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THE STEREOCHEMISTRY OF ASTERISCUNOLIDES

AN X-RAY BASED CORRECTION

ARTURO SAN FELICIANO, ALEJANDRO F. BARRERO, MANUEL MEDARDE, JOSE M. MIGUEL DEL CORRAL and ARRATE ARAMBURU
Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Salamanca, Spain

AUREA PERALES and JOSE FAYOS
Instituto Rocasolano, Serrano 119, Madrid 6, Spain

and

FRANCISCO SANCHEZ-FERRANDO
Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma, Bellaterra (Barcelona), Spain

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Abstract—The application of X-ray diffraction methods has shown that the configurations of Asteriscunolides **A** and **B** at the Δ^9 double bond are *Z*, rather than those previously proposed *E*, while the stereochemistries of Asteriscunolides **C** and **D** were correctly established. Some unexpected NMR data and the new assignment of the spectral signals, based on 2D-NMR C/H correlations and NOE-difference experiments are reported.

Previously, we have reported[1,2] the isolation and structural determination of Asteriscunolides **A**, **B**, **C** and **D**, as the first known humulanolides. These substances have an 11-membered ring and it was postulated that they were two pairs, **A**–**C** and **B**–**D**, of conformationally stable conformers, assuming that their Δ^9 double bond had the *E* configuration in the four substances, because all of them showed ^3J H—H olefinic coupling constants ranging between 13.9 and 16.5 Hz.

X-Ray diffraction determinations have now shown that the constitution of all four Asteriscunolides was correctly proposed. In the cases of Asteriscunolides **C** and **D** even the configuration and conformation in solution were very close to those present in the crystal form.

On the other hand, X-ray analyses of Asteriscunolides **A** and **B** have shown that the configuration at the Δ^9 double bond in both compounds is *Z* rather than *E* as initially proposed. Thus, the differences between Asteriscunolides occur at the Δ^6 and Δ^9 double bond configurations as shown in Fig. 1.

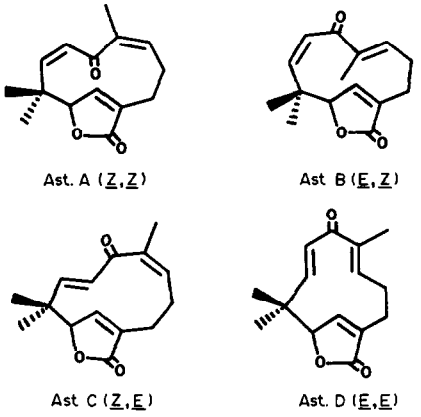

Fig. 1.

RESULTS AND DISCUSSION

Crystal structures

The crystal structures of the four natural isomers (*Z*, *Z*), (*E*, *Z*), (*Z*, *E*) and (*E*, *E*) have been established by X-ray diffraction. Figure 2 shows the X-ray molecular model (Ortep drawing) of Asteriscunolide **C** (*Z*, *E*) as a representative figure of all isomers.

Conformation of the 11-membered ring in each isomer is principally controlled by the stereochemistry of Δ^6 double bond and by the rigidity and almost coplanarity of the C_1—C_4 moiety introduced by the unsaturated lactone ring. Figure 3 shows a perspective view for the X-ray models of the Asteriscunolides where the lactone rings at the bottom are almost hidden.

The less flexible single bonds are, obviously, those close to the lactone ring θ (3–4) = −45° to −96.4° which keeps the two hydrogen atoms at C_5 outside the ring and θ (11–1) = 46.4° to 68° which also moves C_{14} and C_{15} methyl groups outside. The most stable

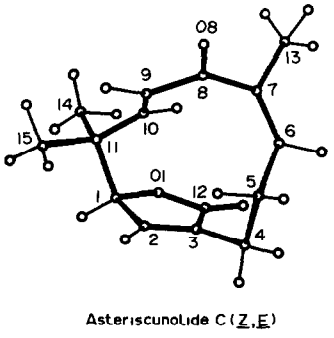

Fig. 2.

