Tetrahedron Letters,Vol.26,No.19,pp 2369-2372,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

ASTERISCANOLIDE. A SESQUITERPENE LACTONE WITH A NEW NATURAL SKELETON.

A. San Feliciano*, A.F. Barrero, M. Medarde, J.M. Miguel del Corral, A. Aramburu
Dept. Organic and Pharmaceutical Chemistry. Fac. of Pharmacy. Salamanca-37007. Spain.
A. Perales and J. Fayos
Instituto Rocasolano. CSIC. Serrano 119. Madrid-28006. Spain.

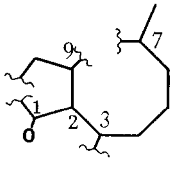
Summary: *A sesquiterpene lactone was isolated from the hexane extract of* Asteriscus aquaticus. *Its constitution and stereochemistry were determined by spectroscopic techniques, principally two-dimensional NMR correlations (COSY, HCCORR, RELAY) and with the interpretation of certain chemical transformations. The results were confirmed by X-ray diffraction and the name asteriscane is proposed for the new natural skeleton.*

By repeated chromatography of a methanol defatted hexane extract of Asteriscus aquaticus L. (familly: Compositae) it was possible to isolate a small amount of a crystalline compound (m.p. 178°, ether), optically active ($[\alpha]_D = 12.1°$, chlorof.), whose remaining properties seemed to correspond to a new sesquiterpene lactone that has been called asteriscanolide.

Its EIMS displayed M^+ at $m/z = 250$[2], corresponding to the formula $C_{15}H_{22}O_3$ and its IR spectrum showed absorption of γ-lactone and ketone groups (1770, 1705 cm^{-1}). Its ^1H-NMR spectrum (fig.1b, table I) showed two methyl singlets and one methyl doublet, as well as a doublet of doublets, centered at 4.29 which was assigned to the proton geminal to the lactonic oxygen, whereas almost all the remaing signals appeared as complex multiplets within the 3 - 1.3 ppm range. These data, together with the absence of olefinic carbons and the large chemical shift of the ketonic carbon (213.9 ppm) in its ^{13}C-NMR spectrum, suggested the existence of a bicyclic carbon skeleton with a seven or eight-membered ring.

In order to confirm this hypotesis and to determine the structure of the substance, several 2D-NMR experiments were carried out. The proton homonuclear correlation spectrum COSY-45[3,4], (fig.1a), displayed correlations for practically all the protons of the asteriscanolide and, besides the normal couplings, other long-range couplings (e.g. H_1-H_{14}, $H_{10\alpha}$-H_{14}, $H_{10\beta}$-H_{15} and H_{14}-H_{15}) could be detected easily. Furthermore, it was possible to locate and differentiate certain signals hidden in the one dimension spectrum, whose later analysis enabled us to obtain the information on δ and J shown in table I.

The RELAY two-dimensional spectrum (RELAYed coherence transfer spectrum)[5,6], which combines one bond C-H correlations with H/H correlations (fig.1c), allowed us to establish the connectivities between carbons bearing, at least, one coupled hydrogen atom[7]. By means of the graphic procedure represented in fig.1c, it was possible to determine the existence of the partial structure 1. Apart from the establishment of a large part of the skeleton, the RELAY experiment also enabled us to unequivocally assign carbon chemical shifts, including those of carbons very close in the



