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# SESQUITERPENE LACTONES FROM *SALVIA PALAEFOLIA*

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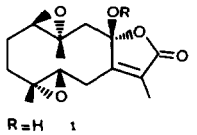
**Key Word Index**—*Salvia palaefolia*; Labiatae; sesquiterpene lactones; eudesmanolide; glechomanolide; glechomafuran; X-ray diffraction analysis; circular dichroism exciton chirality.

**Abstract**—The aerial part of *Salvia palaefolia* yielded (−)-glechomafuran, 1β,10α;4α,5β-diepoxy-8β-hydroxyglechoman-8α,12-olide and the new eudesmanolides: 1α-acetoxy-8α-hydroxy-2-oxo-eudesman-3,7(11)-dien-8,12-olide and 1α,8α-dihydroxy-2-oxo-eudesman-3,7(11)-dien-8,12-olide. The structure of the former new compound was determined from its spectral data and chemical behaviour and its absolute configuration by CD experiments. The absolute configuration of 1β,10α;4α,5β-diepoxy-8β-hydroxyglechoman-8α,12-olide was established by X-ray diffraction analysis.

## INTRODUCTION

In the course of an intensive study of the medical flora of South America, we reported [1] the isolation of the triterpenes squalene, lupeol, taraxerol, taraxerone, β-amyrin, 3-oxo-olean-12-ene, oleanonic, oleanolic and ursolic acid, and 5-hydroxy-7,6,8,4′-tetramethoxyflavone, caryophyllene oxide and (−)-glechomafuran from *Salvia palaefolia* H.B.K., an Andean species used in Colombian folk medicine as an antihypertensive agent. The configuration of glechomafuran was established from its X-ray data. We have now obtained 8-hydroxyglechomanolide (**1**) and two new eudesmanolides (**3** and **4**) from the same plant.



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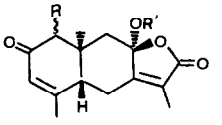
R=Ac 2



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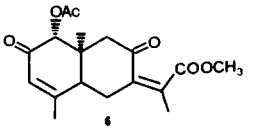
R=αOH R′=H 4
R=αOAc R′=Ac 5
R=αOBz R′=Bz 6
R=βOBz R′=Bz 9
R=α p-BrOBz R′=H 10



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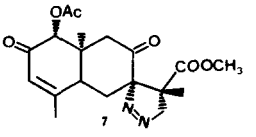

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## RESULTS AND DISCUSSION

Cold acetone extracts of the aerial part of *S. palaefolia* yielded a glechomanolide and two new eudesmanolides which were characterized from their spectral data and chemical behaviour as 1β,10α;4α,5β-diepoxy-8β- hydroxyglechoman-8α,12-olide (**1**), 1α-acetoxy-8α-hydroxy-2-oxo-eudesman-3,7(11)-dien-8,12-olide (**3**) and its deacetoxy derivative (**4**). NOESY and CD experiments established the absolute configuration of **3**.

The high resolution mass spectrum of **1** indicated the molecular formula $C_{15}H_{20}O_5$. A peak at *m/z* 262 corresponds to $[M-H_2O]^+$. In the IR spectrum, hydroxy (3310 $cm^{-1}$), lactone (1740 $cm^{-1}$) and ether bands can be observed. The UV bands at 284 and 305 nm are those appropriate to a conjugated lactone. In the $^1H$ NMR spectrum, the most representative signals are those for three methyls, one of which (at δ1.91) must be situated on the α-carbon atom of the double bond conjugated with the lactone carbonyl while the other two, at δ1.35 and 1.50, are on oxygen-bearing carbons. There are also two protons as double doublets centred at δ2.67 and 2.69 attributable to oxirane protons. Treatment of compound **1** with acetic anhydride in pyridine gave a monoacetate (**2**), ($C_{17}H_{22}O_6$ by HRMS) with no hydroxy signals in the IR spectrum and with an acetate methyl as a singlet at δ2.11 in the $^1H$ NMR spectrum but no signals for the geminal protons of an acetate, signalling that the hydroxy group in compound **1** is tertiary. The $^{13}C$ NMR spectrum showed a signal for a singlet carbon at δ107.3 attributable to a hemiketal carbon which sites the hydroxy group on the lactone closure carbon. These data are all consistent with structure **1** for the natural product, and its physical and $^1H$ NMR spectral data agree with those given in the literature for 1β,10α,4α,5β-diepoxy-8-hydroxy-glechomanolide earlier isolated from *Smyrnium cordifolium* (Umbelliferae) [2]. The absolute configuration of this compound had not, however, been established. It was

