1-Hydroxyditerpenes from Two New Zealand Liverworts, *Paraschistochila pinnatifolia* and *Trichocolea mollissima*

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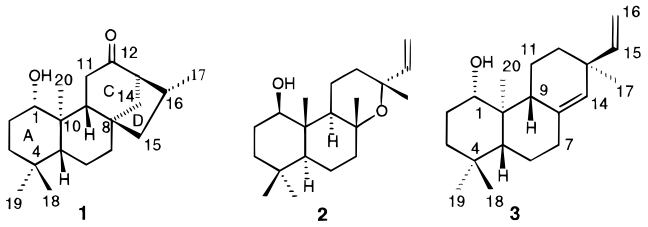
The isolation of two new 1-hydroxyditerpenoids from two species of New Zealand liverwort is described. *ent*-1α-Hydroxykauran-12-one (**1**) was obtained from *Paraschistochila pinnatifolia* and *ent*-1α-hydroxysandaracopimara-8(14),15-diene (**3**) from *Trichocolea mollissima*. The structures were assigned from the NMR spectra.

Liverworts have yielded a wide range of natural products, including some unique diterpenes.[1] We now report two new 1-hydroxylated diterpenes discovered during a search for bioactive natural products from the rich liverwort flora of New Zealand.[2] The liverworts studied were *Paraschistochila pinnatifolia* (Hook.) Schust. (family Schistochilaceae) and *Trichocolea mollissima* (Hook. f. and Tayl.) Gott. (family Trichocoleaceae). *P. pinnatifolia* grows on earth and logs in forests throughout New Zealand, in Tasmania, and on sub-Antarctic islands.[3,4] Asakawa *et al.* used GC−MS to examine an extract of *P. pinnatifolia* from New Zealand.[5] Three kaurane-type diterpene hydrocarbons ([M]$^+$ 272), a diterpene alcohol ([M]$^+$ 288), and an oxygenated diterpenoid ([M]$^+$ 304) were detected, but none was identified. *T. mollissima* is common throughout New Zealand in rain forests and beech forests.[4] A range of isoprenyl phenyl ethers have been isolated from various *Trichocolea* species including *T. mollissima* and *T. lanata*,[6] and a new diterpene, (12*E*)-3α-hydroxylabda-8(17),12,14-triene, has been reported from *T. pluma*.[7]

Reversed-phase flash chromatography of an extract of *P. pinnatifolia* gave most of the mass in the nonpolar fractions eluted with MeOH, MeOH−$CHCl_3$, and $CHCl_3$. Si gel TLC suggested that the fraction eluted with MeOH was mainly one compound, which was purified by chromatography over Sephadex LH-20 and Si gel columns. The mass spectrum of this compound **1** showed an apparent molecular ion at 304.2400 Da, appropriate for the formula $C_{20}H_{32}O_2$. Its IR spectrum revealed a hydroxyl adsorption at 3430 cm^{-1} plus a carbonyl adsorption at 1690 cm^{-1}, consistent with a six-membered ring ketone. The presence of one secondary hydroxyl was demonstrated by the preparation of a monoacetate with a lowest field ^{1}H-NMR signal at 4.51 ppm (1H, dd, J = 11,5 Hz).

The results of COSY, HMQC, and HMBC experiments (Table 1) were consistent with a kaurane skeleton[8] with the hydroxyl at C-1 and the ketone at C-12. The hydroxyl location was supported by the close agreement between the ^{13}C-NMR shifts for the A ring of **1** with those for 1β-hydroxymanoyl oxide (**2**).[9] Positioning of the ketone at C-12 was supported by comparison of ^{13}C-NMR and IR data for kauran-2,12-dione[10] with those for **1**.



