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NEW LABDANE DERIVATIVES FROM *MADIA SATIVA**

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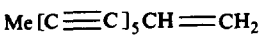
Key Word Index—*Madia sativa*; Compositae; diterpenes; labdane derivatives; *p*-hydroxyacetophenone derivatives.

Abstract—The aerial parts of *Madia sativa* afforded, in addition to known compounds, two labdane derivatives whose structures were elucidated by spectroscopic methods. The absolute configuration was determined by chemical transformations. From the roots a new tremetone derivative was isolated. The constituents indicated close relationships of *Madia* to *Hemizonia*.

INTRODUCTION

The genus *Madia* (tribe Heliantheae) is placed in the subtribe Madiinae[1]. So far little is known about the chemistry of the 18 species of this genus, which are distributed in North and South America. As in the other members of this subtribe, the presence of the widespread pentayne **1** has been reported[2]. We have now investigated *M. sativa* Mol., which contained in addition to known compounds, two new labdane derivatives and a new tremetone derivative.



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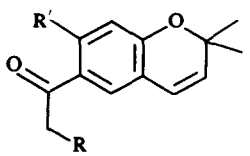
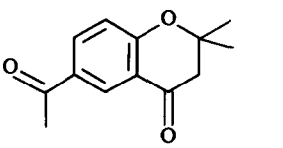
RESULTS AND DISCUSSION

The roots of *M. sativa* afforded lupeyl acetate, stigmasterol, **1**, the chromene derivatives **2–6**, the *p*-hydroxyacetophenone derivative **7**, the thymol epoxides **9–11** and a new tremetone derivative, the hydroxyketone **8**. The structure of **8** followed from the ^{1}H NMR spectral data, which were close to those of the known desoxy compound[3]. As expected, the base peak in the mass spectrum was at [M−



	2	3	4	5
R	H	H	OH	OH
R′	H	OH	OH	OMe



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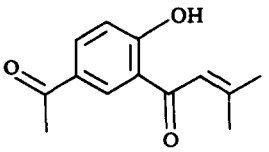

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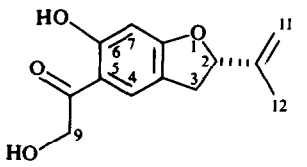

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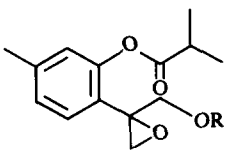
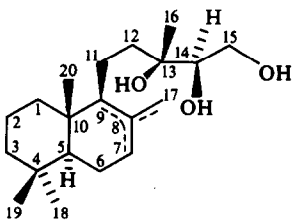


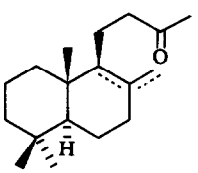
9 R = *i*-Val
10 R = Mebu
11 R = *i*-Bu

*Part 394 in the series "Naturally Occurring Terpene Derivatives". For part 393 see Bohlmann, F., Zdero, C., Robinson, H. and King, R. M. (1982) *Phytochemistry* **21**, 685.

·CH_2OH]$^+$. The aerial parts gave phytol, **1** and a large amount of a mixture of three labdanes. Careful ^{1}H NMR studies and chemical transformation led to the structures **12–14**. **14** had been isolated before from *Hemizonia lutescens* [4]. The structures of **12** and **13** followed from the ^{1}H NMR spectral data (Table 1). The stereochemistry and the absolute configurations could only be established by chemical transformations and degradation to the known hemiacetal **25** [5]. Separation of **12–14** was extremely difficult. The ^{1}H NMR data of **12–14** showed that the triols

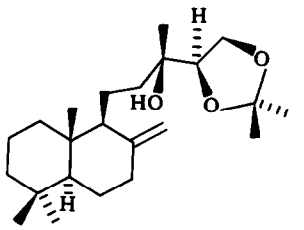


12 Δ 7,8
13 Δ 8,9
14 Δ 8,17



15 Δ 8,17
16 Δ 8,9

differed only in the position of the double bond. In the spectrum of **14** the olefinic methyl signal seen in the spectra of **12** and **13** was replaced by broadened singlets at δ 4.83 and 4.52, indicating the presence of an exocyclic double bond. As the stereochemistry of **14** at C-13 and C-14 as well as the absolute configuration had not been established previously, we attempted to solve these problems by a series of chemical reactions. Periodate splitting of **13** and **14** led to the ketones **15** and **16** respectively. As the rotation of these ketones was dextrorotatory as in manool and epi-manool, the presence of labdane derivatives was very likely. However, determination of the stereochemistry at C-13 and C-14, as well as final confirmation of the absolute configuration, needed further transformations. Reaction of **14** with acetone in the presence of cupric sulphate and sulphuric acid afforded the isomeric acetonides **17** and **18**, as followed from the ^{1}H NMR (Table 1) and the polarity of the two isomers. Oxidation of **18** gave the aldehyde **19**, whose ^{1}H NMR spectral data (Table 1) showed that the aldehyde group and the methyl group at C-13 were probably *cis*-orientated, as the chemical shift of the methyl group was influenced by the introduction of the new carbonyl group. Epoxidation of **14** afforded **20** together with a small amount of the epimeric epoxide, as was deduced from the ^{1}H



