Norditerpene alcohols in the bark of *Thuja plicata* Donn

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The neutral extractives from the bark of western red cedar (*Thuja plicata* Donn) contained, among other components, three alcohols. One was the known diterpene alcohol, isopimarinol, the other two were the new $\Delta^{8(14),15}$-4α- and $\Delta^{8(14),15}$-4β-hydroxy-18-norisopimaradienes. The syntheses of these two alcohols are described. The greater amount of the 4α compound found in nature, and its relative ease of synthesis compared to the 4β isomer, showed it to be formed preferentially.

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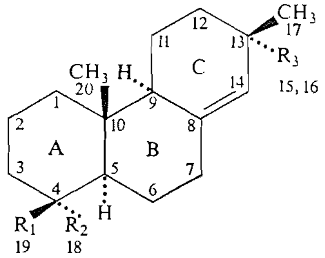
Introduction

The extraction of the outer bark of western red cedar (*Thuja plicata* Donn) with petroleum ether yielded 2.6% (1) of an oil. This has been fractionated and the neutral portion examined chromatographically. This paper describes the characterization and syntheses of three components of the neutral fraction.

Discussion

The neutral fraction of the petroleum ether solubles contained seven components as shown by thin-layer chromatography (t.l.c.). Three of these were new compounds (one ketone and two alcohols), two were known compounds, and the remainder were a hydrocarbon mixture and a fat mixture. One of the known compounds was isopimarinol[3] (**1**), a compound previously isolated from *Cryptomeria japonica* (3), and the other known compound was the ubiquitous β-sitosterol. The identity of **1** was the key to the structures of the two new alcohols. Compound **1** had an infrared (i.r.) spectrum identical with one from the material previously isolated from sugi (3). Comparison with a synthetic sample prepared by reduction of methyl isopimarate (**2**) showed identical nuclear magnetic resonance (n.m.r.) and undepressed mixture melting point. Compound **3** and **4** had spectra similar to **1**, except for the absence of the signals from the methylene carrying the hydroxyl group. The evidence supporting the formulation of compound **3** as $\Delta^{8(14),15}$-4α-hydroxy-18-norisopimaradiene and compound **4** as $\Delta^{8(14),15}$-4β-hydroxy-18-norisopimaradiene is now presented.



R_3 = vinyl
1 $R_1 = CH_3$; $R_2 = CH_2OH$
2 $R_1 = CH_3$; $R_2 = COOCH_3$
3 $R_1 = CH_3$; $R_2 = OH$
4 $R_1 = OH$; $R_2 = CH_3$

R_3 = ethyl
5 $R_1 = CH_3$; $R_2 = OH$
6 $R_1 = OH$; $R_2 = CH_3$
7 $R_1 + R_2 = CH_2$
8 $R_1 = CH_3$; $R_2 = CH_2OH$

The ultraviolet (u.v.) spectra of **1**, **3**, and **4** showed a single maximum at 209 mμ as expected from the unconjugated double bonds. The i.r. spectra showed bands at about 3080, 1640, 1410, 1000, and 906 cm^{-1}, attributed to a vinyl group and about 1660 and 820 cm^{-1} from a trisubstituted double bond. Hydroxyl group absorption in the near i.r. spectra of **1** was at 3642 cm^{-1}. Compounds **5** and **6**, which were the dihydroderivatives of **3** and **4**, absorbed at 3612 cm^{-1} and 3615 cm^{-1}. These data showed that **1** contained a primary hydroxyl group, and that **5** and **6** contained a tertiary hydroxyl group. Extinction coefficients calculated were 61, 30, and 41, respectively, and Bellamy (4) stated that primary alcohols absorbed at 3642 cm^{-1} and tertiary alcohols at 3618 cm^{-1} with extinction coefficients of 70 and 45.

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[3] We are following the nomenclature of Edwards and Rosich (2) who gave the names isopimarane and derivatives to compounds formerly called sandaracopimarane and derivatives.

