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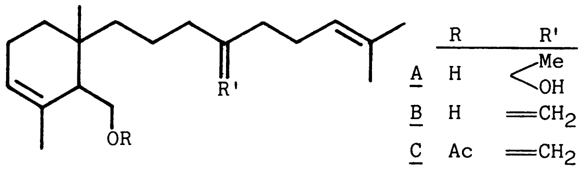
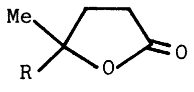
# A REVISED STRUCTURE FOR DITERPENOID MAGYDARDIENDIOL

J. de PASCUAL TERESA,* C. GRANDE, J. R. MORAN, and M. GRANDE[†]
Departamento de Química Orgánica, Facultad de Química,
Universidad de Salamanca, Spain

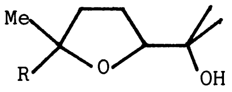
The revised structure and the stereochemistry shown are proposed for magydardiendiol on the basis of chemical and spectral data, mainly 200 MHz $^1$H-NMR and CD spectra. The proposed structure is: (1S,2R,5S,6R) 2-hydroxymethyl-1,5-dimethyl-6-(3-methyl-2-butenyl)-5-(4-methyl-3-pentyl)cyclohexanol.

A few years ago we reported the isolation of a novel diterpenoid, magydardiendiol, MD, and two related terpenoids, magydartrienol, MT, and its acetate, from the aerial parts of Magydaris panacifolia (Vahl)Lange (Umbelliferae).$^{1)}$ The proposed constitution for these substances, A, B and C, was based on spectral data (IR, MS, 60 MHz $^1$H-NMR) as well as on chemical reactivity: acetylation of magydardiendiol ($Ac_2O$/py rt) gave a monoacetate which was dehydrated ($SOCl_2$/py 0°C) to magydartrienol acetate and hydrolysed (KOH/MeOH) to natural trienol, MT. The presence of a $\gamma,\delta$-unsaturated tertiary alcohol was evidenced by oxidation ($Na_2CrO_4$/HOAc-NaOAc) and by epoxidation (m-CPBA/$CH_2Cl_2$) of MD monoacetate. The products from these oxidations were a $\gamma$-lactone, D, ($\nu$ = 1770 cm$^{-1}$) and/or a tetrahydrofurane alcohol, E, structurally related to linalyl oxide,$^{2)}$ respectively.





D



E

To get more information on the constitution and the stereochemistry of magydardiendiol, some NMR experiments were carried out:

1.- Addition of Eu(fod)$_3$ to trienol MT caused an important downfield shift of vinylic protons of the terminal methylene group (P = 13 and 6)$^{3)}$ what means that the hydroxymethyl (P = 25) and methylidene groups are rather close. On the other hand, the low effect of the shift reagent an the vinylic methyls (P = 1.5 and 0.6) pointed out that these methyl groups are away from the hydroxyl.

2.- Dehydration of the primary alcohol of MD (i: p-TsCl/py; ii: 2,6-lutidine, reflux), gave a methylidene derivative in low yield which was not conjugated (UV: end absorption).

3.- Addition of trichloroacetylisocyanate (TAI) to a NMR sample of diol MD, induced an important downfield shift of two previously overlapped proton signals.$^{4)}$ Double irradiation on the primary alcohol protons (esterified as trichloroacetylcarbamate) caused a collapse of the low field deshielded multiplet, arousing a more simplified multiplet but not a singlet as was expected for the constitution A.

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[†] Present address: Dept. Química Orgánica, Apartado 99, Universidad de Alicante, Spain.

All data from these three experiments disagree with the proposed constitution for magydardiendiol and therefore a revision of its structure was necessary.

