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Tricyclic Acylphloroglucinols from *Hypericum lanceolatum* and Regioselective Synthesis of Selancins A and B

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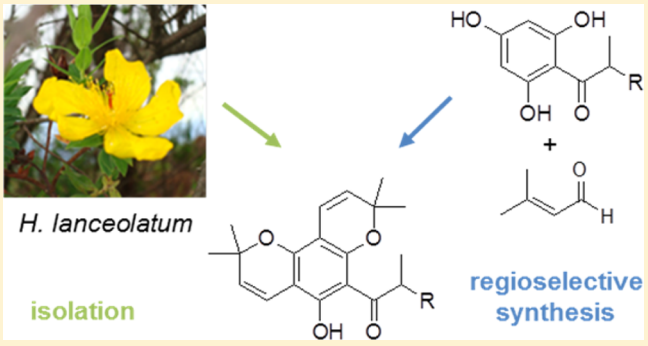
Supporting Information

ABSTRACT: The chemical investigation of the chloroform extract of *Hypericum lanceolatum* guided by ^{1}H NMR, ESIMS, and TLC profiles led to the isolation of 11 new tricyclic acylphloroglucinol derivatives, named selancins A–I (**1**–**9**) and hyperselancins A and B (**10** and **11**), along with the known compound 3-*O*-geranylemodin (**12**), which is described for a *Hypericum* species for the first time. Compounds **8** and **9** are the first examples of natural products with a 6-acyl-2,2-dimethylchroman-4-one core fused with a dimethylpyran unit. The new compounds **1**–**9** are rare acylphloroglucinol derivatives with two fused dimethylpyran units. Compounds **10** and **11** are derivatives of polycyclic polyprenylated acylphloroglucinols related to hyperforin, the active component of St. John's wort. Their structures were elucidated by UV, IR, extensive 1D and 2D NMR experiments, HRESIMS, and comparison with the literature data. The absolute configurations of **5**, **8**, **10**, and **11** were determined by comparing experimental and calculated electronic circular dichroism spectra. Compounds **1** and **2** were synthesized regioselectively in two steps. The cytotoxicity of the crude extract (88% growth inhibition at 50 μg/mL) and of compounds **1**–**6**, **8**, **9**, and **12** (no significant growth inhibition up to a concentration of 10 mM) against colon (HT-29) and prostate (PC-3) cancer cell lines was determined. No anthelmintic activity was observed for the crude extract.



The scientific interest and economic value of *Hypericum perforatum* (St. John's Wort), a medicinal herb mostly used for the treatment of mild to moderate depression, entailed the investigation of bioactive metabolites from other *Hypericum* species.[1−3] The most common secondary metabolites found within the genus *Hypericum* include phloroglucinols,[4−6] xanthones,[7] naphthodianthrones,[8,9] flavonoids,[1,10] and coumarins.[11] Acylphloroglucinols, of which hyperforin from *H. perforatum* is an outstanding example, are among the most relevant bioactive compounds isolated from *Hypericum*.[12−14] Their structures and biological activities have attracted much attention in the medicinal and synthesis chemistry fields since the isolation of hyperforin in 1975.[13] They possess, among others, cytotoxic,[13] antidepressant,[15] antibacterial,[6] and anti-inflammatory activities.[5] The phloroglucinol (1,3,5-trihydroxybenzene) core of these compounds is often substituted by prenyl or geranyl moieties that are susceptible to cyclization and oxidation processes, affording bi-[3,16] or tricyclic[3] derivatives as well as complex cage compounds.[17] Recently, a revised structure for adhyperfirin with a *C*-methylated phloroglucinol core, named hyperpolyphyllirin from *H. polyphyllum*, was reported.[1]

Hypericum lanceolatum Lam. (Hypericaceae) has been prioritized for chemical investigation as part of a metabolomics-driven isolation project aiming to study and compare the metabolomes, biosynthesis, and biological activities of prenylated aromatics and to find new or potential lead compounds from plants including various *Hypericum* species and accessions.[1,2,10,11,18−20] *H. lanceolatum* is a medicinal plant occurring in the mountainous region of West Cameroon (Central Africa).[21] Previous studies on this plant revealed the presence of xanthones, a polyprenylated phloroglucinol (isogarcinol), and terpenoids.[21] In Cameroonian traditional medicine, *Hypericum* plants are multipurpose remedies commonly used for the treatment of tumors, skin infections, epilepsies, infertility, venereal diseases, gastrointestinal disorders, intestinal worms, and viral diseases.[2,21,22] Recently, the first isolation and structural elucidation of biscoumarins from Cameroonian *H. riparium* were reported.[2] The aim of the present study was to isolate and characterize the chemical constituents of *H. lanceolatum* and evaluate their biological activities.

RESULTS AND DISCUSSION

ESIMS, TLC, and particularly ^{1}H NMR-guided fractionation of the chloroform extract of the leaves of *H. lanceolatum* led to the isolation of 11 new acylphloroglucinol derivatives, **1**–**11**, and the known compound 3-*O*-geranylemodin (**12**). The characteristic deshielded proton signals around δ_H 9–14 in the ^{1}H NMR spectrum of acylphloroglucinols are caused by the presence of a

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Table 1. ^{1}H NMR Data [δ, multiplicity, J (Hz)] for Compounds 1−9 (400 MHz, $CDCl_3$)

position	1	2	3	4	5	6	7	8	9
3	5.43, d (10.1)	5.44, d (9.7)	3.81, dd (5.8, 5.3)	3.80, m	5.41, d (10.1)	5.46, d (10.1)	5.46, d (10.1)	5.55, d (10.1)	5.55, d (10.1)
4	6.59, d (10.1)	6.60, d (9.7)	2.85, dd (17.1, 5.3)	2.76, dd (17.1, 5.3)	6.60, d (10.1)	6.43, d (10.1)	6.43, d (10.1)	6.55, d (10.1)	6.55, d (10.1)
			2.60, dd (17.1, 5.8)	2.60, dd (17.1, 5.3)					
7	5.46, d (10.1)	5.46, d (9.7)	5.43, d (10.1)	5.43, d (10.1)	3.80, t (5.3)	5.09, d (3.1)	5.09, d (3.1)	4.85, s	4.85, s
8	6.66, d (10.1)	6.66, d (9.7)	6.66 d (10.1)	6.67, d (10.1)	2.87, dd (17.1, 5.3)	5.83, d (3.1)	5.83, d (3.1)		
					2.65, dd (17.1, 5.3)				
11	1.49, s	1.49, s	1.39, s	1.39, s	1.48, s	1.53, s	1.53, s	1.59, s	1.59, s
12	1.49, s	1.50, s	1.40, s	1.40, s	1.48, s	1.51, s	1.51, s	1.57, s	1.58, s
13	1.44, s	1.44, s	1.43, s	1.43, s	1.38, s	1.44, s	1.44, s	1.39, s	1.39, s
14	1.44, s	1.44, s	1.43, s	1.43, s	1.33, s	1.12, s	1.12, s	1.30, s	1.30, s
2′	3.84, sept (6.6)	3.74, sext (7.0)	3.81, sept (6.8)	3.72, sext (7.0)	3.77, sext (7.0)	3.82, sept (6.6)	3.72, sext (6.6)	3.76, sept (7.0)	3.64, sext (6.6)
3′	1.19, d (6.6)	1.86, m	1.17, d (6.8)	1.85, m	1.86, m	1.19, d (6.6)	1.86, m	1.21, d (7.0)	1.86, m
		1.40, m		1.41, m	1.40, m		1.41, m		1.44, m
4′	1.19, d (6.6)	0.91, t (7.5)	1.17, d (6.8)	0.91, t (7.5)	0.91, t (7.5)	1.19, d (6.6)	0.92, t (7.5)	1.21, d (7.0)	0.93, t (7.0)
5′		1.16, d (7.0)		1.15, d (7.0)	1.16, d (7.0)		1.17, d (6.6)		1.19, d (6.6)
7-OH						8.30, s	8.30, s	8.98, s	8.97, s
8-OH						9.10, s	9.10, s		
9-OH	14.13, s	14.18, s	14.13, s	14.16, s	14.30, s	14.70, s	14.75, s	15.31, s	15.35, s

free hydroxy group hydrogen bonded to the carbonyl group of the acyl moiety. This feature is readily visible in metabolite profiles of fractions and can be used for ^{1}H NMR-guided isolation to reduce replication.[23] The new compounds were trivially named selancins A−I (**1**−**9**) and hyperselancins A and B (**10** and **11**). The assigned compound names are based on the Cameroonian word "*Se*", which is used for *Hypericum* in the local language of Mbouda and also means "God" in the Bamendjida language. "Lancin" is derived from the source plant species *H. lanceolatum*, whose leaves are lanceolated.

