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ISOCAESPITOL, A NEW HALOGENATED SESQUITERPENE FROM *LAURENCIA CAESPITOSA*†

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Abstract—The halogenated sesquiterpene isocaespitol (1) has been isolated from the marine alga *Laurencia caespitosa* Lamx and its structure determined by X-ray crystallography.

In previous communications[1,2] we have established the structure of caespitol by relating it with isocaespitol (1), both compounds being terpenoids which contain bromine and chlorine, isolated from the marine alga *Laurencia caespitosa* Lamx (Rhodomelaceae). The present paper describes the chemical study of 1 and the confirmation of its structure by X-ray analysis.

RESULTS AND DISCUSSION

The air-dried, pulverised plant was extracted with ether, the ether concentrate was washed successively with dil KOH, dil HCl and water, and the neutral oil thus obtained was carefully chromatographed on standard silica gel. The ether-benzene (9:1) eluent contained isocaespitol (1); 0·06% dry weight alga) as a colourless oil which slowly crystallized, m.p. 92–93°/*n*-hexane, $[\alpha]_D = -15°$.

Isocaespitol (1), was analysed for $C_{15}H_{25}O_2Br_2Cl$ by mass spectrometry [*m/e* 434, 432, 430 (M^+); high resolution *m/e* 353·073 ($C_{15}H_{25}O_2{}^{80}Br^{35}Cl$ requires: 353·070), 237·187 ($C_{15}H_{25}O_2$ requires 237·187)], ν_{max}(KBr) 3500, 3320, 1650, 950, 830, 810 and 720 cm^{-1}. The NMR spectrum (100 MHz, $CDCl_3$, τ-scale) and the spin decoupling study indicate the presence of two one-proton signals at 5·54 (s, *W*1/2 5 Hz) and 5·70 (4 lines, X of ABX) corresponding to protons α to halogens, 6·53 (t, *J* 3 Hz, shifted to 5·36 on acetylation) of one proton α to an OH group, and an AB part of an ABXY pattern centred at 7·63 and 7·72. In the upfield region appear signals for four tertiary Me groups at 8·08, 8·62, 8·69 and 8·84. Acetylation of 1 gave the monoacetate 2, from which isocaespitol was regenerated by mild saponification. The mass spectra of

*Part XII in the series "Marine Natural Products of the Atlantic Zone". For Part XI see A. G. González, J. Darias, J. D. Martín and M. Norte, *Tetrahedron Letters* 3951 (1974).

Final Atom Coordinates for Isocaespitol

	x[1]	y	z	B_{ISO}[2]	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
BR1	.8623(4)	.595(1)	.5265(4)	3.2(2)	9.7(5)	4.1(3)	-0.9(6)	0.2(2)	-2.2(4)
BR2	.1107(4)	0	.0806(5)	2.7(2)	8.3(5)	10.0(4)	-4.9(6)	0.7(2)	-1.8(4)
CL	.843(1)	.259(3)	.203(1)	4.5(7)	8.5(14)	6.3(8)	-2.5(14)	2.1(6)	-3.9(9)
O_1	.398(2)	.374(4)	.183(2)	3.1(7)					
O_2	.532(2)	.031(4)	.167(2)	2.8(6)					
H_2O	.481(2)	.682(4)	.051(2)	4.2(7)					
C1	.708(3)	.238(6)	.358(3)	2.3(10)					
C2	.826(4)	.321(8)	.346(4)	5.0(13)					
C3	.842(3)	.563(7)	.352(3)	1.5(8)					
C4	.728(3)	.649(7)	.289(3)	2.3(9)					
C5	.614(3)	.583(9)	.311(3)	3.6(10)					
C6	.602(3)	.380(7)	.281(3)	2.3(10)					
C7	.477(3)	.268(7)	.280(3)	2.4(10)					
C8	.476(3)	.061(7)	.262(3)	2.9(10)					
C9	.344(3)	-.011(7)	.229(3)	2.7(10)					
C10	.274(3)	.121(8)	.123(3)	3.5(10)					
C11	.271(4)	.311(9)	.135(4)	4.7(13)					
C12	.197(3)	.408(6)	.223(3)	2.7(10)					
C13	.233(3)	.426(6)	.019(3)	2.7(10)					
C14	.444(3)	.325(7)	.398(3)	2.0(9)					
C15	.958(3)	.624(8)	.331(3)	4.1(11)					

1) Standard deviations of last significant figures in parenthesis.