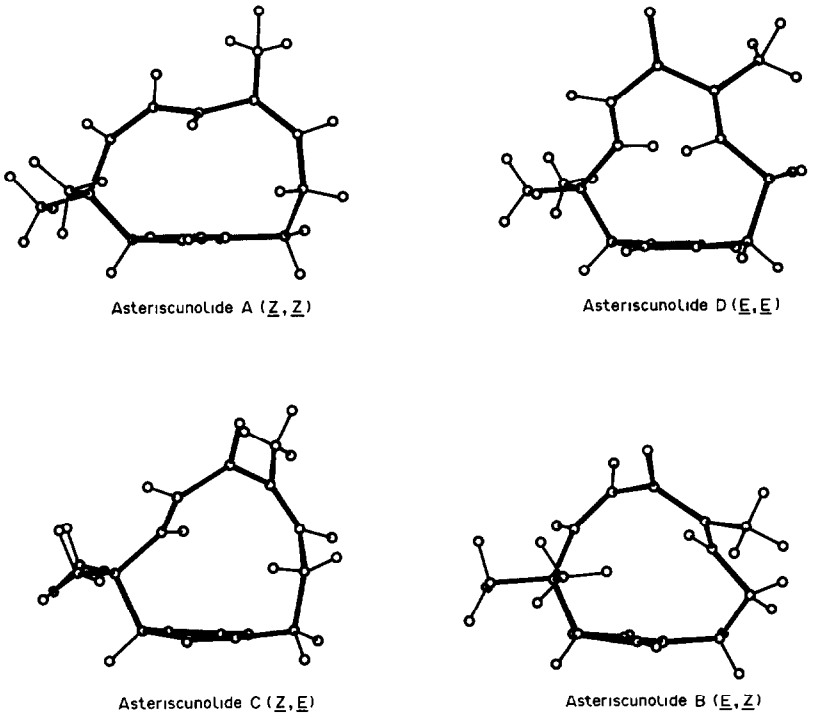

Fig. 3.

conformer for each isomer corresponds to those torsions (Table 4) which move substituents away from the center of the ring. Furthermore, the number of atoms of the ring is not enough to prevent some intraannular short contacts (Table 5), which also affect the conformation of each isomer.

As previously reported[2] Asteriscunolide **A** (*Z*, *Z*) isomerizes quantitatively to Asteriscunolide **C** (*Z*, *E*) by heat and not to Asteriscunolide **B** (*E*, *Z*). The explanation for this result could be readily deduced from the examination with models of the hypothetical evolution pathway during both isomerizations, the

Table 1. Crystal data for the four Asteriscunolides

	A (Z,Z)	B (E,Z)	C (Z,E)	D (E,E)
CRYST. SIZE	.2*.1*.03	.3*.1*.1	.4*.3*.2	.3*.3*.3
A (Å)	11.179(1)	15.572(3)	13.749(1)	14.774(1)
B	5.939(1)	6.418(1)	10.938(1)	10.356(1)
C	9.929(1)	13.871(1)	9.244(1)	8.985(1)
β	90.50(1)	103.78(1)		
V (Å^3)	659.2(1)	1346.5(3)	1390.3(2)	1374.7(2)
SPACE GR.	P21	C2	P212121	P212121
Z	2	4	4	4
D_x (G.CM^{-3})	1.240	1.214	1.176	1.190
D MAX.	60	65	65	65
BIJVOET PAIRS	1962	2400	2744	2253
OBS.I>2σ(I)	1880	1883	2394	1367
R_{obs}/RW_{obs}	.047/.054	.055/.063	.049/.066	.039/.048
NUM.REF/PAR	12	12	15	8
NUM.BIJ.PAIR. ABS.CONF.	115	114	72	74
<BIJ.DIFF.>	.242/.260	.495/.522	.095/.143	.109/.153

Table 2. Atomic parameters for the four Asteriscunolides coordinates (.10**4) and thermal parameters as UEQ = (1/3). Sum (UIJ.AI*AJ*.AI.AJ.Cos(AI,AJ))10**3

