spectral properties; however, a comparison of their proton NMR spectra with that of brasilenone derived from natural brasilenol clearly showed the less polar isomer to be racemic brasilenone (**6a**[8]). With this assignment made, the

(1) For an excellent review on the metabolites of marine algae and herbivorous marine molluscs, see: Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251–280.

(2) (a) Stallard, M. O.; Fenical, W.; Kittredge, J. S. *Tetrahedron* **1978**, *34*, 2077–2081. (b) See also: Fenical, W.; Sleeper, H. L.; Paul, V. J.; Stallard, M. O.; Sun, H. H. *Pure Appl. Chem.* **1979**, *51*, 1865–1874.

(3) Brasilenol may act as a feeding deterrent for both the alga and *Aplysia brasiliana*, which although shell-less, appears to have few predators. For an interesting discussion of the chemical defense and evolutionary ecology of opisthobranchs, see: Faulkner, D. J.; Ghiselin, M. T. *Mar. Ecol. Prog. Ser.* **1983**, *13*, 295–301. See also: Stallard, M. O.; Faulkner, D. J. *Comp. Biochem. Physiol.* **1974**, *49B*, 25–35, and ref 2.

(4) Rhoads, S. J.; Raulins, N. R. *Org. Synth.* **1975**, *22*, 1–252.

(5) (a) See: Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, *3*, 35–85. (b) Hendrickson, J. B.; DeCapite, P. M. *J. Org. Chem.* **1985**, *50*, 2112–2115.

(6) Rubottom, G. M.; Juve, H. D., Jr. *J. Org. Chem.* **1983**, *48*, 422–425.

(7) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102–7104.

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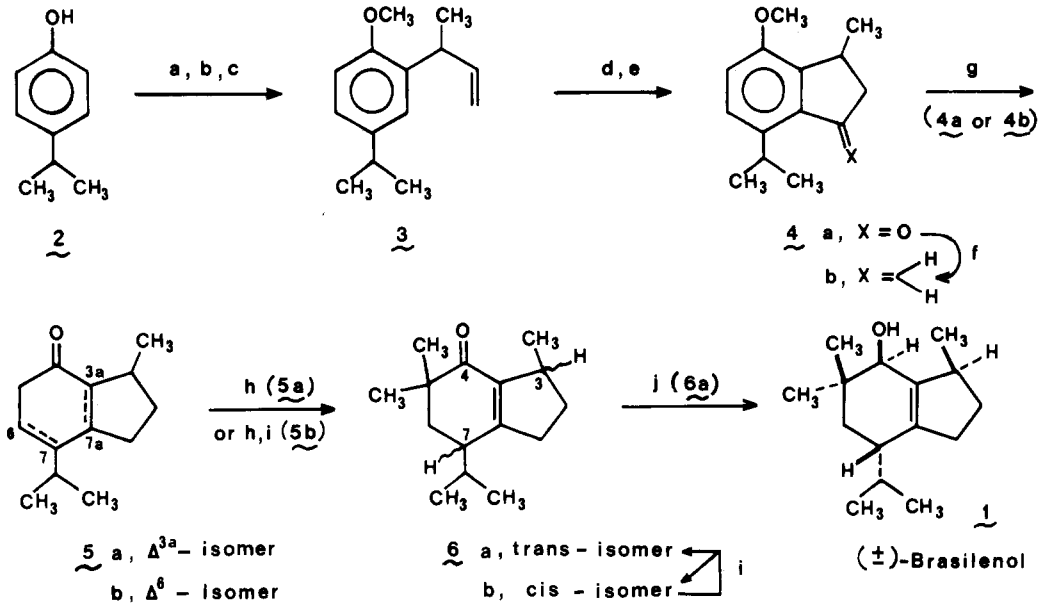
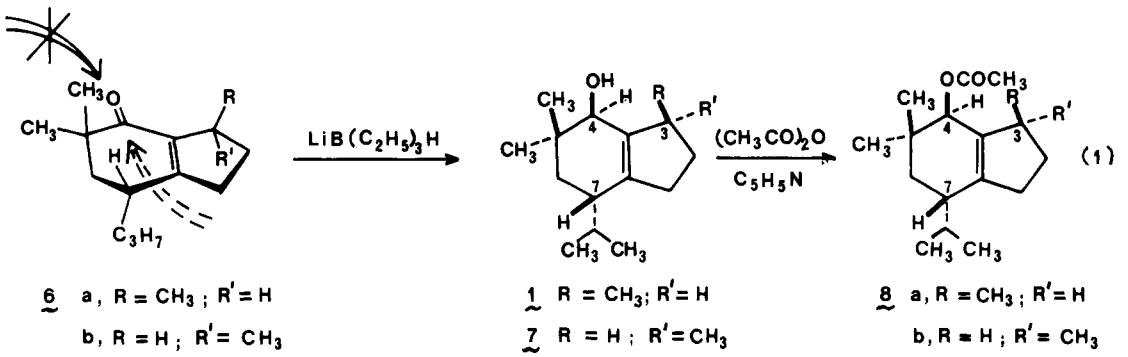
Scheme I[a]