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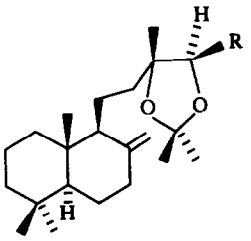
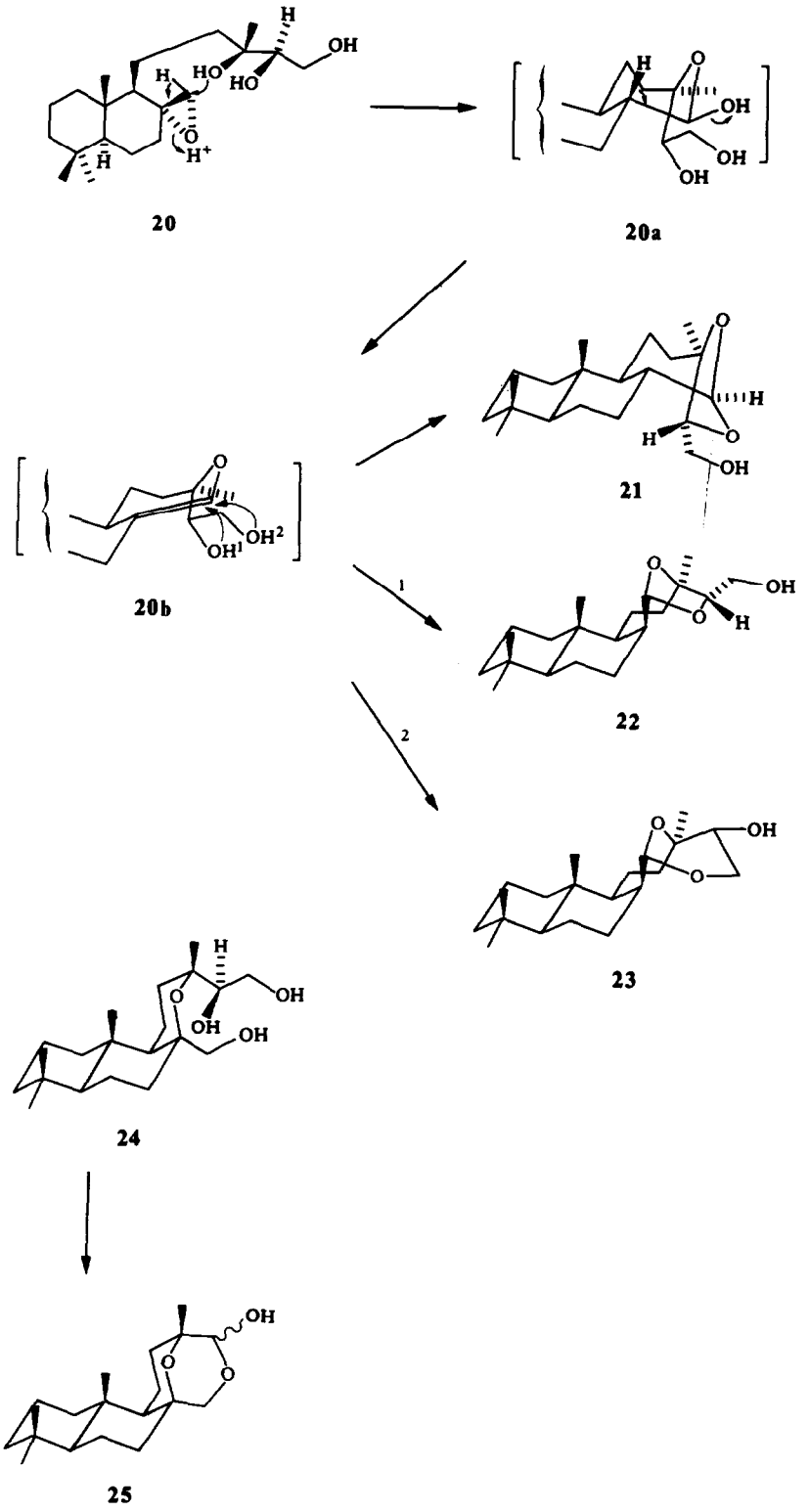


