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Minor Sesquiterpenes from *Maytenus canariensis* with Insecticidal and Antifeedant Activity

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Abstract: One known and four new sesquiterpenes with dihydro-β-agarofuran skeletons were isolated from *Maytenus canariensis* (Celastraceae). Their structures were determined by means of ^{1}H and ^{13}C NMR spectroscopic studies, including homo and heteronuclear correlations, ^{1}H and ^{13}C long range correlation spectra with inverse detection (HMBC) or selective INEPT and NOE experiments. Their absolute configurations were determined by means of CD studies. Two of the compounds which had a new basic polyhydroxylated 3,13-dideoxy-evoninol skeleton exhibited powerful insecticidal activity against *Spodoptera littoralis* and the others proved antifeedant against the same insect in an election test.

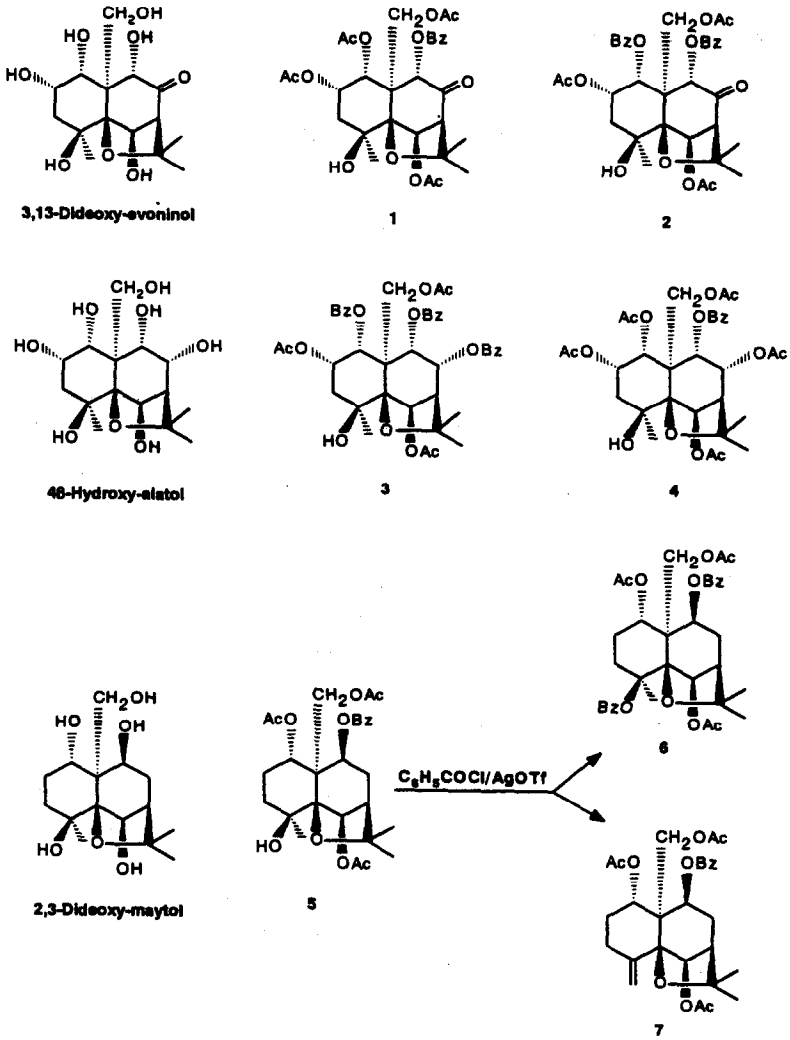
Species of Celastraceae have a long history in traditional medicine. The continued use, for example, of *Catha edulis* ("khat") in North East Africa, Ethiopia, Somalia and the Yemen to offset fatigue and hunger constitutes a sort of addiction, khatism, which has serious social consequences in these areas, the Arabian peninsula, Pakistan and the United Kingdom[1]; a team based at the University of Nottingham has made relevant contributions over the last 20 years on the subject[2,3]. In the Canary Islands shepherds are known to chew the leaves of *Maytenus canariensis* (Loes) Kunk et Sund[4], an endemic species, to ward off fatigue[5].