[a] Key: (a) K_2CO_3, $CH_3CH{=}CHCH_2Br$, 97%; (b) Δ, 93%; (c) NaH, CH_3I, 85%; (d) BH_3; H_2O_2, NaOH; Jones, 73%; (e) PPA, 63%; (f) $LiAlH_4$; H_2, Pd-C, 97%; (g) Li, CH_3NH_2, t-C_4H_9OH; H^+; SiO_2 separation, 43% (44% conversion) from **4a**, 58% (94% conversion) from **4b**, **5a**:**5b** ≃ 1:2; (h) LDA, CH_3I, 2×, 82–85%. From **5a**: SiO_2 separation, **6a**:**6b** = 1:1.7; (i) $RhCl_3$, Δ, SiO_2 separation, 70–85%, **6a**:**6b** ≃ 1:1; (j) $LiB(C_2H_5)_3H$, 73%.



recovered more polar enone **6b** could now be equilibrated with rhodium chloride[7] in ethanol to give anew a separable mixture of enones **6a** and **6b** (~1:1 at equilibrium); through such recycling, an essentially complete conversion of the initial enone mixture to pure brasilenone could eventually be accomplished.

It was most gratifying that brasilenone thus obtained on treatment with lithium triethylborohydride[9] in tetrahydrofuran at −78 °C underwent the anticipated highly selective reduction and produced exclusively racemic brasilenol, mp 63–64 °C, which was readily identified through spectral comparison with the naturally derived material.

Predictably, lithium triethylborohydride reduction of the isomeric enone was also highly stereoselective and gave essentially a single alcohol (eq 1). In both the trans and cis enones the C-5 axial methyl group unquestionably exerts the dominant steric influence on the approach of the bulky hydride reagent, and hence the stereochemistry at C-4 and C-7 must be trans in both alcohols, which differ then only at C-3 (**1** and **7**, respectively). That brasilenol has, in fact, the cis and not the trans relationship at C-4 and C-4 could readily be demonstrated through NMR by comparing the Eu(fod)$_3$-induced proton shift data[10] for alcohols **1** and **7** and the anisotropic shielding effects[11] in the corresponding acetates **8a** and **8b**. Namely, in brasilenol (**1**) the eclipsed methyl group at C-3 experienced a europium-induced shift of 4.04 ppm while the C-3 proton underwent a displacement of 4.31 ppm; in 3-epibrasilenol (**7**), the methyl group and the proton showed the expected opposite relative behavior, with $\Delta\delta$ values of 1.46 ppm and 7.09 ppm, respectively.[12] Concordantly, the C-3 methyl group and proton in brasilenol acetate (**8a**) are shielded by 0.16 ppm and 0.19 ppm relative to those in brasilenol, whereas in the 3-epi series the corresponding $\Delta\delta$ values are 0.13 pm and 0.24 ppm.[13] *Brasilenol, therefore, is correctly depicted in formula 1.*

(8) At this point, the trans stereochemistry was assigned to this isomer solely on the basis of the stereochemistry previously proposed for brasilenone.[2a]

(9) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669–1671. Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1–12.