2) B in $Å^2$ or B_{ij} converted to the same units as B using the equation $B_{ij} = 4\ b_{ij}/a^*_i a^*_j$.

K	L	FOBS	FCAL
****	H=	0	****
0	2	63	64
0	3	159	175
0	4	127	118
0	5	179	191
0	6	80	64
0	7	180	170
0	8	53	32
0	9	57	31
1	1	320	392
1	2	284	308
1	3	285	308
1	4	274	258
1	5	238	228
1	6	157	142
1	7	67	59
1	8	174	164
1	9	78	83
2	0	347	319
2	1	229	270
2	2	261	294
2	3	67	70
2	4	129	122
2	5	251	273
2	6	89	105
2	7	76	71
3	1	284	307
3	2	170	192
3	3	122	143
3	4	121	142
3	5	139	171
3	6	87	106
3	7	79	77
4	0	201	144
4	1	170	208
4	3	62	62
4	4	102	96
4	5	56	56
4	6	99	111
4	7	54	50
5	1	45	78
5	2	45	60
5	3	52	35
****	H=	1	****
0	0	62	162
0	1	84	75
0	-1	67	66
0	-2	799	729
0	3	479	463
0	-3	216	211
0	4	92	93
0	-4	75	76
0	5	418	401
0	-5	99	92
0	6	129	135
0	-6	121	120
0	7	218	212
0	-7	182	177
0	8	77	90
0	-8	76	89

K	L	FOBS	FCAL
0	-9	176	185
0	9	39	11
1	0	535	480
1	-1	151	158
1	1	129	126
1	-2	65	99
1	2	341	355
1	-3	364	382
1	3	231	226
1	-4	141	138
1	4	111	112
1	-5	509	514
1	5	60	59
1	-6	48	47
1	6	136	117
1	-7	145	134
1	7	126	131
1	8	101	96
1	-8	147	150
1	-9	63	61
2	0	282	247
2	1	174	174
2	-1	386	402
2	2	164	180
2	-2	288	359
2	3	212	212
2	-3	141	169
2	4	118	141
2	-4	36	55
2	5	285	281
2	-5	51	38
2	6	204	218
2	-6	79	74
2	7	104	115
2	-7	41	29
2	8	107	111
2	-8	121	129
2	-9	51	55
3	0	399	331
3	-1	189	189
3	1	161	181
3	-2	65	122
3	2	86	83
3	3	104	108
3	-4	90	193
3	4	78	95
3	-5	49	86
3	5	77	99
3	-6	132	191
3	6	91	108
3	-7	80	117
3	7	42	77
3	8	72	85
4	0	61	49
4	1	146	152
4	-1	80	131
4	2	98	111
4	4	200	198
4	5	46	71
4	6	97	100

K	L	FOBS	FCAL
5	0	40	35
5	1	85	105
5	3	57	95
5	4	53	74
****	H=	2	****
0	0	49	42
0	-1	34	39
0	1	62	76
0	-2	79	62
0	2	72	66
0	-3	457	442
0	3	297	282
0	-4	163	167
0	4	169	157
0	-5	257	250
0	5	282	276
0	-6	385	345
0	6	159	172
0	-7	130	120
0	7	69	53
0	8	68	52
0	-8	185	187
0	9	139	147
0	-10	141	134
1	0	485	495
1	1	266	257
1	-1	123	137
1	2	527	481
1	-2	466	447
1	3	249	234
1	-3	162	175
1	4	147	127
1	-4	165	146
1	5	232	204
1	-5	268	265
1	6	48	47
1	-6	103	98
1	7	148	154
1	-7	147	139
1	8	104	117
1	-8	75	83
2	0	114	100
2	-1	327	321
2	1	207	193
2	-2	113	136
2	2	270	277
2	-3	193	199
2	3	268	263
2	-4	130	145
2	4	177	184
2	-5	134	156
2	5	103	117
2	-6	69	75
2	6	96	96
2	7	180	174
2	-7	129	131
2	-8	100	115
2	8	89	71
2	-9	60	85
3	0	257	246

