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Atta-ur-Rahman, K. A. Alvi, S. A. Abbas, T. Sultana,  
Mustafa Shameel, M. Iqbal Choudhary, and Jon C. Clardy

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A DITERPENOID LACTONE FROM *APLYSIA JULIANA*ATTA-UR-RAHMAN,\* K. A. ALVI, S. A. ABBAS, T. SULTANA,<sup>1</sup> MUSTAFA SHAMEEL,<sup>2</sup>

H.E.J. Research Institute of Chemistry, University of Karachi, Karachi 75270, Pakistan

M. IQBAL CHOUDHARY,<sup>3,\*</sup> and JON C. CLARDY

Department of Chemistry, Cornell University, Ithaca, New York 14853-1301

**ABSTRACT.**—A new diterpenoid lactone, angasiol acetate [**1**], has been isolated from the sea hare *Aplysia juliana* collected from the Karachi coastline of the Arabian ocean. The structure, including the absolute configuration of **1**, was determined by single-crystal X-ray diffraction and spectroscopic techniques.

As part of our ongoing efforts in the area of marine natural products, we investigated the sea hare *Aplysia juliana* Quoy and Gaimard (Aplysiidae) and now report the isolation and structure determination of the new diterpenoid lactone angasiol acetate [**1**]. This new brominated diterpene was structurally characterized by X-ray crystallographic and spectroscopic techniques. The absolute configuration of **1** was established from anomalous scattering measurements. The compound was isolated by

extensive solvent-solvent fractionation of the MeOH extracts of the sea hare, followed by cc on Si gel using petroleum ether (40–60°)–Me<sub>2</sub>CO (9:1) as the solvent system to afford **1**. Compound **1** could be recrystallized from MeOH as needles, mp 176°, [ $\alpha$ ]<sub>D</sub> = 27° (CHCl<sub>3</sub>).

The ms of **1** did not show a parent ion, but the [M–HOAc]<sup>+</sup> at *m/z* 458.0458 corresponded to the formula C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>Br<sub>2</sub> (calcd 458.0457). Compound **1** showed only terminal absorption in the uv, while the ir spectrum included bands at

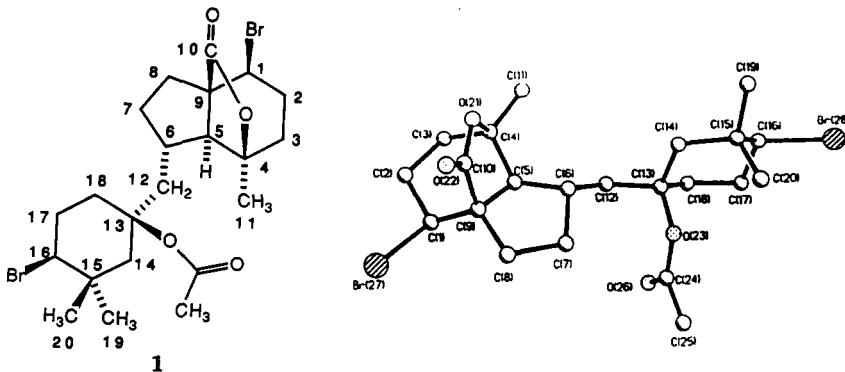


FIGURE 1. A structural drawing of angasiol acetate is shown on the left and a perspective drawing of the final X-ray model is given on the right. Hydrogens are omitted for clarity.

<sup>1</sup>Present address: Center of Excellence, Institute of Marine Biology, University of Karachi.

<sup>2</sup>Department of Chemistry, University of Karachi.

<sup>3</sup>On leave from H.E.J. Research Institute of Chemistry, University of Karachi.

1720 and 1760 cm<sup>-1</sup> indicating the presence of an ester and a  $\gamma$ -lactone (**1**). The structure was established by single crystal X-ray diffraction. Standard heavy atom techniques were used to solve the structure. Full-matrix least square re-