(10) Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, *73*, 553–588.

(11) Bhacca, N. S.; Williams, D. H. *Applications of NMR Spectroscopy in Organic Chemistry*; Holden-Day: San Francisco, 1964.

(12) Our conclusion is in agreement with that of Stallard, Fenical, and Kittredge,[2a] who made the C-3,C-4 cis assignment through comparison of the lanthanide-induced shift data for brasilenol and 4-epibrasilenol. The isopropyl methyl groups in both **1** and **7** showed small displacements in comparison with the shifts measured[2a] for these groups in 4-epibrasilenol, which confirms the C-4,C-7 trans stereochemistry in the two reduction products.

(13) Brasilenol acetate (**8a**) has also been isolated from *Aplysia brasiliana*.[2a]

This first synthesis of brasilenol, which fully confirms both the structure and relative stereochemistry of the compound, has been achieved in approximately 13 steps and 5% overall yield.

Experimental Section

Solvents were normally distilled prior to use. Tetrahydrofuran and ether were distilled from sodium hydride–lithium aluminum hydride and *tert*-butyl alcohol was distilled from calcium hydride. Reaction mixtures were generally stirred under a nitrogen or argon atmosphere. Analytical thin-layer chromatography was performed on Merck $60F_{254}$ (0.25 mm) sheets, which were visualized with molybdophosphoric acid in ethanol. Preparative thick-layer chromatography was effected with Merck $60GF_{254}$ silica gel. Merck 70–230 mesh silica gel 60 was employed for column chromatography. Melting points were obtained on a Büchi-Tottoli apparatus and are not corrected.

(*RS*)-4-Isopropyl-1-methoxy-2-(1-methyl-2-propenyl)benzene (3). To a solution of 20.0 g (147 mmol) of 4-isopropylphenol in 300 mL of acetone were added 20.7 g (150 mmol) of potassium carbonate and 17.0 mL (22.3 g, 165 mmol) of *trans*-crotyl bromide. The mixture was refluxed for 6 h, after which it was cooled and filtered. The solids were washed with 200 mL of acetone and the solvent was then removed from the combined filtrates. The product was isolated with pentane in the normal manner and was purified by vacuum distillation to give 27.1 g (97%) of 1-(2-butenyloxy)-4-isopropylbenzene: bp 100–102 °C (0.5 torr); IR 3020, 1610, 1580, 1510, 1240, 1180, 1010, 960, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.00 (AB q, J = 10 Hz, $\delta_a - \delta_b$ = 21.8 Hz, 4 H), 5.8 (m, 2 H), 4.4 (m, 2 H), 2.85 (septet, J = 6 Hz, 1 H), 1.71 (br d, J = 5 Hz, 3 H), 1.21 (d, J = 6 Hz, 6 H); mass spectrum, m/e 190 (M^+). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.12; H, 9.62. A solution of 25.7 g (135 mmol) of this ether in 250 mL of *N,N*-dimethylaniline was refluxed for 12 h under argon.[4] The reaction mixture was processed with pentane in the usual way and the product was purified by vacuum distillation to provide 24.0 g (93%) of 4-isopropyl-2-(1-methyl-2-propenyl)phenol: bp 110–112 °C (0.5 torr); IR 3450, 3060, 1630, 1605, 1495, 1460, 1425, 1260, 1195, 910, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.0–6.6 (m, 3 H), 6.4–5.9 (m, 1 H), 5.3–5.0 (m, 2 H) 4.91 (br s, 1 H), 3.68 (m, 1 H), 2.85 (septet, J = 7 Hz, 1 H), 1.39 (d, J = 7 Hz, 3 H), 1.21 (d, J = 7 Hz, 6 H); mass spectrum, m/e 190 (M^+). To a stirred suspension of 6.82 g (284 mmol) of oil-free sodium hydride in 280 mL of tetrahydrofuran was added dropwise at 0 °C a solution of 24.0 g (126 mmol) of the above phenol in 70 mL of tetrahydrofuran. After the gas evolution ceased, 40 mL (91.2 g, 643 mmol) of iodomethane was added and the reaction mixture was stirred at room temperature for an additional 2 h. Ice chips were then carefully added to the mixture and the product was isolated with pentane in the usual fashion and purified by distillation to give 22.0 g (85%) of the anisole **3**: bp 80–82 °C (0.5 torr); IR 3070, 1630, 1600, 1490, 1450, 1240, 1030, 905, 805 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.2–6.7 (m, 3 H), 6.3–5.8 (m, 1 H), 5.2–4.9 (m, 2 H), 4.1–3.7 (m, 1 H), 3.78 (s, 3 H), 2.85 (septet, J = 7 Hz, 1 H), 1.30 (d, J = 7 Hz, 3 H), 1.21 (d, J = 7 Hz, 6 H); mass spectrum, m/e 204 (M^+). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 81.96; H, 9.90.

