Pergamon

*Tetrahedron* Vol. 50, No. 9, pp. 2917-2928, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0222-2

# Partial Synthesis of 6β-Eudesmanolides and 6β-Guaianolides from 6α-Eudesmanolides: Synthesis of Analogues of Artepaulin[1], Colartin[2] and Tannunolide D[3]

**José L. Bretón**

Instituto de Productos Naturales Orgánicos.
Consejo Superior de Investigaciones Científicas.
La Laguna. TENERIFE. (Spain)

**Juan J. Cejudo, Andrés García-Granados*, Andrés Parra and Francisco Rivas**

Departamento de Química Orgánica.
Facultad de Ciencias. Universidad de Granada.
18071-GRANADA. (Spain)

*Key Words*: Sesquiterpenoids, sesquiterpenolides, 6β-eudesmanolides, 6β-guaianolides, epimerization

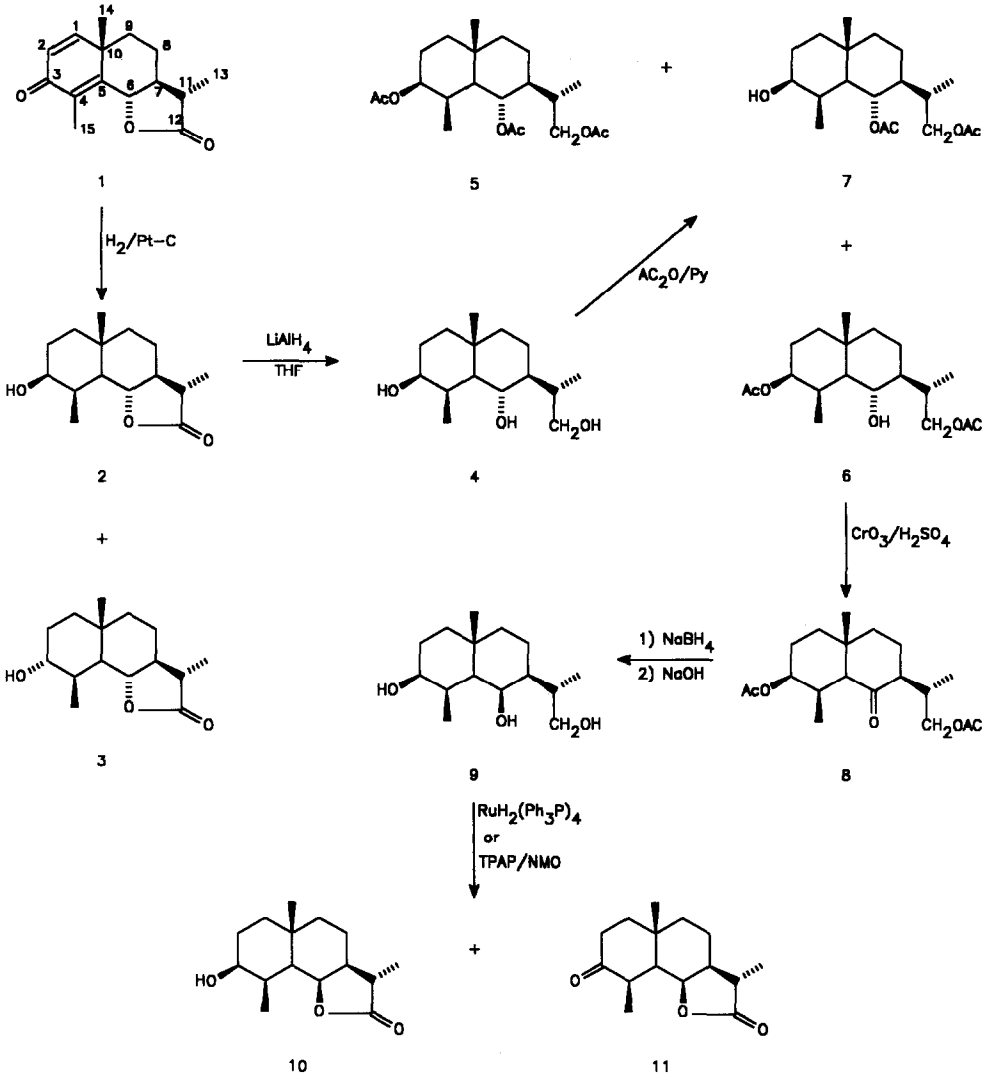
*Abstract:* Epimerization at C-6 of polyfunctionalized 6α-eudesmanolides was achieved by chemical means, to obtain 6β-eudesmanolides and, after rearrangement, 6β-guaianolides. The epimerization process consists of the $LiAlH_4$ reduction of a 6α-lactone, selective protection of the hydroxymethylene group at C-12, oxidation and reduction at C-6 to epimerize this carbon, deprotection at C-12 and finally, lactonization with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine N-oxide (NMO) in yields over 80%. The rearrangement of 1β-hydroxy-6β-colartin allow us to obtain 2,3-dihydro-6β-tannunolide D.

