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A Shorter Route to the Synthesis of (+)-Junenol, Isojunenol, and their Coumarate Esters from (-)-Santonin

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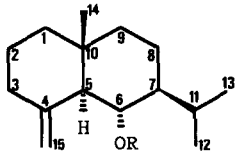
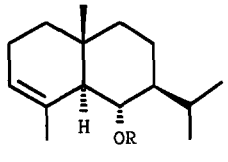
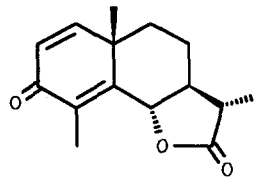
Abstract. This paper reports on the chemical conversion of (-)-santonin into (+)-junenol, isojunenol and their coumarate esters. The identity of (+)-junenol and 8-epi-β-verbesinol is also established.

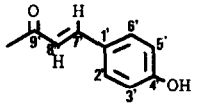
Various cinnamate, coumarate and ferulate esters of sesquiterpenic alcohols were recently isolated from some genera of the *Compositae* family.[1-4] Thus, the coumarate ester of 6-*epi*-β-verbesinol (**1**) was exclusively isolated from two plants of the *Calea* genus (*C. reticulata* and *C. hispida*,[1,2] while the free alcohol **2**, or esterified with other acyl groups (tiglyloyl, angeloyl) were also encountered in other genera.[5,6] The structure proposed for the alcohol (6-*epi*-β-verbesinol) appears to coincide with that of (+)-junenol (**2**),[7] yet there is no literature reference reporting on its identity or enough spectroscopic data to allow for a correct comparison.[1,2,5,6]

Our interest in establishing the relationship between 6-*epi*-β-verbesinol and (+)-junenol as well as their potential biological activity[8] led us, as a continuation of our work on the synthesis of sesquiterpenes[9,10], to develop a method for synthesizing alcohol **2**, its isomer isojunenol (**3**) and their respective coumarate esters (**1**) and (**4**) as enantiomerically pure compounds. We should note that both **2** and **3** are appropriate starting substances for the synthesis of their C_6 epimers and other related esters seemingly typical of the *Verbesina* genus.[3,4]







1 R= 

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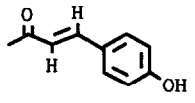
4 R= 

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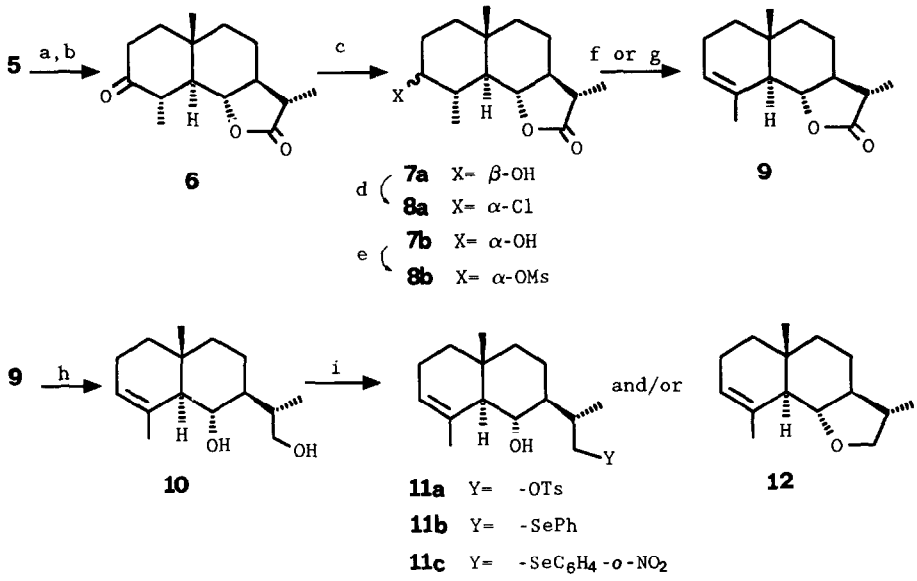
The racemic form of alcohols **2** and **3** were obtained by total synthesis,[11,12] whereas the natural (+) form was prepared from α-santonin according to a procedure reported by Niwa *et al.*[13] We also used α-santonin as starting material because it has the same absolute configuracion at C_6, C_7 and C_{10}. However, Niwa's synthesis is rather lengthly, which makes it difficult to obtain compounds **2** and **3** in amounts large enough to subject them to subsequent transformations. Therefore, we developed a new synthetic pathway for **2** from **5** involving **3** as immediate precursor, which yields **2** by photochemical isomerization of the double bond.[12] Compound **3** was prepared from **5** by changing the dienone function on ring A to $\Delta^{3,4}$-alkene function and obtaining the isopropyl group by reductive elimination of the oxygenated group at C_{12}. Unlike Niwa, we believed it more appropriate to start by the functionalization change on ring A.

RESULTS AND DISCUSION

The starting material **5** was converted into α-tetrahydrosantonin (**6**) by catalytic hydrogenation over Pd/C and epimerization of the resulting mixture with *p*-toluenesulphonic acid/benzene.[8,14] Reduction of the ketone group of **6** with LiAlH(O-*t*-Bu)3 in THF or with $NaBH_4$ in EtOH yielded the epimeric alcohols **7a** and **7b** in a virtually identical ratio (5:1) in both instances. Attempts at the direct dehydration of these alcohols in an acid medium (*p*-TsOH or *p*-TsOH-SiO_2/refluxing toluene),[15] or treatment with $SOCl_2$ in pyridine or quinoline[16] were unsuccessful as they gave rise to the starting alcohol or mixtures with low yields. However, conversion of alcohol **7a** into its 3β-chloro derivative **8a** with $SOCl_2$-pyridine at 80-85°C (yield, 63%)[17] followed by elimination of the purified halide with LiBr-Li_2CO_3/DMF[18] yielded **9** exclusively (yield, 96%). Alkene **9** can also be obtained, though with a lower selectivity ($\Delta^{2,3}/\Delta^{3,4} = 1:9$) from **7b** by formation of mesylate **8b** and subsequent elimination with Li_2CO_3.[18] In this way, the overall yield of conversion of ketone **6** into alkene **9** is 62%.

