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Structure Reassignment of Cryptorigidifoliols E and K

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Abstract

The structures of the α -pyrones cryptorigidifoliols E (**5**) and K (**11**) have been reassigned as **5C** and **11C**.

Graphical abstract

The isolation and structure elucidation of the antimalarial compounds cryptorigidifoliols A – K (**1** – **11**) was reported in this journal in 2015.¹ The position of the distal hydroxyl group in the structure of **5**, and thus of **11** into which it is converted, was assigned based on the ESIMS of **5**, which showed significant ions at m/z 265 and 247, consistent with this assignment.

Since then syntheses of cryptorigidifoliols A (**1**),² B (**2**),³ I (**10**),⁴ E (**5**),⁵ and K (**11**)⁶ have been published. The syntheses of the first three compounds confirmed their structures, but the authors of the last papers noted discrepancies between our published NMR data and the data for their synthetic products.

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Supporting Information

HSQC spectrum of compound **5**, and HSQC, HMBC, and COSY spectra for compound **11**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

We thus reinvestigated the structure of cryptorigidifoliol K (**11**) using the 1 mg sample remaining and subjecting it to additional analysis by NMR spectroscopy. Based on this additional information, the structure of cryptorigidifoliol K is reassigned as **11C** on the basis of the following evidence.

The positive ion HRESIMS for **11C** revealed a peak for a protonated dehydrated molecular ion at m/z 377.3060, and for a sodiated molecular ion at m/z 417.2981, both corresponding to a molecular formula of $C_{24}H_{42}O_4$ for **11C**. Its IR spectrum exhibited bands at 3431 and 1732 cm^{-1} , indicating the presence of hydroxyl and ester carbonyl groups. The presence of a 2,6-dioxabicyclo[3.3.1]nonan-3-one system was indicated by ^1H NMR signals at δH 4.88 (br, H-1), 2.87 (dt 19.3, 1.9, H-4a), 2.79 (dd 19.3, 5.0, H-4b), 4.39 (br, H-5), 2.04–2.00 (m, H-6a), 1.93 (ddt 13.9, 4.0, 1.9, H-6b), 3.98 (ddt, 12.0, 9.4, 2.5, H-7), 2.03 (ddd 14.0, 4.0, 2.5, H-8a), and 1.64 (ddd 14.0, 12.0, 1.9, H-8b) and the ^{13}C NMR signals at δC 72.7 (C-1), 169.2 (C-3), 36.5 (C-4), 65.8 (C-5), 29.7 (C-6), 65.9 (C-7) and 37.1 (C-8). These assignments were confirmed by 2J -HMBC correlations between H-4 and C-3, H-4 and C-5, and by 3J -HMBC correlations between H-1 and C-7, H-5 and C-1/C-3/C-7, H-6 and C-4/C-8 (Figure 1). The long 2'-hydroxyheptadec-3-en-1-yl side chain was indicated by ^1H NMR signals at δH 1.78 (ddd 14.3, 9.4, 7.8, H-1'a), 1.61 (ddd 14.3, 4.3, 2.5, H-1'b), 4.27 (ddd 7.8, 7.1, 4.3, H-2'), 5.42 (ddt 15.0, 7.1, 1.5, H-3'), 5.67 (dt 15.0, 6.8, H-4'), 2.03–1.99 (m, H-5'), 1.39–1.22 (m, 24H, H-6'–H-15'), 1.31–1.28 (m, 2H, H-16'), and 0.88 (t, 6.9, H-17').

Crucially, 3J -HMBC correlations were observed between H-2' and C-7, between H-3' and C-1'/C-5', between H-4' and C-2'/C-6', and between the hydroxyl proton and C-1'/C-3'. These correlations uniquely assign the hydroxyl group to C-2' and the double bond to C-3'. The side chain was connected at C-7 based on 2J -HMBC correlations between H-7 and C-1' and 3J -HMBC correlations between H-8 and C-1' and H-2' and C-7 (Figure 1). In addition, COSY correlations defined the H-7 to H-4' spin system (Figure 2).

