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TRICYCLIC SESQUITERPENES FROM *ARTEMISIA CHAMAEMELIFOLIA*

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Key Word Index—*Artemisia chamaemelifolia* ssp. *chamaemelifolia*; Compositae; Anthemideae; monoterpenes; tricyclic sesquiterpenes; presilphiperfolanes; silphiperfolanes; cadinanes; lignans.

Abstract—The aerial parts of *Artemisia chamaemelifolia* ssp. *chamaemelifolia* yielded, in addition to known compounds, four acids with the silphiperfolane framework, a presilphiperfolane derivative, a bicyclic sesquiterpene formed therefrom by oxidative cleavage, a diacetylated monoterpene diol, a cadinane derivative, three acyclic sesquiterpenes and two tetrahydrofurane lignans.

INTRODUCTION

The large genus *Artemisia* has been the object of numerous chemical studies [1]. As a part of our current research on the chemistry of this genus, we have investigated *Artemisia chamaemelifolia* Vill. ssp. *chamaemelifolia*, collected in the Pyrenees [2, 3]. Several years ago, the closely related *A. cantabrica* Lainz (syn. *A. chamaemelifolia* ssp. *cantabrica*) [3] was shown to contain the sesquiterpene acids **1**–**4**, which display the tricyclic silphiperfolane framework [4]. Other investigations of *A. chamaemelifolia* have focused on the phenolics and essential oil contents [1].

RESULTS AND DISCUSSION

Aerial parts of *A. chamaemelifolia* ssp. *chamaemelifolia* contained the new tricyclic sesquiterpenes **5**–**9**, the bicyclic *seco*-derivative **10**, the acyclic monoterpene **11**, the cadinane derivative **12**, the monocyclic sesquiterpenes **13**–**15** and the two epimeric tetrahydrofurane lignans **17** and **18**. In addition, the known compounds, **3** [4], **4** [4], **16** [5], spathulenol, isofraxidin, *p*-hydroxyacetophenone, 2-*O*-methylphloroacetophenone and (−)-hibalactone [6] were found.

Compounds **5** and **6** were purified as the corresponding methyl esters **5a** and **6a**. Aside from a band of conjugated ester at 1713 cm^{-1}, no other significant absorptions appeared in their IR spectra, which were almost superimposable. A UV band at 229 nm gave further support to the presence of a conjugated ester moiety. The mass spectra of both compounds were also similar and showed the highest mass peak at *m/z* 263, obviously formed by loss of a methyl group from the molecular ion *m/z* 278, in agreement with the molecular formula $C_{17}H_{26}O_3$. The ^1H NMR spectra (Table 1) were close to that of the methyl ester of the co-occurring acid **3**. An additional signal appeared in the spectrum of **5a** and **6a** as a sharp three-proton singlet in the vicinity of δ3.5. Thus, both compounds were likely *O*-methyl derivatives of **3** differing only in the configuration of the carbon atom bearing the methoxyl group (C-5). This conclusion was supported by extensive homo- and heteronuclear 2D-COSY experiments, which additionally permitted the unambiguous assignment of all carbon NMR signals (see Table 2). The configuration at C-5 was determined through NOE difference measurements. These showed for epimer **6** (5β-OMe) clear NOEs between H-5 and H-12, as well as between H-5 and both H-3 hydrogens, in accordance with predictions of molecular modeling using PCMODEL [7]. As expected, the other isomer showed only a strong NOE between H-5 and H-12. In consequence, the latter was assigned structure **5**, with a 5α-methoxyl group. We also carried out 2D NMR measurements on **3** and came to the conclusion that some of the published carbon assignments [4] are erroneous. In fact, the signals of the carbon pairs C-1/C-4 and C-12/C-15 have to be reversed. As regards the absolute configuration of these tricyclic compounds, it may be the depicted one [4], but an unambiguous determination is still needed.

Acids **7** and **8**, isolated as a mixture (*ca.* 2:3), resisted all attempts of separation on either column chromatography or HPLC. GC-MS of the methyl esters (*m/z* 248) indicated the molecular formula $C_{16}H_{24}O_2$. This, and the ^1H NMR spectrum of the mixture (see Experimental), suggested epimeric 7,14-dihydro derivatives of acid **1**,

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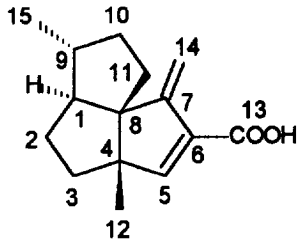

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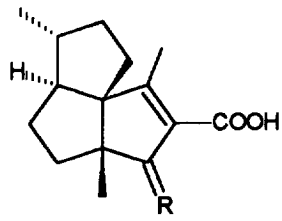

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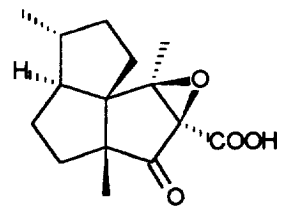
3 R = H, βOH



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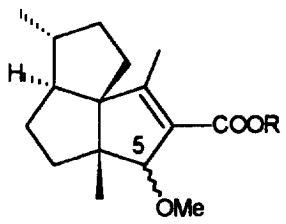
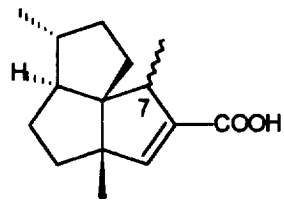
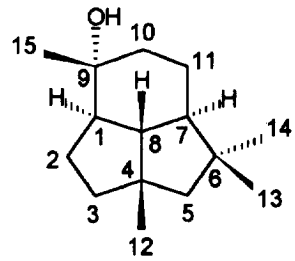


