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Valparane, A New Diterpene Skeleton (Part IV). Absolute Stereochemistry of Valparone, Valparolone and Other Compounds with Valparane Skeleton

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Abstract: The unsaponificable part of the hexane extract of *Halimium viscosum* chemotype (Valparaíso, Zamora, Spain) afforded three hydrocarbons, an epoxide, a ketone (valparone), five allylic alcohols and a *seco* derivative with valparane skeleton and an α,β-unsaturated ketone with valparolane skeleton. The majority of them have been correlated chemically. Chemical correlation between valparanes and valparolanes, absolute stereochemistry determined by means of CD for valparone and the confirmation of the absolute stereochemistry of valparanic and valparolanic compounds have been done by CD curve of the cyclohexanone obtained from valparolone.

INTRODUCTION

Several years ago, the study of *Halimium* species have been initiated in order to exploit the major components of the widely distributed plants of the *Cistaceae*,[1a] as starting materials for biologically active compounds.[1b] Surprinsingly, it was discovered that *Halimium viscosum* exists, until now, as three different chemotypes,[2] according to the collection sites. Since, this was probably important from an ecological point of view, it was decided to study in more detail the extracts of *H. viscosum*.

The extracts from this species are constituted, essentially, by bi- and tricyclic diterpenoids with different carbon skeleton: labdane,[3,4] *ent*-halimane,[5] tormesane,[2] tormesolane,[6] and fregenedane.[7] The neutral part of *H. viscosum* from Valparaíso (Zamora, Spain) mainly contains tricyclic diterpenoids either with valparane[8] or valparolane[9] skeletons: three hydrocarbons (**1**, **2** and **3**), an epoxide (**5**), a ketone (**7**), five allylic alcohols (**4**, **6**, **9**, **10** and **11**) and one *seco* derivative, **12**, all of them of the valparane class, and an α,β-unsaturated ketone (**8**) of the valparolane class (for isolation details see experimental part). In the next pages, it is discussed the structure determination of all of these compounds.

The structure of the main component, **2**, an unsaturated hydrocarbon named valparene, was established by means of spectroscopic methods, specially 2D-heteronuclear ($^1H/^{13}C$, HCCORR) and homonuclear ($^{13}C/^{13}C$, INADEQUATE) techniques. From these data, the carbon backbone was firmly established and confirmed later on by X-ray crystallography of one of its derivatives.[8]

RESULTS AND DISCUSSION

Compound **1**, an isomer of valparene **2**, is an unsaturated hydrocarbon that shows in its ^1H NMR spectrum two angular methyl groups and the groupings -CH=CMe, $-CH_2-CH=C-$ and Me_2CH-. The ^{13}C NMR spectrum shows four quaternary carbon atoms (two of them olefinic) and sixteen protonated carbons sorted by DEPT multiplicity as five methyl groups, six methylenes and five methines (two of them olefinic). The correlations observed in the 2D heteronuclear experiments (one bond and long-range), that are summarized in Table 1, allow the establishment of four partial structures: A, B, C and D (Figure 1) where are mainly shown the correlations observed for the methyl groups. A, B and C are analog to the partial structures

determined for 2[8] and D indicated that the isopropyl group is allylic to a trisubstituted double bond, suggesting that **1** is a structural isomer of **2**.

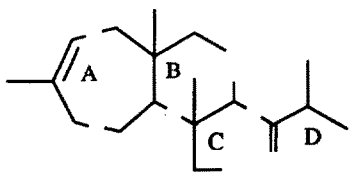


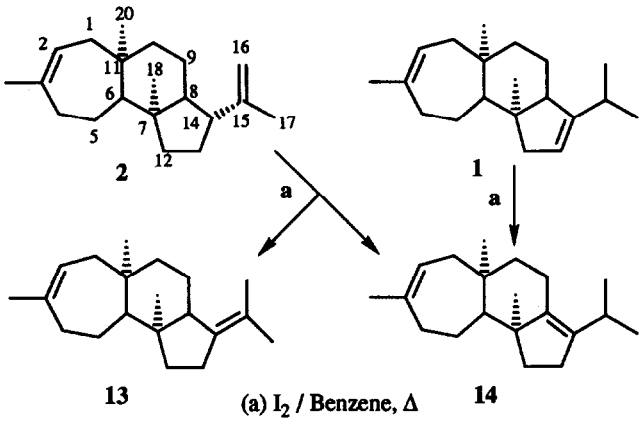
Figure 1.

Table 1. $^{1}H/^{13}C$ (HCCORR) Correlations (One bond and Long Range) Observed for Compound **1**.

C	δ_C	Observed ^{1}H (δ) One Bond Correlation	Observed Long Range Correlation
1	44.4	1.62–2.11 (2H, m)	20
2	122.4	5.39 (1H, tq)	19
3	142.0	—	19
4	33.7	1.91–2.27 (2H, m)	19
5	23.9	1.52 (2H, m)	—
6	57.9	1.33 (1H, m)	12, 20
7	45.7	—	18
8	51.6	2.06 (1H, m)	9, 18
9	27.1	1.42, 1.81 (1H, m, ea)	8
10	43.7	1.90 (2H, m)	20
11	34.1	—	20
12	42.8	1.05, 1.75 (1H, m, ea)	18
13	119.2	5.18 (1H, dt)	8
14	148.2	—	16, 17
15	35.2	1.55 (1H, m)	16, 17
16	21.9	0.89 (3H, d)	—
17	22.0	0.94 (3H, d)	—
18	18.9	0.87 (3H, s)	—
19	25.0	1.75 (3H, s)	4
20	21.6	0.90 (3H, s)	—

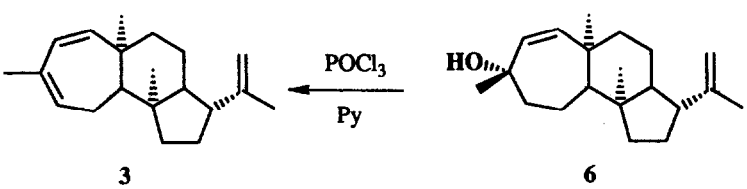
The structure of **1** was confirmed by chemical correlation with **2**. In fact, heating **2** in benzene, in the presence of I_2[10] afforded a mixture of hydrocarbons, **13** and **14**. One of them, **14**, was also obtained when **1** was treated under the same reaction conditions than valparene, **2**.

The exocyclic double bond of **2** migrates giving rise either to a tetrasubstituted double bond of an isopropylidene group as in **13** (δ_C 135.6 and 120.3) or to an endocyclic tetrasubstituted double bond in the five membered ring as in **14** (δ_C 140.2 and 136.1); the latter is the isomer that was also obtained from the isomerization of the trisubstituted double bond of **1**.