## INTRODUCTION

The 6β-sesquiterpene lactones, scarce in nature[4], are the object of interesting studies on the biogenesis of pseudoguaianolides and elemanolides. The chemistry[5], photochemistry[6], biomimetic synthesis[7] and biotransformation[8] of 6α-sesquiterpene lactones have been extensively studied. We have reported the synthesis of 6β-sesquiterpene lactones by chemical and microbiological means[9] and have obtained the lactone function with the aid of two microorganisms, which functionalized non-lactone sesquiterpene compounds[10] at C-11 or C-12.

α-santonin (1) is the classical starting material to obtain 6β-eudesmanolides, because it epimerizes in acidic medium[11]. The special functionalization and the *steric* energy of α-santonin (1) is about 2.1 Kcal/mol greater[12] than that of its epimer at C-6. However, a more general method of epimerizing this type of compounds at C-6, especially those with functionalization at C-1, would allow us to synthesize other 6β-sesquiterpenolide compounds with different skeletons. This type of process is also possible with α-santonin, but the transference of functionalization from C-3 to C-1 is not easy[9a].

## RESULTS AND DISCUSSION




Commercial α-santonin (**1**) was hydrogenated to give the hexahydro derivatives **2** (75%)[9a] and **3** (20%)[9a]. The opening of the lactone ring was achieved by $LiAlH_4$/THF reagent under reflux to give the trihydroxy derivative **4**, a product characterized later as the triacetyl derivative **5**. Acetylation of product **4** under mild conditions gave starting material (5%) and products **6** (75%), **7** (15%) and **5** (5%). The main product (**6**) from acetylation was 3β,12-diacetyl derivative, in which the hydroxyl group at C-6 remained unaltered. Product **7** was the result of acetylation of the hydroxyl groups at C-6 and C-12, and product **5** was the triacetyl derivative, which can be obtained by acetylation of **4** under reflux. The structures of products **5-7** can be easily deduced from their MS, PMR and CMR data (see Experimental and Tables I and II). Oxidation