5 R=H (5α-OMe)
5a R=Me (5α-OMe)
6 R=H (5β-OMe)
6a R=Me (5β-OMe)



7 7α-Me
8 7β-Me



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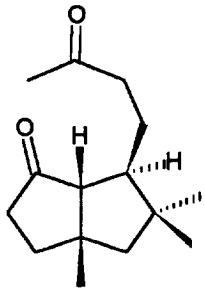

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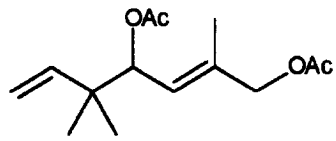

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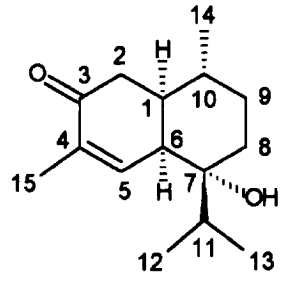
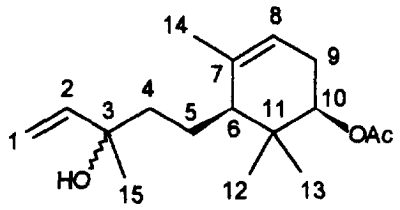


12

differing only in the configuration at C-7. The tentative assignment of the carbon NMR signals for each compound, shown in Table 2, has been based both on their multiplicity and on comparison with the data of acids **3**–**6**. Furthermore, the ^{13}C NMR assignments for two structurally related hydrocarbons (CH_3 instead of CO_2H), isolated from *Silphium* species [8], were also considered.* The proposed structural assignments are based on the results of molecular modeling studies using PCMODEL. These revealed that the methyl group C-14 in **7** is quite close to H-1 (*ca.* 2.5 Å) and to the methyl group C-15 (*ca.* 4 Å between the carbon atoms). In the epimeric compound **8** these distances are markedly higher (>4 Å) and, in addition, C-14 is near to H-11α (*ca.* 2.6 Å). These spatial proximities and the steric compression thereby derived are expected to cause high-field shifts in the corresponding carbon signals. In agreement with these considerations, Table 2 shows that there are actually prominent chemical shift differences between the carbon signals of C-1, C-11, C-14 and C-15.

*The ^{13}C NMR values of these hydrocarbons in Ref. [8] were erroneously interchanged and have therefore to be reversed.



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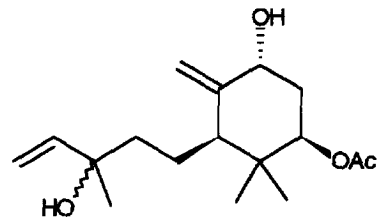

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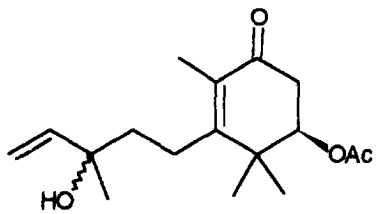

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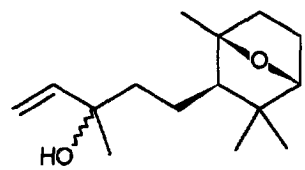

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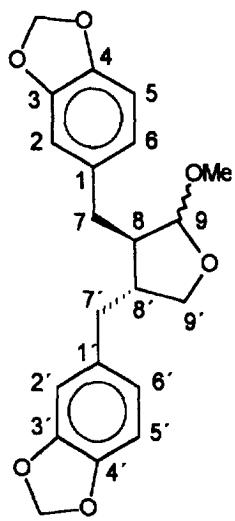

17 9α-OMe
18 9β-OMe

The hydroxyl band at 3400 cm^{-1} was the only structurally significant one in the IR spectrum of **9**, while the parent peak at *m/z* 222 in the mass spectrum indicated the molecular formula $C_{15}H_{26}O$. ^{13}C NMR data (Table 3) pointed out the presence of a tertiary alcohol, as well as the absence of multiple bonds. In consequence, the compound has a tricyclic framework. The interpretation of the ^1H NMR spectrum of tertiary alcohol **9** was rendered quite difficult by considerable overlapping of signals. Addition of $Eu(fod)_3$ spread the proton signals sufficiently to make interpretations feasible. Extensive homo- and heteronuclear 2D-COSY experiments, aided by biogenetic considerations, allowed the unambiguous establishment of the tricyclic carbon framework as that depicted in **9**. The proposed configuration was deduced from the values of the coupling constants and from NOE difference experiments. Particularly significant among the latter were those observed between the geminal methyl groups, H-13 and H-14, with H-8 and H-7, respectively, and between H-8 with H-12 and H-15. After consideration of several possible configurations and molecular modeling with PCMODEL, structure **9** was found to fit best in with the spectral data. As in the previous cases, only the relative configuration could be determined.

