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11,13-DIHYDROEUCANNABINOLIDE, A HELIANGOLIDE FROM *STEVIA MONARDAEFOLIA**

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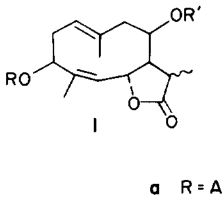
Abstract—Investigation of the chloroform extract of *Stevia monardaefolia* afforded, besides two previously isolated labdane type diterpenes, a new sesquiterpene lactone of the heliangolide type The structure was determined by spectroscopic and chemical data to be 11,13-dihydroeucannabinolide

INTRODUCTION

Different types of sesquiterpene lactones have been isolated from *Stevia* species, one pseudoguaianolide from *S rhombifolia* [1], three guaianolides [2, 3] and one germacrolide from *S serrata* [4], two guaianolides from *S setifera* and one guaianolide from *S boliviensis* [5]

As part of our chemical systematic study of the tribe Eupatorieae, we have investigated *Stevia monardaefolia* and have isolated, in addition to known compounds, two new labdane type diterpenes whose structures were discussed in a previous paper [6] Further investigation of the chloroform extract provided a new sesquiterpene lactone of the heliangolide type which was shown to be 11,13-dihydroeucannabinolide (**1a**) This is the first heliangolide isolated from the genus



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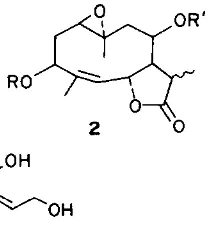

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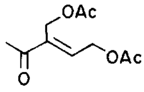

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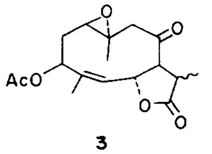
c R = Ac, R' = H

d R = R' = Ac

e R = R' = H



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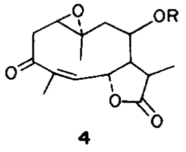

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RESULTS AND DISCUSSION

11,13-Dihydroeucannabinolide (**1a**), $C_{22}H_{30}O_8$, $[\alpha]_D - 93\ 6°$, was a gum which exhibited the typical IR absorption band of a γ-lactone at 1755 cm^{-1} Further absorption at 3430 and 1020, 1740, 1710 cm^{-1} indicated the presence of hydroxyl(s) and ester function(s), respectively

The ^1H NMR spectrum (Table 1) of **1a** lacked the typical doublets of the exocyclic methylene conjugated with the γ-lactone, which must be saturated as indicated by a doublet at δ 1 12 (J = 7 5 Hz) The presence of a two proton singlet at 4 34 and a two proton doublet at 4 40 (J = 6 0 Hz), which shifted downfield upon acetylation, together with a proton triplet at 6 93 (J = 6 0 Hz), strongly suggested the presence of a 4, 5-dihydroxytigloyl moiety as in eucannabinolide [7, 8]

A sharp three proton singlet at δ 2 1 indicated the presence of an acetate These assumptions were supported by the mass spectral fragments at m/z 291 $[M - CH_2(CH_2\text{–}OH) = C(CH_2\text{–}OH)COO]^+$, 363 $[M - AcO]^+$, 230 $[M - CH_2(CH_2\text{–}OH) = C(CH_2\text{–}OH)\text{-}COOH - AcOH]$

The ^1H NMR spectrum of **1a** also showed two vinyl methyl group signals at 1 80 and 1 87, two broad AB doublets centered at 5 40 (J = 11 0 Hz) and 5 90 (J = 11 0 Hz) and a three proton signal at 5 20 These features closely resemble those of eucannabinolide and provincialin, which are heliangolides isolated from *Eupatorium cannabinum* [8] and *Liatris provincialis* [9], both belonging to the tribe Eupatorieae The structure of the isolated sesquiterpene lactone can therefore be represented as the 11,13-dihydro derivative of eucannabinolide (**1a**)

Alkaline hydrolysis of **1a** with potassium carbonate afforded two products The less polar one was the monoalcohol **1c** The ^1H NMR spectrum of **1c**, indicated the loss of the five-carbon atom ester, consequently one of the resonances in the three proton signal at δ 5 20 was shifted upfield to 4 21 and appeared as a multiplet ($W_{1/2}$ ~ 8 Hz) The mass spectrum showed the molecular ion peak at m/z 308 along with peaks at m/z 266 $[M - CH_2CO]^+$, 248 $[M - AcOH]^+$, 230 $[M - AcOH - H_2O]^+$

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Table 1 ^{1}H NMR spectral data of 11,13-dihydroeucannabinolide and its derivatives*