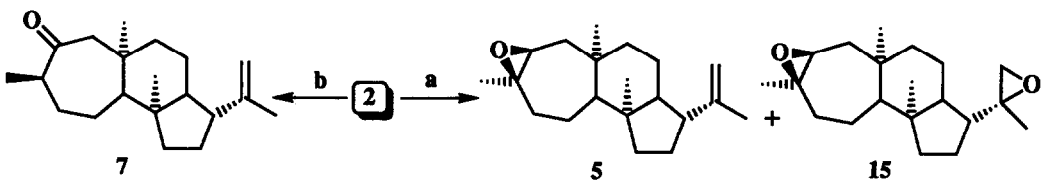
Compound **3** was isolated from the same fractions that afforded **1** and **2**[10b]. According to its mass spectrum it has a $C_{20}H_{30}$ molecular formula ([M+], 270.4584, Δmmu ±0.1) corresponding to a tricyclic diterpene with three unsaturation sites. The ^{13}C NMR spectrum shows twenty carbon atoms, six of them olefinic (three methines, one terminal methylene group and two quaternary carbon atoms). The main signals observed in the ^1H NMR spectrum are two doublets corresponding each one of them to an olefinic proton (δ 5.40, J = 14.2 Hz and 5.35, J = 14.2 Hz), a multiplet (δ 5.86, 1H) that belong to a conjugated system on ring A (UV λ_{max} 261 nm) that could be assigned to the grouping –CH=C(Me)–CH=CH–; the other two olefinic protons correspond to the terminal methylene of the isopropenyl group and four methyl groups: two of them attached to sp^2 hybridized carbons and two angular methyl groups.

The structure proposed for **3**: 1,3,15–valparatriene was confirmed by dehydration of the allylic alcohol **6**.



In the ^1H NMR spectra corresponding to all the compounds described below, except for **10**, the signals corresponding to an isopropenyl group: –C(Me)=CH_2 (δ_H 1.75±0.02, 3H, s; 4.80±0.02, 2H, s), as well as two angular methyl groups are observed.

Compound **5**, isolated as optically active colourless crystals from *n*–hexane (mp 129°C), gave a parent ion at m/z 288 (EIMS), in agreement with a $C_{20}H_{32}O$ molecular formula. The ^1H NMR spectrum shows in addition to the isopropenyl and the two angular methyl groups (δ 1.01 and 0.76) the signals corresponding to a HC$_{\overline{O}}$C(Me) (δ 2.70, 1H, m; 1.33, 3H, s). The signals of twenty carbon atoms in the ^{13}C NMR spectrum correspond to four quaternary carbon atoms (one of them olefinic and one oxiranic at δ 60.5) and sixteen sorted by DEPT as: four methyl groups, eight methylenes (one of them olefinic) and four methines (one oxiranic at δ 60.9). Finally, when **2** was treated with an equimolar amount of *m*CPBA **5** (2,3β–epoxy–15–valparene)[8] was obtained in 94% yield. The diepoxide, **15**, was also obtained in 4% yield.



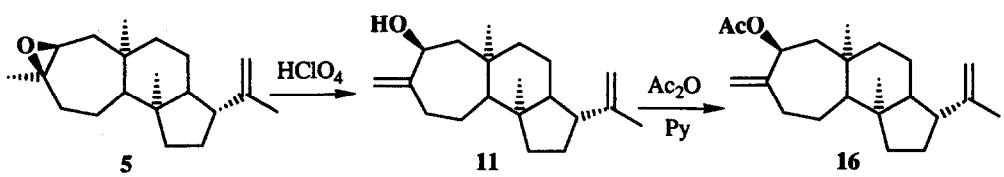
Scheme 1. (a) *m*CPBA; (b) $BF_3 \cdot Et_2O$

Compound **7** was purified by recrystallization from *n*–hexane (mp 76–77°C). According to the IR spectrum (3060, 1702, 1640 and 900 cm^{-1}) it is an unsaturated ketone. The mass spectrum (HREIMS, [M^+], m/z, 288.2444, Δmmu ±0.1) indicated a $C_{20}H_{32}O$ molecular formula, therefore **7** is an isomer of both compounds **5** and **11** (*vide infra*). In fact, the ^1H NMR spectrum allows the identification of the isopropenyl group, the angular methyl groups (δ 0.85 and 0.73) and a doublet methyl group (δ 1.05); and from the ^{13}C NMR spectrum one of the signals of the twenty carbon atoms observed corresponds to a carbonyl group (δ 216.1). Therefore, it could be deduced that the carbonyl function should be at C–2 and the double bond between C–15 and C–16, by comparison with spectral data of other valparanic compounds. Physical properties of **7** (valparone) are identical to those of 15–valparen–7–one, a compound obtained from **5** by reaction with $BF_3 \cdot Et_2O$ and whose structure and relative stereochemistry was confirmed by X–ray diffraction.[8]

The circular dichroism (CD) curve of compound **7** shows a negative Cotton effect, thus, applying the Octant rule[8] and considering the most possible conformation according to the X–ray analysis, the structure and stereochemistry of **7** can be unambiguously assigned as 3*R*,6*R*,7*R*,8*R*,11*R*,14*R*–15–valparen–2–one (Scheme 1).

Compound **11** was recrystallized from *n*–hexane–EtOAc (mp 129–130°C). According to the IR spectrum it possesses a hydroxyl function as well as double bonds (3320, 3080, 1640, 1080 and 890 cm^{-1}) in a tricyclic diterpenic structure with a $C_{20}H_{32}O$ molecular formula (EIMS, [M^+], m/z 288) that is in agreement with the twenty signals observed in the ^{13}C NMR spectrum of which, according to DEPT subspectra, three are methyls, nine methylenes (two of them sp^2), four methines and the remaining are quaternary carbon atoms (two of them olefinic).

The ^1H NMR spectrum shows, in addition to the two angular methyl groups at δ 0.91 and 0.71, respectively, and the isopropenyl group (–C(Me)=CH_2), a terminal methylene group as two broad singlets (δ 5.00 and 4.90) and one hydrogen geminal to a secondary allylic alcohol (δ 4.20, 1H, dd, J_1= 10.5 and J_2= 6.5 Hz). During the treatment of **5** with $HClO_4$,[11] the epoxide ring opened and the tertiary alcohol generated at C–3 was simultaneously dehydrated giving **11**. When **11** was acetylated, a monoacetyl derivative **16** (δ, 5.41, 1H, dd, CHOAc) was obtained, then, the structure of **11** is 3(19),15–valparadiene–2β–ol. Differential nOe experiments demonstrated that the secondary hydroxyl group of **11** is in β position, thus confirming also the β–stereochemistry of the epoxide ring on compound **5**.



