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HELMANTICINE, A PHENYLPROPANOID FROM *THAPSIA VILLOSA*

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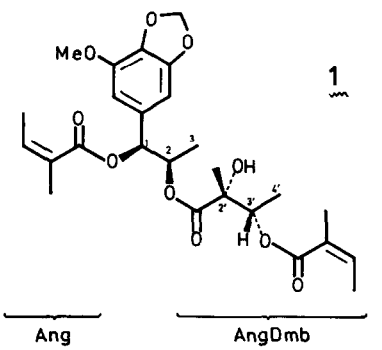
Key Word Index—*Thapsia villosa*; Umbelliferae; phenylpropanoids; helmanticine, latifolone; 12-nonacosanone.

Abstract—Helmanticine, a new phenylpropanoid esterified by angelic and 2,3-dihydroxy-2-methylbutyric acids, was isolated from *Thapsia villosa* and its full structure established by spectroscopic methods and chemical transformations. Hydrocarbons, 12-nonacosanone, sitosterol and latifolone were also isolated.

INTRODUCTION

Thapsia villosa is a perennial plant with wide spherical umbellas of 12–25 radii and yellow flowers, glabrous stem of 10–12 dm, tripinnatifid basal leaves and a robust root. The area of distribution is the west Mediterranean region, including Portugal, Spain, the south of France and the north west of Africa, and it is quite abundant near Salamanca (= Helmantica). The juice of the root of this plant has been used in folk medicine as a purgative, emetic, in plasters against rheuma, etc. [1, 2]. The similar composition of the extracts from *T. villosa* and from *T. transtagana* have been noted in the first phytochemical studies on these plants [3]. Afterwards, some components were identified in *T. villosa*, mainly by analytical methods (TLC, PC, GC), such as scillitol [4], monoterpenes of the essential oil [5], 6-hydroxykynurenic acid [6], coumarins [7, 8], flavonoids and polyacetylenes [8, 9]. In the course of our study,† some works dealing with the chemical components from several species of *Thapsia* have been published [10–19]. Amongst these must be mentioned the isolation of some guaianolides from *T. villosa* [14] related to thapsitranstagine [15–18], substances with a strong irritant activity.‡

In this article we describe the structure of a new phenylpropanoid, **1**, for which the name helmanticine is proposed. This and other phenylpropanoids, some sesquiterpene esters and guaianolides are the main components from the benzene extract of the umbellas and roots of the *T. villosa* studied.



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RESULTS AND DISCUSSION

We have isolated from the less polar fraction of the benzene extracts of *T. villosa* an homologous series of hydrocarbons identified by GC (C_{27} = 37%; C_{29} = 27%) as well as 12-nonacosanone, latifolone (= crocatone), β-sitosterol and the main components, helmanticine and two germacrene derivatives related to shiromodiol.

The position of the carbonyl group in the nonacosanone was established according to mass spectral data. The ketone showed RC ≡ O^+ fragments at *m/z* (%) 183 (18) and 267 (10) in agreement with the C-12 position of the carbonyl group. If the carbonyl group were placed on C-10 or on C-14, RC ≡ O^+ fragments would be observed at *m/z* 155 and 295 for nonacosan-10-one [20] or at *m/z* 211 and 239 for nonacosan-14-one but the relative intensities observed for these ions were negligible. Also even fragments resulting from a McLafferty rearrangement were detected at *m/z* 198 (3) and 282 (1.2), as expected for a carbonyl group at C-12. This uncommon natural ketone had been found previously in *Laserpitium siler* [21].

Helmanticine is a viscous oil, $[\alpha]_D$ +24.5° ($CHCl_3$; *c* 1.1) which showed in the IR spectrum absorption bands for hydroxyl, unsaturated ester and aromatic groups (3500, 1715, 1230–1150, 1625, 1605, 1505 cm^{-1}). The hydroxyl group(s) must be tertiary because the substance was recovered unchanged on treatment with acetic

†Presented at the 12th International Symposium on the Chemistry of Natural Products, Puerto de la Cruz, Tenerife, Spain, September 1980 and at the XV Congreso Latinoamericano de Química, San Juan, Puerto Rico, October 1982.

‡While this paper was in preparation, the isolation from *T. villosa* of a sesquiterpenoid with a new skeleton, named thapsane, was reported [19], but we had also found thapsane derivatives in *T. villosa* L. var. *minor* (Hoff. & Link) Cout., which are absent in the common *T. villosa* L. var. *villosa*. Presented at the R.S.C. Symposium on Natural Products I, Nottingham, U.K., July 1982.

anhydride–pyridine. The ^{1}H NMR spectrum clearly showed the presence of two equivalent protons, one methylenedioxy group and one methoxyl group, all of them on an aromatic ring [δ6.56 (2H), 5.98 (2H), 3.90 (3H)]. This spectrum also showed signals for methyl groups [δ1.32 (3H, *s*), 1.27 (6H, *d*)], geminal protons to ester groups [δ5.15 (3H, *m*)] and signals which could be assigned to angeloyloxy groups [δ6.0 (*m*) and 1.9 (*m*)]. The higher fragment in the mass spectrum appears at *m/z* 488, but the absence of fragments at *m/z* $[488-18]^+$ suggested that the *m/z* 488 ion could be the $[M-18]^+$ fragment, because the presence of a tertiary hydroxyl group and, in consequence, the $[M]^+$ should be $[M]^+$ 506 which corresponds to an empirical formula $C_{26}H_{34}O_{10}$. The presence of fragments at *m/z* 55, 83 (100%), 406 $[M-100]^+$ and 388 $[M-100-18]^+$ confirms the suggested molecular formula and the presence of angelate esters.

