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MILLERENOLIDES, SESQUITERPENE LACTONES FROM *MILLERIA QUINQUEFLORA*

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Key Word Index—*Milleria quinqueflora*; Compositae; sesquiterpene lactones; millerenolides; melampolides; diterpenes; *ent*-pimarenes; *ent*-kaurenes, alicyclic diterpenes; galactoside.

Abstract—The aerial parts of *Milleria quinqueflora* afforded 17 new germacranolides (five melampolides and 12 millerenolides), two *ent*-pimarene and two *ent*-kaurene derivatives as well as two alicyclic diterpenes and a galactoside. The structures were elucidated by NMR spectroscopy. The chemotaxonomic situation is discussed.

INTRODUCTION

The monotypic genus *Milleria* (Compositae, tribe Heliantheae) was traditionally placed in the subtribe Milleriinae [1]. In a revision of the tribe [2] it was noted that recognition of relationships among the genera of this group is difficult. In the latest revision of the tribe Heliantheae [3] several genera of this subtribe were transferred to others and some other genera were placed in the new concept of Milleriinae. So far only the roots of *Milleria quinqueflora* have been studied chemically. The isolated acetylenes are not very characteristic [4]. Therefore, we have investigated the aerial parts of the plant collected in Costa Rica.

RESULTS AND DISCUSSION

The aerial parts of *Milleria quinqueflora* L. afforded germacrene D, squalene, caryophyllenepoxide, phytol, cycloartenol, 17 new sesquiterpene lactones **1**, **2**, **2a**, **3**–**11** and **13**–**17**, two *ent*-pimarenes (**18** and **19**), two *ent*-kaurenic acid derivatives (**20** and **21**), two geranyl nerol derivatives (**22** and **23**) and a galactoside of a glyceride (**24**).

The structures of compounds **3** and **4** followed from the ^{1}H NMR spectra (Table 1) which were close to those of acanthospermal A [5]. The absence of an ester group at C-9 caused the expected upfield shift of the H-9 signal and in the spectrum of **4** the isobutyrate signals were replaced by those of a methacrylate.

The ^{1}H NMR data of **5** were close to those of **4** but the presence of a 4,5-epoxide was indicated by the upfield shifts of the H-5 and H-6 signals which were assigned by spin decoupling. The configurations followed from the couplings and from comparison of the data with those of fluctuadin, the corresponding 14-oic methyl ester with a 9-acetoxy group [6].

The ^{1}H NMR spectra (Table 1) indicated that **6** and **7** were isomeric. In the spectra of **6** and **7** the chemical shifts of H-8 and H-9 clearly indicated the position of the ester groups. The spectrum of **6** was close to that of **4**, only the H-15 methyl signal was replaced by that of an acetoxy methylene group (in C_6D_6 a pair of doublets at δ4.52 and 4.49 as well as a singlet at 1.69). Thus compound **6** was the 15-acetoxy derivative of **4** and **7** was the isomeric 9-*O*-methacrylate.

The main compound was the lactone **11**. Its ^{1}H NMR spectrum (Table 1) was not similar to those of **3**–**7**. However, all signals could be assigned by spin decoupling though a few were overlapped multiplets. Acetylation gave the acetate **12**, its ^{1}H NMR spectrum showed that in **11** a free hydroxyl was at C-5. The corresponding proton showed an unusual chemical shift (δ2.99 *d*). NOE difference spectroscopy allowed the assignment of the stereochemistry. Thus clear NOEs were observed between H-5, H-15 (5%) and H-7 (7%), between H-7, H-1 (4%) and H-8 (8%), between H-6, H-3 (5%) and H-9 (2%), between H-8, H-7 (8%) and H-1 (5%) as well as between H-9, H-14 (15%) and H-6 (5%). Inspection of Dreiding models showed that these data required a conformation with C-14 above and C-15 below the plane. The configuration of the Δ^9-double bond followed from the NOE and the chemical shift of H-14. The ^{13}C NMR data agreed with the structure.

The ^{1}H NMR spectrum of compound **8** (Table 1) was in part similar to that of **11**. All data agreed with the presence of the corresponding precursor of **11**, the $\Delta^{4(15)}$ derivative. Thus a pair of narrowly split doublets at δ5.47 and 5.24 was present and the H-5 signal was shifted downfield. Spin decoupling allowed the assignment of all signals, only those of H-2 and H-3 being overlapped multiplets.

The molecular formulae of compounds **9** and **13** indicated that these lactones were isomers of **8** and **11**, respectively. Inspection of the ^{1}H NMR spectra (Table 1) indicated that the corresponding 9-*Z* isomers were present. Accordingly, the H-14 signals were shifted downfield and those of H-9 were more upfield. Some other differences indicated a changed conformation. NOE difference spectroscopy with **13** gave clear effects between H-7, H-8 (10%) and H-14 (4%), between H-9, H-1 (5%) and H-6 (8%), between H-15 and H-3 (3%) as well as between H-5, H-7 (5%) and H-15′ (6%). These results required a conformation with both, C-14 and C-15, below the plane. The ^{13}C NMR data also supported the structure (Experimental).