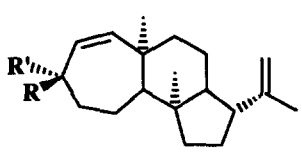
Compounds **4** and **6** are two isomeric hydroxy derivatives (IR 3400 cm^{-1}) that have in their ^1H NMR spectra, in addition to the isopropenyl moiety and the two angular methyl groups, the signals corresponding to the group –C–CH=CH– δ 5.53 (1H, d, J= 9.8 Hz) and 5.12 (1H, d, J= 9.8 Hz), for compound **4** and 5.30 (1H, dd, J= 12.7 and 1.5 Hz) and 5.14 (1H, d, J = 12.7 Hz) for compound **6**, respectively. The ^{13}C NMR spectrum

shows signals for twenty carbon atoms: four methyl groups, seven methylenes (one of them olefinic), five methines (two of them olefinic) and four tetrasubstituted carbon atoms, one of them sp^2 hybridized and one beared the tertiary hydroxyl group: δ 77.0 in compound **4** and 73.6 in compound **6**, respectively.

The parent ion in the mass spectrum shows m/z 288 for both compounds, indicating a $C_{20}H_{32}O$ molecular formula, in agreement with a tricyclic diterpenic alcohol with two double bonds, and only being differentiated by the relative intensity observed for some of the fragments.

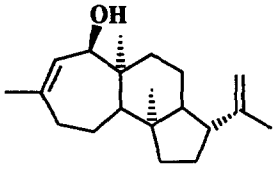
The presence of the isopropenyl and the two angular methyl groups in the ^1H NMR spectra, suggested that the tertiary hydroxyl group should be located in ring A at the allylic position, thus **4** and **6** should be epimers at C–3.

When the signal corresponding to Me–20 in compound **4** was saturated in an nOe experiment, there is an enhancement in the signal corresponding to Me–19, indicating that the hydroxyl group is *trans* respect to Me–20. Furthermore, irradiation of Me–18 generates enhancement in the hydrogens of the isopropenyl group as well as in Me–20; therefore the stereochemistry at C–3 for the hydroxyl group could be assigned as β in compound **4** and α in compound **6**, respectively. Finally, **6** was transformed into the triene **3** by dehydration with $POCl_3$ as it was already discussed.



4 R = OH, R' = Me

6 R = Me, R' = OH



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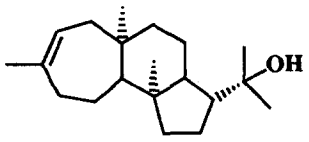


10

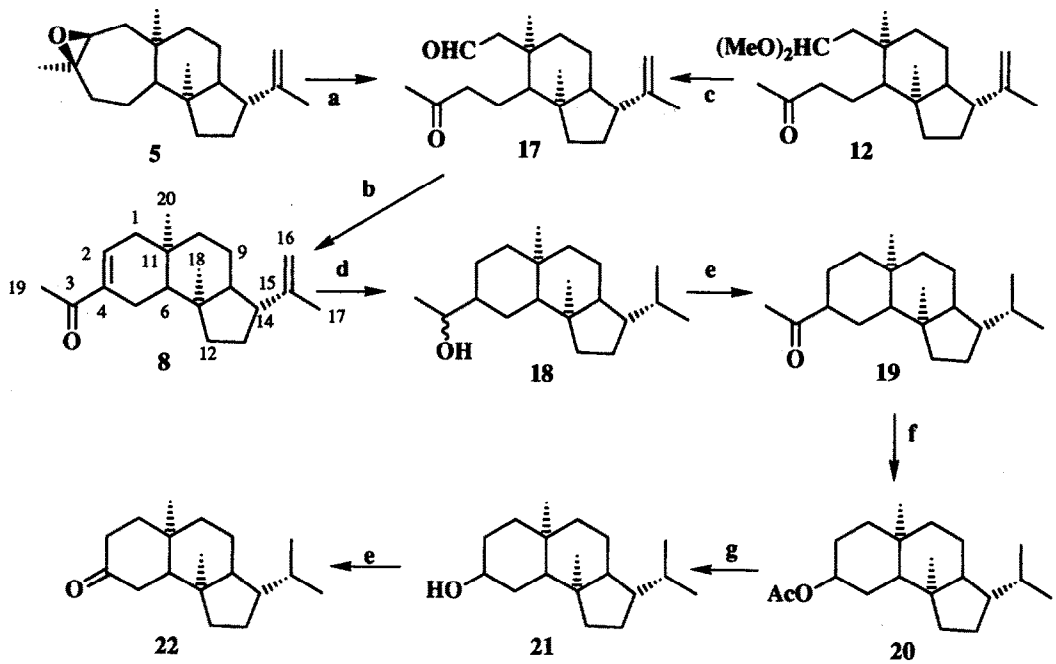
Compound **9** is also an unsaturated alcohol, isomer of **4** and **6** and in its ^1H NMR spectrum shows, in addition to the isopropenyl and the angular methyl groups, a Me–C=CH–CHOH (δ 1.75, 3H, s; 5.65, 1H, d, J= 7.7 Hz; 3.41, 1H, d, J= 7.7 Hz) grouping. Locating the hydroxyl group in the allylic position of the trisubstituted double bond on ring A, the hydroxyl must be at C–1, and considering the magnitude of the coupling constant of the geminal proton at C–1, the stereochemistry of the hydroxyl group should be β. Thus, **9** has the structure of 2,15–valparadien-1β–ol.

The last valparanic compound, **10**, is also a hydroxy derivative with a double bond (IR 3500, 1650 cm^{-1}). It shows in the ^1H NMR spectrum the signals corresponding to the two angular methyl groups but, instead of the isopropenyl group, it shows two methyl singlets geminal to an oxygen function (δ 1.24 and 1.21, 3H ea) that could be assigned to the Me_2C–OH and the grouping Me–C=CH– (δ 1.73, 3H, s; 5.38, 1H, m). When **10** was dehydrated in the presence of $POCl_3$, **13** was obtained, confirming the structure of the former as 2–valparen–15–ol.

Compound **8**, valparolone,[9] is an α,β–unsaturated ketone, whose structure was determined spectroscopically and by chemical correlation with **2** (Scheme 2).