Table 1. $^1$H NMR spectral data for compounds **3**–**5** and **8**–**10**

| H | 3 | 4 | 5 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|
| 1 | 5.08 *s* | 3.82 *s* | 5.12 *s* | 5.91 *s* | 5.45 *s* | 5.35 *s* |
| 2 | — | — | — | — | — | — |
| 2′ | — | — | — | — | — | — |
| 3 | 5.98 *br s* | 6.09 *br s* | 6.03 *br s* | 5.98 *br s* | 6.19 *br s* | 6.09 *s* |
| 3′ | — | — | — | — | — | — |
| 5 | 2.59 *t* | 2.50 *m* | 2.66 *br dd* | 2.67 *t* | 2.81 *m* | 2.57 *m* |
| 6α | 2.96 *br dd* | 2.99 *d* | 3.05 *dd* | 3.19 *dd* | 3.14 *m* | 3.02 *m* |
| 6β | 2.56 *br dd* | 2.50 *m* | 2.43 *br dd* | 2.32 *dd* | 3.31 *m* | 2.50 *m* |
| 9α | 1.62 *d* | 2.71 *d* | 2.94 *d* | 1.56 *d* | 1.81 *d* | 1.88 *d* |
| 9β | 2.44 *d* | 1.79 *d* | 1.57 *d* | 3.47 *d* | 3.08 *d* | 3.02 *m* |
| 13 | 1.82 *br s* | 2.07 *br s* | 1.93 *br s* | 2.11 *s* | 2.02 *s* | 2.08 *s* |
| 14 | 1.19 *s* | 1.07 *s* | 1.12 *s* | 1.25 *d* | 1.34 *s* | 1.31 *s* |
| 15 | 2.03 *br s* | 1.90 *br s* | 2.05 *s* | 2.00 *br s* | 2.08 *br s* | 2.04 *s* |
| OAc | 2.18 *s* | — | 2.05 *s* | — | — | — |
| OAc | — | — | 2.21 *s* | — | — | — |
| OH | — | 3.73 *d* | — | — | — | — |
| $CO_2Me$ | — | — | — | — | — | — |
| Ar-H | — | — | — | 7.23–8.03 | 7.24–8.10 | 7.96–7.50 |
| $-CH_2-N$ | — | — | — | (10H) | (10H) | (4H) |

*J* (Hz): **3**: 9α,9β = 13.6; 6α,6β = 12; 6α,5 = 2; **4**: 9α,9β = 14; 6α,6β = 10; **5**: 9α,9β = 14; 6α,6β = 13; 6α,5 = 3; 6β,5 = 12; **8**: 9α,9β = 15; 6α,6β = 14; 6α,5 = 3; 6β,5 = 13; **9**: 9α,9β = 14; 6α,6β = 14; 6α,5 = 13.

therefore submitted to X-ray crystallographic examination (see Experimental) and the stereochemistry at C-1, C-4, C-5 and C-10 found to be identical with the stereochemistry of the related compound, glechomafuran [1].

