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New Diterpenes with a Valparane Skeleton

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Abstract: Nine new valparane diterpenoids have been isolated from *Halimium viscosum*, Valparaíso. Their structures were determined by spectroscopic methods and/or chemical correlations.

The acid fraction of the *Halimium viscosum* chemotype[1] collected at Valparaíso (Zamora, Spain), provided diterpenic acids with a labdane skeleton and functionalized with a carboxylic function at C-17[2] and the neutral fraction provided diterpenoids belonging to two new and different carbon skeleta: valparane[3] and valparolane.[4]

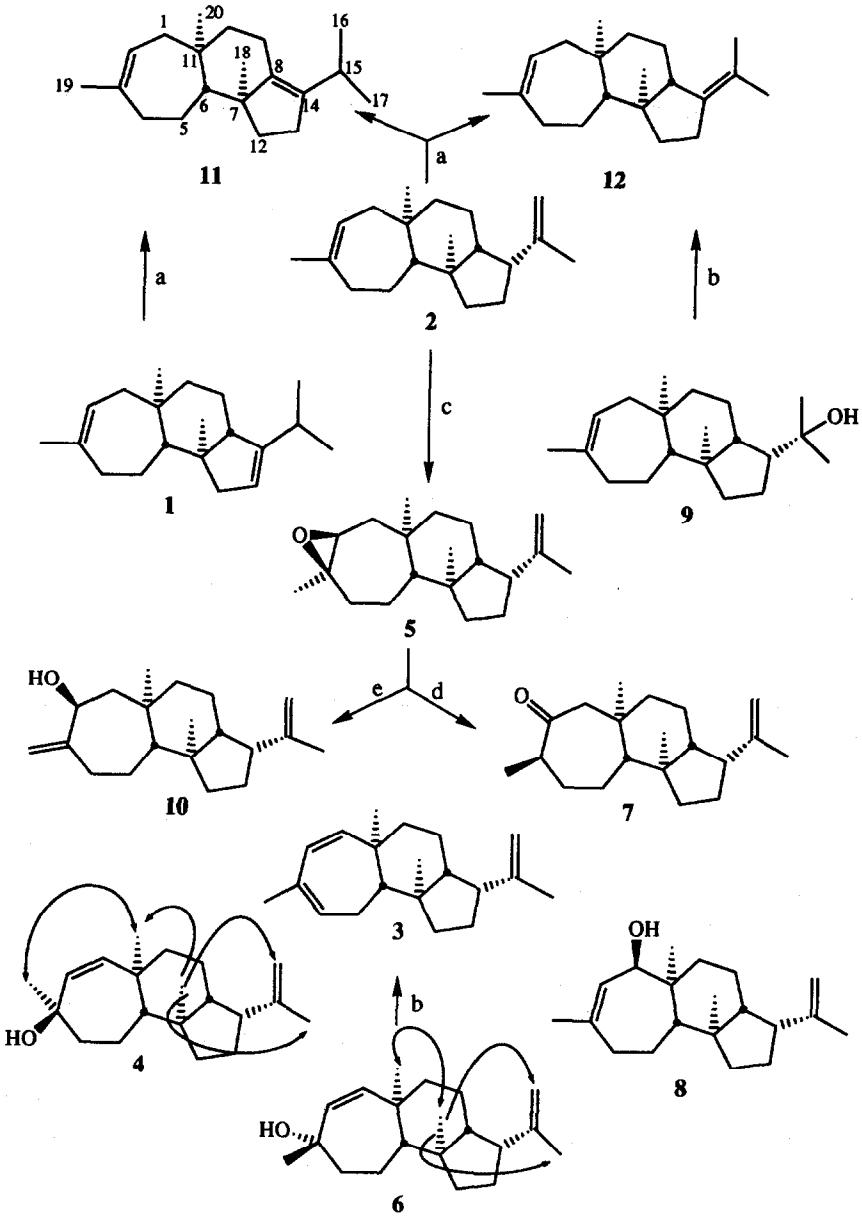
We have isolated a hydrocarbon named valparene, **2** (2,15–valparadiene),[3] that belongs to the valparane class and whose structure has been determined by spectroscopic methods and unambiguously confirmed by X–ray diffraction of one of its derivatives.