When **5** was treated with H_5IO_6[12] **11** and **17** were obtained, the former corresponds to the epoxide ring opening with simultaneous dehydration of the tertiary hydroxyl group and the latter to the ring opening of the non isolated intermediate diol to give the dicarbonyl compound (Scheme 2).

When **17** was treated with KOH/EtOH[13] under aldol reaction conditions **8** was obtained, and valparolone is unambiguously correlated with the previous valparanic compounds already described.



Scheme 2. a) H_5IO_6; b) KOH/EtOH; c) *p*TsOH/Me_2CO; d) H_2/PtO_2; e) Swern Oxidation; f) Baeyer–Villiger Oxidation; g) KOH/MeOH

Due to the fact that the absolute stereochemistry for the valparanic skeleton was established by the CD curve obtained for the cycloheptanone **7**, **8** was correlated to the ketone **22**, whose CD curve was used to establish the absolute stereochemistry of the valparolane skeleton (Scheme 2).

When **8** was hydrogenated over PtO_2 **18** was obtained and, after oxidation under Swern conditions,[14] afforded ketone **19**. Baeyer–Villiger oxidation[15] of the latter provided the ester **20** that was hydrolyzed under alkali conditions to give **21**, that was oxidated under Swern conditions giving ketone **22**. The CD curve of this compound has a negative Cotton effect, thus, applying the octant rule for cyclohexanones[16] and considering the X–ray study of **7**, the stereochemistry could be assigned as 6*R*,7*R*,8*R*,11*R*,14*R* for **22** and therefore valparolone is 6*R*,7*R*,8*R*,11*R*,14*R* ,2(4),15–valparoladien–3–one. This study not only confirmed the absolute stereochemistry of valparanic compounds established by the CD curve of cycloheptanone **7** but also that the approach used for this study has been the correct one, at least in this case.

The numbering of the carbon skeleton is based on the possible biogenetic origin of valparolane skeleton, that is, ring A contraction of valparanic compounds through a suitable *seco*–valparane intermediate or by a rearrangement, similar to the one proposed for cyperolone, of a valparane derivative.[17]

Finally, the most polar natural product isolated until now is **12**, a ketone (IR 1710 cm^{-1}) that shows a ^1H NMR spectrum pattern similar to most of the compounds already described: an isopropenyl group, two angular methyl groups and the groupings: $(MeO)_2$–CH–CH_2– (3.27, 6H, s; 4.44, 1H, t, J= 4.9 Hz) and a methyl ketone (2.12, 3H, s). The ^{13}C NMR spectrum shows twenty two carbon atoms: four tetrasubstituted (one of a carbonyl compound and one olefinic) and eighteen protonated sorted by DEPT as: six methyl groups (two methoxyls), eight methylenes (one olefinic) and four methines. The structure of **12** was established as 2,2–dimethoxy–2,3–*seco*–15–valparen–3–one, due to the fact that acid hydrolysis afforded **17**. Probably **12** could be an artefact produced during the extraction process of the plant.[18]

Table 2. ^{13}C NMR Data for Valparanic and Valparolanic Compounds

C	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	19	21	22
1	44.4	46.3	145.1	130.9	47.0	133.5	59.1	43.5	77.2	46.4	53.7	46.3	46.3	45.8	46.9	51.0	57.1	44.5	33.5	40.4
2	122.4	122.9	128.6	138.2	60.9	142.4	216.1	139.2	125.4	122.8	71.9	102.6	122.9	122.8	60.8	73.7	203.5	25.7	31.6	38.2
3	142.0	141.0	135.5	77.0	60.5	73.6	48.0	199.2	143.9	141.3	155.2	208.9	140.9	141.2	60.5	150.2	208.4	212.0	–	–
4	33.7	34.9	123.6	38.8	36.5	43.2	33.9	139.3	33.8	34.9	32.8	42.9	35.0	34.9	36.4	33.5	42.6	56.4	72.3	210.8
5	23.9	24.0	29.4	23.3	23.8	23.7	27.1	23.0	25.0	24.1	28.5	21.5	23.8	23.9	23.9	28.3	21.4	42.2	43.2	43.2
6	57.9	64.1	52.9	56.8	64.0	57.7	62.9	51.9	52.6	64.5	60.7	56.7	62.9	63.5	64.0	60.4	56.7	52.8	54.7	537
7	45.7	46.9	46.0	46.6	46.7	46.9	46.5	44.5	43.5	46.3	46.9	46.2	46.3	51.6	45.8	46.4	48.2	44.5	44.5	44.69
8	51.6	55.4	54.7	51.0	55.2	54.8	55.3	55.7	54.5	54.6	55.2	55.1	56.6	140.2	54.3	55.2	54.9	55.9	55.5	55.1
9	27.1	22.2	21.4	21.9	21.5	21.6	21.8	21.8	21.7	22.6	21.6	21.3	23.5	20.1	21.4	21.5	21.1	24.1	22.6	22.4
10	43.7	45.1	43.5	46.2	44.8	45.1	45.0	46.8	40.2	45.8	45.9	45.7	44.3	42.9	45.5	45.8	45.1	44.1	43.8	44.1
11	34.1	36.2	41.4	40.4	37.9	40.4	36.6	32.9	41.0	36.1	36.1	37.2	35.8	36.5	37.9	36.2	39.2	34.2	33.8	33.9
12	42.8	41.6	41.6	42.7	41.9	41.7	41.8	41.2	41.6	40.9	41.8	40.6	38.8	41.2	41.4	41.8	41.3	41.8	40.8	40.6
13	119.2	27.3	27.3	27.5	27.1	27.2	27.1	27.7	27.3	26.5	27.2	27.5	28.4	27.5	24.5	27.2	27.4	27.6	27.6	27.6
14	148.2	46.7	46.5	49.3	46.5	46.4	46.4	46.3	46.7	51.3	46.5	45.7	135.6	136.1	45.5	46.4	45.8	47.9	47.9	47.7
15	35.2	148.6	148.1	148.0	148.3	148.4	148.1	148.4	149.0	73.8	148.5	148.1	120.3	26.4	57.9	148.5	147.8	31.9	31.9	31.9
16	21.9	110.2	110.3	110.2	110.2	110.3	110.4	110.4	110.2	28.9	110.3	110.5	20.5	21.8	53.1	110.3	110.8	22.7	22.7	22.6
17	22.0	25.0	25.3	25.8	24.9	24.9	24.9	25.0	25.0	30.9	25.0	24.9	19.4	21.2	23.1	25.0	25.0	23.9	23.6	23.8
18	18.9	16.2	16.2	17.4	16.2	16.2	16.2	15.5	16.6	16.2	16.0	18.5	14.8	18.6	16.5	16.0	18.4	15.6	15.7	14.9
19	25.0	25.7	26.0	28.9	22.7	30.1	19.5	25.2	26.9	25.6	112.3	29.8	25.7	25.5	22.5	114.3	29.9	27.9	–	–
20	21.6	20.8	24.1	21.8	20.0	21.7	20.8	21.0	20.5	21.0	20.1	21.7	22.7	19.1	20.1	20.1	22.2	20.5	20.6	19.6
MeO												52.4								
MeO												52.1								
$MeCO_2$																171.1				
$MeCO_2$																21.8				

Acknowledgements. The authors thank the CICYT for financial support (PB 88-0369).