The presilphiperfolane sesquiterpene skeleton, represented by **9**, is quite uncommon and was initially

Table 1. ^{1}H NMR data of silphiperfolanes **5a** and **6a**

H	5a	6a
1	1.76 *m*	1.76 *m*
2α	1.50 *ddd* (14; 7; 3.7)	1.40 *m*
2β	1.68 *ddd* (14; 9.5; 6.5)	1.73 *m*
3α	1.89 *m*	1.52 *m**
3β	1.39 *m*	1.55 *m**
5	4.00 *br s*	4.01 *br s*
9	1.55 *m**	1.63 *m**
10α	1.25 *m**	1.30 *m*
10β	1.84 *m**	1.83 *m*
11α	1.84 *m**	1.59 *m**
11β	1.30 *m**	1.66 *m**
12	1.07 *s*	1.02 *s*
14	2.03 *d* (1.2)	2.02 *d* (1)
15	0.98 *d* (6.5)	0.97 d (6.5)
OMe	3.51 *s*	3.41 *s*
COOMe	3.73 *s*	3.71 *s*

δ in ppm and *J* (parentheses) in Hz, 400 MHz, $CDCl_3$, 25°.
*Overlapped signal.

Table 2. ^{13}C NMR data of silphiperfolanes **5a**, **6a**, **7** and **8**

C	5a	6a	7*	8*
1	58.6	57.5	52.4	64.5
2	30.1	30.1	30.4	30.0
3	35.4	41.0	37.3	37.5
4	52.5	53.8	57.6	58.6
5	94.5	91.5	154.8	154.3
6	126.0	125.7	136.9	138.6
7	163.6	164.9	47.8	49.9
8	73.2	73.3	65.3	64.0
9	41.4	42.3	42.5	43.1
10	36.9	36.8	35.9	35.6
11	29.5	31.3	34.6	28.9
12	25.2	17.3	19.7	19.9
13	166.4	166.6	171.0	170.7
14	13.5	13.4	14.8	18.0
15	19.3	19.5	19.2	21.7
5-OMe	60.6	59.6	—	—
COOMe	50.9	50.9	—	—

δ in ppm, 100 MHz, $CDCl_3$, 25°.
*Tentative assignments in the spectrum of the mixture.

proposed as an intermediate in the biogenetic formation of silphiperfolane derivatives [8]. The first representative of this compound class was found in *Eriophyllum* [9] and then in some other plant species [10–13]. Further examples have been reported within *Senecio* and *Ursinia* [14, 15]. In fact, we did not find a description of compound **9** in the literature, but then learned that **9** had previously been found among the components of the essential oil of *Artemisia laciniata* [16]. The same group has also achieved a total synthesis of the compound [17] whose details have not yet been published. The ^{1}H NMR spectrum of the synthetic compound was completely superimposable with ours.

Ketone **10** (IR 1710 cm^{-1}) was isolated in very small amount, perhaps because of losses due to its volatility. For this reason, purification was difficult. The ^{13}C NMR spectrum (Experimental) showed the presence of two ketone carbonyls and the absence of any other functions or multiple bonds. The ^{1}H NMR spectrum (Experimental) indicated the presence of four methyl singlets, one of them being part of a methyl ketone fragment, and of five protons contiguous to a carbonyl group. Taking into account the multiplicities of the carbon signals, structure **10** is the only likely one. Such a structure may biogenetically arise from alcohol **9** by enzymatic oxidative cleavage of the C_1–C_9 bond. To the best of our knowledge, this type of 1,9-*seco*presilphiperfolane system has not previously been found in nature.

Compound **11** had 14 carbon atoms (^{13}C NMR), four of them belonging to two acetoxy groups. This suggested a monoterpene diol diacetate. Spin decoupling and 2D heteronuclear correlation experiments supported this idea and evidenced the presence of an irregular, artemisyl-type C_{10} framework [18]. NOE difference experiments indicated that the trisubstituted olefinic bond had an *E*-configuration. The corresponding monoterpene diol has previously been reported in *Othantus maritimus* [19]. Artemisyl monoterpenes are quite common in essential oils of many *Artemisia* species [1].

Compound **12**, $C_{15}H_{24}O_2$ (MS *m/z* 236), showed alcohol and conjugated ketone IR bands at 3490 and 1669 cm^{-1}. NMR data (Table 3) indicated the presence of a tertiary hydroxyl and a ketone conjugated with a trisubstituted double bond. Signals of an isopropyl group, a MeCH fragment and an olefinic methyl group were also noticeable. Extensive decoupling experiments revealed structure fragments only compatible with a cadinane framework. This conclusion was confirmed by heteronuclear 2D measurements. The relative stereochemistry was deduced from the values of some coupling constants and from NOE measurements. While the small value of $J_{1,6}$ indicates a *cis*-decaline system, the NOE between H-14 and the axial proton at C-9 (H-9α) shows that the methyl group cannot be axial, therefore establishing the configuration at C-10. Furthermore, the NOE between H-5 and H-11 is easily explained within the depicted stereochemistry at C-7 (PCMODEL) but would hardly be observed with the opposite configuration. In fact, the NMR spectra of **12** are close to those of a related cadinane lacking the carbonyl group, isolated some years ago from *A. crithmifolia* [20].