The molecular formula of **1** was established as $C_{20}H_{24}O_4$ from the ^{13}C NMR and HRESI-FTMS, which shows the deprotonated molecular ion at m/z 327.1601 $[M - H]^-$, corresponding to nine indices of hydrogen deficiency. The NMR data (Tables 1 and 2) are similar to those of octandrenolone, a tricyclic acetophloroglucinol derivative, isolated from *Melicope erromangensis* (Rutaceae), bearing two nonsymmetrical fused 2,2-dimethyl-2*H*-pyran rings.[24,25] The main difference between the two compounds is that the acyl side chain in **1** is a 2-methylpropanoyl moiety, while an acetyl group is present in octandrenolone.[25] The characteristic signals of the 2-methylpropanoyl group are observed in the ^{1}H NMR spectrum as one methine septet at δ_H 3.84 (1H, sept, J = 6.6 Hz, H-2′) and two equivalent methyl groups at δ_H 1.19 (6H, d, J = 6.6 Hz, Me-3′/Me-4′). The structure assigned to compound **1** (Figure 1) was confirmed based on HMBC correlations from 9-OH to C-10, C-9, and C-8a; from H-8 to C-9, C-8a, C-4b, and C-6; from H-7 to C-8a, C-6, and C-13/C-14; from H-4 to C-10a, C-4b, C-4a, and C-2; from H-3 to C-4a, C-2, and C-11/C-12; and from H_3-3′/H_3-4′ to C-1′ and C-2′ as well as from H-2′ to C-1′ and C-3′/C-4′. The COSY spectrum reveals three spin systems (H-7/H-8, H-3/H-4, and H-2′/Me-3′/Me-4′), whereas five cross-peaks are displayed in the ROESY spectrum (H-7/H-8, H-3/H-4, H-2′/Me-3′/Me-4′, H-7/Me-13/Me-14, and H-3/Me-11/Me-12). The structure of compound **1**, selancin A, was therefore unambiguously defined as 1-(5-hydroxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-yl)-2-methylpropan-1-one.

A difference of 14 atomic mass units between **1** ($C_{20}H_{24}O_4$) and **2** ($C_{21}H_{26}O_4$) was derived from MS and NMR data. A comparison of the 1D and 2D NMR data of **2** with those of **1** shows that the structural differences are restricted to the acyl side chain (Tables 1 and 2). HMBC correlations of Me-4′ with C-3′ (δ_C 26.8) and C-2′ (δ_C 46.0) and HMBC correlations of Me-5′ with C-1′ (δ_C 210.5) as well as with C-3′ and C-4′ clearly showed the replacement of the 2-methylpropanoyl substituent in **1** by a 2-methylbutanoyl side chain in **2**. Hence, the structure of compound **2** (Figure 1), selancin B, was elucidated as 1-(5-hydroxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano-[2,3-*f*]chromen-6-yl)-2-methylbutan-1-one.

The regioselective total synthesis of compounds **1** and **2** (racemic) was performed in two efficient steps (Scheme 1) starting with phloroglucinol. The synthetic routes afforded only one regiomer each (**1** and **2**) in 80% and 85% yield, respectively. The synthesis strategy involved Friedel−Crafts acylation of phloroglucinol followed by an ethylenediamine diacetate (EDDA)-catalyzed double condensation of acylphloroglucinols with 3-methyl-2-butenal. The NMR and MS data of synthetic compounds **1** and **2** (racemic) are identical to those of natural selancins A (**1**) and selancin B (**2**) isolated from the leaves of *H. lanceolatum*. In order to assign the C-2′ absolute configuration of **2**, the sign of its optical rotation was compared with that of synthetic compound (*S*)-**2**, synthesized from (+)-(*S*)-2-methylbutanoic acid (Scheme 2). The specific rotations of (*S*)-**2** and **2** were found to be $[\alpha]^{25}_D$ +2 (*c* 0.24, $CHCl_3$) and $[\alpha]^{26}_D$ +13 (*c* 0.22, $CHCl_3$), respectively. This, supported by matching the experimental electronic circular dichroism (ECD) spectra of natural compound **2** and synthetic (*S*)-**2** (Figure S48, Supporting Information), confirms the 2′*S* configuration of the natural product **2**.

A variation of 18 atomic mass units (addition of H_2O) between **1** ($C_{20}H_{24}O_4$) and **3** ($C_{20}H_{26}O_5$) was derived from MS

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Table 2. ^{13}C NMR Data (100 MHz, $CDCl_3$) for Compounds 1–9[a]

carbon	1		2		3		4		5		6		7		8		9	
2	78.2,	C	78.2,	C	78.5,	C	78.5,	C	77.7,	C	79.3,	C	79.4,	C	81.1,	C	81.0,	C
3	124.5,	CH	124.6,	CH	68.7,	CH	68.7,	CH	124.3,	CH	125.0,	CH	125.0,	CH	125.1,	CH	125.1,	CH
4	116.5,	CH	116.6,	CH	26.8,	CH_2	25.7,	CH_2	116.8,	CH	115.8,	CH	115.8,	CH	114.4,	CH	114.5,	CH
4a	102.1,	C	102.2,	C	98.1,	C	98.1,	C	102.2,	C	98.2,	C	98.3,	C	98.2,	C	98.3,	C
4b	154.8,	C	154.8,	C	157.5,	C	157.5,	C	154.3,	C	163.3,	C	163.3,	C	172.0,	C	171.9,	C
6	78.1,	C	78.1,	C	78.1,	C	78.1,	C	78.4,	C	82.3,	C	82.3,	C	83.4,	C	83.4,	C
7	125.3,	CH	125.3,	CH	125.0,	CH	125.0,	CH	69.1,	CH	91.9,	CH	91.9,	CH	88.8,	CH	88.8,	CH
8	116.3,	CH	116.3,	CH	116.3,	CH	116.3,	CH	25.6,	CH_2	84.7,	CH	84.8,	CH	193.7,	C	193.7,	C
8a	102.5,	C	102.5,	C	102.6,	C	102.6,	C	99.6,	C	102.2,	C	103.8,	C	104.1,	C	104.2,	C
9	161.1,	C	161.1,	C	160.6,	C	160.5,	C	164.3,	C	163.4,	C	163.3,	C	165.6,	C	165.6,	C
10	104.6,	C	105.2,	C	104.6,	C	105.2,	C	105.9,	C	105.3,	C	106.4,	C	105.3,	C	105.8,	C
10a	156.0,	C	156.1,	C	155.1,	C	155.1,	C	154.4,	C	159.0,	C	159.0,	C	163.3,	C	163.3,	C
11	27.9,	CH_3	27.8,	CH_3	24.8,	CH_3	24.8,	CH_3	27.7,	CH_3	28.2,	CH_3	28.2,	CH_3	28.5,	CH_3	28.5,	CH_3
12	27.9,	CH_3	27.8,	CH_3	21.7,	CH_3	21.8,	CH_3	27.8,	CH_3	27.9,	CH_3	27.8,	CH_3	28.5,	CH_3	28.4,	CH_3
13	28.4,	CH_3	28.4,	CH_3	28.5,	CH_3	28.5,	CH_3	24.9,	CH_3	21.3,	CH_3	21.3,	CH_3	21.9,	CH_3	21.9,	CH_3
14	28.4,	CH_3	28.4,	CH_3	28.6,	CH_3	28.6,	CH_3	22.1,	CH_3	19.1,	CH_3	19.1,	CH_3	19.6,	CH_3	19.6,	CH_3
1′	210.7,	C	210.5,	C	210.4,	C	210.3,	C	210.5,	C	210.9,	C	210.8,	C	211.0,	C	210.9,	C
2′	39.3,	CH	46.0,	CH	39.4,	CH	46.1,	CH	45.9,	CH	39.2,	CH	46.0,	CH	39.6,	CH	46.3,	CH
3′	19.4,	CH_3	26.8,	CH_2	19.4,	CH_3	26.8,	CH_2	26.8,	CH_2	19.3,	CH_3	26.7,	CH_2	19.2,	CH_3	26.6,	CH_2
4′	19.4,	CH_3	11.9,	CH_3	19.5,	CH_3	11.9,	CH_3	12.0,	CH_3	19.4,	CH_3	11.9,	CH_3	19.2,	CH_3	11.9,	CH_3
5′			16.9,	CH_3			16.9,	CH_3	16.9,	CH_3			16.8,	CH_3			16.7,	CH_3

[a]Assignment aided by 1D and 2D NMR data including HMBC, HSQC, and DEPT.