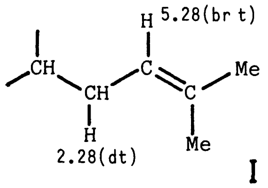
Meanwhile, Prof. H. Nagano gave us to know their success in the transformation of α-santonin into a pair of diastereomeric trienols with the structure B, but the $^1$H-NMR signals of the synthetic trienols were different from those of the natural magydartrienol.$^{5)}$

We have had recently access to a 4.7 T NMR spectrometer (200 MHz for $^1$H; 50.3 MHz for $^{13}$C) whose availability has been decisive for establishing the structure of magydardiendiol proposed now: the vinylic methyls of MD, MT, and those of their acetates, absorb at 60 MHz as one broad singlet or as two signals whose integral was not clearly resolved. Even in the LIS experiment on MT, only two methyl vinylic signals could be observed.

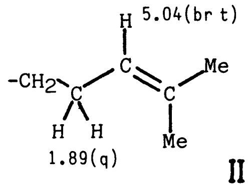
The $^{13}C\{^1H\}$ NMR spectrum of magydardiendiol in $CDCl_3$ showed 19 singlets (at 20 MHz). The off-resonance spectrum allowed us to identify four $C_{sp^2}$ as two >C=CH– units, and the following $C_{sp^3}$: two $\geqslant$C–, two $\geqslant$CH, six $>CH_2$ and five $-CH_3$. The presence of two methine carbons is not compatible with the constitution A and to fit the above signals to an empirical formula $C_{20}H_{36}O_2$ (two hydroxyl groups, two double bonds and one cycle), it is necessary the presence of one methyl more. In fact, the singlet at 25.6 ppm (20 MHz) appears as two signals at 25.76 and 25.70 ppm when recorded on the 50.3 MHz spectrometer. The $^{13}$C spectrum of MT showed also four methyl signals but the NOE supressed integration of the singlet at 25.7 ppm disclosed the presence of two carbon atoms.

The 200 MHz $^1$H-NMR spectrum of magydartrienol showed five independent methyl singlets, four of them were vinylic. These vinylic methyl groups were not resolved in the 200 MHz spectrum of diol MD, but in this case the integral of the methyl signals at 1.68 and 1.59 ppm showed a 9:3 ratio. Hence, it seems evident the presence of two methyl groups on a quaternary $C_{sp^3}$ and two isobutenyl groups, $-CH=C(Me)_2$, in magydardiendiol.

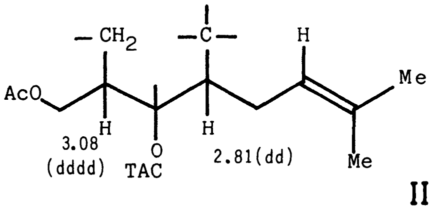
An inspection of the 200 MHz $^1$H-NMR spectrum of MD monoacetate, allowed us to know more structural details. The vinylic protons of two trisubstituted double bonds ($\delta$ = 5.28 and 5.04 ppm) were each coupled with a vicinal methylene. One allylic proton absorbed at 2.28 ppm (1H, dt, $J_d$ = 16 Hz, $J_t$ = 8 Hz) and it was coupled with the 5.28 signal as was evidenced by double irradiation. The allylic protons coupled with the 5.04 signal were detected as a quartet at 1.89 ppm (2H, q, J = 8 Hz). This signal became a triplet by irradiation on the 5.04 ppm signal. These double resonance experiments are consistent with the partial structures I and II:



I



II



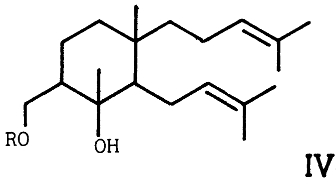
III

The addition of trichloroacetyl isocyanate to a NMR sample of MD monoacetate caused an important downfield shift of two proton signals.$^{4)}$ These signals were nicely resolved (4.7 T FT spectrometer) at 3.08 ppm (1H, dddd, J = 12, 7, 6 and 4 Hz) and at 2.81 ppm (1H, dd, J = 7 and 4 Hz). The first signal was coupled with the $-CH_2OAc$ protons and the 2.81 signal was coupled with the allylic dt proton at 2.28 ppm (confirmed by double resonance). Consequently, the partial structure I can be expanded to III and this was also supported by:

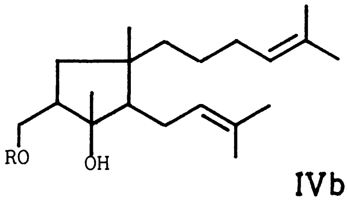
a) Oxidation to a γ-lactone, as mentioned above (partial structures D and E).

b) Oxidation of trienol MT with PCC/$CH_2Cl_2$ to a β,γ-unsaturated aldehyde [$\lambda_{max}$ = 304 nm ($\varepsilon$ = 63, hexane)] which easily evolutions to a α,β-unsaturated aldehyde [$\lambda_{max}$ = 252 nm ($\varepsilon$ = 9,600, EtOH)].

