

AJUGAMARIN, A NEW BITTER DITERPENE
 FROM AJUGA NIPPONENSIS MAKINO

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Summary: The structure of a new bitter neo-clerodane, ajugamarin, isolated from *Ajuga nipponensis* Makino, has been elucidated by spectroscopic studies and confirmed by X-ray crystallographic analysis.

The leaves of *Ajuga nipponensis*, Labiatae, have a bitter taste. A bitter principle, ajugamarin, was isolated from the dry leaves of this plant in 0.2% yield. On spectroscopic and X-ray crystallographic studies we proposed the structure 1 for ajugamarin.

Ajugamarin 1 showed the following data: $C_{29}H_{40}O_{10} \cdot \frac{1}{2}CCl_4$, crystallized from CCl_4 as colorless needles; m.p. 93-95°; M^+ 548 (base peak) by FD-MS; ν_{max} (KBr) 3540, 1780, 1750-1690, and 1640 cm^{-1} ; λ_{max} (95% EtOH) 212 nm (ϵ 20,000). The 1H -NMR spectrum (100 MHz, $CDCl_3$) of 1 showed the presence of the groupings: $C-CH_3$ (δ 0.84 s), $CH-CH_3$ (δ 0.84 d, $J=6$ Hz), 2 $-OCOCH_3$ (δ 2.14 and δ 1.96), $C-CH_2OAc$ (δ 4.91 and 4.45 ABq, $J=12$ Hz), $CH-OH$ (δ 3.35 d, $J=7$ Hz), and $C-O-CH_2$ (δ 3.06 dd, $J=4$ and 2 Hz, and δ 2.32 d, $J=4$ Hz). The presence of an α,β -unsaturated γ -lactone was inferred from the NMR signals (δ 5.85 t, $J=2$ Hz, 14-H and δ 4.78 d, $J=2$ Hz, 16- H_2). The pertinent ^{13}C -NMR data of 1 are summarized in Figure 1.

The combined spectral data suggested that the compound closely related to ajugarins¹ belonging to a clerodane.^{2,3,4}

Tigloyl group was supported with the typical NMR signals (δ 6.72 brq, $J=7$ Hz, δ 1.83 brs, and δ 1.78 brd, $J=7$ Hz). A doublet of triplets at δ 5.84 ($-CH-O-tigloyl$) was assigned to 1-ax-H coupled to 2-ax-H ($J=11$ Hz), 2-eq-H ($J=5$ Hz), and 10-ax-H ($J=11$ Hz)

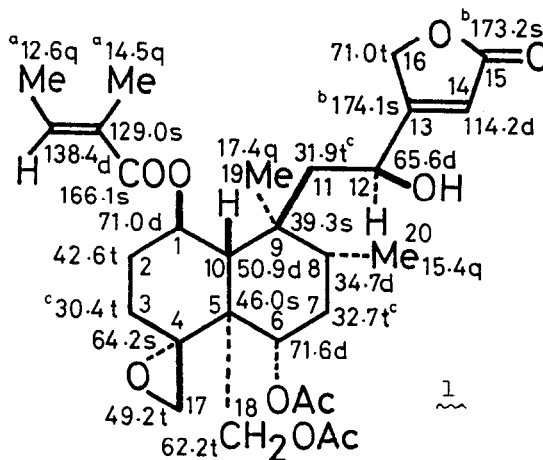


Figure 1 ^{13}C -NMR data of 1
 (δ and multiplicity in $CDCl_3$)
 a,b,c: Assignments are inter-
 changeable.

appearing at δ 2.72. In the oxo-derivative obtained by oxidation of 1 with $\text{CrO}_3/\text{pyridine}$, a $\text{C}-\text{CH}_2-\text{C}=\text{O}$ group (δ 3.05 and 2.85 ABq, $J = 20$ Hz) and a $\text{O}=\text{C}-\text{C}=\text{C}=\text{O}$ group (UV, λ_{max} 290 nm, ϵ 3600) appeared. It follows from the above fact that the hydroxy function is adjacent to the α,β -unsaturated γ -lactone ring.

The full structure and absolute configuration of ajugamarin were confirmed by X-ray analysis of *p*-bromobenzoate of 1. The X-ray study provided the structure 1 assigned to a neo-clerodane^{6,7} for ajugamarin.

The X-ray specimen of about 0.4 x 0.2 x 0.1 mm in size was cut from the platy crystals obtained from EtOH solution. The lattice parameters and intensity data were measured on a Philips PW 1100 diffractometer using graphite monochromated $\text{CuK}\alpha$ radiation. Crystal data: *p*-bromobenzoate of ajugamarin, $\text{C}_{36}\text{H}_{43}\text{O}_{11}\text{Br}$, m.w. 731.6; monoclinic, space group $\text{P}2_1$, $Z = 2$, $a = 11.929(6)$, $b = 16.184(8)$, $c = 9.230(4)$ Å, $\beta = 98.80(6)^\circ$, $U = 1761.0$ Å³, μ for $\text{CuK}\alpha = 10.37$ cm⁻¹, $D_c = 1.380$ g·cm⁻³, $D_m = 1.373$ g·cm⁻³.

The crystal structure was solved by the heavy atom anomalous dispersion method⁵ and refined by the method of block-diagonal least-squares. In determining the absolute configuration, the $|F_c|$ values for the 253 Friedel pairs having the differences in $|F_o|$ greater than $2\sigma(F_o)$ were calculated and compared with $|F_o|$ which showed that 239 pairs gave the consistent result as shown in Figure 2. The R_F value for the 253 pairs was 0.073 while it was 0.093 for the reversed structure. The final R_F value for the 2945 reflections was 0.063 including the corrections for anomalous dispersion but not including the hydrogen atoms.

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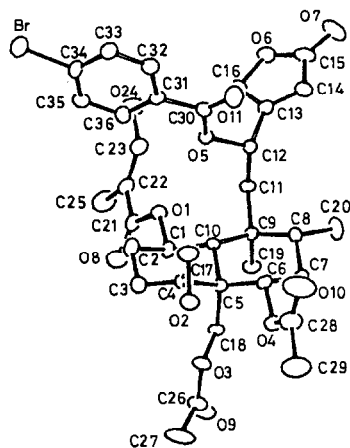


Figure 2 X-ray structure of *p*-bromobenzoate of 1

REFERENCES

- 1: I. Kubo, Y.-W. Lee, V. Balogh-Nair, K. Nakanishi, and A. Chapyra, *Chem. Commun.*, 949 (1976)****2: D.H.R. Barton, H.T. Cheung, A.D. Cross, L.M. Jackman and M. Martin-Smith, *J. Chem. Soc.*, 5061 (1961)****3: N. Kato, M. Shibayama, and K. Munakata, *J. Chem. Soc., Parkin Trans. I*, 712 (1973)****4: F. Camps, J. Coll, A. Cortel, and A. Messeguer, *Tetrahedron Lett.*, 1709 (1979)****5: S.R. Hall and E.N. Maslen, *Acta Cryst.*, 18, 265 (1965)****6: D. Rogers, G.G. Ünal, D.J. Williams, and S.V. Ley, *Chem. Commun.*, 97 (1979)****7: I. Kubo, M. Kido, and Y. Fukuyama, *Chem. Commun.*, 897 (1980)