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MELAMPOLIDES FROM *MAGNOLIA GRANDIFLORA*

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Key Word Index—*Magnolia grandiflora*, Magnoliaceae, parthenolide, melampolides, soulangianolide A, NMR

Abstract—Two isomeric melampolides, melampomagnolide A and melampomagnolide B, were isolated from the newly formed leaves of *Magnolia grandiflora* Their stereochemical structures were established by spectroscopic means, and by chemical correlation with soulangianolide A and parthenolide, respectively

INTRODUCTION

In a continuation [1] of our study of the C-14 partially oxidized melampolides of family Magnoliaceae, examination of the newly formed leaves of *Magnolia grandiflora* L yielded two novel compounds melampomagnolide A (**1**) and melampomagnolide B (**2**) This paper describes the isolation, structure elucidation and correlation of **1** and **2** with soulangianolide A (**3**) and parthenolide (**4**), respectively

RESULTS AND DISCUSSION

An ethanolic extract of the newly formed leaves of *M grandiflora* yielded the hitherto unreported melampolides melampomagnolide A (**1**) and the more polar melampomagnolide B (**2**), upon solvent partitioning then repeated chromatography Melampomagnolide A (**1**), $C_{15}H_{20}O_4$, mp 177–178°, showed IR absorption bands and ^1H NMR signals similar to those reported [1] for soulangianolide A (**3**), except for the absence of the characteristic C-1 olefinic proton The presence of a C-1(10) epoxide group was suggested by the ^{13}C NMR signals at δ62 6 (*d*) and 63 3 (*s*) Also, unlike soulangianolide A (**3**) [1], the hydroxymethyl group appeared in the ^1H NMR spectrum as a pair of double doublets (J = 6 0 and 12 0 Hz) centred at δ3 50 and 3 95 This pattern was attributed to geminal coupling with additional coupling with the hydroxyl proton, as it was sharpened up to a pair of doublets (J = 12 0 Hz) upon deuterium exchange

The stereochemical structure of melampomagnolide A (**1**) was confirmed by monoepoxidation of soulangianolide A (**3**) using *m*-chloroperbenzoic acid, the product was indistinguishable from melampomagnolide A (**1**) Since epoxidation would be expected to proceed peripherally [2], the stereochemistry at both C-1 and C-10 should be *R*

Melampomagnolide B (**2**), $C_{15}H_{22}O_4$, mp 174–175°, could only be separated from melampomagnolide A (**1**) by flash chromatography [3] Its ^1H NMR, ^{13}C NMR signals (Table 1), and IR absorption bands were similar to those reported for parthenolide (**4**), except for the absence of the C-14 methyl group, and the presence instead, of a hydroxymethyl group (see Experimental) In addition, the endocyclic proton (H-1) appeared in the ^1H NMR spectrum as a broad triplet at δ5 75 (J = 7 0 Hz) Its deshielded position relative to that of parthenolide (**4**) suggested a *cis* relationship with the hydroxymethyl group [1]

The structure of melampomagnolide B (**2**) was further confirmed by acetylation to yield the acetate **5** and manganese dioxide oxidation to the α,β-unsaturated aldehyde **6** with ^1H NMR and ^{13}C NMR signals (Table 1) in agreement with their proposed structures The stereochemical structure of **2** was unambiguously established by the regio- and stereo-specific allylic oxidation [4] of parthenolide (**4**) with selenium dioxide and *t*-butyl hydroperoxide Melampomagnolide B (**2**) was the major product of this reaction (79 %) with only a trace isolated of the aldehyde **6**

EXPERIMENTAL

Mps uncorr, IR 7–9 % soln in $CHCl_3$ unless otherwise specified, ^1H NMR 60 or 90 MHz, $CDCl_3$, TMS as int standard, ^{13}C NMR 15 03 MHz, $CDCl_3$, TMS as int standard The plant material was collected in July 1980 on the campus of The University of Mississippi, University, Mississippi, U S A, and was identified by Professor Thomas Bullen, Biology Department of the same university Parthenolide (**4**) and soulangianolide A (**3**) used in this investigation were isolated as previously reported [5, 1, respectively]