The interest generated by polyester sesquiterpenes from the Celastraceae has increased in line with the complexity of the substances isolated and the possibility of their application in the struggle against insect plagues as an alternative to the synthetic insecticides[6].

Earlier papers on *Maytenus canariensis* reported the isolation and structural elucidation of bioactive metabolites[7,8] with diverse structures[9,10] and now we are reporting the isolation and identification of five sesquiterpenes (**1-5**) with a dihydro-β-agarofuran sesquiterpene skeleton separated from the ethanol extract of *Maytenus canariensis*. Except for **4** which had already been isolated from another species of the Celastraceae[11], these sesquiterpenes were new and their structures were determined from ^{1}H and ^{13}C NMR studies, including 2-D homo and heteronuclear experiments, ^{1}H-^{13}C long range correlation spectra with inverse detection (HMBC) or selective INEPT and NOE experiments; the absolute configurations of both natural products and synthetic derivatives were determined by circular dichroism studies using the octant rule[12] or the exciton chirality method[13,14].

Compounds **1** and **2** have a novel basic polyhydroxylated 3,13-dideoxy-evoninol skeleton involving the presence of a carbonyl group in the molecule[15] which, according to our data[16], is probably responsible for the powerful insecticidal activity shown when it is ingested on vegetable disks[17] by *Spodoptera littoralis*, with

a DL_{100} of 1 and 0.1 $\mu g/cm^2$, respectively. This is the first time that such activity has been registered for non-macrocyclic dihydro-β-agarofuran sesquiterpenes. Compounds **3-5** exhibited antifeedant activity on the same insect when the vegetable disk method was used in an election test and compounds, **4** and **5**, proved more powerful than triphenyl tin acetate which is used as standard in this type of assay[17].



After repeated chromatography of the ethanol extract on Sephadex LH-20 and silica gel, five metabolites (**1-5**) were isolated. Compound **1** had the molecular formula, $C_{30}H_{36}O_{13}$ (HREIMS) and its IR had absorption bands for a hydroxy group (3565 cm^{-1}) and ester groups (1745 cm^{-1}). When the product was treated with acetic anhydride in pyridine it remained unaltered, a fact which, when taken in conjunction with its IR and ^1H NMR spectra (where a proton appeared at δ 2.77 interchangeable with D_2O), attested to this molecule

having a tertiary alcohol group. In the UV spectrum absorption for a benzoate chromophore could be observed which was confirmed by the presence of five aromatic protons between δ 7.36-7.98 and a carbon of a conjugated carboxyl at δ 165.17 in its ^{1}H and ^{13}C NMR spectra, respectively. Other notable ^{1}H NMR characteristics (Table 1) were the existence of an AB system assigned to H-1 at δ 5.56 (d, J= 3.3 Hz) and H-2 at δ 5.33 (m) indicating that the substituents on C-1 and C-2 must be axial and equatorial, respectively, in view of their coupling constants; signals were also observed for two protons at δ 3.02 (s) (H-7) and δ 5.90 (s) (H-9) which by their form and shifts must be α to a carbonyl group; four acetate methyl signals were also observed at δ 1.50, 2.06, 2.13 and 2.16. All these data taken together indicated that **1** was a polyester sesquiterpene with a dihydro-β-agarofuran skeleton[18]. Its relative configuration was confirmed by means of a NOE experiment (Figure 1) and regiosubstitution was established by means of a selective INEPT experiment whereby the benzoate group was sited at C-9, as three-bond coupling with the carboxyl of the benzoate group at δ 165.17, with C-1 at δ 74.4 and with C-5 at δ 93.3 was observed when H-9 (δ 5.90) was irradiated, as was two-bond coupling with C-10 at δ 52.6 (Table 2). The absolute configuration of **1** was determined by CD studies with the curve showing a positive Cotton effect at 288.9 nm ($\Delta\varepsilon$ = +3.5) corresponding to the n-π^* transition of the carbonyl group at C-8, application of the octant rule[12] indicates that the absolute configuration of this product should be (1R,2S,4S,5S,6R,7R,9S,10S)-9-benzoyloxy-1,2,6,15-tetra-acetoxy-4-hydroxy-8-oxo-dihydro-β-agarofuran.

