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SESQUITERPENES FROM *PERNETTYA FURENS*

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Key Word Index—*Pernettya furens*; Ericaceae; hierba loca; sesquiterpene carboxylic acid; sesquiterpene alcohol; sesquiterpene aldehyde; pernetic acid A–E; pernetol; pernetal; modified cadalane skeleton.

Abstract—The novel sesquiterpene carboxylic acids, pernetic acid A–E, a new sesquiterpene alcohol, pernetol, a new sesquiterpene aldehyde, pernetal, and pernetic acid A methyl ester, were isolated from the aerial parts of *Pernettya furens*. The structures were established by spectral and X-ray analysis. Pernetic acids D and E have a novel *cis* hydrindane skeleton presuming the oxidative modification from the cadalane skeleton.

INTRODUCTION

The fruits of *Pernettya furens*, called hysh-hued or hierba loca in Chile, are toxic to humans causing mental confusion and madness [1]. While the folklore use is known a little in the southern region of Chile, no phytochemical investigations have been made on this plant [2]. In our current investigations aimed at identifying the chemical constituents of *P. furens*, eight novel sesquiterpenes were isolated from the aerial parts and their structures determined by chemical and spectral methods.

RESULTS AND DISCUSSION

Three low field carbon signals at δ172.4, 143.2, and 130.0, and a vinyl proton signal at 7.41, in addition, the disappearance of a proton signal at 12.04 following D_2O addition, indicated the presence of an $\alpha\beta$-unsaturated carboxylic acid group in pernetic acid A (**1**), which was also corroborated from IR and UV spectra. The presence of a tertiary OH group was supported from a proton signal at δ4.11, a quarternary carbon signal at 75.2, and an intense fragment ion peak at *m/z* 234. The presence of an isopropyl group was corroborated from the one proton quartet of quartets at δ2.17, obviously coupled to two Me protons, together with the strong fragment ion peaks at *m/z* 191 and 43. The assignment of all proton signals and the conformation of the basic *cis*-decalin skeleton of **1** was deduced from extensive ^{1}H NMR double resonance experiments. The large coupling constant ($J_{1\alpha,10\beta}$ = 12 Hz) suggested an antiperiplanar arrangement of H-1α and H-10β. Similarly, the large coupling constant ($J_{9\alpha,10\beta}$ = 13 Hz) also indicated an antiperiplanar arrangement of H-10β and H-9α. The coupling constant ($J_{1\alpha,6\alpha}$ = 5 Hz) suggested a *cis*-axial equatorial relationship between H-1α and H-6α. The W-shaped long range coupling ($J_{6\alpha,8\alpha}$ = 3 Hz) between H-6α and H-8α suggested a 1,3-diequatorial relationship of these protons. The magnitudes of the coupling constants suggested a chair conformation for ring B. The small coupling constants (J = 3 Hz) of H-1α and the protons at C-2 indicated a synperiplanar arrangement, and the large coupling constants ($J_{2\alpha,3\beta}$ = 12 Hz) indicated an antiperiplanar arrangement of H-2α and H-3β. The configuration of the C-7 OH group was formulated as β-equatorial on the basis of the significant $\Delta\delta$ ppm values observed on the protons of 8α, 8β, and 6α. The stereochemical structure of **1** is 9,10-dihydro-7β-hydroxy-muurol-4-en-14-oic acid, and the absolute configuration (1S,6R,7S,10R) was concluded from biogenetic comparison with **5** and **6**.

The IR and UV spectra of compound **2** suggested the presence of a OH group and an $\alpha\beta$-unsaturated ester moiety. The ^{1}H NMR spectrum of **2** was strikingly similar to that of **1** except for the presence of a OMe Me proton signal at δ3.72. The structure of **2** was finally confirmed by spectroscopic comparison with the Me ester of **1**; the two compounds were identical.

The presence of an isopropenyl group in pernetic acid B (**3**) was corroborated from two low field carbon signals at δ111.3 and 146.6, the exo-methylene and a vinyl methyl proton signals, together with an intense fragment ion peak at *m/z* 41. The presence of an $\alpha\beta$-unsaturated carboxylic acid moiety was again clearly confirmed from the spectroscopic data. Extensive ^{1}H NMR double resonance experiments indicated that the structure of **3** was closely related to that of **1** except for the configuration at C-7. The β-equatorial disposition of an isopropenyl group was deduced from the magnitudes of the coupling constants among the four protons. The small coupling constants ($J_{6\alpha,7\alpha}$ = 2 Hz, $J_{8\alpha,7\alpha}$ = 3.1 Hz) indicated a *cis*-equatorial axial relationship of H-6α and H-7α, and of H-8α and H-7α. The large coupling constant ($J_{7\alpha,8\beta}$ = 12.7 Hz) indicated a *trans*-diaxial relationship of H-7α and H-8β. The structure of **3** was thus formulated as (1S,6S,7R,10R)-amorph-4,11-dien-14-oic acid.

Pernetic acid C (**4**) exhibited a similar mass spectrum to that of **3**. The presence of an isopropenyl group and of an $\alpha\beta$-unsaturated carboxylic acid moiety was confirmed by the spectroscopic data. However, the chemical shifts in the

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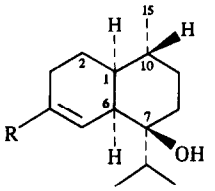
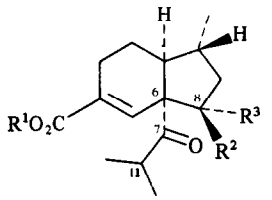
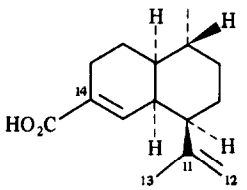


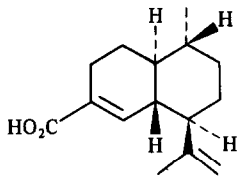
1 R = CO_2H
2 R = CO_2Me
7 R = CH_2OH
8 R = CHO



5 R^1 = H, R^2 = H, R^3 = OH
6 R^1 = H, R^2 = OH, R^3 = H
9 R^1 = $CH_2COC_6H_4Br$, R^2R^3 = O
10 R^1 = Me, R^2 = H, R^3 = OH
10a R^1 = Me, R^2R^3 = O
11 R^1 = Me, R^2 = OH, R^3 = H



3



4

^1H and ^{13}C NMR spectra of **4** were clearly different from those of **3**, and furthermore, the sign of the optical rotation of **4** was opposite to that of **3**. The antiperiplanar relationships among the four protons, H-1α–H-6β–H-7α–H-8β, were indicated from the large coupling constants ($J_{1\alpha,6\beta}$ = 11.5 Hz, $J_{6\beta,7\alpha}$ = 11.5 Hz, $J_{7\alpha,8\beta}$ = 13 Hz). Similarly, the large coupling constants ($J_{8\beta,9\alpha}$ = 13 Hz, $J_{9\alpha,10\beta}$ = 10 Hz) also suggested the antiperiplanar relationships among the three protons, H-8β, H-9α and H-10β. Based on the above observations, the structure of **4** was concluded as the following: ring B held a preferred chair conformation, the isopropenyl group at C-7 had a β-equatorial orientation and the stereochemistry of the ring junction should be *trans*. Thus, the structures of **3** and **4** were identified as a pair of isomers differing in the configuration at C-6. The stereochemical structure of **4** was therefore formulated as (1S,6R,7R,10R)-cadin-4,11-dien-14-oic acid.