1

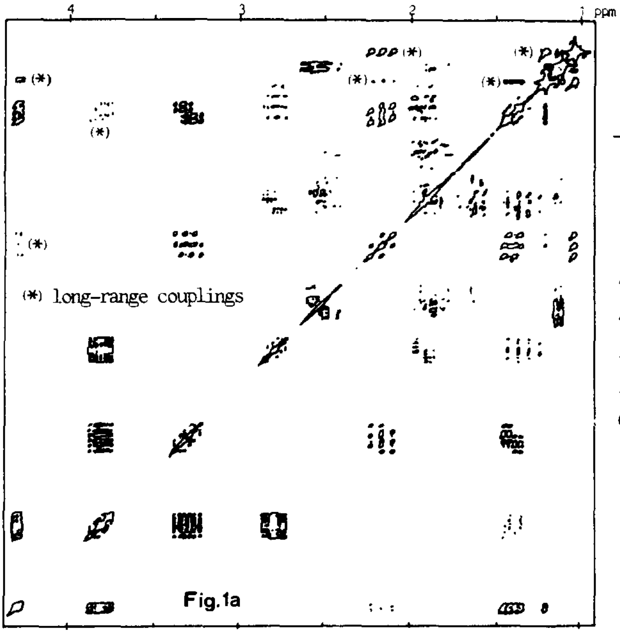
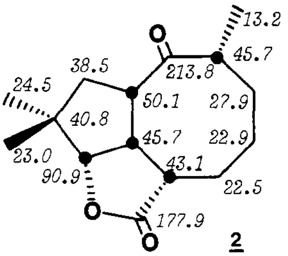
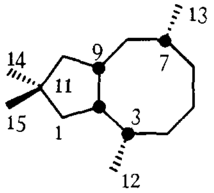


Table I. ^{1}H-NMR data for Asteriscanolide (200MHz, $CDCl_3$, TMS as int.st.)

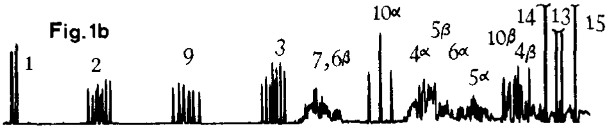
H	δ ppm mult.	H	δ ppm mult.	J (Hz)
1	4.29 *dd*	6β	2.43 *m*	1,2= 5.3 1,10β= 1.1
2	3.79 *ddd*	7	2.53 *m*	2,9= 11.4
3	2.77 *ddd*	9	3.28 *ddd*	2,3= 9.4
4α	1.96 *m*	10α	2.16 *dd*	3,4α= 12.3
4β	1.45 *m*	10β	1.38 *ddd*	3,4β= 4.8
5α	1.58 *m*	13	1.11 *d*	7,13= 6.8
5β	1.93 *m*	14	1.19 *s*	9,10α= 12.9 9,10β= 6.8
6α	1.83 *m*	15	1.02 *s*	10α,10β= 13.3