Partial structures II and III accounts for 18 carbon atoms out of 20. NMR spectra showed that the remaining two carbon atoms were one methyl and one methylene groups. The methyl group must be placed on the tetrasubstituted carbon of formula III, but the $-CH_2-$ and the side chain II could be accommodated as shown:



**IVa**



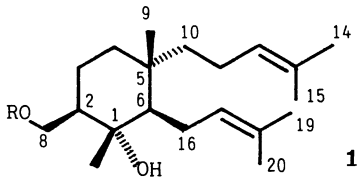
**IVb**

The size of the cycle was evidenced by hydrogenation ($H_2$/$PtO_2$-EtOH), dehydration ($SOCl_2$/py) and ozonolysis ($O_3$/$CH_2Cl_2$-py) of MD monoacetate. The resulting ketone showed a typical cyclohexanone IR absorption ($\nu$ = 1710 $cm^{-1}$) and therefore we concluded that the constitution of magydardiendiol is **IVa**. It is like a dimer of geranyl units linked through $C_1$—$C_{2'}$ and $C_3$—$C_{4'}$.

The **stereochemistry** assigned to magydardiendiol, **1**, is based on the following evidence.

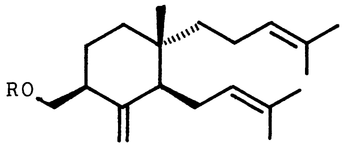
We have mentioned before that dehydration of **1** (or its monoacetate, **2**) with $SOCl_2$/py gave mainly (>90%) the exocyclic alkene magydartrienol, **3** (or **4**), even when dehydration was performed with p-TsOH/$C_6H_6$ reflux. This behaviour suggested us that the tertiary hydroxyl group in **1** must must be equatorial.$^{6,7)}$ Also, the shielding of the C-5 methyl ($\delta$ = 0.80 ppm in **1** and 0.73 ppm in **3**) can be explained if the methyl groups on C-1 and on C-5 are in an 1,3-syn-diaxial arrangement.

The $^1H$-NMR spectrum of the trichloroacetylcarbamate of **2**, showed for H-2 a dddd signal with J = 12, 7, 6, and 4 Hz. The coupling constants of 7 and 6 Hz were also present in the signals of the acetoxymethyl protons and therefore the coupling constants of H-2 with H-3 and H-3' are 12 and



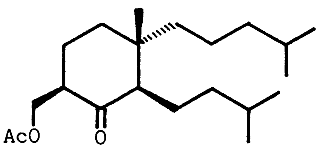
**1**: R = H

**2**: R = Ac

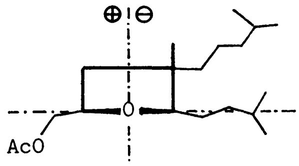


**3**: R = H

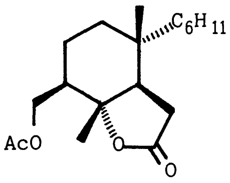
**4**: R = Ac



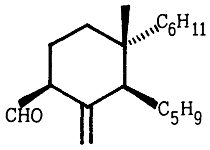
**5**



**5cd**



**6**



**7**

4 Hz. Only an axial configuration for H-2 can explain these couplings.

The *cis* relationship of H-2 and H-6 (equatorial C-6 side chain) was infered from the 8% NOE enhancement of H-2 multiplet (2.61 ppm) observed after irradiation on H-6 signal (2.18 ppm) of ketoester **5**.

Lastly, the absolute stereochemistry of magydardiendiol was established by CD measurements on the derivatives **5**, **6**, and **7**.