CD spectra of **3** and the dihydroderivative **3a** showed the inverse Cotton effects to those of **4** and **4a**. Since the magnitude of ε values of **3** and **4** in the UV spectra was reasonably large, the carboxylic acid group may not be sterically hindered.* If the stereostructures predicted from the NMR analysis were divided into a quadrant by the carbonyl nodal plane, where the C-4–C-5 double bond was coplanar, and a perpendicular symmetry plane was drawn through C-4–C-5, the residual structural unit of **3** or **3a** appeared in the inverse quadrant to that of **4** or **4a** (Fig. 1).† Thus, the opposite Cotton effects may be explained by the structural difference around the αβ-unsaturated carboxylic acid chromophore. Furthermore, in this limited case the signs of the Cotton effects at the transition bands 242–256 nm $n\pi^*$ and 220–226 nm $\pi\pi^*$ seemed to be correlated to the absolute configuration.‡

Pernetic acid D (**5**) and E (**6**) exhibited the same $[M]^+$ peak at *m/z* 266. The presence of an αβ-unsaturated carboxylic acid moiety in **5** and **6** was indicated from the spectroscopic results. The presence of a 2-methyl propionyl group was confirmed from the following results. A carbon signal at δ215.1 was assigned to the C-7 ketone group, which was indicated from the IR absorption at 1700 cm^{-1} (sh). Two secondary Me groups were coupled to the one proton double quartets at δ2.96 (H-11). The strong fragment ion peaks at *m/z* 71 and 195 were due to cleavage of the C-6–C-7 bond. The hydrindene skeleton was suggected from the intense fragment ion peaks shown in Scheme 1. In addition, PCC oxidation of Me ester **10** or **11**, in which the same oxidation product **10a** exhibited a new carbonyl absorption at 1740 cm^{-1}, also demonstrated the hydrindene skeleton. The position of the OH group was proved by extensive double resonance experiments, the results being summarized in the partial structures shown in Fig. 2. The configurations of the C-8 OH group were supported from the following arguments. The appearance of lower field chemical shifts of H-1α and H-9α in **5** was due to the effect of the α oriented C-8 OH group. In comparison, the lower field chemical shift of H-10β in **6** was due to the effect of a β oriented C-8 OH group, and also the lower field chemical shift of H-8α in **6** was due to the neighboring C-7 carbonyl group. The *cis*

*CD double bond/carbonyl group chirality rule, applied for the ene lactones [3], could not be applied in these cases.

†The increment of the rotatory strength at 194–195 nm in **3** and **4** must be due to the contribution of isopropenyl double bond group.

‡In general, the prediction of absolute configuration from the sign of Cotton effects must be done with great care when the Cotton effects are based on a single chiral chromophore.

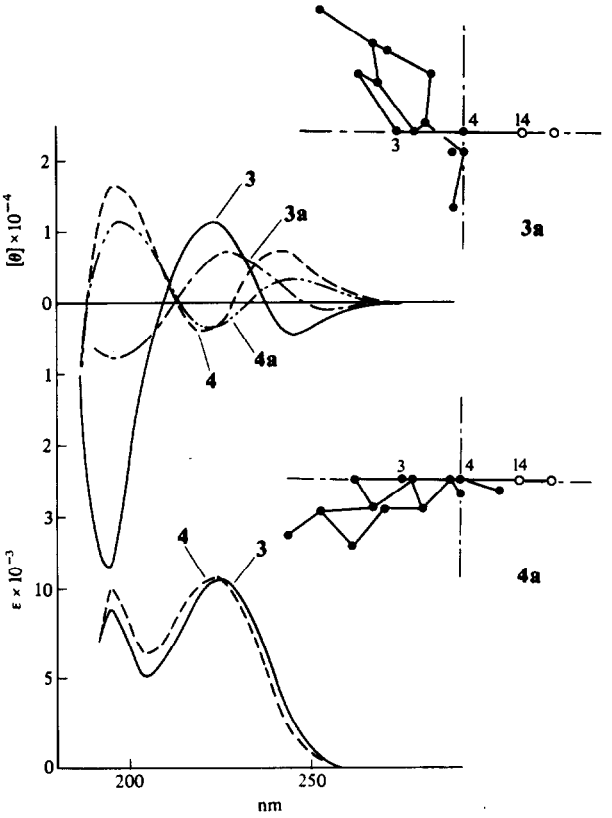
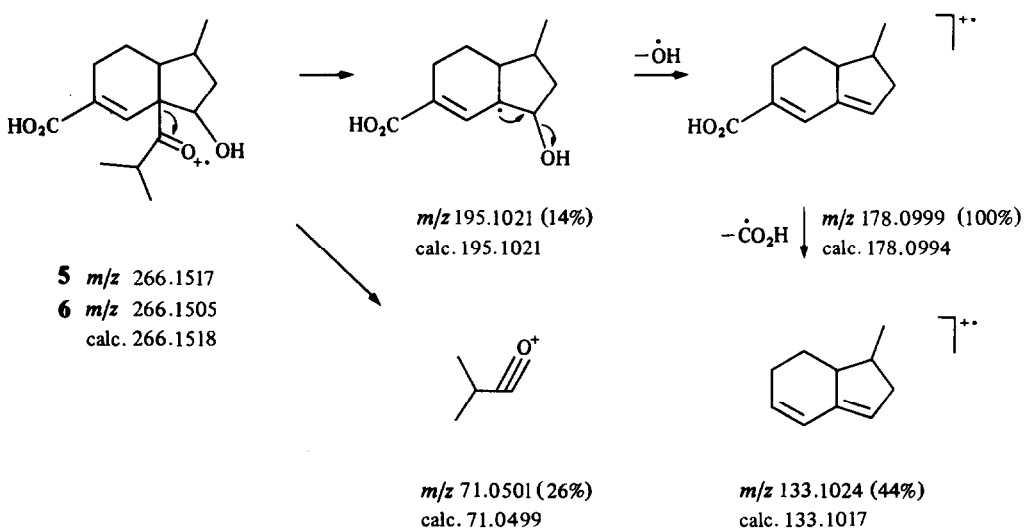


Fig. 1. CD spectra of compounds **3**, **4**, **3a** and **4a**.

ring junction on **5** and **6** was established by the low field chemical shift of H-1α. The structures of **5** and **6** were thus a pair of epimers differing in the configuration of the OH group located at C-8.