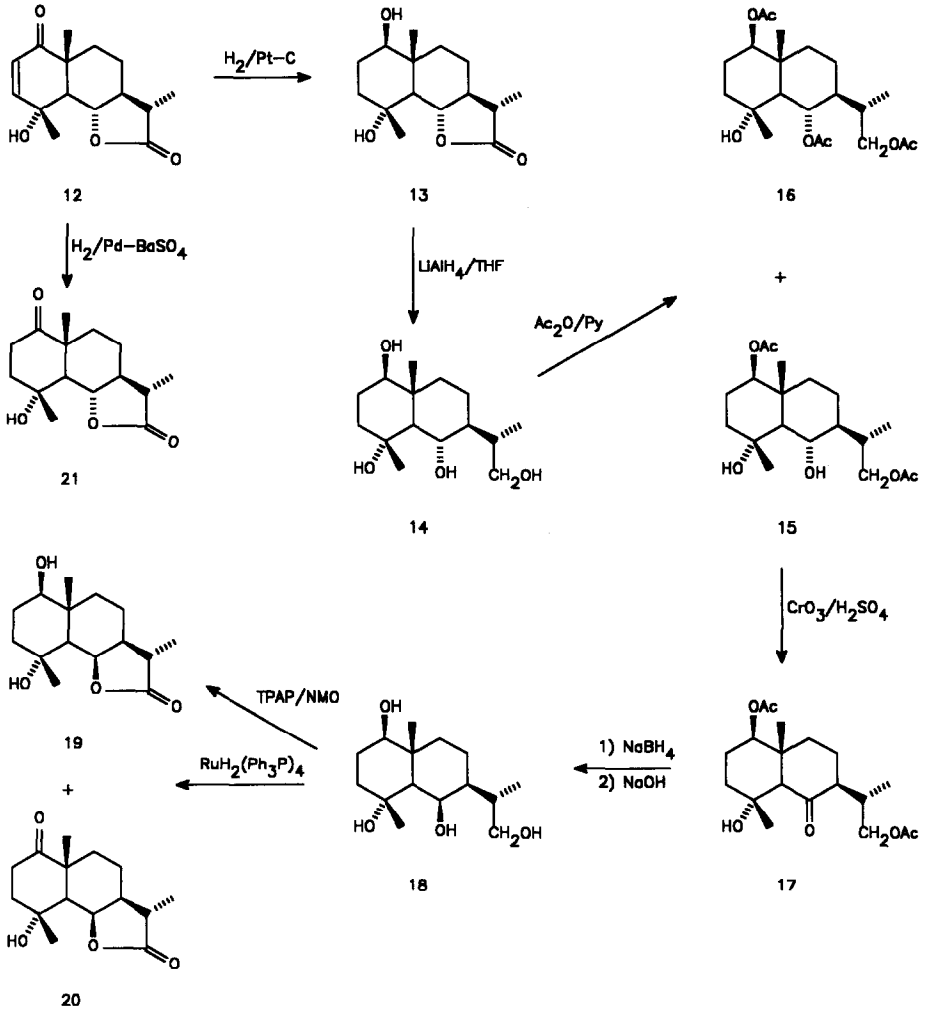
of diacetate **6** with Jones' reagent[13] gave the 6-keto compound **8**, which was treated with $NaBH_4$ to reduce, on the α-face, the keto group at C-6. This ketone (**8**) is the key product of this process, because in this type of 5α-H-sesquiterpenes with *trans*-junction between both rings, the α-face is the less hindered face. This reaction mixture was treated with diluted NaOH to give the trihydroxy compound **9** (90%), for which spectroscopic data indicated a 6β-disposition of the new hydroxyl group at this position (δ 4.04, 1H, bs, see Table I).

Product **9** was oxidized with $RuH_2(Ph_3P)_4$[14] to give products **10** (55%) and **11** (4β,6β-artepaulin, 10%). Both products have been previously described by us[9]. Product **10** was obtained by chemical-microbiological procedures in which *Rhizopus nigricans* epimerized at C-4[9b]. Product **11** was a subproduct of the reaction in which the hydroxyl group at C-3 was oxidized to a ketone group. We have also oxidized product **9** with tetrapropylammoniun perruthenate (TPAP) and 4-methylmorpholine N-oxide (NMO)[15]. These products **10** (80%), **11** (10%) and starting material (**9**, 10%) were isolated after 2 h of reaction. With TPAP, the yield of product **10** was considerably higher. The overall yield of product **10** from the original α-santonin (**1**) was now of 32%, very similar to that described[9b] when was obtained by chemical-microbiological procedures (34%) which included a first epimerization at C-6 of 6α-santonin to 6β-santonin[11]. However, we describe another epimerization process superior to other methods that start with the epimerization of 6α-santonin.

We have also used vulgarin (**12**), a very abundant 6α-sesquiterpene lactone in *Artemisia canariensis* Lees[16], as starting material. Moreover, this product (**12**) possesses functionality at C-1, which is useful for rearranging the eudesmane compounds to other sesquiterpene skeletons. Hydrogenation of vulgarin (**12**) gave the tetrahydro derivative 1β-hydroxycolartin **13** in high yield (95%). Treatment of the dihydroxy derivative **13** with $LiAlH_4$/THF also gave high yield (85%), of the tetrahydroxy derivative **14**. It was necessary to protect the hydroxymethylene group at C-12 to selectively oxidize the hydroxyl group at C-6. Thus, by acetylation of **14** under mild conditions (see Experimental) the diacetyl compound **15** (90%) and the triacetyl compound **16** (5%) were isolated. Not only the hydroxymethylene group at C-12 was acetylated, but acetylation at C-1 was also suitable for this process. The hydroxymethyne group at C-6 of compound **15** remained free and could be oxidized to give product **17** in quantitative yield. Reduction under mild conditions of the keto group at C-6, and saponification of product **17**, gave the tetrahydroxyl derivative **18** in high yield (90%). Its spectroscopic behavior indicated clearly that epimerization at C-6 has been achieved. This configuration at C-6 was the result of the different accessibility between the more hindered β-face and the α-face, of a smaller steric hindrance. Thus, product **15** showed the PMR H-6 signal at δ 3.90 as a double doublet with high coupling constants ($J_1$= $J_2$= 10 Hz). However, the corresponding signal in product **18** was a broad singlet at δ 4.51. CMR data for both compounds **15** and **18** also confirmed the epimer character at C-6 (see Table IV).