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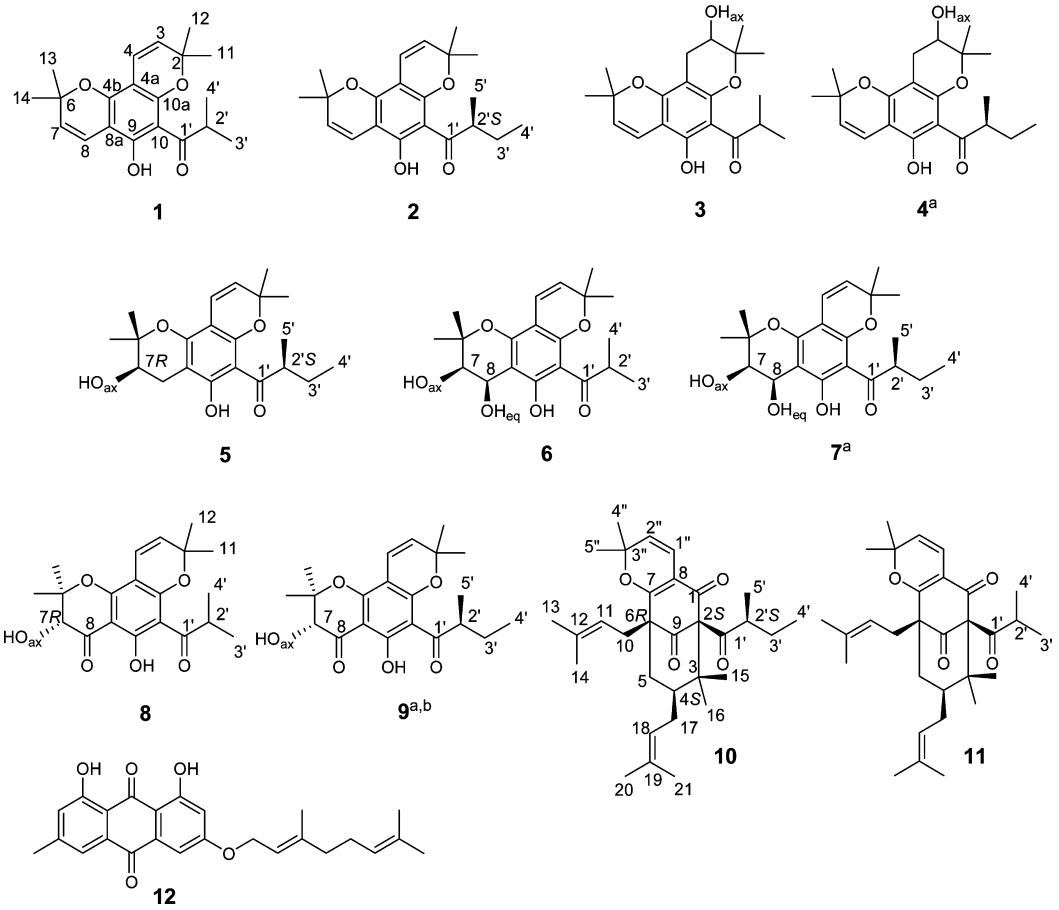
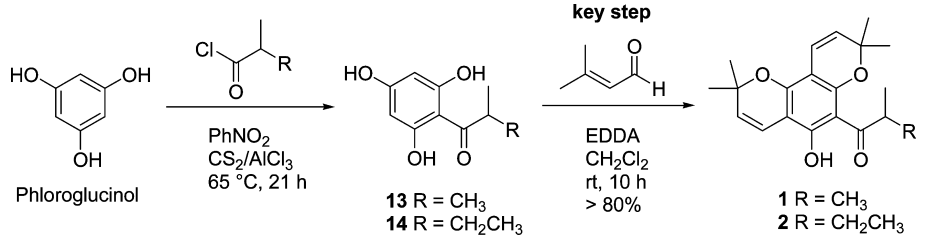
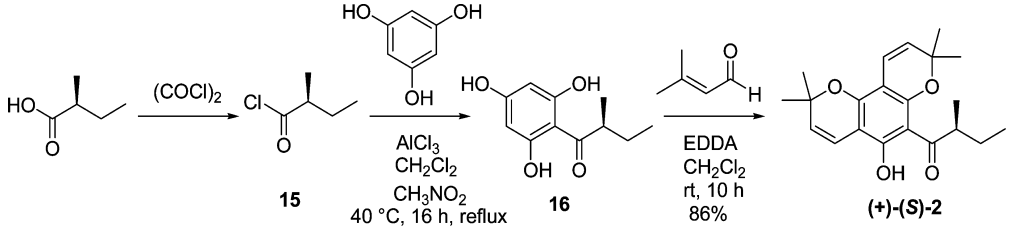


Figure 1. Chemical structures of compounds **1**−**12**. [a]2′*S* configuration tentatively assigned as in **2** due to the same biosynthetic origin.[6,27,38−40] [b]7*R* configuration tentatively assigned as in **8**.

Scheme 1. Regioselective Synthesis of Acylphloroglucinol Derivatives 1 and 2



Scheme 2. Total Synthesis of (+)-(*S*)-2



analysis. This difference was explained by the ^{1}H NMR spectrum (Table 1), which shows the replacement of the two doublets (H-3 and H-4) of a 2,2-dimethyl-2*H*-pyran moiety in **1** by the three signals (δ_H 3.81, dd, J = 5.8, 5.3, H-3; δ_H 2.85, dd, J = 17.1, 5.3, H-4a; and δ_H 2.60, dd, J = 17.1, 5.8, H-4b) of a 3-hydroxy-2,2-dimethyldihydropyran moiety in **3**.[26] The connection of the 3-hydroxy-2,2-dimethyldihydropyran moiety via C-4−C-4a was evident from HMBC correlations of H-4a/H-4b to C-10a, C-4b, C-4a, C-3, and C-2 as well as from H-3 to C-4a, C-11, and C-12. ROESY interactions were observed between H-3/Me-11/Me-12 and H-4a/Me-11 as well as a weak association between H-4b/Me-12. The ROESY interaction between H-3/Me-11/Me-12 and the coupling constant of H-3 (δ_H 3.81, dd, J = 5.8 and 5.3 Hz) required 3-OH to be axial.

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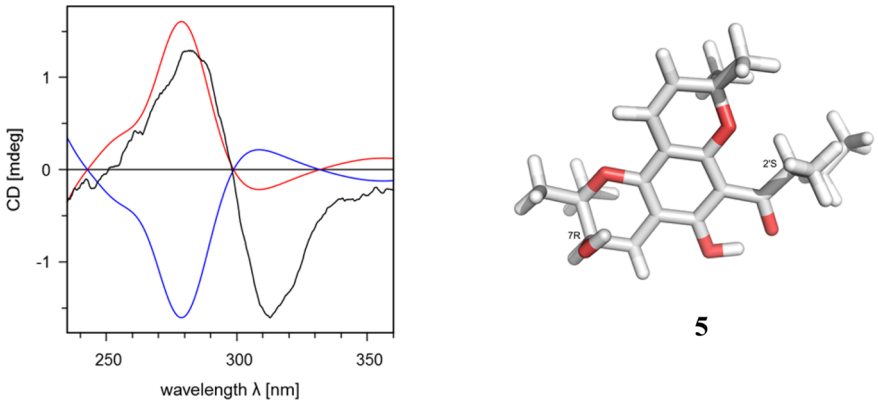

Figure 2. ECD spectra (7*R*, 2′*S*: red, 7*S*, 2′*R*: blue) of **5** in comparison to the experimental one (black). Similarity factor = 0.8963 at 24 nm shift.

However, it is not possible to determine the C-3 absolute configuration based on the axial orientation of 3-OH. On the basis of the above spectroscopic evidence the structure of **3**, selancin C, was defined as 1-(5,9-dihydroxy-2,2,8,8-tetramethyl-9,10-dihydro-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-yl)-2-methylpropan-1-one.

The HRESI-FTMS data of compound **4** exhibits the deprotonated molecule at *m*/*z* 359.1864 $[M - H]^-$, corresponding to the molecular formula $C_{21}H_{28}O_5$, which was also derived from ^{13}C NMR analysis. The 1D and 2D NMR data resemble those of selancin C (**3**), except in the acyl side chain. The difference of 14 mass units in compound **4** is attributed to a methylene group (δ_C 26.8, δ_H 1.85 m/1.41 m, 1H each) in the acyl side chain, which implies the replacement of the 2-methylpropanoyl unit of **3** by a 2-methylbutanoyl moiety in **4** (Tables 1 and 2).[23] Thus, the structure of compound **4**, selancin D, was identified as 1-(5,9-dihydroxy-2,2,8,8-tetramethyl-9,10-dihydro-2*H*,8*H*-pyrano[2,3-*f*]-chromen-6-yl)-2-methylbutan-1-one. Compounds **3** and **4** are, therefore, 3-hydroxylated derivatives of **1** and **2**, respectively (Scheme S1, Supporting Information). On the basis of this consideration, the C-2′ absolute configuration of **4** was tentatively assigned to be *S* as in **2**.

