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FURANOEREMOPHILANES FROM *PETASITES NIVEUS*: HIGH SOLVOLYTIC REACTIVITY AT THE C-6β POSITION BEARING AN α,β-UNSATURATED ESTER GROUP

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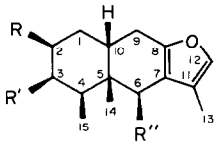
Key Word Index—*Petasites niveus*; Compositae; furanoeremophilanes; C-6 reactivity.

Abstract—Rhizomes and roots of *Petasites niveus* gave some new *cis*-fused, unstable furanoeremophilanes bearing the senecioyloxy group either at C-2β or at C-3β and C-6β, besides the known, unstable 2β-angeloyloxy-10β-H-furanoeremophilane (furanojaponin) and 3β,6β-diangeloyloxy-10β-H-furanoeremophilane. The senecioyloxy or angeloyloxy group at C-6 was easily replaced in alcohols, by the alkoxyl group, leading in medium yields to the ethers with retention of configuration at C-6. Most of the above terpenes prefer the 'non-steroid-like' conformation.

INTRODUCTION

Furanoeremophilanes (1) are widespread in the tribe Senecioneae [1], which, not only has led to an enormous literature dealing with their isolation, but has also stimulated the development of versatile synthetic entries to such sesquiterpenes [2].

Petasites niveus is a common plant in the Trentino area, where it is used as a substitute for *P. officinalis* in folk medicine [3]. We now report on the isolation from this plant of two new, unstable furanoeremophilanes bearing the senecioyloxy group in place of the angeloyloxy group of already known, unstable



	1	2	3	4	5	6	7	8	9
R	H	OAng	OSen	H	H	H	H	H	H
R′	H	H	H	OAng	OSen	OAng	OSen	OAng	OSen
R″	H	H	H	OAng	OSen	OSen	OAng	OEt	OEt

	10	11	12	13	14	15
R	H	H	H	OH	H	H
R′	OAng	OSen	OAng	H	OH	OH
R″	OMe	OMe	OCH_2Ph	H	OH	OC(O)CH(Me)CH(Me)$_2$

	16	17	18
R	H	H	H
R′	OH	OH	OH
R″	OAng	OTigl	OEt

furanoeremophilanes, which have also been found in the same plant. Moreover, we report on the high solvolytic reactivity at the C-6 position of these terpenes.

RESULTS AND DISCUSSION

When fresh rhizomes and roots of *P. niveus* were lyophilized and then extracted with petrol, a series of six closely related furanoterpenes was obtained, three of which are new. The less polar compound proved to be the known furanojaponin (**2**), first isolated from *P. japonicus* [4] and later re-described as a new compound from *Senecio alatus* [6].

The next more polar compound is the senecioyloxy analogue **3** of furanojaponin. (It is stressed that both this and the other furanoeremophilanes reported in this work are particularly unstable in chloroform solutions, whereas in benzene solutions they survive much longer.) Its structure is clearly supported by mass spectral, ^1H and ^{13}C NMR data, and by chemical transformations. Thus, the proton spectrum shows a senecioyloxy group [7], whilst the mass spectrum shows the molecular ion, and two peaks at *m/z* 233 and 216 corresponding to, respectively, the loss of both the acyl and the acid moiety. It also shows, as the base peak, the formation, by retro Diels–Alder fragmentation, of an ion comprising the methylfurane moiety together with the adjacent methylenes. Finally, the change of **3** into the known **13** [4], by either basic hydrolysis or reduction with lithium aluminum hydride, establishes the relationship with furanojaponin, thus giving both the position and the stereochemistry of the ester group.

The next more polar compound was the known **4** [8], followed by a mixture of the known **7** [8] and the new **6** (5:4 ratio), which could not be obtained pure, and whose structure will be dealt with later. The most polar compound was the new 3β,6β-disenecioyloxyfuranoeremophilane (**5**). The structures are supported by the ^1H NMR spectra which show two non-equivalent senecioyloxy groups for **5** and two non-equivalent angeloyloxy groups for **4**. Also, reduction of either **5** or **4** with lithium aluminum hydride to give furanofukinol (**14**) [5], establishes both the position and the stereochemistry of the senecioyloxy groups for **5**.

Going back to the **6** + **7** mixture, both the position and the stereochemistry of the ester groups was established by lithium aluminum hydride reduction to give furanofukinol (**14**) [5]. The presence of both a senecioyloxy and an angeloyloxy group was indicated by solvent-induced differential shifts in the ^1H NMR spectra [7]. Also, because a senecioyloxy group at C-6 shows a resonance for the sp^2 proton at lower field than for the same group at C-3 (as shown by the ^1H NMR spectra in deuterochloroform of the compounds described above), we established that the more abundant component of the mixture is **7**.