Table 1. ^{1}H NMR spectral data of compounds 1–17

	1	2	3	4	5	6(C_6D_6)	7	8
H-1	6.58 *dd*	6.72 *dd*	6.64 *dd*	6.65 *dd*	6.84 *dd*	5.58 *dd*	6.74 *dd*	2.57 *m*
H-2	2.79 *ddd*	3.01 *m*	2.65 m		2.71 *m*	1.98 *m*	3.04 *br ddd*	2.00 *m*
H-2′	2.51 *m*	2.61 *m*	2.39 *m*		2.67 *m*	1.80 *m*	2.68 *m*	
H-3	3.07 *br d*	3.01 *m*	2.44 *m*		2.40 *ddd*	2.07 *ddd*	2.74 *m*	2.55 *m*
H-3′	2.37 *ddd*	2.48 *ddd*	2.10 *m*		1.28 *ddd*	1.38 *ddd*	2.10 *m*	2.21 *br d*
H-5	3.96 *br d*	3.96 *br d*	4.90 *br d*	4.92 *br d*	2.63 *d*	4.49 *br d*	5.10 *br d*	4.19 *br d*
H-6	4.87 *br d*	4.83 *dd*	5.05 *dd*	5.08 *dd*	4.27 *t*	5.09 *t*	5.32 *t*	4.32 *dd*
H-7	2.81 *br s*	3.63 *ddd*	2.58 *m*		2.82 *br d*	2.26 *br d*	2.50 *br d*	3.54 *dddd*
H-8	5.39 *ddd*	—	6.38 *dd*	6.43 *dd*	6.47 *br d*	6.70 *dd*§	5.34 *br d*	6.22 *dd*
H-9	3.01 *dd* 2.51 *m*	5.84 *br s*	3.97 *br t*	3.91 *br t*	4.41 *br d*	4.06 *dd*§	5.18 *dd*	6.44 *d*
H-13	6.29 *d*	6.43 *d*	6.25 *dd*		6.33 *d*	6.20 *d*	6.37 *d*	6.43 *d*
H-13′	5.69 *d*	5.75 *d*	5.68 *d*	5.64 *d*	5.79 *d*	5.62 *d*	5.70 *d*	6.09 *d*
H-14	9.47 *d*	9.52 *s*	9.47 *d*	9.46 *d*	9.53 *d*	9.01 *d*	9.43 *d*	9.45 *d*
H-15	5.06 *br s*	5.11 *br s*	1.91 *d*	1.90 *d*	1.61 *s*	4.52 *d*	4.89 *d*	5.47 *d*
H-15′	4.97 *br s*	5.07 *br s*				4.49 *d*	4.82 *d*	5.24 *d*
OCOR	6.06 *br s*	6.12 *br s*	2.58 *qq*	6.10 *br s*	6.08 *br s*	6.12 *br s*	6.12 *br s*	6.10 *br s*
	5.58 *dq*	5.69 *br s*	1.17 *d*	5.63 *dq*	5.63 *dq*	5.24 *dq*	5.62 *dq*	5.67 *dq*
	1.88 *t*	1.93 *br s*	1.14 *d*	1.95 *t*	1.93 *t*	1.80 *t*	1.92 *t*	1.94 *t*
OH	2.70 *s*		2.65 *m*			1.69 *s* (OAc)	2.13 *s* (OAc)	

*OEt 3.39 *q*, 1.16 *t* (compound **10**: AA′ *q* 3.41).

†OMe 3.25 *s*.

‡Overlapped multiplets.

§In $CDCl_3$ H-8 6.43, H-9 4.15.

J (Hz): compounds **1** and **2**: 1,2 = 12; 1,2′ = 4; 2,2′ = 3,3′ = 13; 2,3 = 2′,3′ = 3.5; 2,3′ = 12; 5,6 = 9; 6,7 ~ 0.5; 7,8 = 2.5; 7,13 = 1.5; 8,9 = 5; 8,9′ = 8; 9,9′ = 13 (compound **2**: 6,7 = 1.5; 1,9 = 2,9 ~ 1); compounds **3**–**7**: 1,2 = 9; 1,2′ = 7; 2,3 = 5; 2′,3 = 3; 2,3′ = 12; 2′,3′ = 3; 3,3′ = 14; 5,6 = 6,7 = 9.5; 7,8 ~ 1; 7,13 = 3.5; 7,13′ = 3; 8,9 = 8; 9,14 = 1 (compounds **6** and **7**: 15,15′ = 12); compounds **8**, **11**, **12** and **14**: 3,15 ~ 2; 5,6 = 9; 6,7 = 7; 7,8 = 5.5; 7,13 = 3; 7,13′ = 2.5; 8,9 = 7 (compounds **11**, **12** and **14**: 15,15′ = 4); compounds **10**, **13**, **15** and **16**: 1,1′ = 13; 1,2 = 4; 1′,2′ = 12; 1′,2 = 5.5; 2,3 = 8; 2′,3′ = 10; 3,3′ = 15; 5,6 = 10; 6,7 = 7,8 = 3.5; 7,13 = 2.5; 7,13′ = 2; 8,9 = 6.5; 9,14 = 1; 15,15′ = 4 (compounds **10**, **15** and **16**: 1,2 = 1,2′ = 2.5); compound **17**: 1,2 = 11; 1,2′ = 8; 2,3 = 11; 2′,3′ ~ 2; 3,3′ = 13; 5,6 = 4; 6,7 = 7; 7,8 = 1.5; 7,13 = 3.3; 7,13′ = 3; 8,9 = 5.5; 15,15′ = 4; OMeacr: 3,4 = 3′,4 ~ 1; OiBu: 2,3 = 2,4 = 7; OAng: 3,4 = 7; 3,5 = 4,5 = 1.

The ^{1}H NMR spectrum of compound **14** (Table 1) was very close to that of **11**. The replacement of the ester group at C-8 by an angelate residue followed from the typical NMR signals.

The ^{1}H NMR spectrum of compound **15** (Table 1) was in part close to that of **13**. However, an additional lowfield broadened triplet at δ4.50 and the typical signal of an *O*-ethyl group required a further oxygen function. Spin decoupling and NOE difference spectroscopy indicated a 1β-ethoxy group. Thus irradiation of the ethoxy methylene gave NOEs with H-1 (4%) and H-9 (2%). Furthermore, a NOE between OH, H-5 (8%) and H-6 (4%) excluded a changed situation of the hydroxy and ethoxy groups. The ^{1}H NMR data of **16** were nearly identical with those of **15**, only the ethoxy signals were replaced by a methoxy singlet. Thus **16** was the 1β-methoxy and **15** the 1β-ethoxy derivative of **13**.

The ^{1}H NMR spectrum of compound **10** (Table 1) was close to that of **15**. However, the absence of the epoxide group clearly followed from the replacement of these signals by a pair of lowfield doublets. Therefore the spectrum of **10** also was close to that of **9**. Accordingly, **10** was the 1β-ethoxy derivative of **9**.