Compound **5**, which has a molecular formula of $C_{21}H_{28}O_5$ as determined from HRESI-FTMS and ^{13}C NMR data, is a regiomer of **4**. They differ in the position of the 2,2-dimethyl-2*H*-pyran and 3-hydroxy-2,2-dimethyldihydropyran moieties, as shown by 1D (Tables 1 and 2) and 2D NMR data. As for **3** and **4**, the ^1H NMR data (Table 1) of **5** show three characteristic signals (δ_H 3.80, t, *J* = 5.3, H-7; δ_H 2.87, dd, *J* = 17.1, 5.3, H-8a; and δ_H 2.65, dd, *J* = 17.1, 5.3, H-8b) for a 3-hydroxy-2,2-dimethyldihydropyran moiety in addition to signals of a hydrogen-bonded hydroxy group (δ_H 14.30, s), a 2,2-dimethyl-2*H*-pyran, and a 2-methylbutanoyl group. The position of the OH group at C-7 was supported by HMBC cross-peaks from Me-13 (respectively, Me-14) to C-6, C-7, and C-14 (respectively, C-13). The key HMBC correlations from 9-OH to C-8a; from H-7 to C-8a; and from H-8a/H-8b to C-9, C-8a, C-4b, and C-7 established the connection of the 3-hydroxy-2,2-dimethyldihydropyran moiety via C-8−C-8a−C-4b on the phloroglucinol core. The linkage of the 2,2-dimethyl-2*H*-pyran moiety via C-4−C-4a−C-10a was indicated by the HMBC correlations from H-4 to C-10a, C-4b, and C-2 as well as from H-3 to C-4a and C-2. The 2-methylbutanoyl residue containing the carbonyl group hydrogen-bonded to the hydroxy group at C-9 was, therefore, deduced to be linked at C-10. Further HMBC correlations were detected from 9-OH to C-9 and C-10 and from H-8a/H-8b to C-6. ROESY interactions were observed between H-7/Me-13/Me-14, which required 7-OH to be axial. On the basis of the above spectroscopic evidence the structure of **5**, selancin E, was defined as 1-(3,5-dihydroxy-2,2,8,8-tetramethyl-3,4-dihydro-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-yl)-2-methylbutan-1-one. The absolute configuration of selancin E (**5**) was investigated by comparing its experimental and calculated ECD spectra. The calculations indicated that compound **5** has a 7*R* configuration with axial orientation of the 7-OH group (Figures 2 and S39, Supporting Information). However, it was not possible to unambiguously distinguish between (7*R*, 2′*S*) and (7*R*, 2′*R*) absolute configurations based on calculated data. Compared to the experimental data the (7*R*, 2′*S*) diastereoisomer exhibits a slightly better similarity factor (0.8963 at 24 nm shift) than the (7*R*, 2′*R*) epimer (0.8580 at 23 nm shift, Figure S39). Likewise, previously reported acylphloroglucinols as well as compound **2** possess the *S* configuration at C-2′.[6,27] Therefore, the 2′*S* configuration (Figure 1) was tentatively assigned for **5**.

The molecular formula of selancin F (**6**, $C_{20}H_{26}O_6$), as determined by HRESI-FTMS and ^{13}C NMR data, differs from that of selancin A (**1**, $C_{20}H_{24}O_4$) by the addition of two hydroxy groups. The NMR data of **1** and **6** are similar, except that signals of one of the two 2,2-dimethyl-2*H*-pyran moieties in **1** are substituted by those of a 3,4-dioxygenated dimethylchromane moiety (Tables 1 and 2; Figure 1).[28,29] The ^1H NMR data (Table 1) of **6** show signals of three hydroxy groups. The chemical shifts at δ_H 5.83 (d, *J* = 3.1 Hz; δ_C 84.7, C-8) and 5.09 (d, *J* = 3.1 Hz; δ_C 91.9, C-7) are assigned to the 3,4-dioxygenated dimethylchromane unit.[28,29] The 2,2-dimethyl-2*H*-pyran moiety of **6** was connected via C-4−C-4a−C-10a as revealed by HMBC correlations from H-4 to C-10a, C-4b, C-4a, and C-2. The connection of the dioxygenated dimethylchromane moiety via C-8−C-8a−C-4b was consequently derived from 2D NMR data analysis. Further HMBC correlations were observed from 9-OH to C-10, C-9, and C-8a; from Me-14 to C-7, C-6, and C-13; and from Me-13 to C-7, C-6, and C-14. The relative configuration depicted in Figure 1 was established by 1D and 2D NMR. The ROESY correlations observed between H-8/Me-14 and H-7/Me-13/Me-14 suggest H-7 and Me-13 to be equatorial, while H-8 and Me-14 are axially oriented. These observations, in addition to the ROESY correlation observed between H-7/H-8 and the small coupling constant ($^3J_{H7-H8}$ = 3.1 Hz), required H-7 and H-8 to be *cis* oriented. Compound **6**, selancin F, was therefore characterized as 1-(3*R**,4*S**,5-trihydroxy-2,2,8,8-tetramethyl-

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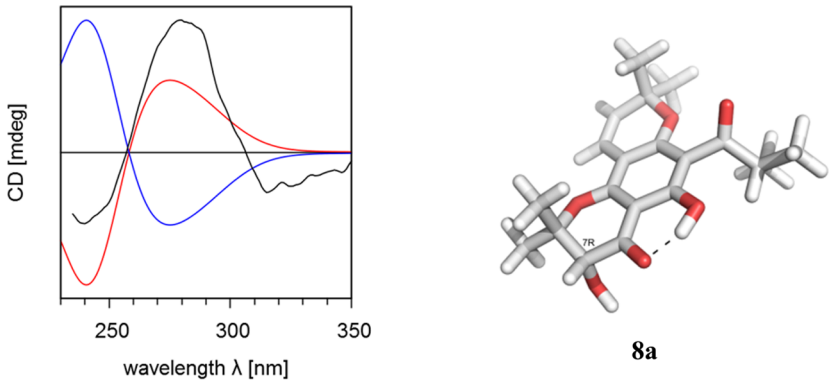

Figure 3. Boltzmann-weighted ECD spectra of **8** (7*R*: red, 7*S*: blue) in comparison to the experimental one (black). Similarity factor = 0.9174 with a shift of −8 nm. Weighting factors see Figure S40: **8a** (48.1%), **8b** (38.2%), and **8c** (13.7%).

3,4-dihydro-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-yl)-2-methylpropan-1-one.

Although selancin G (**7**, $C_{21}H_{28}O_6$) was not of good purity and rapidly decomposed, its ^{1}H and ^{13}C NMR signals could be readily assigned (Tables 1 and 2). The MS and NMR data resemble those of selancin F (**6**, $C_{20}H_{26}O_6$). A variation of 14 atomic mass units as determined from the HRMS data is due to the replacement of a 2-methylpropanoyl unit by a 2-methylbutanoyl moiety (Tables 1 and 2). The chemical shifts and coupling constants of H-7 and H-8 are the same as in **6**, which implies the same relative configuration. The 2′*S* configuration was tentatively assigned for **7** as in **2** and previously reported acylphloroglucinols.[6,27] Compound **7** was therefore assigned the structure 1-(3*R**,4*S**,5-trihydroxy-2,2,8,8-tetramethyl-3,4-dihydro-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-yl)-2*S*-methylbutan-1-one.

The molecular formulas of compounds **8** and **9** were determined as $C_{20}H_{24}O_6$ and $C_{21}H_{26}O_6$ based on their negative ion HRESI-FTMS data, which reveal the $[M - H]^-$ ion peaks at *m*/*z* 359.1573 and 373.1729, respectively. These MS observations were supported by NMR data. Compounds **8** and **9** differ only in the acyl side chain as established by NMR and MS data. Compound **8** is similar to **6** except that C-8 (δ_C 193.7) is oxidized to a carbonyl group in **8**,[30] as revealed by key HMBC correlations from H-7 (δ_H 4.85, s) to C-8, C-6, and C-13/C-14, as well as from Me-14 (respectively, Me-13) to C-7 (δ_C 88.8), C-6 (δ_C 83.4), and C-13 (respectively, C-14). The ROESY spectrum suggests H-7 to be equatorial oriented because it exhibits interactions with both Me-13 and Me-14, thus placing the 7-OH group axial. The absolute configuration of **8** was determined by comparing its experimental and calculated ECD spectra (Figures 3 and S40, Supporting Information). The calculations clearly indicated that compound **8** has a 7*R* configuration with axial orientation of the 7-OH group. The energetically preferred conformation is shown in Figure S40 (Supporting Information). Calculated spectra with equatorial orientation of the 7-OH group do not fit with the experimental spectrum. On the basis of spectroscopic data, the structure of **8** (Figure 1), selancin I, was thus identified as 3*R*,5-dihydroxy-2,2,8,8-tetramethyl-6-(2-methylpropanoyl)-2,3-dihydro-4*H*,8*H*-pyrano[2,3-*f*]chromen-4-one. Similarly, compound **9**, selancin I, is 3*R*,5-dihydroxy-2,2,8,8-tetramethyl-6-(2*S*-methylbutanoyl)-2,3-dihydro-4*H*,8*H*-pyrano[2,3-*f*]chromen-4-one. The (7*R*, 2′*S*) absolute configuration was tentatively assigned for **9** in comparison to its potential biosynthetic precursor (2′*S*)-**2** and its analogue (7*R*)-**8** (Scheme S1, Supporting Information).[6,27]

The absolute configurations of **3**, **4**, and **9** were not determined since no reasonable conclusions could be drawn solely from ECD data. However, it can be presumed that they maintain the same configurations as their structural analogues **2**, **5**, or **8** due to the proposed biogenetic relationship (Scheme S1, Supporting Information). These compounds were not in sufficient quantities for further purification or chemical derivatization.

