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BIOMIMETIC CYCLIZATION OF 4β,5α-EPOXY-6β-ACETOXY-TRANS-GERMACR-1(10)-ENE TO FORM CIS-(1β-H;5β-H)-GUAIANES

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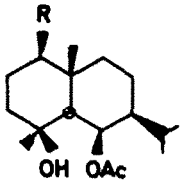
Abstract - A new 4β,5α-epoxy-6β-acetoxy-trans-germacr-1(10)-ene has been isolated from Sideritis varoi subsp. cuatrecasasii. The product has been subjected to several biomimetic cyclizations which have rendered cis-(1β-H,5β-H)-guaianes. One of these guaianes presents the same structure as a product also present in an extract of this plant.

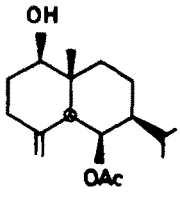
Chemical structure of guaianes have been established by ^{1}H-NMR, ^{13}C NMR, ORD experiences and chemical correlations.

The stereoespecificity of the cyclization is explained according to a conformation in which the 14 and 15 methyl groups are syn.

In a previous report[1] we have described a series of eudesmane and eudesmene sesquiterpenes isolated from Sideritis varoi subsp. cuatrecasasii: 1β,4β-dihydroxy-6β-acetoxy-eudesmane (1); 1β-hydroxy-6β-acetoxy-eudesm-4(15)-ene (2); 1β-hydroxy-6β-acetoxy-eudesm-3-ene (3) and 1β-hydroxy-6β-acetoxy-eudesm-4-ene (4).



1 R=OH
14 R=OTs



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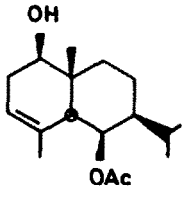

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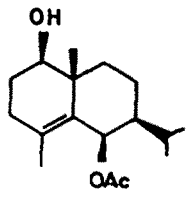

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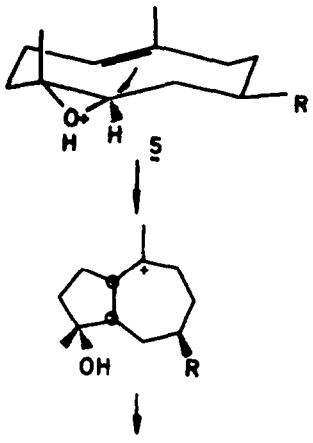
Certain controversy exists with regard to the correlation between the different configurations at C-1 and C-5 of guaianolides and the configurational and conformational situations of their likely biogenetic precursors the germacranolides.[2]

On some occasions, it has been demonstrated that (4α,5β)-epoxy-trans-germacr-1(10)-ene derivatives, give cis-fused (α-H)guaianolides by acid-induced cyclization.[3] However, in this case, the epoxygermacrene must necessarily adopt a crown conformation (5), where the 14 and 15 methyl groups are β-oriented.



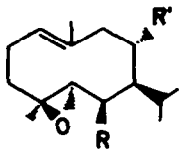
cis-fused guaianolides

In the present paper we report the cyclization of a substrate which presents the same configuration at C-7 than the above mentioned epoxygermacrene, but with reverse configurations at C-4 and C-5. With this purpose, we started from a (4β,5α)-epoxy-*trans*-germacr-1(10)-ene, and studied its cyclization products.

Studies with *S. varoi* subsp. *cuatrecasasii* have allowed for the isolation of product 6, whose mass spectrum shows a molecular ion at 280 m/z, according with the molecular formula $C_{17}H_{28}O_3$. Its IR spectrum shows bands at 1745, 1230 (acetoxy group) and 3110 cm^{-1} (double bond). The ^1H NMR (80 MHz) spectrum presents signals at δ 5.27 (1H,bt) attributable to a vinylic proton coupled with another two protons, in addition to allylic couplings of lesser entity, 4.97 (1H,dd) geminal to an acetoxy group, 2.62 (1H,d) coupled with the above described signal, 2.05 (3H,s) acetoxy group, 1.67 (3H,bs) allylic methyl group, and methyl groups signals at 1.25, 0.96 and 0.85 (3H each).

Saponification of 6 yields a product, also isolated from the more polar fractions, of spectroscopical characteristics identical to those previously reported for *shiromool* (7).[4] Oxidation product of 7 (8) was also spectroscopically similar to the oxidation product of *shiromool*.[4]

Structure of 6 is in agreement with the ^{13}C NMR spectrum obtained for this product. (See table 1).