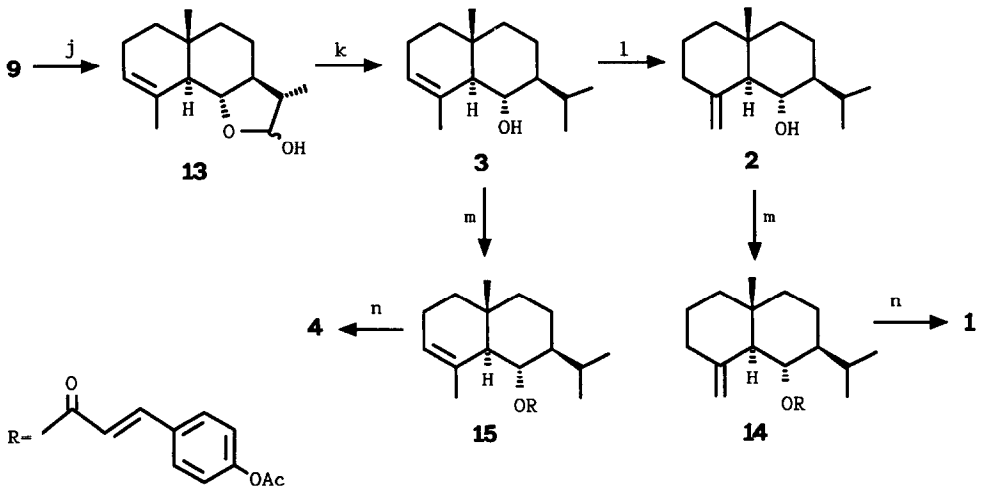


Reagents: (a) H_2, Pd/C; (b) *p*-TsOH; (c) $NaBH_4$ or LiAlH(O-t-Bu)3; $SOCl_2$, pyr.; (e) MsCl, pyr.; (f) LiBr, Li_2CO_3 ; (g) Li_2CO_3; (h) $LiAlH_4$; (i) TsCl, or NPS-n-Bu3P or o-$NO_2C_6H_4SeCN$-n-Bu3P.

The obtainment of the isopropyl unit was first tackled by reducing the lactone to diol **10**[20] and taking advantage of the different reactivity of primary and secondary alcohols to convert it into a 12-monoderivative that could subsequently be reduced to a hydrocarbon (TsO-[20], ArSe-[21]). Despite the fact that **10** was readily obtained with a high yield (92%) from lactone **9** by treatment with $LiAlH_4$/THF, attempts at the selective functionalization of the primary hydroxyl group either with *p*-TsCl,[20] N-phenylselenophtalimide/tri-*n*-butylphosphine (NPS/*n*-Bu_3P)[21] or *o*-$NO_2C_6H_4SeCN$/*n*-Bu_3P[21] did not meet with the desired results, *i.e.* products **11a-c**. The first reagent yielded ether **12** virtually quantitatively, whereas NPS led back to the starting diol. Only *o*-$NO_2C_6H_4SeCN$ yielded the 12-monoarylseleno derivative **11c**, though with low yield (25%) since ether **12** was also obtained preferentially (yield, 58%).

In view of these results we attempted reducing the lactone to a lactol followed by conversion of the aldehyde group of the latter into a methyl group. Despite the reportedly low yield of this conversion,[7] we have carried out the preparation of **3** from **9** with a yield of 87%. Such a transformation involves the reduction of lactone **9** to lactol **13** with DIBAL[22] (5-6 equiv., toluene, at -20°C, yield, 98%; a single epimer by ^1H and ^{13}C NMR spectroscopy) and the application of the Huang-Minlon method[23] to lactol obtained (yield, 89%). It is interesting to note that this procedure makes a straightforward method to the obtainment of β-hydroxyisopropyl groups with high yields from α-methyl-γ-lactones.

Finally, irradiation of a solution of **3** in *i*-PrOH/xylene with a high-pressure 125 W mercury lamp yielded the expected product **2**, which is identical with natural (+)-junenol (IR, ^1H NMR).[7,13] We should note that the above-described synthetic pathway allows one to obtain junenol (**2**) from santonin (**5**) in only 7 steps and with an overall yield higher than the reported by Niwa.[13]



Reagents: (j) DIBAL; (k) NH_2-NH_2, KOH; (l) hν; (m) RCl, pyr.; (n) $NaBH_4$

Once alcohols **2** and **3** were obtained, their coumarate esters **1** and **4** were prepared by acylation with O-acetyl-*p*-coumaroyl chloride/pyridine in benzene and subsequent deprotection of the phenolic hydroxyl group in **14** and **15** by reduction with $NaBH_4$ in dimethoxyethane at room temperature.[24] The physical and spectroscopic properties of product **1** thus obtained coincide with those reported by Bohlman *et al.* for 6-*epi*-β-verbesinol coumarate,[1,2] so (+)-junenol[7] and 6-*epi*-β-verbesinol[5,6] are the same substance.

