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Sampsoniones C-H, a Unique Family of Polyprenylated Benzophenone Derivatives with the Novel Tetracyclo[7.3.1.$1^{3,11}$.$0^{3,7}$]tetradecane-2,12,14-trione Skeleton, from *Hypericum sampsonii*(Guttiferae)

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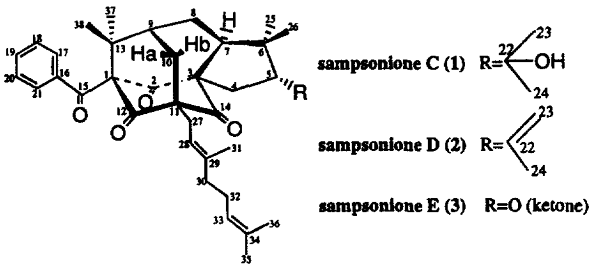
Abstract The structures of sampsoniones C-H, isolated from the aerial parts of *Hypericum sampsonii*, have been elucidated by extensive analysis of 2 D NMR. Sampsoniones C-H are the first polyprenylated benzophenone derivatives with a unique caged tetracyclo[7.3.1.$1^{3,11}$.$0^{3,7}$]tetradecane-2,12,14-trione skeleton.

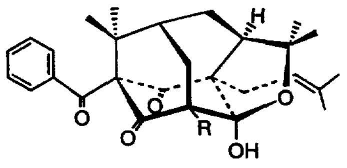
A few structurally complex and biologically active polyprenylated benzophenone derivatives with the rare tricyclo-skeleton have been isolated from Guttiferous plants[1-3]. Our previous work[4] on *Hypericum sampsonii* resulted in the characterization of sampsoniones A and B, with the novel 5-oxatetracyclo-skeleton arising from cyclizations of two prenyl substituents. Continuing investigations on this plant have resulted in the isolation of six new caged compounds, sampsoniones C-H, with an unusual carbotetracyclo-skeleton formed by complex cyclizations of three prenyl substituents.



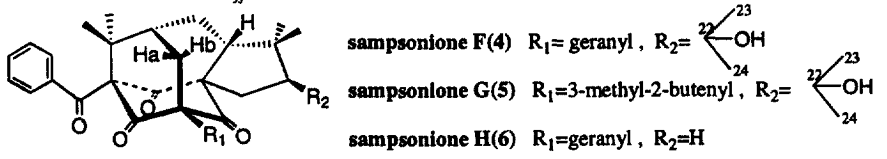
sampsonione C (1) R= (22, 23, 24, OH)

sampsonione D (2) R= (22, 23, 24)

sampsonione E (3) R=O (ketone)



sampsonione A R=geranyl
sampsonione B R=3-methyl-2-butenyl



sampsonione F(4) R_1= geranyl , R_2=

sampsonione G(5) R_1=3-methyl-2-butenyl , R_2=

sampsonione H(6) R_1=geranyl , R_2=H

Sampsonione C (1) was obtained as a colourless oil (10.5 mg, 0.00021%), $[\alpha]_D^{31.2}$ +13.39° (c, 0.174, $CHCl_3$). HREIMS indicated a molecular formula of $C_{38}H_{50}O_5$ (m/z 586.36551). The UV spectrum exhibited maxima at 216 (3.73), 242 (3.84), 278 (3.2), 302 (2.65) nm. The IR spectrum showed strong bands for hydroxyl (3565, 3450 cm^{-1}) and carbonyl groups (1734 1697, 1695 and 1685 cm^{-1}). The ^1H and ^{13}C NMR data of **1** (Table 1) indicated a close structural similarity to sampsonione A[4]. The ^{13}C NMR spectrum of **1** exhibited four signals (δ 206.3, 204.7, 203.9, 192.4 ppm) corresponding to carbonyl groups, while only three were found in sampsonione A. The hemiketal carbon (δ 110.3 ppm) in sampsonione A was replaced by a nonconjugated carbonyl function.

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Table 1: NMR data for sampsoniones C-H.