Compound **3** was isolated as a crystalline solid with the molecular formula $C_{17}H_{20}O_6$ determined by high resolution mass spectrometry. The IR spectrum shows bands for an alcohol group at 3340 $cm^{-1}$, a conjugated carbonyl (1670 $cm^{-1}$) and a conjugated lactone (1750 $cm^{-1}$). The $^1$H NMR data (Table 1) include an acetate methyl as a singlet at δ2.18, two methyls on double bonds as singlets at δ1.82 and 2.03, a proton singlet at δ5.08 and a broad singlet at δ5.98 attributable to the α-proton of an α,β-unsaturated ketone. Hydrolysis of compound **3** gave alcohol **4** with a chemical shift of the proton at δ5.08 in **3** to δ3.82, signifying that this proton is geminal to the acetoxy group in compound **3**. Its low chemical shift (δ5.08) in compound **3** makes this proton α to the ketone group. Acetylation of compound **3** gave the diacetate **5** with no alcohol groups discernible in the IR spectrum, and its $^1$H NMR spectrum shows signals for the two acetate groups as three-proton singlets at δ2.05 and 2.21 but no visible signal for the extra acetoxy group, thus indicating that the hydroxy group in compound **3** is tertiary. In the $^{13}$C NMR spectrum of compound **3**, a carbon singlet at δ102.6 assignable to a hemiketalic carbon situates the tertiary hydroxy group on the lactone closure carbon and this was confirmed chemically, when treatment of compound **3** with diazomethane gave a mixture of **6** and **7** separated by preparative TLC. Compound **7** may have been formed by a cycloaddition process [2+3]. All the data agreed with the structure proposed for compound **3**. A COSY experiment for compound **3** (Fig. 1) allocated all the protons and established from the multiplicity of the H-5 that the lactone closure is at C-8 and not C-6.

When compound **4** was treated with benzoyl chloride, a mixture of the benzoates **8** and **9**, epimeric at C-1, was obtained. This mixture was separated by preparative TLC and differentiated by $^1$H NMR spectroscopy (NOE experiments). Irradiation of H-1 in compound **8** showed a strong NOE effect on H-5 but this was negligible for compound **9**.

The relative configuration of compound **3** was established from NOE experiments. Irradiation of 14-Me showed a strong NOE effect on the OH-8 and H-$6_{ax}$ protons and a slight effect on H-$1_{eq}$ and H-3. Irradiation of H-$1_{ax}$ had a strong NOE effect on H-5 and H-$9_{ax}$.

The absolute configuration of compound **3** was determined by CD as follows. The positive Cotton effect of the $n$-$\pi^*$ transition of the enone moiety at 327 nm, suggesting the absolute configuration shown in compound **3** [3], was confirmed by application of the circular dichroism exciton chirality method to the derivatives **10** and **8** [4, 5]. Their CD spectrum showed a negative first and a positive second Cotton effect at 248/216 nm, and at 242/225 nm, respectively, due to the exciton coupling between the enone and the *p*-bromobenzoate moieties in compound **10** and between the multichromophore system benzoates/enone/unsaturated lactone present in compound **8**. The negative exciton chiralities observed are in agreement with the absolute configuration shown for these derivatives.

From the more polar fractions of the extract compound **4** was obtained as a natural product and its physical and spectral data proved totally superimposable upon those of the sodium bicarbonate hydrolysis product of compound **3**. To the best of our knowledge, this is the first time that sesquiterpene lactones have been isolated from the *Salvia* genus.

## EXPERIMENTAL

The plant material was collected in Cundinamarca (Bogotá plain). Colombia in December 1987. A voucher specimen (No. 293387) is on file in the Herbario Nacional Colombiano and was