The ^{1}H NMR spectrum of compound **17** (Table 1) was different from all the others though the number of lowfield signals corresponded to that of **16** and related lactones. Spin decoupling allowed the assignment of all signals, only those of H-2, H-2′ and H-3 were multiplets. EIMS gave no molecular ion but CIMS showed *m/z* 361 in agreement with $C_{19}H_{20}O_7$. The compound was a methacrylate with two further double bonds, an aldehyde, a lactone carbonyl and an epoxide group and therefore a tetracyclic compound had to be assumed. This required an ether bridge, which could be placed only between C-1 and C-5 if the results of spin decoupling were inspected. The stereochemistry could be deduced by NOE difference spectroscopy. Clear effects were obtained between H-5 and H-15 as well as between H-7 and H-3 while no effect was observed between H-7 and H-1. Accordingly, a 1α-oxygen function could be excluded. Inspection of a Dreiding model showed that the observed couplings, which differed from those of **16**, agreed with the proposed structure.

The ^{1}H NMR spectrum of **1** (Table 1) showed that this aldehyde was the 1(10)*E*-isomer of the Δ^9-aldehyde **8**. The configuration of the double bond followed from the chemical shift of H-14. NOE difference spectroscopy established the stereochemistry and the conformation. Clear NOEs were observed between H-5, H-15′ (5%) and H-7 (4%), between H-8, H-7 (10%), H-9 (5%) and H-13′ (2%), between H-6 and H-2β (5%), between H-3β, H-1 (4%) and H-15 (3%), between OH, H-6 (3%) and H-5

(400 MHz, $CDCl_3$, TMS as internal standard)

9	10*	11	12	13	14	15*	16†	17
	4.46 *brt*	2.59 *m*	2.64 *br d*	2.90 *br dd*		4.50 *br t*	4.42 *br t*	5.30 *dd*
			2.55 *ddd*	1.82 *ddd*				
		1.77 *m*	1.80 *m*	1.70 *m*		1.84 *m*	1.84 *m*	2.35 *m*
‡	‡	1.41 *br t*	1.39 *m*	1.08 *m*	‡	1.16 *m*	1.17 *m*	1.25 *m*
		1.90 *m*	1.89 *m*	2.29 *m*		2.02 *dd*	2.01 *dd*	2.31 *m*
		1.52 *br t*	1.54 *br t*	1.60 *dd*		1.84 *m*	1.80 *dd*	1.78 *dd*
3.97 *br d*	3.94 *br d*	2.99 *br d*	4.28 *d*	2.96 *d*	3.01 *br d*	2.94 *d*	2.95 *d*	4.73 *d*
4.77 *dd*	4.80 *dd*	4.72 *dd*	4.90 *dd*	4.94 *dd*	4.70 *dd*	4.97 *dd*	4.94 *dd*	4.78 *dd*
3.27 *br s*	3.22 *br s*	4.12 *br s*	4.29 *br s*	3.88 *dddd*	4.10 *br s*	3.88 *dddd*	3.90 *dddd*	4.10 *dddd*
6.36 *dd*	6.42 *br d*	6.24 *br t*	6.17 *ddd*	6.47 *dd*	6.30 *dd*	6.50 *dd*	6.49 *dd*	6.20 *dd*
6.03 *br d*	6.37 *d*	6.49 *d*	6.50 *d*	6.07 *d*	6.50 *d*	6.39 *d*	6.38 *d*	6.56 *d*
6.46 *d*	6.46 *d*	6.37 *d*	6.40 *d*	6.42 *d*	6.40 *d*	6.44 *d*	6.45 *d*	6.40 *d*
5.85 *d*	5.85 *d*	5.96 *d*	5.94 *d*	5.89 *d*	5.99 *d*	5.87 *d*	5.89 *d*	5.75 *d*
9.74 *br s*	9.76 *s*	9.43 *br s*	9.44 *d*	9.80 *d*	9.46 *br s*	9.86 *br s*	9.86 *br s*	9.37 *s*
5.03 *d*	5.01 *d*	2.72 *d*	2.89 *d*	2.46 *d*	2.73 *d*	2.47 *d*	2.49 *d*	2.89 *d*
4.91 *d*	4.87 *d*	2.66 *d*	2.61 *d*	2.41 *d*	2.68 *d*	2.38 *d*	2.40 *d*	2.80 *d*
6.05 *br s*	6.08 *br s*	6.10 *br s*	6.12 *br s*	6.06 *br s*	6.19 *qq*	6.08 *br s*	6.10 *br s*	6.09 *br s*
5.61 *dq*	5.63 *dq*	5.65 *dq*	5.66 *dq*	5.61 *dq*	2.01 *dq*	5.63 *dq*	5.65 *dq*	5.64 *dq*
1.87 *t*	1.91 *t*	1.92 *br s*	1.93 *t*	1.90 *t*	1.88 *dq*	1.91 *t*	1.91 *t*	1.92 *t*

(8%) as well as between H-1 and H-14 (10%). These results indicated a conformation with both C-14 and C-15 below the plane.

The ^{1}H NMR spectrum of compound **2** (Table 1), which had two hydrogens less, was an 8,9-dehydro derivative of **1**. Thus spin decoupling showed that no proton was at C-8. As the broadened singlet at δ5.84 was coupled with H-1 and H-2′ the presence of an 8,9-double bond was necessary. The remaining signals were close to those in the spectrum of **1**.

The ^{1}H NMR spectral data of compound **2a** (Experimental) were close to those of **2**. The presence of the corresponding 4,5-epoxide followed from the pair of doublets at δ2.64 and 2.57 and the absence of the methylene protons. NOE difference spectroscopy indicated that this lactone was present in a conformation with C-14 and C-15 below the plane. The double bonds therefore were not in plane. Clear effects were obtained between H-7 and H-5 (6%), between H-6 and H-2β (4%), between H-14 and H-1 (15%), between OH, H-1 (4%) and H-6 (6%), between H-15 and H-3 (3%) as well as between H-15′ and H-5 (6%). Also the ^{13}C NMR data agreed with the structure.

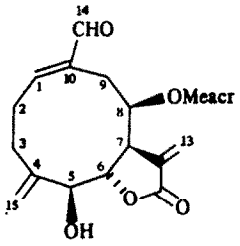
All the lactones are biogenetically related. Most likely **4** is the common precursor of all the compounds. Transformation to **1** could be achieved by reaction with singlet oxygen followed by reduction of the obtained hydroperoxide. Isomerization of the 1,10-double bond would lead to **8** or **9**. All the other lactones could be formed by common transformation. Perhaps compounds **10**, **15** and **16** could be artifacts though only methanol was used for the extraction. The 1,10-dihydro derivative of **1** has been named millerolide. The lactones are related to the repandins [7].