Ast. A (Z,Z)

Atom	X/A	Y/B	Z/C	UEQ
O1	4241(2)	7176(23)	871(2)	55(1)
O8	1041(2)	2910(23)	2237(2)	60(1)
O12	5286(2)	7532(23)	2785(3)	71(1)
C1	3545(3)	5423(23)	215(3)	48(1)
C2	3558(3)	3568(23)	1203(4)	49(1)
C3	4180(3)	4128(23)	2300(3)	45(1)
C4	4414(3)	2784(24)	3552(4)	57(1)
C5	3253(3)	1743(24)	4107(4)	61(1)
C6	2505(3)	3459(24)	4773(4)	63(1)
C7	1662(3)	4802(24)	4237(4)	57(1)
C8	1308(3)	4673(24)	2787(4)	49(1)
C9	1265(3)	6891(23)	2091(4)	52(1)
C10	1665(3)	7556(23)	889(4)	51(1)
C11	2317(3)	6372(23)	-238(3)	47(1)
C12	4634(3)	6403(24)	2086(4)	51(1)
C13	1070(4)	6562(24)	5074(5)	79(2)
C14	2551(3)	8123(24)	-1345(4)	63(1)
C15	1563(3)	4471(23)	-862(4)	60(1)

Ast. B (E,Z)

Atom	X/A	Y/B	Z/C	UEQ
O1	8016(1)	4915(22)	6125(2)	55(1)
O8	7032(2)	-515(22)	9048(2)	104(2)
O12	9254(2)	6632(21)	6827(2)	75(1)
C1	7728(2)	2754(22)	6065(2)	52(1)
C2	8530(2)	1615(21)	6573(3)	53(1)
C3	9184(2)	2899(22)	6953(3)	52(1)
C4	10041(3)	2483(22)	7692(3)	79(2)
C5	9942(3)	1201(22)	8560(4)	87(2)
C6	9052(2)	1510(22)	8761(3)	64(1)
C7	8479(3)	46(23)	8876(2)	63(1)
C8	7552(3)	675(22)	8803(3)	67(2)
C9	7280(2)	2821(22)	8443(3)	65(1)
C10	7050(2)	3542(22)	7521(3)	58(1)
C11	6906(2)	2522(22)	6508(2)	57(1)
C12	8870(2)	5004(22)	6664(2)	49(1)
C13	8690(4)	-2242(23)	9019(4)	96(2)
C14	6133(3)	3644(23)	5810(3)	84(2)
C15	6698(3)	196(24)	6522(3)	81(2)

Ast. C (Z,E)

Atom	X/A	Y/B	Z/C	UEQ
O1	7753(1)	4739(1)	7154(2)	817(5)
O8	6962(2)	- 8(1)	10424(2)	1296(10)
O12	9061(2)	4972(2)	8549(2)	1213(8)
C1	7346(2)	3787(2)	6285(2)	769(7)
C2	8133(2)	2846(2)	6264(2)	716(6)
C3	8821(1)	3126(2)	7165(2)	691(6)
C4	9615(2)	2347(3)	7763(3)	1092(11)
C5	9203(2)	1398(3)	8820(3)	1057(10)
C6	8809(2)	1937(3)	10195(2)	865(8)
C7	7929(2)	1753(2)	10759(2)	681(6)
C8	7158(2)	1016(2)	9998(2)	768(7)
C9	6671(2)	1527(2)	8743(3)	810(7)
C10	6722(1)	2697(2)	8399(2)	686(6)
C11	6398(2)	3307(2)	7020(3)	895(8)
C12	8600(2)	4353(2)	7724(2)	767(7)
C13	7636(2)	2217(2)	12225(2)	883(8)
C14	5740(2)	4406(4)	7357(5)	1343(14)
C15	5920(3)	2419(4)	5953(3)	1420(16)

Ast. D (E,E)