The n.m.r. spectra of **1**, **3**, and **4** showed an ABX signal centered at 4.8 and 5.7 δ from the three protons of a monosubstituted double bond. The position of these signals suggested the $\Delta^{8(14),15}$ isopimaradiene configuration (2,5). However, Edwards and Rosich have shown similar vinyl absorption patterns from $\Delta^{8(9),15}$ pimaradiene and its 18- or 19-derivatives (2). These compounds also showed a broad singlet at about 5.2 δ arising from the proton on a trisubstituted double bond. The spectrum of compound **1** had a quartet from the C-18 methylene centered at 3.2 δ, and this indicated the equatorial configuration (6). Compounds **1**, **3**, and **4** each had three sharp singlets attributed to methyl groups. Since these were not coupled, the methyl groups were therefore all tertiary and the hydroxyl groups of **3** and **4** were probably on position 4. The absence of a signal from a proton on a carbinol in the spectra of **3** and **4** downfield from the methylene protons, showed that the hydroxyl groups were not secondary in these compounds.

The axial methyl groups at C-10 were at about 0.77 δ in the spectra of **1** and **3**. The signal shifted downfield to about 0.95 δ in **4**, showing an interesting effect with changes in structure. Table I shows the positions of the signals from the other two (C-17 and C-19) methyl groups in these compounds. These data indicated that compounds **3** and **4** were norditerpenes with the isopimaradiene configuration.

TABLE I

Chemical shifts of methyl groups in δ

Compound	C-20	C-19	C-17
1	0.79	0.86	1.02
3	0.75	1.08	1.02
4	0.91	1.13	1.01

Parent ion peaks in the low-resolution mass spectra of **1** and **3** to **6** were all visible at the calculated molecular weight. Empirical formulae were confirmed by high-resolution spectra of **1**, **5**, and **6**. The initial fragmentation mode appeared similar in all compounds; *i.e.* an initial loss of a methyl group (perhaps C-17), and loss of water in **3** and **4**. Table II summarizes the spectral data.

It was decided to synthesize the dihydroderivatives (compounds **5** and **6**) of compounds **3** and **4**. The synthesis of **5** was similar to the synthesis of $\Delta^{8(14)}$-4α-hydroxy-18-norpimarene by Grant *et al.* (7). Dihydroisopimaric acid was decarboxylated with lead tetraacetate (6) to a mixture of olefins and an acetoxy substituted compound. The desired product, the $\Delta^{4(19),8(14)}$ olefin **7** was separated by column chromatography on silver nitrate–alumina. Compound **7** was epoxidized (8) and then reduced with lithium aluminium hydride to give $\Delta^{8(14)}$-4α-hydroxy-18-norisopimarene (**5**). Compound **5** was identical (t.l.c. on silver nitrate–silica gel, mixture melting point, n.m.r. spectra) with the product from the hydrogenation of **3**.

The above mixture of hydrocarbons (from the decarboxylation of dihydroisopimaric acid) were examined on the gas chromatograph. They had the same retention times, on two different columns, as the mixture of hydrocarbons obtained from the dehydration of **5** and **6**. These data showed that the location of the hydroxyl group in **5** and **6**, and thus **3** and **4**, was on C-4.

Compound **6**, the dihydro derivative of **4**, was synthesized by the same method as used for the preparation of 4α- and 4β-hydroxy-18-norhibaene from erythroxylol A by Martin and Murray

TABLE II

Major peaks in the low resolution mass spectra*

Compound **1**	Compound **3**	Compound **4**	Compound **5**	Compound **6**
m/e	*m/e*	*m/e*	*m/e*	*m/e*
288 (15)	274 (50)	274 (44)	276 (5)	276 (6)
273 (11)	259 (22)	259 (36)	258 (6)	258 (6)
257 (54)	256 (50)	241 (15)	247 (42)	247 (20)
220 (15)	241 (42)	202 (15)	229 (21)	191 (12)
177 (17)	189 (53)	189 (49)	191 (12)	163 (16)
161 (34)	161 (44)	161 (49)	163 (24)	147 (16)
131 (42)	135 (97)	133 (47)	147 (15)	139 (19)
105 (63)	121 (45)	121 (71)	139 (17)	121 (100)
91 (64)	109 (83)	95 (50)	121 (75)	95 (65)
	95 (61)	81 (73)	95 (46)	81 (72)
			81 (50)	

*Starting from the parent ion peak, with the peak height in parentheses relative to a *m/e* 43 ion of 100 percent.