Saponification of helmanticine (5% KOH–MeOH) gave an alcohol and two acids, angelic acid and (2*R*,3*S*)-2,3-dihydroxy-2-methylbutyric acid, identified by their chemical and spectral data and those of their *p*-phenylpenacyl esters [22]. The neutral product of the hydrolysis, deacylhelmanticine (**2**), is an aromatic alcohol (IR: ν3380, 1625, 1605, 1505, 1080, 1030 cm^{-1}) with an empirical formula $C_{11}H_{14}O_5$ ($[M]^+$ *m/z* 226). The ^{1}H NMR spectrum showed in the aromatic region signals also present in the spectrum of the helmanticine, assignable to one methylenedioxy group, one aromatic methoxyl and two equivalent aromatic protons. The equivalence and the chemical shift of the aromatic protons suggested that the aryl radical is nearly symmetrical, with the alkoxyl groups at C-3, C-4 and C-5. The remaining signals were in agreement with the arrangement Ar–CHOH–CHOH–Me [δ4.48 (1H, *d*, J = 4 Hz), 3.90 (1H, *m*), 1.05 (3H, *d*, J = 6.5 Hz)]. All these data are in agreement with the constitution for deacylhelmanticine, as 1-(3-methoxy-4,5-methylenedioxyphenyl)-1,2-propanediol.

The constitution of deacylhelmanticine is the same as that proposed for the aromatic diol arising from reduction of laserine, a phenylpropanoid isolated from *Laser trilobum* [23]. However, the physical constants of deacylhelmanticine (mp 79°, $[\alpha]_D$ +21.8°) were clearly different from those described for deacyllaserine (mp 111°, $[\alpha]_D$ +2.2°). This discrepancy could be explained if both substances were the *erythro* and *threo* isomers **2** and **3**, so that a sample of both isomers was desirable in order to assign the relative stereochemistry.

A small sample of deacyllaserine was kindly supplied by Dr. Holub [23] and their IR and ^{1}H NMR spectra were recorded and compared with those of deacylhelmanticine. The IR spectra of both diols in a 5×10^{-3} M/CCl_4 solution showed a stronger intramolecular hydrogen bond for deacyllaserine than for deacylhelmanticine ($\Delta\nu$40 and 33 cm^{-1} respectively) [24]. The Newmann projections of **2a** and **3a** suggested that the hydrogen bond in the *threo* isomer must be stronger than that in the *erythro* isomer [25].

The ^{1}H NMR spectra of diols **2** and **3** as well as those of the respective isopropylidene derivatives, **4** and **5**, are also in agreement with an *erythro* configuration for deacylhelmanticine. The coupling constant $J_{1,2}$ for diol **3** is larger than that showed by **2** (Table 1). Protons H-1 and H-2 are *synclinal* in the more favorable conformations (intramolecular H bond) of the *erythro* isomer, **2a** and **2b**, but are *anticlinal* in the conformation **3a** for the *threo* isomer which can justify the larger coupling constant for this last *threo* isomer [26, 27]. The same conclusion was reached when the NMR data were compared with those described for other *erythro–threo* isomers of 1,2-disubstituted arylpropanes [28]. Protons H-1 and H-2 of the isopropylidene derivative of deacylhelmanticine are

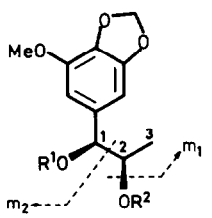
Table 1. ^{1}H NMR data for compounds **2–5** (60 MHz, $CDCl_3$, δ-values)*

	H-1	H-2	Me-3
2	4.48	3.85	1.05
	(*d*, 4.5)	(*m*)†	(*d*, 6.5)
3	4.20	3.74	1.03
	(*d*, 7.5)	(*dq*, 7.5, 7)†	(*d*, 7)
4‡	5.05	4 48	0.85
	(*d*, 6.5)	(*dq*, 6.5, 6)	(*d*, 6)
5‡	4.37	4 13	1.28
	(*d*, 8)	(*m*)†	(*d*, 6)

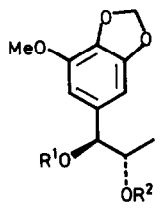
*Coupling constants (J in Hz) are given in parentheses.

†Overlapped by MeO signal.

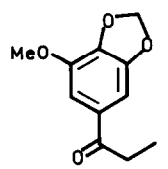
‡*gem*-Me_2: **4**, δ1.60 and 1.42; **5**, δ1.52 and 1.54.