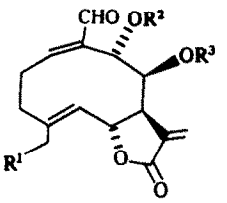
The structure of compound **18** followed from the ^{1}H NMR spectrum and that of the corresponding tetraacetate (Experimental). The spectrum of **18** was in part close to that of darutigenol [8]. However, the lowfield signals indicated an additional hydroxy group. Spin decoupling allowed the assignment of most signals and the configuration at C-2 and C-3 followed from the couplings. The tetraacetate **18a** showed NOEs between H-16 and H-14 (5%), between H-16′ and H-20 (3%) as well as between H-15 and H-17 (4%). Together with the couplings observed and the data of **19** (see below) the conformation and configuration of the quasi-axial side chain can be assigned.

The ^{1}H NMR spectrum of compound **19** (Experimental) showed that this diterpene was the corresponding 15-keto derivative. Accordingly, the signal of H-15 was missing and that of H-16 now was only split to a doublet by a hydroxy coupling. Also, the ^{13}C NMR data agreed with the proposed structure. NOE difference spectroscopy allowed the assignment of the complete stereochemistry. Clear NOEs were observed between H-20, H-19 (5%), H-2 (5%), H-11α (3%) and H-16 (2%), between H-19, H-20 (6%), H-18 (6%), H-2 (6%) and H-3 (5%), between H-18, H-3 (4%) and H-5 (5%), between H-17, H-14 (5%) and H-16 (2%), between H-9, H-5 (7%) and H-11 (5%), between H-16, H-14 (4%) and H-11α (4%) as well as between H-14, H-16 (2%), H-17 (6%) and H-7β (8%). The observed NOEs of H-16 indicated a preferred conformation of the side chain. The CD curve showed a clear positive Cotton effect. Application of the octant rule supported the presence of an *ent*-pimarene derivative.

The structures of compounds **20a** and **21a**, which were prepared from the natural occurring acids, followed from the ^{1}H NMR spectra (Experimental) which were close to that of the 12-acetoxy derivative where the configuration was determined by preparing the epimer [9]. As in similar cases the unsaturated ester group at C-12 (**20a**) caused a small downfield shift of H-12 if compared with the shift of **21a**.

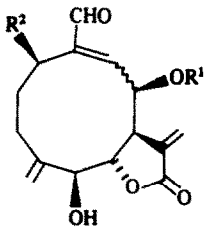
The structures of the last two diterpenes could be deduced also from the ^{1}H NMR spectral data. Spin decoupling allowed the assignment of all signals. The configuration of the Δ^6-double bond followed from the chemical shift of H-19 and that of the Δ^2-double bond was



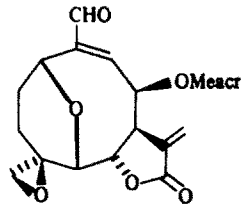


1	2	Δ^8
	2a	Δ^8,4β,15-epoxide

	3	4	5	6	7
R^1	H	H	H	OAc	OAc
R^2	H	H	H	H	Meacr
R^3	iBu	Meacr	Meacr 4α,5β epoxide	Meacr	H



	8	9	10	11*	12*†	13*	14*	15*	16*
R^1	Meacr	Meacr	Meacr	Meacr	Meacr	Meacr	Ang	Meacr	Meacr
R^2	H	H	OEt	H	H	H	H	OEt	OMe
Δ^9	*E*	*Z*	*Z*	*E*	*E*	*Z*	*E*	*Z*	*Z*



17

* 4β,15-epoxide † 5-OAc

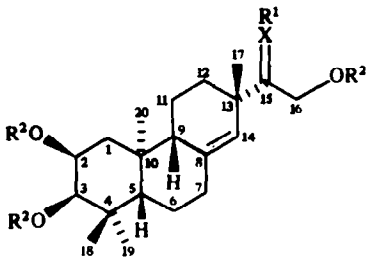
determined by the NOE between H-1 and H-4 (4%). The position of the keto group in **22** followed from the chemical shifts (H-11 and H-13) and from spin decoupling which showed that the broadened doublet at δ3.13 was coupled with two methyl groups. Thus, the aldehyde group must be placed at C-7 and not at C-17 or C-20. Obviously **23** was derived from **22** by allylic oxidation. The configuration of the Δ^{13}-double bond followed from the coupling. Also the mass spectra supported the proposed position of the keto group. In the spectrum of **22** after loss of water, elimination of the dimethyl allyl residue is visible followed by loss of CO. In the spectrum of **23** the base peak *m/z* 124 ($C_8H_{12}O$) must be the result of a McLafferty fragmentation. Loss of ethyl (*m/z* 95) indicated that the keto group was next to the secondary methyl. The ^{13}C NMR spectrum of **23** also agreed with the structure.

The last compound could be purified only as its tetraacetate **24a**. The presence of 1,2-dilinolenyl-3-*O*-β-D-galactopyranosyl-*sn*-glycerol followed from the ^{1}H NMR data which agreed with those in the literature [10].

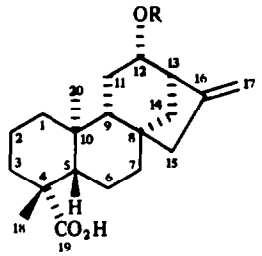
The overall picture of the chemistry of *Milleria* showed a clear relationship to that of *Siegesbeckia* by the nature of the sesquiterpene lactones [11] and also by the co-occurrence of *ent*-pimar-8(14)-enes [11–13] and *ent*-kaurenes [12]. This clearly favours the placement of the two genera in the same subtribe [3]. The subtribe Milleriinae in the latest fashion [3] contains genera which are closely related to those of the subtribe Melampodiinae where sesquiterpene lactones related to those of *Siegesbeckia* and *Milleria* are common [5, 14–17]. The previous placement of *Milleria* [2] cannot be supported by the chemistry. From an *Ichthyothere* species melampolides were reported [17]. Accordingly, its placement in the Milleriinae [3] is also very likely. It would be of interest to know more about the chemistry of the other genera which have been placed in the Milleriinae [3]. Unfortunately very little is known so far about the constituents of these genera.