Atom	X/A	Y/B	Z/C	UEQ
O1	2627(1)	4718(2)	1760(2)	764(7)
O8	1530(2)	521(3)	6299(4)	1331(14)
O12	3855(2)	5289(3)	3048(3)	1074(10)
C1	2296(2)	3579(3)	1018(3)	695(10)
C2	3071(2)	2674(3)	1158(3)	691(10)
C3	3725(2)	3151(3)	1994(3)	659(9)
C4	4537(2)	2521(4)	2637(4)	846(12)
C5	4377(2)	2095(4)	4261(4)	893(13)
C6	3450(2)	1539(3)	4448(3)	724(11)
C7	2879(2)	1616(3)	5592(3)	721(10)
C8	1947(3)	1152(3)	5361(4)	840(13)
C9	1518(2)	1480(3)	3930(4)	803(11)
C10	1691(2)	2622(3)	3287(3)	656(9)
C11	1419(2)	3096(3)	1783(4)	761(11)
C12	3457(2)	4471(3)	2349(3)	722(11)
C13	3105(3)	2105(4)	7115(4)	1012(15)
C14	748(2)	4221(4)	1918(6)	1062(16)
C15	1001(3)	2027(5)	798(5)	1152(17)

second having greater spatial interactions at the transition state, particularly between O_8—Me_{15} and Me_{13}—H_6.

Lactone rings are almost planar in the four cases and display a $^2T_1$ conformation in Asteriscunolides **B**, **C** and **D** and between ^{12}E and $^{12}T_{01}$ in Asteriscunolide **A**. Cremer parameters[3] for these rings have been calculated and are listed in Table 4. Calculations were carried out anticlockwise beginning at C_2.

NMR studies

Once the stereochemistries of the Asteriscunolides were unequivocally established, certain assignments of the NMR signals had to be revised and more complete NOE studies and 2D-NMR C/H correlations were performed. As a result, the previous assignment of doublets at 5.29 and 6.16 ppm in the ^{1}H-NMR spectrum of Asteriscunolide **A**, those at 5.49 and 6.17 ppm in Asteriscunolide **B** and those at 5.74 and 6.10 ppm in Asteriscunolide **D**, respectively, proposed for α and β protons (H_9 and H_{10}) of the *cross*-conjugated carbonyl, have to be reversed (Table 6).

The new chemical shift assignments, which are unexpected in the cases of Asteriscunolides **A** and **B**, are not easily explained in terms only of the "cisoid" conformation and coplanarity of the α,β-unsaturated system ; the presence and spatial disposition of the α,β-unsaturated γ-lactone and of the Δ^6 double bond must, therefore, also influence these values. In the case of Asteriscunolide **D** the relative disposition of H_{10} with respect to the Δ^2 and Δ^6 double bonds could explain its shielding relative to H_9.

EXPERIMENTAL

The X-ray intensity data of the four isomers (*Z*, *Z*), (*E*, *Z*), (*Z*, *E*) and (*E*, *E*) of Asteriscunolides were collected on a four circle diffractometer using graphite monochromated Cu Kα radiation (λ = 1.5418 Å). The Bijvoet pairs HKL and $\overline{HKL}$ reflections were measured alternately. No intensity decay was observed for any of them during the experiment. Table 1 shows the crystal data. The intensities were reduced by Lorentz polarization, but no absorption or secondary extinction corrections were applied. The crystal structure was solved by Multan[4] and refined anisotropically by full-matrix least squares.[5] The H atoms were located on a difference map, and included as fixed contributors for the last cycles of refinement, where all HKL and $\overline{HKL}$ reflexions were used. A weighting

Table 3. Bond distances (Å) and bond angles (deg.)