18 R = CH_2OH
19 R = CHO

NMR spectrum (Table 2). Crystallization, however, afforded the pure epoxide **20**. As the absolute configuration of **25** had already been determined [5], an attempt was made to transform **20** to this hemiacetal by proton catalysed ring opening and intramolecular attack of the hydroxyl at C-13 followed by periodate splitting. Heating of **20** in benzene in the presence of *p*-toluenesulfonic acid, however, gave the acetal **21** and only traces of **24**. We therefore, studied the reaction in a NMR tube. It turned out, that at room temperature a mixture of **21–24** was formed, while on heating the sample slowly, **22** and **23** were transformed to **21**. Obviously **21–23** were formed by rearrangement of the epoxide (see Scheme 1). Protonation of the epoxide caused a hydride shift from C-17 to C-8 followed by nucleophilic addition of the C-13 hydroxyl. The resulting hemiacetal **20a** was then transformed by loss of water to the intermediate **20b**, which by proton-catalysed addition of the C-14 hydroxyl gave **21** or **22**, while addition of OH-15 led to **23**. The formation of **22** and **23** was obviously reversible, as heating of the mixture in the presence of acid finally led to **21**, thermodynamically the more stable isomer. Consequently, the yield of the desired tetrahydropyran derivative **24** could not be *improved*. The structures and stereochemistry of **21–24** followed from the ^{1}H NMR spectra (Table 2). Periodate splitting of **24** afforded the known epimeric hemiacetal **25**, which showed the same rotation as that reported [5]. Consequently, the stereochemistry of **14**, was 13*R*, 14*R*, while that of **12** and **13** was definitely the same.

The chemistry of *M. sativa* shows a close relationship to that of *Hemizonia* [4], supporting the placement of these two genera in the same subtribe. Further investigations of members of the other genera placed in the Madiinae may show whether the labdanes and the aromatic constituents are chemotaxonomic markers of the subtribe. So far very little is known about the chemistry of the other genera belonging to this subtribe. The roots of a *Calycadenia* and several *Layia* species contain the pentayne **1** [2], but no systematic studies have been undertaken.



Scheme 1.

Table 1. ^{1}H NMR spectral data of compounds **12–14** and **16–19** (400 MHz, $CDCl_3$, TMS as int. standard)

	12*	13	14	16†	17‡	18§	19‖
H-14	3.54*t*(*br*)	3.54*t*(*br*)	3.52*t*(*br*)	—	3.96*m*	3.95	4.10*d*
H-15	3.77*d*(*br*)	3.78*d*(*br*)	3.76*d*(*br*)	—	3.81*m*	3.77*dd* 3.64*dd*	9.71*d*
H-16	1.18*s*	1.21*s*	1.17*s*	2.13*s*	1.08*s*	1.08*s*	1.15*s*
H-17	1.68*s*(*br*)	1.57*s*	4.83*s*(*br*) 4.52*s*(*br*)	1.54*s*	4.83*s*(*br*) 4.54*s*(*br*)	4.82*s*(*br*) 4.55*s*(*br*)	4.83*s*(*br*) 4.56*s*(*br*)
H-18	0.86*s*	0.87*s*	0.86*s*	0.86*s*	0.87*s*	0.87*s*	0.86*s*
H-19	0.84*s*	0.82*s*	0.79*s*	0.81*s*	0.81*s*	0.80*s*	0.79*s*
H-20	0.75*s*	0.94*s*	0.67*s*	0.92*s*	0.70*s*	0.69*s*	0.68*s*

*H-8 5.38*s*(*br*).

†H-12 2.48 (2H, *dd*, *J* = 9, 8 Hz), H-11 2.29 (*dt*, *J* = 14, 8 Hz), H-12′ 2.15 (*dt*, *J* = 14, 9 Hz), H-7 1.93 (*dd*, *J* = 17, 6 Hz), H-7′ 2.00 (*ddd*, *J* = 17, 11, 5 Hz).

§Acetonide 1.45*s*, 1.36*s*.

‡Acetonide 1.43*s*, 1.37*s*.

‖Acetonide 1.54*s*, 1.47*s*.

J (Hz): Compounds **12–14**: 14, 15 = 4; compound **17**: 14, 15 = 8; 14, 15 = 4; 15, 15′ = 12; compound **19**: 14, 15 = 2.