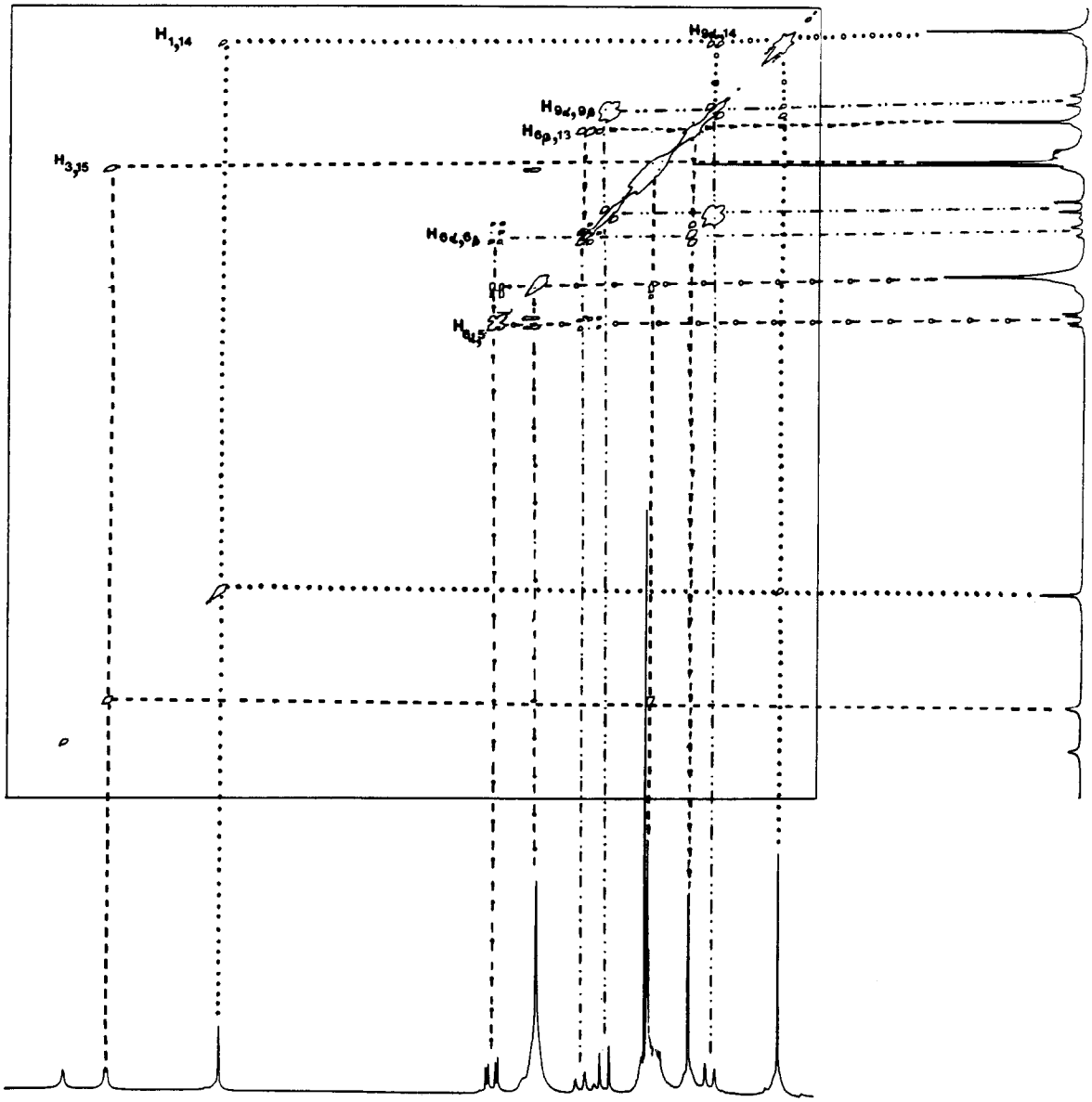


Fig. 1. COSY experiment in acetone-$d_6$ for compound **3**.

identified by Dr. Clara Iris Orozco of the Instituto de Ciencias Naturales of the Universidad Nacional de Colombia. Another voucher specimen has been lodged with the Dept of Botany of the Universidad de La Laguna where its identification has been duly confirmed.

*General.* Mps: uncorr. High and low resolution MS were taken at 15 or 70 eV. NMR spectra were run on 200 MHz spectrometers. Chemical shifts are given in $\delta$. Merck (0.2–0.5 mm) and type G silica gel were used for wet column chromatography and the same silica gel (0.2–0.063 mm) for dry column chromatography. TLC was carried out on type G silica gel plates.

*Plant extraction.* The leaves of *S. palaefolia* were shredded and extracted with cold $Me_2CO$ giving 105 g of extract which was dry-column chromatographed with *n*-hexane as eluant and differing mixtures of *n*-hexane–EtOAc, yielding: squalene (2.8 g); taraxerone (1.5 g); 3-oxo-olean-12-ene (1 g), $\beta$-amyrin (0.5 g); caryophyllene oxide (2.3 g); lupeol (1 g); taraxerol (0.8 g); (−)-glechomafuran (2.5 g); ursolic acid (4 g); oleanonic acid (1 g); oleanolic acid (0.5 g); 5-hydroxy-7,6,8,4′-tetramethoxyflavone (2 g); 1$\beta$,10$\alpha$,4$\alpha$,5$\beta$-diepoxy-8$\beta$-hydroxy-glechoman-8$\alpha$,12-olide (**1**) (0.15 g); 1$\alpha$-acetoxy-8$\alpha$-hydroxy-2-oxo-eudesman-3,7(11)-dien-8,12-olide (**3**) (0.2 g); and its deacetoxy derivative **4** (3 mg).