	C (1)			F (4)			D (2)	E (3)	G (5)	H (6)
Position	H^a	^{13}C^b	HMBC^c	^{1}H^a	^{13}C^b	HMBC^c	^{13}C^b	^{13}C^b	^{13}C^b	^{13}C^b
1		80.9			81.5		80.8	80.8	81.5	81.1
2		203.9			204.2		203.9	203.0	204.1	203.3
3		73.1			73.1		73.9	69.8	73.2	74.8
4	α 2.19 dd (10.9, 6.3)	33.1	3, 5, 6, 7,14, 22	α 2.27 dd (12.5, 5.7)	31.1	2, 3, 5, 6, 14	34.4	42.7	31.0	27.9
	β 2.50 m		2, 3, 4, 5, 6, 7, 22	β 2.75 dd (12.5, 7.1)		2, 3, 5, 6, 14				
5	β 2.48 m	57.5	3, 7, 22, 26	α 2.19 dd (7.2, 5.8)	58.9	3, 6, 7, 22, 23, 24, 25, 26	54.9	217.1	58.9	42.4
6		44.8			46.7		44.3	48.0	46.7	44.2
7	α 2.12 m	57.5	2, 5, 6, 8, 14, 25, 26	β 2.29 dd (12.4, 7.4)	54.6	2, 3, 6, 8, 14, 25, 26	57.2	52.4	54.6	55.3
8	α 2.28 m	28.6	3, 10	α 2.04 m	24.7	10, 13	28.9	29.0	24.7	23.5
	β 1.65 m		6, 7, 10, 13	β 1.77 m		3, 7, 9, 10, 13				
9	2.12 m	43.8	1, 7, 8, 11, 37, 38	2.08 m	42.3	1, 7, 11, 38	43.9	43.8	42.2	42.2
10	a 2.53 m	42.3	8, 11, 12, 14, 27	a 2.49 dd (14.9, 6.8)	35.1	8, 11, 14, 27	42.6	43.9	35.3	35.0
	b1.96 d (13.9)		8, 9, 11, 12, 13, 14, 27	b 2.17 dd (14.9, 3.9)		8, 11, 12, 13, 14				
11		68.9			67.7		68.9	68.5	67.6	67.5
12		204.7			204.4		204.7	204.2	204.3	204.8
13		50.7			47.6		50.7	51.1	47.7	47.5
14		206.3			205.5		206.2	205.6	205.5	203.3
15		192.4			192.8		192.4	192.0	192.7	192.9
16		134.9			134.8		134.8	134.5	134.8	134.8
17	7.11 d (7.1)	128.8	15, 19	7.07 d (7.8)	128.4	15, 19	128.8	128.9	128.4	128.4
18	7.26 t (7.0)	128.0	16, 17	7.28 t (7.5)	128.2	16, 20	127.9	128.0	128.2	128.1
19	7.39 t (7.3)	131.9	17, 21	7.39 t (7.6)	132.2	17, 21	131.3	132.2	132.1	132.1
20	7.26 t (7.0)	128.0	16, 21	7.28 t (7.5)	128.2	16, 20	127.9	128.0	128.2	128.1
21	7.11 d (7.1)	128.8	15, 19	7.07 d (7.8)	128.4	15, 19	128.8	128.9	128.4	128.4
22		73.2			73.1		145.2		73.1	
23	1.38 s	30.0	5, 22, 24	1.35 s	30.3	5, 22	111.8		30.3	
24	1.32 s	30.0	5, 22, 23	1.35 s	31.6	5, 22	23.8		31.6	
25	1.23 s	27.0	5, 6, 7, 26	1.06 s	26.9	5, 6, 7, 26	26.7	27.5	26.8	20.5
26	0.92 s	28.2	5, 6, 7, 25	1.23 s	27.4	5, 6, 7, 25	27.0	20.7	27.4	28.3
27	2.56 m	29.3	10, 11, 12, 14, 28, 29	2.60 m	28.9	10, 11, 12, 14, 28, 29	29.3	29.2	29.1	28.9
28	5.12 t (7.0)	119.0	30, 31	5.25 t (7.4)	118.7	30, 31	118.9	118.2	118.5	118.9
29		138.3			139.0		138.3	139.0	135.3	138.8
30	1.99 m	39.9	28, 29, 31, 32, 33	2.01 m	40.0	28, 29, 31	39.5	39.9	26.0	39.9
31	1.66 s	16.3	28, 29, 30	1.65 s	16.3	28, 29	16.3	16.4	17.9	16.2
32	2.04 m	26.5	30, 33, 34	2.11 m	26.5	30, 33, 34	26.5	26.5		26.5
33	5.06 t (6.9)	124.1	32, 36	5.06 t (5.3)	124.1	32, 36	124.0	123.9		124.1
34		131.3			131.4		131.3	131.4		131.3
35	1.66 s	25.6	33, 34, 36	1.65 s	25.7	33, 34, 36	25.6	25.7		25.7
36	1.58 s	17.6	33, 34, 35	1.58 s	17.6	33, 34, 35	17.6	17.6		17.6
37	1.40 s	22.7	1, 9, 13, 38	1.38 s	22.5	1, 9, 13, 38	22.7	22.8	22.4	22.5
38	1.46 s	25.2	1, 9, 13, 37	1.44 s	25.1	1, 9, 13, 37	25.2	25.2	25.1	25.2