Isolation of melampomagnolides A (**1**) *and B* (**2**) The dried and powdered newly formed tender leaves (1 5 kg) of *M grandiflora* were extracted by cold percolation with 95 % EtOH The extract (102 g) was partitioned between H_2O and $CHCl_3$, and the $CHCl_3$ solubles were further partitioned between *n*-hexane and 10 % aq MeOH Chromatography of the methanolic fraction (29 g) on silica gel using $CHCl_3$ as solvent gave a crystalline fraction (176 mg) that was flash chromatographed on silica gel using MeOH–C_6H_6 (1 9) (R_f values 0 20 and 0 27 on TLC) as solvent to give the following two compounds in the order of their elution

Melampomagnolide A (**1**), crystallized from Et_2O to give fine needles (49 mg), mp 177–178°, $[\alpha]_D$ −19° ($CHCl_3$, *c* 0 12), IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3620 and 3490 (OH), 1758 (CO) and 1662 and 1670 (C=C), ^1H NMR ($CDCl_3$) δ1 85 (3H, *s*, Me-4), 2 52 (1H, *s*, exch OH), 3 50 and 3 95 (2H, each *dd*, J = 6 0 and 12 0 Hz,

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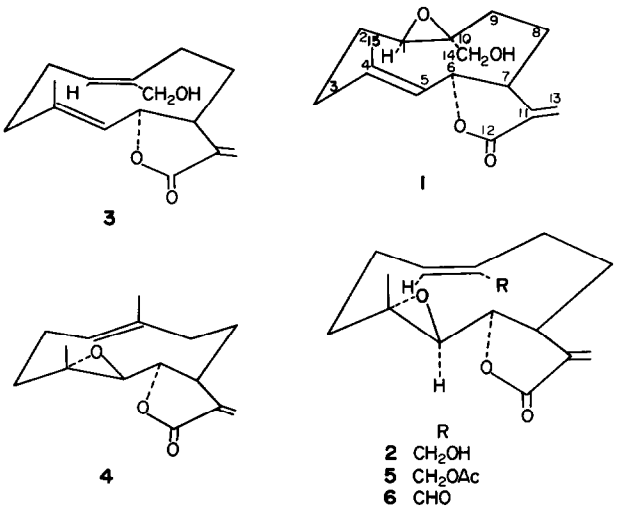

Table 1 ^{13}C NMR data for compounds 1 and 2 and their derivatives (15 03 MHz, $CDCl_3$, TMS as int standard)

C	1	2	5	6	
1	62 6 (*d*)	126 8 (*d*)	130 6 (*d*)	153 5 (*d*)	
2	27 3 (*t*)*	24 2 (*t*)*	25 7 (*t*)*	22 5 (*t*)*	
3	24 2 (*t*)*	36 9 (*t*)*	36 6 (*t*)*	36 1 (*t*)*	
4	142 4 (*s*)	60 3 (*s*)	59 9 (*s*)	59 5 (*s*)	
5	124 4 (*d*)	63 3 (*d*)	63 3 (*d*)	63 1 (*d*)	
6	79 5 (*d*)	81 4 (*d*)	81 1 (*d*)	81 3 (*d*)	
7	46 4 (*d*)	42 8 (*d*)	42 6 (*d*)	42 3 (*d*)	
8	27 3 (*t*)*	25 7 (*t*)†	24 5 (*t*)†	25 0 (*t*)†	double
9	34 6 (*t*)	23 7 (*t*)†	23 8 (*t*)†	25 0 (*t*)†	intensity
10	63 3 (*s*)	139 8 (*s*)‡	130 0 (*s*)	144 0 (*s*)	
11	139 9 (*s*)	139 0 (*s*)‡	139 0 (*s*)	138 4 (*s*)	
12	170 1 (*s*)	169 8 (*s*)	169 4 (*s*)‡	169 3 (*s*)	
13	119 1 (*t*)	120 2 (*t*)	120 0 (*t*)	120 6 (*t*)	
14	64 8 (*t*)	65 4 (*t*)	66 8 (*t*)	195 0 (*d*)	
15	17 4 (*q*)	18 0 (*q*)	17 9 (*q*)	17 9 (*q*)	
Acetate C=O	—	—	170 6 (*s*)‡	—	
Acetate Me	—	—	20 9 (*q*)	—	