When **5** or **6** was kept overnight in aqueous methanol solution, epimerization was observed by TLC with an almost 1:1 ratio between **5** and **6**. The mechanism of epimerization should be reasonably explained by the retro aldol pathway, in which the stereochemistry of the ring junction changes spontaneously to *cis* under thermodynamic control (Scheme 2). From the biosynthetic point of view, **5** or **6** might be formed in the plant. Once an oxoformyl intermediate was formed from suitable precursors, then it might be cyclized immediately and epimerized under the physiological conditions. Thus, **5** and **6** were concluded to be natural products and their stereochemical structures were formulated as 8(7 → 6)*abeo*-8α-hydroxy-7-oxo-cadin-4-en-14-oic acid (**5**) and 8(7 → 6)*abeo*-8β-hydroxy-7-oxo-cadin-4-en-14-oic acid (**6**). The absolute configuration of **5** (1S,6S,8S) and **6** (1S,6S,8R) was confirmed by X-ray crystallographic analysis on the 8-oxo *p*-bromophenacyl ester derivative (**9**). The crystal structure is shown in Fig. 3. Since the configuration of C-1 and C-10 was common to all of the sesquiterpenes isolated from *P. furens*, based on the biogenetic assumption, the absolute configuration of **1**–**4** was consequently defined as the previously proposed structures.

Biogenesis of pernetic acids A–E might involve the further rearrangement of the cadalane type hypothetical intermediate **12** or **13** [4, 5] (Scheme 3). If all the sesquiterpenes were derived from a common cation intermediate, the stereochemistry at C-1 and C-10 should be defined at an early stage of biosynthesis. For instance, the 1,3-hydride shift on the cadinane intermediate **13** could generate a new intermediate **14**, which had the desired stereochemistry for C-1 and C-10. And the following 1,2-hydride shift, route a, or 1,3-hydride shift, route b, could convert **14** to the presumed intermediates **15** and **18**. Another possible route to the cation **15** was a 1,4-hydride shift of the muurolane cation **12**. The rearrangements of the cations could produce **17** and **19**. The formation of **4** is also possible by isomerization at C-6 during the oxidation stages of **17**. Hydroxylation of the cation intermediate **15** followed by the oxidation at C-14 could yield **1**. Oxidation at C-14 of **1** was presumed via pernetol (**7**) and pernetal (**8**), which were isolated as minor constituents in the same plant extract. The precursor of **5**



5 *m/z* 266.1517
6 *m/z* 266.1505
calc. 266.1518

Scheme 1. Mass spectral fragmentation of compounds **5** and **6**.

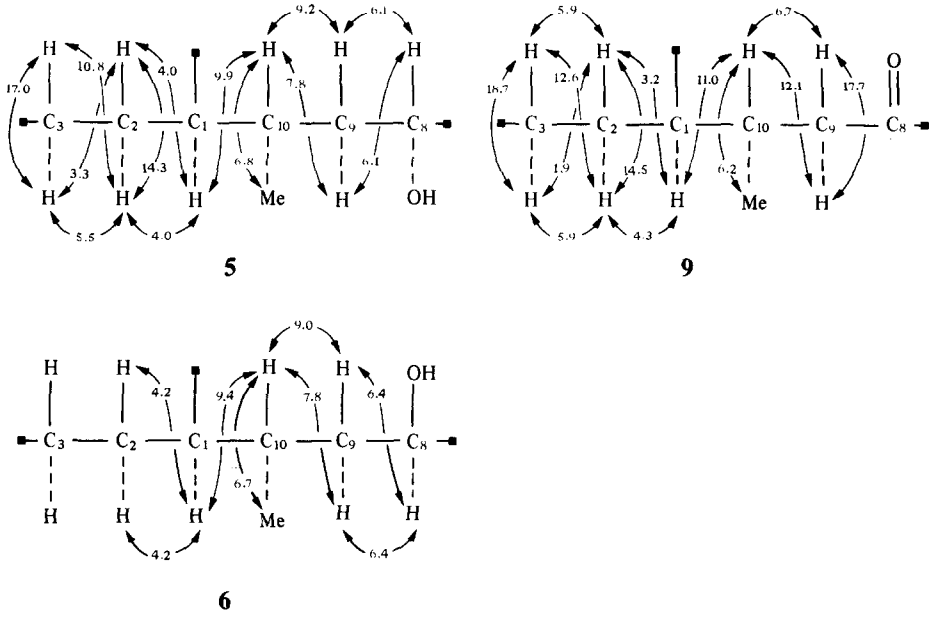
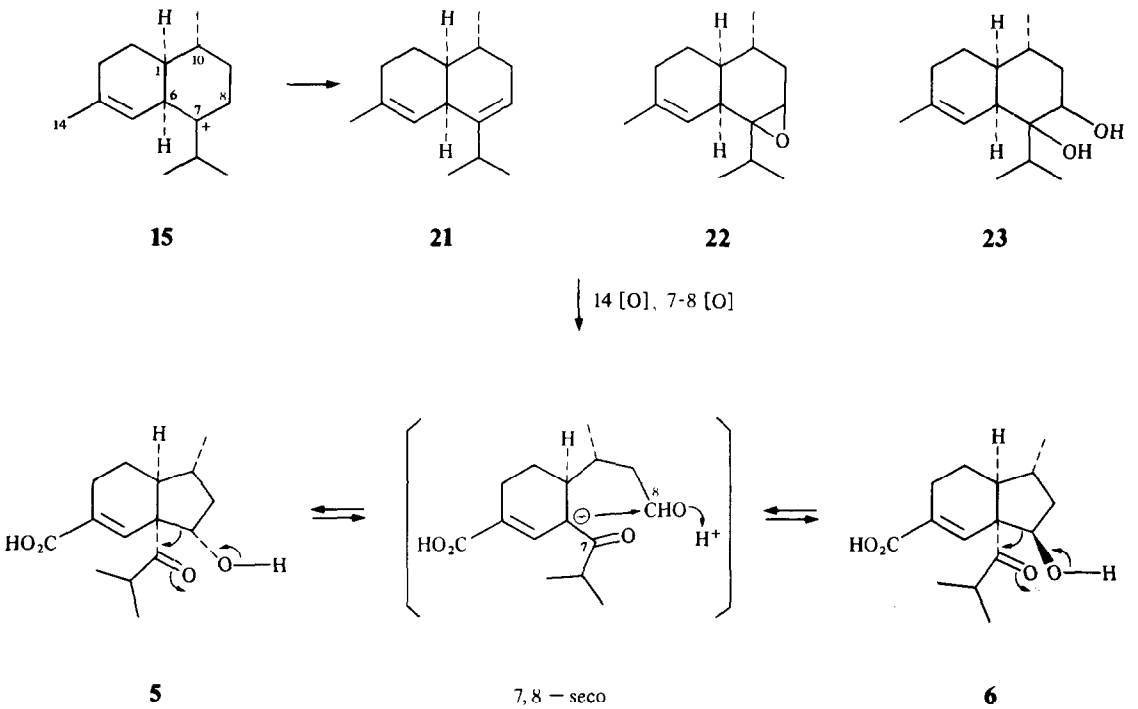


Fig. 2. Partial structure and coupling constants of compounds **5**, **6** and **9**.