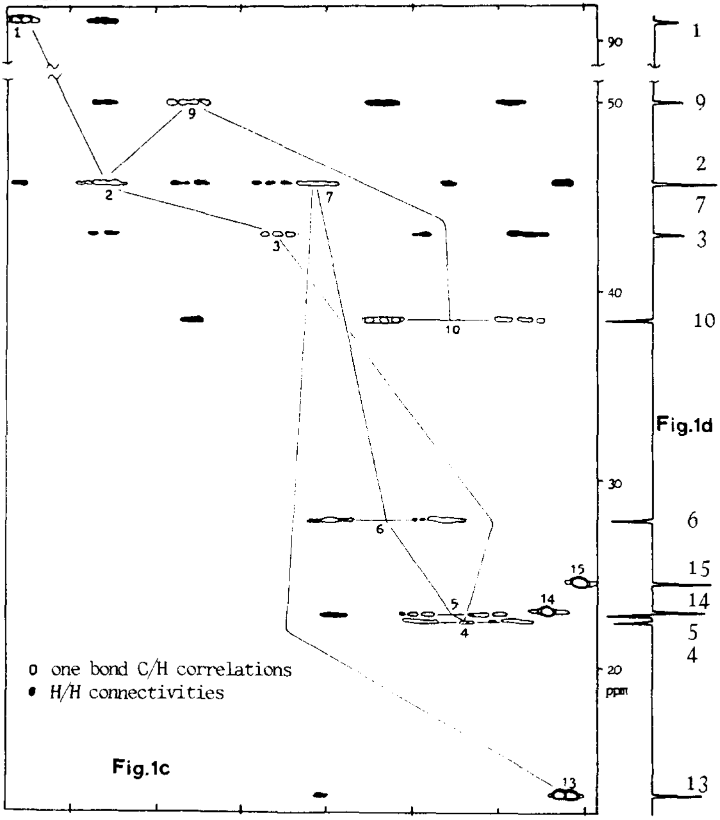


2



ASTERISCANE





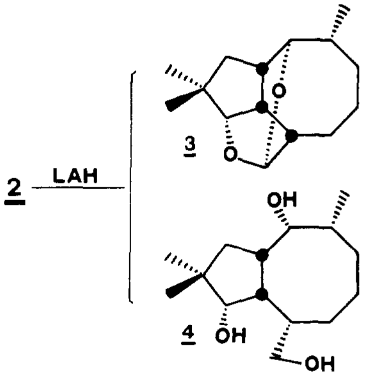


Fig.1a. Symmetrized contour plot of a COSY-45 spectrum of 2

Fig.1b. ^{1}H-NMR spectrum of 2 (200MHz,$CDCl_3$)

Fig.1c. Contour plot of a RELAY spectrum of 2 and graphic procedure for establishing the protonated skeleton of Asteriscanolide

Fig.1d. ^{13}C DEPT spectrum (50.3MHz,$CDCl_3$) showing CH_2 signals (left) and $CH+CH_3$ signals (right) spectrum and bearing the same number of hydrogen atoms (e.g. C_2 at 45.73 and C_7 at 45.68 ppm, or C_4 at 22.5 and C_5 at 22.9 ppm).

As has been reported above, long-range coupling between protons of both methyl singlets and between these methyls and one or more of H_1, $H_{10\alpha}$ and $H_{10\beta}$ were detected, which fixes the location of a gem-dimethyl group between positions 1 and 10, whose existence is further corroborated by the presence of bands at 1375 and 1360 cm^{-1} in the IR spectrum. Accordingly, 2 was proposed as the structure of asteriscanolide.

In order to confirm this, several two-dimensional long-range C/H correlation experiments[8] were performed, the spectra of which are not shown here, to study the surroundings of the quaternary carbons. In this way, non-direct connectivities between the ketonic carbon C_8 and protons H_{13}, $H_{6\alpha}$ and $H_{10\alpha}$; between C_{11} and protons $H_{10\alpha}$, H_{14} and H_{15}, and between the lactonic carbonyl C_{12} and protons H_2 and H_3, were seen to exist.

The relative stereochemistry of ring junctions was deduced from the values of proton couplings (table I) as being all cis, which is confirmed by the formation of asteriscaneacetal 3[10], as well as the expected asteriscanetriol 4[11], in the reduction of 2 by an excess of LAH.

Likewise, as a result from the study of NOE difference and 2D-NOE (NOESY) spectra, it was possible to establish the spatial proximity between the following atoms or groups: Me_{15} is close to protons H_1, H_9, H_2 and $H_{10\beta}$; Me_{14} is close to $H_{10\alpha}$ and H_1; H_1 is close to H_2 and H_3 and H_2 is close to H_3 and $H_{6\beta}$. NOE difference spectra obtained for acetal 3 allowed us to detect, among others, the spatial proximity of H_8 with H_9 and H_{13}, which together with the appearance of H_8 in the proton spectrum as a broadened singlet, permitted us to fix the configuration at C_7 for both substances 3 and 2. Finally, the CD spectrum of 2, which shows a negative Cotton effect associated to the ketone of $\Delta\varepsilon_{305} = -0.17$, allowed us to establish the absolute configuration of asteriscanolide as that depicted in 2.

