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GERMACRANES AND FLAVONOIDS FROM *ACHILLEA AGERATUM*

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Key Word Index—*Achillea ageratum*; Anthemideae; Compositae; ageratriol derivatives; germacranes; flavonoids.

Abstract—Aerial parts of *Achillea ageratum* yielded, in addition to ageratriol 9-*O*-acetylageratriol, 1-dehydroageratriol, a 1(10)-epoxygermacra-5,9-diol, and its monoacetate, as well as 5,4′-dihydroxy-3,7-dimethoxyflavone, chrysosplenetin, penduletin, hispidulin and cirsileol.

INTRODUCTION

More than 20 years ago, Trave and co-workers reported the isolation of the germacranes ageratriol (**1a**) [1–3] from the whole plant and agerol (**2**) [4, 5] from the flowers of Sardinian *Achillea ageratum* L. Biosynthesis of **1a** apparently proceeds via agerol diepoxide rather than by a process mimicking the reaction of **2** with singlet oxygen followed by reduction of the intermediate 1,5-hydroperoxide [5, 6]. The essential oil produced by steam distillation contained approximately 60% 1,8-cineole and some **3**, presumably produced by a Cope rearrangement of **2** [7]. Other workers have reported identification of *E*-dehydromatricaria ester in the root extract [8] and penduletin and vicenin in the leaf [9] of *A. ageratum* collections, the provenance of which was not specified.

RESULTS AND DISCUSSION

Examination of a collection of *A. ageratum* from Mafra, Portugal, has now yielded, in addition to ageratriol, a monoacetate **1b**, an epoxyacetate **4a**, a 2:1 mixture of 1-dehydroageratriol (**5**) and epoxyalcohol **4c** and the flavonoids **6a**, **6b** (chrysosplenetin), **6c** (penduletin), **7a** (hispidulin) and **7b** (cirsiliol). Previously reported ^{1}H NMR data for ageratriol (**1a**), which is insoluble in $CDCl_3$, and its triacetate **1c** are sparse [1] and not useful for comparison with the new compounds. Significant signals in the ^{1}H NMR spectra of **1a** in DMSO-d_6 and **1c** in DMSO-d_6 and $CDCl_3$ are, therefore, included in Table 1, together with those of the new compounds, while the ^{13}C NMR spectra are listed in Table 2. The ^{1}H NMR spectra of **1a–1c** and **5** exhibit three pairs of singlets, characteristic of *exo*-methylenes. Thus, the pair at highest field near δ 4.6, allylically coupled to a vinyl methyl near δ 1.65, is attributable to H-13a, b, while a second pair, which although slightly affected by acetylation remains essentially constant near δ 5.2 throughout the series, can be assigned to H-15a,b. The pair at lowest field (H-14a,b) is replaced in the spectra of monoacetate **4a**, synthetic diacetate **4b** and epoxyalcohol **4c** by a three-proton singlet in the range δ 1.33–1.42, characteristic of methyl on carbon under oxygen. Simultaneously, a *dd* at δ 4.21 (–CHOH) in the spectrum of monacetate **1b** and δ 4.98 (or 5.00) in the spectrum of triacetate **1c** (–CHOAc) has moved upfield to δ 3.11 (from δ 3.17), thus indicating the conversion of partial structure A to B where the CH_2- group could represent C-2 or C-8, but not C-6 (see below). In the spectrum of dehydroageratriol (**5**) the chemical shifts of H-15a, b are not altered, while the paramagnetic shifts of

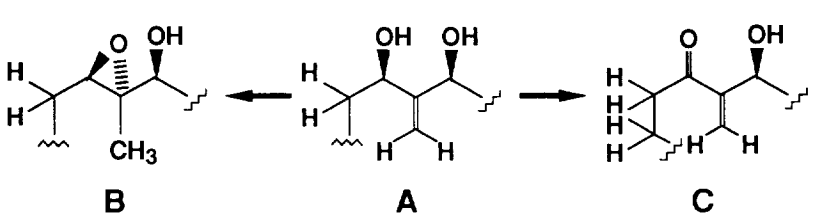

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Table 1. Partial ^{1}H NMR data for compounds **1a–1c**, **4a–4c** and **5** (500 MHz, $CDCl_3$)

