Structures of Inumakilactones B and C, Lactones of Diterpenoid Origin

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Summary The structure of inumakilactone B has been determined spectroscopically, and two alternative structures are put forward for inumakilactone C.

WE have elucidated[1,2] the structure of inumakilactone A (I) and nagilactones C and D,[3] novel C_{18} and C_{19} lactones of diterpenoid origin, isolated from Japanese *Podocarpus* species. The seeds of *P. macrophyllus* D. Don afforded two more new bisnorditerpenoid lactones, inumakilactones B and C, along with (I), nagilactone C, and ponasterone A.[4] We now suggest structures (II) and (III) for inumakilactones B and C.

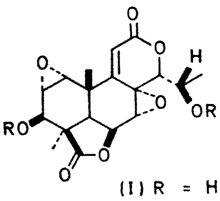
Inumakilactone B (II), $C_{18}H_{18}O_7$, m.p. 295° (dec.) has a hydroxy-group [ν 3350 cm^{-1}, monoacetate (IV), m.p. 385°], a γ-lactone function (ν 1770 cm^{-1}), and an $\alpha\beta$-unsaturated δ-lactone group [λ_{max} 220 nm (ϵ 7300), ν 1720 and 1643 cm^{-1}]. The n.m.r. parameters of (II) (Table) and (IV) revealed their similarity in substitution pattern and in configuration of 1H—6-H and 11-H with (I) and its diacetate (V), respectively. 15-H and 16-H, however, appear in the olefinic proton region for (II), contrary to the case of (I). The presence of a vinyl group suggested by the above difference was verified by the appearance of a newly-formed methyl triplet (δ 1·18, J 8 in pyridine) in the n.m.r. spectrum of dihydroinumakilactone B (VI), m.p. 254—257°, ν 3490, 1773, 1715, and 1645 cm^{-1}, obtained by catalytic reduction (Pd–C) of (II).

For the determination of absolute configuration of the ring system, (II) was hydrogenated catalytically (PtO_2) to give the tetrahydro-compound (VII), m.p. 250—252°, which was oxidized (Jones' reagent) to the corresponding 3-keto-derivative (VIII), m.p. 265—266°, ν 1800, 1753, and 1722 cm^{-1}. The c.d. spectrum of (VIII) having a characteristic negative n–π^* Cotton effect with fine structure, was superimposable upon that of the corresponding derivative of (I).[2] This indicated the same absolute configuration in (I) and (II). The β-orientation of the 3-hydroxy-group was supported by the acetylation shifts of methyl groups [(II) → (IV): $18\text{-}H_3$ +0·15 and $20\text{-}H_3$ −0·20 p.p.m. in pyridine).[2] The coupling constant $J_{6,7}$ (Table) indicated the *trans*-configuration for 6-H/7-H in (II).[1] The α-orientation of the vinyl group at C-14 was assigned from the c.d. spectrum of (II) ($[\theta]_{259}$ −20,300).[1,5]

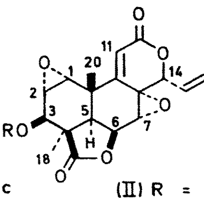
N.m.r. signals of derivatives of inumakilactones B and C

Compd. No.	(II)		(III)	(IX)
Solv.	Py	$(CD_3)_2SO$	$(CD_3)_2SO$ $(+D_2O)$	$CDCl_3$
$18\text{-}H_3$	1·41	1·34	1·31	1·56
$20\text{-}H_3$	1·51	1·07	0·86	1·17
1-H	3·63d (4·0)	3·54d (4·0)	3·36d (4·2)	3·52d (4·0)
2-H	3·51dd (4·0,6·5)	3·34dd (4·0,6·0)	3·29dd (4·2,5·5)	3·45dd (4·0,6·0)
3-H	4·67d (5·6)	4·26d (6·0)	4·25d (5·5)	5·47m
5-H	2·16d (5·2)	2·05d (5·0)	2·04d (6·4)	2·10d (5·0)
6-H	5·10dd (1·2,5·2)	4·96dd (1·2,5·0)	4·63[a]	4·89ddd (1·7,5·0,5·0)
7-H	3·95d (1·2)	3·78d (1·2)	5·00br.d (*ca.* 3)	6·23ddd (1·7,1·7,5·0)
11-H	6·78s	6·42s	4·56[a]	6·17d (1·7)
14-H	5·39d (6·5)	5·40d (6·5)	4·56[a]	5·29ddd (1·7,1·7,4·0)
15-H			4·00m	5·17m
	5·3–6·0	5·4–5·8		
16-H			0·99d (6·5)	1·34d 6·2)

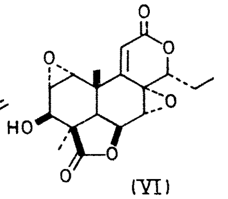
[a] Signals overlap each other.