	R^1	R^2
2	H	H
4	—CMe_2—	
6	Ac	Ac
9	H	Ac
10	Ac	H
11	Ang	AngDmb
12	AngDmb	Ang
13	Ang	H
14	H	AngDmb
15	H	Ang
16	AngDmb	H



	R^1	R^2
3	H	H
5	—CMe_2—	
7	Ac	Ac
8	Ang	Ang



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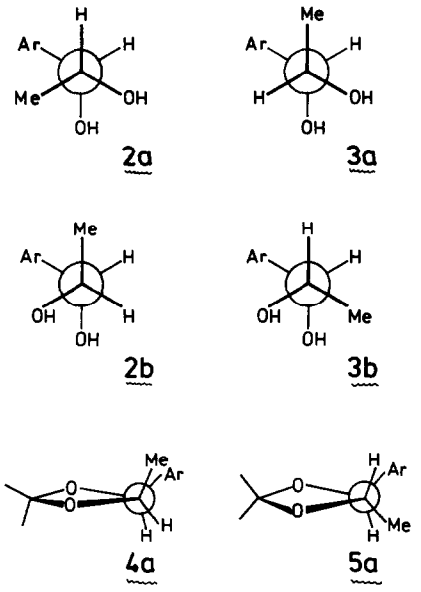
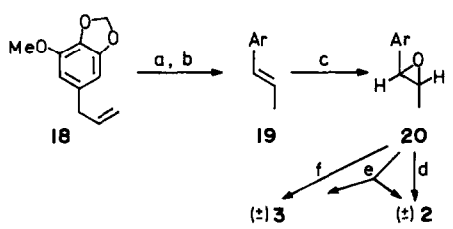


more deshielded and their NMR signal showed smaller coupling constants than those of the isopropylidene derivative of deacyllaserine. These data also suggested an *erythro* configuration for deacylhelmanticine. Moreover, the *quasi*-axial conformation of methyl Me-3 in the *erythro* isomer **4a** give rise to a deformation of the dioxonale ring which can explain the greater difference of chemical shift of isopropylidene methyl groups as compared with those of the more symmetric *threo* isomer **5a** [27, 29].

To confirm the relative configuration suggested for deacylhelmanticine and deacyllaserine, the racemic *erythro* and *threo* isomers were synthesized. Myristicine (**18**), isolated from mace essential oil, was isomerized to *E* and *Z* isomyristicine. The *E* isomer (**19**) purified by silica gel–$AgNO_3$ chromatography, on treatment with *m*-chloroperoxybenzoic acid in CH_2Cl_2–$NaHCO_3$, gave the *trans*-epoxide **20**, which was hydrolysed either by treatment with 2 M KOH–DMSO in a stereospecific way to give the *anti*-product (±)-**2**, or by acid treatment with 3% $HClO_4$–THF or by contact with deactivated silica gel, to give the diols (±)-**2** and (±)-**3** in *ca* 5:4 and 8:2 ratios, respectively [30, 31]. The IR of ^{1}H NMR spectra of synthetic *erythro* (±)-**2** and *threo* (±)-**3** isomers were identical with those of natural deacylhelmanticine and deacyllaserine respectively.



a KOH–EtOH
b Silica gel–10% $AgNO_3$
c *m*-CPBA–CH_2Cl_2–$NaHCO_3$ aq
d 2 M KOH–DMSO
e 3% $HClO_4$–THF
f Silica gel–10% H_2O

The absolute stereochemistry of deacylhelmanticine was deduced by application of the Freudenberg's rule and also by CD measurements. Freudenberg's rule [32] can be applied to diol **2** assuming that the sign of the optical rotation is mainly conditioned by the chirality of the benzylic carbon. In fact, it has been observed that the magnitude of the optical rotation of a phenyl methyl carbinol is higher than that of a benzyl methyl carbinol [33]. If the molecular rotations of (*S*)-phenyl methyl carbinol, M − 52°, and that of its acetate, M − 199° [34] are compared with those of diol **2**, M + 49°, and that of its acetate **6**, M + 117°, it can be deduced that the absolute configuration of C-1 in diol **2** must be opposite to the configuration of the reference substance. This means that the absolute configuration of (+)-deacylhelmanticine must be 1*S*,2*R*. The same absolute configurations was deduced from the circular dichroism curve of deacylhelmanticine in a 10^{-3} M $Ni(acac)_2$–CCl_4 solution [35]. The bisignate CD curve showed Cotton effects at $\Delta\varepsilon_{321}$ − 1.06 and $\Delta\varepsilon_{302}$ + 0.85 which are characteristic for a positive dihedral angle of the hydroxyl groups as they are coordinated to the $Ni(acac)_2$ complex. If it is adopted a conformation in which the bulky Ni complex and the aromatic group are apart, then the absolute configuration of diol **2** must be 1*S*,2*R* for a positive dihedral angle between the hydroxyl groups.* The CD curve of the isopropylidene derivative **4** showed Cotton effects at 282 nm (negative) and 241 nm (positive) of the same sign as those described for analogous aromatic compounds with 1*S*,2*R* configuration [36].