1$\beta$,10$\alpha$,4$\alpha$,5$\beta$-*Diepoxy-8*$\beta$-*hydroxyglechoman-8*$\alpha$,12-*olide* (**1**). $^{13}$C NMR [$(CD_3)_2CO$] $\delta$: 8.80 (*q*, C-13), 17.1 (*q*, C-14), 18.9 (*q*, C-15), 23.9 (*t*, C-3), 25.5 (*t*, C-2), 35.9 (*t*, C-6), 50.0 (*t*, C-9), 58.6 (*s*, C-10), 61.1 (*s*, C-4), 62.2 (*d*, C-1), 67.0 (*d*, C-5), 107.5 (*s*, C-8), 130.0 (*s*, C-11), 158.5 (*s*, C-7), 171.0 (*s*, C-12).

1$\beta$,10$\alpha$,4$\alpha$,5$\beta$-*Diepoxy-8*$\beta$-*acetoxyglechoman-8*$\alpha$,12-*olide* (**2**). Compound **1** (18 mg) was treated with $Ac_2O$–pyridine at room temp. for 10 min to yield **2**: IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3000, 1770, 1385, 1365, 1190, 1115, 1050, 985; UV $\lambda_{max}^{EtOH}$ nm: 225; $^1$H NMR: $\delta$3.27 (1H, *d*, $J$ = 15.0 Hz, H-9$\beta$), 2.88 (1H, *d*, $J$ = 7.5 Hz, H-6$\beta$), 2.69

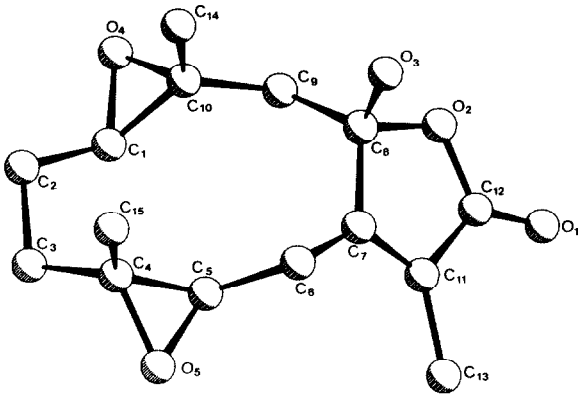


Fig. 2. PLUTO generated view of compound **1**.

(1H, *dd*, $J = 11.0$, 15.0 Hz, H-1), 2.67 (1H, *d*, $J = 7.5$ Hz, H-5), 2.23 (1H, *dd*, $J = 15.0$, 7.5 Hz, H-6α), 2.15 (1H, *br d*, H-2'), 2.25 (1H, *m*, H-3), 2.11 (3H, *s*, $-CO_2Me$), 1.96 (3H, *s*, Me-13), 1.46 (3H, *s*, Me-14), 1.45 (1H, *m*, H-2), 1.33 (3H, *s*, Me-15), 1.27 (1H, *m*, H-3'), 1.16 (1H, *d*, $J = 15.0$ Hz, H-9α); MS *m/z* (rel. int.): 322 $[M]^+$ (1), 280 (1), 262 (5), 220 (36). Calcd for $C_{17}H_{22}O_6$, 322.1584; found, 322.1500 (HRMS).

1α-*Acetoxy*-8α-*hydroxy*-2-*oxo*-*eudesman*-3,7(11)-*dien*-8,12-*olide* (**3**). Mp 115–120°; IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3330, 3005, 2920, 1745, 1680, 1620, 1430, 1375, 1320, 1230, 1175, 1085, 1045, 965, 840; UV $\lambda_{max}$ (EtOH) nm: 228; UV $\lambda_{max}^{MeCN}$ nm: 220; CD $\lambda_{ext}^{MeCN}$ nm: 327 (Δε 0.7), 257 (Δε 1.1), 234 (Δε −6.7), 212 (Δε 10.9); $^1$H NMR: see Table 1; $^{13}$C NMR [$(CD_3)_2CO$]: δ8.25 (*q*, C-13), 12.3 (*q*, C-14), 20.5 (*q*, OAc), 21.9 (*q*, C-15), 23.2 (*t*, C-6), 42.8 (*s*, C-10, 46.1 (*t*, C-9), 49.4 (*d*, C-5), 82.7 (*d*, C-1), 102.6 (*s*, C-8), 123.5 (*s*, C-11), 126.4 (*d*, C-3), 158.2 (*s*, C-4), 159.7 (*s*, C-7), 170.4 (*s*, C-12), 171.8 (*s*, OAc), 192.1 (*s*, C-2); MS *m/z* (rel. int.): 320 $[M]^+$ (7), 302 (6), 292 (1), 278 (52), 260 (55), 242 (46), 232 (24). Calcd for $C_{17}H_{20}O_6$, 320.1272; found, 320.1266 (HRMS).