Table 2. ^{1}H NMR spectral data of compounds **20–25** ($CDCl_3$, TMS as int. standard)

	20	21	22	23	24	25†	
H-7β	—	1.82*dddd*	—	1.73*dddd*	—	—	
H-8α	—	—	2.09*dddd*	2.54*dddd*	—	—	
H-8β	—	1.53*m*	—	—	—	—	
H-9α	—	0.97*dd*	—	1.5*m*	—	—	
H-11α	—	1.67*m*	—	—	—	—	
H-11β	—	1.29*m*	—	—	—	—	
H-12α	—	1.58*m*	—	—	—	—	
H-12β	—	1.98*ddd*	—	1.96*dd*(*br*)	—	—	
H-14	3.72*m**	3.86*dd*	3.90*dd*	3.72*m*	3.59*m**	4.56*d*	4.55*d*
H-15		3.86*m**	3.57*m**	3.79*dd*		—	—
H-15′				3.73*dd*			
H-16	1.09*s*	1.26*s*	1.27*s*	1.25*s*	1.08*s*	1.13*s*	1.12*s*
H-17	2.84*dd*	5.21*d*	5.19*d*	4.83*d*	3.47*d*	3.68*d*	3.60*d*
H-17′	2.54*d*				3.37*d*	2.23*d*	3.49*d*
H-18	0.88*s*	0.85*s*	0.87*s*	0.84*s*	0.89*s*	0.86*s*	
H-19	0.81*s*	0.81*s*	0.84*s*	0.81*s*	0.78*s*	0.86*s*	
H-20	0.78*s*	0.79*s*	0.93*s*	0.92*s*	0.96*s*	1.09*s*	1.07*s*

*Not 1 order.

†OH 3.21 (*d*, *J* = 8), 2.64 (*d*, *J* = 6).

J (Hz): Compound **20**: 9α,17 = 1.5; 17,17′ = 4; compound **21**: 7α,7β = 13; 7α,8β = 10; 6α,7β ~ 2; 6β,7β ~ 4; 7β,8β ~ 3; 8β,9α = 9α,11β = 10.5; 8β,17 = 1.5; 11α,12β = 4; 11β,12β = 4; 12α,12β = 14; 14,15 = 7; 14,15′ = 4.5; compound **22**: 7α,8α = 7β,8α = 8α,9α = 8α,17 ~ 4; 14,15 = 7; 14,15′ = 4.5; compound **23**: 7α,7β ~ 13; 7α,8α ~ 3; 8α,17β = 9; 14,15 ~ 11; 14,15′ ~ 5; 15,15′ ~ 11; compound **24**: 17,17′ = 11.5; compound **25**: 14,OH = 8 and 6; 17,17′ = 12.

EXPERIMENTAL

The air dried plant material (voucher RMK 8402, deposited in the U.S. National Herbarium) was extracted with Et_2O–petrol (1:2), and the resulting extracts were separated by CC (Sigel) and further by repeated TLC (Si gel). Known compounds were identified by comparing the ^{1}H NMR spectra with those of authentic material. The roots (80 g) afforded 10 mg lupeyl acetate, 10 mg stigmasterol, 1 mg **1**, 6 mg **2**, 2 mg **3**, 2 mg **4**, 3 mg **5**, 4 mg **6**, 2 mg **7**, 2 mg **8** (Et_2O–petrol, 1:1) and 2 mg **9**, **10** and **11** (*ca* 1:1:1), while the aerial parts (400 g) gave 30 mg phytol, 5 mg **1** and a mixture of *ca* 3.5 g **12**, 150 mg **13** and 1 g **14**, which was only partially separated by repeated TLC (Et_2O–petrol, 7:3, several times and $AgNO_3$-Si gel–Et_2O).

9-Hydroxydihydroeuparin (**8**). Colourless gum, not completely free from **5**. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500–2700 (OH), 1650 (hydrogen bonded PhCO); MS *m*/*z* (rel. int.): 234.089 [M]$^+$ (31) ($C_{13}H_{14}O_4$), 203 [M − CH_2OH]$^+$ (100); ^{1}H NMR ($CDCl_3$): 5.17 (*dd*, H-2, *J* = 9, 7 Hz), 3.32 (*ddd*, H-3, *J* = 15, 9, 1 Hz), 2.98 (*ddd*, H-3, *J* = 15, 7, 1 Hz), 7.92 (*t*, H-4, *J* = 1 Hz), 6.33

(*s*, H-7), 7.78 (*d*, H-9, $J = 5$ Hz), 5.08 [*s*(*br*), H-11], 4.93 (*dq*, H-11', $J = 1$, 1 Hz), 1.74 [*s*(*br*), H-12], 3.42 (*t*, OH, $J = 5$ Hz).