Table 1. ^{13}C NMR Data of Compounds (7)-(10),(12) and (13) (50.3 MHz, $CDCl_3$, δ values)

C	(7a)	(7b)	(8a)	(8b)	(9)	(10)	(12)	(13)
1	40.7[b]	40.8[a]	40.6[a]	40.6[b]	39.5[a]	40.9[a]	40.4[a]	40.1[b]
2	30.2	28.7	30.4	27.7	23.1[b]	24.1[b]	23.1[c]	23.0[c]
3	76.0	72.3	68.5	85.3[a]	122.2	124.0	121.2	121.4
4	38.7	35.2	35.8	34.8	133.2	136.9	135.1	134.6
5	52.3[a]	46.7	46.9	47.5	50.6	48.6	51.7[b]	51.2[a]
6	83.3	83.2	82.3	82.5[a]	81.9	70.3	82.0	80.0
7	53.5[a]	53.7	53.6	53.6	54.1	54.1	55.6[b]	55.7
8	23.1	23.3	23.1	23.1	22.8[b]	20.2[b]	29.7[c]	22.8[c]
9	39.9[b]	35.4[a]	35.3[a]	35.3[b]	37.8[a]	39.6[a]	38.0[a]	37.9[b]
10	36.7	36.9	36.9	36.6	35.8	35.6	35.2	35.2
11	40.6	40.9	40.7	40.7	40.8	35.1	37.6	46.1[a]
12	179.6	179.8	179.4	179.3	179.7	67.3	74.3	105.1
13	18.8[c]	17.9	19.6[b]	18.1	17.3	17.0	17.4	17.3
14	12.4	12.4	12.4	12.4	12.4	11.4	16.2	14.9
15	16.5[c]	17.9	18.5[b]	18.1	23.6	25.1	23.9	23.9

[a,b,c] Chemical shifts are interchangeable.

EXPERIMENTAL

Melting points were determined in capillary tubes with a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 281 spectrometer, while NMR spectra were run on a Bruker AC-200 instrument (200.1 MHz for ^1H NMR and 50.3 MHz for ^{13}C) by using $CDCl_3$ solutions. Mass spectra were recorded at 70 ev on a Hewlett-Packard 5988A spectrometer. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Reactions were run under atmosphere of argon. Silica gel Merck (0.040-0.063mm) was employed for flash chromatography and silica gel plates 60 F_{254} (Merck) was used for TLC.

3β-Hydroxy- and 3α-hydroxy-5,7αH,4,6,11βH-eudesman-6,12-olide **(7a)** *and* **(7b).**

$NaBH_4$ reduction: To a solution containing 1.544 g (6.17 mmol) of α-tetrahydrosantonin[11] **(6)** in 200 mL of anhydrous EtOH cooled at 0°C, 0.784 g (20.20 mmol) of $NaBH_4$ was added. The resulting mixture was stirred at 0-5°C for 25 min, after which 40 mL of aqueous saturated NH_4Cl was added in small portions. After *in vacuo* evaporation of part of the EtOH, the mixture was extracted with EtOAc and the combined organic layers washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* yielding a foam. Flash chromatography with an 1:9 hexane-ether mixture eluted 0.241 g (15%) of compound **(7b)**: mp 136-137°C (hexane-ether); $[\alpha]_D^{25}$ +13.3° (c 1.36, $CHCl_3$); IR ν_{max} 3480, 3000-2850, 1745, 1460, 1150, 1120, 980, 960 cm^{-1}; ^1H NMR δ 0.93 (*s*,3H,H-14), 1.13 (*d*,3H,J=6.5 Hz,H-15), 1.17 (*d*,3H,J=6.8 Hz,H-13), 2.20 (*dq*,1H,J=6.8 and 12.1 Hz,H-11), 3.74 (*td*,1H,J=2.1 and 4.9 Hz, H-3) and 3.76 (*t*,1H,J=10.7 Hz,H-6); ^{13}C NMR (Table 1).

Table 2. ^{13}C NMR Data of Compounds (1)-(4),(14) and (15) (50.3 MHz, $CDCl_3$, δ values)

C	(1)	(2)	(3)	(4)	(14)[A]	(15)[A]
1	40.2[b]	40.3[a]	39.8[b]	39.6[b]	40.0[b]	39.5[b]
2	24.2[c]	24.0[b]	23.1[c]	23.0[c]	24.0[c]	22.8[c]
3	42.1	41.9	123.5	123.9	42.0	124.1
4	146.3	148.3	135.0	134.1	146.5	134.2
5	55.9[a]	58.3[d]	52.6[a]	50.8[a]	55.8[a]	50.7[a]
6	71.4	67.2	70.4	73.5	71.4	73.6
7	49.6[a]	49.8[d]	53.5[a]	50.5[a]	49.4[a]	50.4[a]
8	18.3[c]	18.3[b]	18.5[c]	18.2[c]	18.1[c]	18.1[c]
9	38.1[b]	37.9[a]	38.2[b]	38.3[b]	37.9[b]	38.2[b]
10	38.1	37.6	34.7	34.9	38.0	34.8
11	26.1	26.0	26.1	25.9	25.9	25.7
12	17.6[d]	17.5[c]	16.7[d]	16.5[d]	17.4[d]	16.3[d]
13	21.4[d]	21.1[c]	21.4[d]	21.6[d]	21.2[d]	21.4[d]
14	16.1	16.2	16.2	16.0[d]	15.9	15.8[d]
15	106.7	106.3	24.6	23.4	106.8	23.3
1'	127.2	-	-	127.1	132.4	132.4
2'	130.0	-	-	130.0	129.3	129.4
3'	115.8	-	-	115.9	122.1	122.2
4'	157.7	-	-	157.9	152.1	152.3
5'	115.8	-	-	115.9	122.1	122.2
6'	130.0	-	-	130.0	129.3	129.4
7'	144.5	-	-	144.6	143.6	143.7
8'	115.8	-	-	116.2	118.9	119.3
9'	167.8	-	-	167.8	167.2	167.3

[A] Acetate carbons: for compound (**14**), 20.9 and 169.4; for compound (**15**), 21.0 and 169.4.
[a,b,c,d] Chemical shifts are interchangeables.