The relative stereochemistry of **1** was determined from proton−proton coupling constants and NOE experiments (Figure 1). The coupling constants for H-1 (10 and 5 Hz) suggested that it was axial in a chair ring A. NOE interactions between H_3-19 and H_3-20, and between H-1 and H-5, supported a *trans* A−B ring junction. The coupling constants for H-5 (12 and 2 Hz) and an NOE interaction between H-5 and H-9 defined a chair conformation for ring B. An NOE interaction between H_3-20 and H-14S (2.23 ppm) showed these groups to be on the same face of ring B. These results showed that **1** had the relative stereochemistry of a kaurane,[8] but the configuration of the 17-CH_3 on C-16 had to be decided. Molecular modeling of the 16*R* and 16*S* configurations was carried out by conformational searching using MacroModel software[11] and the MM2 force field.[12] The predicted most stable conformation for 16*R* showed a coupling of 0.6 Hz from H-13 to H-16, while for the 16*S* configuration this coupling was 6 Hz. The predicted coupling constants from H-13 to the H-14 protons were 5 and 2 Hz for both configurations. Since the ^{1}H NMR spectrum of **1** (Table 1) showed a broad doublet for H-13 with a coupling of 5 Hz, the configuration at C-16 was assigned as *R* (Figure 1). The other observed ^{1}H-NMR coupling constants and NOE interactions for **1** (Table 1) were in good agreement with the predicted most stable conformation (Figure 1).

The absolute stereochemistry of **1** was determined from CD measurements. Applying the octant rule for cyclohexanones to the observed positive CD at 295 nm assigned **1** as *ent*-1α-hydroxykauran-12-one. While several *ent*-kauranoids have been isolated from liverworts, we could not find any references to kauranoids oxygenated (hydroxyl or ketone) at C-12.[1,13,14] A series of *ent*-kauranes α-acetylated at C-1 have just been reported.[15]

The second diterpene studied was isolated from *T. mollissima*. Reversed-phase flash chromatography of a crude extract gave one fraction, eluted with CH_3OH−$CHCl_3$ 3:1, with ^{1}H-NMR signals assignable to an isolated vinyl group. The major component was sepa-

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Table 1. NMR Data for 1α-Hydroxykauran-12-one (**1**)[a]

position	^{13}C	^{1}H	COSY[b]	HMBC[c]
1	81.9	3.26 (dd, 10, 5)	2	2, 3, 3′, 5, 9, 20
2	29.8	1.55		1, 3, 3′
		1.63		
3	39.8	1.22	1, 5	5, 18, 19
3′		1.33 (m, 13, 4)		
4	33.2			5, 18, 19
5	54.3	0.71 (dd, 12, 2)	1, 6, 7	3, 18, 19, 20
6	20.4	1.34		5, 7
6′		1.58		
7	40.1	1.58	5, 6	5, 15*S*
8	46.0			9, 11*S*, 13, 14*R*, 15*R*, 15*S*
9	57.8	1.68 (dd, 10, 2)	11*R*, 11*S*, 20 (w)	1, 5, 11*R*, 11*S*, 14*S*, 15*R*, 15*S*, 20
10	44.6			1, 9, 11*R*, 11*S* ,20
11*R*	37.4	2.46 (dd, 17, 10)	9, 11*R*, 20 (w)	9, 13
11*S*		3.65 (dd, 17, 1)	11*S*, 13, 20 (w)	
12	216.9			9, 11*R*, 11*S*, 13, 14*S*
13	59.9	2.29 (d, 5)	*14R*, 11*S*	11*S*, 15*R*, 17
14*S*	36.8	2.23 (dd, 13, 2)	14*R*, 15*R*	9, 13, 15*R*
14*R*		1.48 (ddd, 13, 5, 2)	14*S*, 13	
15*R*	50.2	1.96 (ddd, 13, 8, 1)	14*R*, 15*S*, 16	13, 14*S*, 17
15*S*		1.16 (dd, 13, 5)	15*R*, 16	
16	35.2	2.12 (m)	15*R*, 15*S*, 17	14*S*, 15*S*, 17
17	22.9	0.99 (d, 7)	16	13, 15*R*, 15*S*
18	33.0	0.83 (s)		5, 19
19	21.2	0.77 (s)		5, 18
20	12.5	0.92 (s)	9 (w), 11*R* (w)	1, 9

[a] In $CDCl_3$. [b] ^{1}H signals showing correlations to this ^{1}H signal, (w) defines weak correlations, italics for TOCSY correlation. [c] ^{1}H signals correlated to this ^{13}C.