[a] Recorded in $CDCl_3$ at 300 MHz. [b] Recorded in $CDCl_3$ at 75 MHz. [c] Carbons that correlate with the proton resonance.

Therefore the tetrahydrofuran-ring of sampsonione A was replaced by a cyclopentane-ring in 1, which was supported by the presence of HMBC cross peaks between: (i) the C_4 methylene protons at δ 2.19, 2.50 ppm and the quaternary carbon signals at δ 203.9 ppm (C_2), 73.1 ppm (C_3), 206.3 ppm (C_{14}), the methine carbon signals at δ 57.5 ppm (C_7 and C_5); (ii) the C_7 methine proton at δ 2.12 ppm and the quaternary carbon signals at δ 203.9 ppm (C_2), 44.8 ppm (C_6), 206.3 ppm (C_{14}), the methine carbon signal at δ 57.5 ppm (C_5); (iii) the C_5 methine proton at δ 2.48 ppm and the quaternary carbon signal at δ 73.1 ppm (C_3), the methine carbon signal at δ 57.5 ppm (C_7).

In addition to the main skeleton, other readily identifiable pendant residues were: (a) the gem-dimethyl group (C_{25} and C_{26}) correlating by HMBC to each other and to C_6 on the main skeleton; (b) the gem-dimethyl group (C_{37} and C_{38}) correlating by HMBC to each other and to C_{13} on the main skeleton; (c) a geranyl side chain (C_{27} to C_{36}); (d) a 2-(2'-hydroxy)propyl group (C_{22} to C_{24}).

The C_{27} methylene protons showed heteronuclear correlation to C_{12} (δ 204.7 ppm), C_{11} (δ 68.9 ppm), C_{14} (δ 206.3 ppm) and C_{10} (δ 42.3 ppm) and NOE interactions with C_{31} methyl, while the C_{28} olefinic proton correlated with C_{30} and showed NOE enhancements with the C_{30} methylene protons. This allowed assignment of a geranyl moiety at C_{11} and revealed that the geometry of the C_{28}-C_{29} olefin was *E*. HMBC correlations observed between the C_{23} and C_{24} methyls (δ 1.38 and 1.32 ppm) and C_5 (δ 54.5 ppm), C_{22} (δ 73.2 ppm) established the attachment of the 2-(2'-hydroxy)propyl at C_5.

Molecular models disclosed that, by its formation, the tetracyclic system itself sets up the relative configurations at the chiral centres C_1, C_3, C_9 and C_{11}. The relative stereochemistry of the remaining chiral carbons at C_5 and C_7 was determined by 2 D NOESY spectra (Figure 1). Cross peaks between the C_7 methine proton (δ 2.12 ppm) and the C_{37} and C_{25} methyl protons (δ 1.40 and 1.23 ppm); the C_{10} methylene proton at δ 2.53 ppm and the C_{38} methyl (δ 1.46 ppm); the C_{10} methylene proton at δ 1.96 ppm and the C_{26} methyl protons (δ 0.92 ppm) established the α configuration of the C_7 methine proton. The 2-(2'-hydroxyl)propyl group at $C_{5\alpha}$ was deduced from the presence of cross peaks between the C_7 methine proton (δ 2.12 ppm) and the C_{23}, C_{24} methyl protons (δ 1.38 and 1.32 ppm); the C_{25} methyl (δ 1.23 ppm) and the C_{23}, C_{24} methyls.