A second product eluted with ether was compound (**7a**) (1.186 g, 76%) with the following features: mp 169-171°C (hexane-ether); $[\alpha]_D^{25}$ +50.3° (c 1.49, $CHCl_3$); IR ν max 3520, 3000-2845, 1755, 1455, 1115, 980 cm^{-1}; ^1H NMR δ 0.95 (*s*,3H,H-14), 1.17 (*d*,3H,J = 6.9 Hz,H-13), 1.18 (*d*,3H,J = 6.3 Hz,H-15), 2.20 (*dq*,1H,J = 6.9 and 12.0 Hz,H-11), 3.11 (*ddd*,1H,J = 5.1,10.1 and 10.6 Hz,H-3) and 3.80 (*t*,1H,J = 10.2 Hz,H-6); ^{13}C NMR (Table 1).

LiAlH(O-t-Bu)3 reduction: α-Tetrahydrosantonin (**6**) (0.032 g, 0.13 mmol) in dry THF (2 mL) was added to a suspension of LiAlH(O-*t*-Bu)3 (0.096 g, 0.38 mmol) in dry THF (0.5 mL) at 0°C and stirred at this temperature for 30 min. The reaction was quenched with aqueous saturated NH_4Cl and after *in vacuo* evaporation of THF and usual workup the mixture was chromatographed yielding (**7b**) (5 mg,15%) and (**7a**) (25 mg,77%).

3α-Chloro-5,7αH,4,6,11βH-eudesman-6,12-olide (**8a**)

To a solution of 0.596 g (2.36 mmol) of compound (**7a**) in dry pyridine (3.5 mL) cooled at 0°C was added dropwise over 5 min a solution 2.38 M of $SOCl_2$ in dry pyridine (12.1 mL, 28.80 mmol) and then quickly warmed to 80-82°C. After stirring 2.25 h at this temperature and cooling, the reaction was quenched by adding 10 mL of 1N aqueous HCl. The mixture was extracted with EtOAc, washed with 1N HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The solid residue was chromatographed on silica gel with 1:1 hexane-ether mixture yielding 0.401 g (63%) of compound (**8a**) and 0.067 g (11%) of starting material. Compound (**8a**) had the following features: mp 145-146°C (hexane-ether);$[\alpha]_D^{25}$ -21.2° (c 1.17, $CHCl_3$); IR ν_{max} 2970-2845, 1760, 1455, 1145, 980, 705 cm^{-1}, ^1H NMR δ 0.95 (*s*,3H,H-14), 1.16 (*d*,3H,J = 6.5 Hz,H-15), 1.18 (*d*, 3H,J = 6.8 Hz,H-13), 2.20 (*dq*,1H,J = 6.8 and 12.0 Hz,H-11), 3.77 (*dd*,1H,J = 9.6 and 9.9 Hz,H-6) and 4.25 (*brd*,1H,J = 2.8 Hz,H-3); ^{13}C NMR (Table 1).

3α-(O-Methanesulfonyl)-5,7αH,4,6,11βH-eudesman-6,12-olide (**8b**)

To a solution of 24 mg (0.095 mmol) of compound (**7b**) in 2 mL of dry pyridine a 0°C was added 40 μL (0.517 mmol) of mesyl chloride. After stirring at 0°C for 5 h, an additional amount (34 μL,0.44 mmol) of MsCl was added and the stirring continued for 12 h at this temperature. Then, the mixture was diluted with EtOAc and the reaction quenched with 5 mL of 2% aqueous HCl. By the usual workup and chromatography with 2:8 hexane-ether mixture as eluent was obtained 30 mg (96%) of compound (**8b**) with the following features: mp 124-125°C (hexane-ether); $[\alpha]_D^{25}$ -23.4°C (c 0.42, $CHCl_3$); IR ν_{max} 3000-2875, 1775, 1460, 1355, 1175, 1160, 975, 760, 670 cm^{-1}; ^1H NMR δ 0.95 (*s*,3H,H-14); 1.17 (*d*,6H,J = 6.9 Hz,H-13 and H-15), 2.19 (*dq*,1H,J = 6.9 and 12.0 Hz,H-11), 2.99 (*s*,3H,CH_3-SO_3-), 3.75 (*t*,1H,J = 10.3 Hz,H-6) and 4.75 (*brd*,1H,J = 2.3 Hz,H-3); ^{13}C NMR (Table 1).

5,7αH,6,11βH-Eudesm-3-en-6,12-olide (**9**).

From compound (**8a**). A suspension of compound (**8a**) (0.985 g, 3.64 mmol), LiBr (0.830 g, 9.56 mmol) and Li_2CO_3 (0.967 g, 13.09 mmol) in dry DMF (9.0 mL) was heated at 138-140°C for 2.25 h. After *in vacuo* removal of the solvent the solid residue was chromatographed with 7:3 hexane:ether mixture as eluent giving 0.795 g (93%) of compound (**9**) with the following features: mp 132-134°C (ether); $[\alpha]_D^{25}$ +71.8° (c 1.11, $CHCl_3$); IR ν_{max} 3020, 2980-2840, 1765, 1450, 990, 980, 850 cm^{-1}; ^1H NMR δ 0.89 (*s*,3H,H-14), 1.19 (*d*,3H,J = 6.8 Hz,H-13), 1.79 (*brd*,3H,J = 2.3 Hz,H-15), 2.30-1.90 (*m*,4H,overlapped signals 2H-2,H-5 and H-11), 3.85 (*dd*,1H,J = 9.6 and 9.7 Hz,H-6) and 5.33 (*brd*,1H,J = 2.3 Hz,H-3); ^{13}C NMR (Table 1).