However, our study of *P. niveus* was started in a different way, by extraction of fresh rhizomes and roots with ethanol. This revealed some interesting facets of the furanoeremophilane chemistry. Thus, we obtained, by chromatographic separations, a series of four furanoeremophilanes. The two less polar compounds proved to be **2** and **3**.

The other two unstable furanoeremophilanes showed, besides an angeloyloxy (**8**) or a senecioyloxy group (**9**), a typical quartet–triplet pattern for an ethoxy group in the ^1H NMR spectrum in deuterochloroform. The presence of an ethoxy group immediately suggested an artifact due to the extraction process. Structures **8** and **9** are proved by both spectral data and chemical transformations. The mass spectrum shows in both cases, a very weak molecular ion and a base peak at *m/z* 152, attributable to a retro Diels–Alder fragmentation into a methylfurane carrying a methylene and a CHOEt group. This serves to establish the position of the ethoxy group. The position and the stereochemistry of the angeloyloxy (**8**) or senecioyloxy group (**9**) was established from chemical transformations. In fact, **4** or **5** underwent either ethanolysis to give, respectively, **8** or **9**, or reduction by lithium aluminum hydride to give furanofukinol (**14**).

The problem of the stereochemistry at C-6 with both **8** and **9** was solved by ^1H NMR experiments which also threw light on the preferred conformations for both these and the other terpenoids. Thus, a broad doublet at δ 2.23 ($CDCl_3$) or 2.09 (C_6D_6) for **8**, and at δ 2.19 ($CDCl_3$) or 2.05 (C_6D_6) for **9**, can be attributed to H-9α for the 'non-steroid-like' conformation [9] in Fig. 1. Conceivably, the doublet arises from coupling of H-9α with H-9β. Also, the signal broadening, corresponding to a coupling constant of *ca* 2 Hz, can be attributed to the coupling of H-9α with H-10, which is consistent with a dihedral angle of *ca* 75° between the planes H-10–C-10–C-9 and C-10–C-9–Hα. A value of only 2 Hz is clearly inconsistent with the 'steroid-like' conformation in Fig. 1, where H-9α and H-10 are antiperiplanar. Moreover, the smaller coupling constant (2.2 Hz) from the *ddd* pattern attributable to H-9β, can be thought to originate from the axial–axial coupling between H-9β and H-6α in the 'non-steroid-like' conformation in Fig. 1 [9]. Such a relationship was proved by irradiation at the resonance level for H-6α, whereby the *ddd* assigned to H-9β became a *dd* (J = 17.0 and 6.0 Hz), whilst the multiplet attributable to H-9α did not change. Clearly, the axial–axial relationship between H-9β and H-6α is consistent with the ethoxy group occupying a C-6β position in the 'non-steroid-like' conformation of Fig. 1.

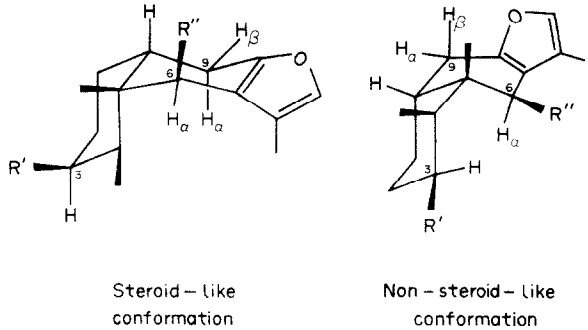


Fig. 1. 'Steroid-like' and 'non-steroid-like' conformation for **8** (R' = OAng; R'' = OEt), **9** (R' = OSen; R'' = OEt) and **12** (R' = OAng; R'' = OCH_2Ph).

Ethanolysis of either **4** or **5** to give, respectively, **8** or **9** has been mentioned. This is an indication that the un-natural terpenoids **8** and **9** in the ethanolic extract from *P. niveus* did really originate from natural **4** and **5** during the extraction process. That the phenomenon of the high solvolytic reactivity of either **4** or **5** at C-6 is general, was proved by methanolysis of either **4** or **5** to give, respectively, **10** or **11** and by the formation of **12** from **4** in benzydrol. Structures **10–12** rest on similar evidence to that offered for **8** and **9**. Moreover, with **12** in deuterochloroform solution, we observed a 28% NOE increase of the resonance due to 6-Hα on irradiation at 3-Hα. This unequivocally supports the β-position for the benzyloxy group in a 'non-steroid-like' conformation (Fig. 1).