EXPERIMENTAL

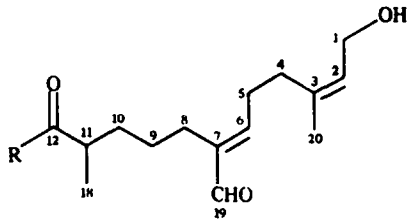
The air dried aerial parts (1 kg, collected in February 1985 in Tilaran, Costa Rica, voucher 108510, deposited in the



	18	18a	19
R	H, αOH	H, αOAc	=O
R^2	H	Ac	H



20 R = Ang
21 R = iVal
(**20a** and **21a** are the methylesters)



22 R = $Me_2C^{16,17}=^{15}CH^{14}CH_2^{13}$
23 R = $Me_2C(OH)CH=CH$ (*E*)

National Herbarium of Costa Rica) was extracted with MeOH–Et_2O–petrol, (1:1:1) and the extract obtained was defatted with MeOH and first separated by CC (silica gel). The less polar fractions (petrol, Et_2O–petrol, 1:10, and Et_2O–petrol, 1:3) gave 10 mg germacrene D, 300 mg squalene, 10 mg caryophyllen-1,10-epoxide, 50 mg phytol, 35 mg cycloartenol and a mixture which was partly separated by prep. TLC (silica gel PF 254, R_f values in Et_2O) affording 50 mg of a mixture of **20** and **21**, which were separated as their methyl esters (C_6H_6–petrol, 1:1, three developments), affording 2 mg pure **20a** and 2.5 mg pure **21a**. The polar CC fractions (Et_2O–MeOH, 10:1) were separated again by flash chromatography (silica gel, ϕ 30–60) into five fractions (F1: Et_2O–petrol, 1:3; F2: Et_2O–petrol, 1:1; F3: Et_2O–petrol, 3:1; F4: Et_2O and F5: Et_2O–MeOH, 9:1). HPLC of F1 (MeOH–H_2O, 7:3; column RP 8; *ca* 100 bar; flow rate *ca* 3 ml/min) gave 22 mg **11** (R_t 3.1 min), 8 mg **8** (R_t 4.4 min) and a mixture (R_t 5.9 min) which was separated by TLC (C_6H_6–CH_2Cl_2–Et_2O, 9:9:2, three developments) affording 0.8 mg **17** (R_f 0.90), 0.9 mg **9** (R_f 0.85), 2.4 mg **10** (R_f 0.70), 8.3 mg **8** (R_f 0.60), 8 mg **22** (R_f 0.50), 22 mg **11** (R_f 0.45) and 0.9 mg **14** (R_f 0.35). Fraction F2 gave by HPLC (MeOH–H_2O, 3:2) 4 mg **15** (R_t 5.7 min). Fraction F3 gave by prep. TLC (C_6H_6–CH_2Cl_2–Et_2O, 2:2:1, three developments) 2.6 mg **7** (R_f 0.47), 8 mg **2** (R_f 0.43), 1.4 mg **16** (R_f 0.30) and 3.5 mg **19** (R_f 0.20). TLC of F4 (C_6H_6–CH_2Cl_2–Et_2O, 1:1:1, three developments) gave 2.8 mg **1** (R_f 0.36), 30 mg **13** (R_f 0.34), 2.5 mg **2a** (R_f 0.28) and 7.5 mg **23** (R_f 0.20). TLC of F5 (Et_2O, three developments) gave 2 mg **3** (R_f 0.34), 2 mg **4** (R_f 0.32), 15.5 mg **6** (R_f 0.28), 13 mg **18** (R_f 0.25), 4.4 mg **5** (R_f 0.20) and crude **24** (R_f 0.10) which was purified as its tetraacetate. Known compounds were identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic material.

Miller-1(10)*Z*-*enolide* (**1**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 1765 (γ-lactone), 1720, 1640 (C=CCO_2R), 2720, 1685 (C=CCHO); MS *m/z* (rel. int.): 346.142 [M]$^+$ (0.3) (calc. for $C_{19}H_{22}O_6$: 346.142), 260 [M − RCO_2H]$^+$ (14), 242 [260 − H_2O]$^+$ (7), 69 [C_3H_5CO]$^+$ (100); $[\alpha]_D^{24°}$ = −255° ($CHCl_3$; *c* = 0.26).

Miller-1(10)*Z*,8*E*-*dienolide* (**2**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (OH), 1765 (γ-lactone), 1725 (C=CCO_2R), 2720, 1690 (C=CCHO); MS *m/z* (rel. int.): 344.126 [M]$^+$ (0.2) (calc. for $C_{19}H_{20}O_6$: 344.126), 258 [M − RCO_2H]$^+$ (3), 240 [258 − H_2O]$^+$ (1), 69 [C_3H_5CO]$^+$ (100); $[\alpha]_D^{24°}$ = −260° ($CHCl_2$; *c* = 0.43).

4β,15-*Epoxymiller*-1(10)*Z*,8*E*-*dienolide* (**2a**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 1765 (γ-lactone), 1720 (C=CCO_2R), 2720, 1690 (C=CCHO); MS *m/z* (rel. int.): 360.120 [M]$^+$ (0.8) (calc. for $C_{19}H_{20}O_7$: 360.121), 274 [M − RCO_2H]$^+$ (1), 245 [274 − CHO]$^+$ (2.5), 69 [C_3H_5CO]$^+$ (100); ^{1}H NMR ($CDCl_3$): δ6.92 (*dd*, H-1), 3.20 (*dddd*, H-2), 2.58 (*br d*, H-2'), 2.18 (*ddd*, H-3), 1.59 (*ddd*, H-3'), 2.80 (*d*, H-5), 5.05 (*dd*, H-6), 4.26 (*ddd*, H-7), 5.92 (*br s*, H-9), 6.43 (*d*, H-13), 5.80 (*d*, H-13'), 9.58 (*s*, H-14), 2.64 and 2.57 (*d*, H-15), 6.14 *br s*, 5.69 *dq* and 1.93 *br s* (OMeacr) *J*(Hz): 1,2 = 1,2' = 2,3' = 3,3' = 12, 1,2' = 4; 2,3 = 2',3 = 3.5; 1,9 = 2,9 1; 5,6 = 10; 6,7 = 1.5; 7,13 = 2; 7,13 = 1.5; 15,15' = 4.5; ^{13}C NMR ($CDCl_3$): δ157.4 *d*, 28.9 *t*, 28.8 *t*, 58.0 *s*, 79.2 *d*, 82.4 *d*, 40.5 *d*, 147.9 *s*, 113.3 *d*, 132.9 *s*, 137.2 *s*, 168.5 *s*, 127.0 *t*, 193.0 *s*, 54.1 *t*; OCOR: 166.1 *s*, 134.7 *s*, 128.4 *t*, 18.2 *q*.