Scheme 2. Possible biosynthetic sequences leading to compounds **5** and **6**, and their epimerization.

and **6** may be **1** or a very closely related compound of **1**, such as **21**–**23** derived from **15** (Scheme 2). Oxidative C-7–C-8 bond cleavage could produce a 7,8-seco intermediate, or its equivalents, then the aldol type cyclization can produce **5** and **6**.

The structures of **7** and **8** were confirmed by the following derivatizations: $NaBH_4$ reduction of the mixed anhydride derivative of **1** gave **7**, and the following PCC oxidation of **7** gave **8**. Consequently, the stereochemical structure was formulated as (1S,6R,7S,10R)-9,10-dihydro-7β-hydroxy-muurolen-14-ol (**7**) and (1S,6R,7S,10R)-9,10-dihydro-7β-hydroxy-muurolen-14-al (**8**).

In conclusion, the biogenesis of the sesquiterpenes isolated in the present work presumed the key inter-

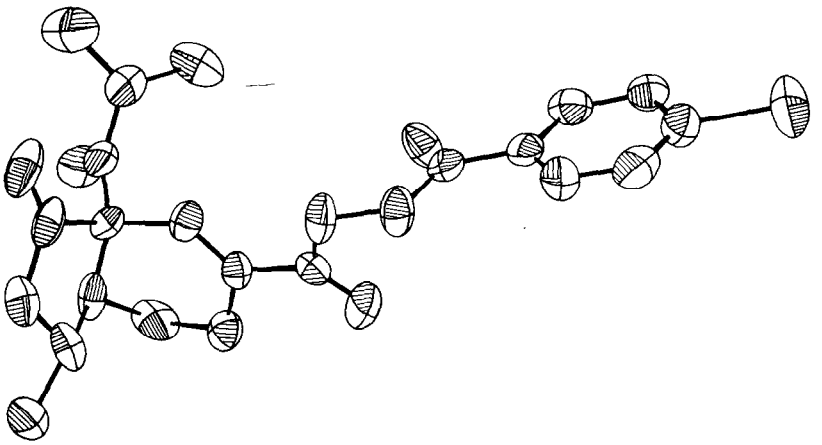
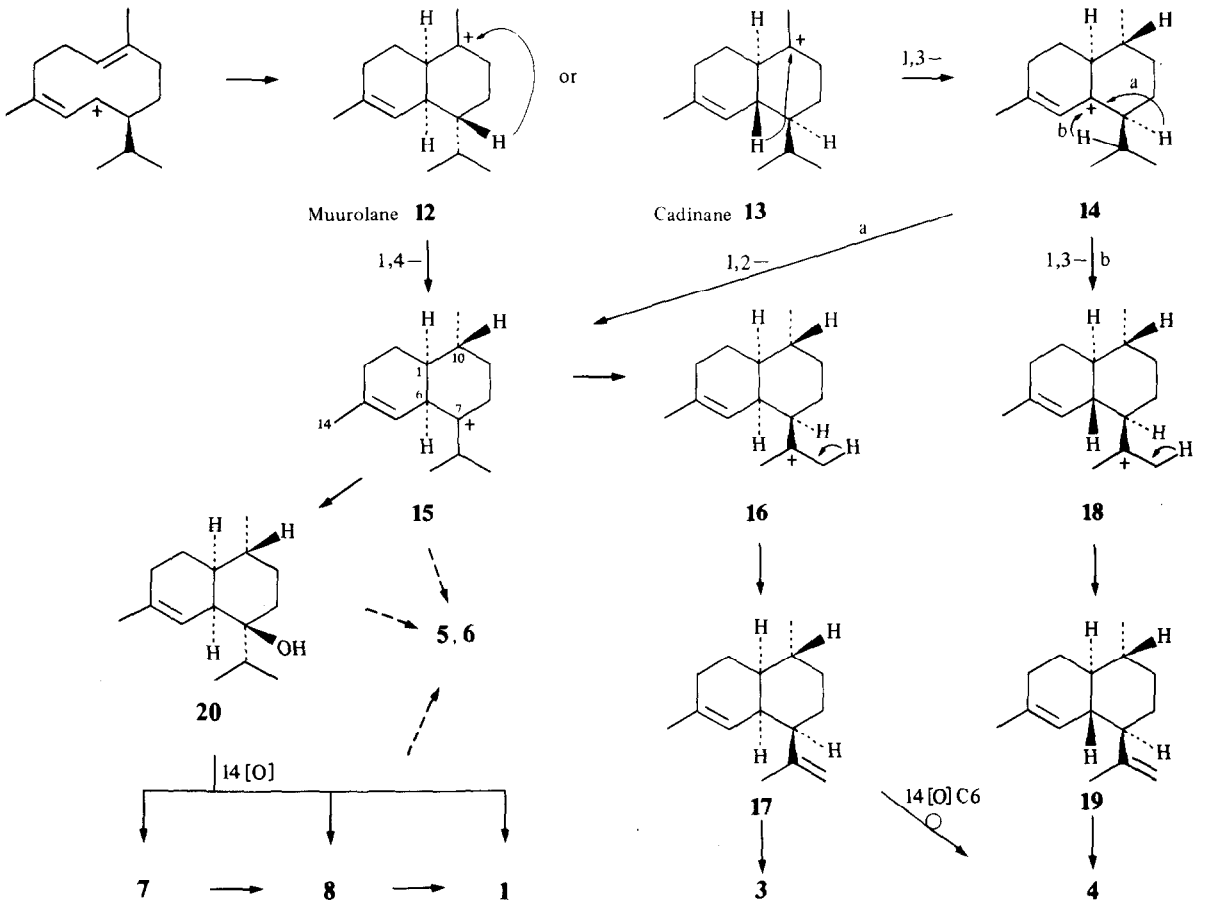


Fig. 3. Molecular structure of 8-oxopernetic acid D *p*-bromophenacyl ester (**9**).



Scheme 3. Hypothetical biogenetic sequences leading to compounds **1**–**4**, **7** and **8**.

mediates possessing a carbonium ion at C-6 or C-7. The rearrangements of the carbonium ion and subsequent oxidations resulted in a variety of different configurations at C-6 and C-7. The oxidative functionalization at C-7, and furthermore, the oxidative modification of skeleton at the positions C-7, C-8, and C-6, were less common on the cadalane type sesquiterpenes. Pernetic acid D and E may be classified as a new class of sesquiterpene.

EXPERIMENTAL

Plant material was collected in the suburb of Tome, 40 km

north of Concepcion, Chile, on December 1980, and was identified as *P. furens* by Professor C. Marticorena of the University of Concepcion. A voucher specimen has been deposited at the harbarium of FCBF. Mps were uncorr. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in the Fourier transfor mode using TMS as int standard. MS were determined at 70 eV using a direct inlet system.