The crystal structure of 2 and its absolute configuration were also determined by a single crystal X-ray diffraction experiment[12]. It crystallizes in the space group P212121, with Z = 4, a=18.970(1)Å, b=10.917(1)Å and c=6.764(1)Å; Mw=250.35 and calculated density Dx=1.182 $g.cm^{-3}$ (13,14). Pentagonal ring conformations were determined by Cremer's parameters Q and ϕ[15]. The cyclooctane ring shows an almost boat conformation $^{2,6}B_{4,8}$; the cyclopentane ring displays an envelope conformation E_{10} and the lactone ring adopts a conformation between E^2 and $^2T_3$. Relevant short contacts are: C_4-C_8 = 2.91Å, C_2-C_6 = 3.13Å, C_8-$H_{4\alpha}$ = 2.54Å and C_2-$H_{6\beta}$ = 2.62Å. Fig.2 shows a computer generated Ortep drawing of asteriscanolide.

Although several synthetic substances possessing the carbon skeleton of asteriscanolide have been described[16], up to the present, as far as the authors know, no natural product has appeared with this kind of skeleton, which has been called asteriscane 5 and its numbering has been carried out according to that of its supposed precursors humulene and farnesol.

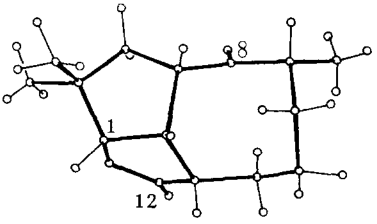


Fig. 2

Acknowledgements: We thank Prof. J. de Pascual (Faculty of Chemistry, Salamanca) the facilities obtained from his laboratory, Prof. S. Garcia-Blanco (Inst. Rocasolano, Madrid) his support and Dr. A. Virgili for the MS. This work received a grant (nº 1857/82) from the Spanish CAICYT.

