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Waihoensene. A New Laurenene-Related Diterpene from *Podocarpus totara var waihoensis*

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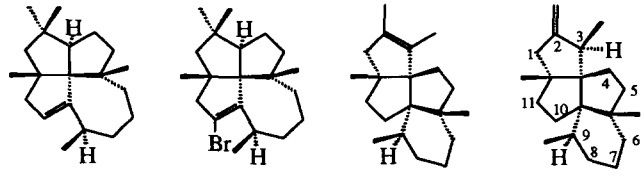
Abstract: New natural sources are reported for the unique rosettane diterpene, (-)-lauren-1-ene (**1**) along with the structure of the first laurenene-related plant metabolite. This new compound (**4**), isolated from the New Zealand podocarp, *Podocarpus totara var waihoensis* and named waihoensene, has a perhydro-4H-pentaleno[6a,1-*c*]indene ring system. Waihoensene is a double bond position isomer of a compound which has been formed previously by acid treatment of laurenene. © 1997 Elsevier Science Ltd.

Lauren-1-ene (**1**) holds a special place among the diterpenes as it is the only naturally occurring compound which has a rosettane ring system[1]. Despite being reported from the New Zealand rimu tree, *Dacrydium cupressinum*, some 18 years ago[2,3], it is particularly surprising that it has not since been identified from any other natural source. Furthermore, no structurally related natural products have been isolated. Laurenene has been regarded as a particularly challenging synthetic target and total syntheses have been achieved on four occasions[4]. In more general terms, rosettanes have attracted attention as synthetic targets as the central carbon has the potential to be progressively flattened by reducing the sizes of the four rings radiating out from it, or by introducing multiple bonds around the periphery[5]. Although the [5.5.5.7]rosettane system found in laurenene does not induce such a high degree of structural deformation, X-ray analysis of 2-bromolauren-1-ene (**2**)[3] revealed central bond angles ranging from 100.3 to 118.9°.



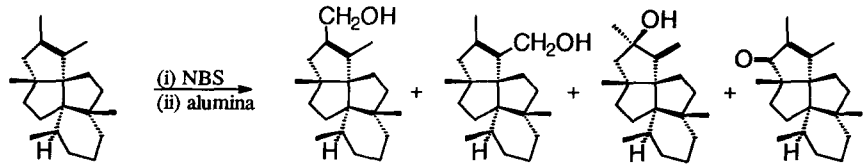
(**1**) (**2**) (**3**) (**4**)

Associated with this inherent strain is a strong tendency towards structural rearrangement. Treatment of (**1**) with various acids has given rise to compounds with four new carbon frameworks[6]. Of particular significance here is the major product (**3**) from the reaction of (**1**) with formic acid in boiling chloroform[2,7], whose structure is closely related to that of the new metabolite, waihoensene (**4**).

GC/MS studies of the foliage oils of 36 specimens of the New Zealand conifer, *Podocarpus hallii*, revealed high levels of a range of diterpenes with compositions varying widely from tree to tree. Significantly, nine of the samples analysed contained measurable levels of lauren-1-ene (0.2-2.9% of total diterpenes). Laurenene isolated from three of the trees tested proved to be identical in all respects to that obtained previously from *D. cupressinum*. Examination of *P. nivalis*, *P. totara* and *P. totara var waihoensis* revealed similar variability of diterpene composition and specimens of each species containing lauren-1-ene were noted. The level of (**1**) reached 60.7% of the total diterpenes in one specimen of *P. totara*.

The samples of *P. totara var waihoensis* which contained high levels of lauren-1-ene (35-50% of total diterpenes) also contained a further component whose GC and MS data matched none of our reference compounds. ^{1}H and ^{13}C NMR results, coupled with MS measurements led to the conclusion that this compound, waihoensene, was a tetracyclic diterpene containing a 1,1-disubstituted double bond and four methyl groups, two of which were attached to quaternary centres and two to tertiary carbons[8]. Such a structural combination has not been encountered previously in a naturally occurring diterpene. Waihoensene was obtained at a level of 5% of the total diterpenes in one specimen, but isolation proved difficult due to the co-occurrence of a range of other diterpene hydrocarbons. Much of the NMR spectral analysis and the chemical transformations undertaken were performed on a sample which contained *c.a.* 25% of rimuene as an impurity. Ultimately, however, a small sample (1.8 mg) free from other diterpenes was isolated by a sequence of chromatographic separations, culminating in centrifugal chromatography on a silver nitrate impregnated silica plate.

The fact that waihoensene was always present in trees with a relatively high level of laurenene, coupled with a strong similarity between the ^{13}C NMR spectrum of waihoensene and that of the laurenene rearrangement product (**3**)[6], hinted that waihoensene may be structurally related to laurenene. This hypothesis was borne out by more detailed NMR studies. ^{1}H and ^{13}C NMR assignments were established by standard methods, and an HMBC study disclosed that the carbon skeleton was indeed as shown in structure (**4**). Attempted epoxidation of (**4**) yielded a mixture of two compounds which we were unable to separate. Nonetheless, it appeared from the ^{1}H and ^{13}C NMR spectra that the major compound was the allylic alcohol (**5**). This compound was subsequently synthesised from the laurenene rearrangement product (**3**) by reaction with N-bromosuccinimide followed by passage of the mixture of crude bromides through an alumina column. Other products of this conversion were the allylic alcohols (**6**) and (**7**) and the unsaturated ketone (**8**) (Scheme 1).



(**3**) (**5**) (**6**) (**7**) (**8**)

Scheme 1.