(*RS*)-7-Isopropyl-4-methoxy-3-methyl-1-indanone (4a). To 25 mL (25 mmol) of a 1 M solution of borane in tetrahydrofuran at 0 °C was added 2.80 g (13.7 mmol) of anisole **3** in 20 mL of tetrahydrofuran. The resulting solution was stirred at room temperature for 5 h, whereupon 5.5 mL of absolute ethanol was added followed by 14 mL (42 mmol) of 3 M aqueous sodium hydroxide. After being cooled to 0 °C, the reaction mixture was treated dropwise with 9.6 mL (96 mmol) of 30% aqueous hydrogen peroxide and then stirred at 50 °C for 4 h. After the addition of 15 g of potassium carbonate, the product was isolated with pentane in the usual manner and purified by dry silica gel chromatography with 20% ethyl acetate in hexane to give 2.28 g (75%) of 3-methyl-3-(5-isopropyl-2-methoxyphenyl)propanol: IR 3350, 1600, 1240, 1030, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.2–6.7 (m, 3 H), 3.85 (s, 3 H), 3.7–3.2 (m, 3 H), 2.85 (septet, J = 7 Hz, 1 H), 1.8 (m, 3 H), 1.30 (d, J = 7 Hz, 3 H), 1.25 (d, J = 7 Hz, 6 H); mass spectrum, m/e 222 (M^+). A stirred solution of 3.20 g (14.4 mmol) of this alcohol in 50 mL of acetone at 0 °C was treated dropwise over 30 min with 22 mL of Jones reagent. The reaction mixture was stirred at 0 °C for an additional 1 h, whereupon 10 mL of 2-propanol was added. The removal of the solvents by rotary evaporation and normal processing of the residue with ethyl acetate then yielded 3.29 g (97%) of 3-methyl-3-(5-isopropyl-2-methoxyphenyl)propionic acid: mp 115–117 °C (ethyl acetate–hexane); IR 3500–2300, 1705, 1595, 1495, 1245, 1025, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.2–6.6 (m, 3 H), 3.81 (s, 3 H), 3.0–2.5 (m, 4 H), 1.30 (d, J = 7 Hz, 3 H), 1.18 (d, J = 7 Hz, 6 H); mass spectrum, m/e 236 (M^+). A 3.40-g (14.4 mmol) sample of this acid, comparable to that described above, in 34 g of polyphosphoric acid was stirred mechanically at 60 °C for 12 h. After being cooled to 0 °C, the reaction mixture was treated with ca. 100 g of ice and then stirred for several minutes. The crude product was isolated with pentane in the normal way and purified by dry silica gel chromatography with 5% ether in pentane to give 1.99 g (63%) of the indanone **4a**: mp 86–87 °C (ethyl acetate–hexane); IR 1695, 1270, 1040, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz), δ 7.10 (AB q, J = 8 Hz, $\delta_a - \delta_b$ = 20.1 Hz, 2 H), 4.15 (septet, J = 7 Hz, 1 H), 3.86 (s, 3 H), 3.40 (m, X of ABX, 1 H), 2.85 (2 d, B of ABX, J_{AB} = 18 Hz, 1 H), 2.20 (2 d, A of ABX, J_{AB} = 18 Hz, 1 H), 1.33 (d, J = 7 Hz, 3 H), 1.23 (d, J = 7 Hz, 3 H), 1.21 (d, J = 7 Hz, 3 H). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.77; H, 8.26.