The CD curve of ketone **5** showed a negative Cotton effect [$\Delta\varepsilon_{292}$ = -2.13(hexane)] as corresponds to the outlined configuration. The intensity of this Cotton effect is also quite similar to that of cyclohexanones with the substituents as they are represented in the projection **5cd**.$^{8)}$

The same absolute configuration was also brought out from the CD curves of the $\gamma$-lactone **6** [$\Delta\varepsilon_{220}$ = +0.4 (hexane)],$^{9)}$ and the $\beta,\gamma$-unsaturated aldehyde **7** [$\Delta\varepsilon_{305}$ = +6.68 and $\Delta\varepsilon_{215}$ = -2.89 (hexane)].$^{10,11)}$

According to the preceding data$^{12)}$ we now propose the structure **1** for magydardiendiol: (-) (1*S*,2*R*,5*S*,6*R*) 2-hydroxymethyl-1,5-dimethyl-6-(3-methyl-2-butenyl)-5-(4-methyl-3-pentyl)-cyclohexanol.$^{13)}$

**References**

1) J. de Pascual Teresa, C. Grande, and M. Grande. Tetrahedron Lett., 1978, 4563.

2) J.F. Biellmann. Bull. Soc. Chim. Fr., 1967, 3459.

3) $P=\Delta\delta/([Eu(fod)_3]/[MT])$. A.F. Cockerill, G.L.O. Davies, R.C. Harden, and D.M. Rackham. Chem. Rev., 73, 553(1973).

4) Z. Samek and M. Budesinsky. Collect. Czech. Chem. Commun., 44, 558(1979).

5) H. Nagano, Y. Ishikawa, Y. Matsuo, and M. Shiota. Chem. Lett., 1982, 1947.

6) J. de Pascual-T., I.S. Bellido, and M.S. González. An. Quím., 74, 91(1978).

7) R.P. Walker and D.J. Faulkner. J. Org. Chem., 46, 1098(1981).

8) D.N. Kirk and W. Klyne. J. Chem. Soc., Perkin Trans. 1, 1974, 1076.

9) M. Legrand and R. Bocourt. Bull. Soc. Chim. Fr., 1967, 2241.

10) P.H. Schippers and H.P.J.M. Dekkers. J. Am. Chem. Soc., 105, 79(1983) and references cited.

11) The PMR spectra of **7** in $CDCl_3$ + $Eu(fod)_3$ showed 14 single proton isolated signals and 5 methyl signals which fully confirm the constitution proposed for this substance. For instance, when $|Eu|/|\mathbf{7}| = 0.7$, $\delta = 16.25$(*s*,br, CHO), 7.30(*s*, H-7a), 7.28(*t*,br, J=6.2, H-2), 6.16(*t*,br, J=6.5, H-17), 6.10(*s*, H-7b), 5.88(*dddd*, J=13.5, 7.5, 6.5, 4, H-3a), 5.51(*t sept*, J=7.5, 1.3, H-12), 4.60(*dddd*, J=13.5, 8, 6, 4.5, H-3b), 4.14(*m*, H-16a), 3.76(*ddd*, J=13.5, 8, 4, H-4a), 3.45(*dd* apparent, H-6), 3.38(*m*, H-16b), 2.87(*ddd*, J=13.5, 7.5, 4.5, H-4b), 2.56(*q*, J=7.5, 2H-11) 2.10(*m*, H-10), 2.08(*s*, Me-20), 1.92(*s*, 3Me), 1.75(*s*, Me-9). The conformation of the six member cycle in **7** must be different from that of **1** to **6** because of overlapping between CHO and C=C groups, as concluded from NMR, UV and CD data.$^{12)}$

12) A full paper on coumarins and terpenoids from *Magydaris panacifolia*, with more detailled information on magydardiendiol and derivatives, will be published elsewhere.

13) In order to confirm the structure **1**, a sample of magydardiendiol was sent for X-ray crystallographic analysis to Prof. H. Nagano, to whom we are indebted, but unfortunatly it has not been possible yet to obtein a single crystal for this study. Professor Nagano is now in agreement with the new structure.

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