K	L	FOBS	FCAL
3	1	251	249
3	-1	244	218
3	2	131	136
3	-2	59	57
3	3	174	181
3	-3	88	112
3	4	109	135
3	-4	133	174
3	5	60	82
3	-5	77	109
3	6	128	120
3	-6	123	157
3	-7	63	71
4	0	63	64
4	-1	55	42
4	1	41	40
4	-2	102	128
4	2	81	99
4	3	126	162
4	4	109	99
4	5	79	70
4	6	56	56
4	-7	44	77
5	0	70	56
5	1	141	123
5	-1	65	105
5	2	50	55
5	3	94	85
5	4	89	87
****	H=	3	****
0	0	580	624
0	1	40	48
0	-1	108	137
0	2	260	253
0	-2	168	160
0	3	40	40
0	-3	519	480
0	4	189	190
0	-4	127	112
0	5	77	100
0	-5	266	248
0	7	85	99
0	-7	179	169
0	-8	78	70
0	8	110	92
0	-10	102	116
1	0	361	360
1	-1	158	162
1	1	378	345
1	-2	258	259
1	2	189	186
1	-3	243	222
1	3	116	112
1	-4	158	154
1	4	161	146
1	-5	113	109
1	5	280	275
1	-6	250	247
1	6	104	116
1	7	192	202

K	L	FOBS	FCAL
1	-7	39	6
1	8	81	71
1	-8	97	104
1	-9	57	53
2	0	153	158
2	1	138	127
2	-1	119	120
2	2	367	340
2	-2	203	202
2	3	194	179
2	-3	223	233
2	4	156	157
2	-4	190	187
2	5	64	65
2	-5	279	315
2	-6	94	112
2	-7	92	95
2	-8	93	104
2	-9	95	106
3	0	186	177
3	-1	249	213
3	1	102	92
3	-2	159	144
3	2	138	132
3	-3	138	155
3	3	142	144
3	-4	33	10
3	4	138	124
3	-5	51	53
3	5	109	117
3	6	143	161
3	-6	57	89
3	7	126	111
3	-8	60	87
4	0	102	101
4	1	242	203
4	-1	135	127
4	2	60	55
4	-2	124	135
4	3	90	92
4	-3	57	71
4	4	66	66
4	-4	124	196
4	-5	40	70
4	5	81	77
4	-7	50	89
5	0	39	22
5	-1	70	75
5	1	139	121
5	2	74	75
5	3	67	89
****	H=	4	****
0	0	365	406
0	-1	172	184
0	1	61	48
0	2	381	381
0	-3	288	262
0	3	709	208
0	-4	81	82

K	L	FOBS	FCAL
0	4	114	117
0	-5	40	65
0	5	195	205
0	-6	38	42
0	-7	203	193
0	7	193	195
0	-8	47	42
0	-9	55	76
1	0	138	125
1	1	147	136
1	-1	324	313
1	2	150	150
1	-2	93	97
1	3	271	267
1	-3	261	264
1	4	125	114
1	-4	125	123
1	5	219	206
1	-5	335	323
1	-6	109	103
1	-7	118	129
1	7	108	113
1	-8	219	211
1	-9	40	47
2	0	294	253
2	-1	210	203
2	1	247	211
2	-2	231	217
2	2	335	318
2	-3	112	114
2	3	158	147
2	-4	207	215
2	4	103	97
2	-5	168	172
2	5	192	180
2	-6	108	111
2	6	150	145
2	7	91	117
2	-8	60	56
2	-9	40	60
3	0	90	77
3	1	43	54
3	-1	104	91
3	2	134	126
3	-2	164	150
3	3	132	136
3	-3	142	144
3	4	73	61
3	-4	124	132
3	5	130	127
3	-6	114	144
3	6	92	71
3	-7	116	131
3	-8	43	50
4	0	88	85
4	-1	140	128
4	1	256	231
4	-2	74	74
4	2	130	136