EXPERIMENTAL SECTION

Spectral Analysis. NMR spectra were obtained on a 200 MHz spectrometer, operating at 200 MHz for ^1H and 50.3 MHz for ^{13}C, respectively. Chemical shifts are given in ppm and are referenced in $CDCl_3$ to the residual $CHCl_3$, 7.26 ppm for ^1H and 77.0 ppm for ^{13}C, respectively, unless otherwise stated. Coupling constants are given in Hz. ^{13}C NMR data are given in Table 2. Melting points were determined in a Kofler type hot–stage apparatus and are uncorrected. IR spectra were recorded in a BOMEM MB–100 FTIR spectrometer. Mass spectra were obtained in a VG TS 250 Mass spectrometer by Electron Ionization with a potential of 70 eV. Accurate Mass Spectra were done in a VG–ZAB–E instrument.

Extraction and Isolation. The extraction of the aerial parts of *Halimium viscosum* (Valparaíso, Zamora, Spain) was previously described.[4] The neutral fraction (45 g) was saponified with 10% KOH/MeOH and the neutral part (12.5 g) was chromatographed on a silica gel column and eluted with *n*-hexane–EtOAc mixtures of increasing polarity, affording seven main fractions: A, B, C, D, E, F and G. Compounds **1** (120 mg), **2** (420 mg) and **3** (12 mg) were isolated from fraction A (*n*–hexane, 8.7 %) by CC over $SiO_2/AgNO_3$. From fraction B(*n*–hexane–EtOAc, 97:3, 13.5 %)by CC over $SiO_2/AgNO_3$ were isolated the hydroxy derivatives **4** (60 mg), **5** (96 mg) and **6** (58 mg). From fraction C (*n*–hexane–EtOAc, 95:5, 2 %) by crystallization from *n*–hexane **7** (53 mg) was isolated. The mother liquor afforded by CC (*n*–hexane–EtOAc, 97:3) over SiO_2 **8** (52 mg). Alcohols **9** (12 mg) and **10** (35 mg) were isolated from fraction D(*n*–hexane–EtOAc, 9:1, 13.8 %) by PTLC (Benzene–EtOAc, 9:1, two times) and **11** (45 mg) by CC over SiO_2. Compound **12** (22 mg) was isolated by CC (*n*–hexane–EtOAc, 85:15) over $SiO_2/AgNO_3$ from fraction E (*n*–hexane–EtOAc 8:2, 28.8 %). Fraction F (*n*–hexane–EtOAc, 1:1, 29.7 %) and fraction G (EtOAc, 3.5 %) complete the weight recovered from the first chromatography.

2,13-valparadiene: **1**. Colourless oil. $[\alpha]_D$ + 36.7 ($CHCl_3$, c 1.2). IR ν_{max} (film) cm^{-1}: 1640, 1460, 1380, 1100 and 840. ^1H δ: 5.39 (1H, tq, J= 1.8 and 7.3, H-2), 5.18 (1H, dt, J= 1.4 and 3.8, H-13), 1.75 (3H, s, Me-19), 0.94 (3H, d, J= 6.7, Me-16), 0.90 (3H, s, Me-20), 0.89 (3H, d, J= 6.7, Me-17), 0.87 (3H, s, Me-18). ^{13}C δ: see Table 2.

2,15-valparadiene: **2**. Colourless oil. $[\alpha]_D$ + 11.4 ($CHCl_3$, c 1.2). IR ν_{max} (film) cm^{-1}: 3090, 1640, 1450, 1380, 890 and 840. ^1H δ: 5.37 (1H, m, H-2), 4.80 (2H, s, H-16), 2.72 (1H, m, H-14), 1.76 (3H, s, Me-17), 1.74 (3H, s, Me-19), 0.82 (3H, s, Me-20) and 0.72 (3H, s, Me-18). ^{13}C δ: see Table 2. EIMS m/z (rel. int.): 272 [M^+] (5), 257(2), 243(2), 229(4), 203(4), 189(100), 173(4), 161(10), 159(4), 147(11), 133(22), 121(22), 119(24), 107(18), 105(24), 91(19), 81(43), 69(10), 67(48), 55(65), 43(67), 41 (90).

1,3,15-valparatriene: **3**. Colourless oil. $[\alpha]_D$ + 10.3 ($CHCl_3$, c 0.8) IR ν_{max} (film) cm^{-1}: 3090, 1640, 1600, 1470, 1390 and 890. ^1H δ: 5.86(1H, m, H-4), 5.40 and 5.36(1H, m, ea, H-1 and H-2), 4.81(2H, s, H-16), 2.71(1H, m, H-14), 1.78(3H, s, ea, Me-17 and Me-19), 1.03 and 0.76(3H, s, ea, Me-20 and Me-18). ^{13}C δ: see Table 2. UV λ_{max} (nm) 261 log ε: 3.88. EIMS m/z (rel. int.): 270 [M^+] (6), 255(3), 227(16), 187(100), 173(19), 159(70), 134(39), 105(50), 91(68), 79(80).

1,15-valparadien-3β-ol: **4**. Colourless oil. $[\alpha]_D$ -60.9 ($CHCl_3$, c 1.2). IR ν_{max} (film) cm^{-1}: 3400 (broad), 3060, 1640, 1470, 1380, 1160, 890 and 840. ^1H δ: 5.53 and 5.12(1H, d, ea, J= 9.8, H-1 and H-2), 4.82(2H, s, H-16), 2.72(1H, m, H-14), 1.77(3H, s, Me–17), 1.32(3H, s, Me-19), 1.07(3H, s, Me-20) and 0.92(3H, s, Me-18). ^{13}C δ: see Table 2. EIMS m/z (rel. int.): 288 [M^+] (3), 270(30), 255(45), 242(4), 227(30), 201(20), 187(60), 173(35), 159(86), 134(62), 105(85), 91(89), 79(100), 55(40).