The stereochemical outcome of the solvolytic reactions is noteworthy. In fact, at the level of sensitivity of the ^{1}H NMR technique, the epimers at C-6 of compounds **10–12** could not be detected. Also, **8–10**, and **12** proved to be HPLC pure. Conceivably, the stereospecificity (or high stereoselectivity) of these solvolytic reactions can be rationalized on the basis of an intermediate C-6 carbonium ion whose β-face can be more easily approached than the α-face by the alcohol reactant. It seems safe to argue that formation of a carbonium ion at C-6 is favoured by its special, allylic-type position involving conjugation of the furane oxygen. α,β-Unsaturation in the carboxylate-leaving group is also a favouring factor.

We conclude that the high nucleophilic reactivity, and stereospecificity, at C-6 discovered here is not the result of chance, but has been tailored by nature. Perhaps, it might constitute a mechanism for blocking enzyme-active nucleophilic sites.

EXPERIMENTAL

^{1}H NMR spectra were taken with a Varian CFT 20 spectrometer modified for proton spectra and equipped with a microprobe for ^{13}C spectra. Chemical shifts are given in δ-values (TMS as int. standard), in the same sequence as the indicated solvents. Multiplicities in ^{13}C NMR data are from off-resonance expts.

Prep. HPLC was carried out on a Yobin–Yvon Miniprep liquid chromatograph, equipped with a Jasco Unidec 100-II detector (using Lichroprep SI 60, 15–25 μm, 50 g, and monitoring at 254 nm). Analytical HPLC was carried out on a Perkin–Elmer Series 3B liquid chromatograph. TLC was carried out on Merck Kieselgel 60 F_{254} plates. Petrol refers to petroleum ether (40–60°). MS were obtained at either 70 or 20 eV.

Extraction with EtOH. Rhizomes and roots (0.8 kg, collected at Passo Cimirlo, Trento, in April 1980 and April 1981) were extracted (Soxhlet) with EtOH until colourless (24 hr). The EtOH extract was evaporated *in vacuo* and the aq. residue continuously extracted with petrol. The brown, oily residue (4.5 g) from evaporation of the petrol was subjected to CC on Kieselgel 60, 70–230 mesh (400 g). The eluant, petrol–Et_2O (19:1), was collected in 30 ml fractions. Fractions 27–57 gave 0.75 g of a mixture of **2**, **3**, **8** and **9** (TLC R_f 0.6, 0.5, 0.4 and 0.35, respectively, with petrol–Et_2O (19:1); all spots were Erlich reactive: violet for R_f 0.35 and 0.4, initially brown and then changing into blue for R_f 0.5 and 0.6). HPLC of the residue from fractions 27–57 with petrol–Et_2O (97:3), gave pure oily **2** (0.054 g), **3** (0.048 g), **8** (0.150 g) and **9** (0.180 g). These compounds were stable in C_6H_6, whereas they quickly decomposed, to give a multitude of unidentified products, in $CHCl_3$. Even when fresh rhizomes and roots were extracted by making a homogenate in a Waring blendor with 95% EtOH at room temp. only **2**, **3**, **8** and **9** could be obtained.

Extraction with petrol. Rhizomes and roots (0.8 kg) were lyophilized and then extracted (Soxhlet) with petrol (×3 each for 3 hr). Evaporation of the petrol extract gave a brown, oily residue (3.6 g) which was subjected to CC (Kieselgel conditions as before) using two-step gradient elution from petrol–Et_2O (19:1) to petrol–Et_2O (9:1). Fractions 24–26 (30 ml each) gave a mixture of **2** and **3** (0.43 g), whereas fractions 28–41 gave a mixture of **4**, **5**, **7** and **6** [0.71 g; TLC R_f 0.6, 0.5, 0.35, 0.25 and 0.30, respectively (Erlich-positive), with petrol–Et_2O (19:1)]. Repeated HPLC, using the above conditions, gave pure oily **2** (0.21 g) and **3** (0.13 g). Further, by changing to petrol–Et_2O (24:1), HPLC gave **4** (0.178 g), **4**+**6**+**7** (0.135 g), **6**+**7** (0.255 g), **5**+**6**+**7** (0.190 g), and **5** (0.165 g).