(9). Partial hydrogenation of **1** gave **8** which was reacted with chromium trioxide in acetic acid. The major product was the putative aldehyde. The t.l.c. in two solvent systems showed both **5** and **6** as minor products. The latter was isolated in 1% yield. Other evidence supporting structure **4** was the similarities for it (and **3**) with the spectral data reported (7) for the 4α- and 4β-hydroxy-18-norhibaenes. Thus the methyl group resonance reported in Table I for **4** agreed within 0.06 δ with the data for 4α-hydroxy-18-norhibaene, and within 0.05 δ for **3** and the 4β-isomer.

Experimental

Melting points were uncorrected. Infrared spectra were taken of carbon tetrachloride solutions with Perkin–Elmer 421 and Beckman DK-2 spectrophotometers. Nuclear magnetic resonance spectra were taken in deuteriochloroform solutions containing tetramethylsilane (δ = 0) with Varian A-60 or HA-100 instruments. Low-resolution mass spectra were taken on an Atlas CH-4 and high-resolution mass spectra on an AEI-MS9 double-focusing spectrometer. Thin-layer chromatography was on Merck silica gel G with dichloromethane developing solvent and nitric–sulphuric acid detecting reagent unless otherwise noted. Petroleum ether was the 65–100° fraction.

Isolation of Compounds

Petroleum ether solubles (3.60 g) from the extraction of western red cedar bark (1) were placed on a column (5 × 40 cm) of Woelm alumina (activity III). The column was eluted with petroleum ether for the first 400 ml, followed by mixtures of petroleum ether containing increasing amounts of benzene (10% more every 200 ml); fractions were collected every 50 ml and examined by t.l.c. Fractions 1–4, 498 mg, contained a straight-chain hydrocarbon mixture which was not examined further. Fractions 5–6, 71 mg, contained a fat also not examined. Fractions 11–12, 33 mg, contained an unknown ketone (m.p. 50°, λ_{max} 267 mμ) whose structure has not yet been determined. Fraction 13–16, 43 mg, contained compound **4**. Fractions 17–20, 54 mg, contained compound **1**. Fractions 21–24, 62 mg, contained compound **3**. Fractions 25–28, 85 mg, contained β-sitosterol, m.p. 137°, mixture m.p. undepressed with an authentic sample, also identical t.l.c. R_f values. Yields quoted above were those obtained after the compound had been purified via preparative-layer chromatography. Compounds **1**, **3**, **4**, in ethanol absorbed at 209 mμ in the ultraviolet (u.v.) region. They all had a vinyl signal in their n.m.r. spectra, with the AB portion centered at 4.80 δ and the X at 5.70 δ, with $J_{AB} = 2$, $J_{AX} = 10$, and $J_{BX} = 18.5$ Hz: also a broad singlet at 5.15 δ (W 1/2, 3.5 Hz) from the proton on C-14. Other spectral data are summarized in Tables I and II.

Isopimarinol (1)

Compound **1** $[\alpha]_D - 1.5°$ (*c*, 0.2 ethanol) had identical i.r. and n.m.r. spectra with isopimarinol, m.p. 43–45°, mixture m.p. undepressed with a sample synthesized by reduction of methyl isopimarate $[\alpha]_D - 7.9°$ (*c*, 1 ethanol); both had R_f 0.26.

Calcd. (mass spectrum) for $C_{20}H_{32}O$: 288.245303. Found: 288.243135.

$\Delta^{8(14),15}$-*4α-Hydroxy-18-norisopimaradiene (3) and* $\Delta^{8(14)}$-*4α-Hydroxy-18-norisopimarene (5)*

Compound **3** had R_f 0.20, spectra very similar to **1** (except methylene components) and crystallized from ethanol–water to needles, m.p. 100–101°. Compound **3** (20 mg) in ethanol (5 ml) plus platinum oxide (5 mg) was treated with hydrogen at 2 atm and room temperature for 10 min. After isolation, the product **5** crystallized as needles from acetone–water, m.p. 93–95°. Both **3** and **5** had similar R_f values and colour reactions (purple) on the chromatoplate. On silver nitrate–silica gel G plates, however, **3** hardly moved from the origin whilst **5** had R_f 0.2.

Calcd. (mass spectrum) for $C_{19}H_{32}O$ (**5**): 276.245303. Found: 276.244319.

$\Delta^{8(14),15}$-*4β-Hydroxy-18-norisopimaradiene (4) and* $\Delta^{8(14)}$-*4β-Hydroxy-18-norisopimarene (6)*

Compound **4** had R_f 0.31, spectra similar to **3**, and did not crystallize. It was hydrogenated to **6**, as above, which crystallized from ethanol–water as plates, m.p. 82–84°. R_f values were again similar; on the argentous plate, **6** had R_f 0.5 and **4** had 0.1.