	1a	**1b**	**1c**	**1d**	**1e**	**2a**	**2c**	**2d**	**3**
H-1	5 20 *m*	5 14 *m*	†	†	†	†	†	†	†
H-3	5 20 *m*	5 14 *m*	5 20 *t*	5 27 *m*	4 42 *br t*	5 19 *m*	5 2 *m*	5 2 *m*	5 54 *m*
H-5	5 40 *br d*	5 26 *br d*	5 34 *br d*	5 27 *m*	5 26 *br d*	5 49 *br d*	5 44 *br d*	5 38 *dd*	5 34 *m*
H-6	5 90 *br d*	5 72 *br d*	5 72 *br d*	5 72 *br d*	6 16 *br d*	6 12 *br d*	5 98 *br d*	5 95 *dd*	5 54 *m*
H-8	5 20 *m*	5 14 *m*	4 21 *m*	5 27 *m*	4 04 *br t*	5 19 *m*	4 17 *m*	5 20 *m*	—
H-13	1 12 *d*	1 12 *d*	1 26 *d*	1 39 *d*	1 34 *d*	1 09 *d*	1 25 *d*	1 40 *d*	1 32 *d*
H-14	1 80 *s*	1 70 *s*	1 81 *s*	1 76 *s*	1 72 *s*	1 46 *s*	1 60 *s*	1 48 *s*	1 40 *s*
H-15	1 87 *br s*	1 76 *br s*	1 92 *s*	1 82 *s*	1 77*s*	1 94 *br s*	1 90 *s*	1 90 *s*	1 93 *s*
H-3′	6 93 *t*	6 84 *t*	—	—	—	6 96 *t*	—	—	—
H-4′	4 40 *d*	4 79 *d*	—	—	—	4 41 *d*	—	—	—
H-5′	4 34 *s*	4 72 *s*	—	—	—	4 34 *s*	—	—	—
AcO	2 1 *s*	1 96,2 0 *s*	2 0 *s*	2 06 *s*	—	2 16 *s*	2 12 *s*	2 08,2 12 *s*	2 06 *s*

*Run at 100 MHz in $CDCl_3$ with TMS as int standard Values are in ppm (δ)

†Signal obscured J (Hz) 3,2 = 3, 5,6 = 11, 5,15 = 2, 6,7 = 2, 11,13 = 7, 3′,4′ = 6

Acetylation of **1c** gave a crystalline diacetate **1d**, mp 178–179°, which was treated with *m*-chloroperbenzoic acid to give the epoxy-derivative **2d**, mp 210–213° (lit 209–211° [10])

The more polar hydrolysis product was the corresponding diol **1e**, mp 127–128°, which was a mixture of C-11 epimers

Treatment of **1a** with *m*-chloroperbenzoic acid afforded the monoepoxide **2a**, as indicated by the ^{1}H NMR spectrum, which lacked one vinyl proton signal and exhibited an upfield shift of one of the vinyl methyl group signals to δ 1 46 Mild alkaline hydrolysis of **2a** gave the epoxyalcohol **2c** which was also obtained by epoxidation of **1c**

Finally, confirmation of the relative position of the esters was achieved by oxidation of **2c** with pyridinium dichromate to give the keto-derivative **3**, which clearly showed three IR carbonyl absorption bands at 1775, 1735 and 1710 cm^{-1} The UV absorption at 216 nm (ε 1398) supported structure **3**, rather than the alternative α, β-unsaturated formulation as in tetrahydroheliangmone (**4**)

EXPERIMENTAL

Stevia monardaefolia H B K was collected 35 km south of Mexico City on the Mexico–Cuernavaca road, in December 1978 A voucher is on deposit at the Herbarium of the Instituto de Biología (UNAM), Mexico

A 1 25 kg sample of the aerial parts of the plant was extracted first with petrol, secondly with $CHCl_3$ The $CHCl_3$ extract after removing long-chain hydrocarbons was separated by CC over Si gel (1 kg) From the low polar fractions, 6α-angeloyloxysclareol, kaurenoic acid, sitosterol and stigmasterol were isolated

11,13-*Dihydroeucannabinolide* (**1a**) From fractions eluted with $CHCl_3$–EtOAc (7 3), after repeated purification by TLC (Et_2O–Me_2CO, 9 1) 1 2 g **1a**, as an amorphous solid, was obtained Mp 51–60° $[\alpha]_D - 93\ 6°$ ($CHCl_3$) UV λ_{max}^{EtOH} nm (ε) 211 (3808) IR ν_{max}^{film} cm^{-1} 3430, 1755, 1740, 1710, 1665, 1020 MS m/z 422 $[M]^+$, 407 $[M-15]^+$, 404 $[M-H_2O]^+$, 43 $[C_2H_3O]^+$ (100 0)

Alkaline hydrolysis of **1a** To a soln of 100 mg **1a** in 8 ml MeOH, 100 mg K_2CO_3 were added and the mixture refluxed under N_2 The reaction mixture was cooled, acidified with HCl, extracted with EtOAc and the residue purified by TLC ($CHCl_3$–MeOH, 9 1)

