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Structures of Norditerpene Lactones from *Podocarpus* Species

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The crystal structure of sellowin B bromohydrin acetate ($C_{20}H_{21}O_7Br$) has been determined. The space group is $P2_1$ with cell dimensions a = 10.060 (5), b = 6.127 (4), c = 16.037 (6) Å, β = 96.02 (2)°, and Z = 2. The structure, solved using MULTAN and refined to R = 0.053, indicates sellowin B and related compounds to be 2,3-β rather than 1,2-α epoxides. Earlier chemical results are interpreted in light of the new structure.

In recent years, many norditerpene dilactones showing important biological activities have been isolated from *Podocarpus* species, ancient gymnosperms growing in scattered parts of the southern hemisphere.[3] These compounds are usually highly polar and hydrophilic, heavily oxygenated, and chemically refractory, in spite of the presence of the lactones and (usually) epoxide groups. The small number of interpreted reactions reported[4-7] includes almost exclusively simple functional group derivatization (alcohol to acetate or ketone) and unexpected transformations of the molecules.

Perhaps due to this refractory response to usual chemical reagents, and to unusual spectral characteristics of the compounds as well, recent x-ray analyses have revised the majority of the published structures[3] in the group. Thus, inumakilactone A, long supposed to possess a 1,2-α epoxide in ring A,[6] was shown by x-ray analysis to be in fact a 1,2-β epoxide (**1**).[8] This structural modification affected, by extension, the accepted constitutions of at least ten other compounds isolated from eight *Podocarpus* species in three continents and New Zealand, including the most widely distributed member of the group, nagilactone C (**2**).[3,7,8] By x-ray analysis of its *p*-bromobenzoate, podolactone A was shown to possess a 2,3-β epoxide (**3**)[9] rather than the 1,2-α group widely accepted.[3,10] By extension, at least five additional lactones from three *Podocarpus* species are subject to a similar modification. The present paper confirms that the structure of one of these five, from the Brazilian *P. sellowii*, likewise must be modified from a 1,2-α epoxide to a 2,3-β epoxide. Thus, no ring A epoxide in the series remains with its originally proposed structure, and interpretations of the chemistry of this group in these compounds[4,5] must be revised. Even a ring A alcohol, nagilactone A, was definitively assigned stereochemistry (**4**) only after an x-ray analysis.[11] It is also possible that a ring A olefin, podolactone D, could possess a 2,3 rather than a 1,2 double bond; unfortunately, this olefin does not react with peracid to form an epoxide,[12] and the reverse deepoxidation in nagilactone C (**2**) gave complete saturation of the ring,[4] though in the absence of a neighboring hydroxyl group olefin formation might be favored. The presence of a 2,3 double bond in podolactone D is rendered more probable by the x-ray study[13] which shows the closely related podolide (**5**) to contain this structural feature.

Reaction of sellowin B (published structure **6**)[3,4,14] with *N*-bromoacetamide under forcing conditions, in an attempt to functionalize the double bond and thereby give entry to a three-carbon side chain, gave exclusively a hygroscopic ring A bromohydrin, mp 204–208 °C, which was directly acetylated to a beautifully crystalline bromohydrin acetate. This compound was selected for x-ray analysis over the less satisfactorily crystalline tribromide (olefin dibromide + epoxide bromohydrin) produced by direct bromination of sellowin B.

X-ray analysis of the bromohydrin acetate revealed it to possess structure **7**, with the conformation depicted in Figure 1. Figure 2 gives bond lengths and bond angles, Figure 3 packing in the unit cell, Table I atomic coordinates, and Table II torsion angles for the rings in the molecule. The torsion angles reveal that rings A, B, and C approximate chair, 1,2-diplanar (sofa), and 1,3-diplanar conformations.[15] The torsion angles involving the acetate group are C2–C3–O17–C17 (124.7°), C4–C3–O17–C17 (−108.4°), C3–O17–C17–C21 (−174.8°), and C3–O17–C17–O18 (4.0°).