From compound (**8b**). A suspension of (**8b**) (13 mg, 0.039 mmol) and Li_2CO_3 (24 mg, 0.33 mmol) in dry DMF (1 mL) was heated at 110-120°C for 1.5 h. Then the temperature was raised to 148-150°C and the mixture was kept at this temperature for 2 h. After *in vacuo* removal of solvent and chromatography as above was obtained 8 mg (87%) of compound (**9**).

5,7αH,11βH-Eudesm-3-en-6α,12-diol (**10**).

A solution of compound (**9**) (0.693 g, 2.96 mmol) in dry THF (20 mL) was added dropwise over 10 min to a 0°C cooled suspension of 0.236 g (6.22 mmol) of $LiAlH_4$ in dry THF (15 mL). After stirring at 0°C for 1.5 h the reaction was quenched with 5% aqueous H_2SO_4 (70 mL) and extracted with ether. The product was worked up as usual and chromatographed with ether as eluent yielding 0.659g (92%) of compound (**10**) with the following features: mp 158-160°C (ether); Anal. Calcd. for $C_{15}H_{26}O_2$: C, 75.58, H, 10.99. Found: C, 75.51, H, 11.12.; $[\alpha]_D^{25}$ +33.8° (c 1.41, MeOH); MS *m/e* 220 (M^+-H_2O, 37%), 187 (26%), 161 (41%), 131 (38%), 109 (100%), 107 (99%), 95 (53%), 81 (46%), 41 (51%); IR ν_{max} 3360-3280, 3020, 2960-2820, 1490-1435, 1065, 1040, 1045, 1025, 860 cm^{-1}; ^1H NMR δ 0.75 (*s*,3H,H-14), 0.88

(*d*,3H,J = 7.2 Hz,H-13), 1.73 (*brs*,2H,2-OH), 1.88 (*brd*,3H,J = 1.7 Hz,H-15), 2.10-1.95 (*m*,1H,H-2), 2.13 (*ddd*,1H,J = 0.7,6.7 and 13.5 Hz,H-2ß), 3.45-3.62 (*m*,3H,overlapped signals H-6 and 2 H-12) and 5.35 (*brs*,1H,H-3); ^{13}C NMR (Table 1).

6α,12-Oxy-5,7αH,6,11βH-eudesm-3-ene (**12**).

A solution of 30 mg (0.125 mmol) of compound (**10**) and 64 mg (0.34 mmol) of tosyl chloride in 2 mL of dry pyridine was stirred at 5-8°C for 5 h. After diluting with EtOAc (1 mL) the reaction was quenched with 1 mL of aqueous saturated $NaHCO_3$ and then the mixture was poured on 2N aqueous HCl and extracted as usual. After chromatography with 8:2 hexane-EtOAc mixture as eluent was isolated 27.5 mg(100%) of compound (**12**) as a colourless oil: Anal. Calcd. for $C_{15}H_{24}O$: C, 81.78, H, 10.98. Found: C, 81.81, H, 11.10; $[\alpha]_D^{25}$ +10.3° (c 2.63, $CHCl_3$); MS *m/e* 220 (M^+,35%), 187 (14%), 151 (27%), 109 (40%), 107 (100%), 79 (26%), 41 (41%); IR ν_{max} 3010, 2980-2840, 1450, 1375, 1025-975, 840 cm^{-1}; ^{1}H NMR δ 0.81 (*s*,3H,H-14), 1.00 (*d*,3H,J = 6.6 Hz,H-13), 1.77 (*brs*,3H,H-15), 1.80-2.20 (*m*,2H,2H-2), 3.26 (*t*,1H,J = 10.2 Hz,H-6), 3.38 (*t*,1H,J = 8.4 Hz,H-12), 4.01 (*t*,1H,J = 8.4 Hz,H-12') and 5.27 (*brd*,1H,J = 2.8 Hz,H-3); ^{13}C NMR (Table 1).

12-(o-Nitrophenylseleno)-5,7αH,11βH-eudesm-3-en-6α-ol (**11c**)

To a -20°C cooled solution of compound (**10**) (0.117 g,0.49 mmol) and *o*-nitrophenylselenocyanate (0.295 g,1.30 mmol) in dry THF (6 mL) was added 320 μL (1.30 mmol) of *n*-Bu_3P. The mixture was stirred at -10/-20°C for 4.5 h and then warmed to 0°C and kept at this temperature for 2.5 h. After precipitation with ether and removal of the solid, the remaining solution was evaporated *in vacuo* giving a dark brown oil which by preparative TLC (hexane-EtOAc, 8:2) gives 0.063 g (58%) of compound (**12**) and 0.051 g (25%) of (**11c**) as a low melting point yellow solid with the following features: $[\alpha]_D^{25}$ +6.5° (c 0.51, $CHCl_3$); MS *m/e* 423(M^+,11%), 221 (24%), 201 (35%), 161 (29%), 121 (32%), 109 (58%), 107 (69%), 95 (100%), 81 (84%), 41 (83%); IR ν_{max} 3550-3420, 3080-3060, 3015, 2980-2840, 1590, 1565, 1510, 1450, 1330, 1095, 1035, 850, 770, 730 cm^{-1}; ^{1}H NMR δ 0.77 (*s*,3H,H-14), 1.06 (*d*,3H,J = 6.8 Hz,H-13), 1.87 (*brs*,3H,H-15), 2.56 (*brq*,1H,J = 6.8 Hz,H-2), 2.89 (*d*,2H,J = 7.4 Hz,2 H-12), 3.51 (*brt*,1H,J = 7.6 Hz,H-6), 5.35 (*brs*,1H,H-3), 7.30-7.50 (*m*,3H,overlapped signals, aromatic H in *meta* and *para* to -NO_2) and 8.25 (*dd*,1H,J = 0.9 and 8.5 Hz, aromatic H *orto* to NO_2).