(*RS*)-4-Isopropyl-7-methoxy-1-methylindane (4b). A 2.00-g (9.17 mmol) sample of indanone **4a** in 20 mL of tetrahydrofuran was added to a stirred suspension of 690 mg (18.2 mmol) of lithium aluminum hydride in 20 mL of tetrahydrofuran. After being stirred for 2 h, the mixture was carefully treated at 0 °C with 1.4 mL of water and 1.12 mL of 10% aqueous sodium hydroxide. After being allowed to warm to room temperature, the mixture was filtered and the solvent was removed by rotary evaporation to afford 2.00 g (99%) of 7-isopropyl-4-methoxy-3-methyl-1-indanol as an amorphous solid: IR 3325, 1600, 1265, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 6.95 (AB q, J = 8 Hz, $\delta_a - \delta_b$ = 26 Hz, 2 H), 5.35 (m, 1 H), 3.80 and 3.78 (2 s, 3 H), 3.7–3.1 (m, 3 H), 2.8–1.6 (m, 2 H), 1.5–1.1 (m, 9 H); mass spectrum, m/e 220 (M^+). A 1.00-g (4.6 mmol) sample of the above alcohol and 100 mg of 10% palladium on carbon in 30 mL of glacial acetic acid containing one drop of 70% aqueous perchloric acid were stirred under hydrogen for 2 h. Normal processing of the mixture with pentane gave the crude product, which was purified by dry silica gel chromatography with 5% ether in pentane to afford 907 mg (98%) of the indane **4b**: IR 1600, 1260, 1080, 800 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 6.84 (AB q, J = 8 Hz, $\delta_a - \delta_b$ = 28 Hz, 2 H), 3.80 (s, 3 H), 3.5–1.5 (m, 6 H), 1.23 (d, J = 7 Hz, 3 H), 1.21 (d, J = 7 Hz, 6 H); mass spectrum, m/e 204 (M^+). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.44; H. 9.96.

(3*RS*,7*RS*,*SR*)-1,2,3,5,6,7-Hexahydro-7-isopropyl-3-methyl-4*H*-inden-4-one (5a) and Δ^6-Isomer 5b. (A) Via Birch Reduction of Indanone 4a. In a 500-mL three-necked flask equipped with a dry ice condenser, a solution of 500 mg (2.29 mmol) of indanone **4a** in 40 mL of tetrahydrofuran and 60 mL of *tert*-butyl alcohol at −40 °C was diluted with 200 mL of dry methylamine and then treated with 1.39 g (200 mmol) of lithium in small pieces.[5] After the appearance of the coloration, the mixture was stirred at −40 °C for an additional 30 min, whereupon ca. 60 mL of *tert*-butyl alcohol was added to discharge the coloration, followed by 30 g of ammonium chloride. After the evaporation of the methylamine, the crude dienol ethers were isolated with pentane in the usual way and purified by dry chromatography (silica gel–2% triethylamine) with pentane to give 91 mg of the dienol ethers and 281 mg of recovered indanone **4a**. The dienol ethers were hydrolyzed by stirring for 5 min in ether–5% aqueous hydrochloric acid to provide after separation by dry silica gel chromatography with 5% ether in pentane 25 mg (13%, based on consumed **4a**) of enone **5a** and 58 mg (30%, based on consumed **4a**) of enone **5b**.