K	L	FOBS	FCAL
4	-3	52	52
4	3	63	72
4	4	135	127
4	-6	105	138
5	0	52	31
5	1	122	114
5	-1	47	59
5	2	62	42
5	-2	109	109
****	H=	5	****
0	0	287	283
0	1	153	162
0	-1	106	95
0	2	227	225
0	-2	226	222
0	3	136	148
0	-3	37	67
0	-4	109	103
0	5	271	276
0	-5	106	90
0	-6	296	289
0	6	53	55
0	-7	54	48
0	7	137	143
0	-8	96	96
1	0	327	314
1	-1	339	322
1	1	224	218
1	-2	304	260
1	2	343	335
1	-3	315	289
1	3	39	25
1	-4	81	57
1	4	138	135
1	-5	154	149
1	5	81	89
1	-6	152	152
1	-7	96	98
1	-8	85	90
1	-9	74	72
2	0	269	268
2	1	54	36
2	-1	300	286
2	2	95	105
2	-2	215	209
2	3	156	147
2	-3	31	38
2	4	154	156
2	-4	140	135
2	-5	32	43
2	5	134	126
2	-6	88	97
2	6	118	110
2	-7	62	90
2	-8	82	92
3	0	142	128
3	-1	142	131
3	1	208	195
3	-2	190	179

K	L	FOBS	FCAL
3	2	86	66
3	-3	216	219
3	3	174	145
3	-4	151	155
3	4	99	96
3	-5	64	87
3	5	61	62
3	-6	92	104
3	-7	74	95
4	0	139	141
4	-1	100	90
4	1	130	118
4	2	82	79
4	-3	61	81
4	3	73	47
4	-5	85	75
4	-6	40	43
5	-1	133	135
5	-2	96	89
****	H=	6	****
0	0	62	65
0	-1	266	269
0	1	86	79
0	-2	73	72
0	-3	363	367
0	3	135	148
0	4	195	199
0	-5	107	121
0	5	181	192
0	-6	279	259
0	6	57	79
0	-7	99	124
0	-8	87	95
1	0	255	269
1	1	139	158
1	-1	78	89
1	2	266	289
1	-2	131	135
1	-3	279	271
1	4	182	193
1	-4	58	60
1	-5	133	133
1	5	184	186
1	-6	121	130
1	-7	86	94
1	-9	68	70
2	0	120	121
2	-1	217	208
2	-2	116	105
2	2	52	57
2	-3	176	164
2	3	102	97
2	-4	145	141
2	4	55	67
2	-5	118	104
2	5	119	112
2	-6	97	98
2	-7	129	125
2	-8	177	183

K	L	FOBS	FCAL
3	0	132	126
3	1	141	127
3	-1	188	191
3	2	163	147
3	-3	49	62
3	3	155	144
3	-4	132	109
3	4	92	96
3	-5	56	60
3	-6	97	99
4	-1	101	97
4	-2	199	199
4	2	62	79
4	-3	40	33
4	-4	71	61
4	-5	52	48
****	H=	7	****
0	0	247	248
0	-1	262	282
0	2	276	284
0	-2	73	77
0	-3	382	381
0	3	37	41
0	-4	33	8
0	4	57	42
0	-5	48	34
0	5	50	57
0	-6	36	34
0	-7	137	143
0	-8	126	125
1	0	197	213
1	-1	162	172
1	1	55	109
1	-2	104	111
1	2	99	96
1	-3	57	68
1	3	134	150
1	-4	126	130
1	4	64	79
1	-5	37	55
1	-6	175	170
1	-8	153	161
2	0	105	99
2	1	135	137
2	-1	149	160
2	-2	126	116
2	2	198	184
2	-3	184	198
2	3	151	159
2	-4	167	160
2	4	127	129
2	-5	167	160
2	-6	75	84
3	0	116	107
3	-1	136	118
3	1	122	119
3	-2	57	49
3	2	104	107
3	-4	100	86

K	L	FOBS	FCAL
3	-5	69	58
3	-6	84	59
4	-1	49	79
4	-2	108	107
4	-3	53	52
****	H=	8	****
0	0	241	244
0	-1	124	123
0	1	154	169
0	-2	138	143
0	2	141	166
0	-3	70	61
0	3	101	94
0	-4	107	109
0	-5	218	224
0	-6	131	132
1	0	45	29
1	-1	202	210
1	1	81	80
1	-2	56	65
1	2	92	96
1	-3	163	160
1	3	109	106
1	-4	38	51
1	-5	130	140
1	-6	190	186
2	0	160	157
2	-1	122	136
2	1	130	94
2	2	136	144
2	-2	49	46
2	-3	61	63
2	-4	139	137
2	-5	80	81
2	-6	46	45
3	0	133	141
3	-1	96	109
3	-2	117	118
3	-3	117	124
3	-4	115	119
****	H=	[illegible]	****
0	1	105	95
0	-1	90	103
0	-2	76	90
0	-3	41	63
0	-4	42	22
0	-5	44	72
0	-6	217	222
1	0	112	113
1	1	145	146
1	-1	215	238
1	-2	165	133
1	-3	148	155
1	-5	125	142
2	-1	103	113
2	-3	55	50
2	-4	83	95
****	H=	[illegible]	****
5	-4	61	114