6 R=OAc R'=H
7 R=OH R'=H
9 R=OH R'=OH
10 R=OAc R'=p-bromobenzoate

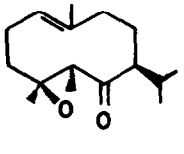


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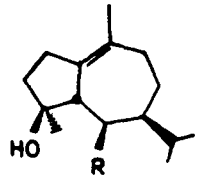
Table 1. ^{13}C NMR spectral data for compounds 6 and 7.

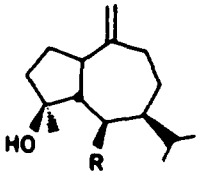
Carbon Nº	6	7
C-1	123.59(d)	123.25
C-2	22.97(t)	23.06
C-3	37.17(t)	37.44
C-4	59.60(s)	60.73
C-5	66.06(d)	68.90
C-6	74.13(d)	71.81
C-7	45.97(d)	47.05
C-8	26.61(t)	26.12
C-9	38.25(t)	38.95
C-10	136.75(s)	137.35
C-11	31.43(d)	31.81
C-12	20.66(q)	21.12
C-13	20.66(q)	21.12
C-14	16.45(q)	16.46
C-15	18.61(q)	18.62
$\underline{C}H_3$-CO	20.98(q)	-
CH_3-$\underline{C}O$	170.00(s)	-

Stereochemistry of *shiromool* (7) was assumed to be the same of *shiromodiol* (9). Both products 7 and 9 were jointly isolated and X-ray difraction experiments were performed[5] with derivative 10 of product 9.

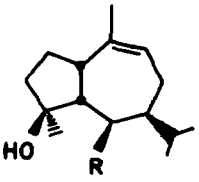
Treatment of 6 with dry HCl gas in anhydrous ether at 0º for 5 minutes rendered a mixture of products (11, 12, 13) as a result of a transanular cyclization.



11 R = OAc
17 R = =O
18 R = OH



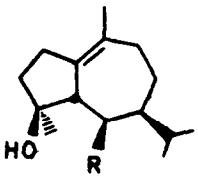
12 R = OAc
23 R = OH



13 R = OAc

In order to determine the stereochemistry of those products we proceeded to obtain a guaiane of known stereochemistry, following the method described by Heathcock-Ratcliffe,[6] using product 1 as starting material. Solvolysis of tosylate of 1 (14) in 80% aqueous EtOH yields products 15 and 16.

The ^{1}H NMR of 15 differs from that of product 11. To eliminate the possibility that the difference was due to the configuration at C-4, dehydration of 11 was carried out but gave such a unstable product that it could not be studied, and therefore its chemical behaviour was very different to that of the product 16 which is a stable product.



15 R = OAc
19 R = OH

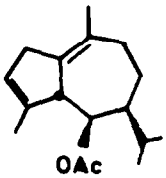


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Table 2
^{13}C NMR spectral data for compounds 11, 12, 13, 15 and 23

Carbon Nº	11	12	13	15	23
C-1	133.09	45.00	42.66	133.34	42.93
C-2	28.12	26.87	26.40	27.24	27.39
C-3	39.42	39.16	39.67	39.35	40.62
C-4	79.87	79.16	80.00	78.69	80.86
C-5	60.22	62.07	56.65	56.72	59.67
C-6	72.56	74.13	77.10	71.05	72.66
C-7	43.38	46.16	46.91	53.66	48.37
C-8	23.86	26.78	25.30	23.63	23.28
C-9	31.50	36.67	124.75	35.95	35.67
C-10	127.96	152.42	138.65	131.70	152.58
C-11	31.09	31.40	28.86	31.77	29.10
C-12	20.42*	21.09	21.70	21.05	21.70
C-13	20.60*	21.09	20.87	21.05	21.70
C-14	20.95*	108.25	22.97	20.45	108.21
C-15	23.28	25.24	24.49	28.93	24.09
CH_3-CO	172.46	172.57	171.46	173.00	-
CH_3-CO	21.58	21.63	21.70	21.71	-

* These values could be interchangeables.

In any event ^{13}C NMR spectra of products 11 and 15 have enough differences (See table 2) to be exclusively due to a different configuration of the hydroxyl group at C-4.