2,3β-epoxy-15-valparene: **5**. Colourless crystals. mp 129-130°C (*n*–hexane). $[\alpha]_D$ -23.9 ($CHCl_3$, c 2.4). IR ν_{max} (film) cm^{-1}: 3090, 1660, 1460, 1380, 1170 and 890. ^1H δ: 4.80(2H, s, H-16), 2.72(1H, m, H-14), 2.70(1H, m, H-2), 1.76(3H, s, Me-17), 1.33(3H, s, Me-19), 1.01 and 0.76(3H, s, ea, Me-20 and Me-18 respectively). ^{13}C δ: see Table 2. EIMS m/z (rel. int.): 288 [M^+], (1), 270(2), 255(4), 245(1), 227(5), 203(8), 189(11), 173(8), 159(13), 135(20), 119(25), 107(29), 91(38), 70(45), 55(100).

1,15-valparadien-3α-ol: **6**. Colourless oil. $[\alpha]_D$ -34.2 ($CHCl_3$, c 1.4). IR ν_{max} (film) cm^{-1}: 3400 (broad), 3080, 1640, 1100 and 890.^1H δ: 5.30(1H, dd, J= 12.7 and 1.5 Hz, H-1), 5.14(1H, d, J= 12.7 Hz, H-2), 4.80(2H, s, H-16), 2.71(1H, m, H-14), 1.75(3H, s, Me-17), 1.33(3H, s, Me-19), 1.00(3H, s, Me-20) and 0.78(3H, s, Me-18). ^{13}C δ: see Table 2. EIMS m/z (rel. int.): 288[M^+] (5), 270(31), 255(50), 242(2), 227(28), 201(19), 187(50), 173(29), 159(81), 134(49), 105 (72), 91(99), 79(100), 55(60). To **6** (41 mg, 0.14 mmol) dissolved in pyridine (4 ml), cooled in an ice bath and stirred, was added $POCl_3$ (0.34 ml, 13.64 mmol) freshly distilled. The mixture was maintained in the ice–bath for an hour and then seven hours at room temperature, monitoring the reaction by TLC. The mixture was then poured into ice, warmed to room temperature and extracted with ether. The organic phase was washed with 2N HCl and water, dried over Na_2SO_4. Evaporation of the solvent afforded **3** (32 mg, 83%).

15-valparen-2-one: **7**. Needle crystals. mp 76-77°C (*n*–hexane). $[\alpha]_D$ + 11.3 ($CHCl_3$, c 1.2)IR ν_{max} (film) cm^{-1}: 3060, 1702, 1640, 1460, 1390, 1030 and 900. ^1H δ: 4.80 (2H, bs, H-16), 2.71(1H, m, H-14), 2.58 and 2.02(1H, d, ea, J= 12.5, H-1), 1.75(3H, s, Me-17), 1.05(3H, d, J= 7.2, Me-19), 0.86(3H, s, Me-20), 0.73(3H, s, Me-18). ^{13}C δ: see Table 2. EIMS m/z (rel. int.): 288[M^+] (15), 273(7), 260(100), 246(24), 232(14), 217(31), 203(19), 189(43), 177(37), 163(52), 147(92), 133(58), 121(48), 109(64),105(48), 93(52), 79(46), 55(50), 43(71), 41(61). HREIMS: calculated for $C_{20}H_{32}O$: 288.2453; observed 288.2444. Anal. found: C 83.37 %, H 11.27 %. Anal. calculated: C 83.33 %, H 11.11%. CD (nm): $\Delta\varepsilon_{305}$ –0.85, $\Delta\varepsilon_{296}$ –0.87.

Valparolone: **8**. Colourless crystals. mp 128-129°C.$[\alpha]_D$ +10.1 ($CHCl_3$, c 2.0). IR ν_{max} (film) cm^{-1}: 3080, 1680, 1640, 1470, 1390, 1300 and 890. ^1H δ: 6.79(1H, m, H-2), 4.80(2H, s, H-16), 2.71(1H, m, H-14), 2.27(3H, s, Me-19), 1.75(3H, s, Me-17), 0.85(3H, s, Me-20) and 0.82(3H, s, Me-18). ^{13}C δ: see Table 2. UV λ_{max} (nm) 231 log ε 4.6.

2,15-valparadien-1β-ol: **9**. Colourless oil. $[\alpha]_D$ –1.4 ($CHCl_3$, c 0.7). IR ν_{max} (film) cm^{-1}: 3400 (broad), 3080, 1640, 1040, 890.^1H δ: 5.65(1H, d, J= 7.7, H-2), 4.82(2H, s, H-16), 3.41(1H, d, J= 7.7, H-1), 2.72(1H, m, H-14), 1.75(6H, s, Me–17 and Me–19), 0.86 and 0.74(3H, s, ea, Me-20 and Me-18).^{13}C δ: see Table 2.

2-valparen-15-ol: **10**. Colourless oil. $[\alpha]_D$ –5.0($CHCl_3$, c 0.5). IR ν_{max} (film) cm^{-1}: 3500 (broad), 1650, 950.^1H δ: 5.38(1H, m, H-2), 1.73(3H, s, Me-19), 1.24 and 1.21 (3H, s, ea, Me-16 and Me-17), 0.82 and 0.75(3H, s, ea, Me-20 and Me-18). ^{13}C δ: see Table 2. To **10** (30 mg, 0.10 mmol) solved in pyridine(6 ml), cooled in an ice bath and stirred, was added $POCl_3$ (0.23 ml, 2.50 mmol) freshly distilled. The mixture was maintained in the ice–bath for an hour and then six hours at room temperature, monitoring the reaction by TLC. The mixture was then poured into ice, warmed to room temperature and extracted with ether. The organic phase was washed with 2N HCl and water, dried over Na_2SO_4. Evaporation of the solvent and purification by CC eluted with hexane afforded 24 mg (88%) of **13** (*vide infra*).

3(19),15-valparadien-2β-ol: **11**. Needle crystals. mp 129-130°C (*n*–hexane–EtOAc).$[\alpha]_D$ +23.6 ($CHCl_3$, c 0.7). IR ν_{max} (film) cm^{-1}: 3320, 3080, 1640, 1080, 1040, 910 and 890. ^1H δ: 5.00 and 4.92(1H, s, ea, H-19), 4.79(2H, s, H-16), 4.24(1H, dd, J=10.5 and 6.3), 2.70(1H, m, H-14), 1.75(3H, s, Me-17), 0.91(3H, s, Me-20),

0.71(3H, s, Me-18). ^{13}C δ: see Table 2. EIMS m/z (rel. int.): 288[M+] (1), 270(5), 255(6), 245(1), 227(6), 201(7), 187(11), 173(10), 159(21), 146(70), 119(30), 105(48), 91(85), 79(87), 55(100).