Asteriscunol.	A	B	C	D
2=3	1.33	1.32	1.297	1.319
3-4	1.50	1.50	1.492	1.484
4-5	1.54	1.50	1.534	1.543
5-6	1.48	1.49	1.503	1.495
6=7	1.34	1.33	1.332	1.332
7-8	1.49	1.48	1.506	1.473
8-9	1.49	1.49	1.452	1.473
9=10	1.34	1.33	1.321	1.340
10-11	1.51	1.52	1.506	1.493
11-1	1.55	1.55	1.561	1.550
1-2	1.46	1.47	1.494	1.486
3-12	1.46	1.46	1.469	1.458
12-O 1	1.36	1.36	1.344	1.361
O 1-1	1.45	1.45	1.432	1.440
12=O 12	1.21	1.20	1.200	1.207
7-13	1.49	1.51	1.503	1.497
8=O 8	1.22	1.22	1.214	1.232
11-15	1.54	1.53	1.533	1.546
11-14	1.54	1.53	1.536	1.535
2=3-4	129	130	129.5	130.5
3-4-5	112	114	110.6	111.7
4-5-6	111	111	114.0	110.9
5-6=7	129	127	126.9	130.1
6=7-8	122	118	122.5	117.7
7-8-9	114	118	119.5	116.8
8-9=10	132	129	122.7	119.9
9=10-11	134	134	128.1	129.0
10-11-1	113	112	105.7	106.4
11-1-2	118	117	112.3	113.8
1-2=3	111	112	110.9	112.1
2=3-12	107	107	107.0	106.2
3-12-O 1	109	109	109.2	109.6
12-O 1-1	109	109	109.3	109.4
O 1-1-2	104	103	102.9	102.4
4-3-12	124	123	122.9	123.1
3-12=O 12	130	129	129.1	129.8
O 1-12=O 12	121	121	121.8	120.6
O 1-1-11	110	110	109.0	110.1
6=7-13	121	125	123.1	125.7
8-7-13	117	117	114.4	116.6
7-8=O 8	123	121	119.8	122.9
9-8=O 8	123	121	120.7	120.3
10-11-15	112	113	113.0	113.0
10-11-14	107	108	110.5	110.6
1-11-15	109	107	106.9	108.1
1-11-14	107	108	108.4	109.3
15-11-14	108	109	112.0	109.3

Averaged L.S.S.D. are .01, .02, .005, .006 Å and 1.0, 1.0, 0.3, 0.3 deg

Table 4. Internal torsional angles (deg.) and Cremer parameters for the 5-membered rings

Asterisc.	A	B	C	D
2=3	179	166	164.0	168.4
3-4	- 49	- 45	- 70.2	- 96.4
4-5	- 75	- 28	- 68.1	40.4
5-6	88	129	127.3	-144.2
6=7	3	-164	- 4.6	169.9
7-8	-132	10	- 72.9	- 41.1
8-9	135	81	- 14.1	- 35.8
9=10	0	5	169.1	172.6
10-11	- 60	- 99	-114.1	-127.8
11-1	67	68	46.7	46.4
1-2	-122	-116	-108.4	-112.8
3=2	- 1	- 4	- 6.8	- 5.4
2-1	0	5	8.7	6.0
1-O 1	1	- 4	- 6.9	- 4.1
O 1-12	- 2	2	3.4	1.2
12-3	2	1	2.3	2.7

Averaged L.S.S.D. are 1.0, 1.0, 0.3 and 0.5 for Asteriscunolides A, B, C and D.

scheme was applied, therefore, to normalize $\langle W\Delta F\rangle$ vs $\langle F_o\rangle$ and $\langle \sin\theta/\lambda\rangle$.

The absolute configuration was determined by comparing the more significant Bijvoet pairs with greater ΔF_c. The number of these pairs and the average Bijvoet differences for each isomer are listed in Table 1. All four isomers have the same absolute configuration at C_1, which can be seen in Fig. 3. Table 2 shows the final isotropic parameters. Table 3 contains the bond length and bond angles. Anisotropic thermal parameters, H-atom parameters and $F_o - F_c$ tables are given as supplementary material.

Table 5. Significant intraannular short distances (Å)

Asterisc.	A	B	C	D
3-6	3	2.72	3.09	2.80
10-O 1	2.89	2.86	2.88	2.92
10-C 2	3	3	2.77	2.80
H 6-C 9	-	-	-	2.58
H 10-C 7	-	-	-	2.56
C 8-C 2	3.05	-	-	-
O 8-C 2	3.03	-	-	-

Averaged L.S.S.D. are 0.01 Å.