Hyperselancin A (**10**) has the molecular formula $C_{31}H_{44}O_4$ based on the HRESI-FTMS (*m*/*z* 481.3303, $[M + H]^+$) and ^{13}C NMR data. The assignment of carbon and proton signals of this compound was based on 1D and 2D NMR data, including DEPT, HSQC, HMBC, COSY, and ROESY. The ^{1}H NMR data (Table 3) of **10** indicate signals of four olefinic protons including two doublets of a 2,2-dimethyl-2*H*-pyran moiety at δ_H 6.49 (1H, d, *J* = 10.1 Hz, H-1″) and 5.38 (1H, d, *J* = 10.1 Hz, H-2″) as well as two triplets at δ_H 4.99 (1H, t, *J* = 6.6 Hz, H-11) and δ_H 4.92 (1H, t, *J* = 6.6 Hz, H-18) consistent with two prenyl units.[24,31] They also indicate signals of six methyls at oxygenated and nonoxygenated sp^3 C atoms and the four methyl groups of the two prenyl chains. The ^{13}C NMR data of **10** (Table 3) exhibit 31 carbon signals, including characteristic signals of a polyprenylated polycyclic acylphloglucinol (PPAP) containing a bicyclo[3.3.1]nonane-2,4,9-trione skeleton with two nonconjugated carbonyl groups (δ_C 208.6, C-1′; 206.8, C-9), one enolized keto group (δ_C 188.8, C-1; 114.1, C-8; 171.7, C-7), three quaternary carbons (δ_C 81.2, C-2; 55.1, C-6; 48.2, C-3), one methine (δ_C 44.7, C-4), one methylene (δ_C 38.4, C-5), and two methyl groups at C-3 (δ_C 26.5, C-16; 22.1, C-15).[13,24,31] Signals of the 2-methylbutanoyl moiety of PPAP-type compounds (δ_H 0.83, 3H, t, *J* = 7.5 Hz, Me-4′; 1.02, 3H, d, *J* = 6.1 Hz, Me-5′; 1.94 m/1.32 m, 1H each, diastereotopic C-3′ protons; 1.84, 1H, m, H-2′) are also displayed in the ^{1}H NMR spectrum of **10** (Table 3).[13,24,31] The COSY spectrum of **10** displays proton spin systems of H-1″/H-2″, H_2-10/H-11, H-18/H-17a/H-17b/H-4/H-5a, and H_3-5′/H-2′/H-3′a/H-3′b/H_3-4′. Inspection of the HMBC spectrum of **10** permitted the unambiguous placement of each substituent on the core structure. ROESY correlations were observed between H-17b/H-3′b, H-17b/H-5a, H-5a-H_2-10, and H-17a/Me-15. In addition to the COSY data, HMBC correlations from H-10 to C-6, C-7, C-9, C-11, and C-12; from H-5a (δ_H 2.11) to C-4, C-6, C-7, C-9, and C-17; from H-5b (δ_H 2.06) to C-7, C-9, and C-17; from H-1″ to C-7 and C-3″; and from H-2″ to C-8 and

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Table 3. ^{13}C and ^{1}H NMR Data [δ, multiplicity, J (Hz)] for Compounds 10 and 11 ($CDCl_3$)[a]

	10			11		
position	δ_C		δ_H	δ_C		δ_H
1	188.8,	C		187.6,	C	
2	81.2,	C		81.1,	C	
3	48.2,	C		48.0,	C	
4	47.7,	CH	1.36, m	47.7,	CH	1.36, m
5	38.4,	CH_2	2.11, m	38.1,	CH_2	2.11, m
			2.06, m			2.06, m
6	55.1,	C		55.0,	C	
7	171.7,	C		171.8,	C	
8	114.1,	C		114.2,	C	
9	206.8,	C		206.7,	C	
10	30.5,	CH_2	2.45, d (6.6)	30.5,	CH_2	2.45, d (6.6)
11	119.7,	CH	4.99, t (6.6)	119.7,	CH	5.02, t (6.6)
12	133.6,	C		133.5,	C	
13	26.0,	CH_3	1.65, s	25.9,	CH_3	1.67, s
14	18.1,	CH_3	1.69, s	18.1,	CH_3	1.53, s
15	22.1,	CH_3	1.32, s	22.1,	CH_3	1.32, s
16	26.5,	CH_3	1.19, s	26.5,	CH_3	1.20, s
17	29.5,	CH_2	2.10, m	29.4,	CH_2	2.10, m
			1.87, m			1.87, m
18	125.0,	CH	4.92, t (7.0)	125.0,	CH	4.92, t (7.5)
19	132.1,	C		132.1,	C	
20	25.8,	CH_3	1.65, s	25.8,	CH_3	1.65, s
21	18.1,	CH_3	1.53, s	18.1,	CH_3	1.68, s
1′	208.6,	C		208.9,	C	
2′	48.9,	CH	1.84, m	41.9,	CH	2.15, m
3′	26.7,	CH_2	1.94, m	21.7,	CH_3	1.03, d (6.6)
			1.32, m			
4′	11.7,	CH_3	0.83, t (7.5)	20.6,	CH_3	1.14, d (6.6)
5′	18.0,	CH_3	1.02, d (6.1)			
1″	115.5,	CH	6.49, d (10.1)	115.4,	CH	6.49, d (10.1)
2″	124.0,	CH	5.38, d (10.1)	124.0,	CH	5.38, d (10.1)
3″	82.5,	C		82.5,	C	
4″	29.3,	CH_3	1.51, s	29.3,	CH_3	1.51, s
5″	28.2,	CH_3	1.37, s	28.1,	CH_3	1.36, s

[a]Assignment aided by 1D and 2D NMR data including HMBC, HSQC, and DEPT.

C-3″ confirmed the position of the prenyl and 2,2-dimethyl-2*H*-pyran groups. HMBC correlations from Me-15/Me-16 to C-2 (δ_C 81.2, C), C-3 (δ_C 48.2, C), C-4 (δ_C 47.7, CH), and C-16/C-15 require Me-15/Me-16 at C-3. Me-5′ of the C-2 acyl chain correlates to C-1′, C-2′, and C-3′. The chemical shift of the highly deshielded and nonoxygenated quaternary carbon C-2 (δ_C 81.2) indicates that it is surrounded by three carbonyl groups as extensively reported for PPAP-type compounds.[13,24,31] The connectivity inferred by the HMBC spectrum is compatible only with structure **10**. According to these NMR data, the structure of compound **10** resembles therefore androforin A, scrobiculatone A, and papuaforin C, which were previously isolated from Guttiferae plants.[24,31,32] Owing to the rigid structure of the bridged ring system, the substituents at C-2 and C-6 must be *cis* oriented, as extensively reported for PPAPs.[13,24,33] The C-4 relative configuration of **10** was assessed by NMR analysis. ROESY correlations observed between H-17b/H-5a, H-5a/H_2-10, and H-17a/Me-15 indicated that CH_2-17, Me-15, and CH_2-10 are β-oriented. The absolute configuration of compound **10** was determined by comparing its experimental and calculated ECD spectra. The results (Figure 4) suggest the configuration at the four stereogenic centers to be (2*S*, 4*S*, 6*R*, 2′*S*). The most stable conformer agrees with ROESY analysis and literature evidence where the chemical shift of C-4 (δ_C 45−49) in PPAPs with an α-oriented H-4 can be readily distinguished from that of C-4 (δ_C 41−44) in PPAPs with a β-oriented H-4.[31−33] On the basis of the above data, the structure of compound **10**, hyperselancin A, was established as 2,2,7,7-tetramethyl-6*S*-(2*S*-methylbutanoyl)-8*S*,10*R*-bis(3-methylbut-2-enyl)-2,6,7,8,9,10-hexahydro-5*H*-6,10-methanocycloocta[*b*]pyran-5,11-dione.