As reported in our original paper,¹ compound **11C** had no significant δ (H) difference between its *R*- and *S*-MPA derivatives, so its absolute configuration at C-2' could not be determined.

Regrettably no sample of cryptorigidifoliol E was available, but since it can be converted to its isomer cryptorigidifoliol K (**11C**) on treatment with acid,¹ its structure can be reassigned as **5C**.

We also took the opportunity to redetermine the NMR spectra of all the isolated compounds except **5**, and have made some minor adjustments of these assignments. The results are included in Tables 1 and 2. The data for cryptorigidifoliol E (**5C**) are reassigned from the original data.

EXPERIMENTAL SECTION

General Experimental Procedures

1D and 2D NMR spectra were recorded on a Bruker Avance 500 spectrometer in CDCl₃, with residual CHCl₃ as internal reference. The high resolution ESI mass spectrum was obtained on an Agilent 6220 mass spectrometer.

Cryptorigidifoliol K (11C)—colorless oil; $[\alpha]_D^{21}$ -8 (*c* 0.6, MeOH); UV (MeOH) λ_{max} (log ϵ): 204 (3.10) nm; IR ν_{max} 3431, 2956, 2867, 1732, 1036 cm⁻¹; ¹H and ¹³C NMR data, see Table 2; HRESIMS m/z [M+Na]⁺ 417.2981 (calcd for C₂₄H₄₂O₄Na⁺, 417.2975), [M+H-H₂O]⁺ 377.3060 (calcd for C₂₄H₄₁O₃⁺, 377.3050).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

¹H and ¹³C NMR Spectroscopic Data for Compounds 1–5.^a

posd	1	2	3	4	5
	δ_{H}^b	δ_{C}^c	δ_{H}^b	δ_{C}^c	δ_{H}^b
2		164.6 (C)		164.8 (CH ₂)	163.5 (C)
3	6.03 dt (9.8, 1.7)	121.3 (CH)	6.04 dt 9.8, 1.7	121.3 (CH)	121.2 (CH)
4	6.89 dt (9.8, 4.5)	145.0 (CH)	6.90 dt 9.8, 4.5	145.0 (CH)	145.0 (CH)
5	2.35–2.38 m	30.1 (CH ₂)	2.38–2.34 m	30.1 (CH ₂)	29.3 (CH ₂)
6	4.75 tdd (9.6, 6.3, 2.2) 1.92 ddd	74.8 (CH)	4.75 tdd 9.6, 4.5, 2.5 1.92 ddd 14.5,	75.1 (CH)	74.7 (CH)
	(14.5, 9.6, 2.2)		9.6, 2.2		
1'	1.65 ddd (14.5,	41.2 (CH ₂)	1.64 ddd 14.5,	42.3 (CH ₂)	37.3 (CH ₂)
	9.6, 3.2)		9.6, 2.9		
2'	4.00 br s	67.3 (CH)	4.01 br	67.3 (CH)	69.2 (CH)
3'	1.50–1.44 m	38.2 (CH ₂)	1.49–1.45 m	37.9 (CH ₂)	42.9 (CH ₂)
4'	1.46–1.39 m 1.34–1.29 m	25.7 (CH ₂)	1.47–1.44 m	25.0 (CH ₂)	72.0 (CH)
5'	1.35–1.22 m	29.6 (CH ₂)	1.36–1.32 m	29.6 (CH ₂)	131.4 (CH)
6'	1.35–1.22 m	29.6 (CH ₂)	1.35–1.22 m	29.6 (CH ₂)	132.4 (CH)
7'	1.35–1.22 m	29.6 (CH ₂)	1.35–1.22 m	29.6 (CH ₂)	32.2 (CH ₂)
8'	1.35–1.22 m	29.6 (CH ₂)	1.35–1.22 m	27.0 (CH ₂)	29.3 (CH ₂)
9'	1.35–1.22 m	29.6 (CH ₂)	2.05–1.98 m	27.3 (CH ₂)	29.5 (CH ₂)
10'	1.35–1.22 m	29.6 (CH ₂)	5.41–5.28 m	130.0 (CH)	29.5 (CH ₂)
11'	1.35–1.22 m	29.6 (CH ₂)	5.41–5.28 m	129.8 (CH)	29.5 (CH ₂)
12'	1.35–1.22 m	29.6 (CH ₂)	2.05–1.98 m	27.3 (CH ₂)	29.5 (CH ₂)
13'	1.27–1.23 m	32.0 (CH ₂)	1.35–1.22 m	29.6 (CH ₂)	29.5 (CH ₂)
14'	1.31–1.28 m	22.8 (CH ₂)	1.35–1.22 m	29.6 (CH ₂)	29.5 (CH ₂)
15'	0.88 t (7.0)	14.2 (CH ₃)	1.27–1.23 m	32.0 (CH ₂)	29.5 (CH ₂)
16'			1.31–1.28 m	22.8 (CH ₂)	29.5 (CH ₂)