finements of atomic parameters converged at  $R = 0.033$  for the 2590 observed reflections. Absorption corrections ( $\mu = 0.54 \text{ mm}^{-1}$ ) were made for the observed data, and  $F_o$ ,  $F_c$ , were compared for both enantiomers. A computer-generated drawing of the better model (0.033 vs. 0.042) is given in Figure 1. Fractional coordinates of the non-hydrogen atoms are given in Table 1. The  $^1\text{H}$ -nmr spectrum (400 MHz,  $\text{CDCl}_3$ ) showed four singlets at  $\delta$  1.02, 1.09, 1.40, and 1.99, due to three quaternary methyls and one acetyl methyl protons, respectively. Double doublets at  $\delta$  3.89 ( $J_{1a,2a} = 12.5 \text{ Hz}$ ,  $J_{1a,2e} = 4.1 \text{ Hz}$ ) and 4.07 ( $J_{16,17a} = 11.8 \text{ Hz}$ ,  $J_{16,17b} = 5.9 \text{ Hz}$ ) were assigned to the axial protons attached to the Br-bearing C-1 and C-16, respectively. The couplings at C-1 and C-16 protons were

consistent with an equatorial disposition of both bromine atoms. The  $^{13}\text{C}$ -nmr spectrum was completely consistent with the structure given as **1**. The multiplicity assignments were made by using DEPT experiments. The  $^{13}\text{C}$ -nmr spectrum of **1** showed twenty-two carbons. The four methyl carbons appearing at  $\delta$  21.73, 22.82, 32.32, and 21.20 were assigned to C-19, C-20, C-11 and acetate methyl carbons, respectively. Two downfield methines which appeared at  $\delta$  51.43 and 64.40 were assigned to the bromine-bearing C-16 and C-1 respectively. The presence of  $\gamma$ -lactone was indicated by the peak at  $\delta$  176.60.

Angasiol acetate [**1**] is related to the previously reported metabolites irieol A (**2**), pinnaterpene C (**3**) and angasiol (**4**). The absolute configuration of angasiol

TABLE 1. Fractional Coordinates and Equivalent Thermal Parameters for the Non-hydrogen Atoms with Estimated Standard Deviations in Parentheses.

Atom	x	y	z	B( $\text{\AA}^2$ )
C-1	532 (5)	10080 (1)	9060 (1)	40 (2)
C-2	824 (5)	11277 (5)	8874 (1)	48 (2)
C-3	481 (6)	11255 (5)	8481 (1)	49 (2)
C-4	858 (5)	10040 (5)	8304 (1)	42 (2)
C-5	208 (5)	8999 (4)	8497 (1)	33 (2)
C-6	256 (5)	7659 (4)	8363 (1)	37 (2)
C-7	219 (6)	6907 (5)	8708 (2)	46 (2)
C-8	800 (6)	7701 (5)	9000 (1)	46 (2)
C-9	947 (5)	8973 (5)	8843 (1)	36 (2)
C-10	2248 (5)	9220 (5)	8698 (2)	42 (2)
C-11	761 (6)	10077 (6)	7911 (1)	59 (2)
C-12	-826 (5)	7389 (4)	8110 (1)	42 (2)
C-13	-889 (4)	6118 (5)	7934 (1)	38 (2)
C-14	240 (5)	5873 (5)	7705 (1)	41 (2)
C-15	250 (5)	4687 (5)	7479 (1)	40 (2)
C-16	-990 (6)	4639 (5)	7285 (1)	50 (2)
C-17	-2102 (5)	4786 (5)	7513 (2)	48 (2)
C-18	-2051 (5)	6014 (5)	7706 (1)	48 (2)
C-19	1306 (6)	4819 (6)	7214 (2)	61 (2)
C-20	476 (6)	3537 (5)	7701 (1)	52 (2)
O-21	2164 (3)	9825 (4)	8390 (1)	49 (1)
O-22	3216 (4)	8962 (4)	8833 (1)	63 (2)
O-23	-871 (3)	5134 (3)	8197 (1)	37 (1)
C-24	-1764 (5)	4989 (6)	8434 (2)	47 (2)
C-25	-1497 (6)	3913 (6)	8666 (2)	60 (2)
O-26	-2647 (3)	5658 (4)	8468 (1)	61 (2)
Br-27	1277 (1)	10115 (1)	9529 (1)	63 (1)
Br-28	-1169 (1)	3082 (1)	7010 (1)	71 (1)

had been assigned using the anomalous dispersion method (4), but the level of refinement at which the discrimination was made was not sufficient for a definitive assignment. In the current analysis, which agrees completely with the earlier result (4), the overall agreement factor and the discrimination of the anomalous scattering are much more reliable. Angasiol acetate **[1]** is most plausibly acquired by *A. juliana* from dietary sources (5).