We now report the structure determination of nine new valparanic compounds: **1** and **3** to **10** (Scheme 1). Their isolation has been achieved by repeated column chromatographies over SiO_2 and /or SiO_2–$AgNO_3$. The less polar compound, **1**, is a hydrocarbon that contains in its ^{13}C NMR spectrum (Table 1)[5] twenty carbon atoms: five methyl groups, six methylenes, five methines (two of them are sp^2) according to the DEPT subspectra, and four quaternary carbon atoms, two of them are sp^2. The MS spectrum shows a molecular ion peak at m/z 272 corresponding to the formula $C_{20}H_{32}$ (HR EIMS 272.4741, Δ 0.2 mmu), thus compound **1** must be a tricyclic molecule with two unsaturation sites. The ^1H NMR spectrum exhibited characteristic signals of a valparane skeleton:[6] two olefinic hydrogens (δ 5.39 and 5.18) and five methyl groups: one of them is a singlet at δ 1.75 attached to an sp^2 carbon, two doublets (δ 0.94 and 0.89) corresponding to the gem-dimethyl of an isopropyl group with restricted rotation and two angular methyl groups at 0.90 and 0.87 ppm.

These deductions were confirmed by 2D Heteronuclear correlation experiments (one bond and long–range): specially significant are the couplings observed between Me–18, –19 and –20 because of the similarity with those observed for the same methyl groups in valparene, **2**. Furthermore, the long range couplings between H–16 and H–17 with the olefinic carbon atom at δ (148.2) indicate that the isopropyl group must be attached to an olefinic carbon and, thus the methyl groups are allylic to a trisubstituted double bond. All these data suggest that the unsaturation site must be located at C-13 on ring C to agree with a valparane structure and therefore **1** must be an isomer of **2**, that can be designated as 2,13–valparadiene.

Compounds **1** and **2** were also chemically correlated by transformation of each one into an isomeric diene **11**. When **1** was dissolved in benzene and refluxed with a catalytic amount of I_2, **11** was obtained. When **2** was treated under the same conditions a mixture of dienes (**11** and **12**), that can be separated by column chromatography over SiO_2–$AgNO_3$, was obtained.

A third hydrocarbon, **3**,[7] was isolated from the same fractions that contained **1** and **2**. Its ^{13}C NMR spectrum shows peaks corresponding to twenty carbon atoms, six of them olefinic (three methines, two quaternaries and one terminal methylene group). According to the MS spectrum the formula should be $C_{20}H_{30}$ (m/z 270.4582, M^+ Δ 0.1 mmu), that is in agreement with a tricyclic diterpene with three unsaturation sites.



Scheme 1. a) I_2, C_6H_6; b) $POCl_3$; c)*m*CPBA; d) BF_3•Et_2O; e) $HClO_4$

Similar spectroscopic features, with those of compounds **1** and **2** suggested a valparane skeleton. Scrutiny of the ^1H NMR spectrum shows five olefinic hydrogens (two of them correspond to a terminal methylene group such as in **2**) and four methyl groups (two of them attached to sp^2 carbons and two angular

methyl groups). The main difference between **3** and **2** is the presence of a conjugate double bond system on ring A (UV: λ_{max} 261 nm), therefore the structure of **3** is determined as 1,3,15–valparatriene.

Compounds **5** and **7** were identified by their spectroscopic properties. Their structures are chemically correlated with **2**, that upon treatment with an equimolar amount of *m*CPBA, provided an epoxide **5** (2,3–β–epoxy–15-valparene).[3] When **5** was treated with BF_3•Et_2O led to a cycloheptanone, **7** (15–valparen –2–one).[3]

The more polar compounds are a series of hydroxy derivatives: **4**, **6**, **8**, **9** and **10**. Analysis and comparison of the spectroscopic properties of **4** and **6** (IR, ^{1}H NMR, ^{13}C NMR and MS)[8] indicate that both have the same skeleton and that they should be epimers at C-3. **4** corresponds to 1,15-valparadien-3β-ol and **6** to 1,15-valparadien-3α-ol. The configuration at C-3 for each one of them has been determined by differential nOe experiments (Scheme 1). Furthermore, **6** could also be transformed in **3** by treatment with $POCl_3$. Compound **8**, according to its spectroscopic properties,[9] is an isomer of **4** and **6**, but instead of being a tertiary allylic alcohol, it is a secondary allylic alcohol (δ 3.41, 1H, d, J =7.7 Hz) with a trisubstituted double bond on ring A (δ 5.65, 1H, d, J = 7.7 Hz; 1.75, 3H, s), feature that is confirmed by 2D Homonuclear correlation spectroscopy (^{1}H–^{1}H COSY). The configuration for the hydroxyl group at C-1 was determined considering the value of the coupling constant for the *gem*-hydrogen, thus **8** has the structure of 2,15-valparadien-1β-ol.