The less polar compound was the acetate **1c** $[\alpha]_D$ $-56\ 12°$ ($CHCl_3$) UV λ_{max}^{EtOH} nm (ε) 218 (2350) IR ν_{max}^{film} cm^{-1} 3450, 1760, 1740, 1670, MS m/z 308 $[M]^+$, 248 $[M-AcOH]^+$, 230 $[M-AcOH-H_2O]^+$, 43 $[C_2H_3O]^+$ (100 0)

The more polar reaction product was a crystalline compound which was identified as the diol **1e**, mp 127–128° $[\alpha]_D - 40\ 8°$ ($CHCl_3$) UV λ_{max}^{EtOH} nm (ε) 218 (2058) IR ν_{max}^{film} cm^{-1} 3450, 1740, 1665, MS m/z 266 $[M]^+$, 248 $[M-H_2O]^+$, 230 $[M-2H_2O]^+$

Acetate **1b** A soln of 50 mg **1a** in 0 5 ml pyridine and 0 5 ml Ac_2O was allowed to stand at room temp for 30 min After the usual work-up, the residual acetate was purified by TLC ($CHCl_3$–Me_2CO, 9 1) giving 22 mg **1b** as an oil $[\alpha]_D - 61\ 8°$ ($CHCl_3$) UV λ_{max}^{EtOH} nm (ε) 210 (10 524), IR ν_{max}^{film} cm^{-1} 1765, 1740, 1715, 1665 MS m/z 506 $[M]^+$, 447 $[M-AcO]^+$, 404 $[M-AcO-Ac]^+$, 387 $[M-AcO-AcOH]^+$, 43 $[C_2H_3O]^+$ (100 0)

Acetate **1d** Acetylation of **1c** (50 mg) provided 35 mg of the acetate **1d** after TLC purification ($CHCl_3$–MeOH, 97 3) $[\alpha]_D$ $-88\ 0°$ ($CHCl_3$) UV λ_{max}^{EtOH} nm (ε) 217 (1193), IR ν_{max}^{film} cm^{-1} 1765, 1740, 1665, MS m/z 350 $[M]^+$, 308 $[M-C_2H_2O]^+$, 290 $[M-AcOH]^+$, 248 $[M-C_2H_2O-AcOH]^+$, 230 $[M-2AcOH]^+$, 43 $[C_2H_3O]^+$ (100 0)

Epoxidation of **1a** To a soln of 50 mg **1a** in 4 ml $CHCl_3$, was added 50 mg *m*-chloroperbenzoic acid and the mixture allowed to react for 1 hr After the usual work-up, the residue was purified by TLC ($CHCl_3$–Me_2CO, 1 1), to give 15 mg **2a** Mp 75–77°, $[\alpha]_D$ $-45\ 9°$ ($CHCl_3$) UV λ_{max}^{EtOH} nm (ε) 222 (7043), IR ν_{max}^{film} cm^{-1} 3450, 1760, 1745, 1715, 1650, 850; MS m/z 420 $[M-H_2O]^+$, 378 $[M-H_2O-C_2H_2O]^+$, 360 $[M-H_2O-AcOH]^+$, 43 $[C_2H_3O]^+$ (100 0)

Epoxidation of **1d** Epoxidation of **1d** (50 mg) under the same conditions as described before, afforded 40 mg of the epoxy derivative **2d** after TLC purification ($CHCl_3$–Me_2CO, 1 1) Mp 210–213° (lit 209–211° [10]), $[\alpha]_D - 46\ 2°$ ($CHCl_3$) IR ν_{max}^{film} cm^{-1} 1765, 1740, 1670, 860; MS m/z 350 $[M-16]^+$, 324 $[M-C_2H_2O]^+$, 307 $[M-AcO]^+$, 263 $[M-AcOH-Ac]^+$, 246 $[M-2AcOH]^+$, 43 $[C_2H_3O]^+$ (100 0)

Alkaline hydrolysis of **2a** Hydrolysis with K_2CO_3 of **2a** (70 mg) as described before, provided 37 mg **2c**, as an amorphous solid Mp 68–75°, $[\alpha]_D - 68\ 6°$ ($CHCl_3$) UV λ_{max}^{EtOH} nm (ε) 216 (458), IR ν_{max}^{film} cm^{-1} 3470, 1760, 1740, 1670, 860 The same compound (**2c**) was obtained by epoxidation of **1c**

Oxidation of **2c** To a soln of **2c** (30 mg) in 5 ml CH_2Cl_2, 25 mg pyridinium dichromate were added and the mixture stirred for 5 hr, then diluted with Et_2O, filtered, concd and the reaction mixture purified by TLC (pentane–$CHCl_3$–Me_2CO, 2 6 2) to yield 15 mg **3** as a crystalline compound Mp 222–224°, $[\alpha]_D$ $-165\,6°$ ($CHCl_3$) UV λ_{max}^{EtOH} nm (ε) 216 (1398), IR ν_{max}^{film} cm^{-1} 1775, 1735, 1710, MS *m/z* 322 $[M]^+$, 280 $[M - C_2H_2O]^+$, 262 $[M - AcOH]^+$

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