Data for known compounds. 2β - Angeloyloxy - 10β - H-furanoeremophilane (*furanojaponin*) (**2**) [4]. Colourless oil. $[\alpha]_D^{22}$ −33.5° ($CHCl_3$; *c* 1.17); IR ν_{max}^{film} cm^{-1}: 1710, 1650, 1571; MS *m/z* (rel. int.): 316 [M]$^+$ (3), 233 (3), 216 (M − angelic acid]$^+$ (10), 108 (100), 55 (30); UV $\lambda_{max}^{cyclohexane}$ nm (log ϵ): 219 (4.00); ^{1}H NMR (CCl_4, $CDCl_3$, C_6D_6): δ 6.87, 7.04, 7.02 (1H, *m*, H-12), 5.92, 6.03, 5.74 (1H, *qd*, *J* = 6.9, 1.2 Hz, =CHMe), 5.07, 5.17, 5.15 (1H, *m*, H-2α), 1.97, 1.98, 2.01 (3H, *dq*, *J* = 6.9, 1.4 Hz, =CHMe), 1.87, 1.90, 1.79 (3H, *d*, *J* = 1.3 Hz, Me-13), 1.85, 1.90, 1.89 [3H, *m*, =CMe–C(O)O–] 0.99, 1.00, 0.79 (3H, *s*, Me-14), 0.96, 0.96, 0.81 (3H, *d*, *J* = 7.0 Hz, Me-15), 2.3–1.3 (10H, series of *m*); ^{13}C NMR (C_6D_6): δ 166.63 (*s*, C=O), 148.54 (*s*, C-8), 137.69 (*d*, =CHMe or C-12), 137.36 (*d*, =CHMe or C-12), 128.68 (*s*, =CMeCOO–), 119.53 (*s*, C-7), 115.54 (*s*, C-11), 69.78 (*d*, C-2), 35.75, 34.62, 32.73 (*t*), 29.98 (*t*), 26.39 (*t*), 22.81, 22.70, 20.95 (*q*), 16.95 (*q*), 15.83 (*q*), 8.14 (*q*).

3β,6β - *Diangeloyloxy* - 10β - H - *furanoeremophilane* (**4**) [8]. Colourless oil; $[\alpha]_D^{22}$ −64.3° ($CHCl_3$; *c* 1.18); IR ν_{max}^{film} cm^{-1}: 1713, 1650, 1570; UV $\lambda_{max}^{n\text{-hexane}}$ nm (log ϵ): 218 (4.18); ^{1}H NMR ($CDCl_3$, C_6D_6): δ 7.04, 6.90 (1H, *m*, H-12), 6.46, 6.64 (1H, *m*, H-6), 6.05, 5.76 (1H, *qd*, *J* = 7.0, 1.1 Hz, =CHMe at ring C-6), 5.95, 5.76, (1H, *qd*, *J* = 7.0, 1.1 Hz, =CHMe at ring C-3), 5.42, 5.58 (1H, *ddd*, *J* = 10, 5, 5 Hz, H-3), 2.85, 2.55 (1H, *m*, H-9β), 2.37 (not evident in C_6D_6) (1H, *m*, H-9α) 1.91, 1.90 (3H, *d*, *J* = 1.1 Hz, Me-13), 1.07, 0.98 (3H, *s*, Me-14), 0.99, 0.89 (3H, *d*, *J* = 7.1 Hz, Me-15), 2.4–1.1, 2.2–1.0 (18H, series of *m*).

2β - *Senecioyloxy* - 10β - H - *furanoeremophilane* (**3**). Colourless oil. Found: C, 75.89; H, 8.97. $C_{20}H_{28}O_3$ requires C, 75.91; H, 8.92%; $[\alpha]_D^{22}$ −51.3° ($CHCl_3$; *c* 0.85); IR ν_{max}^{film} cm^{-1}: 1709, 1650, 1570; MS *m/z* (rel. int.): 316 [M]$^+$ (3), 233 (3), 216 [M − 100]$^+$ (13), 108 (100); UV $\lambda_{max}^{cyclohexane}$ nm (log ϵ): 218 (4.01); ^{1}H NMR ($CDCl_3$, C_6D_6): δ 7.03, 7.01 (1H, *m*, H-12), 5.66, 5.76 [1H, *m*, =CHC(O)O–], 5.16, 5.18 (1H, *m*, H-2), 2.17, 2.16 [3H, *d*, *J* = 1.2 Hz, Me *cis* to –C(O)O–], 1.90, 1.78 (3H, *d*, *J* = 1.1 Hz, Me-13), 1.89, 1.47 [3H, *d*, *J* = 1.2 Hz, Me *trans* to –C(O)O–], 1.00, 0.80 (3H, *s*, Me-14), 0.93, 0.81 (3H, *d*, *J* = 7.0 Hz, Me-15); 2.7–1.2, 2.6–1.1 (10H, *m*); ^{13}C NMR (C_6D_6): δ 165.63 (*s*, C=O), 155.62 (*s*, =CMe$_2$), 148.68 (*s*,C-8), 137.65 (*d*, C-12), 119.56 (*s*, C-7), 117.20 (*d*, =CHCOO–), 115.58 (*s*, C-11), 69.08 (*d*, C-2), 35.70, 34.60, 32.71, 30.00, 26.99 (*q*), 26.41, 22.76 (*q*), 20.02 (*q*), 16.90 (*q*), 8.16 (*q*).