The last step in obtaining 6β,12-eudesmanolides was the selective oxidation of the hydroxymethylene group at C-12 to a carboxyl group, and cyclization to form a 6β,12-eudesmanolide. Oxidation was also done with two different ruthenium reagents. Dihydrotetrakis-(triphenylphosphine)-ruthenium (II) ($RuH_2(Ph_3P)_4$[14] gave two lactone compounds, **19** (1β-hydroxy-6β-colartin, 58%) and **20** (1-oxo-6β-colartin, 8%). The main lactone product (**19**) showed a narrow signal at δ 5.11 (1H, dd, $J_1$= 4.2, $J_2$= 2.7Hz) in its PMR spectrum, which was assigned to the 6α-H proton. This product (**19**) maintained the hydroxyl group unaltered at C-1, as can be seen from its spectroscopic data (see Tables III and IV). The minor product **20** showed a 6α-H signal similar to that of product **19**, but different from the corresponding geminal proton to the hydroxyl group at C-1. Its CMR spectrum clearly indicated that this hydroxyl group was also oxidized to a ketone group. Its

epimer at C-6 (**21**) was obtained by mild hydrogenation of vulgarin (**12**) to confirm its structure. No starting material (**18**) was isolated from this oxidation process, which needed energetic conditions (see Experimental). This oxidation reaction was the limiting step in the process, through which 1β-hydroxy-6β-colartin (**19**) was obtained at an overall yield of 38%. Another ruthenium reactive has been used to improve the yield of this oxidation step. Thus, tetrapropylammonium perruthenate (TPAP) in presence of 4-methylmorpholine N-oxide (NMO) produced the oxidation of tetrol **18** to the 6β-lactone **19** at a higher yield (85%). Moreover, some quantity of tetrol **18** (10%), which can be reoxidized, was recovered unaltered in this procedure. With this reagent 1β-hydroxy-6β-colartin (**19**) was obtained at an overall yield of 52%. This type of 6β-lactone was also obtained at lower yields from the commercial α-santonin (**1**) in a process initiated by epimerization of product **1**, at C-6, with nine chemical steps (overall yield of 18%)[9a] or eight chemical-microbiological steps (overall yield of 10%)[9a].



This type of compound (**19**) was a suitable starting material to obtain 6β-guaianolide compounds. Thus, mesylation of compound **19** (see Experimental) gave the mesyl derivative **22** (90%), which was solvolized in KOAc/HOAc under reflux for 72 h, after which starting material (**22**, 10%) and products **23** (20%), **24** (10%) and **25** (40%) were isolated. MS spectrometry of products **23-25** indicated the elimination of MsOH in the process. Moreover, PMR spectra of product **23** and **24** indicated that both products possessed two vinyl protons (see Table III). This group was confirmed in the corresponding CMR spectra (see Table IV). The spectroscopic behavior of product **23** indicated that this compound was the result of the normal elimination process of the mesyloxy group at C-1. Product **24** showed similar PMR signals to H-1, H-2 and H-6. However, the H-11 signal appeared to be more deshielded as a double quartet ($J_1$= $J_2$= 7.2 Hz), instead of as a quartet (J= 7.7 Hz, no observable coupling between H-6 and H-7, dihedral angle near 90°). These data are in accordance with those described for 6β-eudesmanolide epimers at C-11[10]. Thus, products **23** and **24**, epimers at C-11, are the result of elimination of the mesyloxy group at C-1. Product **25** did not give a vinyl proton signal in its PMR spectrum. However, two signals of quaternary ethylene carbons (δ 128.9 and 131.2, see Table IV) were observed in its CMR spectrum. The H-6 signal appeared at δ 4.86 (1H, dd, $J_1$= 7.5, $J_2$= 1.5 Hz), and was more shielded that the corresponding signals of the 6β-eudesmanolides described above (see Table III). Moreover, a signal of an allylic methyl group was present (δ 1.55, 3H, bs). These data indicated that the expected rearrangement to a 6β-guaianolide compound had been achieved. Thus, product **25** was 4α-hydroxy-5α,11β-H-guai-1(10)-en-6β,12-olide (2,3-dihidro-6-*epi*-tannunolide D). The overall procedure also allowed us to obtain not only 6β,12-eudesmanolide compounds, but also 6β,12-guaianolide compounds.