Table 6. ^{1}H-NMR data for Asteriscunolides

Asteriscunolide	H_9	H_{10}	H_{14}	H_{15}
A (Z,Z)	6.16 d (J=13.9)	5.29 d	1.41	1.20
B (E,Z)	6.17 d (J=14.1)	5.49 d	1.38	1.04
C (Z,E)	5.91 d (J=16.5)	6.27 d	1.36	1.28
D (E,E)	6.10 d (J=16.5)	5.74 d	1.28	1.30

Table 7. Nuclear Overhauser enhancements (%)

	irrad.	observed H_1	H_2	H_6	H_9	H_{10}	H_{13}	H_{14}	H_{15}
Asteriscunolide A	{15}	7.7	10					#	
	{14}	8.5				9.9			#
	{13}			14.0	8.5				
	{ 1 }		>5					#	#
	{ 2 }	>5							#
Asteriscunolide B	{15}	6.0	7.8				2.3	#	
	{14}	6.1				5.8			#
	{13}		2.5						
	{ 1 }		3.1					3.7	3.0
	{ 2 }	4.4					2.1		3.6
Asteriscunolide C	{15}	7.0	5.0		7.4				
	{14}	5.2				4.8			
	{13}			15.0		4.2			
	{ 1 }		5.2					4.4	4.8
	{ 2 }	4.8				1.7			#
Asteriscunolide D	{15}	7.8	7.0		8.4				
	{14}	8.2				8.6			
	{ 1 }		>5					#	#
	{ 2 }	5.9		8.2					#

Small not quantitated NOEs

Table 8. ^{13}C-NMR spectral data for Asteriscunolides

	Atom	1	2	3¶	4	5	6	7¶	8	9	10	11	12	13	14	15
Asteriscunol.	A	88.1	147.9	138.8	23.0	29.9	138.3	133.7	198.5	133.1	136.5	42.5	173.5	21.3	30.0	24.7
	B	88.7	153.1	138.3	23.9	21.7	151.6	131.8	199.7	133.1	136.8	42.7	173.5	10.9	31.1	23.9
	C	85.6	149.7	138.6	22.8	33.9	128.4	135.6	202.6	129.5	156.4	40.7	173.7	21.1	24.6	21.0
	D	87.3	150.3	139.3	24.5*	22.8*	145.2	133.9	202.9	129.8	155.3	41.0	172.5	12.6	24.2	21.5

Assignments are based on DEPT experiments and C/H 2D-NMR correlations, except for Asteriscunolide B which were performed through comparison with those other Asteriscunolides, and by off-resonance and selective decoupling experiments.

* Assignment of C_4 and C_5 in Asteriscunolide D has been based on the height of the projection peak on the carbon dimension of the 2D C/H spectrum, being smaller for C_5 (with more coupled and spreaded proton signals) than for C_4.

¶ Assignments of quaternary C_3 and C_7 signals were performed through selective H_2, H_6 and H_{13} irradiation in lactones C and D.

Results of some NOE difference experiments on the four stereoisomers (Table 7) show that the conformations of Asteriscunolides in solution are close to those in the crystal form. These experiments were performed after N_2 degassing and in each case, the frequency and power of the on-resonance irradiation were carefully adjusted to properly saturate the signal being irradiated. Off-resonance irradiations were 30–50 Hz apart from the top of the signals, at frequencies without absorption. Quantitative NOE values were calculated as percent proportion between areas of observed nuclei respect to that of irradiated nuclei.

C/H 2D-NMR correlations were obtained through a HCCORR Bruker pulse sequence using a 1 K × 256 w sized matrix. Recycle delay 1.5–2 s and optimization of resonance for $^1J_{CH} = 140$ Hz. Temperature was stabilized at 297 K during acquisition.

NMR experiments were performed in $CDCl_3$ solution in a Bruker WP 200 SY spectrometer using TMS as internal standard.

In Table 8 the new ^{13}C assignments based on C/H 2D-NMR correlation are shown.

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