Hyperselancin B (**11**) has the molecular formula $C_{30}H_{42}O_4$ based on the HRESI-FTMS (m/z 467.3156, $[M + H]^+$) and ^{13}C NMR data. A difference of 14 atomic mass units is observed between **10** and **11**. The 1D and 2D NMR data of **11** indicate that signals of the 2-methylbutanoyl group in **10** are replaced by signals of a 2-methylpropanoyl group (δ_H 1.14, 3H, d, J = 6.6 Hz, Me-4′; 1.03, 3H, d, J = 6.6 Hz, Me-3′; 2.15, 1H, m, H-2′) in **11**. This is confirmed by HMBC correlations from Me-4′/Me-3′ to C-1′ (δ_C 208.9). The ROESY data of **11** exhibit similar correlations to those in **10**, which implies the same relative configuration. The absolute configuration of **11** was determined to be (2*S*, 4*S*, 6*R*) by comparing the experimental and calculated ECD spectra (Figure 5). The results are consistent with NMR analysis. Analogues of hyperselancins A and B (PPAPs), including hyperforin,[1] androforins,[31] hypercohins,[13]

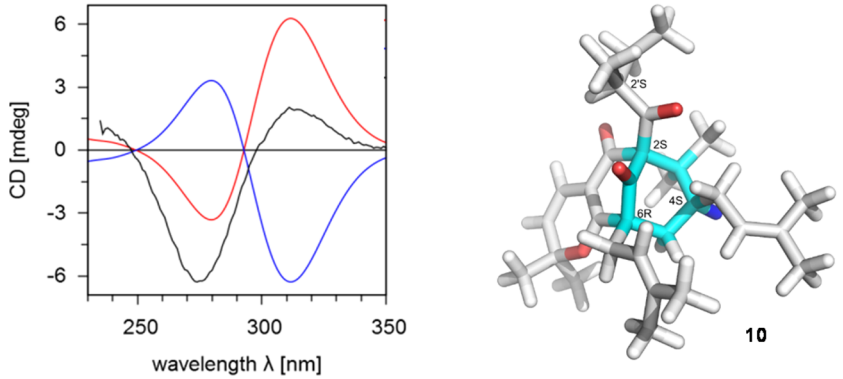

Figure 4. ECD spectra (red: calculated, black: experimental) and structure of **10** with 2*S*, 4*S*, 6*R*, 2′*S* configuration in boat conformation at 4*S* (cyan ring). Similarity factor = 0.9529, 9 nm shift. Blue spectrum: calculated spectrum with 2*R*, 4*R*, 6*S*, 2′*R* configuration.

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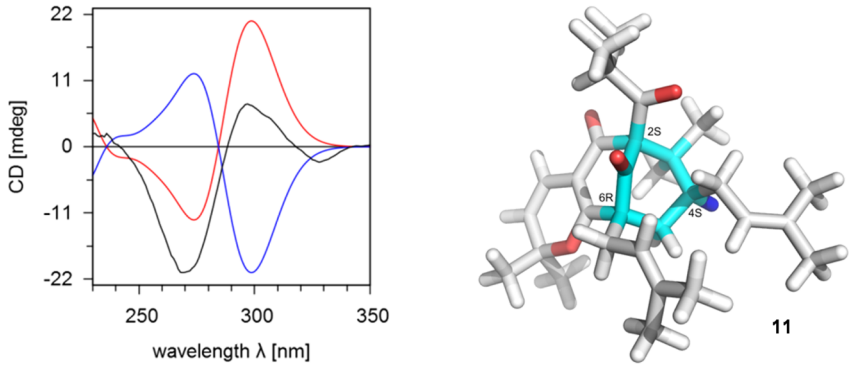

Figure 5. ECD spectra (red: calculated, black: experimental) and structure of compound **11** in 2*S*, 4*S*, 6*R* configuration with boat conformation (cyan ring). Similarity factor = 0.9695, shift 2 nm. Blue spectrum: calculated spectrum with 2*R*, 4*R*, 6*S* configuration.

and papuaforins,[24] have been previously reported from *Hypericum* species.

The structure of 3-*O*-geranylemodin (**12**) was established by comparing its observed and reported spectroscopic data.[20,34] 3-*O*-Geranylemodin is the first geranylated anthraquinone isolated from the genus *Hypericum*, although simple anthraquinones (e.g. emodin) and bisanthraquinones have been reported from this genus.[35,36]

Compounds **1**–**9** belong to the rare group of acylphloroglucinol derivatives bearing two fused dimethylpyran units around a central benzene core. Only 18 compounds showing such structural features have been reported from nature, and they occur mainly in *Clusia ellipticifolia* (Clusiaceae or Guttiferae) and *Melicope erromangensis* (Rutaceae).[25,37] Some of the new derivatives reported here are partially oxidized. Compounds **8** and **9** are the first natural products that have a 6-acyl-2,2-dimethylchroman-4-one core fused with an additional dimethylpyran unit. Two key steps presumably govern the biosynthesis of compounds **1** and **2**: the diprenylation of the acylphloroglucinol core intermediate followed by cyclization. Compounds **3**–**9** might henceforth derive from **1** or **2** via oxidation processes.[38−40] The biosynthesis and diprenylation mechanisms of acylphloroglucinol intermediates have been disclosed.[41]

Considering that *Hypericum* species are used in Cameroonian folk medicine for the treatment of various diseases including intestinal worms, the crude MeOH extract obtained from the whole leaf powder of *H. lanceolatum* was tested in an anthelmintic assay. The anthelmintic activity against the model organism *Caenorhabditis elegans* was determined in a modified microtiter plate assay by enumeration of living and dead nematodes using a simple microscopic view.[42] At a test concentration of 500 μg/mL, the extract showed a nematode death percentage of only 2.52 ± 2.20% (no activity). In contrast, the same extract induced significant growth inhibition of the prostate cancer cell line PC-3 (88.6 ± 0.6%) and the colon cancer cell line HT-29 (88.7 ± 1.8%) at a concentration of 50 μg/mL. No cytotoxicity (less than 2% growth inhibition) was observed at a concentration of 0.5 μg/mL. Compounds **1**–**6**, **8**, **9**, and **12** were also screened for cytotoxicity against HT-29 and PC-3 cancer cell lines. However, up to a concentration of 10 μM no significant growth inhibition was determined. These results suggest a potential synergistic cytotoxic effect of *H. lanceolatum* constituents. Compounds **7** and especially **10** and **11** were not tested for any biological activity because they readily decomposed after isolation and spectroscopic measurements.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured using a JASCO P-2000 digital polarimeter. UV spectra were obtained on a JASCO V-560 UV/Vis spectrophotometer. ECD spectra in $CHCl_3$ were recorded using a JASCO J-815 spectrometer. IR (ATR) spectra were recorded using a Thermo Nicolet 5700 FT-IR spectrometer, in MeOH or $CHCl_3$. ^1H and ^{13}C NMR and 2D (gDQCOSY, ROESY (mixing time 200 ms), gHSQCAD, gHMBCAD) spectra were recorded on an Agilent DD2 400 NMR spectrometer at 399.915 and 100.569 MHz, respectively. The ^1H NMR chemical shifts are referenced to internal TMS (δ_H 0.0); ^{13}C NMR chemical shifts are referenced to internal $CDCl_3$ (δ_C 77.0). The low-resolution electrospray (ESI) mass spectra were performed on a SCIEX API-3200 instrument (Applied Biosystems, Concord, Ontario, Canada) combined with an HTC-XT autosampler (CTC Analytics, Zwingen, Switzerland). The samples were introduced via autosampler and loop injection. The HRESI mass spectra of compounds **1**–**12** as well as the corresponding MS^n measurements were obtained from an Orbitrap Elite mass spectrometer (Thermofisher Scientific, Bremen, Germany) equipped with an HESI electrospray ion source (spray voltage 4 kV, capillary temperature 275 °C, source heater temperature 40 °C, FTMS resolution 30.000). Nitrogen was used as sheath gas. The sample solutions were introduced continuously via a 500 μL Hamilton syringe pump with a flow rate of 5 μL/min. The data were evaluated by the Xcalibur software 2.7 SP1.

HPLC was performed on a Varian PrepStar instrument equipped with a Varian ProStar PDA detector using an RP18 column (10 μm, 250 × 10 mm; flow rate 8.9 mL/min; detection 210 nm) and acetonitrile (HPLC grade, LiChrosolv, Merck KGaA, Germany) and double distilled water as solvents. Before HPLC separation samples were filtered using solid phase extraction through a Chromabond C18ec SPE cartridge (Macherey-Nagel, 1 mL/100 mg). Column chromatography (CC) was run on silica gel (Merck, 63–200 and 40–63 μm) and Sephadex LH-20 (Fluka), while TLC was performed on precoated silica gel F_{254} plates (Merck). Spots were visualized with a UV lamp at 254 and 366 nm or by spraying with vanillin–H_2SO_4–MeOH followed by heating at 100 °C.