13R,14R,15-*Trihydroxylabd-7-ene* (**12**). Colourless gum, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3630, 3400 (OH), 1600, 890 (C=CH); MS *m/z* (rel. int.): 324.266 $[M]^+$ (1) ($C_{20}H_{36}O_3$), 306 $[M-H_2O]^+$ (1), 291 $[306-Me]^+$ (1), 273 $[291-H_2O]^+$ (1), 245 $[273-CO]^+$ (9), 204 $[C_{15}H_{24}]^+$ (100) (McLafferty), 191 $[C_{14}H_{23}]^+$ (12), 189 $[204-Me]^+$ (12);

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\text{ nm}}{+4.1 \quad +4.2 \quad +4.3 \quad +4.6}$$

($CHCl_3$; *c* 1.0).

13R,14R,15-*Trihydroxylabd-(8,9)-ene* (**13**). Colourless gum, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH); MS *m/z* (rel. int.): 324.266 $[M]^+$ (10) ($C_{20}H_{36}O_3$), 306 $[M-H_2O]^+$ (3), 291 $[306-Me]^+$ (8), 273 $[291-H_2O]^+$ (4), 245 $[273-CO]^+$ (38), 204 $[C_{15}H_{24}]^+$ (100), 191 $[C_{14}H_{23}]^+$ (95), 189 $[204-Me]^+$ (48).

10 mg **13** in 1 ml MeOH were stirred for 30 min with 20 mg H_5IO_6. TLC (Et_2O–petrol, 1:10) afforded 5 mg **16**, colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725 (C=O); ^{1}H NMR see Table 1;

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\text{ nm}}{+43 \quad +51 \quad +55 \quad +85}$$

($CHCl_3$; *c* 0.1).

Preparation of **17** *and* **18**. 500 mg **14** in 10 ml Me_2CO containing a drop of H_2SO_4 was stirred for 15 min in the presence of 500 mg $CuSO_4$ at room temp. TLC (Et_2O–petrol, 1:3) afforded 400 mg **17** and 80 mg **18**. 20 mg **18** in 0.5 ml CH_2Cl_2 was stirred for 4 hr with 50 mg pyridinechlorochromate. TLC (Et_2O–petrol, 1:10) afforded 5 mg **19**, ^{1}H NMR see Table 1.

Epoxidation of **14**. 100 mg **14** in 2 ml CH_2Cl_2 was stirred for 1 hr with 1 ml $NaHCO_3$–soln and 100 mg *m*-chloroperbenzoic acid. Usual work-up and TLC (Et_2O–petrol, 1:1) afforded 100 mg **20** containing *ca* 5% epimeric epoxide, Crystallization from Et_2O gave pure **20**, colourless crystals, mp 96°, ^{1}H NMR see Table 2.

10 mg **20** in 0.5 ml C_6H_6 were heated for 1 hr with 5 mg *p*-toluenesulfonic acid. TLC (Et_2O–petrol, 1:3) afforded 5 mg **21** (^{1}H NMR see Table 2) and traces of **24**. 40 mg **20** in 2 ml C_6H_6 were stirred at room temp. with 20 mg *p*-toluenesulfonic acid. After 1 hr, usual work-up and TLC (Et_2O–petrol, 1:3 and C_6H_6–Et_2O, 5:1, several times) afforded 5 mg **21**, 3 mg **22**, 10 mg **23** and 3 mg **24** (^{1}H NMR see Table 2). **23**: colourless crystals, mp 211°; MS *m/z* (rel. int.): 307.127 $[M-Me]^+$ (2) ($C_{19}H_{31}O_3$), 279 $[307-CO]^+$ (80), 261 $[279-H_2O]^+$ (40), 243 $[261-H_2O]^+$ (60), 233 $[261-CO]^+$ (12), 177 $[C_{13}H_{21}]^+$ (43), 123 $[C_9H_{15}]^+$ (100).

Preparation of **25**. 3 mg **24** in 1 ml MeOH were stirred for 15 min with 10 mg $NaIO_4$ in 0.1 ml H_2O. TLC (Et_2O–petrol, 1:1) afforded 2 mg **25** (epimers at C-14, *ca* 3:2), ^{1}H NMR see Table 2; MS *m/z* (rel. int.) 293.212 $[M-Me]^+$ (1) ($C_{18}H_{29}O_3$), 123 (100);

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\text{ nm}}{+42 \quad +43 \quad +44 \quad +72}$$

($CHCl_3$; *c* 0.1).

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