	1	2	3	4	5
posd	δ_{H}^b	δ_{C}^c	δ_{H}^b	δ_{C}^c	δ_{H}^b
17'		1.27-1.23 m	31.9 (CH ₂)	0.88 t 7.0	14.2 (CH ₃)
18'		1.31-1.28 m	22.7 (CH ₂)	1.31-1.28 m	22.8 (CH ₂)
19'		0.88 t 7.0	14.1 (CH ₃)	0.88 t 7.0	14.1 (CH ₃)

^a Spectra obtained in CDCl₃; assignments based on analysis of 2D NMR spectra.

^b Data (δ) measured at 500 MHz; brs = broad singlet, brd = broad doublet, t = triplet, ddd = doublet of doublets of doublets, dt = doublet of triplets, m = multiplet. *J* values are in Hz and are omitted if the signals overlapped as multiplets. The overlapped signals were assigned from HSQC and HMBC spectra without designating multiplicity.

^c Data (δ) measured at 125 MHz; CH₃, CH₂, CH, and C multiplicities were determined by an HSQC experiment.

Table 2
¹H and ¹³C NMR Spectroscopic Data for Compounds 6–9 and 11, ^a and ¹H NMR Spectroscopic Data for Compound 10.

posn	6	7	8	9	10	11	δ_c
	δ_H^b	δ_c^c	δ_H^b	δ_c^c	δ_H^b	δ_c^c	
1	4.89 tt 4.0, 2.0	73.1 (CH)	4.88 tt 4.0, 2.0	73.4 (CH)	4.91 tt 4.0, 2.0	72.9 (CH)	72.7 (CH)
3		169.7 (C)		170.1 (C)		169.7 (C)	169.2 (C)
4	2.89 ddd 19.3, 2.0, 2.0 2.78 dd 19.3, 5.4	36.4 (CH ₂)	2.87 ddd 19.2, 2.0, 2.0 2.77 dd 19.2, 5.3	36.7 (CH ₂)	2.89 ddd 19.2, 2.0, 2.0 2.80 dd 19.2, 5.3	36.4 (CH ₂)	36.5 (CH ₂)
5	4.36 br	66.0 (CH)	4.35 br	65.9 (CH)	4.38 br	66.1 (CH)	65.8 (CH)
6	2.03-1.98, m 1.94-1.89, m	29.7 (CH ₂)	2.06-2.01 m 1.92 dddd 13.8, 4.0, 2.0, 2.0	30.0 (CH ₂)	2.05-1.99 m 1.94 dddd 13.8, 4.0, 2.0, 2.0	29.6 (CH ₂)	29.7 (CH ₂)
7	4.10 ddt 11.1, 7.8, 3.1	63.6 (CH)	3.73 dddd 11.5, 7.5, 4.6, 2.8	65.8 (CH)	4.12 ddt 11.1, 7.1, 3.2	63.6 (CH)	65.9 (CH)
8	2.00-1.95, m 1.72-1.66, m	36.8 (CH ₂)	2.08-2.02 m 1.61-1.55 m	36.7 (CH ₂)	2.03-1.98 m 1.74-1.69 m	36.8 (CH ₂)	37.1 (CH ₂)
1'	1.68-1.63 m 1.62-1.57 m	42.2 (CH ₂)	1.58-1.53 m 1.48-1.44 m	36.0 (CH ₂)	1.69-1.65 m 1.63-1.60 m 1.63-	42.0 (CH ₂)	43.0 (CH ₂)
2'	3.81 dddd, 10.2, 7.7, 5.2, 3.3	68.3 (CH)	1.45-1.39 m 1.33-1.30 m	25.4 (CH ₂)	3.82 br	68.5 (CH)	72.0 (CH)
3'	1.50-1.38 m	37.8 (CH ₂)	1.35-1.22 m	29.5 (CH ₂)	1.51-1.45 m 1.44-1.40 m	37.7 (CH ₂)	131.8 (CH)
4'	1.45-1.39 m, 1.32-1.26, m	25.7 (CH ₂)	1.35-1.22 m	29.5 (CH ₂)	1.42-1.39 m 1.37-1.32 m	25.8 (CH ₂) 2	132.5 (CH)
5'	1.32-1.26 m	29.6 (CH ₂)	1.35-1.22 m	29.5 (CH ₂) 2	1.30-1.23 m	29.7 (CH ₂)	32.4 (CH ₂)