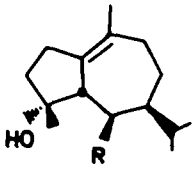
These observations allow us to affirm that proton in C-5 of the cyclization products has a H-β configuration which is supported by ORD studies carried out on ketone 17, product obtained by oxidation[7] of the product of saponification 18.

Although the conformational mobility of cycloheptanones difficulties ORD stu-

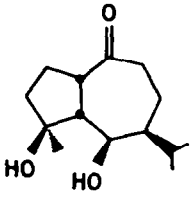
dies, the negative Cotton effect showed by ketone 17 is only compatible with the assigned stereochemistry, as no other stable conformation exist for epimer at C-5 with a negative sign. In addition, the configuration at C-4 has been deduced as follows: Considerations on Dreiding models, indicate that in 4β-OH derivatives (products 11 and 18) chemical shifts of the α-proton at C-6 must be smaller than the corresponding shifts in products 15 and 19. On the other hand, this proton at C-6 in products 20 and 21 must be higher than in products 15 and 19.

In effect, chemical shifts of H-6, in products 11 and 18 (δ 5.05 and 4.00 respectively) are lower than those observed for 15 and 19 (δ 5.45 and 4.18 respectively).

We therefore conclude that products resulting from transanular cyclization have a 4β-OH configuration.



20 R = OAc
21 R = OH



22

The results found for the configurations at C-4 and C-5 are in agreement with the stereochemistry of the shiromool epoxide assuming a concerted transanular cyclization.

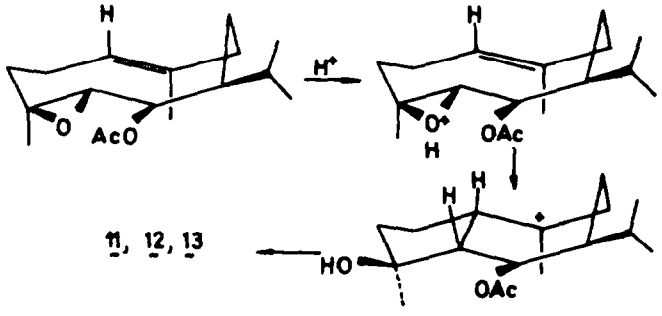
Configuration of C-1 in products 12 and 13 was determined by measuring the coupling constant between H-1 and H-5, since there is an appreciable difference in the corresponding values for a trans-fused guaiane or for a cis-fused guaiane.[8]

Experiments of single and double ^{1}H NMR (200 MHz) were done on product 23 obtaining a value for $J_{1,5}$=10 Hz, which indicates that this product is a cis-fused guaiane, so H-1 has a β-disposition. This configuration is confirmed again by ORD studies performed on cycloheptanone 22 which was obtained by ozonolisis of 12, product formed by saponification of 23.

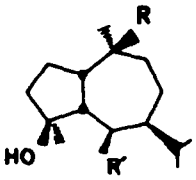
The positive Cotton effect shown is only compatible with the proposed stereochemistry, as the epimer molecule at C-1 of 22 has no stable conformation with this positive sign.

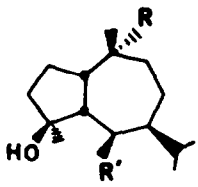
On the other hand, product 23 has been isolated from the plant extract, but due to the great facility of shiromool to cyclate we do not know if it is a natural product or an artifact obtained during the extraction process.

These results imply that for the formation of 1β,5β-cis fused guaianes, the ten-membered ring must adopt the same flattened conformation found in 5. This observation is in agreement with the conformation observed by means of X-ray experiments for shiromodiol derivatives[5] in which the 14 and 15 methyl groups are syn and its α-orientation is locked in by the 4,5-epoxide system.



11, 12, 13





24 R=OAc R'=OAc
25 R=OH R'=OAc
28 R=OH R'=OH

26 R=OAc R'=OA
27 R=OH R'=OAc

Cyclization achieved by solvolysis of 6 with 80% AcOH/H_2O, rendered two main products 24 and 25 together with product 11. This supports the idea that the principal way takes place in a concerted form although minority products 26 and 27 are also isolated which can be obtained only via a previous carbocation at C-10.

If the formation of these products was exclusively via carbocation possibly such a big difference in the proportion of the obtained products would not exist.