Table 1: ^{1}H NMR (200 MHz) Data (δ, $CDCl_3$) of **1-7** (J are given in Hz in brackets)

	1	**2**	**3**	**4**	**5**[1]	**6**	**7**
H-1	5.56 d (3.3)	5.89 d (3.3)	5.82 d (3.7)	5.47 d (3.8)	5.78 dd (3.9,12.6)	5.60 dd (3.9,12.6)	5.69 dd (3.8,12.6)
H-2	5.32 m	5.44 m	5.48 m	5.34 m			
H-3			1.86,2.39 d (2.4)	1.86, 2.02 d (2.3)			
H-6	6.68 s	6.70 s	7.12 s	6.96 s	6.26 s	6.36 s	5.96 s
H-7	3.02 s	3.03 s	2.63 d (3.7)	2.39 d (3.8)	2.20 m	2.21 m	2.20 m
H-8			5.75 dd (3.7,6.1)	5.57 dd (3.8,6.1)	2.49 m	2.56 m	2.57 m
H-9	5.90 s	6.02 s	5.87 d (6.1)	5.65 d (6.1)	5.87 d (7.0)	5.45 d (7.2)	5.52 d (7.8)
H-15	4.60,5.02 d_{AB}(13.1)	4.76,5.17 d_{AB}(12.8)	4.85,5.47 d_{AB}(13.6)	4.86,5.07 d_{AB}(13.4)	4.62,4.90 d_{AB}(12.4)	4.51,4.76 d_{AB}(12.7)	4.38 s
-OOC-Me							
1	1.50 s			1.48 s	1.43 s	1.56 s	1.51 s
2	2.06 s	2.08 s	2.05 s	2.05 s			
6	2.13 s	2.14 s	2.04 s	2.13 s	1.75 s	1.95 s	2.11 s
8				2.09 s			
15	2.16 s	2.18 s	2.17 s	2.23 s	1.99 s	2.30 s	2.24 s

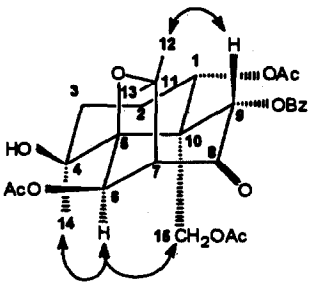
[1] C_6D_6

Table 2: ^{13}C NMR (50 MHz) Data (δ, $CDCl_3$) of **1, 3 and 5**

	1	3	5
1	74.4 d	76.4 d	72.6 d
2	66.3 d	68.3 d	24.0 t
3	42.0 t	42.1 t	38.7 t
4	69.8 s	69.9 s	71.3 s
5	93.3 s	92.6 s	92.1 s
6	74.4 d	75.3 d	78.1 d
7	64.9 d	53.7 d	49.3 d
8	197.1 s	70.8 d	34.9 t
9	79.7 d	72.3 d	69.9 d
10	52.6 s	53.2 s	54.8 s
11	85.1 s	82.8 s	84.4 s
12	24.5 q	24.5 q	25.7 q
13	29.3 q	29.4 q	29.4 q
14	21.3 q	24.2 q	24.0 q
15	61.0 t	61.1 t	65.2 t

Data are based on ^1H-^{13}C bidimensional experiments.