Compounds **13–15** are all closely related and also to the known compound **16** [5]. Their NMR spectra (Table 4) showed signals which indicated the presence of a vinyl methyl carbinol side-chain as in the latter compound. Furthermore, a *gem*-dimethyl moiety and an acetate group were also present. Compound **13** additionally displayed a trisubstituted double bond bearing a methyl group. Extensive spin decoupling experiments and 2D correlations established the structure of **13** as depicted, with the same carbon framework as **16**. The absolute and

Table 3. ^{1}H and ^{13}C NMR data of compounds **9** and **12**

H	9	9*	12	C	9	12
1	1.73 *m*†	7.20 *br m*	2.18 *br dddd* (11; 4.5; 2.5; 2)	1	62.2	40.8
				2	29.7	42.4
2α	1.73 *m*†	4.45 *br m*	2.36 *dd* (16.5; 4.5)	3	45.3	199.6
2β	1.48 *m*†	4.10 *br dddd* (12; 12; 12; 4)	2.75 *dd* (16.5; 2.5)	4	42.1	136.7
				5	58.7	142.9
3α	1.60 *m*†	2.62 *ddd* (12; 12; 4)	—	6	46.6	45.0
3β	1.48 *m*†	2.22 *dd* (12; 4.5)	—	7	60.8	74.4
				8	63.8	32.5
5α	1.60 *d* (13)	2.40 *d* (13)	6.43 *br s*			
5β	1.43 *d* (13)	2.16 *d* (13)	—	9	76.0	29.8
				10	45.4	28.1
6	—	—	2.78 *br ddq* (2; 2; 15)			
				11	26.9	33.0
7	1.28 *ddd* (10.5; 10.5; 2.5)	3.15 *br m*	—	12	30.9	16.1‡
8α	—	—	1.75 *dddd* (13.5; 3.5; 3; 1.5)	13	22.0	15.7‡
				14	28.8	19.3
8β	1.34 *dd* (10.5; 10.5)	4.00 *br dd* (10; 10)	1.18 *ddd* (13.5; 13.5; 4)	15	21.7	16.1
9α	—	—	1.34 *dddd* (13.5; 13.5; 13.5; 3.5)			
9β	—	—	1.47 *m*†			
10α	1.48 *m*†	7.40 *br m*	—			
10β	1.87 *ddd* (13; 4; 2)	6.50 *br d* (12)	1.47 *m*†			
11α	1.60 *m*†	3.00 *br m*				
			1.96 *quint* (7)			
11β	1.20 *m*†	3.15 *br m*				
12	1.03 *s*	2.00 *s*	0.97 *d* (7)‡			
13	0.88 *s*	1.68 *s*	0.94 *d* (7)‡			
14	0.93 *s*	1.40 *s*	0.87 *d* (6.5)			
15	1.22 *s*	5.56 *br s*	1.76 *dd* (1.5; 1.5)			

δ in ppm and J (parentheses) in Hz, 400 MHz (^{1}H) and 100 MHz (^{13}C), $CDCl_3$, 25°.
*After addition of 0.2 equiv. of $Eu(fod)_3$.
†Overlapped signal.
‡Interchangeable signals.

relative stereochemistry, however, could not be completely determined with the data available. Only the observation of a NOE between H-6 and H-10 suggests that the side chains bound to C-6 and C-10 atoms are *cis* to each other.

Compound **14** is similar to **13**. An additional OH or OOH group is present, however, and an exocyclic methylene replaces the trisubstituted C=C bond. The presence of a hydroperoxide was excluded by the fact that the compound was recovered unchanged after treatment with dimethyl sulfide. Structure **14** was confirmed by spin decoupling and 2D experiments. As above, H-6 and H-10 showed a mutual NOE but not with H-8, which showed in turn a marked NOE with one of the H-14 protons. Here again, it follows that the substituents at C-6 and C-10 are *cis* to each other but *trans* to the hydroxyl group at C-8. Most likely, compound **14** is formed from **13** by enzymatic oxidation, perhaps via an intermediate hydroperoxide.

The only significant difference between **15** and compounds **13** and **14** is the presence in the former of a ketone group conjugated with a tetrasubstituted double bond (UV λ_{max} 248 nm). Structure **15** was confirmed as above by spin decoupling and 2D correlations. Compound **15** is most likely derived from **14** by alcohol oxidation and double-bond isomerization.

The aromatic compounds **17** and **18** were obviously epimers, in view of the close similarity between their