Isolation of sesquiterpenes. Air dried and finely ground leaves and twigs (20 kg) were extracted successively with hexanes under reflux. The hexanes extract (200 g) was loaded on to a silica gel column which was eluted with a C_6H_6–EtOAc gradient with increasing amounts of EtOAc afforded the following fractions: Frs 1 (18 g)–2 (16 g) (C_6H_6), 3 (23 g)–4 (28 g) (C_6H_6–EtOAc, 9:1), 5 (17 g)–6 (17 g) (8:2), 7 (8 g)–8 (7 g)–9 (2.8 g)–10 (1.3 g) (1:1). Fr. 2 (11 g) was diluted with hot MeCN (150 ml) and then allowed to cool, the ppt (1.5 g) of triterpenes as sepd by centrifugation. The MeCN soln was concd and subjected to silica gel CC eluting with C_6H_6–EtOAc. Further purification on a Robar RP-8 column eluted with MeCN–H_2O (7:3) furnished **2** (80 mg). Fr. 3 (16 g) was treated with hot MeCN as described for Fr. 2. After silica gel CC of the MeCN fraction, the crude crystalline compounds were sepd into **3** (250 mg) and **4** (45 mg) by prep. HPLC on ODS developed with MeCN–H_2O (3:2). Fr. 5 (12 g) was subjected to silica gel CC, Merck 40–63 μm, eluted with EtOAc–C_6H_6 (1:4), and then the fraction was purified by prep. HPLC on ODS developed with MeCN–H_2O (3:2), to yield **1** (640 mg). Fr. 6 was chromatographed over alumina eluted with C_6H_6–MeOH and subsequent prep. silica gel TLC developed with EtOAc–C_6H_6 (1:4), gave **8** (12 mg). In the same manner, **7** (6 mg) was obtained from Fr. 8. Frs 9 and 10 were combined and purified on a Robar RP-8 column, MeCN–H_2O (7:3), followed by silica gel CC, eluted with EtOAc–*n*-hexane (1:1), furnishing **5** (170 mg) and **6** (160 mg). Compound **1** (1.2 g) was also obtained from Fr. 4 (18 g) by standard acid–base partition followed by the silica gel CC.

Pernetic acid A (**1**). Colourless prisms, mp 143–144° (MeCN–H_2O), $[\alpha]_D$ +2.7° ($CHCl_3$, *c* 1.64). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1680 (acid C=O), 1630 (C=C), 1450, 1270, 1100, 985. MS *m/z* (rel. int.): 252.1734 $[M]^+$ (0.4), $C_{15}H_{24}O_3$ calc. 252.1726, 234.1626 $[M-H_2O]^+$ (48), 206.1679 $[C_{14}H_{22}O]^+$ (44), 191.1074 $[C_{12}H_{15}O_2]^+$ (52), 125. 0609 $[C_7H_9O_2]^+$ (31), 107.0499 $[C_7H_7O]^+$ (100), 43 (35). UV λ_{max}^{MeOH} 219 nm (ε12 000). CD (MeOH) $\Delta\varepsilon_{248}$ −0.64, $\Delta\varepsilon_{223}$ +1.15. ^{1}H NMR ($CDCl_3$): δ1.54 (*dddd*, H-1α), 1.51 (*dddd*, H-2β), 2.07 (*dddd*, H-2α), 2.20 (*ddddd*, H-3β), 2.30 (*dddd*, H-3α), 7.41 (*br m*, H-5), 2.63 (*br m*, H-6α), 1.29 (*ddd*, H-8β). 1.70 (*dddd*, H-8α), 1.57 (*dddd*, H-9β), 1.10 (*dddd*, H-9α), 1.42 (*qddd*, H-10β), 2.12 (*qq*, H-11), 0.91 (*d*, Me-12, 13), 0.90 (*d*, Me-15), 4.11 (DMSO-d_6), OH-7, 12.04 (DMSO-d_6) CO_2H-14; *J* (Hz): 1α,10β = ~ 12, 1α,6α = ~ 5, 2α,3β = 12, 2α,3α = 6, 3α,3β = 18, 3α,5 = 3β,5 = 2, 3α,6 = 3β,6 = 3, 6,8α = 3, 8α,8β = 8β,9α = 13, 8α,9β = 8β,9β = 8α,9α = 9β,10β = 4, 9α,9β = 9α,10β = 13, 10β,15 = 7, 11,12 = 11,13 = 7; $\Delta\delta$ ppm ($CDCl_3$–C_5D_5N): −0.03 (H-2β), 0.03 (H-2α), −0.25 (H-3β), −0.32 (H-3α), −0.69 (H-5), −0.26 (H-6), −0.26 (H-8β), −0.20 (H-8α), 0.07 (H-9β), 0.02 (H-10), −0.05 (H-11), −0.23(Me-12), −0.18(Me-13), 0.02(Me-15). ^{13}C NMR ($CDCl_3$): δ28.2 (*d*, C-1), 25.0 (*t*, C-2), 20.6 (*t*, C-3), 130.0 (*s*, C-4), 143.2 (*d*, C-5), 43.7 (*d*, C-6), 75.2 (*s*, C-7), 32.2 (*t*, C-8), 30.3 (*t*, C-9), 37.5 (*d*, C-10), 30.0 (*d*, C-11), 15.9 (*q*), 16.0 (*q*, C-12, 13), 172.4 (*s*, C-14), 19.3 (*q*, C-15).

Pernetic acid A methyl ester (**2**). Colourless prisms, mp 96–97° (EtOAc–petrol), $[\alpha]_D$ +2.9° ($CHCl_3$, *c* 2.17). IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 1703 (ester C=O), 1635 (C=C), 1435, 1270, 1242, 1103, 1060. MS *m/z* (rel. int.): 266 $[M]^+$ (3.9), 248 $[M-H_2O]^+$ (1.9), 234 $[M-MeOH]^+$ (47.3), 206 (39), 191 (53.9), 139 (47.3), 107 (100), 43 (29). UV λ_{max}^{MeOH} 223 nm (ε11 800). CD (MeOH) $\Delta\varepsilon_{247}$ −0.85, $\Delta\varepsilon_{223}$ +1.09. ^{1}H NMR ($CDCl_3$): δ1.55 (H-1α), 1.51 (H-2β), 2.08 (H-2α), 2.20 (H-3β), 2.30 (H-3α), 7.25 (H-5), 2.60 (H-6), 1.28 (H-8β), 1.70 (H-8α), 1.63 (H-9β), 1.09 (H-9α), 1.42 (H-10), 2.12 (*qq*, *J* = 7, 7 Hz, H-11), 0.92 (*d*, *J* = 7 Hz Me-12, 13), 0.90 (*d*, *J* = 7 Hz, Me − 15), 3.72 (*s*, OMe). *Esterification of* **1**. A soln of **1** (100 mg) in MeOH (5 ml) was treated with CH_2N_2–Et_2O at 0°. The reaction product was purified by the short silica gel CC eluted with EtOAc–benzene (1:4) and was crystallized from EtOAc–petrol to give **2** (92 mg).