Plant Material. The leaves of *H. lanceolatum* Lam. were collected in August 2011 at Mount Bamboutos (Mbouda) in the West Region of Cameroon. The plant was identified by Mr. Nana Victor, botanist at the National Herbarium of Cameroon, where a voucher specimen (No. 32356/HNC) is deposited.

Extraction and Isolation. The air-dried and powdered leaves (750 g) of *H. lanceolatum* were sequentially and successively extracted with $CHCl_3$ (3 × 3 L) and MeOH (2 × 2 L) for 1 day under shaking to give the respective extracts, namely, the $CHCl_3$ (68.82 g) and MeOH (15.63 g) extracts, after solvent evaporation under reduced pressure. For the evaluation of anthelmintic and cytotoxic activities, the whole powdered leaves (3 g) of *H. lanceolatum* were extracted in 80% MeOH (30 mL) under sonification for 30 min to afford a crude extract (140.2 mg) after filtration and solvent removal.

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A portion of the $CHCl_3$ extract (42 g) was subjected to silica gel column flash chromatography, eluted with step gradients of *n*-hexane−EtOAc and EtOAc−MeOH, to afford 23 fractions of 400 mL each, which were combined on the basis of their TLC profiles into seven main fractions (Fr.1−Fr.7). Fr.1 (7.65 g), obtained from *n*-hexane−EtOAc (100:0 and 90:10), was further chromatographed on a SiO_2 column, eluted with *n*-hexane−EtOAc, to afford eight subfactions ($Fr.1_1$−$Fr.1_8$). $Fr.1_1$ (1.96 g, from *n*-hexane−EtOAc, 90:10 and 80:20) also afforded eight subfractions ($Fr.1_{1a}$−$Fr.1_{1h}$) after CC on silica gel, eluted with step gradients of *n*-hexane−EtOAc (98:2, 95:5, 90:10, 0:100). Repeated chromatography of $Fr.1_{1a}$ (558 mg, obtained from *n*-hexane−EtOAc, 98:2) on silica gel CC and preparative TLC, as well as final purification by reversed phase HPLC, eluted with H_2O−MeCN (30% → 100% MeCN 0−20 min, 100% MeCN 20−25 min, 100% → 30% MeCN 25−27 min, 30% MeCN 27−30 min), afforded compounds **1** (7.79 mg, t_R 6.43 min) and **2** (4.5 mg, t_R 7.25 min). $Fr.1_{1c}$ (151.4 mg), also obtained from *n*-hexane−EtOAc (98:2), was dissolved in THF and purified by semipreparative HPLC, eluted with H_2O−MeCN (70% → 100% MeCN 0−20 min, 100% MeCN 20−25 min, 100% → 70% MeCN 25−27 min, 70% → 50% MeCN 27−30 min), to yield **6** (4.04 mg, t_R 9.08 min), **7** (2.9 mg, t_R 9.85 min), **8** (4.4 mg, t_R 9.34 min), **9** (1.8 mg, t_R 10.10 min), **10** (1.8 mg, t_R 17.42 min), **11** (1.78 mg, t_R 16.98 min), and **12** (2.2 mg, t_R 18.51 min). Fr.2 (3.1 g), obtained from *n*-hexane−EtOAc (90:10 and 80:20), was further subjected to silica gel CC eluted with *n*-hexane containing increasing amounts of EtOAc to yield eight subfractions ($Fr.2_1$−$Fr.2_8$). $Fr.2_4$ (252.7 mg), obtained from *n*-hexane−EtOAc (80:20 and 70:30), was suspended in isopropyl alcohol, filtered by SPE, and finally purified by semipreparative HPLC, eluted with H_2O−MeCN (30% → 100% MeCN 0−20 min, 100% MeCN 20−25 min, 100% → 30% MeCN 25−27 min, 30% MeCN 27−30 min), to afford compounds **3** (6.5 mg, t_R 3.88 min), **4** (3.5 mg, t_R 4.29 min), and **5** (2.6 mg, t_R 4.61 min).

*Selancin A (**1**), 1-(5-hydroxy-2,2,8,8-tetramethyl-2H,8H-pyrano[2,3-f]chromen-6-yl)-2-methylpropan-1-one:* yellow oil; UV ($CHCl_3$) λ_{max} (log ε) 273 (4.49), 379 (3.38) nm; IR (ATR) ν_{max} (cm^{-1}) 3604, 2974, 2928, 2872, 1640, 1592, 1462, 1381, 1132, 997, 871, 709, 660; ^1H NMR data see Table 1; ^{13}C NMR data see Table 2; negative ion ESI-FTMS *m*/*z* 327.1601 $[M - H]^-$ (calcd for $C_{20}H_{23}O_4^-$, 327.1602).

*Selancin B (**2**), 1-(5-hydroxy-2,2,8,8-tetramethyl-2H,8H-pyrano[2,3-f]chromen-6-yl)-2S-methylbutan-1-one:* yellow oil; $[\alpha]^{26}_D$ +13 (*c* 0.2, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 273 (4.47), 378 (3.37) nm; ECD ($CDCl_3$) $\Delta\varepsilon$ (nm) +1.8 (279) and −0.8 (317); IR (ATR) ν_{max} (cm^{-1}) 3594, 2970, 2926, 2874, 1639, 1591, 1461, 1382, 1132, 880, 709, 660; ^1H NMR data see Table 1; ^{13}C NMR data see Table 2; negative ion ESI-FTMS *m*/*z* 341.1756 $[M - H]^-$ (calcd for $C_{21}H_{25}O_4^-$, 341.1758).

*Selancin C (**3**), 1-(5,9-dihydroxy-2,2,8,8-tetramethyl-9,10-dihydro-2H,8H-pyrano[2,3-f]chromen-6-yl)-2-methylpropan-1-one:* yellow oil; $[\alpha]^{25}_D$ +2 (*c* 0.3, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 279 (4.33), 354 (3.42) nm; ECD ($CDCl_3$) $\Delta\varepsilon$ (nm) +0.2 (293) and −0.04 (327); IR (ATR) ν_{max} (cm^{-1}) 3444, 2975, 2929, 2872, 1634, 1594, 1424, 1381, 1125, 751, 717, 666; ^1H NMR data see Table 1; ^{13}C NMR data see Table 2; negative ion ESI-FTMS $[M - H]^-$ at *m*/*z* 345.1712 (calcd for $C_{20}H_{25}O_5^-$, 345.1707).

*Selancin D (**4**), 1-(5,9-dihydroxy-2,2,8,8-tetramethyl-9,10-dihydro-2H,8H-pyrano[2,3-f]chromen-6-yl)-2S-methylbutan-1-one:* yellow oil; $[\alpha]^{25}_D$ +12 (*c* 0.3, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 279 (4.58), 357 (3.65) nm; ECD ($CDCl_3$) $\Delta\varepsilon$ (nm) +0.9 (292) and −0.6 (322); IR (ATR) ν_{max} (cm^{-1}) 3444, 2972, 2929, 2874, 1613, 1594, 1423, 1379, 1123, 752, 718, 666; ^1H NMR data see Table 1; ^{13}C NMR data see Table 2; negative ion ESI-FTMS *m*/*z* 359.1867 $[M - H]^-$ (calcd for $C_{21}H_{27}O_5^-$, 359.1864).

*Selancin E (**5**), 1-(3R,5-dihydroxy-2,2,8,8-tetramethyl-3,4-dihydro-2H,8H-pyrano[2,3-f]chromen-6-yl)-2S-methylbutan-1-one:* yellow oil; $[\alpha]^{25}_D$ +7 (*c* 0.2, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 287 (5.04), 360 (4.12) nm; ECD ($CDCl_3$) $\Delta\varepsilon$ (nm) +0.6 (281) and −0.8 (313); IR (ATR) ν_{max} (cm^{-1}) 3450, 2966, 2924, 2873, 1638, 1596, 1417, 1380, 1126, 754, 716, 666; ^1H NMR data see Table 1; ^{13}C NMR data see Table 2; negative ion ESI-FTMS *m*/*z* 359.1867 $[M - H]^-$ (calcd for $C_{21}H_{27}O_5^-$, 359.1864).

*Selancin F (**6**), 1-(3R*,4S*,5-trihydroxy-2,2,8,8-tetramethyl-3,4-dihydro-2H,8H-pyrano[2,3-f]chromen-6-yl)-2-methylpropan-1-one:* yellow oil; UV ($CHCl_3$) λ_{max} (log ε) 269 (4.76), 279 (4.75) nm; IR (ATR) ν_{max} (cm^{-1}) 3400, 2977, 2933, 2873, 1650, 1615, 1423, 1367, 1127, 1058, 749, 666; ^1H NMR data see Table 2; ^{13}C NMR data see Table 2; positive ion ESI-FTMS *m*/*z* 385.1625 $[M + Na]^+$ (calcd for $C_{20}H_{26}O_6Na^+$, 385.1622).