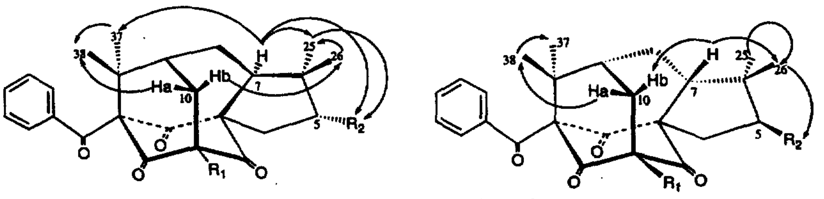
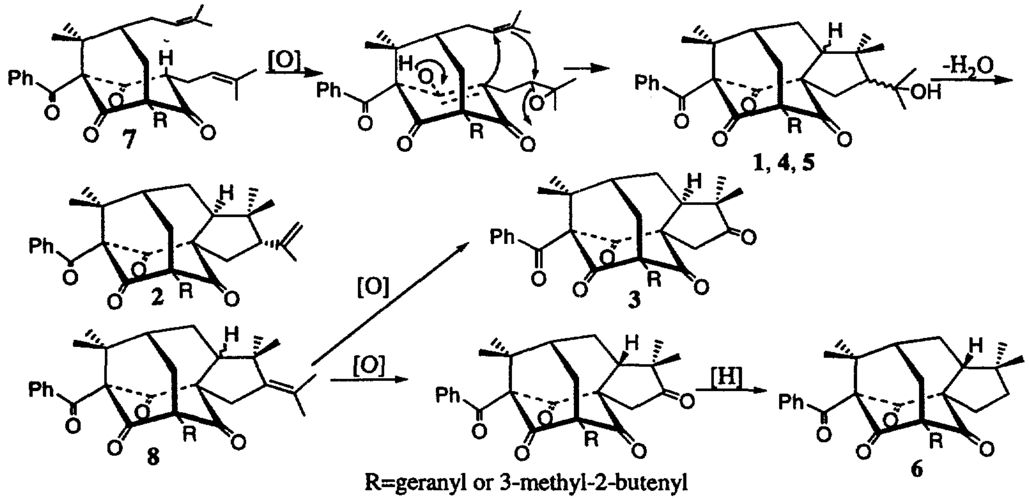


Figure 1. Selected NOE Correlations for Sampsoniones C-H (1-6)

Sampsonione F (4) (54.8 mg, 0.00110%) was isolated as a colourless oil, $[\alpha]_D^{31.2}$ +14.52° (c, 1.096, $CHCl_3$), with the following spectral characteristics: IR (film) ν_{max} 3591, 3409, 1732, 1695, 1691,1686 cm^{-1}; UV (MeOH) λ_{max} (log ε) 322 (2.94), 274 (3.61), 240 (4.52), 214 (3.97) nm; ^1H and ^{13}C NMR, Table 1. HREIMS indicated a molecular formula of $C_{38}H_{50}O_5$ (m/z 586.36697). Extensive analyses of 1 D (^1H, ^{13}C) and 2 D (^1H-^1H COSY, HMQC, and HMBC) NMR spectra of 4 established that it is a diastereomer of 1.The relative configuration of the $C_{7\beta}$ methine proton and the $C_{5\beta}$ 2-(2'-hydroxyl)propyl group in sampsonione F was established from the 2 D NOESY spectrum (Figure 1), in which the C_7 methine proton (δ 2.29 ppm) was correlated with the C_{26} methyl protons (δ 1.23 ppm) and the C_{10} methylene proton at δ 2.17 ppm; the C_{10} methylene proton at δ 2.49 ppm was correlated with the C_{38} methyl protons(δ 1.41 ppm); the C_{26} methyl protons (δ 1.23 ppm) showed correlations with the C_{23} (δ 1.06 ppm) and C_{24} (δ 1.23 ppm) methyl protons.