3β,6β - *Disenecioyloxy* - 10β - H - *furanoeremophilane* (**5**). Colourless oil. (Found: C, 72.27; H, 8.53. $C_{25}H_{34}O_5$

requires C, 72.43; H, 8.27%); $[\alpha]_D^{22} - 80.8°$ ($CHCl_3$; *c* 1.07); IR ν_{max}^{film} cm^{-1}: 1717, 1651, 1572; UV $\lambda_{max}^{n\text{-hexane}}$ nm (log ϵ): 218 (4.23); ^1H NMR ($CDCl_3$, C_6D_6): δ 7.03, 6.99 (1H, *m*, H-12), 6.40, 6.68 (1H, *m*, H-6), 5.73, 5.75 [1H, *m*, =CHC(O)O– at C-6], 5.66, 5.66 [1H, *m*, =CHC(O)O– at C-3], 5.37, 5.62 (1H, *ddd*, *J* = 10, 5, 5 Hz, H-3), 2.21, 2.13 (3H, *d*, *J* = 1.2 Hz, Me *cis* to H at C-6), 2.18, 2.10 [3H, *d*, *J* = 1.3 Hz, Me *cis* to –C(O)O– at C-3], 1.89, 1.97 (3H, *d*, *J* = 1.2, Me-13), 1.89, 1.44 [3H, *m*, Me *trans* to –C(O)O– at C-6], 1.85, 1.44 [3H, *m*, Me *trans* to –C(O)O– at C-3], 1.04, 1.06 (3H, s, Me-14), 0.97, 0.96 (3H, *d*, *J* = 7.0 Hz, Me-15), the remaining protons were at 2.90–1.15 in $CDCl_3$ (8H, series of *m*) or at 2.85–1.00 (8H, series of *m*); ^{13}C NMR (C_6D_6): δ 166.21 (*s*, C=O at C-3 or C-6), 165.19 (*s*, C=O at C-3 or C-6), 156.97 (*s*, =$\underline{C}Me_2$ at C-3 or C-6), 155.37 (*s*, =$\underline{C}Me_2$ at C-3 or C-6), 150.45 (*s*, C-8), 138.80 (*d*, C-12), 120.06 (*s*, C-7), 117.11 [*d*, =$\underline{C}$(H)C(O)O– at C-3 or C-6], 116.30 [*d*, =$\underline{C}$(H)C(O)O– at C-3 or C-6], 116.05 (*s*, C-11), 71.24 (*d*, C-6), 67.70 (*d*, C-3), 41.99 (*s*, C-5), 36.67 (*d*), 36.45 (*d*), 27.11 (*q*), 27.00 (*q*), 26.70, 26.33 (*t*), 26.21 (*t*), 20.25 (*q*), 19.97 (*q*), 8.78 (*q*).

From a mixture of **6** + **7**. 3β - *Angeloyloxy* - 6β - *senecioyloxy* - 10β - **H** - *furanoeremophilane* (**6**). ^1H NMR ($CDCl_3$ or C_6D_6, given in parenthesis, when recognizable) δ 7.04, (6.96), (1H, *m*, H-12), 6.35, (6.71) (1H, *m*, H-6), 5.94 (1H, *qd*, *J* = 6.9, 1.2 Hz, =C$\underline{H}$Me), 5.68 [1H, *m*, =CHC(O)O–], 5.35 (1H, *ddd*, *J* = 10, 5, 5 Hz, H-3), 2.83, (2.63) (1H, *m*, H-9β), 2.31 (1H, *m*, H-9α), 1.93 (3H, *d*, *J* = 1.1 Hz, Me-13). 3β - *Senecioyloxy* - 6β - *angeloyloxy* - 10β - H - *furanoeremophilane* (**7**). ^1H NMR ($CDCl_3$ or C_6D_6, given in parenthesis, when recognizable): δ 7.04, (6.96) (1H, *m*, H-12), 6.42, (6.71) (1H, *m*, H-6), 6.04 (1H, *qd*, *J* = 6.9, 1.2 Hz, =C$\underline{H}$Me), 5.62 [1H, *m*, =CHC(O)O–], 5.35 (1H, *ddd*, *J* = 10, 5, 5 Hz, H-3), 2.83, (2.63) (1H, *m*, H-9β), 2.31 (1H, *m*, H-9α), (1.93) (3H, *d*, *J* = 1.1 Hz, Me-13); ^{13}C NMR (C_6D_6): significantly, the mixture showed four carbonyl singlets at δ 167.28, 166.42, 166.29 and 165.22 and four doublets at δ 72.05, 71.17, 68.48 and 67.74 for C-3 and C-6.