Isomerization of **1** *with* I_2 */ benzene*: *2,8(14)-valparadiene* : **14**. Compound **1** (61 mg, 0.22 mmol) was dissolved in 8 ml of dry C_6H_6, I_2 (traces) was added and the mixture was heated under reflux for 17 hours. Benzene was added and the reaction mixture was washed with $Na_2S_2O_3$ solution and water, affording, after CC, 45 mg (74%) of **14** as a colourless oil. IR(film) ν_{max} cm^{-1}: 1650, 1470, 1390, 840. ^1H δ: 5.38 (1H, m, H-2), 2.65 (1H, m, H-15), 1.74 (3H, s, Me-19), 0.99 and 0.93 (3H, d, ea, J= 6.8, Me-16 and Me-17), 0.90 (3H, s, Me-20) and 0.81 (3H, s, Me-18). ^{13}C δ: see Table 2.

Isomerization of **2** *with* I_2 */ benzene*: *2,14–valparadiene*: **13** *and 2,8(14)-valparadiene*: **14**. Compound **2** (56 mg, 0.21 mmol) was dissolved in 8 ml of dry C_6H_6, I_2 (traces) was added and the mixture was heated under reflux for 2.5 hours, monitoring the reaction by ^1H NMR. Benzene was added and the reaction mixture was washed with $Na_2S_2O_3$ solution and water, affording, after PTLC over SiO_2–$AgNO_3$(15%) 8 mg (14%) of **13** and 17 mg (30%) of **14** (*vide supra*). Compound **13**. Colourless oil. IR(film) ν_{max} cm^{-1}: 1640, 1470, 1390, 840. ^1H δ: 5.42 (1H, m, H-2), 1.74(9H, s, Me-19, Me-16, Me-17), 0.85 (3H, s, Me-20) and 0.57 (3H, s, Me-18). ^{13}C δ: see Table 2.

Treatment of **2** *with* m*CPBA*: **5**. To compound **2** (139 mg, 0.51 mmol) dissolved in CH_2Cl_2 (3 ml) freshly distilled, cooled in an ice–bath was added *m*CPBA (86 mg, 0.50 mmol). The reaction was vigorously stirred at room temperature for 15 minutes. After the usual work–up, the crude reaction product afforded after CC 127 mg (86%) of **5** and 6 mg (4%) of **15**. The latter was obtained as the only reaction product when **2** was treated with an excess of *m*–CPBA (3mmol/mmol). *2,3–β-15,16-diepoxy-valparane*: **15**. ^1H δ: 2.71(1H, m, H-2), 2.52(2H, m, H-16), 1.32(6H, s, Me-17 and Me-19), 1.01(3H, s, Me-20), 0.78(3H, s, Me-18). ^{13}C δ: see Table 2.

Treatment of **5** *with* BF_3•Et_2O: **7**. To compound **5** (62 mg, 0.22 mmol) dissolved in dry benzene (4ml) was added a drop of BF_3•Et_2O. The mixture was stirred at room temperature for 12 minutes. Then, water was added and the mixture extracted with ether, washed with 5% $NaHCO_3$ and water and dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude reaction product (57 mg) was chromatographed (*n*–hexane:EtOAc, 95:5) affording **7** (42 mg).

Treatment of **5** *with* $HClO_4$:**11**. To compound **5** (25 mg, 0.09 mmol) disssolved in DMF was added two drops of 60% $HClO_4$. The mixture was stirred at room temperature for 9 hours .Then, water (20 ml)was added and the mixture was extracted with ether. After usual work–up, the crude reaction product was chromatographed affording 18 mg of **11**. The latter (18 mg) was acetylated with Ac_2O/Pyridine affording 17 mg of *2β- acetoxy-3(19),15-valparadiene*: **16**. Colourless oil. IR(film) ν_{max} cm^{-1}: 3080, 1750, 1650, 1480, 1390, 1250 and 910 cm-1. ^1H δ: 5.41(1H, dd, J_1= 10.7, J_2= 5.4 Hz, H-2), 5.04 and 4.98(1H, s, ea, H-19), 4.80(2H, s, H-16), 2.02(3H, s, Me-CO_2), 1.75(3H, s, Me-17), 0.97(3H, s, Me-20), 0.72(3H, s, Me-18). ^{13}C δ: see Table 2.

Treatment of **5** *with* H_5IO_6, *3–oxo–2,3–*seco*–15–valparen–2–al*: **17**. To compound **5** (102 mg, 0.35 mmol) dissolved in THF (3 ml) and water (0.6 ml) was added H_5IO_6 (159 mg, 0.70 mmol) and stirred at room temperature for 9 hours. Then water was added and the mixture extracted with ether, washed with $Na_2S_2O_3$, 5% $NaHCO_3$, water and dried over Na_2SO_4. Removal of the solvent afforded 98 mg of crude product that was chromatographed affording **11** (32 mg, 35 %) and **17** (60 mg, 59 %). *3-oxo-2,3-*seco*-15-valparen-2-al*: **17**. Colourless oil. IR(film) ν_{max} cm^{-1}: 3080, 1705, 1640, 1460, 1380, 1205 and 880.^1H δ: 9.85(1H, t, J= 3.2, H-2), 4.82(1H, q, J=1.1, H_a-16), 4.79(1H, s, H_b-16), 2.69(1H, m, H-14), 2.49(2H, q, J= 8.1, H-4), 2.33 and 2.23(1H,

dd, ea, J= 14.5 and 3.2, H-1), 2.13(3H, s, Me-19), 1.75(3H, d, J= 1.1, Me-17), 1.02(3H, s, Me-20), 0.81(3H, s, Me-18). ^{13}C δ: see Table 2.

Treatment of **17** *with KOH/EtOH: Valparolone,* **8**. To **17** (42 mg) dissolved in EtOH (4 ml), under N_2 atmosphere, 3M KOH/EtOH (0.15 ml) was added. The mixture was mantained at room temperature for 32 hours. After that time, water was added and the mixture was extracted with ether. The organic phase was washed with 2N HCl and dried over Na_2SO_4. The residue was chromatographed to afford **8** (45 mg).