6α,12-Oxy-5,7αH,11βH-eudesm-3-en-12 -ol (**13**)

To a solution of 0.377 g (1.61 mmol) of compound (**9**) in dry toluene (12 mL) at -20°C was added dropwise over 10 min a solution of 1M diisobutylaluminium hydride (DIBAL) in *n*-hexane (9 mL, 9.0 mmol). After stirring at -20°C for 45 min the reaction was quenched at 0°C with 9 mL of a 2M solution of *i*-PrOH in toluene-water (9:1). The mixture was diluted with EtOAc, treated with anhydrous Na_2SO_4 (2 g) and Kieselgur (0.9 g) and then filtered on silica gel from which EtOAc and acetone eluted 0.371 g (98%) of compound (**13**): mp 87-89°C (EtOAc-acetone); Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23, H, 10.23. Found: C, 76.19, H, 10.43; $[\alpha]_D^{25}$ +109.2° (c 1.21, MeOH); MS *m/e* 236(M^+,10%), 221 (9%), 218 (10%), 189 (4%), 167 (13%), 160 (46%), 145 (25%), 109 (87%), 107 (100%), 79 (35%), 41 (51%); IR $_{max}$ 3390, 3010, 2960-2830, 1455-1430, 1075, 1060, 980, 960, 940, 930, 850 cm^{-1}; ^{1}H NMR δ 0.82 (*s*,3H,H-14), 1.09 (*d*,3H,J = 6.6 Hz,H-13), 1.77 (*brs*,3H,H-15), 3.69 (*t*,1H,J = 10.4 Hz,H-6), 5.07 (*d*,1H,J = 4.4 Hz,H-12) and 5.27 (*brs*,1H,H-3); ^{13}C NMR (Table 1).

6-Epi-α-verbesinol or isojunenol (**3**)

A solution of compound (**13**) (0.295 g, 1.25 mmol), KOH (0.355g, 5.38 mmol) and 80% aqueous hydrazine (0.387 g, m6.18 mmol) in diethylenglycol (17 mL) under deoxygenated argon was heated to

110-115°C for 1.75 h. Then the $N_2H_4.H_2O$ excess was distilled and the temperature of the mixture raised to 200-205°C. After stirring at this temperature for 3.75 h the mixture was poured on 0.5 N aqueous HCl (15 mL) and extracted with EtOAc. After usual workup the mixture was chromatographed with a 9:1 hexane-EtOAc mixture yielding compound (**3**) (0.240 g, 87%): mp 62-64°C (hexane-EtOAc); $[\alpha]_D^{25}$ +23.1° (c 5.20, Cl_3CH); MS *m/e* 222 (M^+,3%), 204 (13%), 189 (30%), 161 (36%), 133 (21%), 109 (100%), 107 (63%), 81 (41%), 41 (59%); IR ν max 3420-3350, 3015, 2960-2840, 1450, 1380, 1375, 1015, 975, 835 cm^{-1}; ^1H NMR δ 0.75 (*s*,3H,H-14), 0.84 and 0.93 (two *d*, 3H each, J = 6.8 Hz, H-12 and H-13), 1.83 (*brd*,1H,J = 9.8 Hz,H-5), 1.89 (*brd*,3H,J = 1.8 Hz,H-15), 2.03 (*m*,1H,H-2ß), 2.22 (*d quint*,1H,J = 2.6 and 7.1 Hz,H-2), 3.49 (*t*,1H,J = 9.8 Hz,H-6) and 5.34 (*brs*,1H,H-3); ^{13}C NMR (Table 2).

6-Epi-ß-verbesinol or (+)-junenol (**2**).

A solution of 75 mg (0.34 mmol) of compound (**3**) and xylene (2 mL) in 220 mL of degasified *i*-PrOH was irradiated with a 125 W high pressure Hanovia lamp at room temperature over 1 h. After *in vacuo* removal of solvent the mixture was chromatographed with (9:1) hexane-ether mixture as eluent yielding (**2**) (38 mg, 50%) with the following features: mp 53-54°C (hexane-ether) ; $[\alpha]_D^{25}$ +48.0° (c 6.96, $CHCl_3$) ; IR ν max 3420-3350, 3015, 2960-2840, 1450, 1380, 1375, 1015, 975, 835 cm^{-1}; MS *m/e* 222 (M^+,5%), 205 (2%), 204 (15%), 179 (18%), 161 (23%), 135 (13%), 109 (100%), 81 (32%), 41 (34%); ^1H NMR δ 0.71 (*t*,3H,H-14), 0.85 (*d*,3H,J = 7.1 Hz,H-12 or H-13), 0.93 (*d*,3H,J = 6.8 Hz,H-12 or H-13), 3.63 (*dt*, 1H, J = 1.9 and 9.4 Hz, H-6), 4.64 (*d*,1H, J = 0.9 Hz, H-15) and 4.95 (*d*,1H,H = 0.9 Hz, H-15'). ^{13}C NMR (Table 2).