(B) Via Birch Reduction of Indane 4b. In an analogous manner, a solution of 500 mg (2.45 mmol) of indane **4b** in 50 mL of tetrahydrofuran, 100 mL of *tert*-butyl alcohol, and 300 mL of methylamine was treated at −40 °C with 1.50 g (216 mmol) of lithium and then stirred for 15 min.[5] Processing the mixture as above gave, in addition to 30 mg of **4b**, 89 mg (20%, based on consumed **4b**) of enone **5a** and 166 mg (38%, based on consumed **4b**) of enone **5b**. Enone **5a**: 1665, 1615, 1295, 1200, 1175, 1140,

940 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 3.3–1.3 (m, 11 H), 1.12, 1.10 (2 d, J = 7 Hz, 3 H), 1.09 (d, J = 7 Hz, 3 H), 0.81 (d, J = 7 Hz, 3 H). Enone **5b**: 3040, 1705, 1220, 1210, 1080, 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 5.35 (br t, J = 4 Hz, 1 H), 3.2–1.2 (m, 10 H), 1.06 (d, J = 6 Hz, 6 H), 1.2–0.8 (m, 3 H); mass spectrum, m/e 192 (M^+).

(3*RS*,7*RS*)-1,2,3,5,6,7-Hexahydro-7-isopropyl-3,5,5-trimethyl-4*H*-inden-4-one (6a) and 3*RS*,7*SR* Isomer 6b. (A) From Enone 5a. To a stirred solution of 42 mg (0.22 mmol) of enone **5a** in 2 mL of tetrahydrofuran under argon at −78 °C was added 0.24 mL (0.24 mmol) of a 1 M solution of lithium diisopropylamide in tetrahydrofuran.[6] After being stirred for 20 min, the reaction mixture was treated with 15 μL (34 mg, 0.24 mmol) of iodomethane and then stirred for an additional 1 h. The residue (50 mg) obtained on workup was dissolved in 3 mL of tetrahydrofuran and at −78 °C under argon treated with 0.27 mL (0.27 mmol) of the LDA solution and after 20 min with 16 μL (36 mg, 0.26 mmol) of iodomethane. After being stirred for an additional 1 h at −78 °C, the reaction mixture was processed with pentane in the usual way to yield the crude mixture **6a,b**. Separation of these enones was effected by preparative thick-layer chromatography with 5% ether in pentane (three developments: R_f(**6a**) 0.72, R_f(**6b**) 0.67) to yield 15 mg (31%) of enone **6a** and 26 mg (54%) of enone **6b**.

(B) From Enone 5b. Dimethylation[6] of 32 mg (0.17 mmol) of **5b** as described above in A for **5a** gave 30 mg (82%) of the Δ^6 isomer after purification by dry silica gel chromatography with 5% ether in pentane: IR 3040, 1700, 1020, 860 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 5.23 (s, 1 H), 1.2–0.9 (m, 15 H). A mixture of this material (30 mg, 0.14 mmol) and 0.7 mg (0.003 mmol) of rhodium chloride trihydrate in 26 μL of absolute ethanol was stirred under argon in a sealed tube at 100 °C for 24 h.[7] After being allowed to cool, the reaction mixture was diluted with pentane and filtered. The crude product was isolated with pentane and then purified by preparative thick-layer chromatography to give 21 mg (70%) of enones **6a** and **6b** (~1:1).