H	**1a***	**1b**	**1c***	**1c†**	**4a**	**4b†**	**4c‡**	**5‡**
1	3.87 *dt*¶ (10, 5.5)	4.21 *dd* (11, 5)	4.85 *dd* (10, 5)	4.98 *dd* (11, 5.5)	3.11 *dd* (10, 4.5)	3.17 *dd* (10, 4.5)	obsc.	—
5	3.64 *dt*‖ (8.5, 3.5)	3.90 *dd* (12, 3.5)	4.88 *dd* (11, 4)	5.00 *dd* (11, 4.5)	3.96 *dd* (12, 3)	5.01 *dd* (12, 3)	3.94 *dd* (12, 2)	3.98 *dd* (10.5, 4.5)
9	3.87 *dt*¶ (10, 5)	4.70 *dd* (12, 5.5)	5.47 *dd* (11, 3)	5.58 *dd* (11.5, 3)	4.24 *dd* (12, 5)	4.31 *dd* (12, 5)	Obsc.	4.78 *dd* (10.5, 5.5)
12§	1.62 *brs*	1.68 *brs*	1.65 *brs*	1.68 *brs*	1.68 *brs*	1.69 *brs*	1.65 *brs*	1.64 *brs*
13a	4.64 *brs*	4.67 *brs*	4.72 *brs*	4.77 *brs*	4.68 *brs*	4.75 *brs*	4.66 *brs*	4.63 *brs*
13b	4.64 *brs*	4.65 *brs*	4.72 *brs*	4.74 *t* (1)	4.65 *brs*	4.74 *brs*	4.62 *brs*	4.59 *brs*
14a	5.29 *s*	5.42 *brs*	5.57 *s*	5.60 *s*	1.37 *s*§	1.42 *s*§	1.33 *s*§	6.06 *s*
14b	5.16 *s*	5.36 *brs*	5.57 *s*	5.50 *s*				5.94 *s*
15a	4.96 *s*	5.16 *brs*	5.25 *s*	5.34 *s*	5.17 *brs*	5.32 *brs*	5.09 *brs*	5.16 *brs*
15b	4.94 *s*	5.12 *br*	5.24 *s*	5.32 *s*	5.16 *brs*	5.31 *brs*	5.09 *brs*	5.09 *brs*
Ac§	—	2.01 *s*	1.98 *s*, 1.96 *s* 1.93 *s*	2.09 *s*, 2.01 *s* 1.98 *s*	2.06 *s*	2.07 *s* 2.01 *s*		

*At 300 MHz, DMSO-d_6.
†At 300 MHz, $CDCl_3$.
‡From an approximately 1 : 2 mixture of **4c** and **5**.
§Intensity three protons.
¶Coupled to –OH signals at 4.69 *d* (5) and 4.60 *d* (5).
‖Coupled to –OH signal at 4.51 *d* (3.5).

Table 2. ^{13}C NMR spectra of compounds **1a–1c**, **4a–4c** and **5** (75 MHz)