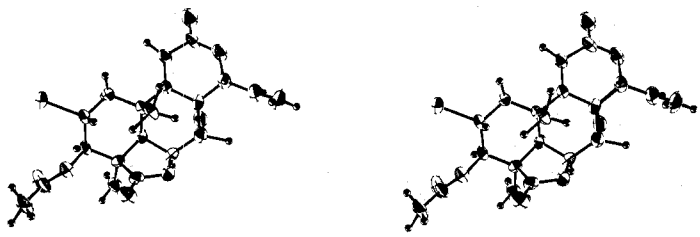


Figure 1. Stereoscopic view of the molecule. Hydrogen atoms are depicted as spheres, and other atoms as 50% probability ellipsoids.

The constitution revealed by the x-ray study of the bromohydrin acetate (**7**) leaves no doubt that the correct structure for sellowin B is **8**, identical with the published structure in all details except for the position and configuration of the ring A epoxide. This corresponds, however, to the modification required in podolactone A (**3**)[9] which can be extended to podolactone C (**9**) because of the extremely close similarity of chemical shifts and coupling constants for the ring A protons in the NMR spectra of the two compounds,[12] and because the two lactones coexist in *P. neriifolius*.

By arguments similar to the above, the revised ring A structure can be extended from sellowin B (**6**) to sellowin A (**10**) and also hallactone B (**11**)[16] which is obtained by oxidation of podolactone C (**9**).[12] The NMR spectra of the latter compound in Me_2SO and pyridine, however, are more suggestive of the presence of at least one β proton on the epoxide;[3] this may be simply another case of the unusual spectral characteristics of these compounds, which seem to obey few of the rules derived from observations on less polar natural products with more scattered functional groups.

The direction of opening of the epoxide ring in sellowin B (**8**) to give after acetylation bromoacetate **7** violates the axial attack rule, and is probably the result of unfavorable steric interactions (C18 methyl group with bromine, C20 methyl group with the developing hydroxyl group) in the transition state leading to the unobserved bromohydrin. The observed

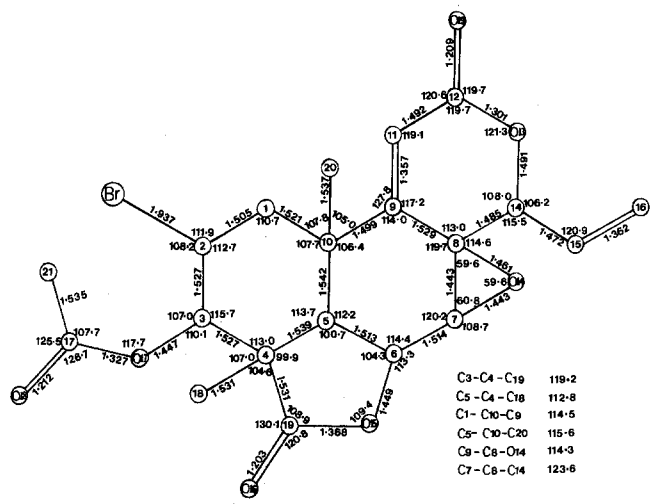


Figure 2. Bond lengths (Å) and bond angles (deg) in the molecule, with standard deviations in Br–C, C–C, and C–O lengths of 0.007, 0.008, and 0.009 Å, respectively, and in Br–C–C, C–C–C, and C–C–O angles of 0.4, 0.5, and 0.5°, respectively.