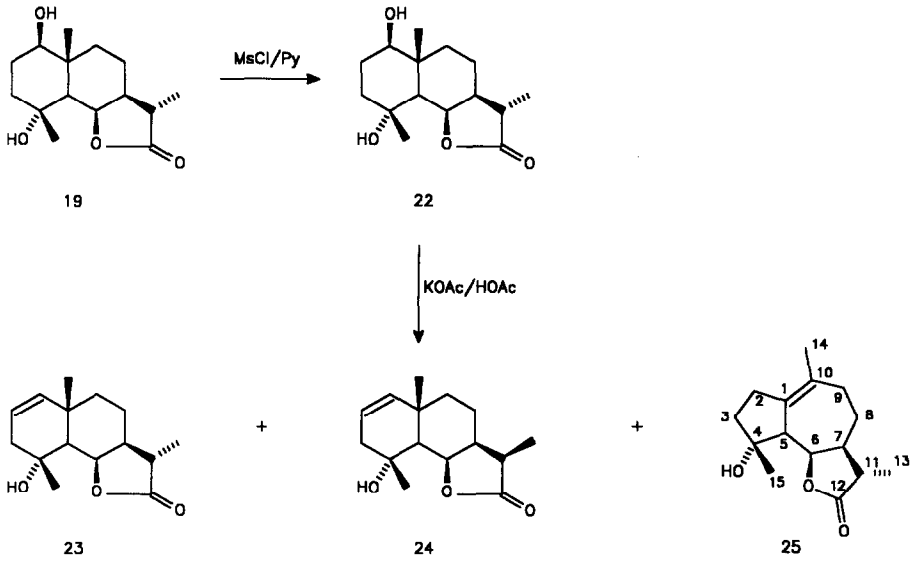


**TABLE I**

| Hydr. | 2 | 3 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H-1α | | | | | | | | | | | **3.35dd** J1=11.1Hz J2=6.9Hz |
| H-2α | | | | | | | | | **2.26ddd** J1=J2=3.2Hz J3=14.8Hz | **6.58d** J=15.0Hz | |
| H-2β | | | | | | | | | **2.80ddd** J1=6.2Hz J2=J3=14.7Hz | | |
| H-3α | **3.72ddd** J1=J2=6.5Hz J3=11.0Hz | | **4.75ddd** J1=J2=4.7Hz J3=12.5Hz | **4.76ddd** J1=J2=4.7Hz J3=12.7Hz | **3.65ddd** J1=J2=6.1Hz J3=11.2Hz | **4.67ddd** J1=J2=4.5Hz J3=11.9Hz | **3.67ddd** J1=J2=6.7Hz J3=10.9Hz | **3.71ddd** J1=4.7Hz J2=9.8Hz J3=11.6Hz | | **5.86d** J=15.0Hz | |
| H-3β | | **3.85ddd** J1=J2= J3=2.8Hz | | | | | | | | | |
| H-4α | **2.40dd** J1=J2=5.2Hz | **2.10m** | | **2.56m** | **2.09m** | | | **2.20m** | **2.61dq** J1=7.7Hz J2=6.3Hz | | |
| H-5α | | **2.03dd** J1=6.0Hz J2=11.6Hz | | | | | | | | **2.40d** J=6.4Hz | |
| H-6α | | | | | | | **4.04ss** | **4.53dd** J1=2.7Hz J2=4 2Hz | **4.51dd** J1=2.8Hz J2=4.0Hz | | |
| H-6β | **3.95dd** J1=11.7Hz J2=9.9Hz | **3.93dd** J1= 1.6Hz J2=10.0Hz | **5.08dd** J1=J2=0.7Hz | **3.55dd** J1=10.6Hz J2=9.3Hz | **5.09dd** J1=J2=10.8Hz | | | | | **4.14dd** J1=6.4Hz J2=7.8Hz | **4.10dd** J1=J2=9.5 Hz |
| H-11β | **2.33dq** J1=12.3Hz J2=6.9Hz | **2.32dq** J1=6.9Hz J2=12.4Hz | | **2.43m** | | | | **2.30q** J=7.7Hz | **2.34q** J=7.7Hz | **2.32dq** J1=11.9Hz J2=6.9Hz | **2.26dq** J1=11.7Hz J2=6.9Hz |
| H-12 | | | **3.89dd** J1=10.8Hz J2=12.4Hz | **3.96** | **3.90** | **3.9ldd** J1=10.9Hz J2=14.0Hz | **3.60dd** J1=10.6Hz J2=17.5Hz | | | | |
| H-12′ | | | **3.92dd** J1=10.9Hz J2=12.4Hz | **3.96** | **3.90** | **3.93dd** J1=11.1Hz J2=14.0Hz | **3.65dd** J1=16.3Hz J2=17.5Hz | | | | |
| Me | **1.00s** | **1.02s** | **0.95s** | **0.90s** | **0.91s** | **0.91s** | **1.21s** | **1.07s** | **1.29s** | **1.18s** | **0.93s** |
| Me | **0.96d** J=7.4Hz | **0.99d** J=7.6Hz | **0.90d** J=7.0Hz | **0.92d** J=7.4Hz | **0.90d** J=7.4Hz | **1.08d** J=7.1Hz | **0.96d** J=7.1Hz | **1.19d** J=7.4Hz | **1.28d** J=7.7Hz | **1.53s** | **1.29s** |