C	**1a***	**1b***	**1c†**	**1c***	**4a†**	**4b†**	**4c*‡**	**4c†‡**	**5*‡**	**5†‡**
1	76.6 *d*	74.1 *d*[a]	76.2 *d*[a]	77.1 *d*	59.9 *d*	59.3 *d*	58.8 *d*	60.5 *d*	203.3 *s*	203.4 *s*
2	32.1 *t*	31.6 *t*	29.9 *t*	28.0 *t*	25.7 *t*	25.5 *t*	25.5 *t*	26.0 *t*	38.6 *t*	39.1 *t*
3	22.5 *t*	21.7 *t*	21.8 *t*	22.6 *t*	21.1 *t*	22.9 *t*	22.0 *t*	22.0 *t*	24.8 *t*	25.7 *t*
4	150.4 *s*	150.7 *s*	150.0 *s*	143.3 *s*	147.3 *s*[a]	142.7 *s*	148.2 *s*	147.7 *s*[a]	148.1 *s*[a]	146.6 *s*[a]
5	69.3 *d*	69.4 *d*	70.7 *d*	73.2 *d*	75.6 *d*	77.6 *d*	76.0 *d*	76.0 *d*	66.7 *d*	69.1 *d*
6	36.9 *t*	36.5 *t*	36.4 *t*	33.8 *t*	35.9 *t*	33.7 *t*	36.4 *t*	35.8 *t*	37.4 *t*	37.6 *t*
7	37.7 *d*	37.6 *d*	37.9 *d*	37.1 *d*	38.4 *d*	38.1 *d*	38.1 *d*	38.9 *d*	36.8 *d*	37.8 *d*
8	44.4 *t*	39.8 *t*	40.1 *t*	39.6 *t*	36.0 *t*	36.1 *t*	39.7 *t*	38.4 *d*	44.0 *t*	42.5 *t*
9	72.0 *d*	74.5 *d*[a]	77.2 *d*[a]	70.4 *d*	80.9 *d*	80.7 *d*	78.1 *d*	79.9 *d*	73.7 *d*	75.3 *d*
10	154.4 *s*	149.5 *s*	147.3 *s*[b]	145.7 *s*	59.4 *s*	59.9 *s*	61.2 *s*	62.2 *s*	153.0 *s*	152.3 *d*
11	148.7 *s*	148.0 *s*	147.8 *s*[b]	146.9 *s*	146.4 *s*[a]	146.0 *s*	148.2 *s*	147.5 *s*[a]	147.4 *s*[a]	147.8 *s*[a]
12	18.4 *q*	18.2 *q*	18.0 *q*	18.0 *q*	18.2 *q*	18.2 *q*	18.3 *q*	18.1 *q*	18.0 *q*	18.2 *q*
13	110.6 *t*	110.1 *t*	111.0 *t*	111.0 *t*	111.2 *t*	111.7 *t*	110.0 *t*	111.0 *t*	109.7 *t*	110.8 *t*
14	109.7 *t*	113.6 *t*	114.7 *t*	117.5 *t*	11.5 *q*	11.6 *q*	10.6 *q*	10.6 *q*	122.6 *t*	123.1 *t*
15	112.8 *t*	113.2 *t*	115.4 *t*	117.5 *t*	115.9 *t*	118.4 *t*	113.9 *t*	116.1 *t*	114.9 *t*	116.9 *t*
Ac		169.5 *s* 21.0 *q*	171.7 *s* 22.0 *q*	170.1 *s*, 169.1 *s*, 168.9 *s*, 21.0 *q*, 20.9 *q*, 20.9 *q*	170.0 *s* 21.2 *q*	169.9 *s*, 169.7 *s* 21.2 *q*, 21.1 *q*				

*In DMSO-*d*.
†In $CDCl_3$.
‡From mixture of **4c** (minor) and **5** (major).
[a,b]In the same column, interchangeable signals.

H-14a, b are indicative of conjugation with the new carbonyl group, the presence of which is also responsible for strongly deshielding a proton under a hydroxyl as in C, of necessity at C-1 if the carbonyl is at C-9, or at C-9 if the carbonyl group is at C-1. That the latter arrangement is correct is shown by the ^{1}H NMR spectrum, where two mutually coupled protons at relatively low field (δ 3.25 and 2.71) are each coupled to a second pair of mutually coupled protons at δ 2.57 and 2.44; this is only possible if the carbonyl group is at C-1. Consequently, the ketodiol is identified as **5**, which is reflected in the ^{13}C NMR spectrum by pronounced paramagnetic shifts of three triplets (b) now assignable to C-2, C-3 and C-14 when compared with **1a** in the same solvent (DMSO-d_6).