REFERENCES AND NOTES

1. Presented, in part, at the 14th Intl. Symp. on the Chemistry of Natural Products; Poznań (Poland), July 9-14, 1984.
2. MS of 2; m/z (rel.abond.%): 250(7), 235(1), 222(43), 208(6), 184(9), 165(12), 136(11), 128(11), 107(12), 95(100).
3. a) A. Bax and R. Freeman; J. Magn. Reson., 44, 542 (1981). b) A. Bax; Two-dimensional NMR in liquids, p. 78 Delft-Reidel. Dordrecht, Holland. 1983; and references therein.
4. 32 FID's were coadded with appropriate phase cycling[17] for each value of t_1 which was incremented from 5 μsec to 256 msec in 256 steps. The 1024 x 512 data matrix was Fourier transformed using Bruker DISNMR.82 software. All NMR experiments were performed on a Bruker WP 200 SY instrument.
5. a) P.H. Bolton; J. Magn. Reson., 48, 336 (1982). b) H. Kessler, M. Bernd, H. Kogler, J. Zarbock, O.W. Sørensen, G. Bodenhausen and R.R. Ernst; J. Am. Chem. Soc., 105, 6944 (1983).
6. 128 FID's were coadded with appropriate phase cycling for each value of t_1 which was incremented from 3 μsec to 128 msec in 256 steps. The 1024 x 512 data matrix was transformed with sine-bell filters in both domains.
7. Prior to the RELAY experiment a 2D one bond C-H correlation (HCCORR microprogram) was performed to differentiate which of the signals of a given horizontal in fig.1c corresponds to a C-H correlation and with to H/H connectivities.
8. a) J.N. Shoolery; J. Nat. Products (Lloydia), 47, 226 (1984). b) H. Kessler, C. Criesinger, J. Zarbock and H.R. Loosli J. Magn. Reson., 57, 331 (1984).
9. In these experiments, response of correlation resonance was optimized for $^nJ_{CH}$ values ranging between 6 and 12 Hz.
10. ^{1}H NMR of 3; proton δ ppm (multip., J Hz): *H-1* 3.74(d, 3.2), *H-2* 2.64(ddd, 8.2, 3.2, 3.2), *H-3* 2.22(m), *H-8* 3.54(bs), *H-9* 2.32(m), *H-10α* 1.63(dd, 13.6, 2.0), *H-10β* 2.03(dd, 13.6, 8.5), *H-12* 5.12(d, 3.7), *H-13* 0.96(d, 6.5), *H-14* 1.21(s) and *H-15* 0.98(s). Assigments based on a 2D-COSY experiment.
    ^{13}C NMR of 3; δ ppm (type): 22.1, 24.6 and 30.4 (primary); 22.4, 28.2, 32.7 and 54.0 (secondary); 40.6, 41.9, 42.8, 45.2, 82.2, 94.5 and 99.5 (tertiary); 42.0 (quaternary).
11. ^{1}H NMR of 4: *H-1* 3.58(d, 3.7), *H-8* 3.65(bd, 3.3), *H-10α* 1.52(dd, 13.6, 4.3), *H-10β* 1.97(dd, 13.6, 9.3), *H-12α* 3.80(dd, 10.3, 7.1), *H-12β* 3.65(dd, 10.3, 4.3), *H-13* 1.00(d, 7.2), *H-14* 1.06(s) and *H-15* 0.99(s).
    ^{13}C NMR of 4: 19.3, 24.3 and 30.9 (primary); 25.5, 26.2, 29.1, 47.9 and 68.5 (secondary); 38.2, 40.6, 45.9, 47.2, 79.8 and 82.6 (tertiary); 40.6 (quaternary).
12. Atomic co-ordinates, bond lengths and angles for this work are available from the Director of the Cambridge Crystallographic Data Center; University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. Any request should be accompanied by the full literature citation for this communication.
13. The intensities of 2370 independent reflections to a $\theta = 65^\circ$ were alternatelly collected on an automated four circle refractometer using graphite monochromated CuKα radiation. After usual correction for background, Lorentz and polarization effects, 1997 reflections were judged observed when $I > 2\sigma(I)$ and they were used for structure determination and refinement. No absorption correction was applied and atomic scattering factors and anomalous dispersion corrections were taken from the literature[18].
14. The structure was solved by MULTAN[19] and refined by full-matrix least-squares method with anisotropic thermal parameters for non-hydrogen atoms. Hydrogen atoms were placed at their expected positions, checked in a Fourrier difference map and included as fixed isotropic contributors in the refinement. Several cycles of weighted anisotropic refinement[20], including (hkl) and $(\bar{h}\bar{k}\bar{l})$ reflections gave for the correct enantiomer the discrepance indices R = 0.041 and Rw = 0.52. The absolute configuration[21] was determined using 28 pairs with $\Delta F_c > 0.08$. The total averaged Bijvoet difference was 0.095 for the right enantiomer vs. 0.210 for the wrong one.
15. a) D. Cremer and J.A. Pople; J. Am. Chem. Soc., 97, 1354 (1975) b) Values of Q(Å) and ϕ(°); cyclopentane: $Q = 0.390(2)$ $\phi = 99.9(3)$, γ-lactone: $Q = 0.315(2)$ $\phi = -8.9(4)$.
16. a) K. Sakai, T. Ohtsuka, S. Misumi, H. Shirahama and T. Matsumoto; Chem. Lett., 355 (1981). b) G. Pattenden and S.J. Teague; Tetrahedron Lett., 25, 3021 (1984).
17. G. Wider, S. Macura, A. Kamur, R.R. Ernst and K. Wüthrich; J. Magn. Reson., 56, 207 (1984).
18. International Tables for X-ray crystallography. Kinoch Press. Birmingham, UK. 1974. vol. IV
19. P. Main. MULTAN. Department of Physics, University of York, UK. 1980.
20. M. Martinez-Ripoll and F.H. Cano. PESOS. Instituto Rocasolano, CSIC. Serrano 119. Madrid, Spain. 1975.
21. M. Martinez-Ripoll and J. Fayos. CONFAB. Instituto Rocasolano, CSIC. Serrano 119. Madrid, Spain. 1977.

(Received in UK 4 March 1985)