Table 4. ^{1}H and ^{13}C NMR data of compounds **13–15**

H	13	14	15	C	13	14	15
1	5.04 *dd* (10.7; 1.2)	5.05 *dd* (10.8; 1.2)	5.12 *dd* (10.7; 1.2)	1	111.7	111.7	112.6
				2	145.0	145.2	144.1
1′	5.19 *dd* (17.4; 1.2)	5.19 *dd* (17.4; 1.2)	5.27 *dd* (17.4; 1.2)	3	73.5	73.3	73.2
2	5.90 *dd* (17.4; 10.7)	5.90 *dd* (17.4; 10.8)	5.91 *dd* (17.4; 10.7)	4	44.1	41.0	40.1
				5	22.8	20.1	25.0
4	1.74 *m*	1.30 *m* (1H)	1.64 *m*				
	1.48 *m*		(2H)	6	49.4	49.7	161.9
5	1.68 *m**	1.70–1.50 *m* (3H)	2.29 *m*	7	136.7	148.7	131.4
	1.28 *m**		(2H)				
6	1.60 *m*	2.12 *br d* (10.5)	—	8	117.5	70.0	195.5
8	5.19 *m**	4.37 *dd* (6; 4.7)	—	9	28.6	36.3	39.3
9	2.25 *br dd* (18; 6.5)	1.90 *ddd* (13.5; 6: 4.1)	2.75 *dd* (17; 4)	10	76.4	76.6	75.6
				11	36.8	39.3	40.5
9′	2.00 *br dd* (18; 6.5)	1.83 *ddd* (13.5; 8; 4.7)	2.54 *dd* (17; 7.7)	12	25.7	26.3	25.0
10	4.67 *dd* (6.5; 6.5)	4.97 *dd* (8; 4.1)	5.03 *dd* (7.7; 4)	13‡	18.6	17.9	22.0
				14	22.7	109.9	11.4
12‡	0.88 *s*	0.97 *s*	1.16 *s*				
				15	27.7	27.7	28.0
13‡	0.86 *s*	0.80 *s*	1.14 *s*				
				OAc	170.8	170.4	170.4
14	1.68 *br s*	5.10 *br s*	1.76 *s*				
		4.78 *br s*			21.1	21.2	21.1
15	1.26 *s*	1.27 *s*	1.33 *s*				
OAc	2.00 *s*	2.04 *s*	2.03 *s*				

δ in ppm and J (parentheses) in Hz, 400 MHz (^{1}H) and 100 MHz (^{13}C), $CDCl_3$, 25°.
*Overlapped signal.
‡Interchangeable signals.

NMR spectra (Experimental). These suggested a lignan of the bisbenzyltetrahydrofuran type [6]. The presence of two piperonyl side chains in either compound followed from the ^{1}H NMR spectra and from mass spectral data (base peak at *m/z* 135). The *trans*-orientation of these benzyl side chains was deduced from the ^{13}C NMR spectra (Experimental) and comparison with literature data [6]. Furthermore, the methoxyl singlets at *ca.* δ3.30 indicated *O*-methyl derivatives of a lactol-type lignan. Finally, compounds **17** and **18** were identified as the two epimeric *O*-methyl derivatives of the lignan cubebin [21]. The orientation of the methoxy group at C-9 in each compound was deduced from the value of $J_{8,9}$ and from NOE measurements. Irradiation of H-9 in **17** caused NOE in the signals of the H-7 protons but not in those of H-7′. Finally, comparison with the physical and spectral data of the closely related, epimeric lignans α- and β-intermedianol [22] provided firm support for our proposal.

EXPERIMENTAL

NMR spectra at 400 MHz (^{1}H) and 100 MHz (^{13}C). Optical rotations at 23°. MPCC: silica gel Merck (particle size 25–40 μ), gradient elution with the solvent mixts indicated in each case. HPLC: LiChrosorb RP-8 (250 mm × 8 mm), elution with MeOH–H_2O mixts. GC-MS: Varian 3700 Gas Chromatograph coupled with a Varian MAT 44S mass spectrometer. GC column: Chrompack CPSil 5, 25 m × 0.25 mm, injector temp. 300°.

Plant material. Aerial parts of *A. chamaemelifolia* were collected at 1600 m altitude in the vicinity of Canillo, Pyrenees of Andorra (September, 1991). A voucher specimen (BCF-36710) has been deposited in the herbarium of the Laboratory of Botany, Faculty of Pharmacy, University of Barcelona, Spain.

Extraction and chromatography. The plant material (800 g of aerial parts) was processed according to our standard procedure [23]. The defatted extract was prefractionated by CC on silica gel (A, hexane–EtOAc 6:1; B, hexane–EtOAc 3:1; C, hexane–EtOAc 1:1; D, EtOAc). The four frs were subjected to further chromatographic sepns as described below. The partial frs resulting from chromatography of fr. D were discarded after a preliminary examination by TLC and NMR, which only showed the presence of ill-defined, highly polar compounds.

MPCC of Fr. A (elution with hexane–EtOAc, 10:1), followed where necessary by CC or prep. TLC, allowed the isolation and spathulenol (6 mg), 2-*O*-methylphloroacetophenone (20 mg), a mixture of **7** and **8** (ca. 10 mg), **9** (50 mg), **10** (4 mg), **11** (17 mg), **12** (30 mg), **13** (60 mg), **17** (5 mg) and **18** (6 mg). Two frs containing compounds **5** and **6** were methylated with ethereal diazomethane and purified by CC (hexane–Et_2O, 3:1) to yield **5a** (14 mg) and **6a** (86 mg), respectively. The fr. containing **7/8** was methylated in the same manner. MPCC of fr. B (hexane–EtOAc 4:1), followed by prep. TLC or HPLC, yielded (−)-hibalactone (10 mg), *p*-hydroxyacetophenone (35 mg), **4** (5 mg), **15** (20 mg) and **16** (5 mg). Finally, fr. C gave isofraxidin (*ca.* 1 g), **3** (100 mg) and **14** (38 mg).