Desacetylacanthospermal A (**3**). Colourless oil; MS *m/z* (rel. int.): 348.157 [M]$^+$ (0.2) (calc. for $C_{19}H_{24}O_6$: 348.157), 260 [M − RCO_2H]$^+$ (10), 242 [260 − H_2O]$^+$ (9.5), 71 [C_3H_7CO]$^+$ (100).

9α-*Hydroxy*-8β-*methacryloyloxy*-14-*oxo*-*acanthospermolide* (**4**). Colourless oil; MS *m/z* (rel. int.): 260.105 [M − RCO_2H]$^+$

(10) (calc. for $C_{15}H_{16}O_4$: 260.105), 242 [260 − H_2O]$^+$ (5), 69 [C_3H_5CO]$^+$ (100).

9α-Hydroxy-8β-methacryloyloxy-14-oxo-acanthospermolide-4α,5β-epoxide (**5**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 2720, 1690 (C=CCHO), 1775 (γ-lactone), 1720 (C=CCO_2R); MS *m/z* (rel. int.): 362.136 [M]$^+$ (0.1) (calc. for $C_{19}H_{22}O_7$: 362.137), 276 [M − RCO_2H]$^+$ (2), 69 [C_3H_5CO]$^+$ (100); $[\alpha]_D^{24°}$ = −53° ($CHCl_3$; *c* = 0.32).

15-Acetoxy-9α-hydroxy-8β-methacryloyloxy-14-oxo-acanthospermolide (**6**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 2720, 1685 (C=CCHO), 1740 (OAc), 1720 (C=CCO_2R); MS *m/z* (rel. int.): 404.147 [M]$^+$ (0.1) (calc. for $C_{21}H_{24}O_8$: 404.147), 319 [M − OCOR]$^+$ (1.3), 318 [M − RCO_2H]$^+$ (0.3), 258 [318 − HOAc]$^+$ (5), 240 [258 − H_2O]$^+$ (3.5), 212 [240 − CO]$^+$ (6), 69 [C_3H_5CO]$^+$ (100).

15-Acetoxy-9α-methacryloyloxy-8β-hydroxy-14-oxo-acanthospermolide (**7**). Colourless crystals, mp 188°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 2720, 1690 (C=CCHO), 1770 (γ-lactone), 1735 (OAc), 1720 (C=CCO_2R); MS *m/z* (rel. int.): 386.138 [M − H_2O]$^+$ (0.2) (calc. for $C_{21}H_{22}O_7$: 386.138), 258 [M − HOAc, RCO_2H]$^+$ (6), 69 [C_3H_5CO]$^+$ (100).

Miller-9E-enolide (**8**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3580 (OH), 2720, 1695 (C=CCHO), 1775 (γ-lactone), 1720 (C=CCO_2R); MS *m/z* (rel. int.): 346.141 [M]$^+$ (0.2) (calc. for $C_{19}H_{22}O_6$: 346.142), 260 [M − RCO_2H]$^+$ (3.3), 242 [260 − H_2O]$^+$ (3), 231 [260 − CHO]$^+$ (6.5), 213 [231 − H_2O]$^+$ (6), 69 [C_3H_5CO]$^+$ (100); $[\alpha]_D^{24°}$ = −5.0° ($CHCl_3$; *c* = 0.6).

Miller-9Z-enolide (**9**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 2720, 1690 (C=CCHO), 1765 (γ-lactone), 1705 (C=CCO_2R); MS *m/z* (rel. int.): 346.142 [M]$^+$ (0.2) (calc. for $C_{19}H_{22}O_6$: 346.142), 260 [M − RCO_2H]$^+$ (2), 69 [C_3H_5CO]$^+$ (100).

1β-Ethoxymiller-9Z-enolide (**10**). Colourless oil; MS *m/z* (rel. int.): 390.167 [M]$^+$ (0.1) (calc. for $C_{21}H_{26}O_7$: 390.168), 344 [M − HOEt]$^+$ (0.1), 258 [344 − RCO_2H]$^+$ (2.4), 229 [258 − CHO]$^+$ (2.5), 201 [229 − CO]$^+$ (2.5), 69 [C_3H_5CO]$^+$ (100); $[\alpha]_D^{24°}$ = −17° ($CHCl_3$; *c* = 0.24).

4β,15-Epoxymiller-9E-enolide (**11**). Colourless crystals, mp 196–198°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 2720, 1690 (C=CCHO), 1765 (γ-lactone), 1710 (C=CCO_2R); MS *m/z* (rel. int.): 362.136 [M]$^+$ (0.5) (calc. for $C_{19}H_{22}O_7$: 362.137), 334 [M − CO]$^+$ (0.1), 258 [M − H_2O, RCO_2H]$^+$ (0.5), 229 [258 − CHO]$^+$ (1.3), 69 [C_3H_5CO]$^+$ (100); ^{13}C NMR ($CDCl_3$): δ 24.8 *t*, 18.9 *t*, 22.0 *t*, 55.7 *s*, 79.2 *d*, 81.4 *d*, 42.7 *d*, 72.8 *d*, 149.9 *d*, 144.2 *s*, 134.3 *s*, 169.0 *s*, 125.3 *t*, 194.0 *d*, 51.0 *t*; OMeacr: 166.0 *s*, 135.0 *s*, 127.5 *t*, 18.1 *q*; $[\alpha]_D^{24°}$ = −131° ($CHCl_3$; *c* = 1.8).

Compound **11** (5 mg) was heated for 1 hr with Ac_2O at 70°. TLC afforded 2.4 mg **12**, colourless oil; MS *m/z* (rel. int.): 404.147 [M]$^+$ (4) (calc. for $C_{21}H_{24}O_8$: 404.147), 258 [M − RCO_2H, AcOH]$^+$ (2), 69 [C_3H_5CO]$^+$ (100).