3β - *Angeloyloxy* - 6β - *ethoxy* - 10β - H - *furanoeremophilane* (**8**). Colourless oil; $[\alpha]_D^{22} - 25.7°$ ($CHCl_3$; *c* 0.43); IR ν_{max}^{film} cm^{-1}: 1706, 1635, 1560; MS *m/z* (rel. int.): 360 $[M]^+$ (0.5), 152 (100), 123 (27), 108 (11), 83 (13), 55 (22); UV $\lambda_{max}^{cyclohexane}$ nm (log ϵ): 220 (3.98); ^1H NMR ($CDCl_3$, C_6D_6): δ 7.04, 7.03 (1H, *m*, H-12), 6.05, 5.69 (1H, *qd*, *J* = 6.9, 1.1 Hz, =C$\underline{H}$Me), 5.39, 5.43 (1H, *m*, H-3), 4.61, 4.56 (1H, *m*, H-6), (OCH_2 in $CDCl_3$ appeared as two quartets centred at δ 3.92 and 3.91, *J* = 7.0 Hz, whilst in C_6D_6 the two quartets were centred at 4.05 and 3.85, *J* = 7.0 Hz), 2.80, 2.60 (1H, *m*, which, on irradiation at H-12, became a *ddd*, *J* = 17.0, 6.0, 2.2 Hz, H-9β), 2.23, 2.09 (1H, *m*, which, on irradiation at H-6α, became a *dd*, *J* = 17, 1.5 Hz, H-9α), 2.04, 2.00 (3H, *d*, *J* = 1.3 Hz, Me-13), 1.99, 2.00 (3H, *dq*, *J* = 6.9, 1.4 Hz, =CHMe), 1.94, 1.94 [3H, *m*, =C(Me)C(O)O–], 1.26, 1.22 (3H, *t*, *J* = 7.0 Hz, $CH_2\underline{Me}$), 0.99, 0.88 (3H, *d*, *J* = 7.1 Hz, Me-15), 0.99, 1.01 (3H, *s*, Me-14), the other six protons were at δ 2.30–1.20 in $CDCl_3$ and at 2.18–1.16 in C_6D_6 as a series of *m*; ^{13}C NMR (C_6D_6): δ 166.94 (*s*, C=O), 149.41 (*s*, C-8), 138.58 (*d*, C-12 or =$\underline{C}$HMe), 137.61 (*d*, C-12 or =$\underline{C}$HMe), 128.66 [*s*, =$\underline{C}$MeC(O)O–], 120.56 (*s*, C-7), 118.30 (*s*, C-11), 76.17 (*d*, C-6), 72.12 (*d*, C-3), 68.81 (*t*, $\underline{C}H_2Me$), 43.47, 36.62, 36.08, 27.17, 26.67, 26.37, 20.95, 19.97, 16.07, 15.90, 9.52, 8.58.

3β - *Senecioyloxy* - 6β - *ethoxy* - 10β - H - *furanoeremophilane* (**9**). Colourless oil; $[\alpha]_D^{22} - 25.2°$ ($CHCl_3$; *c* 0.40); IR ν_{max}^{film} cm^{-1}: 1704, 1653, 1560; MS *m/z* (rel. int.): 360 $[M]^+$ (0.5), 260 (0.5), 152 (100), 123 (60), 108 (23), 83 (17), 55 (5): UV $\lambda_{max}^{cyclohexane}$ nm (log ϵ): 219 (3.96); ^1H NMR ($CDCl_3$, C_6D_6): δ 7.03, 7.04 (1H, *m*, H-12), 5.70, 5.81 [1H, *m*, =CHC(O)O–], 5.33, 5.46 (1H, *m*, H-3), 4.60, 4.65 (1H, *m*, H-6), (OCH_2 in $CDCl_3$ appeared as two quartets centred at 3.89 and 3.88, *J* = 7.0 Hz, whilst in C_6D_6 the two quartets were centred at 4.10 and 3.87, *J* = 7.0 Hz), 2.78, 2.65 (1H, *m*, which, on irradiation at H-12, became a *ddd*, *J* = 17.0, 6.1, 2.2 Hz, H-9β), 2.19, 2.05 (1H, *m*, H-9α), 2.17, 2.13 [3H, *d*, *J* = 1.2 Hz, Me *cis* to –C(O)O–], 2.03, 2.01 (3H, *d*, *J* = 1.2 Hz, Me-13), 1.89, 1.45 [3H, *d*, *J* = 1.2 Hz, Me *trans* to –C(O)O–], 1.25, 1.24 (3H, *t*, *J* = 7.0 Hz, $CH_2\underline{Me}$), 0.97, 1.03 (3H, *s*, Me-14), 0.95, 0.99 (3H, *d*, *J* = 7.1 Hz, Me-15); the other six protons were at δ 2.30–1.20 in $CDCl_3$ and at δ 2.10–1.15 in C_6D_6 as a series of *m*; ^{13}C NMR (C_6D_6): δ 165.55 (*s*, C=O), 155.77 (*s*, =$\underline{C}Me_2$), 149.18 (*s*, C-8), 138.48 (*d*, C-12), 120.45 (*s*, C-7), 118.26 (*s*, C-11), 117.0 (*d*, =$\underline{C}$HMe), 76.07 (*d*, C-6), 71.18 (*d*, C-3), 68.72 (*t*, OCH_2), 43.45 (*s*, C-5), 36.63, 36.22, 27.36, 27.01, 26.66, 26.48, 19.96, 16.04, 9.48, 8.38.

