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NEW MACROCYCLIC ALPHA- AND GAMMA-PYRONES FROM THE MARINE RED ALGA PHACELOCARPUS LABILLARDIERI

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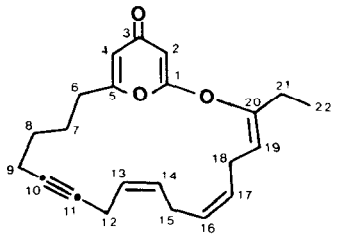
Summary: Along with several of the previously reported gamma-pyrones, a new collection of the Australian red alga Phacelocarpus labillardieri (Sphaerococcaceae) has now been shown to produce structurally similar alpha-pyrones. The structure determinations of four new compounds, two new alpha-pyrones (3, 5) and two new gamma-pyrones (2, 6), are reported herein. These, and the previously reported compounds, remain as the sole examples of this interesting new class of macrocyclic enol-ethers.

In 1982, Kazlauskas et al.[1] reported the isolation of several unprecedented macrocyclic enol-ethers, containing gamma-pyrone functionalities, from the Australian red marine alga Phacelocarpus labillardieri. The major metabolites were 1 and 4, and these compounds are unique in their biogenetic origins, especially considering bromination and enol-pyrone formation. In this paper we wish to report the results of a second investigation of P. labillardieri which has resulted in the isolation of 2 new alpha-pyrones, and 2 new gamma-pyrones, as well as a suggestion for the C-19-C-20 geometry in the previously described macrocyclic pyrone 1.

P. labillardieri was collected at Flinders Reef, near Melbourne, Australia on 8 April, 1984. The alga was immediately frozen, it was next freeze-dried, and then exhaustively extracted with 80% $CHCl_3$/MeOH. The condensed extract (10g) was initially fractionated over TLC grade Si gel, selected fractions were then combined, and a second chromatography was performed. Fractions which chromatographed with 35% EtOAc/isooctane yielded compounds 3 and 5 by final HPLC purification (0.2 % ext. each), those chromatographing with 75% EtOAc/isooctane yielded 2 and 4 (12 and 0.7 % ext.), and fractions chromatographing with 100% EtOAc yielded the more polar metabolite 6 (0.06 % ext.).

The major metabolite, 2, analysed for $C_{22}H_{27}O_3$ by high resolution FAB mass spectral measurement of its M^+ +H ion. The compound lacked significant rotation at the Na D line, and was recognized to be almost identical spectrally to the metabolite described earlier by Kazlauskas from collections of this alga made near Adelaide, Australia.[1,2] Complete analysis of the ^1H NMR data for 2 allowed all protons to be confidently assigned. However, a careful comparison of the ^1H and ^{13}C NMR spectra of 2 (see the Table) with those published for 1,



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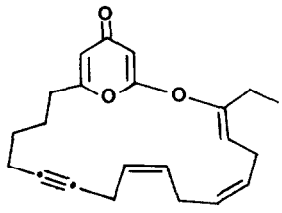

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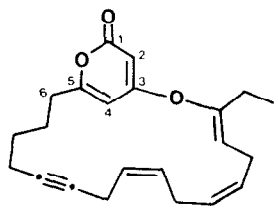

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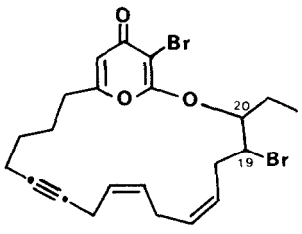

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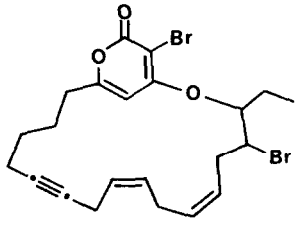

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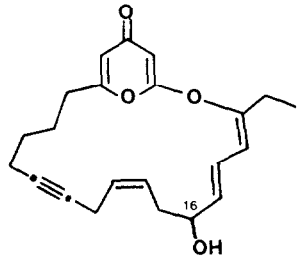


6

showed they were not identical. Major differences in the proton shifts for the C-19 olefin protons were very obvious (2 5.20 ppm, verses 1 4.70 ppm), and unlike the reports for 1, there was a complete lack of allylic coupling between the C-21 and C-19 protons. It is known that beta olefin protons, trans-oriented in enol ethers, appear at higher fields.[3] Also, allylic coupling is known to be accentuated in the cis relationship. Irradiation of the C-19 proton in 2 failed to induce significant **nOe** enhancement of the C-21 protons. Hence, with this comparison now available, the olefin geometries for 1 and 2 are suggested as **Z** and **E**, respectively.