To complete the structural determination of helmanticine it was necessary to know how the diol **2** is esterified by angelic and 2,3-dihydroxybutyric acids. It was mentioned above that helmanticien has a tertiary hydroxyl group and the molecular formula led us to assume the presence of one molecule of diol **2**, two angelic acids and one 2,3-dihydroxy-2-methylbutyric acid. These fragments can be arranged as shown in the structures **11** and **12**. Mild hydrolysis of helmanticine (0.5 M KOH–MeOH, 15 min) yielded a crude reaction product from which was isolated the partially hydrolysed substances **13** and **14**. The more polar compound showed ^{1}H NMR signals of one 3-methoxy-4,5-methylenedioxyphenyl group, one angeloyl group and signals at δ 5.58 (*d*, *J* = 5.5 Hz, H-1), 4.06 (*dq*, *J* = 5.5 and 6.5 Hz, H-2) and 1.22 (*d*, *J* = 6.5 Hz, Me-3) for the propyl side chain. The shielding of the H-2 signal as compared with that of helmanticine allowed us to assign the structure **13** for this substance. The ^{1}H NMR signals of the less polar partially hydrolysed compound, particularly those of H-1 [δ 4.61 (*d*, *J* = 4.5 Hz)], H-2 [δ 4.97 (*m*)] and the methyl protons [δ 1.32 (3H, *s*), 1.16 (6H, *d*, *J* = 6.5 Hz)], led us to assign structure **14** for this substance. An internal migration of acyl groups is possible during the hydrolysis and, in fact, the C-2 angelate **15** could be isolated while the C-2 AngDmb ester **16** was not detected. This migration was observed in the monoacetates **9** and **10**

*A small negative Cotton effect was observed at 284 nm for diol (+)-**3** [cf. (+)-**2**, $\Delta\varepsilon_{284}$ − 1 7] that suggested the 1*S*,2*S* configuration for laserin (**8**).

(Ac_2O–pyridine, 75 min, 0°) which can be readily equilibrated to a 1:1 mixture in acidic media, including silica gel.

The proportions of the hydrolysis products and the absence of **16**, are indicative that the primary products of partial hydrolysis must be **13** and **14**, and this led us to conclude that helmanticine has the structure shown in **11** but not that in **12**. Structure **11** was also supported by mass spectrometry. Indeed, the distinctive fragments m_1 and m_2 were observed at *m/z* 290 $[M-AngDmbOH]^+$ and at *m/z* 263 $[M-AngDmbO{-}CH{-}Me]^+$, respectively, as corresponds with structure **11**, whereas the analogous ions for the alternative structure **12**, m_1 *m/z* 406 and m_2 *m/z* 379, were absent. In consequence, we propose for (+)-helmanticine the structure **11** = **1**: (1*S*,2*R*)-2-{(2*R*,3*S*)-2-hydroxy-2-methyl-3-[(*Z*)-2-methyl-2-butenoyloxy]-butanoyloxy}-1-[(*Z*)-2-methyl-2-butenoyloxy]-1-(3-methoxy-4,5-methylenedioxyphenyl)propane.

Although laserine (**8**) and latifolone (**17**) are two phenylpropanoids structurally related to helmanticine that were isolated some time ago [23, 37], only in recent years has the isolation of related substances been reported. Laserine oxide and latifolone were found in *Guillonea scabra* [38], laserine in *Ferula loscosii* [39], 3′-demethyllatifolone in *F. elaeochytris* [40] and we have also isolated helmanticine and latifolone from *F. communis*. In a study on germination inhibitory substances from *Daucus carota*, the racemates (±)-**2** and (±)-**3** have been isolated but only the *threo* isomer was active [K. Nakanishi, personal communication]. It should be noted that in all these cases the plants belong to the Umbelliferae.

EXPERIMENTAL

Plant material. Roots of *T. villosa* L. were collected in Villamayor near Salamanca and identified by Prof. B. Casaseca, Head of the Department of Botany, University of Salamanca, where a voucher specimen (no. 3586) was deposited.

Extraction and purification. Air dried and powdered roots of *T. villosa* were extracted in a Soxhlet with C_6H_6. The concd extract (9.5% dry wt roots) was chromatographed over a silica gel column with hexane and hexane–EtOAc mixtures. Fractions were monitored by TLC on silica gel, hexane–EtOAc (7:3) and C_6H_6–EtOAc (9:1) as eluents and visualized with H_2SO_4–EtOH (1.3) or phosphomolybdic acid in EtOH

Hydrocarbons. Main constituents of the less polar fractions. GC analysis: dual FID, 2 m × 1/8″ packed with 5% OV-1, isothermal 240°, N_2 at 30 ml/min: C_{19} (0.8%), C_{21} (0.7), C_{22} (0.3), C_{23} (1.6), C_{24} (0.7), C_{25} (9.8), C_{26} (2.8), $C_{26\text{-}iso}$ (3.8), C_{27} (36.7), C_{28} (6.3), $C_{29\text{-}iso}$ (10), C_{29} (26.6).