(1S*,4R*,5R*,8R*,9R*)-5-*Methoxysilphiperfol*-6-*en*-13-*oic acid* (O-*methyl*-5-*epicantabrenolic acid*) (**5**). Purified as the methyl ester **5a**, oil, $[\alpha]_D$ + 3° ($CHCl_3$; *c* 1.3); IR $\tilde{\nu}_{max}^{film}$ cm^{-1}: 1713 (ester C=O), 1646, 1458, 1442, 1373, 1343, 1251, 1159, 1092, 1067, 968, 736; UV λ_{max}^{MeOH}: 229 nm; EIMS (probe) *m/z* (rel. int.): 263 $[M - Me]^+$ (2), 248 $[M - CH_2O]^+$ (24), 247 $[M - OMe]^+$ (35), 231 $[M - MeOH - Me]^+$ (7), 219 $[M - COOMe]^+$ (100), 215 $[M - MeOH - OMe]^+$ (13), 187 (15), 145 (12), 131 (10), 119 (9), 105 (11), 91 (14); NMR, Tables 1 and 2.

(1S*,4R*,5S*,8R*,9R*)-5-*Methoxysilphiperfol*-6-*en*-13-*oic acid* (O-*methylcantabrenolic acid*) (**6**). Purified as the methyl ester **6a**, oil, $[\alpha]_D$ −61° ($CHCl_3$; *c* 3.3); IR $\tilde{\nu}_{max}^{film}$ cm^{-1}: 1713 (ester C=O), 1643, 1455, 1443, 1372, 1342, 1325, 1249, 1203, 1164, 1124, 1091, 1069, 964, 792, 738; UV λ_{max}^{MeOH}: 229 nm; EIMS (probe) *m/z* (rel. int.): 263 $[M - Me]^+$ (3), 248 $[M - CH_2O]^+$ (30), 247 $[M - OMe]^+$ (46), 231 $[M - MeOH - Me]^+$ (7), 219 $[M - COOMe]^+$ (100), 215 $[M - MeOH - OMe]^+$ (17), 187 (18), 145 (15), 131 (14), 119 (12), 91 (20); NMR, Tables 1 and 2.

(1S*,4R*,7S*,8R*,9R*)- *and* (1S*,4R*,7R*,8R*,9R*)-*Silphiperfol*-5-*en*-13-*oic acid* (**7** *and* **8**). Isolated as a *ca* 2:3 mixture of epimers at C-7, which could not be separated by either silica gel chromatography or by HPLC. The corresponding methyl esters proved equally inseparable. Only GC-MS of the latter permitted the determination of the individual mass spectra. Separation conditions: 2 min at 70°, then temperature gradient of 5° min^{-1}. Retention times: methyl ester of **7**, 25.8 min, methyl ester of **8**, 25.5 min. Mass spectral data: methyl ester of **7**, EIMS (probe) *m/z* (rel. int.): 248 $[M]^+$ (8), 233 $[M - Me]^+$ (10), 216 $[M - MeOH]^+$ (10), 189 $[M - COOMe]^+$ (45), 173 (25), 166 (7), 161 (18), 159 (18), 148 (100), 147 (35), 135 (21), 133 (55), 131 (26), 119 (50), 107 (44), 105 (50), 102 (48), 95 (40), 93 (50), 91 (58), 81 (26), 79 (42), 77 (39), 69 (18), 67 (27), 65 (19), 59 (22), 55 (40); methyl ester of **8**, EIMS (probe) *m/z* (rel. int.): 248 $[M]^+$ (38), 233 $[M - Me]^+$ (21), 219 (42), 216 $[M - MeOH]^+$ (30), 189 $[M - COOMe]^+$ (100), 173 (45), 166 (40), 161 (31), 159 (50), 148 (38), 147 (51), 135 (65), 133 (82), 131 (50), 119 (88), 107 (77), 105 (88), 95 (72), 93 (75), 91 (87), 81 (40), 79 (70), 77 (70), 69 (20), 67 (40), 65 (28), 59 (45), 55 (73); ^1H NMR of the mixture **7/8** ($CDCl_3$, 400 MHz, 25°): δ6.58 (1H, *s*; H-5, major epimer), 6.49 (1H, *d*, *J* = 2.5 Hz; H-5, minor epimer), 2.97 (1H, *qd*, *J* = 7, 2.5 Hz; H-7, minor epimer), 2.82 (1H, *q*, *J* = 7 Hz; H-7, major epimer), 2.00–1.25 (complex overlapped signals), 1.21 (3H, *d*, *J* = 7 Hz; H-14, minor epimer), 1.06 (3H, *d*, *J* = 7 Hz; H-14, major epimer), 1.06 (3H, *s*; H-12, major epimer), 1.00 (3H, *s*; H-12, minor epimer), 0.98 (3H, *d*, *J* = 6.5 Hz; H-15, major epimer), 0.97 (3H, *d*, *J* = 6.5 Hz; H-15, minor epimer); ^{13}C NMR, Table 2.

(1R*,4S*,7R*,8S*,9R*)-*Presilphiperfolan*-9-*ol* (**9**). Oil, $[\alpha]_D$ −31.5° ($CHCl_3$; *c* 4); IR $\tilde{\nu}_{max}^{film}$ cm^{-1}: 3400 (br, OH), 2938, 2868, 1689, 1454, 1374, 1241, 1137. EIMS (probe) *m/z* (rel. int.): 222 $[M]^+$ (10), 207 $[M - Me]^+$ (5), 204 $[M - H_2O]^+$ (2), 189 $[M - Me - H_2O]^+$ (8), 177 (6), 161 (7), 149 (15), 137 (24), 124 (29), 109 (30), 95 (45), 81 (39), 71 (33), 55 (31), 43 (100). NMR, Table 3.