Compound 3 was isomeric with 2 as determined by both FAB mass spectrometry and ^{13}C NMR methods. Analysis of the ^{1}H NMR spectrum confirmed that the identical macrocyclic component of the compound (C-6 to C-22) was intact in this derivative. There were major differences, however, in the UV, IR and ^{13}C NMR spectra which indicated that major modifications of the gamma-pyrone ring had been made. Infrared bands at 1710, 1640 and 1565 cm^{-1}, UV absorption at 282 nm, and the carbonyl carbon resonance at 167 or 169 ppm, clearly indicated the presence of an alpha-pyrone.[4-7] In the latter case, a comparison of the ^{13}C NMR shifts assigned to the alpha-pyrone ring with those of a suitable comparison compound, 4-methoxy-6-methyl-2-pyrone, gave excellent agreement.[7]

Once the structure of alpha-pyrone 3 had been assigned, the relationship of a closely related dibromo derivative, pyrone 5, was readily determined. A molecular formula of $C_{22}H_{26}Br_2O_3$ was suggested by FAB mass spectrometry, which clearly illustrated the isotopic cluster for a dibromo compound. The complete assignment of 5 followed quite easily from the ^{1}H NMR data which were analogous to those of the known pyrone 4, at least as far as the macrocyclic portion is concerned. Here too, spectral data supported the assigment of this new

^1H and ^{13}C NMR Spectra for Compounds 1-6.

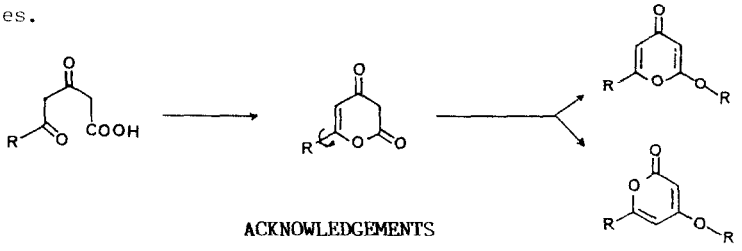
Carbon #	1		2		3		4		5		6	
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
1	—	165.8 s[a]	—	166.3 s[a]	—	166.9 s[a]	—	162.9 s[a]	—	166.0 s[a]	—	166.1 s[a]
2	5.48,d(2)	115.1 d[b]	5.48,d(1.5)	115.7 d[b]	5.20,d(1.9)	114.2 d	—	91.8 s	—	90.3 s	5.50,d(1.8)	116.5 d[b]
3	—	181.8 s	—	180.7 s	—	169.0 s	—	175.4 s	—	165.9 s[a]	—	180.0 s
4	6.01,bd(2)	112.6 d[b]	6.02,bd(1.5)	113.1 d[b]	5.89,d(1.9)	99.0 d	6.10,s	111.2 d	6.01,s	95.9 d	6.04,d(1.8)	113.3 d[b]
5	—	165.1 s[a]	—	165.6 s[a]	—	165.1 s[a]	—	161.6 s[a]	—	161.1 s[a]	—	N.O.
6	2.54,t(7)	32.7 t[c]	2.54,t(6.8)	32.9 t[c]	2.48,t(6.8)	32.3 t[c]	2.58,t(7)	33.2 t[c]	2.45,dt(15.3,7.5) 2.63,dt(15.3,7.5)*	33.6 t[c]	2.54,t(7.1)	35.4 t[c]
7	1.84,m	27.5 t[c]	1.84,m	28.3 t[c]	1.82,m	27.3 t[c]	1.88,m	32.3 t[c]	1.82,m	32.9 t[c]	1.75,m	32.9 t[c]
8	1.52,m	26.0 t[c]	1.52,m	26.7 t[c]	1.56,m	25.5 t[c]	1.60,m	27.5 t[c]	1.54,m	27.3 t[c]	1.52,m	28.8 t[c]
9	2.22,dt(7,2.5)	25.3 t[c]	2.22,m	25.9 t[c]	2.20,bt(7.1)	25.3 t[c]	2.22,bt	26.1 t[c]	2.21,bt(6.4)*	26.7 t[c]	2.18,tt(7.4,2.3)	27.7 t[c]
10	—	79.0 s	—	79.6 s[e]	—	79.3 s[e]	—	78.8 s[e]	—	79.2 s[e]	—	79.9 s[e]
11	—	79.0 s	—	79.4 s[e]	—	78.9 s[e]	—	78.5 s[e]	—	79.0 s[e]	—	79.3 s[e]
12	2.87,dt(7,2.5)	25.1 t[c]	2.88,m	25.6 t[c]	2.87,bd(7.5)	25.0 t[c]	2.88,m	26.1 t[c]	2.87,m	25.9 t[c]	2.87,bt(7.4)	26.3 t[c]
13	5.46-5.40,m	130.2 d[d]	5.46-5.40,m	130.7 d[d]	5.44-5.29,m	130.5 d[d]	5.40,m	130.3 d[d]	5.65-5.38,m	130.8 d[d]	5.67,bdt(10.5,7.4)	138.9 d[d]
14	5.46-5.40,m	128.4 d[d]	5.46-5.40,m	128.8 d[d]	5.44-5.29,m	128.4 d[d]	5.40,m	128.9 d[d]	5.65-5.38,m	129.7 d[d]	5.48,bdt(10.5,7.4)	128.4 d[d]
15	2.86,t(7)	23.6 t[c]	2.86,m	24.1 t[c]	2.77, t(7.0)*	23.8 t[c]	2.88,m	25.7 t[c]	2.80,m	25.4 t[c]	2.33,bdd(7.4,6.4)	19.1 t[c]
16	5.46-5.40,m	126.5 d[d]	5.46-5.40,m	127.5 d[d]	5.44-5.29,m	126.6 d[d]	5.40,m	125.5 d[d]	5.65-5.38,m	125.6 d[d]	4.20,ddt(5.5,0.9 6.4)	72.9 d[d]
17	5.46-5.40,m	124.4 d[d]	5.46-5.40,m	125.2 d[d]	5.44-5.29,m	124.4 d[d]	5.40,m	124.6 d[d]	5.65-5.38,m	124.8 d[d]	5.79,dd(15.4,5.5)	127.2 d[d]
18	2.77,t(7)	18.4 t[c]	2.77,t(7.2)	18.7 t[c]	2.66,t(7.1)	18.1 t[c]	2.72,bt(7)	18.2 t[c]	2.70,m	18.2 t[c]	6.19,ddd(15.4,10.9 0.9)	121.9 d[d]
19	4.70,tt(7,1)	91.3 d	5.20,t(7.2)	91.4 d	5.11,t(7.1)	89.6 d	4.14,ddd(5,6,7)	54.9 d	4.11,ddd(8.5,5.6 2.9)	54.7 d	5.76,d(10.9)	92.0 d
20	—	150.1 s	—	150.9 s	—	151.0 s	4.90,dt(6,5)	84.2 d	4.35,dt(2.9,6.4)	82.8 d	—	152.1 s
21	2.24,dq(7,1)	16.9 t[c]	2.24,q(7.4)*	17.1 t[c]	2.21,q(7.4)	16.9 t[c]	1.92,m	17.0 t[c]	1.94,m	17.0 t[c]	2.34,q(7.4)	17.3 t[c]
22	1.07,t(7)	11.2 q	1.07,t(7.4)	11.5 q	1.10,t(7.4)	11.0 q	1.00,t(7)	9.3 q	1.00,t(7.4)	9.7 q	1.15,t(7.4)	11.4 q