Product 24 has been correlated with product 25 as saponification of both give the same product 28.

EXPERIMENTAL

Mps. (Koffler apparatus) are uncorr. ^{1}H NMR 80 MHz or 200 MHz $CDCl_3$, TMS as internal standard. ^{13}C NMR 20.13 MHz, CDCl (which also provided the lock signal), TMS as internal reference. Assignments of ^{13}C chemical shifts were made with the aid of broad-band proton decoupling and SFORD experiments, setting the decoupler frequency in the middle of the proton range in the former and 2 ppm to the right of TMS in the latter; also assignations are made with the aid of distortionless enhancement by polarization transfer (DEPT), using a "flip angle" of 135º. Silica gel, Merck 7729 (less than 0.08 mm) was used for CC. Voucher specimens have been deposited at the Herbarium of the Faculty of Pharmacy (University of Granada).

Isolation of Sesquiterpenes. Dried plant (1.8 Kg) collected in Carboneras (Almeria) in May 1980 were processed to give 30 g of a sirup which was treated as indicated in ref. 9 yielding apart from the eudesmanes and eudesmenes previously described [1] the following products in order of elution: 4β,5α-epoxy-6β-acetoxy-trans-germacr-1(10)-ene (6) (1.6 g), 4β,5α-epoxy-6β-hydroxy-trans-germacr-1(10)-ene (7) (35 mg), 4β,6β-dihydroxy-(1βH,5βH)-guai-10(14)-ene (23) (40 mg). 4β,5α-Epoxy-6β-acetoxy-trans-germacr-1(10)-ene (6). M.p. 45-47ºC; $[\alpha]_D^{20}$= +48.4º ($CHCl_3$, c 1); IR ν_{max}^{KBr} cm^{-1} : 3110, 2980, 1745, 1230 and 860; ^{1}H NMR (80 MHz, $CDCl_3$): δ 5.27 (1H, bt, J=7 Hz, H-1), 4.97 (1H, dd, J_1=8 J_2=1.5 Hz, H-6), 2.62 (1H, d, J=8 Hz, H-5), 2.05 (3H, s, AcO-group), 1.67 (^{1}3H,bs, C-14 Me group), 1.25 (3H, s, C-15 Me group), 0.96 and 0.85 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups); ^{13}C NMR: See table 1; MS m/z (rel. int.): 280 [M$^+$] (3), 262 (3), 251 (3), 237 (8), 220 (10), 205 (13), 202 (10), 195 (10), 191 (15), 187 (10), 177 (55), 162 (30), 159 (45), 149 (38), 147 (38), 135 (50), 122 (55), 107 (100); Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.85; H, 10.09. 4β,5α-Epoxy-6β-hydroxy-trans-germacr-1(10)-ene (7). Colourless gum; $[\alpha]_D^{20}$= +63.3º ($CHCl_3$, c 1); IR ν_{max}^{neat} cm^{-1}: 3430, 2950, 1670, 1380, 1250, 850 and 820; ^{1}H NMR (80 MHz, $CDCl_3$): δ 5.25 (1H, bt, J=7 Hz, H-1), 3.62 (1H, dd, J_1=8 J_2=1.5 Hz, H-6), 2.62 (1H, d, J=8 Hz, H-5), 1.67 (3H, bs, C-14 Me group), 1.22 (3H, s, C-15 Me group), 1.01 and 0.95 (3H each, d, J=6.5, C-12 and C-13 Me groups); ^{13}C NMR: See table 1; MS m/z (rel. int.): 238 [M$^+$] (10), 220 (7), 205 (12), 193 (12), 177 (34), 167 (22), 153 (43), 135 (52), 121 (74), 109 (100). This product has been also prepared by saponification of product 6 in basic media.

Oxidation of 7. 20 mg of 7 were oxidized with pyridinium dichromate[10] to give after cc, 17 mg of 4β,5α-epoxy-germacr-10-en-6-one (8). M.p. 45-6ºC; IR ν_{max}^{KBr} cm^{-1}:3130, 2980, 1710 and 1240; ^{1}H NMR (80 MHz, $CDCl_3$): δ 5.30 (1H, bt, J=7.5 Hz, H-1), 3.53 (1H, s, H-5), 1.63 (3H, s, C-14 Me group), 1.25 (3H, s, C-15 Me group), 0.97 and 0.93 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups); MS m/z (rel. int.): 236 [M$^+$] (22), 222 (18), 220 (2), 219 (2), 207 (4), 203 (5), 193 (43), 179 (18), 178 (21), 175 (40), 167 (24), 166 (19), 164 (16), 152 (30), 135 (46), 123 (86), 107 (100); $[\alpha]_{20}^{\lambda}$= $\frac{589 \quad 578 \quad 546 \quad 436 \quad 365}{-1 \quad -1.5 \quad -3.3 \quad -45.7 \quad 0}$ ($CHCl_3$, c 1).