4β,15-Epoxymiller-9Z-enolide (**13**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 2740, 1690 (C=CCHO), 1765 (γ-lactone), 1720 (C=CCO_2R); MS *m/z* (rel. int.): 362.137 [M]$^+$ (1) (calc. for $C_{19}H_{22}O_7$: 362.137), 334 [M − CO]$^+$ (0.6), 276 [M − RCO_2H]$^+$ (0.7), 258 [276 − H_2O]$^+$ (1), 230 [258 − CO]$^+$ (2), 229 [258 − CHO]$^+$ (2), 69 [C_3H_5CO]$^+$ (100); $[\alpha]_D$ = −27° ($CHCl_3$; *c* = 0.35); ^{13}C NMR ($CDCl_3$): δ 22.3 *t*, 17.0 *t*, 32.4 *t*, 55.2 *s*, 78.6 *d*, 80.0 *d*, 44.0 *d*, 72.3 *d*, 142.3 *d*, 133.5 *s*, 137.1 *s*, 169.2 *s*, 125.5 *t*, 190.5 *d*, 48.4 *t*; OMeacr: 166.3 *s*, 135.1 *s*, 126.9 *t*, 18.0 *q*.

4β,15-Epoxy-8-desacylmiller-9E-enolide-8-O-angelate (**14**). Colourless oil; MS *m/z* (rel. int.): 376.152 [M]$^+$ (1) (calc. for $C_{20}H_{24}O_7$: 376.152), 277 [M − OCOR]$^+$ (2.3), 83 [C_4H_7CO]$^+$ (100), 55 [83 − CO]$^+$ (74).

1β-Ethoxy-4β,15-epoxymiller-9Z-enolide (**15**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590 (OH), 2740, 1690 (C=CCHO), 1765 (γ-lactone), 1720 (C=CCO_2R); MS *m/z* (rel. int.): 406.162 [M]$^+$ (6) (calc. for $C_{21}H_{26}O_8$: 406.163), 320 [M − RCO_2H]$^+$ (2), 274 [320 − EtOH]$^+$ (3.5), 245 [274 − CHO]$^+$ (3), 69 [C_3H_5CO]$^+$ (100).

1β-Methoxy-4β,15-epoxymiller-9Z-enolide (**16**). Colourless oil; MS *m/z* (rel. int.): 392.147 [M]$^+$ (2) (calc. for $C_{20}H_{24}O_8$: 392.147), 306 [M − RCO_2H]$^+$ (1), 69 [C_3H_5CO]$^+$ (100).

4β,15-Epoxy-1β,5β-oxidomiller-9E-enolide (**17**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone), 1720 (C=CCO_2R), 1700 (C=CCHO); MS *m/z* (rel. int.): 69 [C_3H_5CO]$^+$ (100); CIMS *m/z* (rel. int.): 361 [M + 1]$^+$ (23) ($C_{19}H_{20}O_7$ + 1), 330 [361 − CH_2OH]$^+$ (40), 312 [330 − H_2O]$^+$ (100).

2β,3β,15,16-Tetrahydroxy-ent-pimar-8(14)-en (**18**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH); MS *m/z* (rel. int.): 277.217 [M − CH(OH)CH_2OH]$^+$ (88) (calc. for $C_{18}H_{29}O_2$: 277.217), 259 [277 − H_2O]$^+$ (81), 241 [259 − H_2O]$^+$ (29), 109 [C_8H_{13}]$^+$ (100); CIMS *m/z* (rel. int.): 339 [M + 1]$^+$ (6), 321 [339 − H_2O]$^+$ (100), 303 [321 − H_2O]$^+$ (22), 285 [303 − H_2O]$^+$ (10); ^{1}H NMR ($CDCl_3$): δ 1.64 (*dd*, H-1) 1.52 (*m*, H-1'), 3.98 (*ddd*, H-2), 3.45 (*d*, H-3), 1.44 (*dd*, H-5), 1.53 (*m*, H-6), 1.30 (*dddd*, H-6'), 2.27 (*ddd*, H-7), 2.06 (*br ddd*, H-7'), 1.83 (*br t*, H-9), 1.53 (*m*, H-11), 1.91 (*br dt*, H-12), 1.03 (*m*, H-12'), 5.12 (*br s*, H-14), 3.57 (*t*, H-15), 3.74 (*d*, H-16), 1.03 (*s*, *H*-17), 0.89 (*s*, H-18, H-19), 0.82 (*s*, H-20), *J* (HZ): 1,1' = 1',2 = 12; 1,2 = 4; 2,3 = 5,6 = 2.5; 5,6' = 6,6' = 6',7 = 7,7' = 12; 6,7 = 2; 9,11 = 8; 11,12 = 4; 12,12' = 13; 15,16 = 9; $[\alpha]_D^{24°}$ = −28° ($CHCl_3$; *c* = 0.86).

Acetylation (Ac_2O, 2 hr, 70°) gave **18a**; colourless oil; MS *m/z* (rel. int.): 506.288 [M]$^+$ (0.2) (calc. for $C_{28}H_{42}O_8$: 506.288), 446 [M − HOAc]$^+$ (1.3), 386 [446 − HOAc]$^+$ (1.2), 361 [M − CH(OAc)CH_2OAc]$^+$ (100), 301 [361 − HOAc]$^+$ (12), 241 [301 − HOAc]$^+$ (82); ^{1}H NMR ($CDCl_3$): δ 5.20 (*ddd*, H-2), 5.00 (*d*, H-3), 5.17 (*br s*, H-14), 5.13 (*dd*, H-15), 4.36 (*dd*, *J* = 2.5, 9 Hz, H-16) and 4.07 (*dd*, *J* = 9, 12 Hz, H-16), 1.03 (*s*, H-17), 0.96, 0.94, 0.88 (*s*, H-18, H-19, H-20), 2.11, 2.08, 2.02, 1.97 (*s*, OAc).