Pernetic acid B (**3**). Colourless needles, mp 147–149° (MeCN–H_2O), $[\alpha]_D$ −31.7° ($CHCl_3$, *c* 0.51). IR ν_{max}^{KBr} cm^{-1}: 1667 (acid C=O), 1640 (C=C), 1442, 1405, 1215, 885. MS *m/z* (rel. int.): 234.1606 $[M]^+$ (100), $C_{15}H_{22}O_2$ calc. 234.1619, 219 (25.4), 191 (19.2) 189 (39.4), 149 (70), 133 (27), 107 (36), 91 (37), 79 (43), 67 (29), 41 (46). UV $\lambda_{max}^{isooctane}$ nm (ε): 224 (10 500), 195 (8900). CD (isooctane) $\Delta\varepsilon_{246}$ −1.27, $\Delta\varepsilon_{223}$ +3.40, $\Delta\varepsilon_{194}$ −11.2. ^{1}H NMR ($CDCl_3$, *J* in Hz): δ1.44 (*dddd*, 10.5, 3.5, 3.5, 3.5, H-1α), 2.08 (*dddd*, 12.5, 5.2, 3.5, 1.5, H-2β), 1.55 (*dddd*, 12.5, 12.5, 6.1, 3.5, H-2α), 2.16 (*ddddd*, 18.3, 12.5, 5.2, 2.1, 1.2, H-3β), 2.29 (*ddddd*, 18.3, 6.1, 1.5, 1.5, 1.2, H-3α), 6.87 (*ddd*, 2.1, 1.9, 1.2, H-5), 2.69 (*dddddd*, 3.5, 3, 1.9, 1.5, 1.2, 3.1, H-6α), 2.11 (*ddddd*, 12.7, 3.1, 3, 1.6, 1.6, H-7α), 1.19 (*dddd*, 12.7, 12.7, 12.7, 3.2, H-8β), 1.60 (*dddd*, 12.7, 3.1, 3.1, 3.1, H-8α), 1.70 (*dddd*, 13.0, 3.2, 3.2, 3.1, H-9β), 1.01 (*dddd*, 13.0, 13.0, 12.7, 3.1, H-9α), 1.32 (*qddd*, 6.1, 13.0, 10.5, 3.2, H-10β), 4.73 (*dd*, 1.6, 1.6, H-12a), 4.96 (*ddq*, 1.6, 1.6, 1.2, H-12b), 1.76 (*d*, 1.2, Me-13), 0.92 (*d*, 6.1, Me-15). ^{13}C NMR ($CDCl_3$): δ28.8 (*d*, C-1), 20.5 (*t*, C-2), 25.2 (*t*, C-3), 130.6 (*s*, C-4), 142.6 (*d*, C-5), 47.5 (*d*, C-6), 39.3 (*d*, C-7), 27.1 (*t*, C-8), 35.3 (*t*, C-9), 41.3 (*d*, C-10), 146.6 (*s*, C-11), 111.3 (*t*, C-12), 22.5 (*q*, C-13), 172.4 (*s*, C-14), 19.6 (*q*, C-15).

Pernetic acid C (**4**). Colourless needles, mp 158–160° (MeCN–H_2O), $[\alpha]_D$ +32.9° ($CHCl_3$, *c* 0.42). IR ν_{max}^{KBr} cm^{-1}: 1675 (acid C=O), 1636 (C=C), 1428, 1275, 935, 880. MS *m/z* (rel. int.): 234.1617 $[M]^+$ (100), $C_{15}H_{22}O_2$ calc. 234.1619, 219 (26.3), 191 (66.6), 189 (41.2), 149 (77.1), 133 (43.8), 107 (45.6), 91 (63.1), 79 (56.1), 67 (42.9), 41 (71.9). UV $\lambda_{max}^{isooctane}$ nm (ε): 223 (10 700), 195 (10 000). CD (isooctane) $\Delta\varepsilon_{242}$ +2.27, $\Delta\varepsilon_{220}$ −1.20, $\Delta\varepsilon_{195}$ +4.96. ^{1}H NMR ($CDCl_3$, *J* in Hz): δ ~ 1.3 (*m*†, H-1α), ~ 1.0 (*m*†, H-2β), ~ 2.2 (*m*†, H-2α), 2.46 (*br ddd*, 17.9, 6, H-3β), ~ 2.17 (*m*†, H-3α), 6.79 (*br m*, H-5), 1.90 (*m*, 11.5, H-6β), 1.85 (*m*, 11.5, H-7α), 1.45 (*dddd*, 13, 13, 13, 4, H-8β), 1.70 (*dddd*, 12.5, 3.5, 3.5, 3.5, H-8α), 1.75 (*dddd*, 12.5, 3.5, 3.5, 3.5, H-9β), 0.81 (*dddd*, 12, 10, 10, 2.5, H-9α), ~ 1.2 (*m*†, H-10), 4.85 (*br s*, H-12a), 4.75 (*br s*, H-12b), 0.97 (*d*, 6.8, Me-15). †Obscured due to overlapping signals. ^{13}C NMR ($CDCl_3$): δ36.8 (*d*, C-1), 26.0 (*t*, C-2, 8), 24.9 (*t*, C-3), 129.7 (*s*, C-4), 144.2 (*d*, C-5), 50.4 (*d*, C-6), 45.4 (*d*, C-7), 36.8 (*t*, C-9), 44.0 (*d*, C-10), 147.4 (*s*, C-11), 112.4 (*t*, C-12), 19.4 (*q*, C-13), 173.4 (*s*, C-14), 19.6 (*q*, C-15).

Hydrogenolysis of **3** *and* **4**. Compound **3** (10 mg) in C_6H_6 (10 ml) was stirred with Wilkinson catalyst under the atm. pres. of H_2 at amb temp for 2 days. After filtration, the soln was concd to yield a colourless amorphous powder of **3a**. IR ν_{max}^{KBr} cm^{-1}: 1685 (acid C=O). MS *m/z* 236 $[M]^+$. CD (isooctane) $\Delta\varepsilon_{255}$ −0.23, $\Delta\varepsilon_{226}$ +2.26, $\Delta\varepsilon_{195}$ −2.36. ^{1}H NMR ($CDCl_3$, *J* in Hz): δ1.30 (*m*, H-1α), 2.06 (*dddd*, 12.5, 5.9, 2.1, 2.1, H-2β), 1.54 (*dddd*, 12.5, 12.5, 6.2, 2.1, H-2α), 2.15 (*ddddd*, 18.2, 12.5, 5.9, 2.1, 2.0, H-3β), 2.30 (*dddd*, 18.2, 6.2, ~ 2, ~ 1, H-3α), 7.05 (*br s*, H-5), 2.68 (*br s*, $W_{1/2}$ = 6.5 Hz, H-6α), 1.06 (*dddd*, 11.8, 10.2, 3.2, 2.9, H-7α), 0.84 (*ddd*, 12.6, 12.6, 2.9, H-8β), 1.75 (*ddddd*, 12.6, 2.9, 2.9, 2.7, 2.0, H-8α), 1.66 (*dddd*, 12.6, 2.9, 2.9, 2.9, H-9β), 0.94 (*dddd*, 12.6, 12.6, 12.6, 2.7, H-9α), 1.33 (*qddd*, 6.0, 12.6, 11, 2.9, H-10β), ~ 1.7 (H-11), 0.96 (*d*, 6.5, Me-12), 0.92 (*d*, 6.5), 0.89 (*d*, 6.0). Compound **4a**, colourless amorphous powder, IR ν_{max}^{KBr} cm^{-1}: 1670 (acid C=O). MS *m/z* 236 $[M]^+$. CD (isooctane) $\Delta\varepsilon_{244}$ +0.96, $\Delta\varepsilon_{222}$ −1.04, $\Delta\varepsilon_{196}$ +3.42. ^{1}H NMR ($CDCl_3$, *J* in Hz): δ1.15 (*m*†, H-1α), 1.17 (*m*†, H-2β), 2.11 (*dddd*, 13.2, 5.1, 2.1, 2.1, H-2α), 2.44 (*m*, 17.9, 4.2, H-3β), 2.20 (*dddd*, 17.9, 12, 6, 4.5, H-3α), 7.25 (*br s*, H-5), 1.77 (*m*, H-6β), 0.82 (*ddd*, ~ 12, 10, 3.5, H-7α), 1.12 (*dddd*, 11.7, 12.9, 10, 3.2, H-8β), 1.69 (*ddd*, 11.7, 3.5, 3.5, H-8α), 1.78 (*dddd*, 12.9, 3.2, 3.2, 3.2, H-9β), 1.02 (*dddd*, 12.9, ~ 12, ~ 12, 3.5, H-9α), 2.21 (*qddd*, 7, 12, 12, 3.2, H-10β), 2.21 (*qq*, 6.8, 6.8, H-11), 0.93 (*d*, 6.8, Me-12, 13), 0.79 (*d*, 7,