Acid-catalized Rearrangement of Product 6. Product 6 (400 mg) was treated with dry HCl gas in ether at 0ºC for 5 min. The reaction soln. was diluted with H_2O, whased with satd. aq. $NaHCO_3$ and the ether layer dried and evapd. After column chromatography products: 4β-hydroxy-6β-acetoxy-5βH-guai-1(10)-ene (11, 52 mg), 4β-hydroxy-6β-acetoxy-cis-1βH,5βH-guai-10(14)-ene (12, 190 mg) and 4β-hydroxy-6β-acetoxy-cis-1βH, 5βH-guai-9-ene (13, 64 mg) were isolated. 11.- Colourless gum; $[\alpha]_D^{20}$= +33.7º ($CHCl_3$, c 0.8); IR ν_{max}^{neat} cm^{-1}: 3500, 1725 and 1250; ^1H NMR (80 MHz, $CDCl_3$): δ 5.05 (1H, d, J=1.2 Hz, H-6), 2.05 (3H, s, AcO-group), 1.65 (3H, bs, C-14 Me group), 1.18 (3H, s, C-15 Me group), 0.90 (6H, d, J=6.5 Hz, C-12 and C-13 Me groups); ^{13}C-NMR: See table 2. 12.- Colourless gum; $[\alpha]_D^{20}$ = +2.1º ($CHCl_3$, c 1); IR ν_{max}^{neat} cm^{-1}: 3450, 1735, 1250 and 890; ^1H-NMR (80 MHz, $CDCl_3$): δ 5.25 (1H, dd, J_1=5 J_2=1.5 Hz, H-6), 4.76 (2H, m, $w_{1/2}$=8 Hz, 2H-14), 2.05 (3H, s, AcO-group), 1.28 (3H, s, C-15 Me group), 0.93 and 0.90 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups); ^{13}C NMR: See table 2. 13.- Colourless gum; $[\alpha]_D^{20}$ = +22º ($CHCl_3$, c 1); IR ν_{max}^{neat} cm^{-1}: 3400, 1740, 1640 and 1250; ^1H-NMR (80 MHz, $CDCl_3$): δ 5.45 (1H, m, $w_{1/2}$=14 Hz, H-9), 5.30 (1H, dd, J_1=8 J_2= 2 Hz, H-6), 2.05 (3H, s, AcO-group), 1.73 (3H, bs, C-14 Me group), 1.27 (3H, s, C-15 Me group), 0.92 and 0.87 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups); ^{13}C-NMR: See table 2.

Preparation of Tosylate 14. Product 1 (300 mg) was dissolved in pyridine (4 ml), tosyl chloride (245 mg) was added, and the solution was kept at room temperature for 3 days. Work-up in the usual way, and after cc, 400 mg of 1β-tosyloxy-4β-hydroxy-6β-acetoxy-eudesmane were collected. Colourless gum; α_D^{20} =+37.4º ($CHCl_3$, c 1); IR ν_{max}^{neat} cm^{-1}: 3560, 1750, 1610 and 1260; ^1H NMR (80 MHz, $CDCl_3$): δ 7.80 and 7.40 (2H each, A_2B_2 system, J=9 Hz, aromatic protons of Ts-group), 5.70 (1H, bs, H-6), 4.20 (1H, dd, J_1=11 J_2=4 Hz, H-1), 2.50 (3H, s, Ts-Methyl group), 2.05 (3H, s, AcO-group), 1.40 and 1.35 (3H each, s, C-14 and C-15 Me groups).