(4S*,7R*,8S*)-1,9-*Secopresilphiperfolan*-1,9-*dione* (**10**). Oil, $[\alpha]_D$ −24° ($CHCl_3$; *c* 1.3); IR $\tilde{\nu}_{max}^{film}$ cm^{-1}: 1710 (*br*, ketone C=O), 1450, 1365, 1260, 908, 730; ^1H NMR ($CDCl_3$ 400 MHz, 25°): δ2.72 (1H, *ddd*, *J* = 18, 9, 5 Hz; CH–CO–), 2.45 (2H, *m*; CH–CO–), 2.30 (2H, *m*; CH–CO–), 2.12 (3H, *s*; COMe), 2.10–1.40 (complex absorption), 1.19 (3H, *s*), 1.02 (3H, *s*), 0.90 (3H, *s*); ^{13}C NMR ($CDCl_3$, 100 MHz, 25°): δ221.5 (*s*), 209.2 (*s*), 66.0 (*d*), 57.3 (*t*), 52.9 (*d*), 46.2 (*s*), 44.7 (*s*), 42.1 (*t*), 37.8 (*t*), 37.4 (*t*), 30.0 (*q*), 29.2 (*q*), 29.0 (*q*), 24.0 (*q*), 23.9 (*t*).

3,3,6-*Trimethylhepta*-1,5-*dien*-4,7-*diol diacetate* (**11**). Oil, $[\alpha]_D$ −11° ($CHCl_3$; *c* 1.4); IR $\tilde{\nu}_{max}^{film}$ cm^{-1}: 1736 (acetate C=O), 1459, 1366, 1239, 1123, 1022, 911, 798; EIMS (probe) *m/z* (rel. int.): 185 $[M - \text{ketene} - CH{=}CH_2]^+$ (3), 143 $[M - 2 \times \text{ketene} - CH{=}CH_2]^+$ (5), 135 $[M - \text{ketene} - HOAc - CH{=}CH_2]^+$ (4), 83 (100), 43 (45); ^1H NMR ($CDCl_3$, 400 MHz, 25°: δ5.83 (1H, *dd*, *J* = 17.3, 10.7 Hz; H-2), 5.35 (1H, *br d*, *J* = 10 Hz; H-5), 5.32 (1H, *d*, *J* = 10 Hz; H-4), 5.02 (1H, *dd*, *J* = 10.7, 1.2 Hz; H-1), 4.99 (1H, *dd*, *J* = 17.3, 1.2 Hz; H-1'), 4.46, 4.43 (2H, AB system, *br d*, *J* = 13 Hz; H-7, H-7'), 2.06, 2.03 (2 × 3H, *s*; 2 × OAc), 1.75 (3H, *br s*; Me-C_6), 0.99 (6H, *s*; 2 × Me-C_3); ^{13}C NMR ($CDCl_3$, 100 MHz, 25°): δ170.7, 170.3 (acetyl carbonyl), 143.7 (C-2), 135.8 (C-6), 123.2 (C-5), 113.0 (C-1), 75.8 (C-4), 68.8 (C-7), 40.8 (C-3), 23.7, 22.0 (Me_2C), 21.1, 20.9 (acetyl Me), 14.6 (Me-C_6).

(1S*,6R*,7R*,10R*)-7-*Hydroxycadin*-4-*en*-3-*one* (**12**). Oil, $[\alpha]_D$ +19° ($CHCl_3$; *c* 1.2); IR $\tilde{\nu}_{max}^{film}$ cm^{-1}: 3490 (br, OH), 1669 (ketone C=O), 1458, 1376, 1150, 982, 914; UV λ_{max}^{MeOH}: 244 nm; EIMS (probe) *m/z* (rel. int.): 236 $[M]^+$ (8), 218 $[M - H_2O]^+$ (5), 193 $[M - \text{iso-Pr}]$ (12), 175 $[M - \text{iso-Pr} - H_2O]^+$ (16), 148 (57), 109 (100), 108 (52), 86 (18), 71 (18), 43 (47). NMR, Table 3.

3-(3-*Hydroxy*-3-*methylpent*-4-*enyl*)-2,2,4-*trimethylcyclohex*-4-*enyl acetate* (**13**). Oil, $[\alpha]_D$ −27° ($CHCl_3$; *c* 4); IR $\tilde{\nu}_{max}^{film}$ cm^{-1}: 3475 (OH), 1727 (acetate C=O), 1447, 1372, 1253, 1025, 918; EIMS (probe) *m/z* (rel. int.): 220 $[M - HOAc]^+$ (2), 202 $[M - HOAc - H_2O]^+$ (5), 187 $[M - HOAc - H_2O - Me]^+$ (4), 159 (3), 134 (100), 121 (38), 119 (64), 107 (20), 71 (26), 55 (18), 43 (66). NMR, Table 4.

3-(3-*Hydroxy*-3-*methylpent*-4-*enyl*)-5-*hydroxy*-2,2-*dimethyl*-4-*methylene-cyclohexyl acetate* (**14**). Oil, $[\alpha]_D$ +12° ($CHCl_3$; *c* 0.84); IR $\tilde{\nu}_{max}^{film}$ cm^{-1}: 3440 (OH), 1722 (acetate C=O), 1653, 1449, 1372, 1260, 1029, 916,

739, 706; EIMS (probe) *m/z* (rel. int.): 218 $[M - HOAc - H_2O]^+$ (7), 203 $[M - HOAc - H_2O - Me]^+$ (12), 190 (6), 185 (6), 175 (10), 149 (20), 137 (27), 133 (29), 121 (24), 109 (23), 95 (26), 81 (33), 71 (50), 69 (44), 55 (35), 43 (100). NMR, Table 4.