12-Nonacosanone. Crystalline compound, mp 75° (hexane–Et_2O). IR ν_{max}^{film} cm^{-1}: 1705, 1465 and 720. EIMS (probe) 70 eV, *m/z* (rel. int.): 422 $[M]^+$ (0.6), 267 $[M-155]^+$ (10), 239 $[M-183]^+$ (17), 183 $[M-239]^+$ (18), 155 $[M-267]^+$ (12), 85 (61), 71 (100), 57 (88) and 43 (38).

β-Sitosterol. Isolated as a crystalline substance, mp 135–137° (MeOH), $[\alpha]_D$ −31.4° ($CHCl_3$; *c* 0.97).

Helmanticine (**1**). Colourless gum; $[\alpha]_D$ +25.0° ($CHCl_3$; *c* 1.08). IR ν_{max}^{film} cm^{-1}: 3500, 1715, 1625, 1605, 1505, 1230, 1150. ^1H NMR (60 MHz, $CDCl_3$): δ6.55 (2H, *s*, 2H-Ar), 6.00 (2H, *m*, H-3 Ang × 2), 5.95 (2H, *s*, O–CH_2–O), 5.90 (1H, *d*, *J* = 4.5 Hz, H-1), 5.10 (2H, *dq*, *J* = 4.5, 6.5 Hz, H-2; *q*, *J* = 6.5 Hz, H-3′), 3.90 (3H, *s*, MeO-Ar), 2.05–1.80 (12H, *m*, vinyl-Me Ang × 4), 1.27 (3H, *s*, Me-2′), 1.22 (6H, *d*, *J* = 6.5 Hz, Me-3 and Me-4′). UV λ_{max}^{EtOH} nm: 214 (ε2000). EIMS (probe) 70 eV, *m/z* (rel. int.): 488 $[M-H_2O]^+$ (4), 388 $[M-H_2O-AngOH]^+$ (5), 307 $[M-AngDmb]^+$ (2), 290 $[M-AngDmbOH]^+$ (10), 263 $[M-AngDmbOCHMe]^+$ (3), 208 $[307+H-AngOH]^+$ (15), 191 (36), 179 $[263-Ang]^+$ (41), 83 $[Ang]^+$ (100), 55 $[83-CO]^+$ (15).

Hydrolysis of helmanticine (**1**). A soln of helmanticine (1 g) in 2 M NaOH in MeOH (4 ml) was kept at room temp for 2 hr. After dil. with H_2O the soln was extracted with Et_2O yielding deacylhelmanticine (**2**, 390 mg). The aq. residual soln was neutralized (pH 7) and EtOH (20 ml), *p*-phenylphenacyl bromide (1 g) and 18-crown-6 ether (50 mg) were added. The soln was refluxed for 30 min and then evapd to dryness. The dry product was extracted with $CHCl_3$ and purified by silica gel CC to give *p*-phenylphenacyl angelate (593 mg) and *p*-phenylphenacyl-(2*R*,3*S*)-2,3-dihydroxy-2-methylbutyrate (258 mg).

p-Phenylphenacyl angelate. Mp 89–91° (hexane); lit. 88.5–89° [22]. IR ν_{max}^{Nujol} cm^{-1}: 2950, 1740, 1710, 1660, 1610, 1470, 1250, 1140, 1390, 1230, 1150, 1040, 980, 850, 760, 700. ^1H NMR (60 MHz, CCl_4): δ7.85 and 7 50 (2H each, 2*d*, *J* = 8 Hz, A ring), 7.40 (5H, *m*, B ring), 6.05 (1H, *qq*, *J* = 7 and 1.5 Hz, H-3 Ang), 5.30 (2H, *s*, CH_2O) 2.00 (3H, *dq*, *J* = 7 and 1.5 Hz, Me-4 Ang), 1.96 (3H, *dq*, *J* = 1.5 Hz, Me-2 Ang). EIMS (probe) 70 eV, *m/z* (rel. int.): 294 $[M]^+$ (2), 196 (35), 181 (100), 167 (30), 165 (30), 153 (70), 152 (70), 127 (15), 83 (80), 82 (80), 55 (50).

p-Phenylphenacyl-(2R,3S)-2,3-dihydroxy-2-methylbutyrate. Mp 167–169° (hexane); $[\alpha]_{365}^{25}$ −97.4° ($CHCl_3$; *c* 0.27); lit. mp 165°; $[\alpha]_{364}^{25}$ −84° [22]. IR ν_{max}^{KBr} cm^{-1}: 3400, 2940, 1770, 1610, 1420, 1250, 1140, 1090, 980, 770, 700. ^1H NMR (60 MHz C_5D_5N): δ8.00 and 7.50 (2H each, 2*d*, *J* = 7 Hz, A ring), 7.50 (5H, *m*, B ring), 5.65 (2H, *br s*, 2-OH), 4.56 (1H, *q*, *J* = 6 Hz, H-3), 1.75 (3H, *s*, Me-5 Dmb), 1.55 (3H, *d*, *J* = 6 Hz, Me-4 Dmb). EIMS (probe) 70 eV, *m/z* (rel. int.): 284 (7), 213 (14), 196 (50), 181 (90), 152 (60), 43 (100), 29 (60).