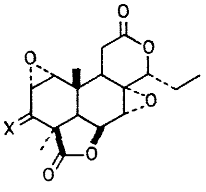
(I) R = H
(V) R = Ac



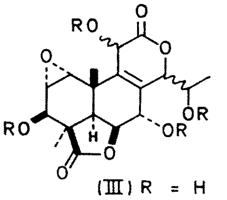
(II) R = H
(IV) R = Ac



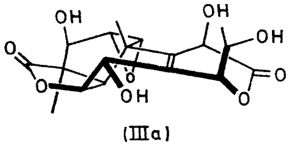
(VI)



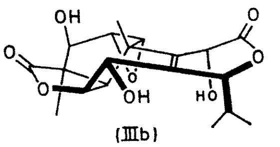
(VII) X = β-OH,α-H
(VIII) X = O



(III) R = H
(IX) R = Ac



(IIIa)



(IIIb)

Inumakilactone C (III), $C_{18}H_{22}O_9$, m.p. 263—265° (dec.), contains a γ-lactone group (ν 1760 cm^{-1}), a δ-lactone group (ν 1700 cm^{-1}, $[\theta]_{225\cdot5}$ −9350, $[\theta]_{200}$ +19,970!), and four hydroxy-groups [ν 3300 cm^{-1}; tetra-acetate (IX), m.p. 253—255°, ν 1783, 1730, and 1700 cm^{-1}]. Although no u.v. maximum and no n.m.r. signal due to an olefinic hydrogen were observed, the presence of a double bond in (III) was detected by a positive colour reaction with $C(NO_2)_4$.

The n.m.r. spectrum of (IX), and extensive double resonance experiments, disclosed the presence of two tertiary and one secondary methyl groups and an isolated proton 11-H, and the vicinal arrangements of 1-H, 2-H, 3-H; 5-H, 6-H, 7-H; and 14-H, 15-H, 16-H (Table). From the acetylation shifts on going from (III) to (IX) [1·16, 1·46, 1·74, and *ca.* 1·15 p.p.m. for 3-H, 7-H, 11-H, and 15-H, respectively, in $(CD_3)_2SO$], hydroxy-groups were assigned at C-3, C-7, C-11, and C-15. The substitution pattern and the relative configuration of ring A were easily deduced from the similarity of the n.m.r. signals of (III) and (IX) with those of (I) and (V)[1] and the nuclear Overhauser effect (NOE) (11%) observed between 3-H and $18\text{-}H_3$ (3-H and 4-Me *cis*). The small $J_{6,7}$ suggested 6-H/7H to be *trans*, unlike the nagilactone C series[3]; thus 7-H has an equatorial orientation. The large NOE (18%) between 1-H and 11-H

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† The Dreiding model indicates the distance between 7(eq)-oxygen and 14(eq)-carbon is 2·2—2·4 Å and that between 1-H and 11(eq)-oxygen is 1·8—1·9 Å for both boat conformations of ring C. In chair conformations of ring C these distances are somewhat longer (2·3—2·5 Å and 2·3 Å, respectively) but the repulsion would still be large.

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confirmed the latter to be equatorial. The magnitude of the homoallylic coupling constant ($J_{7,11}$ 1·7 Hz) is in good agreement with the above conclusions; 7(ax)-H and 11(eq)-H.[6] The homoallylic coupling constants $J_{11,14}$ (~0) and $J_{7,14}$ (1·7 Hz) are explicable on the basis that 14-H is equatorial (eq–eq and ax–eq, respectively).

All these observations point to the four stereostructures, (IIIa), (IIIb), and their mirror images, if the greater stability of a 3,6-dihydro-2-pyrone in the boat conformation[7] is taken into account. Although the limited amount of material available has prevented further study, the rather unusual axial disposition of the substituents at C-11 and C-14 can be rationalized on the basis of serious steric and electronic interactions in a diequatorial conformation: The non-bonded interactions between the 7(eq)-acetoxy-group and the 14(eq)-substituent and between 1-H and the 11(eq)-acetoxy-group,† as well as the dipole–dipole interaction between the 11-acetoxy-group and the lactone carbonyl in this conformation, would be minimized when the substituents are axial.

The close similarity of the structure (III) with (I) implies the same absolute configuration and an intimate biogenetic relationship between these compounds.‡

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