Four other isolated analogues, sampsoniones D[5] (6.6 mg, 0.000132%), E[6] (7.8 mg, 0.000156%), G[7] (1.3 mg, 0.000026%), H[8] (6.6 mg, 0.000132%), HREIMS $[M]^+$ 568.35120, 542.31356, 518.30061, 528.32658, calcd. for $C_{38}H_{48}O_4$, $C_{35}H_{42}O_5$, $C_{33}H_{42}O_5$, $C_{35}H_{44}O_4$, respectively, had UV and IR spectral features similar to those of 1. A combined analysis of their NMR data (including 1 D and 2 D) showed that sampsoniones D and E have the main skeleton of 1, with the C_7 methine proton at α configuration, while sampsoniones G and H have the main skeleton of 4, with the C_7 methine proton at β configuration. They differ only in the substituents at C_5 and C_{11}. Sampsonione D has a geranyl side chain at C_{11}, a 2-propenyl group at $C_{5\alpha}$; E has a geranyl side chain at C_{11}, a carbonyl function at C_5; G has a 3-methyl-2-butenyl side chain at C_{11}, a 2-(2'-hydroxy)propyl group at $C_{5\beta}$; H has a geranyl side chain at C_{11} and no substituents at C_5.

Sampsoniones C-H are the first six of polyprenylated benzophenone derivatives possessing a novel rigid caged tetracyclo[7.3.1.1^{3,11}.0^{3,7}]tetradecane-2,12,14-trione skeleton. They are presumably biosynthesized from the biogenetically acceptable intermediate 7[4], which also leads to sampsoniones A and B. Epoxidation and intramolecular cyclization of 7 afford sampsoniones C (1), F (4) and G (5), which subsequently dehydrate to form sampsonione D (2) and 8. The intermediate 8 undergoes oxidation and reduction to yield sampsoniones E (3) and H (6) (Fig 2).