5-Acetoxy-3-(3-hydroxy-3-methylpent-4-enyl)-2,4,4-trimethylcyclohex-2-enone (**15**). Oil, $[\alpha]_D$ +6° ($CHCl_3$; *c* 2); IR $\bar{\nu}_{max}^{film}$ cm^{-1}: 3470 (OH), 1735 (acetate C=O), 1663 (ketone C=O), 1611, 1453, 1372, 1242, 1029, 924, 736; UV λ_{max}^{MeOH}: 248 nm; EIMS (probe) *m/z* (rel. int.): 234 $[M - HOAc]^+$ (10), 219 $[M - HOAc - Me]^+$ (3), 216 $[M - HOAc - H_2O]^+$ (4), 201 $[M - HOAc - H_2O - Me]^+$ (17), 173 (10), 165 (46), 149 (24), 135 (40), 121 (22), 107 (18), 71 (60), 55 (23), 43 (100). NMR, Table 4.

(9R)-9-O-*methylcubebin* (**17**). Oil, $[\alpha]_D$ −16° ($CHCl_3$; *c* 0.35); IR $\bar{\nu}_{max}^{film}$ cm^{-1}: 1465, 1420, 1225, 1165, 1075, 1010, 900, 830, 780; EIMS (probe) *m/z* (rel. int.): 370 $[M]^+$ (6), 338 $[M - MeOH]^+$ (8), 203 (14), 173 (10), 161 (34), 135 (100), 99 (36), 81 (21), 77 (25); ^1H NMR ($CDCl_3$, 400 MHz, 25°): δ6.68, 6.66 (2 × 1H, *d*, *J* = 8.5 Hz; H-5, H-5′), 6.55–6.45 (4H, *br m*, H-2, H-2′, H-6, H-6′), 5.92 (4H, two overlapped AB systems, *J* = 2 Hz; methylenedioxy groups), 4.68 (1H, *d*, *J* = 1.4 Hz; H-9), 3.98 (1H, *dd*, *J* = 8.8, 7.1 Hz; H-9′$_a$), 3.60 (1H, *dd*, *J* = 8.8, 8 Hz; H-9′$_b$), 3.29 (3H, *s*; OMe), 2.65 (1H, *dd*, *J* = 14, 7.5 Hz; H-7$_a$), 2.50 (2H, *d*, *J* = 7 Hz; H-7′), 2.39 (1H, *dd*, *J* = 14, 8 Hz; H-7$_b$), 2.10 (2H, *m*; H-8, H-8′); ^{13}C NMR ($CDCl_3$, 100 MHz, 25°): δ147.6, 147.5, 145.8, 145.7 (C-3, C-3′, C-4, C-4′), 134.3, 133.4 (C-1, C-1′), 121.7, 121.4 (C-6, C-6′), 109.9 (C-9), 109.2, 108.9 (C-2, C-2′), 108.1 (C-5, C-5′), 100.8, 100.7 (OCH_2O), 72.0 (C-9′), 54.7 (OMe), 52.4 (C-8), 45.8 (C-8′), 39.2 (C-7′), 38.8 (C-7).

(9S)-9-O-*methylcubebin* (**18**). Oil, not completely free from **17**, $[\alpha]_D$ +12° ($CHCl_3$; *c* 0.5); IR $\bar{\nu}_{max}^{film}$ cm^{-1}: 1445, 1410, 1110, 1025, 915, 730; EIMS (probe) *m/z* (rel. int.): 370 $[M]^+$ (8), 338 $[M - MeOH]^+$ (6), 203 (34), 173 (14), 161 (12), 135 (100), 99 (11), 81 (15), 77 (19); ^1H NMR ($CDCl_3$, 400 MHz, 25°): δ6.70–6.50 (6H, *br m*, H-2, H-2′, H-5, H-5′, H-6, H-6′), 5.92 (4H, *s*: methylenedioxy groups), 4.64 (1H, *d*, *J* = 4.4 Hz; H-9), 3.97 (1H, *dd*, *J* = 8.2, 8.2 Hz; H-9′$_a$), 3.56 (1H, *dd*, *J* = 8.2, 7 Hz; H-9′$_b$), 3.30 (3H, *s*; OMe), 2.70 (2H, *m*; H-7$_a$, H-7′$_a$), 2.50–2.30 (3H, *m*; H-7$_b$, H-7′$_b$, H-8′), 2.00 (1H, *m*; H-8); ^{13}C NMR ($CDCl_3$, 100 MHz, 25°): δ147.6, 147.4, 145.8, 145.6 (C-3, C-3′, C-4, C-4′), 134.7, 134.0 (C-1, C-1′), 121.6, 121.4 (C-6, C-6′), 109.3, 108.9, 108.2, 108.1 (C-2, C-2′, C-5, C-5′), 105.4 (C-9), 100.8, 100.7 (OCH_2O), 72.2 (C-9′), 54.5 (OMe), 52.1 (C-8), 43.2 (C-8′), 39.3 (C-7′), 33.6 (C-7).

Known compounds were identified by comparison of their spectra with those of authentic samples or with literature data.

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