^1H NMR data were recorded at 360 MHz in $CDCl_3$ solution. ^{13}C NMR data were recorded at 50 MHz in both $CDCl_3$ (1,3-5) and Me_2CO-d_6 (2,6). ^1H NMR assignments are based upon complete decoupling experiments, and coupling constants are in Hz. The asterisk indicates that J values were only measurable in decoupled spectra. ^{13}C assignments are based solely upon comparison with model compounds and the notations a-e indicate that similar values may certainly be interchanged. ^{13}C multiplicities were obtained using SFORD techniques.

metabolite as an alpha-pyrone.[2] Although the compound is chiral, no attempt was made to establish the relative and absolute stereochemistry at C-19 and C-20.

Finally, a new polar compound, the alcohol 6, was isolated as a minor constituent of the extract. The alcohol analysed for $C_{22}H_{26}O_4$ by high resolution FAB mass spectrometry[2], and the additional oxygen atom was immediately ascribed to an alcohol constellation on the basis of a broad IR absorption at 3600 cm^{-1}, and a consistent ^{13}C NMR band at 72.9(d) ppm. The overall spectral data for 6 were similar to those from 2, except for bands from the diene system. What remained was to locate the position of hydroxylation on the macrocyclic ring. This was readily accomplished by proton NMR experiments which established the alcohol at C-16 (see Table). Although NMR data indicate the hydroxyl group to be un-epimerized, thus creating a chiral molecule, alcohol 6 did not show substantive rotation at the Na D line. The olefin geometry at C-19 could not be determined in this derivative.

To our knowledge macrocyclic enol-pyrones of this type have not been found in other natural sources. The recognition that both alpha- and gamma-pyrones occur in P. labillardieri points to the intermediacy of a linear diketo acid which can cyclize via two pathways yielding both alpha-and gamma-pyrones.



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REFERENCES AND NOTES

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2. Additional spectral data for new compounds: **For 2:** FABMS obs. 339.1968, calc. 339.1961; IR ($CHCl_3$) 3020, 2970, 1660, 1615, 1580, 1410, 1240, and 860 cm^{-1}; UV (MeOH) 240 nm (ε=10,000); **For 3:** FABMS obs. 339.1966, calc. 339.1961; IR ($CHCl_3$) 3010, 2970, 1710, 1640, 1565, 1420 and 825 cm^{-1}; UV (MeOH) 282 nm (ε=7650), no rotation at Na D line; **For 5:** FABMS obs. 501, 499, 497 amu (no high resolution avail.); IR ($CHCl_3$) 3010, 2930, 1712, 1638, 1532, 1410, 1300 and 1051 cm^{-1}; UV (MeOH) 304 nm (ε=7350); $[\alpha]_D$ -41° (c 0.5, $CHCl_3$); **For 6:** FABMS obs. 355.1898, calc. 335.1910; IR ($CHCl_3$) 3600, 3020, 2920, 1660, 1610, 1585, 1420, and 920 cm^{-1}; UV (MeOH) 231 nm (ε=18,000); no observable rotation at Na D line.

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