Reaction of **4** *with EtOH*. A soln of **4** (0.005 g) in 5 ml 95% EtOH was refluxed under N_2 for 16 hr. The solvent was then evaporated *in vacuo* and the residue was subjected to HPLC, petrol–Et_2O (24:1) to give **8** (0.002 g, 57%), and unreacted **4** (0.001 g).

Reaction of **5** *with EtOH*. Both the reaction and the work-up were carried out as just described. Thus, from 0.006 g **5**, we obtained 0.0025 g **9** (58%) and 0.001 g unreacted **5**.

Reaction of **4** *with MeOH*. **4** (0.035 g) was refluxed in 10 ml MeOH for 21 hr under N_2. Work-up as above gave 0.008 g (27%) 3β - angeloyloxy-6β - methoxy - 10β - H - furanoeremophilane (**10**) as a colourless oil; ^1H NMR (C_6D_6): δ 7.02 (1H, *m*, H-12), 6.02 (1H, *qd*, *J* = 6.9, 1.1 Hz, =C$\underline{H}$Me), 5.40 (1H, *m*, H-3), 4.50 (1H, *m*, H-6), 3.70 (3H, *s*, OMe), 2.78 (1H, *m*, which on irradiation at H-12 became a *ddd*, *J* = 17.0, 6.1, 2.2 Hz, H-9β), 2.25 (1H, *m*, which on irradiation at H-6 became a *dd*, *J* = 17, 1.5 Hz, H-9α), 2.03 (3H, *d*, *J* = 1.1 Hz, Me-13), 1.95 (3H, *dq*, *J* = 6.9, 1.4 Hz, =CH$\underline{Me}$), 1.90 [3H, *m*, =C$\underline{Me}$C(O)O–], 0.97 (3H, *s*, Me-14), 0.96 (3H, *d*, *J* = 7.0 Hz), 2.20–1.10 (6H, series of *m*).

Reaction of **5** *with MeOH*. The reaction and the work-up were carried out as just described. Thus, from 0.035 g **5** we isolated 0.015 g (51%) of 3β - senecioyloxy - 6β - methoxy - 10β - *H* - furanoeremophilane (**11**) as a colourless oil; ^1H NMR (C_6D_6): δ 6.97 (1H, *m*, H-12), 5.73 [1H, *m*, =CHC(O)O–], 5.39 (1H, *m*, H-3), 4.43 (1H, *m*, H-6), 3.71 (3H, *s*, OMe), 2.14 [3H, *d*, *J* = 1.1 Hz, Me *cis* to C(O)O–], 2.00 (3H, *d*, *J* = 1.2 Hz, Me-13), 1.47 [3H, *d*, *J* = 1.0 Hz, Me *trans* to C(O)O–], 1.00 (3H, *s*, Me-14), 0.93 (3H, *d*, *J* = 7.2 Hz, Me-15), 2.84–1.05 (8H, series of *m*).

Reaction of **4** *with benzydrol*. A soln of **4** (0.016 g) in 5 ml benzydrol was maintained at 65° under N_2 for 3 days. Work-up as in the above case of **4** with EtOH gave 0.007 g (60%) 3β - angeloyloxy - 6β - benzyloxy - 10β - *H* - furanoeremophilane (**12**) as a colourless oil; ^1H NMR ($CDCl_3$ C_6D_6); δ 7.01, 7.00 (1H, *m*, H-12), 7.34, 7.15 (5H, *m*, Ph, 6.02, 5.45 (1H, *qd*, =C$\underline{H}$Me), 5.42, 5.71 (1H, *m*, H-3), (the benzylic protons appeared as a *s* at 4.93 in $CDCl_3$, whilst in C_6D_6 they appeared as an AB system at 4.87 and 5.15, *J* = 11 Hz), 4.76, 4.72 (1H, *m*, H-6) 2.03, 1.98 (3H, *d*, *J* = 1.2 Hz, Me-13), 1.96, (not detectable in C_6D_6) [3H, *dq*, Me *cis* to C(O)O–], 1.93, not detectable in C_6D_6, [3H, *m*, =CMeC(O)O–], 1.08, 1.04 (3H, *s*, Me-14), 0.96, 0.84 (3H, *d*, *J* = 7.2 Hz, Me-15). Irradiation at the H-3 resonance gave a NOE 28% enhancement of the H-6 resonance. Unreacted **4** (0.005 g) was also recovered. When this reaction was carried out at reflux, no **12** could be recovered because of extensive decomposition.