Solvolysis of Tosylate 14. 400 mg of 14 were dissolved in 80% aqueous EtOH (35 ml) and refluxed for 48 hours. Work-up in the usual way and after column chromatography, product 14 (128 mg), 4β-hydroxy-6β-acetoxy-5αH-guai-1(10)-ene (15, 50 mg) and 6β-acetoxy-5αH-guaian-1(10),3-diene (16, 40 mg) were obtained. 15.- Colourless gum; $[\alpha]_D^{20}$ =+42.2º ($CHCl_3$, c 0.8); IR ν_{max}^{neat} cm^{-1}: 3460, 1720 and 1250; ^1H NMR (80 MHz, $CDCl_3$): δ 5.45 (1H, bs, H-6), 2.05 (3H, s, AcO-group), 1.70 (3H, bs, C-14 Me group), 1.23 (3H, s, C-15 Me group), 0.90 (6H, d, J=6.5 Hz, C-12 and C-13 Me groups); ^{13}C NMR: See table 2. 16.- Colourless gum; $[\alpha]_D^{20}$ =+13.6º ($CHCl_3$, c 1); IR ν_{max}^{neat} cm^{-1}: 3060, 1720 and 1250; ^1H NMR (80 MHz, $CDCl_3$): δ 5.43 (2H, bs, H-3 and H-6), 3.15 (1H, bs, H-5), 2.85 (2H, bs, Hβ-2 and Hα-2), 1.93 (3H, s, AcO-group), 1.80 and 1.73 (3H each, bs, C-14 and C-15 Me groups), 0.95 and 0.90 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups).

Dehydration of Product 11. Product 11 (25 mg), was dissolved in pyridine (2 ml) at 0ºC and $SOCl_2$ (0.25 ml) recently destilled was added drop by drop while stirring for 15 minutes. The soln. was poured over iced water, sat. $NaHCO_3$ aq. was added and the mixture extracted with $CHCl_3$. (See results and discussion).

Saponification of Product 11. Product 11 (27 mg) was dissolved in alcoholic KOH and stirred for 2h. Work-up in the usual manner 22 mg of 4β-6β-dihydroxy-5βH-guai-1(10)-ene (18) were isolated. M.p.=88-90ºC; $[\alpha]_D^{20}$ = -10.7º ($CHCl_3$, c 1); IR ν_{max}^{KBr} cm^{-1}: 3350; ^1H NMR (80 MHz, $CDCl_3$): δ 4.00 (1H, bd, J=10 Hz, H-6), 1.58 (3H, bs, C-14 Me group), 1.30 (3H, s, C-15 Me group), 1.05 and 0.95 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups).

Oxidation of Product 18. 25 mg of 18 were dissolved in CH_2Cl_2, 50 mg of pyridinium dichromate were added and the mixture stirred at room temperature for 10 hours. After column chromatography 23 mg of 4β-hydroxy-5β-H-guai-1(10)-en-6-one (17) were obtained. Colourless gum; IR ν_{max}^{neat} cm^{-1}: 3420 and 1720; ^1H NMR (80 MHz, $CDCl_3$): δ 1.65 (3H, bs, C-14 Me group), 1.35 (3H, s, C-15 Me group), 0.95 (6H, d, J=6.5 Hz, C-12 and C-13 Me groups; $[\alpha]_D^{20}$ = $\frac{589 \quad 578 \quad 546 \quad 436 \quad 365}{-121.3 \quad -129.1 \quad -155.1 \quad -390.8 \quad -1014.8}$ ($CHCl_3$, c 0.72).

Saponification of Product 15. 8 mg of 15 dissolved in basic media were stirred for 3 h. After cc 5 mg of 4β,6β-dihydroxy-5α-H-guai-1(10)-ene (19) were isolated. ^1H NMR (80 MHz, $CDCl_3$): δ 4.3 (1H, bd, J=7 Hz, H-6), 1.85 (3H, bs, C-14 Me group), 1.65 (3H, s, C-15 Me group), 1.10 and 1.05 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups).

Saponification of Product 12. 50 mg of 12 dissolved in MeOH aq/KOH were stirred at room temperature for 2 h. yielding 40 mg of 4β,6β-dihydroxy-cis-1β-H,5β-H-guai-10(14)-ene (23). Colourless gum; $[\alpha]_D^{20}$ =+6.1º ($CHCl_3$, c 1); IR ν_{max}^{neat} cm^{-1}: 3450, 1660 and 890; ^1H NMR (200 MHz, $CDCl_3$): δ 4.71 (2H, d, J=5 Hz, 2H-14), 4.05

(1H, dd J_1=9.5 J_2=3.7 Hz, H-6), 1.35 (3H, s, C-15 Me group, 1.03 and 0.98 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups); ^{13}C NMR: See table 2. This product appeared to be identical to a product isolated from the plant.