This chemical correlation between (**3**) and (**4**) established the relative configuration of waihoensene at all stereogenic centres except for that allylic to the double bond (C-3). The orientation at this center was determined by ^{1}H NMR NOE difference experiments where a reciprocal enhancement involving both H-3 and the remaining methine proton, H-9 was obtained. Thus waihoensene is (3α,3a*R**,5aα,9α,9a*R**,11aα)-3,5a,9,11a-tetramethyl-1,2,3,5,5a,6,7,8,9,10,11,11a-dodecahydro-4H-pentaleno[6a,1-*c*]indene. The absolute stereochemistry has not been determined but the sample isolated was dextrorotatory.

A comprehensive conformational search of (**4**) (Macromodel/MM2*)[9] revealed two low energy conformers. Both are similar (Figure 1) except for the conformation of the six-membered ring. The lower energy form has a twist boat ring while another form with a chair ring bearing an axial methyl group is calculated to be 1.2 kcal mol^{-1} higher in energy. Both forms have H-3 and H-9 in close proximity (2.12 and 2.17Å respectively) but only the form with the chair ring has H-3 close to one of the C-8 hydrogens (2.16Å). The observation of a moderate enhancement of the H-8 NMR signal upon irradiation of H-3 suggests that the chair conformation contributes significantly to the solution structure of (**4**).

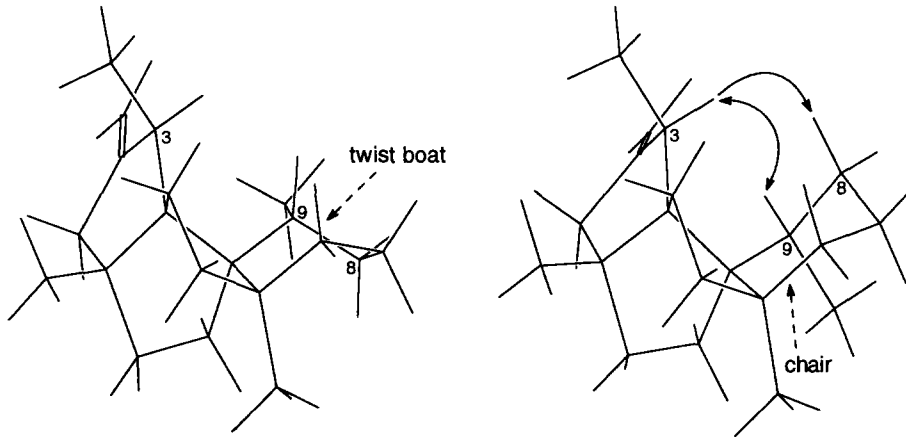


Figure 1. Low energy conformations of 2 showing key NOE.

All evidence so far indicates that waihoensene is a genuine metabolite. Although it was isolated from a steam distillate, GC and ^{1}H NMR studies show that it is also present in cold hexane extracts of the foliage. Despite the fact that lauren-1-ene is readily rearranged under acidic conditions, we have found no evidence for the formation of waihoensene during these transformations and, to date we have been unable to interconvert (**3**) and (**4**) by acid treatment. Indeed, the shape of (**3**) is such that protonation at C-3 from the *si*-face to generate the correct C-3 stereochemistry for (**4**) is highly improbable, and we have found that (**3**) is quite resistant to further transformation under acidic conditions. The discovery of waihoensene is significant on two counts; its skeleton is unique among the known diterpenes, and it is the first metabolite to be discovered whose structure can be related readily to that of lauren-1-ene.

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8. Waihoensene had GC retention indices: on DB-1; 1917 (170°), 1441 (190°); on CW20M 2201 (170°). $[\alpha]_D^{22}$ = +43.9° ($CHCl_3$; *c* 0.09). IR (GC-IR): 3075, 1655, 880 ($C=CH_2$) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.89 (d, *J*=7 Hz, 9-CH_3); 0.99 (s, 11a-CH_3); 1.00 (s, 5a-CH_3); 1.02 (d, *J*=7 Hz, 3-CH_3); 1.12 (m, H-6); 1.15 (m, H-5); 1.25 (m, H-11); 1.27 (m, H-5); 1.36 (m, H-8); 1.42 (m, H-7); 1.43 (m, H-11); 1.50 (m, H-4); 1.54 (m, H-10); 1.55 (m, H-7); 1.56 (m, H-6); 1.64 (m, H-4); 1.79 (m, H-9); 2.20 (br.s., *J*=1 Hz H-2); 2.69 (q, *J*=7, 3 Hz, H-3a); 4.69 (q, *J*=2 Hz, 2-CH_2). ^{13}C NMR ($CDCl_3$): δ 17.61, C-7; 19.23, 3-CH_3; 19.90, 9-CH_3; 25.06, 11a-CH_3; 25.42, 5a-CH_3; 28.75, C-4; 30.35, C-10; 30.55, C-8; 31.93, C-9; 36.03, C-6; 40.98, C-11; 42.07, C-5; 43.92, C-5a; 44.76, C-3; 48.12, C-1; 52.58, C-11a; 60.50, C-9a; 68.35, C-3a; 102.96, 2-CH_2; 159.70, C-2. MS: *m/z* 272 (M) (4), 257 (14), 203 (35), 175 (6), 161 (9), 147 (14), 134 (45), 120 (29), 121 (32), 105 (44), 91 (44), 79 (33), 67 (42), 55 (40), 41 (100). HREIMS (M^+): Found 272.25082. Calc. for $C_{20}H_{32}$ 272.25040. All other compounds reported gave satisfactory microanalytical and spectral data.
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