(C) From Enone 6b. A mixture of this material (30 mg, 0.14 mmol) and 0.8 mg (0.003 mmol) of rhodium chloride trihydrate[7] in 26 μL of absolute ethanol was stirred under argon in a sealed tube at 100 °C for 15 h, and an identical mixture was allowed to react for 30 h. In the former, 12 mg (40%) of **6a** and 13 mg (43%) of **6b** were isolated; in the latter, 11 mg (37%) of **6a** and 14 mg (47%) of **6b**. Enone **6a**: IR 1660, 1620, 1280, 1250, 1130 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 3.17 (m, 1 H), 2.3–2.0 (m, 3 H), 1.9–1.8 (m, 2 H), 1.6–1.2 (m, 3 H), 1.20 (s, 3 H), 1.15 (d, J = 6.9 Hz, 3 H), 0.96 (s, 3 H), 0.78 (d, J = 6.9 Hz, 3 H), 0.57 (d, J = 6.9 Hz, 3 H). This spectrum matched perfectly in every respect that of brasilenone from natural brasilenol. Anal. Calcd for $C_{15}H_{24}O$: M_r, 220.18272. Found: M_r (mass spectrum), 220.18325. Enone **6b**: mp 47–49 °C (pentane); IR 1660, 1620, 1295, 1250, 970, 920 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 3.07 (m, 1 H), 2.45–2.30 (m, 1 H), 2.15 (m, 1 H), 2.0–1.8 (m, 3 H), 1.6–1.3 (m, 3 H), 1.27 (d, J = 6.9 Hz, 3 H), 1.22 (s, 3 H), 0.97 (s, 3 H), 0.78 (d, J = 6.9 Hz, 3 H), 0.60 (d, J = 6.9 Hz, 3 H). Anal. Calcd for $C_{15}H_{24}O$: M_r, 220.18272. Found: M_r (mass spectrum), 220.18237.

(3*RS*,4*SR*,7*RS*)-2,3,4,5,6,7-Hexahydro-7-isopropyl-3,5,5-trimethyl-1*H*-inden-4-ol [(±)-Brasilenol (1)] and Acetate [(±)-Brasilenol Acetate (8a)]. To a 30-mg (0.14 mmol) sample of enone **6a** in 0.5 mL of tetrahydrofuran at −78 °C was added 0.20 mL (0.20 mmol) of a 1 M solution of lithium triethylborohydride in tetrahydrofuran. After being stirred at −78 °C for 40 min, the solution was treated with 90 μL of 3 M aqueous sodium hydroxide and 90 μL of 30% aqueous hydrogen peroxide and then allowed to warm to room temperature. The product was isolated with pentane in the usual way and purified by dry silica gel chromatography with 3% ether in pentane to give 22 mg (73%) of (±)-brasilenol (1): mp 63–64 °C (pentane); IR 3450, 1380, 1260, 1125, 1070, 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.01 (br s, 1 H), 2.76 (m, 1 H), 2.25–1.95 (m, 5 H), 1.6–1.2 (m, 4 H), 1.11 (d, J = 6.8 Hz, 3 H), 1.03 (s, 3 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.83 (s, 3 H), 0.67 (d, J = 6.8 Hz, 3 H).[2a] This spectrum corresponded perfectly to that of natural brasilenol: ^{13}C NMR ($CDCl_3$, 75.4 MHz) 142.0, 138.7, 77.7, 40.4, 39.0, 36.2, 35.5, 33.4, 30.7, 28.7, 27.9, 21.3, 20.1, 18.7, 16.3;[2a] mass spectrum, m/e 222 (M^+). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79; M_r, 222.19836. Found: C, 81.13; H, 11.77; M_r (mass spectrum), 222.19835.