1α,8α-*Diacetoxy*-2-*oxo*-*eudesman*-3,7(11)-*dien*-8,12-*olide* (**5**). Compound **3** (10 mg) was treated with $Ac_2O$–pyridine at room temp. for 10 min to give compound **5**: IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3010, 2911, 2825, 1775, 1729, 1685, 1365, 1319, 1220, 1150, 1085, 1040, 984, 965; $^1$H NMR: see Table 1; MS *m/z* (rel. int.): 362 $[M]^+$ (10), 320 (5), 303 (100), 278 (6), 261 (59), 242 (31), 214 (30).

1α,8α-*Dihydroxy*-2-*oxo*-*eudesman*-3,7(11)-*dien*-8,12-*olide* (**4**). Compound **3** (32 mg) was treated with 0.2 M $NaHCO_3$ with MeOH as solvent and refluxed at 60° for 24 hr to give compound **4** (26.4 mg). For $^1$H NMR, see Table 1.

*Methylation of compound* **3**. Compound **3** (20 g) was treated with $CH_2N_2$–$Et_2O$ to give a mixture of **6** and **7** which were separated by prep. TLC using 60% *n*-hexane–EtOAc.

*Product* **6** (4.7 *mg*). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3010, 3005, 2909, 2820, 1730, 1729, 1721, 1685, 1591, 1431, 1340, 1232, 1172, 1153, 1091, 1060; UV $\lambda_{max}^{EtOH}$ nm: 225; $^1$H NMR: δ6.11 (1H, *br s*, H-3), 5.33 (1H, *s*, H-1), 3.70 (3H, *s*, $CO_2Me$), 3.11 (1H, *dd*, $J = 15.0$, 12.0 Hz, H-6β), 2.44 (1H, *d*, $J = 10.0$ Hz, H-9β), 2.20 (3H, *s*, $CO_2Me$), 1.95 (3H, *s*, Me-15), 1.82 (1H, *dd*, $J = 15.0$, 4.0 Hz, H-6α), 1.41 (3H, *d*, Me-13), 1.10 (3H, *s*, Me-14), 0.92 (1H, *d*, $J = 10.0$ Hz, H-9α); MS *m/z* (rel. int.): 306 (3), 288 (28), 274 $[M-60]^+$ (80). Calcd for $C_{16}H_{18}O_4$, $[M-60]^+$, 274.1249; found, 274.1227 (HRMS).

*Product* **7** (10.6 *mg*): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3005, 2935, 2920, 2909, 1740, 1735, 1725, 1715, 1699, 1680, 1615, 1430, 1370, 1300, 1265, 1225, 1154, 1142, 1122, 1081; UV $\lambda_{max}^{EtOH}$ nm: 232, 283, 330; $^1$H NMR: δ6.11 (1H, *br s*, H-3), 5.50 (1H, *s*, H-1), 4.80 (2H, *s*, $-CH_2-N$), 4.11 (1H, *br t*, H-5), 3.70 (3H, *s*, $CO_2Me$), 2.72 (1H, *d*, $J = 14.0$ Hz, H-9α), 2.48 (1H, *d*, $J = 14.0$ Hz, H-9β), 2.48 (1H, *m*, H-6α), 2.48 (1H, *m*, H-6β), 2.21 (3H, *s*, $CO_2Me$), 2.08 (3H, *s*, Me-15), 1.10 (3H, *s*, Me-13), 1.04 (3H, *s*, Me-14); MS *m/z* (rel. int.): 376 $[M]^+$ (1), 348 $[M-N_2]^+$ (8), 306 (10), 289 (100), 274 (35), 261 (25), 229 (61). Calcd for $C_{19}H_{24}O_6N_2$, 376.1732; found, 376.1683 (HRMS).