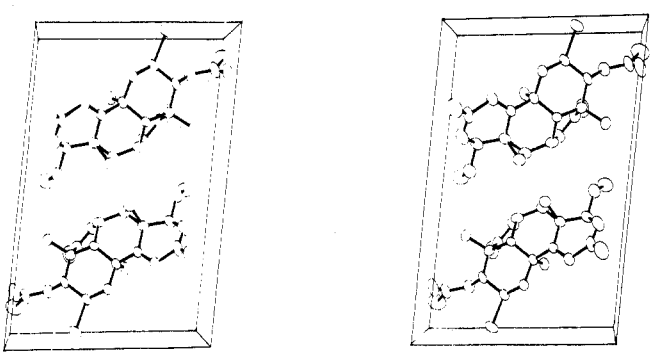
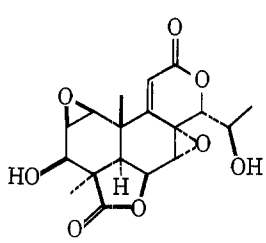


Figure 3. Stereoscopic view of a unit cell, *b* axis projection, *a* axis horizontal.



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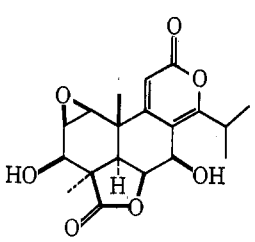

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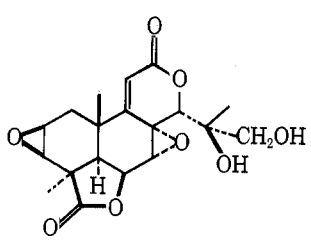

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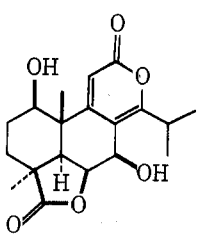

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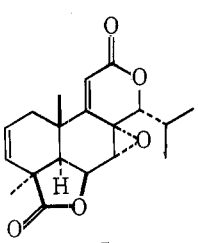

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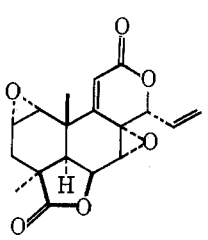

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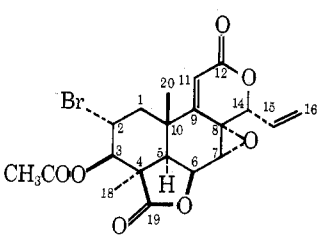

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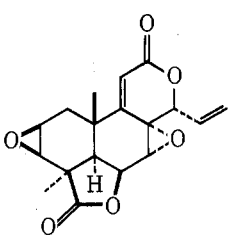

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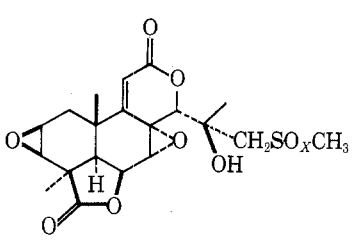
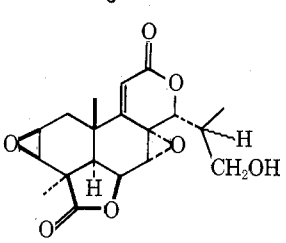


9, $X = 1$
11, $X = 2$



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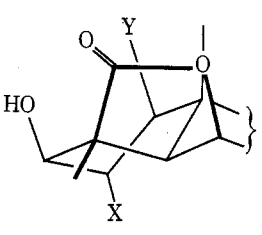

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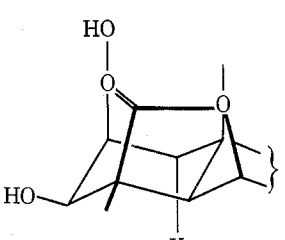