Hydrogenation of **8**: *valparolan-3-ol* **18**. To compound **8** (97 mg, 0.34 mmol) dissolved in dry ether (12 ml) was added PtO_2 (8 mg). The reaction flask was purged with H_2 and the reaction was maintained under H_2 atmosphere for 1.5 hours. Then, ether was added, the mixture filtered and the solvent evaporated to afford **18** (96 mg, 97%) as a colourless oil. IR(film) ν_{max} cm^{-1}: 3370(broad), 1460, 1380, 1070, 1010. ^1H δ: 3.60(1H, m, H-3), 1.18(3H, d, J= 6.7, Me-19), 0.82 and 0.93(3H, d, ea, J= 5.9, Me-16 and Me-17), 0.88(3H, s, Me-20) and 0.70(3H, s, Me-18). ^{13}C δ: 44.9, 25.5, 72.5, 56.6, 44.9, 46.2, 44.7, 55.7, 22.7, 44.2, 34.3, 40.9, 27.6, 48.0, 32.0, 22.7, 23.9, 15.7, 25.9, 20.5.

Swern oxidation of **18**: *Tetrahydrovalparolone* **19**. To a solution of oxalyl chloride (0.03 ml, 0.34 mmol), CH_2Cl_2 (3 ml), under N_2 atmosphere and at –60°C was slowly added a solution of DMSO/CH_2Cl_2 (0.06 ml, 0.84 mmol/ 1 ml). After 30 minutes **18** (96 mg, 0.33 mmol) in CH_2Cl_2 (3 ml) was added and maintained for 1 hour under those conditions. Then, Et_3N (2 ml) was added and the reaction warmed to room temperature. After 5 minutes, water is added and the mixture was extracted with ether, washed with 2N HCl and water. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. The crude reaction product afforded after CC **19** (78 mg, 82%) as a colourless oil. IR(film) ν_{max} cm^{-1}:1710, 1460, 1390. ^1H δ: 3.02(1H, m, H-4), 2.14(3H, s, Me-19), 0.92 and 0.81(3H, d, ea, J= 6.3, Me-16 and Me-17), 0.90(3H, s, Me-20) and 0.70(3H, s, Me-18). ^{13}C δ: see Table 2.

Bayer-Villiger Reaction of **19**: *3,19-di*nor-*4-acetoxy-valparolane*: **20**. To **19** (78 mg, 0.27 mmol) dissolved in CH_2Cl_2 (5 ml), was added *m*–CPBA (65 mg, 0.38 mmol), the mixture was stirred under N_2 atmosphere during 8 days, monitoring the reaction by TLC. The solvent was removed and the residue extracted with ether. After the usual work–up, the crude reaction product was chromatographed affording **20** (59 mg, 72%). Colourless oil. IR(film) ν_{max} cm^{-1}: 1740, 1470, 1370, 1250. ^1H δ: 4.74(1H, m, J= 5.4, H-4), 2.03(3H, s, $MeCO_2$), 0.94(3H, s, Me-20), 0.92 and 0.81(3H, d, ea, J= 6.3, Me-16 and Me-17), 0.70(3H, s, Me-18).

Hydrolysis of **20**: *3,19-di*nor-*valparolan-4-ol*, **21**. **20** (19 mg, 0.06 mmol) dissolved in 5 ml of 10% K_2CO_3/MeOH was stirred during four hours at room temperature. After the usual work–up, **21** (17 mg, 98%) was obtained as a colourless oil. IR(film) ν_{max} cm^{-1}: 3400, 1470, 1390, 1050 and 950. ^1H δ: 3.63(1H, m, J= 6.0, H-4), 0.93(3H, s, Me-20), 0.93 and 0.82(3H, d, ea, J= 6.0, Me-16 and Me-17), 0.71(3H, s, Me-18). ^{13}C δ: see Table 2.

Swern oxidation of **21**: *3,19-di*nor-*valparolan-4-one*: **22**. To a solution of oxalyl chloride (0.02 ml, 0.2 mmol), CH_2Cl_2 (1 ml), under N_2 atmosphere and at –60°C was slowly added DMSO(0.05 ml, 0.7 mmol) in CH_2Cl_2 (0.5 ml). After 30 minutes **21** (9 mg, 0.03 mmol) in CH_2Cl_2 (1 ml) was added and maintained for 1 hour under those conditions. Then, Et_3N (0.5 ml) was added and the reaction warmed to room temperature. After 5 minutes, water was added and the mixture was extracted with ether, washed with 2N HCl and water. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to afford after CC **22** (6 mg, 67%) as a colourless oil. IR(film) ν_{max} cm^{-1}: 1705, 1460, 1380, 1160, 1070, 1040 and 1010. ^1H δ: 1.12(3H, s, Me-20), 0.95 and 0.82(3H, d, ea, J= 6.4, Me-16 and Me-17), 0.74(3H, s, Me-18).^{13}C δ: see Table 2. EIMS m/z

(rel. int.): 262[M+] (29), 247(6), 219(57), 201(45), 191(12), 177(20), 149(55), 123(26), 109(28), 95(100), 67(61), 55(72). CD: $\Delta\varepsilon_{298}$ -0.84.

2,2-dimethoxy-2,3-seco-15-valparen-3-one: **12**. Colourless oil. $[\alpha]_D$ -4.9($CHCl_3$, c 1.8). IR ν_{max} (film) cm^{-1}: 3060, 1710, 1640, 1110, 1060, 1040 and 890. ^1H δ: 4.80(2H, bs, H-16), 4.44(1H, t, J= 4.9, H-2), 3.27(6H, s, OMe), 2.67(1H, m, H-14), 2.49(2H, d, J= 6.8, H-4), 2.12(3H, s, Me-19), 1.75(3H, s, Me-17), 0.87(3H, s, Me-20) and 0.81(3H, s, Me-18). ^{13}C δ: see Table 2. **12** (20 mg, 0.06 mmol) was hydrolyzed in the presence of TsOH (20 mg, 0.12 mmol) in 3 ml of acetone, during 12 hours. The solvent was removed and the residue was taken–up in ether, washed with 5% $NaHCO_3$ and water, dried over anhydrous Na_2SO_4. After filtration and evaporation **17** (18 mg, 98 %) was obtained.

References and Notes

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   It has been observed a typing mistake in the $[\alpha]_D$ sign of valparene **2** (2,15–valparadiene) and valparone **7** (15–valparen–2–one). The correct values have been included in the experimental part of this paper.
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18. According to the referee's comment, we thought that the extraction conditions and purification processes are not so drastic to induce the formation of artefacts, except in this case. More over, we cannot discard the existence of a biogenetic route from a common precursor, *e. g.* **5** that could lead to the triene **3** and to the isomeric allylic alcohols, a common functionalization found in natural products.