Figure 1: NOE experiment of **1**



A detailed study of the spectroscopic data of compound **2** which had the molecular formula, $C_{25}H_{36}O_{13}$ (HREIMS) showed it to be related to **1** with the most notable ^1H NMR differences being the disappearance of one of the acetate methyls at δ 1.50 and the existence of ten aromatic protons between δ 7.17-7.58 instead of five as in **1**, and the corresponding shift of the H-1 from δ 5.56 to 5.89[19] (Table 1) thus establishing its regiosubstitution. The absolute configuration was ascertained by studying the CD curve which showed a positive Cotton effect at 290.7 nm ($\Delta\varepsilon$ = +3.3); its absolute configuration was accordingly determined as (1R,2S,4S,5S,6R,7R,9S,10S)-1,9-dibenzoyloxy-2,6,15-triacetoxy-4-hydroxy-8-oxo-dihydro-β-agarofuran.The basic polyhydroxy 3,13-dideoxy-evoninol[15] skeleton of compounds **1** and **2** had not previously been reported.

Product **3** with the molecular formula, $C_{42}H_{44}O_{14}$ (HREIMS) was shown in a study of its IR, UV, ^1H and ^{13}C NMR data (Tables 1 and 2) and a two-dimensional ^1H-^1H (COSY) experiment to be a dihydro-β-agarofuran skeleton sesquiterpene with three benzoate groups, three acetate groups and one tertiary alcohol, positioned at 1α, 2α, 4β, 6β, 8α, 9α and 15. An HMBC experiment (Table 3) enabled the regiosubstitution pattern to be established with acetate groups on C-2, C-6 and C-15, benzoates at C-1, C-8 and C-9 and the tertiary alcohol at C-4. Its absolute configuration was determined from its CD curve data[10], by application of the exciton chirality method with a split curve with a first negative Cotton effect at 235.8 nm ($\Delta\varepsilon$ = -32.2) and a second positive Cotton effect at 219.8 nm ($\Delta\varepsilon$ = +13.4) and hence the absolute configuration of **3** was determined as (1R,2S,4S,5S,6R,7R,8R,9S,10S)-2,6,15-triacetoxy-1,8,9-tribenzoyloxy-4-hydroxy-8-oxo-dihydro-β-agarofuran.

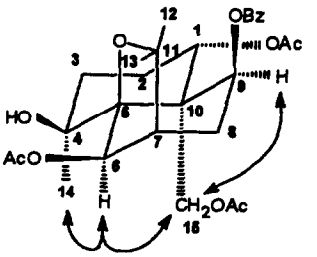
Detailed study of product **4** established its structure as 9α-benzoyloxy-1α,2α,6β,8α,15-penta-acetoxy-4β-hydroxy-dihydro-β-agarofuran which coincided with the published data for celangulin, isolated earlier from the Celastraceae species, *Celastrus angulatus*[11]. Compounds **3** and **4** had a basic 4β-hydroxyalatol polyhydroxylated skeleton[18].

Table 3: Three-bond ^{1}H-^{13}C couplings (HMBC) in compounds **3** and **5**

	3	**5**
H-1	C-15, C*-10, C-9, C_6H_5-COO-	C-15, C-9, CH_3-COO-
H-2	CH_3-COO-	
H-6	C-11, C*-5, CH_3-COO-	C-8, C*-7, CH_3-COO-
H-7	C-9, C*-8, C*-6, C-5	C-9
H-8	C-10, C*-9, C-6, C_6H_5-COO-	C*-7, C-6
H-9	C-15, C*-10, C-1, C_6H_5-COO-	C-15, C-7, C_6H_5-COO-
H-15	C*-10, C-9, C-5, C-1, CH_3-COO-	C-9, C-1, CH_3-COO-
Me-12	C-13, C*-11, C-7	C-13, C*-11, C-7
Me-13	C-12, C*-11, C-7	C-12, C*-11, C-7
Me-14	C-5, C*-4, C-3	C*-4, C-3

*Two-bond coupling enhancement observed.