O-Acetyl-p-coumaroyl chloride

$SOCl_2$ (3.6 mL) was added to 0.101 g (0.49 mmol) of O-acetyl-*p*-coumaric acid at 0°C, stirred at this temperature for 10 min and then heated to 70-75°C for 1.5 h. The excess of $SOCl_2$ was distilled *in vacuo* and the remaining solid dried and used in the acylation reaction without further purification.

6α- O-Acetyl-p-coumaroyloxy -5,7αH-eudesm-4(15)-ene (**14**)

To a stirred solution of 0.110 g (0.49 mmol) of O-acetyl-*p*-coumaroyl chloride in dry benzene (1 mL) at 0°C was added dropwise 1.2 mL of dry pyridine. After 10 min a solution of 12 mg (0.054 mmol) of compound (**2**) in dry benzene (1 mL) was added and the mixture was stirred at 0°C for 10 h. After quenching with 10% aqueous HCl (10 mL) the mixture was worked up as usual and chromatographed on silica gel from which a 8:2 hexane-ether mixture eluted 17 mg (76%) of compound (**14**) with the following features: mp 116-118°C (hexane-EtOAc); Anal. Calcd. for $C_{26}H_{34}O_4$: C, 76.10, H, 8.37. Found: C, 76.06, H, 8.35; $[\alpha]_D^{25}$ -61.8° (c 3.04, $CHCl_3$); MS *m/e* 205 (12%), 204 (74%), 189 (24%), 161 (100%), 147 (63%), 133 (20%), 105 (19%), 91 (24%), 81 (12%), 43 (35%); IR ν max 2920-2840, 1760, 1695, 1630, 1595, 1500, 1200, 1175, 1000, 980, 900, 830 cm^{-1}; ^1H NMR δ 0.78 (*s*,3H,H-14), 0.89 (*d*,6H,H-12 and H-13), 2.10 (*brd*,1H,J = 9.8 Hz,H-5), 2.28 (*s*,3H,CH_3-CO), 4.53 (*brs*,1H,H-15), 4.74 (*brs*,1H,H-15'), 5.16 (*t*,1H,J = 9.8 Hz,H-6), 6.33 (*d*,1H,J = 16.0 Hz,H-8'), 7.08 (*brd*,2H,J = 8.6 Hz,H-2' and H-6'), 7.50 (*brd*,2H,J = 8.6 Hz,H-3' and H-5') and 7.60 (*d*,1H,J = 16.0 Hz,H-7'); ^{13}C NMR (Table 2).

6-Epi-ß-verbesinol or (+)-junenol coumarate (**1**).

To a solution of 14 mg (0.034 mmol) of compound (**14**) in dimethoxyethane (DME) (0.7 mL) was added 6 mg (0.16 mmol) of $NaBH_4$ and the mixture stirred for 24 h. The reaction was quenched with saturated aqueous NH_4Cl and worked up and chromatographed as usual. A mixture of 8:2 hexane-ether eluted 12 mg (97%) of compound (**1**) as a colourless oil.Compound (**1**) had the following features: Anal. Calcd. for $C_{24}H_{32}O_3$: C, 78.22, H, 8.75. Found: C, 78.19, H, 8.72;

$[\alpha]^{25}$ -60.0 -63.4 -74.6 -160.0 (c 0.62, $CHCl_3$)
D 578 546 436 nm

MS *m/e* 368 (M+,3%), 205 (13%), 204 (71%), 189 (15%), 164 (100%), 147 (83%), 133 (22%), 119 (29%), 105 (22%), 91 (34%), 81 (13%), 55 (15%), 41 (17%); IR ν max 3360-3300, 2960-2840, 1670, 1630, 1585, 1510, 1440, 1200-1155, 1005, 980, 905, 825 cm^{-1}; ^1H NMR δ 0.77 (*s*,3H,H-14), 0.88 (*d*,6H,J = 7.0 Hz, H-12 and H-13), 2.09 (*brd*,1H,J = 9.6 Hz,H-5), 4.54 (*brs*,1H,H-15), 4.73 (*brs*,1H,H-15'), 5.16 (*brt*,1H,J = 9.9 Hz,H-6), 6.23 (*d*,1H,J = 16.0 Hz,H-8'), 6.80 (*brd*,2H,J = 8.5 Hz, H-2' and H-6'), 7.38 (*brd*,2H,J = 8.5 Hz,H-3' and H-5') and 7.56 (*d*,1H,J = 16.0 Hz,H-7'); ^{13}C NMR (Table 2).

6α- O-Acetyl-p-cumaroyloxy -5,7αH-eudesm-3-ene (**15**)

Compound (**3**) (26 mg, 0.117 mmol) in dry benzene (1.5 mL) was added to a solution of O-acetyl-*p*-coumaroyl chloride (0.186 g, 0.83 mmol) and dry pyridine (2 mL) in benzene (1 mL) as for compound (**14**) and stirred at 0°C for 65 h. After chromatography (hexane-ether, 8:2) 15 mg (32%) of compound (**15**) was obtained. Compound (**15**) had the following features: mp 112-114°C (hexane-EtOAc); Anal. Calcd. for $C_{26}H_{34}O_4$: C, 76.10, H, 8.37. Found: C, 76.05, H, 8.36; $[\alpha]_D^{25}$ +2.3° (c 0.75, $CHCl_3$); MS *m/e* 204 (58%), 189 (88%), 147 (100%), 120 (69%), 105 (95%), 81 (28%), 43 (80%); IR ν max 3010, 2950-2840, 1760, 1700, 1630, 1600, 1500, 1450, 1200, 1175, 1165, 1005, 980, 830 cm^{-1}; ^1H NMR δ 0.83 (*s*,3H,H-14), 0.88 (*d*,6H,J = 7.0 Hz, H-12 and H-13), 1.62 (*brs*,3H,H-15), 2.28 (*s*,3H,CH_3COO-), 5.08 (*dd*,1H,J = 8.7 and 10.7 Hz,H-6), 5.32 (*brs*,1H,H-3), 6.38 (*d*,1H,J = 16.0 Hz,H-8'), 7.10 (*brd*,2H,J = 8.6 Hz,H-2' and H-6'), 7.52 (*brd*,2H,J = 8.6 Hz, H-3' and H-5') and 7.63 (*d*,1H,J = 16.0) Hz, H-7'); ^{13}C NMR (Table 2).