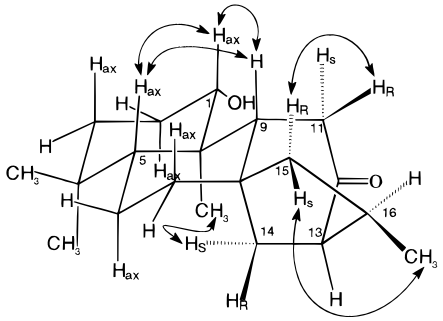

Figure 1. Most stable conformation of **1**, showing selected NOE interactions.

rated from this fraction by repeated chromatography on Si gel. The mass spectrum showed an apparent molecular ion at 288.2449 Da, appropriate for the formula $C_{20}H_{32}O$. The IR spectrum showed a strong O−H stretch and the NMR spectra showed two C=C bonds. The structure of this compound **3** was determined by a combination of NMR experiments, mainly with C_6D_6 (Table 2) as the solvent, since this gave a more dispersed ^{1}H-NMR spectrum than did $CDCl_3$.

The most common tricyclic diterpene dienes have a vinyl group at C-13 (see structure **3** for numbering) and a trisubstituted double bond in either the 7,8 or 8(14) positions,[8] although 9,11 double bonds are known.[16] The proton on the trisubstituted double bond in **3** showed only long-range (2 Hz) couplings, so an 8(14) location seemed likely. A COSY experiment confirmed this, showing allylic coupling from H-14 to H-7ax and to H-9 (see Table 2). H-12 eq also showed a 2 Hz coupling to H-14, interpreted as a "W"-coupling. ^{13}C data matched those for a sandaracopimaradiene with the vinyl group *cis* to H-9 rather than a pimaradiene with the epimeric arrangement at C-13.[17]

With the B and C rings assigned, the hydroxyl could only be in ring A. Since the carbinol proton showed just two vicinal couplings, of 5 and 11 Hz in C_6D_6, the hydroxyl had to be equatorial at either C-1 or C-3. The ^{13}C-NMR data for **3** showed a poor match with data reported recently for the A ring of a pimaradiene with an equatorial 3-OH[18] but did match the ^{13}C-NMR data for the A ring signals of **1** (Table 1) and **2**.[9]

Table 2. NMR Data for 1α-Hydroxysandaracopimara-8(14),15-diene (**3**)

position	^{13}C[a]	^{1}H[a]	COSY[a,b]	NOE[a,c]
1	79.4	3.41 (dd, 11, 5)	2	9, 2, 11
2	31.0	1.5−1.7 (m)	1, 3	NR[d]
3	40.7	1.3−1.5	2	NR
4	30.9?			
5	55.0	1.05 (dd, 12, 3)	6	NR
6	23.5	1.60 (m)	7, 5	NR
7ax	37.5	2.24 (m)	14, 9, 7eq, 6	NR
eq		2.50 (ddd, 14, 4, 2)	7ax, 6	14, 7ax, 6
8	138.0			
9	52.6	2.04 (ddt, 9, 6, 2)	14, 7ax, 11	NR
10	45.0			
11	23.4	2.25 (m)	9, 12	NR
12ax	36.1	1.64 (m)	12eq, 11	NR
eq		1.84 (dtd, 12, 4, 2)	12ax, 11, 14	
13	38.3			
14	130.8	5.67 (q, 2)	7ax, 9, 12eq	7eq
15	150.3	6.13 (dd, 17, 11)	16*Z*, 16*E*	16*E*, 17
16*Z*	110.9	5.31 (dd, 17, 2)	15	NR
E		5.22 (dd, 11, 2)	15	NR
17	26.6	1.41 (s)		NR
18	34.1	0.99 (s)		NR
19	22.5	0.98 (s)		NR
20	9.8	1.10 (s)		NR

[a] In C_6D_6. [b] ^{1}H signals showing correlations to this ^{1}H signal. [c] ^{1}H signals enhanced upon irradiation of this ^{1}H signal. [d] Not resolved, so not irradiated.