Figure 2: ROESY experiment of **5**



Compound **5** with molecular formula $C_{28}H_{36}O_{10}$ (HREIMS) had IR bands for hydroxy and ester groups. When acetylated under normal conditions unreacted starting material was obtained so it can be concluded that a tertiary alcohol was present. The ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) revealed its most significant features to be signals for three acetate groups, a benzoate group, and the geminal protons. These data as a whole indicated a polyester sesquiterpene with a dihydro-β-agarofuran skeleton. A ^{1}H-^{1}H COSY experiment and analysis of a ROESY experiment (Figure 2) settled the substitution positions and the relative configuration as 1α, 6β, 9β and 15. The regiosubsitution was solved by an HMBC experiment (Table 3). To determine the absolute configuration of **5** it was necessary to introduce another chromophore group and the tertiary alcohol on C-4 was the only position available so that when **5** was treated with benzoyl chloride and silver triflate in pyridine it yielded **6** and **7** the structures of which were determined on the basis of their spectral data. The derivative **6** was benzoylated at C-4, the first time that this ester group has been found at this position; compound **7** had an exocyclic methylene at C-4. Compound **6** was suitable for CD analysis and showed a split curve with a first negative Cotton effect at 235.1 ($\Delta\varepsilon$ = -14.9) and a second positive Cotton effect at 219.7 ($\Delta\varepsilon$ = +3.8) so that the absolute configuration of **6** was established as (1S,4S,5S,6R,7R,9S,10S)-4,9-dibenzoyloxy-1,6,15-triacetoxy-dihydro-β-agarofuran and therefore the absolute configuration of **5** could be determined as (1S,4S,5S,6R,7R,9S,10S)-9-benzoyloxy-1,6,15-triacetoxy-4-hydroxy-dihydro-β-agarofuran. The basic polyhydroxylated skeleton of **5** is that of 2,3-dideoxymaytol[19].

In an earlier paper on *Maytenus canariensis* we reported the isolation of sesquiterpenes with basic polyhydroxylated isoalatol and 4β-hydroxyalatol skeletons; as can be seen above, the new compounds possess 3,13-dideoxyevoninol, 4β-hydroxyalatol and 2,3-dideoxymaytol skeletons, indicating that this species has a special ability to manufacture a variety of sesquiterpenes.

EXPERIMENTAL

The plant was collected in Icod, Tenerife, in October 1986 and a voucher specimen is on file with the Departamento de Biología Vegetal, Facultad de Ciencias Biológicas, Universidad de La Laguna.

The aerial part of the plant (7 Kg) was extracted with cold EtOH and 100 g of this solid extract was chromatographed on Sephadex LH-20 using n-hexane-$CHCl_3$-MeOH (2:1:1) as eluant, followed by repeated chromatography on silica gel with mixtures of n-hexane-EtOAc and n-hexane-dioxan to give **1** (18 mg), **2** (8 mg), **3** (7 mg), **4** (5 mg) and **5** (14 mg). IR data were taken in $CHCl_3$. The products used in the CD study were purified by HPLC using a semi-preparative μ Porosil column and mixtures of n-hexane-EtOAc and n-hexane-dioxan as eluants.

(1R,2S,4S,5S,6R,7R,9S,10S)-9-Benzoyloxy-1,2,6,15-tetra-acetoxy-4-hydroxy-8-oxo-dihydro-β-agarofuran (1).- Was obtained as a white amorphous solid, mp 117-118ºC (from $CHCl_3$); $[\alpha]_D^{25}$= -6.8º ($CHCl_3$, c = 0.63); CD λ_{ext} (MeCN) nm: 288.9 ($\Delta\varepsilon$= +3.5); UV λ_{max} (MeCN) nm: 230; IR ν_{max} cm^{-1}: 3565, 3028, 1745, 1451, 1369, 1269, 1228, 1109, 1049, 750, 710; ^1H NMR ($CDCl_3$) δ : 1.54 (3H, s), 1.61 (3H, s), 1.66 (3H, s), 2.77 (1H, s), 7.46 (3H, m), 7.98 (2H, m), for other signals, see Table 1; ^{13}C NMR ($CDCl_3$) δ: 20.3, 20.6, 21.2, 21.3 (4x $\underline{C}H_3$-COO-), 128.7-133.6 ($\underline{C}_6H_5$-COO-), 165.2 (C_6H_5-$\underline{C}$OO-), 169.2, 169.4, 169.5, 170.2 (4x CH_3-$\underline{C}$OO-), for other signals, see Table 2; EIMS m/z (%): 589 [M^+-15] (2), 544 (8), 502 (12), 484 (28), 482 (2), 442 (1), 422 (1), 380 (5), 320 (1), 281 (2), 260 (2), 105 (100); HREIMS [M^+ -CH_3COOH] at m/z 544.2026 (calc. for $C_{28}H_{32}O_{11}$, 544.1986).