2β,3β,16-Trihydroxy-ent-pimar-8(14)-en-15-one (**19**). Colourless oil; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 3420 (OH), 1700 (C=O); MS *m/z* (rel. int.): 277.217 [M − $COCH_2OH$]$^+$ (100) (calc. for $C_{18}H_{29}O_2$: 277.217), 259 (66), 241 (35), 109 (88); CIMS *m/z* (rel. int.): 337 [M + 1]$^+$ (78), 319 [337 − H_2O]$^+$ (100); ^{1}H NMR ($CDCl_3$) as for **18** except 5.40 (*br s*, H-14), 4.36 (*d*, H-16), 1.13 (*s*, H-17), 1.04 (*s*, H-18), 0.89 (*s*, H-19), 0.71 (*s*, H-20), 3.18 (*t*, OH, *J* = 3 Hz); ^{13}C NMR ($CDCl_3$): δ 39.8 *t*, 66.5 *d*, 78.8 *d*, 39.3 *s*, 50.6 *d*, 21.6 *t*, 35.5 *t*, 142.1 *s*, 47.1 *d*, 38.3 *s*, 21.6 *t*, 32.5 *t*, 46.8 *s*, 123.7 *d*, 214.5 *s*, 65.8 *t*, 28.6 *q*, 27.3 *q*, 22.0 *q*, 15.3 *q*; CD (MeCN): $\Delta\varepsilon_{294}$ + 0.25.

Methyl-12α-angeloyloxy-ent-kaur-16-en-19-oate (**20a**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725 (CO_2R), 1710, 1650 (C=CCO_2R); MS *m/z* (rel. int.): 414.277 [M]$^+$ (6.5) (calc. for $C_{26}H_{38}O_4$: 414.277), 314 [M − RCO_2H]$^+$ (90), 255 [314 − CO_2Me]$^+$ (7), 83 [C_4H_7CO]$^+$ (100); ^{1}H NMR ($CDCl_3$): δ 1.23 (*d*, H-9), 1.98 (*ddd*, H-11), 1.70 (*d*, H-11'), 4.86 (*t*, H-12), 2.80 (*br t*, H-13), 2.26 (*d*, H-14), 1.09 (*dd*, H-14'), 2.14 (*br s*, H-15), 4.98, 4.85 (*br s*, H-17), 1.19 (*s*, H-18), 0.90 (*s*, H-20), OAng: 6.03 *qq*, 2.00 *dq*, 1.87 *dq*; OMe: 3.65 *s*; *J* (Hz): 9,11 = 9; 11,11' = 14; 11,12 = 12,13 = 4; 13,14' = 4; 14,14' = 12; $[\alpha]_D^{24°}$ = −13° ($CHCl_3$; *c* = 0.21).

Methyl-12α-isovaleroyloxy-ent-kaur-16-en-19-oate (**21a**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730 (CO_2R); MS *m/z* (rel. int.): 416.292 [M]$^+$ (5) (calc. for $C_{26}H_{40}O_4$: 416.292), 314 [M − RCO_2H]$^+$ (100), 299 [314 − Me]$^+$ (44), 109 (56), 85 [C_4H_9CO]$^+$ (10); ^{1}H NMR ($CDCl_3$) as **20** except 4.78 (*t*, H-12), 2.75 (*br t*, H-13), 2.21 (*d*, H-14), OiVal: 2.14 (*m*), 0.96 (*d*, *J* = 7 Hz).

6E-12,19-Dioxo-10,11-dihydrogeranyl nerol (**22**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 2750, 1690 (C=CCHO), 1710 (C=O); MS *m/z* (rel. int.): 320.235 [M]$^+$ (2) (calc. for $C_{20}H_{32}O_3$: 320.235), 302 [M − H_2O]$^+$ (18), 233 [302 − Me_2C=$CHCH_2$]$^+$ (33), 205 [233 − CO]$^+$ (20), 95 (94), 93 (100), 81 (93), 69 (90); ^{1}H NMR ($CDCl_3$): δ 4.13 (*br d*, H-1), 5.51 (*br t*, H-2), 2.22 (*br t*, H-4), 2.44 (*dt*, H-5), 6.44 (*t*, H-6), 2.27 (*t*, H-8), 1.60 and 1.35 (*m*,

H-9, H-10), 2.57 (*tq*, H-11), 3.13 (*br d*, H-13), 5.27 (*tqq*, H-14), 1.78 (*q*, H-16), 1.62 (*br s*, H-17), 1.05 (*d*, H-18), 9.35 (*s*, H-19), 1.74 (*br s*, H-20), *J* (Hz): 1,2 = 4,5 = 5,6 = 8,9 = 10,11 = 11,18 = 13,14 = 7; 13,16 = 14,16 = 14,17 = 1.

6E, 13E-15-*Hydroxy*-12,19-*dioxo*-13,14-*dehydro*-10,11,14,15-*tetrahydrogeranyl nerol* (**23**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 2700, 1690 (C=CCHO), 1690, 1625 (C=CCO); MS *m/z* (rel. int.): 318.219 $[M-H_2O]^+$ (37) (calc. for $C_{20}H_{30}O_3$: 318.219), 303 $[M-Me]^+$ (2), 300 $[M-H_2O]^+$ (11), 275 $[303-CO]^+$ (75), 124 $[C_8H_{12}O$, McLafferty$]^+$ (100), 95 $[124-Et]^+$ (85); $[\alpha]_D^{24^\circ} = +1^\circ$ ($CDCl_3$; $c = 0.2$); ^{1}H NMR ($CDCl_3$): δ4.12 (*br d*, H-1), 5.49 (*br t*, H-2), 2.25 (*br t*, H-4), 2.44 (*dt*, H-5), 6.44 (*t*, H-6), 2.23 (*t*, H-8), 1.67, 1.35 (*m*, H-9, H-10), 2.74 (*tq*, H-11), 6.38 (*d*, H-13), 6.90 (*d*, H-14), 1.38 (*s*, H-16, H-17), 1.09 (*d*, H-18), 9.34 (*s*, H-19), 1.78 (*br s*, H-20), *J* (Hz): 1,2 = 4,5 = 5,6 = 8,9 = 10,11 = 11,18 = 7; 13,14 = 16; ^{13}C NMR ($CDCl_3$): δ58.8 *t*, 125.5 *d*, 143.6 *s*, 33.0 *t*, 26.5 *t*, 152.8 *d*, 138.2 *s*, 27.7 *t*, 24.0 *t*, 30.9 *t*, 44.4 *d*, 204.3 *s*, 124.2 *d*, 154.1 *d*, 70.9 *s*, 29.5 *q* (2 ×), 16.7 *q*, 195.0 *s*, 23.4 *q*.

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