| Me | **1.19d** J=6.9Hz | **1.20d** J=6.9Hz | **0.86d** J=7.4Hz | **0.89d** J=7.0Hz | **0.86d** J=7.4Hz | **0.86d** J=7.0Hz | **1.25d** J=7.4Hz | **1.27d** J=7.6Hz | **1.41d** J=7.7Hz | **1.22d** J=6.9Hz | **1.17d** J=6.9Hz |
| MeCOO | | | **2.03s** | **2.02s** | **2.03s** | | | | | | |
| MeCOO | | | **2.04s** | **2.04s** | **2.04s** | | | | | | |
| MeCOO | | | **2.05s** | | | | | | | | |

**TABLE II**

| C | 2 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 40.2 | 39.8 | 33.9 | 40.1 | 39.1 | 41.3 | 40.7 | 41.1 | 201.7 | 80.8 |
| 2 | 25.9 | 21.4 | 22.6 | 26.0 | 22.1 | 26.7 | 26.2 | 34.7 | 151.8 | 28.2 |
| 3 | 73.0 | 70.7 | 68.1 | 71.0 | 75.7 | 74.8 | 74.2 | 213.4 | 125.6 | 38.2 |
| 4 | 34.4 | 31.4 | 31.4 | 34.1 | 31.0 | 41.3 | 40.2 | 49.9 | 70.1 | 71.3 |
| 5 | 49.7 | 44.4 | 47.1 | 44.5 | 50.2 | 49.5 | 43.4 | 42.9 | 54.6 | 56.0 |
| 6 | 80.1 | 76.2 | 76.6 | 74.1 | 209.7 | 73.9 | 82.7 | 81.2 | 79.6 | 78.2 |
| 7 | 53.6 | 50.3 | 52.4 | 50.6 | 58.1 | 49.7 | 47.7 | 47.7 | 52.4 | 53.2 |
| 8 | 23.5 | 20.7 | 20.8 | 19.3 | 22.1 | 22.4 | 24.1 | 24.0 | 22.7 | 23.3 |
| 9 | 43.3 | 42.8 | 43.1 | 42.9 | 42.4 | 44.9 | 42.0 | 41.6 | 34.3 | 39.3 |
| 10 | 35.9 | 34.6 | 34.4 | 34.6 | 38.3 | 33.9 | 32.4 | 32.5 | 46.3 | 41.8 |
| 11 | 41.9 | 31.4 | 31.0 | 31.5 | 30.3 | 37.7 | 43.4 | 43.4 | 40.6 | 40.5 |
| 12 | 178.7 | 67.8 | 68.2 | 67.9 | 66.9 | 66.3 | 180.4 | 180.7 | 178.3 | 178.4 |
| 13 | 12.6 | 11.2 | 11.4 | 11.2 | 12.7 | 16.0 | 13.9 | 13.9 | 12.5 | 12.5 |
| 14 | 21.1 | 20.7 | 20.8 | 20.7 | 21.5 | 22.4 | 21.2 | 20.3 | 19.8 | 13.7 |
| 15 | 8.8 | 9.2 | 8.9 | 8.4 | 10.1 | 10.0 | 9.5 | 15.8 | 23.8 | 24.3 |
| $CH_3$ | | 21.4 | 21.4 | 21.0 | 21.2 | | | | | |
| $CH_3$ | | 21.1 | 21.1 | 21.0 | 20.9 | | | | | |
| $CH_3$ | | --- | | | | | | | | |
| CO | | 170.8 | 171.3 | 171.2 | 171.1 | | | | | |
| CO | | 170.6 | 170.6 | 170.7 | 170.4 | | | | | |
| CO | | 170.6 | | | | | | | | |