(1R,2S,4S,5S,6R,7R,9S,10S)-1,9-Dibenzoyloxy-2,6,15-triacetoxy-4-hydroxy-8-oxo-dihydro-β-agarofuran (2).- Was obtained as an oil; $[\alpha]_D^{25}$= +11.6º ($CHCl_3$, c= 0.68); CD λ_{ext} (MeCN) nm: 290.7 ($\Delta\varepsilon$= +3.3), 242.1 ($\Delta\varepsilon$= -5.6), 260.1 ($\Delta\varepsilon$= 0); UV λ_{max} (EtOH) nm: 260, 275; IR ν_{max} cm^{-1}: 3558, 3020, 1745, 1369, 1220, 1120, 1049, 738, 710; ^1H NMR ($CDCl_3$) δ: 1.61 (3H, s), 1.65 (3H, s), 1.68 (3H, s), 2.81 (1H, s), 6.94 (2H, m), 7.17 (3H, m), 7.33 (3H, m), 7.58 (2H, m), for other signals, see Table 1; EIMS m/z (%):606 [M^+-60] (2), 588 (1), 564 (3), 546 (1), 544 (1), 504 (1), 442 (3), 382 (1), 320 (2), 284 (2), 218 (18), 202 (7), 105 (100); HREIMS [M^++H^+] at m/z 667.2466 (calc. for $C_{35}H_{39}O_{13}$, 667.2428).

(1R,2S,4S,5S,6R,7R,8R,9S,10S)-2,6,15-Triacetoxy-1,8,9-tribenzoyloxy-4-hydroxy-dihydro-β-agarofuran (3).- Was obtained as an oil; $[\alpha]_D^{25}$= +49.0º ($CHCl_3$, c= 0.68); CD λ_{ext} (MeCN) nm: 235.8 ($\Delta\varepsilon$= +3.3), 219.8 ($\Delta\varepsilon$= +13.4), 225.4 ($\Delta\varepsilon$= 0); UV λ_{max} (EtOH) nm: 274, 283; IR ν_{max} cm^{-1}: 3562, 3022, 1731, 1369, 1275, 1208, 1100, 756; ^1H NMR ($CDCl_3$) δ: 1.49 (3H, s), 1.63 (3H, s), 1.74 (3H, s), 2.79 (1H, s), 6.89 (2H, m), 7.10 (4H, m), 7.44 (5H, m), 7.98 (4H, m), for others signals, see Table 1; ^{13}C NMR ($CDCl_3$) δ: 21.0, 21.4, 21.6 (3x $\underline{C}H_3$-COO-), 127.8-133.2 (3x $\underline{C}_6H_5$-COO-), 164.3, 164.9, 166.1 (3x C_6H_5-$\underline{C}$OO-), 169.7 (CH_3-$\underline{C}$OO-), 171.0 (2x CH_3-$\underline{C}$OO-), for other signals, see Table 2; (EIMS m/z (%): 650 [M^+-122] (2), 608 (1), 591 (1), 548 (1),

530 (1), 450 (1), 426 (2), 411 (1), 408 (1), 336 (2), 304 (3), 268 (3), 244 (7), 202 (30), 105 (100); HREIMS [M^+-CH_2=CO] at m/z 730.2305 (calc. for $C_{40}H_{42}O_{13}$, 730.2465).