Deacylhelmanticine (**2**). Mp 79°, $[\alpha]_D^{20}$ +21.8° ($CHCl_3$; *c* 0.6). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3380, 2870, 1625, 1605, 1505, 1190, 1080, 1030, 990. ^1H NMR (60 MHz, $CDCl_3$): δ6.57 (2H, *s*, Ar), 5.98 (2H, *s*, O–CH_2–O), 4.48 (1H, *d*, *J* = 4.5 Hz, H-1), 3.90 (3H, *s*, OMe), 4.1–3.7 (1H, *m*, H-2), 2.6 (2H, *br s*, 2-OH) and 1.05 (3H, *d*, *J* = 7 Hz, Me-3). EIMS (probe), 70 eV, *m/z* (rel. int.): 226 $[M]^+$ (39), 208 $[M-H_2O]^+$ (3), 181 $[M-Me-CH_2O]^+$ (100), 165 (15), 153 (42), 151 (14), 149 (4), 135 (8), 123 (71), 121 (8), 107 (8), 95 (55), 93 (13), 43 (11) y 29 (11)

Isopropylidene derivative **4**. To a soln of **2** (20 mg) in dry Me_2CO (2 ml) was added 2,2-dimethoxypropane (0.5 ml) and a small crystal of *p*-TsOH. After 5 min the reaction was complete and a few crystals of Na_2CO_3 were added, the soln filtered and concd to give **4** (19 mg) as a gum. IR ν_{max}^{film} cm^{-1}: 1630, 1605 (w), 1510, 1375, 1205, 1135, 1085, 1030, 950 (w), 925, 855. ^1H NMR (60 MHz, $CDCl_3$): δ6.50 (2H, *s*, Ar), 5.90 (2H, *s*, O–CH_2–O), 5.05 (1H, *d*, *J* = 6.5 Hz, H-1), 4.48 (1H, *dq*, *J* = 6.5 and 6 Hz, H-2), 3.90 (3H, *s*, OMe), 1.60 and 1.45 (3H each, *s*, *gem*-Me_2) and 0.85 (3H, *d*, *J* = 6 Hz, Me-3).

Diacetate **6**. (Ac_2O–pyridine, room temp). Colourless oil, $[\alpha]_D$ +37° ($CHCl_3$; *c* 1.5). IR ν_{max}^{film} cm^{-1}: 3040, 2870, 1735, 1620, 1515, 1225. ^1H NMR (60 MHz, $CDCl_3$): δ6.55 (2H, *s*, Ar), 5 95 (2H, *s*, O–CH_2–O), 5.78 (1H, *d*, *J* = 4.5 Hz, H-1), 5.15 (1H, *dq*, *J* = 4.5 y 6.5 Hz, H-2), 3.85 (3H, *s*, OMe), 2 10 (3H, *s*, AcO), 1.95 (3H, *s*, AcO) and 1 16 (3H, *d*, *J* = 6.5 Hz, Me-3). EIMS (probe) 70 eV, *m/z* (rel. int.): 310 $[M]^+$ (13), 250 $[M-60]^+$ (38), 221 (8), 208 (78), 180 (100), 153 (31).

Monoacetates **9** *and* **10**. To a soln of diol **2** (500 mg) in dry pyridine (1.3 ml) was added Ac_2O (1.3 ml) and the mixture kept at 0° for 75 min. After usual workup the crude product obtained (572 mg) showed on TLC the presence of the substances **2**, **6**, **9** and **10** which were isolated by silica gel CC (hexane–EtOAc, 7·3)

Monoacetate **9**. $[\alpha]_D^{20}$ +8.84° ($CHCl_3$; *c* 1.47). IR ν_{max}^{film} cm^{-1}: 3400, 2760, 1730, 1625, 1605, 1500, 1230, 1070. ^1H NMR

(60 MHz, $CDCl_3$): δ6.55 (2H, *s*, Ar), 5.95 (2H, *s*, O–CH_2–O), 5.02 (1H, *dq*, *J* = 4.5 and 7 Hz, H-2), 4.69 (1H, *d*, *J* = 4.5 Hz, H-1), 3.90 (3H, *s*, OMe), 2.05 (3H, *s*, AcO) and 1.13 (3H, *d*, *J* = 7 Hz, Me-3). EIMS (probe) 70 eV, *m/z* (rel. int.): 268 $[M]^+$ (12), 250 $[M-H_2O]^+$ (2), 224 (13), 208 (25), 181 (25), 180 (100), 153 (25) y 122 (21). *Monoacetate* **10**. $[\alpha]_D^{20}$ +34.0 ($CHCl_3$; *c* 0.37). IR ν_{max}^{film} cm^{-1}: 3400, 2760, 1730, 1625, 1605, 1500, 1230, 1090. ^1H NMR (60 MHz, $CDCl_3$): δ6.55 (2H, *s*, Ar), 5.95 (2H, *s*, O–CH_2–O), 5.45 (1H, *d*, *J* = 6 Hz, H-1), 3.98 (1H, *dq*, *J* = 6 and 6 5 Hz, H-2), 3.85 (3H, *s*, OMe), 2.1 (3H, *s*, AcO) and 1.17 (3H, *d*, *J* = 6.5 Hz, Me-3). EIMS (probe) 70 eV, *m/z* (rel. int.): 268 $[M]^+$ (12), 250 $[M-H_2O]^+$ (2), 224 (13), 208 (37), 181 (23), 180 (100), 153 (30), 122 (28).