In the case of epoxide monoacetate **4a** and the

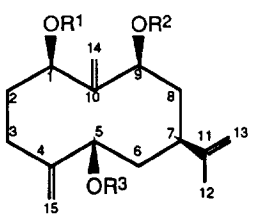
minor constituent of the **4c**–**5** mixture, superposition of ^{1}H NMR signals presented considerable difficulties. However, it could be shown that the epoxidic signal of **4a** at δ 3.11 was vicinally coupled to two neighbouring protons at δ 2.41 and 1.5, the former of which exhibited three additional couplings, thus leading to formula **4a** for the monoacetate and **4c** for the diol with the epoxide closed from C-1 to C-10. Acetylation of **4a** produced the diacetate **4b**. In the ^{1}H NMR spectrum this was accompanied by a paramagnetic shift of the signal at δ 3.96 associated with H-5 (compare with **1b** and **5**) to δ 5.01. Thus the *dd* of **4a** at δ 4.24 (δ 4.31 in **4b**) which was unaffected by acetylation, had to be associated with H-9 under the acetate originally present in **4a**, and its high-field position can be ascribed to shielding by the epoxide (compare with H-9 at δ 3.20 of unacetylated C-9 in the NMR spectrum of synthetic agerol diepoxide [9]). The carbon shift changes accompanying the conversions **4c** → **4a** → **4b** when measured in the same solvent are also in accordance with structure **4a** of the epoxide monoacetate.

Finally, we consider the location of the acetate moiety in the naturally occurring monoacetate of ageratriol. Clearly, the acetate was not at C-5 (Tables 1 and 2) but superposition of signals in the high-field region of the ^{1}H NMR spectrum again caused difficulties. However, the signal at δ 4.21 was clearly coupled to multiplets at δ 2.23 and 2.04, at least one of which was further coupled to multiplets at δ 2.17 and 2.08, thus indicating that the signal at δ 4.21 represents H-1. Hence the signal at lower field (δ 4.70) had to be ascribed to C-9, from which the inference could be drawn that the acetate was at C-9. The changes in the ^{13}C NMR spectra in the same solvent, in particular the upfield shift of the C-8 frequency accompanying the change from **1a** to **1b** and the upfield shift of the C-2 resonance in going from **1b** to **1c**, are in accordance with this formulation.

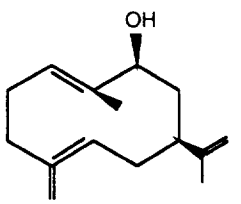
EXPERIMENTAL

Plant material. Achillea ageratum L. was collected in Mafra, Portugal, in July 1992. A voucher specimen was deposited in the Herbarium of the Instituto Superior de Agronomia, Lisbon.

Extraction and isolation. Powdered dry aerial parts (2 kg) were percolated with MeOH at room temp. to exhaustion. Evaporation of the solution at red. pres. gave 500 g of crude material, which was dissolved in $CHCl_3$, filtered and evaporated at red. pressure. The



1a R^1, R^2, R^3 = H
b R^1, R^3 = H, R^2 = Ac
c R^1, R^2, R^3 = Ac



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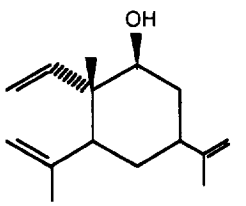

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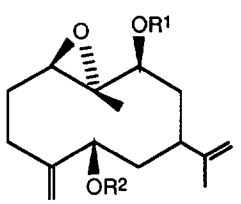
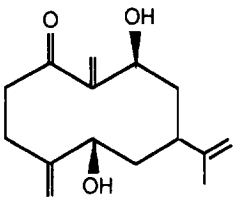