(1S,4S,5S,6R,7R,9S,10S)-9-Benzoyloxy-1,6,15-triacetoxy-4-hydroxy-dihydro-β-agarofuran (5).- Was obtained as a crystalline solid, mp 188-190ºC (from n-hexane-Et_2O); $[\alpha]_D^{25}$= -19.6º ($HCCl_3$, c=0.25); IR ν_{max} cm^{-1}: 3630, 3530, 3010, 2920, 1725, 1595, 1445, 1365, 1275, 1090; ^1H NMR ($CDCl_3$) δ: 1.31 (3H, s), 1.50 (3H, s), 1.53 (3H, s), 1.55 (3H, s), 2.09 (3H, s), 2.24 (3H, s), 4.44- 4.62 (2H, d_{AB}, J= 12.0 Hz), 5.38 (1H, dd, J= 4.0 Hz), 5.39 (1H, d, J= 6.0 Hz), 6.07 (1H, s), 7.50 (3H, m), 8.02 (2H, m); ^1H NMR (C_6D_6) δ: 1.34 (3H, s), 1.43 (3H, s), 1.45 (3H, s), 7.17 (3H, m), 8.37 (2H, m), for other signals, see Table 1; ^{13}C NMR (C_6D_6) δ: 20.4, 20.6, 21.0 (3x $\underline{C}H_3$-COO-), 128.0-133.4 ($\underline{C}_6H_5$-COO-), 165.5 (C_6H_5-$\underline{C}OO$-), 169.1, 169.7, 170.0 (3x CH_3-$\underline{C}OO$-), for other signals, see Table 2; EIMS m/z (%): 472 [M^+-60] (1), 430 (1), 412 (2), 395 (1), 368 (1), 350 (2), 335 (1), 308 (2), 293 (3), 290 (3), 267 (6), 248 (11), 230 (6), 215 (5), 202 (10), 105 (100), 77 (37); HREIMS [M^+-HOAc] at m/z 472.2143 (calc. for $C_{26}H_{32}O_8$, 472.2097).

Benzoylation of 5.- Compound **5** (6 mg) was dissolved in CH_2Cl_2 and benzoyl chloride (6 mg), silver triflate (14 mg), and some crystals of 4-dimethylamino-pyridine were added under argon atmosphere. The mixture was refluxed for 6 hours, poured over water, extracted with ethyl ether and purified on a preparative column on silica gel with a mixture of n-hexane-ethyl acetate (7:3), to give **5** (2 mg), **6** (1.5 mg), and **7** (1 mg) .

(1S,4S,5S,6R,7R,9S,10S)-4,9-Dibenzoyloxy-1,6,15-triacetoxy-dihydro-β-agarofuran (6).- Was obtained as an oil; CD λ_{ext} (MeCN) nm: 235.1 (Δ ε = -14.9), 219.7 (Δ ε = +3.8), 224.6 (Δ ε = 0),; UV λ_{max} (MeCN) nm: 228; ^1H NMR ($CDCl_3$) δ: 1.57 (3H, s), 1.65 (3H, s), 1.80 (3H, s), 7.38-7.60 (6H, m), 8.06-8.10 (4H, m), for other signals, see Table 1; EIMS m/z (%): 594 [M^+-42] (0.2), 472 (13), 412 (10), 350 (4), 290 (3), 230 (4), 202 (21), 187 (4), 172 (5), 105 (100).

9-Benzoyloxy-1,6,15-triacetoxy-4-dehydro-dihydro-β-agarofuran (7).- Was obtained as an oil. ^1H NMR ($CDCl_3$) δ: 1.46 (3H,s), 1.51 (3H,s), 1.58 (6H,s), 2.31 (1H, d, J= 4.8 Hz), 4.72 (1H, s), 5.12 (1H, s), 7.43-7.60 (3H, m), 8.04-8.07 (2H, m); EIMS m/z (%): 514 [M^+] (0.3), 412 (7.2), 350 (2.8), 290 (1.8), 262 (1.3), 230 (3.2), 215 (2.1), 202 (14.2), 105 (100).

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