Assignments are based on comparison with reported chemical shift values for related compounds See refs [1, 6, 7]

*, †, ‡ Assignments bearing the same superscript in the same column may be interchangeable

CH_2OH), 4 60 (1H, *t*, *J* = 10 0 Hz, H-6), 5 25 (1H, *d*, *J* = 10 0 Hz, H-5), 5 45 (1H, *d*, *J* = 3 0 Hz, H-13) and 6 17 (1H, *d*, *J* = 3 0 Hz, H-13), ^{13}C NMR ($CDCl_3$) Table 1, MS *m/z* 264 $[M]^+$ (< 1%) (Found C, 68 25, H, 7 77 $C_{15}H_{20}O_4$ (264) requires C, 68 16, H, 7 63%)

Melampomagnolide B (2), crystallized from Et_2O to give prisms (39 mg), mp 174–175°, $[\alpha]_D$ −46° ($CHCl_3$, *c* 0 18), IR ν_{max}^{KBr} cm^{-1} 3475 (OH), 1748 (CO) and 1671 (C=C), ^1H NMR ($CDCl_3$): δ 1 50 (3H, *s*, Me-4), 2 80 (1H, *d*, *J* = 9 5 Hz, H-5), 3 84 (1H, *t*, *J* = 9 5 Hz, H-6), 4 12 (2H, *s*, CH_2OH), 5 62 (1H, *d*, *J* = 3 0 Hz, H-13), 5 70 (1H, *t*, *J* = 9 0, H-1) and 6 28 (1H, *d*, *J* = 3 0 Hz, H-13), ^{13}C NMR ($CDCl_3$) Table 1, MS *m/z* 264 $[M]^+$ (1%). (Found C, 69 35, H, 7 72 $C_{15}H_{20}O_4$ (264) requires C, 68 16, H, 7 63%)

Both melampomagnolide A (1) and melampomagnolide B (2) were found only in newly formed tender leaves, although they were not detected in all collections made For other constituents isolated and previously reported see ref [6]

m-Chloroperbenzoic acid oxidation of soulangianolide A (3) *to melampomagnolide A* (1) Compound 3 (100 mg) was stirred in $CHCl_3$ soln for 4 hr with 79 mg of *m*-chloroperbenzoic acid (peroxy content 80%) The mixture was worked up in the usual manner [5] to give 93 mg of 1 as fine needles from Et_2O, identical with the natural material (mp, mmp, IR and ^1H NMR)

Oxidation of melampomagnolide B (2) *to the aldehyde* (6) Compound 2 (50 mg) was stirred in CH_2Cl_2 soln with 500 mg of MnO_2 overnight Filtration and evaporation of the filtrate provided the aldehyde 6 as a colourless oil homogeneous on TLC (R_f 0 75 on silica gel with EtOH–$CHCl_3$, 1 19), $[\alpha]_D$ −73° ($CHCl_3$, *c* 0 41); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1678 (CHO) and no OH bands,