the alcohol and acetate showed base peaks at (257, 255, 253) and (299, 297, 295) respectively, arising from the fragment [*a*] as is shown in 1. The C-10 halogen was located when it was shown that treatment of the alcohol (1) with Jones reagent gave the unstable monoketone (3) which easily loses HBr to yield the α,β-unsaturated ketone (4). On the basis of the aforesaid, the relative position of the chlorine and bromine at C-3 and C-4 could not be assigned.

In order to definitively elucidate the structure, a single-crystal of isocaespitol was subjected to X-ray diffraction analysis. One suitable crystal was obtained by recrystallization from carbon tetrachloride. The compound crystallized in the monoclinic system, with systematic extinctions in its diffraction pattern for 0k0 with k = 2n + 1. Since the sample of isocaespitol used is optically active, the space group is uniquely fixed as $P2_1$. Unit cell constants were determined from a least squares fit of 12 carefully centred reflections measured on a Picker FACS-II automated differactometer (MoK_{α_1}; λ = 0·70926 Å) to be: a = 11·548 (13), b = 6·961 (9), c = 11·859 (12) Å and β = 104·27 (3)°.

Three-dimensional intensity data were collected on the above diffractometer, using MoK_α radiation made monochromatic by Bragg reflection from a graphite crystal, scanning reflections in the $2\theta-\theta$ mode at a scan rate of 1°/min and a scan range of 2·0°, and taking background counts of 10 sec at each end of the scan. Of 649 unique reflections having 2θ values less than 35°, 583 remained after rejection of those with intensities less than 1·5 σ. These were put on a common scale using the intensities of three standards (collected every 100 reflections) and corrected for Lorentz-polarization effects. The structure was solved by the heavy atom method, successive cycles of Fourier synthesis, and full-matrix least squares refinement. Ambiguities remained concerned the location of OH and O atoms as well as the identity of a foreign peak in a difference synthesis made very late in the refinement. Careful analysis of the temperature factors associated with each atom led to satisfactory locations for all oxygens in the natural product and a very strong indication that the foreign peak represents a water of crystallization. The H-bonding scheme between the alleged water and the OH and ether moieties reinforces that conclusion. Even though anomalous scattering from the Br and Cl atoms was carefully considered we were unable to arrive at an absolute configuration.

In 1 we show the geometry of isocaespitol. The final weighted residue, wR, was 0·087, and the standard deviation of an observation of unit weight is 1·72. All bond distances and angles agree well with generally accepted values within experimental error.[3]