Hydrolysis of **8** *or* **9**. A soln of **8** (0.0025 g) in 10 ml 5%

NaOH in EtOH–H_2O (3:2) was refluxed for 40 min under N_2. The mixture was then evaporated *in vacuo* and the aq. residue was extracted (×3) with Et_2O to give 0.0011 g (57%) 3β - hydroxy - 6β - ethoxy - 10β - *H* - furanoeremophilane (**18**). ^1H NMR ($CDCl_3$, C_6D_6): δ 7.01, 7.01 (1H, *m*, H-12), 4.50, 4.31 (1H, *m*, $W_{1/2}$ = 5.0 Hz, H-6), 4.23, 3.83 (1H, *m*, $W_{1/2}$ = 2.2 Hz, H-3), (OCH_2 appeared as two *q*, *J* = 7.1 Hz, at 3.76 and 3.77 in $CDCl_3$ and at 3.54 and 3.55 in C_6D_6), 2.79, 2.63 (1H, *m*, H-9β), 2.18, 2.06 (1H, *m*, H-9α), 2.03, 1.99 (3H, *d*, *J* = 1.2 Hz, Me-13), 1.26, 1.13 (3H, *t*, *J* = 7.1 Hz, CH_2 Me), 0.98, 0.87 (3H, *d*, *J* = 7.0 Hz, Me-15), 0.99, 1.03 (3H, *s*, Me-14). The hydrolysis of **9** (0.013 g) was carried out similarly to give **18** (0.007 g, 66%).

Hydrolysis of **4**. A soln of **4** (0.025 g) in 4% KOH in 95% EtOH was maintained at room temp. under N_2, for 20 hr. The mixture was then diluted with H_2O (15 ml), evaporated *in vacuo* and the aq. residue extracted with Et_2O. HPLC of the residue from evaporation of the Et_2O with petrol–Et_2O (1:1) gave the known [8] 3β - hydroxy - 6β - angeloyloxy - 10β - *H* - furanoeremophilane (**16**) (0.006 g, 30%), besides 3β - hydroxy - 6β - tigloyloxy - 10β - *H* - furanoeremophilane (**17**) (0.007 g, 35%), ^1H NMR ($CDCl_3$): δ 7.00 (1H, *m*, H-12), 6.88 (1H, *q*, *J* = 6.4 Hz, =CHMe), 6.38 (1H, *m*, $W_{1/2}$ = 5.0 Hz, H-6), 4.39 (1H, *ddd*, *J* = 10, 5, 5 Hz, H-3), 2.86 (1H, *m*, H-9β), 2.20 (1H, *m*, H-9α), 1.87 [3H, *br s*, =CMeC(O)O–], 1.84 (3H, *d*, *J* = 6.4 Hz, =CHMe), 1.79 (3H, *d*, *J* = 1.1 Hz, Me-13), 1.02 (3H, *s*, Me-14), 0.95 (3H, *d*, *J* = 7.0 Hz, Me-15).

Reactions with $LiAlH_4$. A mixture of the appropriate furanoeremophilane was refluxed, under N_2 for 0.5 hr, in Et_2O and $LiAlH_4$ (3:2 w/w). H_2O was then added and the mixture was extracted with Et_2O. The residue from the Et_2O layer was subjected to HPLC. Thus, from **2** (0.030 g), chromatography with petrol–Et_2O (:1) gave 0.035 g 3β-Analogously, **3** gave **13** (0.008 g). Also, from **4** (0.015 g), chromatography with Et_2O gave **14**, mp 179–180° (lit.) 178–180° (dec.) [4] (0.009 g). Finally, the **4** + **5** + **6** + **7** mixture (0.325 g) described above was reduced with 0.070 g $LiAlH_4$; chromatography with petrol–Et_2O (1:1) gave 0.035 g 3β - hydroxy - 6β - (2 - methyl)butanoyloxy - 10β - *H* - furanoeremophilane (**15**) and 0.03 g of furanofukinol (**14**). ^1H NMR (C_6D_6): δ 6.91 (1H, *m*, H-12), 6.50 (1H, *m*, $W_{1/2}$ = 5 Hz, H-6), 4.24 (1H, *m*, $W_{1/2}$ = 2.2 Hz, H-3), 2.31 [1H, *m*, CH(Me)CH_2], 1.89 (3H, *d*, *J* = 1.1 Hz, Me-13), 0.97 (3H, *s*, Me-14), 1.13 [3H, *d*, *J* = 6.9 Hz, –O(O)CCH(Me)CH_2], 0.96 (3H, *d*, *J* = 7.0 Hz, Me-15), 0.86 (3H, *t*, *J* = 7.0 Hz, CH_2Me).

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