Thus, **3** is the previously unreported 1α-hydroxysandaracopimara-8(14),15-diene (**3**), with the common *ent* stereochemistry assumed. Variations in the coupling constants for H-1 between $CDCl_3$ and C_6D_6 suggested some conformational flexibility. This was explored by conformational searching of the proposed structure **3**.[11,12] The three most stable conformations predicted all had a chair A ring and were rotamers about the

13−15 bond. The observed coupling constants and NOE interactions in C_6D_6 (Table 2) were consistent with these conformations. The next two most stable conformations had a twist-boat A ring and again were rotamers about the 13−15 bond. The different vicinal coupling constants for H-1 in $CDCl_3$ could be explained by a higher population of the twist-boat conformations in this solvent.

Kaurane **1** showed weak cytotoxicity (IC_{50} 15 μg/mL) against the P-388 leukemia cells and weak activity against the yeast *Candida albicans*. Recently, other oxygenated *ent*-kauranoids have been reported as selectively cytotoxic to some human cancer cell lines.[19] Sandaracopimaradiene **3** did not show any activity in antimicrobial or cytotoxicity assays.

Experimental Section

General Experimental Procedures. All solvents were distilled before use and were removed by rotary evaporation at temperatures up to 45 °C. Octadecyl-functionalized Si gel (Aldrich) was used for reversed-phase flash chromatography, and Davisil, 35−70 μm, 150 Å was used for Si gel flash chromatography. TLC was carried out using Merck DC-Plastikfolien Kieselgel 60 F_{254}, visualized with an UV lamp, then by dipping in a vanillin solution (1% vanillin, 1% H_2SO_4 in EtOH), and heating. Mass and IR spectra were recorded on Kratos MS80 (electron impact, 70 eV) and Perkin-Elmer 1600 spectrometers, respectively. NMR spectra, in C_6D_6 or $CDCl_3$ solutions at 25 °C, were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C on a Varian VXR-300 spectrometer. Chemical shifts are given in ppm on the δ scale referenced to the solvent peaks C_6HD_5 at 7.40 and C_6D_6 at 128.70 or $CHCl_3$ at 7.25 and $CDCl_3$ at 77.00. Details of antimicrobial, antiviral, and P-388 assays have been given previously.[20] Our method of conformational searching has been described elsewhere.[21]

Plant Material. *P. pinnatifolia* and *T. mollissima* were collected from near Lake Ellery, on the west coast of the South Island of New Zealand, in June 1993 (Otago University Herbarium specimens *P. pinnatifolia* OTA 046628; *T. mollissima* OTA 046636).

Isolation of 1. Dried *P. pinnatifolia* (59 g) was extracted by blending with EtOH (300 mL and then 4 × 100 mL) to give a crude extract (2.5 g, P388 IC_{50} 18 μg/mL). This extract was submitted to flash chromatography over C18 (precoated on 2.5 g of C18, loaded on a 10 g C18 column) with a H_2O/MeOH/$CHCl_3$ gradient. The MeOH fraction (360 mg) was chromatographed over Sephadex LH20 (5 g), eluting with MeOH−$CHCl_3$ 1:1. The main fractions were combined (260 mg) and rechromatographed over a Si gel column (10 g) with a hexane/$CHCl_3$/EtOH gradient. A fraction eluted with $CHCl_3$ contained pure **1** (0.069 g).