## EXPERIMENTAL

**MATERIAL AND ISOLATION.**—The sea hare *A. juliana* (10 kg) were collected from the intertidal zone of the Karachi coastline and were identified by Dr. M. Moazzam Khan, National Institute of Oceanography, Karachi, where a voucher specimen has been deposited. The whole animals were homogenized and dipped in MeOH, and the extract was concentrated to a gum (200 g). H<sub>2</sub>O (1 liter) was then added and shaken with EtOAc (1.5 liters). The EtOAc extract was evaporated and the gum chromatographed on a Si gel column (flash chromatography) using petroleum ether (40–60°)–Me<sub>2</sub>CO (9:1) as the solvent system to afford a semicrystalline mass, which was recrystallized from MeOH as fine needles: mp 176°;  $[\alpha]_D +26.9^\circ$ ; ir (CHCl<sub>3</sub>) 1720, 1760 cm<sup>-1</sup>; <sup>1</sup>H nmr (400 MHz, CDCl<sub>3</sub>);  $\delta$  1.02 (s, Me-20), 1.09 (s, Me-19), 1.40 (s, Me-11), 1.99 (s, Ac), 2.52 (dd,  $J_{12a,12b} = 14.7$ ,  $J_{12a,6} = 3.6$  Hz, H-12a), 3.89 (dd,  $J_{1a,2a} = 12.5$ ,  $J_{1a,2e} = 4.1$  Hz, H-1), 4.07 (dd,  $J_{16,17a} = 11.8$ ,  $J_{16,17b} = 5.9$  Hz, H-16), 2.04 (m, CH<sub>2</sub>-2); <sup>13</sup>C nmr (100 MHz, CDCl<sub>3</sub>)  $\delta$  64.40 (C-1), 30.88 (C-2), 38.09 (C-3), 82.78 (C-4), 63.60 (C-5), 36.07 (C-6), 30.17 (C-7), 44.31 (C-8), 61.42 (C-9), 176.60 (C-10), 32.32 (C-11), 46.59 (C-12), 83.53 (C-13), 32.73 (C-14), 36.49 (C-15), 51.43 (C-16), 31.35 (C-17), 37.15 (C-18), 21.73 (C-19), 22.82 (C-20), 170.80 (C-24), 21.20 (C-25); eims  $m/z$  (%) [M–OAc]<sup>+</sup> 458.0458 (3) (C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>Br<sub>2</sub>), 414.0548 (5) (C<sub>19</sub>H<sub>28</sub>Br<sub>2</sub>), 279 (3), 274 (15), 272 (5), 255 (15), 213 (20), 147 (80), 133 (100), 121 (30), 109 (31), 105 (61), 91 (81), 79 (61), 67 (39).

### X-RAY CRYSTAL STRUCTURE ANALYSIS.—

The crystals from MeOH belonged to the tetragonal space group *P*4<sub>1</sub>2<sub>1</sub>2 with  $a = b = 10.8629$  (11) and  $c = 38.087$  (4) Å,  $V = 4494$  Å<sup>3</sup>,  $Z = 4$ , C<sub>22</sub>H<sub>32</sub>O<sub>4</sub>Br<sub>2</sub>, MW = 518. A complete set of Friedel pair diffraction maxima with  $2\theta \leq 112^\circ$  were collected using  $\theta:2\theta$  scans with graphite monochromated CuK $\alpha$  radiation (1.54178 Å) on

a computer-controlled four-circle diffractometer at room temperature. Of the 2843 unique reflections, 2590 (91%) had  $|F_o| \leq 3\sigma(F_o)$  and were judged observed. The structure was solved by a standard heavy atom approach. Initial bromine atom coordinates were derived from the Patterson map, and the remaining non-hydrogen atoms were located in a series of weighted and difference Fourier syntheses. The structure was refined by full-matrix least-squares methods to a final discrepancy index of 0.033 for the observed data. Absorption corrections ( $\mu = 0.54$  mm<sup>-1</sup>) were applied to the observed data and  $F_o$ ,  $F_c$  were compared for both enantiomers. A computer-generated drawing of the better model (0.033 vs. 0.042) given in Figure 1.<sup>4</sup>

The Nicolet (Siemens) R3M/V automated diffractometer was used for diffraction data collections. Crystallographic calculations were performed on MicroVAX II computer by using SHELXTL PLUS structure solving package (6).

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<sup>4</sup>Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, UK.