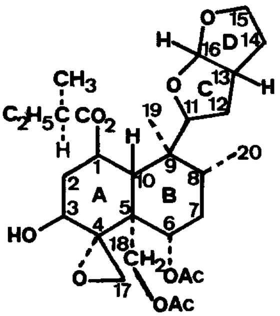
Tetrahedron Letters No. 19, pp 1709 - 1712.
0040-4039/79/0501-1709$02.00/0

AJUGAREPTANSIN, A NEW DITERPENOID FROM AJUGA REPTANS (L.)

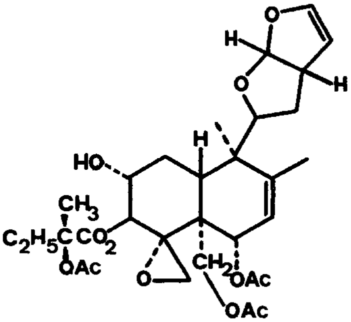
F. Camps, J. Coll, A. Cortel and A. Messeguer
Instituto de Química Orgánica Aplicada de Cataluña (C.S.I.C.)
c/ Jorge Girona Salgado, Barcelona 34. Spain

Summary: The structure of a new clerodane diterpene, isolated from *Ajuga reptans*, has been elucidated by chemical and spectral means and confirmed by X-ray crystallographic studies of the corresponding *p*-bromobenzoate.

During the study of phytoecdysones from *Ajuga reptans* (Labiatae), fractionation of an ethanol plant extract by reversed phase chromatography according to an established procedure[1] allowed us to concentrate the ecdysoid activity in the 70% methanol fraction and to isolate from the 100% methanol fraction ajugareptansin (I)(0.025% yield from dry plant), a new diterpene with a clerodane structure, related to clerodendrin A (II)[2] and to ajugarins[3].



I



II

Ajugareptansin is an amorphous solid, $[\alpha]_D^{20}$=-28º(CCl$_4$, c=8.30), *p*-bromobenzoate, m.p. 210-2º(EtOH), with the molecular formula $C_{29}H_{44}O_{10}$ (Calcd C% 63.10 H% 8.03; Found, C% 62.78, H% 7.99; M^++1, 553 by chemical ionization MS with methane). Among other features its ^{1}H-NMR spectrum (100 MHz in CDCl$_3$ referred to TMS, δ=0) shows four methyl groups (0.84 s; 0.90 d, J= 6Hz; 0.90 t, J= 6Hz and 1.12 d, J= 6Hz), two acetoxy groups (1.90 and 2.10), -CH$_2$OAc AB q, (5.00

and 4.15, J= 13Hz) and CH-OAc double doublet (4.80, J= 10 and 5.5 Hz).

Evidence for the presence of a saturated furofuran ring followed from O-CH-O doublet (5.62, J= 6Hz), which was shown by irradiation studies to be coupled to a complex signal centered at 2.75, the X double doublet of an ABX system (4.21, J= 7 and 8.5 Hz) and complex CH_2-O absorption (2H, centered at 3.84). Likewise, the fragmentation pattern attributable to that ring[2] appeared in the MS: base peak (m/e= 113), formed by scission of the C_9-C_{11} bond and related intense peaks (85, 83, 81 and 69 (m^* 42.1)).

The presence of one secondary hydroxy group was inferred from IR absorption (3460 cm^{-1}) and MS features of the trimethylsilylderivative of I which exhibited characteristic 73 mu shifts and the absence of typical fragments of trimethylsilylated primary alcohols (m/e= 103, $CH_2=\overset{+}{O}-Si(CH_3)_3$)[4]. Furthermore, MS of the above p-bromobenzoate showed 182 mu shifts. The mild reaction conditions used for preparation of these derivatives ruled out the presence of a tertiary hydroxy group.

The ^{13}C-NMR spectrum of I (Table 1) provides evidence for three carbonyl ester groups (two acetates, singlets at 169.4 and 170.0, and singlet at 175.2). The above ^{1}H methyl absorptions suggested the 2-methylbutyrate moiety as possible alternative for the third ester group. This assumption was confirmed by lithium aluminum hydride reduction of I and GLC identification of the resulting 2-methylbutanol by comparison with an authentic sample. Likewise, chemical ionization MS of I exhibited an intense peak at m/e= 103, attributable to protonated 2-methylbutyric acid ion.

It is worth of note that the 17-methylene epoxide protons absorption appearing as a broad singlet (2.92), instead of the typical AB quartets reported in similar cases[2,3,5], as well as the 5-6 ppm shielding of the C-17 absorption (43.4, t) compared to related structures[3,5] could point to a deformation of the chair conformation of the ring A of the decalin, promoted by the steric congestion of C-1 and C-9 substituents.