*Selancin G (**7**), 1-(3R*,4S*,5-trihydroxy-2,2,8,8-tetramethyl-3,4-dihydro-2H,8H-pyrano[2,3-f]chromen-6-yl)-2S-methylbutan-1-one:* yellow oil; ^1H NMR data see Table 1; ^{13}C NMR data see Table 2; positive ion ESI-FTMS *m*/*z* 399.1774 $[M + Na]^+$ (calcd for $C_{21}H_{28}O_6Na^+$, 399.1778). $[\alpha]_D$, UV, and IR were not determined because of compound degradation.

*Selancin H (**8**), 3R,5-dihydroxy-2,2,8,8-tetramethyl-6-(2-methylpropanoyl)-2,3-dihydro-4H,8H-pyrano[2,3-f]chromen-4-one:* yellow oil; $[\alpha]^{25}_D$ +1 (*c* 0.4, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 265 (4.88), 357 (3.84) nm; ECD ($CDCl_3$) $\Delta\varepsilon$ (nm) +0.2 (279) and −0.03 (321); IR (ATR) ν_{max} (cm^{-1}) 3401, 2978, 2933, 2874, 1703, 1645, 1613, 1467, 1378, 1141, 1111, 747, 688, 666; ^1H NMR data see Table 1; ^{13}C NMR data see Table 2; negative ion ESI-FTMS *m*/*z* 359.1505 $[M - H]^-$ (calcd for $C_{20}H_{23}O_6^-$, 359.1500).

*Selancin I (**9**), 3R,5-dihydroxy-2,2,8,8-tetramethyl-6-(2S-methylbutanoyl)-2,3-dihydro-4H,8H-pyrano[2,3-f]chromen-4-one:* yellow oil; $[\alpha]^{25}_D$ +10 (*c* 0.3, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 266 (5.12), 357 (4.04) nm; ECD ($CDCl_3$) $\Delta\varepsilon$ (nm) +1.3 (271) and −0.7 (308); IR (ATR) ν_{max} (cm^{-1}) 3401, 2972, 2930, 2875, 1704, 1645, 1609, 1462, 1366, 1137, 1111, 749, 689, 667; ^1H NMR data see Table 1; ^{13}C NMR data see Table 2; negative ion ESI-FTMS *m*/*z* 373.1659 $[M - H]^-$ (calcd for $C_{21}H_{25}O_6^-$, 373.1657).

*Hyperselancin A (**10**), 2,2,7,7-tetramethyl-6S-(2S-methylbutanoyl)-8S,10R-bis(3-methylbut-2-enyl)-2,6,7,8,9,10-hexahydro-5H-6,10-methanocycloocta[b]pyran-5,11-dione:* yellow oil; $[\alpha]^{25}_D$ −1 (*c* 0.3, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 237 (4.65), 270 (4.63) nm; ECD ($CDCl_3$) $\Delta\varepsilon$ (nm) −3.6 (274) and +1.2 (311) cm^2 $mmol^{-1}$; IR (ATR) ν_{max} (cm^{-1}) 2973, 2929, 1722, 1600, 1461, 1369, 1129, 751, 667; ^1H NMR and ^{13}C NMR data see Table 3; positive ion ESI-FTMS *m*/*z* 481.3303 $[M + H]^+$ (calcd for $C_{31}H_{45}O_4^+$, 481.3312).

*Hyperselancin B (**11**), 2,2,7,7-tetramethyl-8S,10R-bis(3-methylbut-2-enyl)-6S-(2-methylpropanoyl)-2,6,7,8,9,10-hexahydro-5H-6,10-methanocycloocta[b]pyran-5,11-dione:* yellow oil; $[\alpha]^{25}_D$ −9 (*c* 0.2, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 235 (4.73), 271 (4.72) nm; ECD ($CDCl_3$) $\Delta\varepsilon$ (nm) +1.4 (269), 0.5 (298), and −0.2 (328); IR (ATR) ν_{max} (cm^{-1}) 2973, 2928, 1721, 1614, 1456, 1371, 1259, 1085, 752, 667; ^1H NMR and ^{13}C NMR data see Table 3; positive ion ESI-FTMS *m*/*z* 467.3147 $[M + H]^+$ (calcd for $C_{30}H_{43}O_4^+$, 467.3156).

Synthesis. The synthetic procedure and spectroscopic data for compounds **13**, **14**, **15**, **16**, and (+)-(*S*)-**2** are in the Supporting Information.

*Synthesis of Selancin A (**1**), 1-(5-hydroxy-2,2,8,8-tetramethyl-2H,8H-pyrano[2,3-f]chromen-6-yl)-2-methylpropan-1-one.* Ethylene diamine diacetate (36 mg, 0.2 mmol) was added to a solution of 1-(2,4,6-trihydroxyphenyl)-2-methylpropanone (**13**, 196 mg, 1 mmol) and 3-methyl-2-butenal (252 mg, 289 μL, 3.0 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 10 h. After evaporation of the solvent under reduced pressure, the mixture was chromatographed over a silica gel column, eluted with *n*-hexane−EtOAc (95:5), to give selancin A (**1**) as a yellow oil (80%, 261 mg, 0.8 mmol, R_f = 0.5 in *n*-hexane−EtOAc (95:5)): ^1H NMR ($CDCl_3$) δ 14.14 (1H, s), 6.66 (1H, d, *J* = 10.1 Hz), 6.59 (1H, d, *J* = 10.1 Hz), 5.45 (1H, d, *J* = 10.1 Hz), 5.43 (1H, d, *J* = 10.1 Hz), 3.85 (1H, sept, *J* = 6.6 Hz), 1.49 (6H, s), 1.44 (6H, s), 1.19 (6H, d, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 210.5, 161.1, 156.0, 154.8, 125.3, 124.5, 116.5, 116.3, 104.6, 102.5, 102.1, 78.2, 78.1, 39.3, 28.4, 27.9, 19.4; positive ion ESI-FTMS $[M + H]^+$ at *m*/*z* 329.1749 (calcd for $C_{20}H_{25}O_4^+$, 329.1747).

*Synthesis of Selancin B (**2**), 1-(5-hydroxy-2,2,8,8-tetramethyl-2H,8H-pyrano[2,3-f]chromen-6-yl)-2-methylbutan-1-one.* EDDA (36 mg, 0.2 mmol) was added to a solution of 1-(2,4,6-trihydroxyphenyl)-2-methylbutanone (**14**, 210 mg, 1 mmol) and 3-

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methyl-2-butenal (252 mg, 289 μL, 3.0 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 10 h. After removal of the solvent by evaporation under reduced pressure, the reaction mixture was chromatographed over a silica gel column, eluted with *n*-hexane−EtOAc (95:5), to give selancin B (**2**) as a yellow oil (85%, 290.1 mg, 0.85 mmol, R_f = 0.71 in *n*-hexane−EtOAc (95:5)): ^{1}H NMR ($CDCl_3$) δ 14.18 (1H, s), 6.66 (1H, d, J = 10.1 Hz,), 6.60 (1H, d, J = 10.1 Hz,), 5.45 (1H, d, J = 10.1 Hz), 5.44 (1H, d, J = 10.1 Hz), 3.74 (1H, sext, J = 6.6 Hz), 1.86 (1H, m), 1.50 (3H, s), 1.49 (3H, s), 1.44 (6H, s), 1.41 (1H, *m*), 1.17 (3H, d, J = 6.6 Hz), 0.91 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 210.4, 161.1, 156.1, 154.7, 125.3, 124.6, 116.5, 116.3, 105.2, 102.5, 102.2, 78.2, 78.1, 46.0, 28.4, 28.3, 27.8, 26.8, 16.8, 11.9; positive ion ESI-FTMS $[M + H]^+$ at m/z 343.1907 (calcd for $C_{21}H_{27}O_4^+$, 343.1904).

Biological Assays. The cytotoxicity of the methanolic crude extract and isolated compounds against HT-29 and PC-3 cancer cell lines was determined using a modified XTT assay as previously described.[2] The anthelmintic assay against the model organism *Caenorhabditis elegans* was performed as described in Thomsen et al. (2012).[42]

Computational Methods. See the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b00673.

^{1}H and ^{13}C NMR spectra of isolated compounds **1**−**11** and synthesized compounds **1**, **2**, **13**, **14**, **16**, and (+)-(*S*)-**2**; synthesis procedures of compounds **13**, **14**, **15**, **16**, and (+)-(*S*)-**2** and computational methods (PDF)

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Notes

The authors declare no competing financial interest.

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