A 14-mg (0.06 mmol) sample of (±)-brasilenol in 1.5 mL of acetic anhydride and 2.0 mL of pyridine was stirred at 40 °C for 15 h. Workup of the reaction mixture and purification of the product by dry silica gel chromatograpy with 3% ether in pentane gave 11 mg (66%) of (±)-brasilenol acetate (**8a**): IR 1740, 1370, 1240, 1020, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.38 (m, 1 H), 2.57 (br t, 1 H), 2.3–1.8 (m, 5 H), 2.09 (s, 3 H), 1.60–1.25 (m, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.92 (s, 3 H), 0.89 (d, J = 6.9 Hz, 3 H), 0.88 (s, 3 H), 0.68 (d, J = 6.9 Hz, 3 H).[2a] Anal. Calcd for $C_{15}H_{24}$: M_r, 204.18780. Found: M_r (mass spectrum), 204.18835 ($M^+ - CH_3CO_2H$).

(3*RS*,4*RS*,7*SR*)-2,3,4,5,6,7-Hexahydro-7-isopropyl-3,5,5-trimethyl-1*H*-inden-4-ol (7) and Acetate (8b). To an 18-mg (0.08 mmol) sample of enone **6b** in 0.3 mL of tetrahydrofuran at −78 °C was added 0.12 mL (0.12 mmol) of a 1 M solution of lithium triethylborohydride in tetrahydrofuran. After being stirred at −78 °C for 2 h, the solution was treated with 55 μL of 3 M aqueous sodium hydroxide and 55 μL of 30% aqueous hydrogen peroxide and then allowed to warm to room temperature. The product was isolated with pentane in the normal way and purified by dry silica gel chromatography with 3% ether in pentane to give 12 mg (66%) of alcohol **7**: IR 3400, 1385, 1365, 1260, 1080, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.96 (br s, 1 H), 2.85 (br s, 1 H), 2.39 (m, 1 H), 2.2–1.9 (m, 4 H), 1.7–1.1 (m, 4 H), 1.06 (s, 3 H), 1.05 (d, J = 6.8 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H), 0.81 (s, 3 H), 0.68 (d, J = 6.8 Hz, 3 H).

A 12-mg (0.05 mmol) sample of alcohol **7** in 1.5 mL of acetic anhydride and 2.0 mL of pyridine was stirred at 40 °C for 15 h. Workup of the reaction mixture and purification of the product by dry silica gel chromatography with 3% ether in pentane gave 10 mg (70%) of the acetate **8b**: IR 1740, 1365, 1235, 1020, 960, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.43 (m, 1 H), 2.61 (m, 1 H), 2.40 (m, 1 H), 2.2–1.9 (m, 4 H), 2.10 (s, 3 H), 1.65–1.25 (m, 3 H), 0.94 (s, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.89 (d, J = 6.9 Hz, 3 H), 0.86 (s, 3 H), 0.69 (d, J = 6.9 Hz, 3 H). Anal. Calcd for $C_{15}H_{24}$: M_r 204.18780. Found: M_r (mass spectrum), 204.18795 ($M^+ - CH_3CO_2H$).

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Registry No. (±)-**1**, 104485-27-0; (±)-**3**, 104395-26-8; (±)-**4a**, 104395-32-6; (±)-**4b**, 104395-33-7; (±)-**5a** (isomer 1), 104395-34-8; (±)-**5a** (isomer 2), 104395-35-9; **5b**, 104395-36-0; **6** (Δ^6 isomer), 104395-37-1; (±)-**6a**, 104485-25-8; (±)-**6b**, 104485-26-9; (±)-**7**, 104485-29-2; (±)-**8a**, 104485-28-1; (±)-**8b**, 104486-07-9; *trans*-crotyl bromide, 29576-14-5; (*E*)-1-(2-butenyloxy)-4-isopropylbenzene, 104395-27-9; 4-isopropyl-2-(1-methyl-2-propenyl)phenol, 104395-28-0; (±)-3-methyl-3-(5-isopropyl-2-methoxyphenyl)-propanol, 104395-29-1; (±)-3-methyl-3-(5-isopropyl-2-methoxyphenyl)propanoic acid, 104395-30-4; 7-isopropyl-4-methoxy-3-methyl-1-indanol, 104395-31-5; 4-isopropylphenol, 99-89-8.