6-Epi-α-verbesinol p-coumarate (**4**).

Compound (**15**) (14 mg, 0.034 mmol) in DME (0.7 mL) was treated with $NaBH_4$ (6 mg, 0.16 mmol) for 20 h as for compound (**14**). After chromatography 10 mg (79%) of compound (**4**) was obtained as a colourless oil with the following features: Anal. Calcd. for $C_{24}H_{32}O_3$: C, 78.22, H, 8.75. Found: C, 78.20, H, 8.77;

$[\alpha]^{25}$ -16.3 -17.5 -20.3 -43.1° (c 0.36, $CHCl_3$)
D 578 546 436 nm

MS *m/e* 205 (M^+-RCOO,10%), 204 (M^+-RCOOH,59%), 189 (82%), 164 (19%), 161 (31%), 147 (100%), 120 (49%), 119 (48%), 105 (85%), 91 (42%), 81 (31%), 55 (26%), 41 (28%); IR ν max 3360-3220, 2950-2840, 1665, 1625, 1595, 1505, 1435, 1190-1160, 975, 820 cm^{-1}; ^1H NMR δ 0.85 (*d*,6H,J = 8.7 Hz,H-12 and H-13), 0.90 (*s*,3H,H-14), 1.64 (*brs*,3H,H-15), 5.08 (*brt*,1H,J = 10.4 Hz,H-6), 5.32 (*brs*,1H,H-3), 6.29 (*d*,1H,J = 16.0 Hz,H-8'), 6.82 (*d*,2H,J = 8.5 Hz,H-2' and H-6'), 7.41 (*d*,2H,J = 8.5 Hz,H-3' and H-5') and 7.60 (*d*,1H,J = 16.0 Hz,H-7'); ^{13}C NMR (Table 2).

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REFERENCES

1. Bohlmann, F.; Borthakur, N.; King, R.M.; Robinson, H. *Phytochemistry* **1982**, *21*, 1793.
2. Bohlmann, F; Gupta, R.K.; Jakupovic, J.; King,R.M.; Robinson, H. *Phytochemistry* **1982**, *21*, 2899.
3. Bohlmann, F.; Zdero, C. *Phytochemistry* **1979**, *18*, 1751.
4. Jakupovic, J.; Ellmauerer, E.; Jia, Y.; Bohlmann, F.; Dominguez, X.A.; Schmeda-Hirschmann, G. *Planta Med.* **1987**, 39. and lit. cited therein.
5. Bohlmann, F; Jakupovic, J. *Phytochemistry* **1979**, *18*, 1987.
6. Bohlmann, F.; Ahmed, M.; King, R.M.; Robinson, H. *Phytochemistry* **1983**, *20*, 983 (and lit. cited therein).
7. Bhattacharyya, S.C.; Rao, A.S.; Shaligram, A.M. *Tetrahedron* **1962**, *18*, 969.
8. Van Beek, T.A.; DeGrot, A. *Recl.Trv.Chim.Pays-Bas* **1986**, *105*, 513.
9. Blay,G.; Fernández,I.; García,B.; Pedro,J.R. *Tetrahedron* **1989**, *45*, 5925.
10. Blay, G.; Cardona, M.L.; García, B.; Pedro, J.R. *J.Org.Chem* . **1991**, *56*, 6172.
11. Banerjee, A.K.; Hurtado, H.E.; Carrasco, M.C. *J.Chem.Soc.Perkin Trans.I* **1982**, 2547.
12. Schwartz, M.A. Crowell, J.D.; Musser, J.H. *J.Am.Chem.Soc.* **1972**, *94*, 4361.
13. Niwa, M.; Iguchi, M.; Yakamura, S. *Bull.Chem.Soc.Jpn.* **1976**, *49*, 3145.
14. Cocker W.; McMurry, T.B.M.*J.Chem.Soc.* **1956**, 4549.
15. D'Onofrio, F.; Scettri, A. *Synthesis* **1985**, 1159.
16. Fried, J.H.; Arth, G.E.; Sarett, L.H. *J.Am.Chem.Soc.* **1959**, *81*, 1235.
17. Piacenza, L.P.L. *J.Org.Chem* **1977**, *42*, 3778.
18. Corey, E.J.; Hortman, A.G. *J.Am.Chem.Soc.* **1965**, *87*, 5736.
19. Piazenza, L.P.L. *J.Org.Chem.* **1977**, *42*, 3778.
20. Greene, A.E. *J.Am.Chem.Soc.* **1980**, *102*, 5337.
21. Grieco, P.A.; Jaw, J.Y., *J.Org.Chem.* **1981**, *46*, 1215.
22. Schmidlin, J.; Wettstein, A. *Helv.Chim.Acta.* **1963**, *46*, 2799.
23. Huang-Minlon, *J.Am.Chem.Soc.* **1946**, *68*, 2487.
24. Quick, J.; Crelling, J.K. *J.Org.Chem.* **1978**, *43*, 155.