***ent*-1α-Hydroxykauran-12-one (1):** yellowish wax; IR ($CDCl_3$) ν_{max} 3430, 1690 cm^{-1}; CD (dioxane) λ_{ext} 291 ($\Delta\epsilon$ 1.926), 299 ($\Delta\epsilon$ 1.869) nm; HREIMS *m/z* 304.2400 (58, M^+, $C_{20}H_{32}O_2$ requires 304.2402, 286.2288 (73, $M^+ - H_2O$), 271.2072 (64, $M^+ - H_2O - CH_3$), 161.1323 (24), 139.1157 (30), 123.1174 (43), 121.1014 (43), 107.0863 (90), 95.0870 (78), 94.0781 (86), 93.0699 (76), 91.0555 (41), 81.0736 (100); ^{1}H- and ^{13}C-NMR spectra see Table 1. Compound **1** gave a 25% cytotoxic effect against BSC-1 cells at 90 μg/disk; a 3-mm zone of inhibition of *C. albicans* at 90 μg/disk; and an IC_{50} of 15 μg/mL against P-388 leukemia cells.

Acetylation of 1. *ent*-1α-Hydroxykauran-12-one (**1**) (7 mg) was stirred overnight in pyridine (0.5 mL) and acetic anhydride (0.5 mL). After addition of CH_2Cl_2 (5 mL), the solution was washed with HCl (0.5 M; 4 × 3 mL), H_2O (5 mL), and brine and then dried over anhydrous $MgSO_4$. Evaporation gave the monoacetate, which was purified by chromatography over (20% EtOAc−hexane) to give *ent*-1α-acetoxykauran-12-one (6 mg) as an oil: IR ν_{max} ($CDCl_3$) 2950, 1700, 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.80 (3H, s, H-19), 0.83 (1H, t, J = 17 Hz, H-5), 0.85 (3H, s, H-18), 0.99 (3H, d, J = 8 Hz, H-17), 1.02 (3H, s, H-20), 1.16 (1H, dd, J = 14, 5 Hz, H-15), 1.49 (1H, ddd, J = 13, 5, 2 Hz, H-14), 1.70 (1H, d, J = 8 Hz, H-9), 1.93 (1H, ddd, J = 14, 9, 2 Hz, H-15), 2.20 (1H, d, J = 12 Hz, H-14), 2.29 (1H, d, J = 5 Hz, H-13), 2.41 (1H, dd, J = 17, 9 Hz, H-11), 2.71 (1H, d, J = 17 Hz, H-11), 4.51 (1H, dd, J = 11, 5 Hz, H-1); ^{13}C-NMR ($CDCl_3$) δ 215.1 (C-12), 170.7 (CH_3CO), 84.0 (C-1), 59.4 (C-13), 56.5 (C-9), 54.6 (C-5), 50.1 (C-15), 45.8 (C-8), 43.4 (C-10), 40.2 (C-7), 39.3 (C-3), 37.1 (C-11), 36.7 (C-14), 35.1 (C-16), 33.1 (C-4), 33.0 (C-18), 25.2 (C-2), 22.8 (C-17), 22.0 (CH_3CO), 21.4 (C-19), 20.2 (C-6), 13.2 (C-20); HREIMS *m/z* 346.2515 (1, M^+, $C_{22}H_{34}O_3$ requires 346.2508), 302.2254 (5, $M^+ - C_2H_4O$), 286.2298 (63, M^+ − AcOH), 272.2080 (25), 271.2041 (100, M^+ − AcOH − CH_3), 230.1700 (11), 217.1604 (16) 121.1018 (59), 107.0860 (62), 95.0842 (59), 93.0689 (53), 91.0535 (57), 81.0728 (56), 79.0585 (59).