Me-15). †Obscured due to overlapping signals.

Pernetic acid D (**5**). Colourless needles, mp 134.5–135.5° (EtOAc–petrol), $[\alpha]_D$ −21.7° ($CHCl_3$, *c* 0.94). IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 1700 sh (C=O), 1680 (acid C=O), 1628 (C=C). MS *m/z* (rel. int.): 266.1517 $[M]^+$ (1.8), $C_{15}H_{20}O_4$ calc. 266.1518, 195.1021 $[M-C_4H_7O]^+$ (14), 178.0999 $[195-OH]^+$ (100), 133.1024 $[178-CO_2H]^+$ (44), 71.0501 $[C_4H_7O]^+$ (26), 43 (95). UV λ_{max}^{MeOH} nm (ε): 217 sh (7900), 231 (10100), 291 (540). CD(MeOH) $\Delta\varepsilon_{293}$ +7.4, $\Delta\varepsilon_{230}$ −12.0. ^{1}H NMR ($CDCl_3$, *J* in Hz): δ2.36 (*ddd**, H-1α), 1.79 (*dddd*, H-2β), 1.62 (*dddd*, H-2α), 2.16 (*dddd*, H-3β), 2.34 (*dddd*, H-3α), 7.26 (*br s*, H-5), 4.17 (*dd*, H-8β), 1.32 (*ddd*, H-9β), 2.27 (*ddd*, H-9α), 1.70 (*dddd*, H-10β), 2.96 (*qq*, 6.8, 6.8, H-11), 1.02 (*d*, Me-12, 13), 1.06 (*d*, 6.8, Me-15). ^{13}C NMR ($CDCl_3$): δ44.1 (*d*, C-1), 21.0† (*t*, C-2), 43.2 (*t*, C-3), 131.7 (*s*, C-4), 140.5 (*d*, C-5), 65.4 (*s*, C-6), 215.1 (*s*, C-7), 80.4 (*d*, C-8), 19.9† (*t*, C-9), 32.5 (*d*, C-10), 38.9 (*d*, C-11), 19.8‡ (*q*, C-12), 19.5‡ (*q*, C-13), 171.9 (*s*, C-14), 18.7 (*q*, C-15). *Coupling constants shown in Fig. 2. †‡Assignment may be interchanged.

Pernetic acid E (**6**). Colourless needles, mp 134.5–136° (EtOAc–petrol), $[\alpha]_D$ −128.5° ($CHCl_3$, *c* 0.85). IR ν_{max}^{KBr} cm^{-1}: 3375 (OH), 1700 sh (C=O), 1678 (acid C=O), 1630 (C=C). MS *m/z* (rel. int.): 266.1505 $[M]^+$ (1.7), the fragment ion peaks observed in **6** were exactly the same as in **5**. UV λ_{max}^{MeOH} nm (ε): 217 sh (7800), 232 (9600), 291 (500). CD (MeOH): $\Delta\varepsilon_{314}$ −0.98, $\Delta\varepsilon_{284}$ +0.39, $\Delta\varepsilon_{221}$ −2.57. ^{1}H NMR ($CDCl_3$, *J* in Hz): δ2.07 (*ddd**, H-1α), 1.70 (*m*†, H-2α,2β), 2.33 (*m*†, H-3α,3β), 7.32 (*br s*, H-5), 4.58 (*dd*, H-8α), 1.16 (*ddd*, H-9β), 1.75 (*ddd*, H-9α), 1.90 (*dddd*, H-10β), 3.04 (*qq*, 6.7, 6.7, H-11), 1.02 (*d*, 6.7, Me-12), 1.03 (*d*, 6.7, Me-13), 1.06 (*d*, 6.7, Me-15). *Coupling constants shown in Fig. 2. †Obscured due to overlapping signals.

Esterification of **5** *and* **6**. A soln of **5** (20 mg), or **6**, in Et_2O was treated with CH_2N_2–Et_2O at 0° for 30 min. The product was a mixture of **10** and **11** in a 1:1 ratio. **10** and **11** were sepd by prep. silica gel TLC developed with EtOAc–C_6H_6 (1:4), furnishing a colourless gum. **10**, MS *m/z* (rel. int.): 280 $[M]^+$ (2.8), 249 (1.4), 209 (15), 192 (100). ^{13}C NMR ($CDCl_3$): δ44.0 (*d*, C-1), 21.0 (*t*, C-2), 43.3 (*t*, C-3), 131.7 (*s*, C-4), 138.3 (*d*, C-5), 65.3 (*s*, C-6), 214.9 (*s*, C-7), 80.4 (*d*, C-8), 20.3 (*t*, C-9), 32.5 (*d*, C-10), 38.7 (*d*, C-11), 19.8 (*q*, C-12), 19.6 (*q*, C-13), 167.5 (*s*, C-14), 18.7 (*q*, C-15), 51.8 (*q*, OMe); **11**, 45.6 (*d*, C-1), 22.4 (*t*, C-2), 41.8 (*t*, C-3), 134.1 (*s*, C-4), 135.7 (*d*, C-5), 65.6 (*s*, C-6), 215.3 (*s*, C-7), 77.0 (*d*, C-8), 20.8 (*t*, C-9), 32.5 (*d*, C-10), 37.5 (*d*, C-11), 20.3 (*q*, C-12), 19.7 (*q*, C-13), 167.5 (*s*, C-14), 19.4 (*q*, C-15), 51.8 (*q*, OMe). A soln of **5** (20 mg) in 10 ml of DMF was treated with 25 mg of *p*-bromophenacyl bromide and 14 mg of K_2CO_3 at 20° for 30 min. The esterified product was a mixture of the C-8 epimers.