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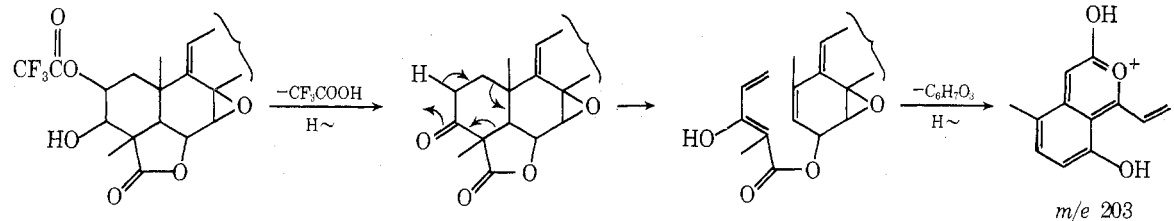
Scheme I



sellowin B + trifluoroacetic acid

m/e 203

Table I. Fractional Coordinates (×10⁴ for Nonhydrogens and ×10³ for Hydrogens) and Estimated Standard Deviations

Atom	*x/a*	*y/b*	*z/c*
Br	3479 (1)	1755 (5)	9892 (1)
C1	4982 (6)	1764 (13)	8473 (4)
C2	3939 (6)	456 (13)	8859 (4)
C3	2656 (6)	174 (11)	8269 (4)
C4	2844 (6)	−424 (10)	7365 (4)
C5	4040 (5)	746 (11)	7039 (4)
C6	4197 (7)	−573 (13)	6258 (4)
C7	5536 (8)	−303 (17)	5920 (4)
C8	6573 (6)	993 (11)	6371 (4)
C9	6370 (5)	1889 (12)	7239 (3)
C10	5317 (6)	715 (11)	7661 (4)
C11	7281 (6)	3353 (11)	7582 (4)
C12	8332 (6)	4168 (11)	7070 (5)
O13	8616 (5)	3059 (9)	6420 (3)
C14	8002 (7)	882 (10)	6219 (4)
C15	8253 (7)	389 (17)	5351 (6)
C16	8831 (10)	−1530 (21)	5158 (6)
C17	637 (7)	−970 (19)	8769 (6)
C18	1520 (6)	50 (15)	6835 (4)
C19	3170 (6)	−2788 (12)	7155 (5)
C20	5909 (6)	−1555 (13)	7875 (4)
C21	64 (12)	−2897 (27)	9228 (7)
O14	5690 (5)	1950 (12)	5686 (3)
O15	3927 (5)	−2799 (9)	6494 (3)
O16	8903 (6)	5871 (10)	7243 (4)
O17	1868 (5)	−1480 (11)	8633 (3)
O18	57 (6)	722 (17)	8581 (5)
O19	2814 (6)	−4470 (10)	7448 (5)
H1C1	572 (8)	160 (16)	893 (5)
H2C1	446 (8)	316 (16)	829 (5)
HC2	438 (6)	−133 (11)	893 (4)
HC3	204 (6)	145 (13)	823 (4)
HC5	387 (8)	209 (17)	680 (5)
HC6	351 (10)	−0 (22)	582 (6)
HC7	605 (6)	−114 (12)	531 (4)
HC11	739 (8)	379 (14)	818 (5)
HC14	824 (7)	−27 (14)	651 (4)
HC15	823 (8)	142 (19)	487 (4)
H1C16	885 (9)	−124 (18)	449 (6)
H2C16	882 (8)	−269 (15)	561 (5)
H1C18	154 (6)	−42 (12)	642 (4)
H2C18	120 (6)	195 (11)	678 (4)
H3C18	76 (8)	− 63 (16)	697 (5)
H1C20	515 (6)	−272 (13)	821 (4)
H2C20	695 (9)	−124 (18)	811 (6)
H3C20	628 (6)	−239 (12)	741 (4)
H1C21	30 (9)	−460 (20)	920 (5)
H2C21	102 (9)	−299 (20)	916 (5)
H3C21	54 (7)	−266 (16)	975 (5)

product results from ring opening to a twist-boat conformation **12** (X = Br; Y = H), which quickly equilibrates to a chair conformation similar to that depicted in Figure 1. The correction in the stereochemistry of inumakilactone A (**1**)[8] also requires modification of the stereochemistry of its 1,2-epoxide ring opening products, which from the reported ^{1}H NMR coupling constants[5] must be represented by either **12** or **13** (X = Br, Cl, or OH; Y = OH). **13**, the product of axial attack, fits the observed ^{1}H NMR constants, but so does **12** (Y = OH) provided that it remains predominantly in the twist-boat conformation.