Calcd. (mass spectrum) for $C_{19}H_{32}O$ (**6**): 276.245303. Found: 276.243768.

Synthesis of $\Delta^{8(14)}$-*4α-Hydroxy-18-norisopimarene (5)*

Dihydroisopimaric acid (1.5 g) in dry benzene (45 ml) and pyridine (3 ml) under nitrogen was treated with lead tetraacetate (3.26 g) with stirring at room temperature for 1 h and refluxing for 3 h. The mixture was filtered, the filtrate was washed with water, and the solvent was evaporated to yield a yellow oil (1.20 g) which was placed on a column of silver nitrate–silica gel (40 g, 10%). The column was first eluted with 1 l of petroleum ether to yield a fraction (330 mg) of an oil believed to be a mixture of $\Delta^{3,8(14)}$- and $\Delta^{4(5),8(14)}$-18-norisopimaradienes. Elution of the column with 1 l of ether–petroleum ether (1:9) gave the desired crude **7** (345 mg), recognized from the *exo*-methylene signals in its i.r. (890 cm^{-1}) and n.m.r. (4.40, 4.68 δ broad singlets) spectra. Further elution of the column with ether–petroleum ether (2:8) gave an unknown product containing an acetoxy group. The crude **7** was purified on a similar column to give pure $\Delta^{4(19),8(14)}$-18-norisopimaradiene (245 mg), $R_f = 0.75$ on argentous plates (petroleum ether developed) vs. R_f 0.95 for the first fraction eluted from the column.

Compound **7** (113 mg) in chloroform (8 ml) was treated with *m*-chloroperbenzoic acid (86 mg) at about 0° for 1 day. Removal of the acid left the crude epoxide (86 mg) which was dissolved in ether (5 ml) and added to a stirred solution of lithium aluminium hydride (120 mg) in ether (10 ml). The mixture was refluxed under nitrogen for 2 h and worked up in the usual manner. The product, 71 mg recrystallized from ethanol–water, had m.p. 91–94°, undepressed on admixture with **5**; i.r. and n.m.r. spectra and chromatographic behaviour all identical to **5**. Its mass spectrum is given in Table II.

Syntheses of $\Delta^{8(14)}$*-4β-Hydroxy-18-norisopimarene (6)*

Compound **8** (650 mg), chromium trioxide (200 mg), acetic acid (15 ml), and water (0.50 ml) were stirred 2 h at room temperature. The reaction mixture was taken up in ether and washed with sodium bicarbonate. After ether evaporation, the product (0.475 g) was fractionated chromatographically on a small column of silica gel (10 g) with petroleum ether going to ether as the eluant. Concentration of the fractions and further chromatographic purification of the appropriate ones on preparative layer plates of silica gel G (dichloromethane eluant) gave crude **6** (7 mg), m.p. 83–85°, mixture m.p. undepressed. The identity was confirmed by R_f values in two t.l.c. systems, and the position of the methyl groups signals in the n.m.r. spectrum of the synthesized **6**.

Dehydration of 5 and 6 and Gas-liquid Chromatography

Compound **5** (14 mg) and compound **6** were each treated with phosphoryl chloride (0.5 ml) and pyridine (1.5 ml) in sealed tubes at 125° for 3.5 h. The products were isolated in the usual manner and examined with the aid of the gas chromatograph. Compounds **5** and **6** both gave the same mixture of three hydrocarbons, believed to be the $\Delta^{3,8(14)}$-, $\Delta^{4,8(14)}$-, and $\Delta^{4(18),8(14)}$-18-norisopimaradienes. The same 3 were isolated from the decarboxylation of dihydroisopimaric acid by lead tetraacetate above. Gas chromatographic columns used were 5′ × 1/8″ 25% SE-30 on Gas Chrom. Q (4.3, 4.8, 5.2) at 225°, and 5′ × 1/8″ 3% OV-1 on Gas Chrom. Q (4.8, 5.9, 6.5) at 175°, retention time in min for the 3 hydrocarbons are given in parentheses. Nitrogen carrier gas at 25 ml/min was used and the flame ionization detector was at 300°. The 3 olefins from each experiment also had the same R_f values on silver nitrate impregnated thin-layer plates.

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