Oxidation of esters. A soln of either **10** or **11**, and or a mixture of **10** and **11**, in CH_2Cl_2 was treated with PCC at 20° for 1 hr. The product was purified by prep. silica gel TLC developed with EtOAc–C_6H_6 (1:4), furnishing the 8-oxoMe ester (**10a**), colourless amorphous powder; IR ν_{max}^{KBr} cm^{-1}: 1740 (cyclopentanone C=O), 1720 (C=O), 1712 (ester C=O). MS *m/z* (rel. int.): 278 $[M]^+$ (6), 247 (0.8), 208 (100). UV λ_{max}^{MeOH} nm (ε): 217 (7800), 241 (9200), 294 (780), 303 (750), 314 sh, 326 sh: $\lambda_{max}^{isooctane}$ nm (ε): 211 (9100), 246 (8100), 276 sh, 285 (660), 294 (740), 302 (700), 314 (510), 326 (250). ^{1}H NMR ($CDCl_3$): δ2.69 (H-1α), 1.52 (H-2α), 2.01 (H-2β), 2.43 (H-3α), 2.13 (H-3β), 7.02 (H-5), 2.06 (H-9α), 2.50 (H-9β), 1.95 (H-10β), 3.28 (H-11), 1.02 (*d*, *J* = 6.8 Hz, Me-12), 1.07 (*d*, *J* = 6.8 Hz, Me-13), 1.16 (*d*, *J* = 6.1 Hz, Me-15), 3.76 (MeO). The foregoing mixture of *p*-bromophenacyl esters was oxidized with PCC and the product was purified by silica gel CC eluted with CH_2Cl_2 followed by crystallization from 65% EtOH to yield a single crystal of **9**. Colourless needles, mp 86–87°. IR ν_{max}^{KBr} cm^{-1}: 1747, 1713, 1700, 1625. MS *m/z* (rel. int.): 462 $[M]^+$ (1.46), 460 $[M]^+$ (1.57), 176 (100). ^{1}H NMR ($CDCl_3$, *J* in Hz): δ2.73 (*ddd**, H-1α), 2.01 (*dddd*, H-2β), 1.58 (*dddd*, H-2α), 2.20 (*dddd*, H-3β), 2.50 (*dddd*, H-3α), 7.19 (*dd*, 2.4, 1.6, H-5), 2.53 (*dd*, H-9β), 2.08 (*dd*, H-9α), 1.95 (*dddd*, H-10β), 3.31 (*qq*, 6.7, 6.7, H-11), 1.08 (*d*, 6.7, Me-12), 1.05 (*d*, 6.7, Me-13), 1.18 (*d*, 6.7, Me-15), 5.35 (*d*, 16.3), 5.38 (*d*, 16.3, O–CH_2–C=O), 7.65 (*dd*, 8.8, 1.9, arom. *o*-H), 7.79 (*dd*, 8.8, 1.9, arom. *m*-H). *Coupling constants shown in Fig. 2.

X-ray crystallographic analysis. Crystal data: $C_{23}H_{25}O_5Br$, monoclinic, space group $P2_1$, a = 11.260(5), b = 5.932(2), c = 16.979(8) Å; β = 98.31(4)°, D_x = 1.37 g.cm^{-3}, Z = 2 and μ(Mo*K*α) = 19.7 cm^{-1}. Intensity data for 1313 reflections [$I > 1.96\sigma(I)$] were collected using an ω-scan mode within 2θ less than 50°. The structure was solved by the heavy atom method. The final *R* value was 0.052 assuming anisotropic thermal mortions for non-H atoms and isotropic ones for H atoms. The absolute configuration of **9** was determined by Bijove's anomalous-dispersion method based on the observed and calculated structure factors of Friedel pairs. The lists of 'atomic coordinations and thermal parameters', 'bond distances and angles', and 'comparison of the observed and calculated structure factors', have been deposited at the Cambridge Crystallographic Data Center.

Pernetol (**7**). Colourless amorphous powder, $[\alpha]_D$ +14.09° ($CHCl_3$, 0.908). IR ν_{max}^{KBr} cm^{-1}: 3300 (OH); MS *m/z* (rel. int.): 220 $[M]^+$ (42.1), 202 (29.8), 195 (31.5), 177 (63), 159 (69), 134 (96), 71 (100), 43 (97). ^{1}H NMR ($CDCl_3$, *J* in Hz): δ1.52 (H-1α), 1.48 (H-2β), 2.01 (*m*†, H-2α,3β), 2.04 (H-3α), 5.89 (*br s*, H-5), 2.52 (*br s*, H-6α), 1.36 (H-8β), 1.60 (H-8α), 1.49 (H-9β), 1.09 (H-9α), 1.38 (H-10β), 2.07 (*qq*, 6.7, 6.7, H-11), 0.89 (*d*, 6.7, Me-12), 0.90 (*d*, 6.7, Me-13), 0.91 (*d*, 6.0, Me-15), 4.02 (CH_2-14). †Obscured due to overlapping signals. *Derivation from* **1**. A soln of **1** (100 mg) in 10 ml of dry C_6H_6 was treated with 0.25 ml of Et chloroformate and 0.25 ml of Et_3N at 10° for 1 hr. The reaction mixture was dil with 50 ml of C_6H_6 and washed with H_2O. The resulting mixed anhydride in 20 ml of THF was treated with an aq soln of $NaBH_4$ at 0°. Removal of solvent *in vacuo* followed by extraction with EtOAc yielded **7** (81 mg).

Pernetal (**8**). Colourless gum, $[\alpha]_D$ +17.8° ($CHCl_3$, *c* 1.06). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590 (OH), 1670 (CHO), 1625 (C=C). UV $\lambda_{max}^{cyclohexane}$ 232 nm (ε13900). CD (cyclohexane) $\Delta\varepsilon_{230}$ +4.29. MS *m/z* (rel. int.): 236 $[M]^+$ (8.6), 218 (11), 193 (11), 175 (12), 109 (100), 43 (38). ^{1}H NMR ($CDCl_3$, *J* in Hz): δ1.60 (H-1α), 1.50 (H-2β), 2.07 (*m*†, H-2α,3β), 2.29 (H-3α), 7.16 (*br s*, H-5), 2.73 (*br s*, H-6α), 1.28 (H-8β), 1.72 (H-8α), 1.56 (H-9β), 1.09 (H-9α), 1.33 (H-10β), 2.17 (*qq*, 6.8, 6.8, H-11), 0.91 (*d*, 6.8, Me-12), 0.94 (*d*, 6.8, Me-13), 0.93 (*d*, 7.5, Me-15), 9.45 (*s*, CHO-14). †Obscured due to overlapping signals.

Derivation from **7**. A soln of **7** (70 mg) in CH_2Cl_2 was treated with PCC at 25°. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. Resulting **8** was purified by silica gel CC eluted with EtOAc–C_6H_6 (1:4) to yield 63 mg.

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