When compound **4** was treated with BzCl–pyridine and refluxed for 72 hr at 60°, a mixture of **8** and **9** was obtained and subsequently separated by prep. TLC with 70% *n*-hexane–EtOAc as eluant.

1α,8α-*Dibenzoyloxy*-2-*oxo*-*eudesman*-3,7(11)-*dien*-8,12-*olide* (**8**). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 2950, 2919, 2842, 1770, 1730, 1724, 1685, 1280, 1260, 1112, 1065, 980; UV $\lambda_{max}^{EtOH}$ nm: 214, 240, 258; UV $\lambda_{max}^{MeCN}$ nm: 232; CD $\lambda_{ext}^{MeCN}$ nm: 330 (Δε 2.0), 280 (Δε 1.7), 242 (Δε −27.6), 225 (Δε 9.6); $^1$H NMR: see Table 1; MS *m/z* (rel. int.): 486 $[M]^+$ (1), 380 (1), 364 (16), 242 (7), 105 (100).

1β,8α-*Dibenzoyloxy*-2-*oxo*-*eudesman*-3,7(11)-*dien*-8,12-*olide* (**9**). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1950, 1920, 1843, 1775, 1730, 1725, 1685, 1265, 1105, 1065, 982; UV $\lambda_{max}^{EtOH}$ nm: 214, 242, 259; $^1$H NMR: see Table 1; MS *m/z* (rel. int.): 486 $[M]^+$ (1), 365 (5), 364 (6), 260 (1), 242 (14), 227 (8), 105 (100).

When Compound **4** was treated with *p*-bromobenzoyl chloride–pyridine and DMAP as catalyst at room temp for 6 hr, product **10** was obtained: UV $\lambda_{max}^{MeCN}$ nm: 224; CD $\lambda_{ext}^{MeCN}$ nm: 335 (Δε 0.7), 248 (Δε −18.0), 216 (Δε 7.9); $^1$H NMR data: see Table 1.

*Crystallographic data collection and absolute configuration determination of compound* **1**. $C_{15}H_{20}O_5$. $M_r$ 280.3, orthorhombic, space group $P2_12_12_1$, $a = 7.940(1)$, $b = 9.779(1)$, $c = 18.136(2)$Å; $V = 1408.2(2)$ Å$^3$, $z = 4$; $D_c = 1.32$ g $cm^{-3}$, $F(0, 0, 0) = 600$. Reflections were measured on a four-circle computer-controlled Siemens AED diffractometer, with $\omega:\theta$ scan mode and using graphite monochromated Cu$K_\alpha$ radiation ($\lambda = 1.5418$ Å). Cell constants were determined by a least-squares fit to $\pm 2\theta$ values of 30 strong reflections in the range $20° \leq 2\theta \leq 38°$. Of the 1219 independent reflections measured in the range $3 \leq 2\theta \leq 120°$, 1159 $I > 3\sigma$ ($I$) were considered as observed and corrected for Lorentz and polarization factors; no absorption correction was made ($\mu = 7.78$ $cm^{-1}$). The structure was solved by direct methods [6] and successive Fourier syntheses [7]. Most of the hydrogen atoms were located on a difference synthesis map and the remainder placed on calculated positions. Refinement with anisotropic thermal parameters for the non-hydrogen atoms and the hydrogen as isotropic fixed contribution converged to a standard crystallographic residual of $R = 0.075$.

The absolute configuration was established as 1(*R*),4(*R*), 5(*R*),8(*S*),10(*R*) with the CONFAB program [8], using 25 Bijvoet pairs measured at very slow scan speed, with $F_o > 10\sigma(F_o)$ and $|F_c(h) - F_c(\bar{h})| > 0.05$, which are in the ranges 5. $\leq F_o \leq 50$. and $0.15 \leq \sin\theta/\lambda \leq 0.40$ Å$^{-1}$. The averaged Bijvoet differences are 0.296 for the correct enantiomer (Fig. 2) vs 0.367 for the wrong one.

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