4a R^1 = Ac, R^2 = H
b R^1, R^2 = Ac
c R^1, R^2 = H



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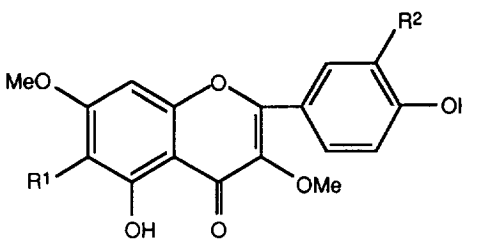
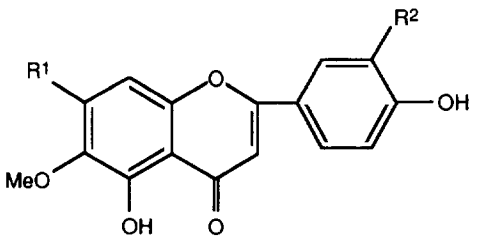


6a R^1, R^2 = H
b R^1 = OMe, R^2 = OH
c R^1 = OMe, R^2 = H



7a R^1 = OH, R^2 = H
b R^1 = OMe, R^2 = OH

residue (115 g) was taken up in hot EtOH, mixed with hot H_2O containing $Pb(OAc)_2$, and HOAc, allowed to stand overnight, filtered, concentrated at red. pressure to remove EtOH, and extracted with $CHCl_3$. Concentration of the dried extract in vacuo furnished 59 g of residue which was chromatographed on silica gel 60 (200 g), eluents petrol–$CHCl_3$ and $CHCl_3$–Me_2CO (1000 ml frs) as follows: Frs 1–35 (petrol–$CHCl_3$, 4 : 1), frs 36–84 (petrol–$CHCl_3$, 3 : 2), frs 85–108 (petrol–$CHCl_3$, 2 : 3), frs 109–129 (petrol–$CHCl_3$, 1 : 4), frs 130–155 ($CHCl_3$), frs 156–186 ($CHCl_3$–Me_2CO, 9 : 1), frs 187–207 ($CHCl_3$–Me_2CO, 4 : 1), frs 208–231 ($CHCl_3$–Me_2CO, 7 : 3), frs 232–248 ($CHCl_3$–Me_2CO, 3 : 2), frs 249–271 ($CHCl_3$–Me_2CO, 1 : 1), frs 272–281 ($CHCl_3$–Me_2CO, 2 : 3), and frs 282–294 ($CHCl_3$–Me_2CO, 1 : 4). Frs 1–47 contained non-polar material which was not studied further. Frs 48–53 were combined (1.2 g) and subjected to CC (silica gel 60, 129), 50-ml subfrs being collected as follows: subfrs 1–30 (petrol–$CHCH_3$, 4 : 1), subfrs 31–40 (petrol–$CHCl_3$, 3 : 2), subfrs 41–60 (petrol–$CHCl_3$, 1 : 4), subfrs 61–66 ($CHCl_3$–Me_2CO, 9 : 1), subfr 67 (Me_2CO), subfr 68 (MeOH). Subfrs 17–30 (560 mg) were combined and purified by prep. TLC (silica gel, petrol–EtOAc–HCO_2H, 70 : 30 : 1) to give 296 mg of **4a**. Frs 54–59 (1 g) were combined, but were not purified further. Frs 60–63 (0.6 g) were combined; recryst. from petrol–$CHCl_3$ afforded 0.4 g of chrysoplenetin (**6b**) identified by MS, UV and NMR spectrometry and conversion of 30 mg of **6b** to 12 mg of 4′-acetoxy-5-hydroxy-3,6,7,3′-tetramethoxyflavone, ^{1}H NMR (DMSO-d_6) δ 12.45 (*brs*, 5-OH), 7.77 (*d*, J = 2 Hz, H-2′), 7.69 (*dd*, J-8.5 and 2 Hz, H-6′), 7.33 (*d*, J = 8.5 Hz, H-5′), 6.97 (*s*, H-8), 3.93, 3.89, 3.87, 3.74 (each *s* and 3p, –OMe), 2.40 and 2.31 (each *s* and 3p, 4′-OAc), and 16 mg of 5,4′-diacetoxy-3,6,7,3′-tetramethoxyflavone, ^{1}H NMR (DMSO-d_6) δ 7.76 (*d*, J = 2 Hz, H-2′), 7.67 (*dd*, J = 8.5, 2 Hz, H-6′), 7.38 (*s* H-8), 7.32 (*d*, J = 8.5 Hz, H-5), 3.99, 3.89, 3.78, 3.74 (each *s* and 3p, –OMe) 2.40, 2.31 (each *s* and 3p, 4′-OAc). Purification of the mother liquor of **6b** by reverse phase PTLC (RP-18, MeOH–H_2O, 7 : 3) afforded an additional 20 mg of **4a**. Frs 64–84 were combined, but contained a mixture of components with similar R_f values and were not examined further.