C	1	3	4	6	8	9
1	44.4	145.1	130.9	133.5	77.2	46.4
2	122.4	128.6	138.2	142.4	125.4	122.8
3	141.9	135.5	77.0	73.6	143.9	141.3
4	33.7	123.5	38.8	43.2	33.8	34.9
5	27.1	29.4	23.3	23.7	24.9	24.1
6	57.9	52.9	56.8	57.7	52.6	64.5
7	45.7	46.5	46.6	46.9	43.5	46.2
8	51.6	54.7	51.0	54.8	54.5	54.6
9	23.9	21.4	21.9	21.6	21.7	22.6
10	43.7	43.5	46.2	45.1	40.2	45.8
11	34.1	41.4	40.4	40.4	40.5	36.1
12	42.8	41.6	42.7	41.7	41.6	40.9
13	119.2	27.3	27.5	27.2	27.3	26.5
14	148.2	46.5	49.3	46.4	46.7	51.3
15	35.2	148.1	148.0	148.4	148.9	73.8
16	22.0	110.3	110.2	110.3	110.2	28.9
17	21.9	25.3	25.8	24.9	25.0	30.9
18	18.9	16.2	17.4	16.2	16.6	16.2
19	25.0	26.0	28.9	30.1	26.9	25.6
20	21.6	24.1	21.8	21.7	20.5	21.0

Table 1. ^{13}C NMR data (50.3 MHz, $CDCl_3$) δ ppm

The hydroxy derivative **9** exhibited as characteristic signals: in its ^{1}H NMR spectrum:[10] five methyl groups (one attached to an sp^2 carbon, two of them deshielded by an oxygen function and two angular methyl groups) and twenty carbon atoms in its ^{13}C NMR spectrum. Comparison of these data with those of valparene **2**, enable the structure to be elucidated as 2–valparen-15-ol, that is confirmed by dehydration of **9** with $POCl_3$ to obtain **12**, a valparadiene already obtained from **2**.

Finally, the new natural product **10**, is identical to a hydroxy derivative obtained by treatment of the epoxide **5** with $HClO_4$,[4] thus confirmed its structure as 3(19),15–valparadien–2β–ol.

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5. ^{13}C NMR data for compounds **1**, **3**, **4**, **6**, **8**, **9** are given in Table 1.
6. Compound **1**: $[\alpha]_D$ =+ 36.7 ($CHCl_3$, c = 1.24 %). IR ν_{max} (film) cm^{-1}: 1640, 1460, 1380, 1100, 840. ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.39 (1H, tq, J=1.8 and 7.3 Hz, H-2), 5.18 (1H, dt, J=1.4 and 3.7 Hz, H-13) , 1.75 (3H, s, H-19) , 0.94 (3H, d, J= 6.6Hz, H-16), 0.90 (3H, s, H-20), 0.89 (3H, d, J=6.6 Hz, H-17), 0.87 (3H, s, H-18).
7. Compound **3**: UV λ_{max} : 261 nm (ε: 7500). IR ν_{max} (film) cm^{-1}: 3090, 1640, 1600, 1470, 1390, 890. ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 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(6H, s, H-17 and H-19), 1.03 and 0.76(3H, s, ea., H-20 and H-18).
8. Compound **4**: $[\alpha]_D$ = – 60.8 ($CHCl_3$, c = 1.25 %). IR ν_{max} (film) cm^{-1} : 3400 (broad), 3060, 1640, 1470, 1380, 1160, 890, 840. ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.53 and 5.12(1H, d, ea., J=9.7 Hz, H-1 and H-2), 4.82(2H, s, H-16), 2.72(1H, m, H-14), 1.77(3H, s, H-17), 1.32(3H, s, H-19), 1.07(3H, s, H-20) and 0.92(3H, s, H-18).
   Compound **6**: $[\alpha]_D$ = –34.2 ($CHCl_3$, c=1.42 %). IR ν_{max} (film) cm^{-1}: 3400 (broad), 3080, 1640, 1100, 890. ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.30(1H, dd, J=12.7 and 1.4 Hz, H-1), 5.14(1H, m, H-2), 4.80 (2H, s, H-16), 2.71 (1H, m, H-14), 1.75 (3H, s, H-17), 1.33 (3H, s, H-19), 1.00 (3H, s, H-20), 0.78(3H, s, H-18). MS 70eV m/z: 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).
9. Compound **8**: $[\alpha]_D$ = –1.4 ($CHCl_3$, c = 0.74 %). IR ν_{max} (film) cm^{-1}: 3400 (broad), 3080, 1640, 1040, 890.^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.65(1H, d, J=7.7Hz, H-2), 4.82(2H, s, H-16), 3.41(1H, d, J=7.7 Hz, H-1), 2.72(1H, m, H-14), 1.75(6H, s, H-17 and H-19), 0.86 and 0.74(3H, s, ea., H-20 and H-18).
10. Compound **9**: $[\alpha]_D$ = –5.0 ($CHCl_3$, c = 0.54 %). IR ν_{max} (film) cm^{-1}: 3500 (broad), 1650, 950. ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.38(1H,m, H-2), 1.73(3H, s, H-19), 1.24, 1.21, 0.82 and 0.75 (3H,s, ea., H-16, H-17, H-20 and H-18).

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