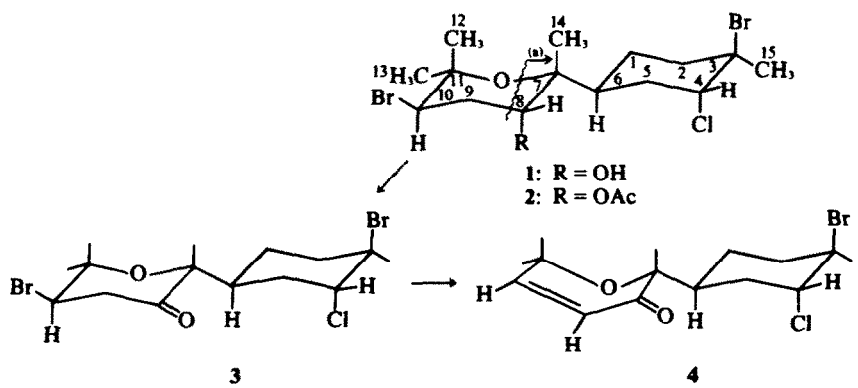
EXPERIMENTAL

The m.ps were determined on a Kofler block and are uncorrected. UV spectra, recorded with a Beckman DB-GT spectrophotometer, refer to EtOH solns. IR spectra, measured with a Unicam SP1100 spectrometer in KBr if not otherwise indicated. NMR spectra were taken with a Perkin-Elmer R-12 (60 MHz) or a Varian HA-100 (100 MHz) instrument for $CDCl_3$ solns with TMS as internal standard, $W1/2$ refers to the width of a band at half height. MS were recorded on an A.E.I. MS-902 or a Hitachi-Perkin-Elmer RMU-7 instrument. Column and dry column chromatography was performed on silica gel 0·2–0·5 and 0·063–0·20 mm respectively, TLC and PLC on silica gel G, the spray reagent was 6N H_2SO_4. Petrol, refers to the fraction b.p. 40–60°. Anhys Na_2SO_4 was used for drying solns.

Isolation of isocaespital (1). Air dried seaweed (2·0 kg) was extracted with ether and the ether soln was concentrated *in vacuo*. The residue was washed succesively with 5% KOH aq and then with 1N HCL to remove acidic and basic components. The neutral oil thus obtained (25 gr) was carefully chromatographed on standard silica gel. Fractions eluted with ether-benzene (9:1) on removal the solvents, left a crystalline substance. Recrystallization from *n*-hexane gave 1 (1·2 g) as monoclinic crystals, m.p. 92–93°, [α] −15 (c, 0·12). (Found: C, 40·04; H, 6·02. $C_{15}H_{25}O_2Br_2Cl.H_2O$ requires: C, 39·94; H, 5·99%). IR: see text. NMR: see text. MS: *m/e* (%) 434, 432, 430 (M^+, 2): 355, 353, 351 (16): 268, 266 (70): 257, 255, 253 (100): 237 (5): 223, 221 (94): 205, 203 (22): 175, 173 (93): and 137, 135, 133 (60).

Acetylation of isocaespitol. Isocaespitol (30 mg) was allowed to react overnight in a soln of Ac_2O (2 ml) in pyridine (1 ml). The soln was poured into water and the product isolated with ether, purified by elution from silica gel with benzene, and crystallised from *n*-hexane as long needles, m.p. 125–128°. (Found: C, 41·50; H, 5·94. $C_{17}H_{27}O_3Br_2Cl.H_2O$ requires: C, 41·42; H, 5·88%); IR: 3500, 2980, 2935, 1735, 1380, 820, 790 and 720 cm^{-1}; NMR: 8·77, 8·66, 8·60, 8·08, 7·90 (each 3H, s), 5·89 (1H, q, J = 12 and 6 Hz), 5·54 (1H, bs, $W1/2$ = 6 Hz) and 5·36 (1H, t, J = 3 Hz). MS: *m/e* (%) 476, 474, 472 (M^+, 3); 397, 395, 393 (20); 310, 308 (64); 299, 297, 295 (100); 279 (16); 265, 263 (80); and 175, 173 (92).

Oxidation of isocaespitol. To a stirred soln of 1 (100 mg) in Me_2CO (20 ml) at room temp. Jones reagent (0·3 ml) was added dropwise till a permanent orange colour resulted. After a further 5 min stirring the mixture was worked up giving the unstable ketone 3 (94 mg); IR: 2985, 2930, 1710, 900 and 710 cm^{-1}; NMR: 8·72, 8·58, 8·54 and 8·08 (each 3H, s), 7·04 (1H, d, J = 8 Hz), 7·03 (1 H, d, J = 10 Hz), 5·76 (1H, q, J = 10 and 8 Hz) and 5·54 (1H, bs, $W1/2$ = 4 Hz). Without further purification, 3 was chromatographed on alumina yielding 4 (54 mg) as a crystalline substance. Recrystallization from *n*-hexane gave plates m.p. 67–68°; UV 224 nm (ϵ 16,900); IR: ν_{max}(CCl_4) 2980, 2930, 1685, 1375, 1100, 1070, 1020, 820 and 730 cm^{-1}; NMR: 8·70 (3H, s), 8·60 (6H, s), 8·09 (3H, s), 5·43 (1H, bs, $W1/2$ = 6 Hz), 4·19 and 3·26 (each 1H, d, J = 11 Hz). MS: *m/e* (%) 353, 351, 349 (M^+, 2); 257, 255, 253 (100); 219, 217 (20); 175, 173 (48) and 139 (34).



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