Table II. Endocylic Torsion Angles (deg)

Ring	Bond	Angle	Ring	Bond	Angle
A	Cl–C2	−57.1	C	C8–C9	30.5
	C2–C3	44.5		C9–C11	6.1
	C3–C4	−38.2		C11–C12	−19.9
	C4–C5	45.5		C12–O13	−5.6
	C5–C10	−57.5		O13–C14	40.8
	C10–C1	63.0		C14–C8	−51.4
B	C5–C6	−41.3	γ-Lactone	C4–C5	37.9
	C6–C7	4.6		C5–C6	−38.2
	C7–C8	6.0		C6–O15	23.0
	C8–C9	19.9		O15–C19	2.3
	C9–C10	−53.8		C19–C4	−26.2
	C10–C5	65.8			

The published mass spectral fragmentation schemes for sellowin B (**8**) and derivatives[4] are not substantially changed by the modification in its structure; even the retro-Diels–Alder cleavage of ring A can proceed in identical fashion through an enol, or in slightly modified form through a ketone, as in Scheme I.

Experimental Section

Sellowin B Bromohydrin Acetate (7). Sellowin B (**8**, 70 mg, mp 316–317 °C) in hot acetone (50 ml) was treated with a 2% aqueous solution of *N*-bromoacetamide (5 ml), agitating for 6 days at room temperature. The reaction mixture was treated with water (10 ml) and the mixture extracted with chloroform (5 × 15 ml), giving after drying (anhydrous Na_2SO_4) and evaporation a crude product (77 mg). Crystallization from pyridine gave 73 mg (87%) of poorly crystalline, highly insoluble material: mp 204–208 °C; ir (KBr) ν_{max} 3530 (sharp, strong), 1780, 1730, 1670, 1250, 1095, 1070, 1050, 1025, 1000, 973, 890, 765, 700, 600, and 550 cm^{-1}, with many additional weaker sharp peaks giving a pattern much more complex than that of sellowin B; NMR showing all three vinyl protons in a pattern similar to that of sellowin B, but lacking the epoxide proton signals, giving instead new one-proton peaks near δ 3.8 and 4.0. This compound was not further purified, but was directly acetylated in pyridine (6 ml) and acetic anhydride (2 ml) for 12 h at room temperature. Workup with water (10 ml) and chloroform (5 × 8 ml) gave 74 mg, crystallized from methanol to provide 64 mg (79%): mp 241–243 °C; ir (KBr) ν_{max} 1780, 1730 i, 1720, 1215, 1015, 880, 760, 695 cm^{-1}; MS *m/e* 452/4 (M^+), 410/2 (M − CH_2CO), 367/9 (410/2 − CO_2 + H), 339/41 (367/9 − CO), 331 (M − Br), 313 (331 − H_2O), 213 (base peak)[4]; ^{1}H NMR (100 MHz, Py-d_5) δ 6.46 (1 H s, 11-H), 5.97 (1 H septet, *J* = 8, 10, 17 Hz, 15-H), 5.66 (1 H d, *J* = 11 Hz, 3α-H), 5.54 (1 H dd, *J* = 2, 11 Hz, 16-trans-H), 5.40 (1 H dd, *J* = 3, 10 Hz, 16-cis-H), 5.36 (1 H d, *J* = 8 Hz, 14-H), 5.23 (1 H dd, *J* = 1.5, 4 Hz, 6α-H), 4.74 (1 H ddd, *J* = 5, 11, 12.5 Hz, 2β-H), 3.97 (1 H d, *J* = 1.5 Hz, 7β-H), 2.68 (1 H dd, *J* = 5, 12.5 Hz, 1β-H), 2.38 (1 H d, *J* = 4 Hz, 5α-H), 2.25 (3 H s, OAc), ~2.2 (1 H t?, *J* ~ 12.5 Hz, 1α-H), 1.47 and 1.29 (2 × 3 H s, 2 C-Me).