	6	7	8	9	10	11	
used	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}	
6'	1.32-1.26 m	29.6 (CH ₂)	1.30-1.23 m	29.7 (CH ₂)	1.35-1.22 m	29.5 (CH ₂)	29.2 (CH ₂)
7'	2.05-1.98 m	27.3 (CH ₂)	1.30-1.23 m	29.7 (CH ₂)	1.98 m 2.09-	29.5 (CH ₂)	29.8 (CH ₂)
8'	5.37-5.28 m	129.82(CH)	1.30 - 1.23 m	29.7 (CH ₂)	5.42 -5.27 m	29.5 (CH ₂)	29.8 (CH ₂)
9'	5.37-5.28 m	130.2 (CH)	1.30 -1.23 m	29.7 (CH ₂)	5.42-5.27 m	29.5 (CH ₂)	29.8 (CH ₂)
10'	2.05-1.98 m	27.3 (CH ₂)	1.30 -1.23 m	29.7 (CH ₂)	2.09-1.98 m	29.5 (CH ₂)	29.8 (CH ₂)
11'	1.32-1.26 m	29.6 (CH ₂)	1.30 -1.23 m	29.7 (CH ₂)	1.35- 1.22 m	29.5 (CH ₂)	29.8 (CH ₂)
12'	1.32-1.26 m	29.6 (CH ₂)	1.28-1.24 m	32.0 (CH ₂)	1.35-1.22 m	29.5 (CH ₂)	29.8 (CH ₂)
13'	1.32-1.26 m	29.6 (CH ₂)	1.32-1.27 m	22.7 (CH ₂)	1.35-1.22 m	29.5 (CH ₂)	29.8 (CH ₂)
14'	1.32-1.26 m	29.6 (CH ₂)	0.88 t 7.0	14.1 (CH ₃)	1.35-1.22 m	29.5 (CH ₂)	29.8 (CH ₂)
15'	1.27-1.23 m	32.0 (CH ₂)			0.88 t 7.0	31.9 (CH ₂)	32.2 (CH ₂)
16'	1.31-1.28 m	22.7 (CH ₂)				22.7 (CH ₂)	22.9 (CH ₂)
17'	0.88 t 6.9	14.1 (CH ₃)				14.4 (CH ₃)	14.1 (CH ₃)
18'							
19'							
20'							
OH	2.43, d 5.2		2.25 d 5.1			2.77	

^aSpectra obtained in CDCl₃; assignments based on analysis of 2D NMR spectra.

^bData (6) measured at 500 MHz; s = singlet, br d = broad doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, m = multiplet. *J* values are in Hz and are omitted if the signals overlapped as multiplets. The overlapped signals were assigned from HSQC and HMBC spectra without designating multiplicity.

^cData (6) measured at 125 MHz; CH₃, CH₂, CH, and C multiplicities were determined by an HSQC experiment.