R=geranyl or 3-methyl-2-butenyl

Figure 2. Possible biosynthesis pathway of sampsoniones C-H

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4. Hu LH, Sim KY. *Tetrahedron Lett.*, 1998, 39, 7999-8002 .
5. Sampsonione D (2): colourless oil; $[\alpha]_D^{31.2}$ +12.27(*c*, 0.156, $CHCl_3$); IR (film) ν_{max} 1736, 1693, 1690, 1687 cm^{-1}; UV (MeOH) λ_{max} (log ε) 306 (2.76), 280 (3.23), 260 (3.62), 240 (3.63), 214 (3.50) nm; ^1H NMR ($CDCl_3$, 300 MHz): 2.63 (t, 12.6 Hz, 4α), 2.08 (dd, 12.4, 8.8 Hz, 4β), 3.12 (dd, 12.0, 8.9 Hz, 5β), 2.03 (m, 7α), 2.28 (m, 8α), 1.71 (m, 8β), 2.13 (m, 9), 2.52 (dd, 14.0, 8.6 Hz, 10a), 1.88 (d, 14.1 Hz, 10b), 7.11 (2H, d, 7.7 Hz, 17, 21), 7.26 (2 H, t, 7.9 Hz, 18, 20), 7.39 (t, 7.7 Hz, 19), 4.91 (s, 23), 4.84 (s, 23), 1.80 (s, 24), 0.86 (s, 25), 0.93 (s, 26), 2.47 (2 H, t, 5.9 Hz, 27), 5.11 (t, 5.7 Hz, 28), 1.98 (2 H, m, 30), 1.66 (s, 31), 2.03 (2 H, m, 32), 5.05 (t, 4.3 Hz, 33), 1.65 (s, 35), 1.57 (s, 36), 1.40 (s, 37), 1.46 (s, 38).
6. Sampsonione E (3): colourless oil; $[\alpha]_D^{31.2}$ 57.69 (*c*, 0.026, $CHCl_3$); IR (film) ν_{max} 1743, 1735, 1698, 1690, 1687 cm^{-1}; UV (MeOH) λ_{max} (log ε) 306 (3.35), 276 (3.69), 254 (4.07), 246 (4.09), 214 (4.00) nm; ^1H NMR ($CDCl_3$, 300 MHz): 3.22 (d, 17.7 Hz, 4α), 2.76 (d, 17.7 Hz, 4β), 2.28 (t, 9.6 Hz, 7α), 2.48 (m, 8α), 1.75 (ddd, 15.4, 9.3, 1.2 Hz, 8β), 2.23 (brt, 6.8 Hz, 9), 2.22 (dd, 14.0, 7.3 Hz, 10a), 1.88 (d, 14.1 H7, 10b), 7.10 (2H, d, 8.0 Hz, 17, 21), 7.27 (2 H, dd, 7.9, 7.0 Hz, 18, 20), 7.41 (t, 7.0 Hz, 19), 1.09 (s, 25), 0.95 (s, 26), 2.54 (2 H, t, m, 27), 5.02 (m, 28), 1.94 (2 H, t, 7.4 Hz, 30), 1.65 (s, 31), 2.00 (2 H, m, 32), 5.02 (m, 33), 1.65 (s, 35), 1.57 (s, 36), 1.47 (s, 37), 1.51 (s, 38).
7. Sampsonione G (5): colourless oil; $[\alpha]_D^{31.2}$ 10.00 (*c*, 0.012, $CHCl_3$); IR (film) ν_{max} 3594, 3411, 1733, 1697, 1690, 1687 cm^{-1}; UV (MeOH) λ_{max} (log ε) 320 (3.12), 276 (3.59), 242 (4.63), 214 (4.03) nm; ^1H NMR ($CDCl_3$, 300 MHz): 2.26 (m, 4α), 2.75 (dd, 13.6, 6.6 Hz, 4β), 2.19 (m, 5α), 2.32 (dd, 12.8, 5.3 Hz, 7β), 2.02 (m, 8α), 1.77 (m, 8β), 2.10 (m, 9), 2.47 (dd, 14.9, 6.6 Hz, 10a), 2.20 (m, 10b), 7.07 (2H, d, 6.1 Hz, 17, 21), 7.29 (2 H, t, 6.3 Hz, 18, 20), 7.39 (t, 6.0 Hz, 19), 1.36 (6 H, 23, 24), 1.22 (s, 25), 1.07 (s, 26), 2.60 (2 H, m, 27), 5.22 (t, 7.5 Hz, 28), 1.73 (2 H, m, 30), 1.67 (s, 31), 1.39 (s, 37), 1.41 (s, 38).
8. Sampsonione H (6): colourless oil; $[\alpha]_D^{31.2}$ +5.15 (*c*, 0.07, $CHCl_3$); IR (film) ν_{max} 1738, 1694, 1691, 1689 cm^{-1}; UV (MeOH) λ_{max} (log ε) 322 (2.53), 282 (3.10), 262 (3.39), 242 (3.43), 216 (3.30) nm; ^1H NMR ($CDCl_3$, 300 MHz): 2.37 (dd, 13.7, 6.7 Hz, 4α), 2.43 (dd, 13.7, 7.0 Hz, 4β), 1.72 (m, 5α), 1.92 (m, 7β), 1.92 (m, 8α), 1.72 (m, 8β), 2.07 (m, 9), 2.50 (dd, 14.4, 5.3 Hz, 10a), 2.21 (d, 14.8 Hz, 10b), 7.10 (2H, d, 8.0 Hz, 17, 21), 7.27 (2 H, dd, 7.9, 7.0 Hz, 18, 20), 7.39 (t, 7.0 Hz, 19), 0.95 (s, 25), 1.03 (s, 26), 2.62 (2 H, m, 27), 5.30 (t, 7.4 Hz, 28), 2.06 (2 H, m, 30), 1.67 (s, 31), 2.07 (2 H, m, 32), 5.07 (brs, 33), 1.67 (s, 35), 1.58 (s, 36), 1.39 (s, 37), 1.42 (s, 38).