Frs 85–87 (0.8 g) were rechromatographed (silica gel 60), 50-ml subfrs being collected as follows: subfrs 1–13 (petrol–$CHCl_3$, 4 : 1), subfrs 14–50 (petrol–$CHCl_3$, 3 : 21), subfrs 51–72 (petrol–$CHCl_3$, 2 : 3). Purification of subfrs 14–46 by TLC (silica gel, toluene–EtOAc–Me_2CO–HCO_2H, 60 : 35 : 5 : 1) gave 0.32 g of **1b**. Recryst. of fr. 88 gave 27 mg of flavone **6a** identified by MS, UV and NMR spectrometry. Frs 100–111 (2.3 g) were combined. Purification by TLC (silica gel, $CHCl_3$–Me_2CO–HCO_2H, 90 : 10 : 1) afforded 56 mg of penduletin (**6c**) identified by UV and NMR spectrometry and conversion of 24 mg of the flavone to 4′-acetoxy-5-hydroxy-3,6,7-trimethoxyflavone (12 mg), ^{1}H NMR (DMSO-d_6) δ 12.45 (*brs*, 5-OH), 8.13 (*d*, J = 8.5 Hz, H-3′ and H-5′), 7.83 (*d*, J = 8.5 Hz, H-2′ and H-6′), 6.96 (*s*, H-8) 3.93 (*s*, 3p, 7-OMe), 3.85 (*s*, 3p, 3-OMe), 3.74 (*s*, 3p, 6-OMe), 2.33 (*s*, 3p OAc), and 5,4′-diacetoxy-2,6,7-trimethoxyflavone (8 mg), ^{1}H NMR (DMSO-d_6) δ 8.11 (*d*, 2p, J = 9 Hz, H-3′ and H-5′), 7.37 (*s*, H-8), 7.37 (*d*, 2p, J = 9Hz, H-2′ and H-6′), 3.98 (*s*, 3p, 7-OMe) 3.76 (*s*, 3p, 3-OMe), 3.73 (*s*, 3p, 7-OMe), 2.39 and 2.32 (both *s* and 3p, –OMe). Frs 112–126 contained a mixture of components with similar R_f values and were not studied further.