Crystal Structure Determination. Oscillation and Weissenberg photographs of a needle 0.2 × 0.2 × 0.4 mm of **7** indicated monoclinic space group $P2_1$. The cell parameters were found by least-squares fitting of the settings for the four angles of ten reflections on a Picker

FACS-I diffractometer (Cu Kα, λ = 1.54178 Å, graphite monochromator) to be a = 10.060 (5), b = 6.127 (4), c = 16.037 (6) Å, β = 96.02 (2)°, ρc = 1.53 g/ml, and Z = 2. Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan, 2°/min scan rate, 10-s background counts, attenuators when the count rate exceeded 10^4 counts/s, and a 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 1620 independent reflections measured, 1591 > $3\sigma(I)$ were considered observed. Lorentz and polarization corrections were applied, but no correction was made for absorption. No significant decrease was observed in the intensities of standards.

The structure was solved using MULTAN.[17] The first E map revealed Br and seven other atoms. The rest of the nonhydrogen atoms were located by difference synthesis. The structure was refined by full matrix least-squares techniques to a final R of 0.053. Anisotropic thermal parameters were assumed for nonhydrogen atoms, and all hydrogen atoms were located and included in the refinement. The scattering factors used were those of Hanson et al.[18] Anomalous scattering factors were used for bromine, but the absolute configuration was not determined and is assumed to be as established earlier.[14] The refinement was based on F_o, the quantity minimized being $\Sigma w(F_o - F_c)^2$. The weighting scheme used was based on counter statistics,[19] with p = 0.04.

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Registry No.—**7**, 58934-07-9; **8**, 34294-03-6; *N*-bromoacetamide, 79-15-2.

Supplementary Material Available. A table of temperature factors (1 page). Ordering information is given on any current masthead page.

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Some Chemical Constituents of the Digestive Gland of the Sea Hare *Aplysia californica*

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The digestive gland of the sea hare *Aplysia californica* contains halogenated metabolites which are obtained from its algal diet. We have isolated three halogenated sesquiterpenes, prepacifenol epoxide (**1**), the diol **5**, and the epoxide **6**, and two halogenated monoterpenes **7** and **11**, which had not been isolated from algae. The structure of the epoxide **6** was elucidated by single-crystal x-ray diffraction analysis, and the remaining four compounds by chemical and spectroscopic techniques.

We previously reported[2] that the chemical constituents of the digestive gland of the herbivorous opisthobranch mollusc *Aplysia californica* (Cooper) were identical with metabolites of the red algae which form a major portion of the sea hare's diet. In a few instances we were able to demonstrate that chemical transformations had occurred within the digestive gland.[3] We found that the sea hare obtained halogenated sesquiterpenes from *Laurencia* sp. and halogenated monoterpenes from *Plocamium* sp. The mixture of halogenated monoterpenes in *Aplysia* was so complex that we chose to investigate these metabolites from *P. cartilagineum*[4] and *P. violaceum*[5] separately. In recent studies of the chemical constituents of the digestive gland of *Aplysia*, we found compounds which have not been detected in local red algae. We wish to report the structural elucidations of three sesquiterpenes and two monoterpenes.

During 1973 and 1974, we made three collections of *Aplysia californica* at three locations in the vicinity of La Jolla, Calif. Each collection of *Aplysia* was investigated separately, resulting in three digestive gland extracts having different compositions. In the first collection, the major constituents were sesquiterpenes, while the two later collections each contained a different monoterpene as the major component.

A group of 50 *Aplysia* were collected at Sunset Cliffs, San Diego, Calif., during August 1973, and the digestive glands