Substitution and configuration in ring B were deduced both from above ^{1}H and ^{13}C-NMR data and were in agreement with previous reported assignments[2,3,5]. On the other hand, ^{1}H-NMR double doublet H-COH absorption (4.55, J= 11 and 6 Hz) indicates a OH substituent at C-3[2] and it is consistent with a plausible deshielding of the proton signal by the vicinal epoxide ring. Furthermore, the above couplings substantiate the proposed configuration at C-3 and the absence of substituents at C-2. The configuration at C-1 was assigned by decoupling

Table 1. ^{13}C-NMR spectrum of I

C-Atom			C-Atom			C-Atom		
1	69.5	d	11	83.6	d	$\underline{C}H_3CHCOO$	14.2	q (b)
2	33.9	t (a)	12	37.9	t (a)	$\underline{C}H_3CH_2CHCOO$	11.4	q
3	63.7	d	13	41.0	d	$\underline{C}H_3COO$	21.2	q (c)
4	66.5	s	14	34.1	t (a)	$CH_3\underline{C}OO$	170.0	s
5	44.7	s	15	67.7	t	$CH_3\underline{C}OO$	169.4	s
6	71.3	d	16	108.2	d	$C_4H_9\underline{C}OO$	175.2	s
7	32.67	t	17	43.5	t	$C_2H_5\underline{C}H(CH_3)$	42.0	d
8	32.73	d	18	61.5	t	$CH_3\underline{C}H_2CH$	26.9	t
9	41.55	s	19	18.6	q			
10	51.7	d	20	15.8	q (b)			

23 MHz, $CDCl_3$, δ relative to TMS= 0. Multiplicity assigned by selective ^{1}H-^{13}C decoupling. (a,b) Assignments may be interchanged. (c) Double intensity.

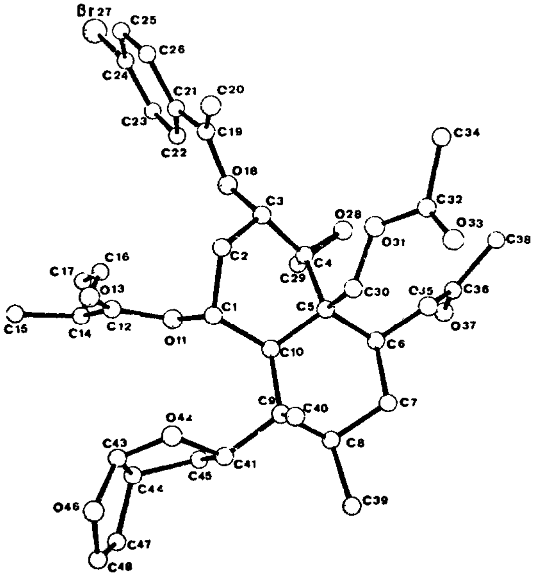


Fig. 1: ORTEP perspective drawing of p-bromobenzoate of I. Hydrogens are not included.

studies on complex signal at 5.6, which revealed coupling constants J= 10, 6 and 4.5 Hz.

As shown in Fig 1, tentative structure *I* has been confirmed by X-ray crystallographic studies of the corresponding *p*-bromobenzoate[6]. Crystals of this derivative are monoclinic, space group $P2_1$, with *a* = 14.152 (5), b= 15.662(4), c= 8.182(2) Å, β= 93.31(3)º and Z=2. The structure was refined to R= 0.070 for 1591 observed reflections. The absolute configuration was determined by the Bijvoet method and it is related to that of clerodendrin A *p*-bromobenzoate chlorohydrin[7]. Rings C and D of the hexahydrofurofuran group exhibit an envelope and planar conformation respectively with a *cis* junction. In the *trans* decalin system, rings A and B adopt a distorted boat and a normal chair conformation respectively, O(18)-C(29) being the shortest intramolecular distance, which could account for the above mentioned apparent magnetic equivalence of the 17-methylene protons.

Acknowledgements: Financial support from the Comisión Asesora de Investigación Científica y Técnica is gratefully acknowledged. The authors thank Dr. J. Rivera of this Institute for MS determinations, Prof. A. Alemany of Instituto de Química Orgánica General (C.S.I.C.), Madrid, for ^{13}C-NMR and 100 MHz ^{1}H-NMR spectra, Drs. C. Miravitlles and X. Solans of Instituto Jaime Almera (C.S.I.C.) Barcelona, for X-ray crystallographic studies and Prof. C. Pascual of Universidad Autónoma de Madrid for helpful discussions.

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(Received in UK 8 March 1979)