Isolation of 3. Dried *T. mollissima* (31.5 g) was extracted with EtOH (1 × 600 mL and 3 × 150 mL) and $CHCl_3$ (1 × 100 mL) by homogenizing and filtering to give a dark green gum (1.4 g). Flash chromatography over C18 (1.4 g precoated on 5.6 g of C18, loaded on a 14 g C18 column) was developed in 20 mL steps from H_2O through CH_3OH to $CHCl_3$. The fraction eluted with CH_3OH−$CHCl_3$ 3:1 (brown oil, 181 mg) was precoated onto Si gel (0.3 g) and loaded onto a column of Si gel (4 g). This column was developed with hexane, 9:1, 3:1, 1:1, and 1:3 hexane:EtOAc, and EtOAc (4 × 3 mL of each). Fraction 10 (yellow solid, 12 mg), eluted with 3:1 hexane:EtOAc, was mainly one component by Si TLC. This compound was purified by a further stage of chromatography on a Si gel column (2 g), developed with hexane−EtOAc 19:1. Fractions eluted from 10 to 20 mL were combined to give pure **3** (3 mg).

***ent*-1α-Hydroxysandaracopimara-8(14),15-diene (3):** colorless wax; Si gel TLC R_f 0.6 (3:1 hexane: ethyl acetate); $[\alpha]_D$ +4°, $[\alpha]_{577}$ +7, $[\alpha]_{546}$ +5, $[\alpha]_{535}$ −10, $[\alpha]_{405}$ −7 (*c* 0.5; $CHCl_3$); IR ν_{max} (film) 3401, 3090, 2943, 1632, 1600, 1458, 1387, 1153, 1076, 1017, 989, 908, 859 cm^{-1}; HREIMS (70 ev) 288.2453 (64, M^+, $C_{20}H_{32}O$ requires 288.2453), 273.2208 (50, $M^+ - CH_3$), 270.2336 (47, $M^+ - H_2O$), 255.2117 (81), 242.2026 (32), 187.1484 (29), 173.1336 (31), 159.1187 (29), 152.1199 (85), 147.1158 (40), 145.1004 (40), 139.1127 (54), 136.1247 (43), 135.1170 (62), 134.1089 (43), 133.1018 (62), 131.0861 (42), 123.1186 (34), 122.1096 (31), 121.1027 (85), 120 (29), 119 (65), 117 (44), 109 (40), 107 (67), 105 (84), 95 (51), 93 (82), 91 (100), 81 (60), 79 (64), 77 (48); ^{1}H-NMR ($CDCl_3$) δ 0.83 (6H, s, H-18 and H-19), 0.86 (3H, s, H-20), 0.99 (1H, dd, J = 12, 2 Hz, H-5), 1.04 (3H, s, H-17), 2.01 (1H, br td, J = 13, 6 Hz, H-7ax), 2.25 (1H, ddd, J = 14, 5, 2 Hz, H-7eq), 3.46 (1H, dd, J = 9, 7 Hz, H-1), 4.86 (1H, dd, J = 11, 1 Hz, H-16), 4.91 (1H, dd, J = 18, 1 Hz, H-16), 5.25 (1H, q, J = 2 Hz, H-14), 5.77 (1H, dd, J =

18, 11 Hz, H-15); ^{13}C-NMR ($CDCl_3$) δ 149.3 (C-15), 136.8 (C-8), 129.7 (C-14), 109.8 (C-16), 79.2 (C-1), 54.2 (C-5), 51.5 (C-9), 44.1 (C-10), 39.8 (C-3), 37.1 (C-13), 36.3 (C-7), 34.7 (C-12), 33.2 (C-18), 29.9 (C-2), 25.6 (C-17), 22.5 (C-6), 22.4 (C-11), 21.7 (C-19), 8.8 (C-20); ^{1}H- and ^{13}C-NMR spectra (C_6D_6) in Table 2. Compound **3** had an IC_{50} against P388 leukemia cells of >25 μg/mL and gave neither antimicrobial effects nor cytotoxicity against BSC cells, at 60 μg/disk.

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