Deacyllaserine (**3**). Sample kindly supplied by Dr. Holub [23]. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3400, 3020, 2870, 1670, 1600, 1500, 1450, 1120, 1080, 1040. ^1H NMR (60 MHz, $CDCl_3$): δ6.60 (2H, *s*, Ar), 5.98 (2H, *s*, O–CH_2–O), 4 20 (1H, *d*, *J* = 7 5 Hz, H-1), 3.90 (3H, *s*, OMe), 3.74 (1H, *dq*, *J* = 8 and 7.5 Hz, H-2), 1.03 (3H, *d*, *J* = 7 Hz, Me-3).

Isopropylidene derivative (**5**). ^1H NMR (60 MHz, $CDCl_3$): δ6.50 (2H, *s*, Ar), 5.95 (2H, *s*, O–CH_2–O), 4.37 (1H, *d*, *J* = 8 Hz, H-1), 4.13 (1H, *dq*, *J* = 8 and 6 Hz, H-2), 3.90 (3H, *s*, MeOH), 1.65 and 1.50 (3H each, *s*, *gem*-Me_2) and 1.28 (3H, *d*, *J* = 6 Hz, Me-3).

Diacetate **7**. (Ac_2O–pyridine room temp). IR ν_{max}^{KBr} cm^{-1}: 3080, 3040, 2870, 1730, 1620, 1510, 1230, 750. ^1H NMR (60 MHz, $CDCl_3$): δ6.50 (2H, *s*, Ar), 5.90 (2H, *s*, O–CH_2–O), 5.60 (1H, *d*, *J* = 7 Hz, H-1), 5.20 (1H, *dq*, *J* = 7 and 6 Hz, H-1), 3.90 (3H, *s*, OMe), 2.02 (3H, *s*, AcO), 2.00 (3H, *s*, AcO) and 1.08 (3H, *d*, 6 Hz, Me-3).

Partial hydrolysis of helmanticine (**1**). A soln of **1** (500 mg) in 0.5 M KOH in MeOH (9 ml) was left at room temp for 20 min. The soln was dil. with H_2O (9 ml), vacuum distilled to remove MeOH and extracted with Et_2O to give a crude reaction product (350 mg) from which the compounds **13** (25 mg), **14** (35 mg) and **15** (20 mg) were isolated by prep. TLC, besides **1** and **2**.

Compound **13**. ^1H NMR (60 MHz, $CDCl_3$): δ6.58 (2H, *s*, Ar), 5.97 (2H, *s*, O–CH_2–O), 6.10 (1H, *qq*, *J* = 7 and 1.5 Hz, H-3 Ang), 5.58 (1H, *d*, *J* = 6 Hz, H-1), 4.06 (1H, *dq*, *J* = 6 and 6.5 Hz, H-2), 2.02 (3H, *br d*, *J* = 7 Hz, Me-4 Ang), 1.98 (3H, *br s*, Me-2 Ang) and 1.22 (3H, *d*, *J* = 6 Hz, Me-3).

Compound **14**. ^1H NMR (CCl_4): δ6.48 (2H, *s*, Ar), 5.97 (1H, *qq*, *J* = 7 and 1.5 Hz, H-3 Ang), 5 88 (2H, *s*, O–CH_2–O), 5.06 (2H, *dq* + *q*, *J* = 4 5 and 6.5 Hz, H-2 and H-3′), 4.68 (1H, *d*, *J* = 4.5 Hz, H-1), 3.84 (3H, *s*, MeO), 1.90 (3H, *br d*, *J* = 7 Hz, Me-4 Ang), 1.84 (3H, *br s*, Me-2 Ang), 1.32 (3H, *s*, Me-2′) and 1.16 (6H, *d*, *J* = 6.5 Hz, Me-3 and Me-4′).

Compound **15**. ^1H NMR (CCl_4): δ6.50 (3H, *s*, MeO), 6.00 (1H, *qq*, *J* = 7 and 1.5 Hz, H-3 Ang), 5.90 (2H, *s*, O–CH_2–O), 5.02 (2H, *dq*, *J* = 4.5 and 7 Hz, H-2 and H-3′), 4.69 (1H, *d*, *J* = 4.5 Hz, H-1), 3.89 (3H, *s*, MeO), 1.95 (3H, *br d*, *J* = 7 Hz, Me-4 Ang), 1.87 (3H, *br s*, Me-2 Ang) and 1.13 (3H, *d*, *J* = 7 Hz, Me-3).