Ozonolisis of 23. Product 23 (10 mg) was dissolved in CH_2Cl_2 (6 ml) at -70ºC and an O_3 stream was passed for 1 minute. Reductive decomposition of ozonide is achieved by addition of triphenylphosphine. After column chromatography 4β,6β-dihydroxy-cis-1β-H, 5β-H-guaian-10-one (22, 8 mg) was isolated. M.p.=64-66ºC; IR ν_{max}^{KBr} cm^{-1}: 3510, 3420, 1700; ^{1}H NMR (80 MHz, $CDCl_3$): δ 4.20 (1H, ddd, J_1=10 J_2=4 J_3=3 Hz, H-6), 1.30 (3H, s, C-15 Me group), 1.05 and 0.97 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups); $[\alpha]_{20}^{\lambda}$=

589	578	546	436	365
+54.1	+54.1	+60.1	+102.8	+144.7

($CHCl_3$, c 0.8).

Cyclization in Acetic Acid Media AcOH/H_2O 80%. 80 mg of 6 were dissolved in AcOH /H_2O 80% and the soln. refluxed for 15 hours and then neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. After cc the following products were isolated in order of elution: 1 (10 mg), 4β-hydroxy-6β,10β-diacetoxy-cis-1β-H,5β-H-guaiane (24, 10 mg), 4β-hydroxy-6β,10α-diacetoxy-1β-H,5β-H-guaiane (26, 2.5 mg), 4β,10β-dihydroxy-6β-acetoxy-cis-1β-H,5β-H-guaiane (25, 9 mg), and 4β,10α-dihydroxy-6β-acetoxy-cis-1β-H,5β-H-guaiane (27, 2.5 mg). 24.- Colourless gum; $[\alpha]_D^{20}$ = -9º ($CHCl_3$, c 1); IR ν_{max}^{neat} cm^{-1}: 3460, 1730 and 1250; ^{1}H NMR (80 MHz, $CDCl_3$): δ 5.25 (1H, t, J=3 Hz, H-6), 2.07 and 1.95 (3H each, s, AcO-groups), 1.37 and 1.28 (3H each, s, C-14 and C-15 Me groups), 0.94 and 0.87 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups). 25.- Colourless gum; $[\alpha]_D^{20}$ =+24º ($CHCl_3$, c 0.7); IR ν_{max}^{neat} cm^{-1}: 3460, 1720, 1260; ^{1}H NMR (80 MHz, $CDCl_3$): δ 5.25 (1H, t, J=2 Hz, H-6), 2.07 (3H, s, AcO-group), 1.27 and 1.22 (3H each, s, C-14 and C-15 Me-groups), 0.80 and 0.75 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups). 26.- ^{1}H NMR (80 MHz, $CDCl_3$): δ 5.27 (1H, t, J=2 Hz, H-6), 2.07 and 2.00 (3H each, s, AcO-groups), 1.50 and 1.25 (3H each, s, C-14 and C-15 Me groups), 0.80 and 0.75 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups). 27.- ^{1}H NMR (80 MHz, $CDCl_3$): δ 5.30 (1H, t, J=2 Hz, H-6), 2.07 (3H, s, AcO-group), 1.25 and 1.20 (3H each, s, C-14 and C-15 Me groups), 0.92 and 0.87 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups).

Saponification of Product 24. 10 mg of 24 stirred in basic media for two hours yields 7 mg of 4β,6β,10β-trihydroxy-cis-1β-H,5β-H-guaiane (28, 7 mg). Colourless gum; $[\alpha]_D^{20}$=+26.6º ($CHCl_3$, c 1); IR ν_{max}^{neat} cm^{-1}: 3460; ^{1}H NMR (80 MHz, $CDCl_3$): δ 4.27 (1H, dd, J_1=8 J_2=4 Hz, H-6), 1.30 and 1.27 (3H each, s, C-14 and C-15 Me groups), 1.05 and 0.98 (3H each, d, J=6.5 Hz, C-12 and C-13 Me groups).

Saponification of Product 25. 8 mg of 25 dissolved in ether were refluxed for 1 hour with 5 mg of H_4AlLi, obtaining 4.5 mg of product 28.

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