Frs 127–136 were combined and recryst. from MeOH to give 20 mg of hispidulin (**7a**) identified by UV and NMR spectrometry. Purification of the mother liquor by TLC (silica gel, toluene–EtOAc–Me_2CO–HCO_2H, 60 : 35 : 5 : 1) gave a 2 : 1 mixture of **5** and **4c**. Frs 137–147 contained a mixture of components with similar R_f values and were not studied further. Frs 142–155 (2.5 g) were combined and recryst. from $CHCl_3$ to give cirsiliol (**7b**, 150 mg) identified by MS, UV and NMR spectrometry and conversion of 20 mg to 17 mg of 3′,4′-diacetoxy-5-hydroxy-3,6,7-trimethoxyflavone, ^{1}H NMR (DMSO-d_6) δ 12.41 (*brs*, 5-OH), 8.06 (*d*, J = 8.5 Hz, H-6′), 7.98 (*s*, H-2′), 7.52 (*d*, J = 8.5 Hz, H-5′), 3.92, 3.87, 3.74 (each *s* and 3p, –OMe, 2.34 (*s*, 6p, 2 –OAc). TLC (silica gel, toluene–EtOAc–Me_2CO–HCO_2H, 60 : 35 : 5 : 1) of the mother liquor afforded an additional 70 mg of **7b**. Frs 156–167 contained mixtures of compounds with similar R_f. Frs 168–186 (2 g) were combined. Recryst. from Me_2CO afforded 168 mg of pure ageratriol (**1a**).

Ageratriol (**1a**). Crystals. Found: mp 191–193°; $[\alpha]_D$ + 30° (*c* 0.005 g ml^{-1}, MeOH). Lit.[1]: mp 195°, $[\alpha]_D$ + 30.5 (*c* 2 MeOH). MS PCI *m/z* (rel. int.) 253 ([M + H$^+$] 8), 235 (50), 217 (100), 199 (89), 189 (58), 157 (37), 147 (38), 133 (44), 121 (49), 107 (12). ^{1}H NMR in Table 1; ^{13}C NMR in Table 2.

Acetylation of **1a** (22 mg) with Ac_2O-Py and work-up in the usual manner afforded the triacetate **1c** (16 mg) as a viscous liquid. ^{1}H NMR spectrum in Table 1; ^{13}C NMR in Table 2.

(1R*,5R*,7S*,9S*)-9-*Acetoxy*-1,5-*dihydroxy*-*germacra*-4(15),-10(14),11(13-*triene* (*ageratriol* 9-*acetate*) (**1b**). Viscous liquid, $[\alpha]_D$ −18° (*c* 0.0006 g ml^{-1}; $CHCl_3$). MS PCI *m/z* (rel. int.) 295 ([M + H$^+$] 8.7), 277 (23.5), 235 (53.4), 233 (27.3), 217 (100), 199 (25.3), 197 (68.0). ^{1}H NMR (500 MHz, $CDCl_3$) in Table 1; ^{13}C NMR in Table 2.

(1R*,5R*,7S*,9S*,10S*)-9-*Acetoxy*-1(10)-*epoxy*-5-*hydroxygermacra*-4(15),11(13)-*diene* (**4a**). Viscous liquid; $[\alpha]_D$ −46 (*c* 0.0041 g ml^{-1}; $CHCl_3$). MS PCI (rel. int.) 295 ([M + H$^-$] 18.9), 277 (100), 253 (32.8), 235 (66.1), 217 (42.8). IR (film), ν_{max}, cm^{-1}: 3600–3200, 3070, 2940, 2870, 1740, 1645, 1460, 1375, 1240, 1080, 1030, 995, 905, 855. ^{1}H NMR in Table 1; ^{13}C NMR in Table 2.

Acetylation of **4a** (20 mg) with Ac_2O–pyridine followed by the usual work-up furnished 13 mg of **4b**. ^{1}H NMR in Table 1; ^{13}C NMR in Table 2.

Mixture of (5R*,7S*,9S*)-5,9-*dihydroxy*-1-*oxogermacra*-4(15),10(14),11(13)-*triene and* (1R*,5R*,7S*,

9S*,10S*)-5,9-*dihydroxy*-1(10)-*epoxygermacra*-4(15), 11(13)-*diene* (**5** *and* **4c**). MS (PCI) *m/z* (rel. int.) 251 ([M + H^+ of **5**] 1), 233 (16), 215(8), 173(5), 121(S), 85(11, 83(23), 57(77), 43(100). ^1H NMR (500 MHz, $CDCl_3$) in Table 1; ^{13}C NMR of mixture in Table 2.

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