Latifolone (**17**). Mp 86–88° (MeOH). IR ν_{max}^{KBr} cm^{-1}: 3060, 2790, 1675, 1625, 1600, 1520, 925. ^1H NMR (60 MHz, $CDCl_3$): δ7.12 and 7.00 (2H, 2*d*, *J* = 2 Hz, Ar), 5.95 (2H, *s*, O–CH_2–O), 3.88 (3H, *s*, MeO), 2.85 (2H, *q*, *J* = 7.5 Hz, H-2) and 1.18 (3H, *t*, *J* = 7.5 Hz, Me-3). EIMS (probe) 70 eV, *m/z* (rel. int.): 208 $[M]^+$ (28), 179 (100), 151 (26).

trans-*Isomyristicine* (**19**). Vacuum distillation of mace essential oil (105°/20 mm) left a residue which was chromatographed on silica gel to isolate pure myristicine (**18**). IR ν_{max}^{film} cm^{-1}: 3040, 2870, 1630, 1605, 1500, 990, 915 ^1H NMR (60 MHz, CCl_4): δ6.45 (2H, *s*, Ar), 5.95 (2H, *s*, O–CH_2–O), 5.70 (1H, *m*, H-2), 5.1–4.9 (2H, *m*, H-3), 3.85 (3H, *s*, OMe) and 3.20 (2H, *d*, *J* = 7 Hz, H-1). A soln of myristicine (4.4 g) in 10% KOH in EtOH (50 ml) was refluxed for 15 hr, dil with H_2O, neutralized, concd to remove EtOH and extracted with Et_2O to give *ca* 17:3 (GC) mixture of *trans*- and *cis*-isomyristicine (2.9 g). The *trans*- isomer **19** was purified by $AgNO_3$–silica gel (1:9) CC to give crystals mp 38°. IR ν_{max}^{nujol} cm^{-1}: 3030, 2860, 1670, 1600, 1500, 1430, 1225, 970. ^1H NMR (60 MHz, CCl_4): δ6.47 (1H, *d*, *J* = 1.5 Hz, H-Ar), 6.38 (1H, *d*, *J* = 1.5 Hz, H-Ar), 6.20 (1H, *d*, *J* = 16 Hz, H-1), 5.95 (1H, *dq*, *J* = 16 and 5 Hz, H-2), 5.82 (2H, *s*, O–CH_2–O) 3.80 (3H, *s*, OMe) and 1.79 (3H, *d*, *J* = 5 Hz, Me-3). EIMS (probe) 70 eV, *m/z* (rel. int.): 192 $[M]^+$ (100), 177 $[M-Me]^+$ (15), 165 (20) 161 (50), 147 (37), 131 (60) y 119 (50).

trans-*Epoxide* **20**. To a soln of **19** (300 mg) in CH_2Cl_2 (25 ml), was added *m*-chloroperbenzoic acid (1.03 g) in satd aq. $NaHCO_3$ (25 ml) and the mixture stirred for 2 hr at 37°. After addition of 1 N Na_2SO_3 (10 ml) and CH_2Cl_2 (25 ml), the washed and dried organic extract was concd to give crystalline **20** (217 mg), mp 90° (CCl_4). IR ν_{max}^{KBr} cm^{-1}: 3080, 3020, 2870, 1630, 1600, 1500, 1430, 1260, 930, 810. ^1H NMR (60 MHz, CCl_4): δ6.50 (2H, *s*, 2H-Ar), 5.90 (2H, *s*, O–CH_2–O), 3.90 (3H, *s*, OMe), 3.80 (1H, *d*, *J* = 5.5 Hz, H-1), 3.26 (*dq*, *J* = 5.5 and 5 Hz, H-2) and 1.11 (3H, *d*, *J* = 5 Hz, Me-3).

Hydrolysis of **20**. (a) A soln of **20** (50 mg) in 2 M KOH–DMSO (1:4, 20 ml) was left at room temp for 24 hr. After usual work-up, crystalline diol (±)-**2** was isolated, mp 89°. IR and ^1H NMR data identical to natural (+)-**2**. (b) Epoxide **20** (40 mg) was left overnight at room temp in contact with partially deactivated silica gel (10% H_2O). After elution (hexane–EtOAc, 9:1 to 6:4), diol (±)-**3** (32 mg) was obtained lightly contaminated with (±)-**2** (*ca* 10%, ^1H NMR) together with small amounts of unchanged **20** and a rearranged alcoxybenzyl methyl ketone. Crystalline (±)-**3** had mp 118°. IR and ^1H NMR data identical to natural (+)-**3**. (c) To a soln of **20** (90 mg) in THF (10 ml), 3% $HClO_4$ (1 ml) was added and the mixture kept at room temp for 2 hr. After usual work-up, a crude reaction product (111 mg) was obtained which contained mainly the diols (±)-**2** and (±)-**3** in a *ca* 5:4 ratio.

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