^{1}H NMR ($CDCl_3$) δ1 57 (3H, *s*, Me-4), 2 75 (1H, *d*, *J* = 9 5 Hz, H-5), 3 81 (1H, *t*, *J* = 9 5, C-6), 5 55 (1H, *d*, *J* = 3 0 Hz, H-13), 6 20 (1H, *d*, *J* = 3 0 Hz, H-13), 6 70 (1H, *t*, *J* = 9 0 Hz, H-1) and 9 52 (1H, *s*, CHO), ^{13}C NMR ($CDCl_3$) Table 1, MS *m/z* 262 $[M]^+$ (< 1%) (Found C, 68 57, H, 7 02 $C_{15}H_{18}O_4$ (262) requires C, 68 68, H, 6 92)

Acetylation of melampomagnolide B (**2**) *to* **5** Compound **2** (60 mg) was stirred with 2 ml C_5H_5N–Ac_2O (1 1) for 24 hr Usual work-up provided **5** (69 mg) as colourless prisms from isopropyl ether, mp 143–144°, $[\alpha]_D$ −27° ($CHCl_3$, *c* 0 12), IR $\nu_{max}^{CHCl_3}$ cm^{-1} same pattern as for **2** with a band at 1727 (AcO), ^{1}H NMR ($CDCl_3$) same pattern as for **2** with a signal at δ2 05 (3H, *s*, AcO) and an AB system centred at δ4 52 (2H, *dd*, *J* = 12 5 Hz, –CH_2OAc), ^{13}C NMR ($CDCl_3$) Table 1, MS *m/z* 306 $[M]^+$ (< 1%) (Found C, 66 69, H, 7 27 $C_{17}H_{22}O_5$ (306) requires C, 66 65, H, 7 24%)

Oxidation of parthenolide (**4**) *to melampomagnolide B* (**2**) Compound **4** (248 mg), *tert*-BuOOH (0 50 ml of 70% soln in H_2O), SeO_2 (56 mg) were stirred in 10 ml of CH_2Cl_2 for 8 hr Flash chromatography [3] of the product on silica gel using EtOH–$CHCl_3$ (1 19) yielded 206 mg of **2** identical with the natural product (mp, mmp, IR and ^{1}H NMR), 7 mg of a product identical with **6** and 17 mg of unreacted **4**

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ESSENTIAL OILS OF SOME AMAZONIAN *MIKANIA* SPECIES

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Key Word Index—*Mikania amara*, *M congesta*, *M banisteriae*, Compositae, essential oils, aliphatic alcohols, aldehydes and acids, monoterpenes, sesquiterpenes

Abstract—Terpenoid constituents were identified in the essential oils of *Mikania banisteriae* and *M congesta* *M amara* contains aliphatic alcohols, aldehydes and acids besides *p*-cymene and thymol

INTRODUCTION

Mikania banisteriae DC (called salsa branca) and *M congesta* DC grow wild in Peixe-Boi and Bujaru, State of Pará, while *M amara* Willd, known as 'cipó catinga', is distributed throughout Brazil and is esteemed for a number of medicinal properties, including use against fever, whooping cough and rheumatism [1] Flavonoids [2, 3], sesquiterpenoid lactones [4, 5], kaurenoid diterpenes [6] and triterpenoids [7, 8] have been reported from several species of *Mikania* Mono- and sesquiterpenes were identified in the essential oil of *M micrantha* [9] As part of an ongoing study of the essential oils of Amazonian plants, we have analysed the volatile components of *M amara*, *M banisteriae* and *M congesta* by GC/MS

RESULTS AND DISCUSSION

The essential oil of *M amara* exhibited a chemical composition quite different from that of *M banisteriae* and *M congesta* In these two latter species only mono- and sesquiterpenoids were found The monoterpene α-pinene (43 3%) is the major component in the oil of *M banisteriae* while limonene, β-cubebene, β-caryophyllene, germacrene B and an unidentified oxygenated sesquiterpene comprise 70% of the oil of *M congesta* The essential oil from *M amara* is dominated by the presence of dodecanal, 1-dodecanol and tetradecanal, in addition to a large number of other aliphatic alcohols, aldehydes and acids

Identification of most of the components was accomplished by comparison of both the mass spectrum and