## TABLE III

| Hydr. | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H-1α | 3.45dd | 4.54dd J1=3.9Hz J2=11.0Hz | 4.56dd J1=3.9Hz J2=11.1Hz | 4.72dd J1=6.0Hz J2=11.3Hz | 3.20dd J1=4.0Hz J2=10.7Hz | 3.25dd J1=4.2Hz J2=10.6Hz | | | 4.32dd J1=4.8Hz J2=11.4Hz | 5.39m | 5.39m | |
| H-2α | | | | | | | 2.41ddd J1=4.7Hz J2=6.0Hz J3=15.3Hz | 2.41ddd J1=4.8Hz J2=6.6Hz J3=16.2Hz | | 5.39m | 5.39m | |
| H-2β | | | | | | | 2.69ddd J1=6.2Hz J2=12.0Hz J3=15.3Hz | 2.54ddd J1=6.7Hz J2=10.4Hz J3=16.2Hz | | | | |
| H-5α | | | | 2.39m | | | | 2.17d J=10.4Hz | | | | |
| H-6α | | | | | 4.51m | 5.11dd J1=2.7Hz J2=4.2Hz | 5.10dd J1=2.5Hz J2=4.2Hz | | 5.11dd J1=2.7Hz J2=4.2Hz | 5.23dd J1=2.2Hz J2=4.7Hz | 4.99dd J1=2.2Hz J2=4.0Hz | 4.86dd J1=1.5Hz J2=7.5Hz |
| H-6β | 3.90dd J1=J2=10.0 Hz | 3.88dd J1=J2=10.2 Hz | 5.32dd J1=J2=10.6 Hz | | | | | 4.05dd J1=10.4Hz J2=11.4Hz | | | | |
| H-7α | | | | | | | | | | 2.0ddd J1=4.7Hz J2=6.8Hz J1=11.6Hz | | |
| H-11β | | | | | | 2.31q J=7.7Hz | 2.33q J=7.3Hz | 2.29dq J1=12.4Hz J2=6.9Hz | 2.33q J=7.7Hz | 2.33q J=7.7Hz | 2.76dq J1=J2= 7.2Hz | 2.44dq J1=7.4Hz J2=4.8Hz |
| H-12 | 3.65 | 3.92dd J1=7.1Hz J2=11.0Hz | 3.85dd J1=6.9Hz J2=10.9Hz | 3.91dd J1=6.3Hz J2=11.0Hz | 3.57dd J1=3.2Hz J2=10.8Hz | | | | | | | |
| H-12′ | | 3.97dd J1=7.6Hz J2=11.0Hz | 3.91dd J1=6.0Hz J2=10.9Hz | 3.94dd J1=6.1Hz J2=11.0Hz | 3.63dd J1=6.7Hz J2=10.8Hz | | | | | | | |
| Me | 1.30s | 0.92s | 0.98s | 0.92s | 1.17s | 1.04s | 1.25s | 1.15s | 1.10s | 1.15s | 1.14s | 1.35s |
| Me | 0.80s | 1.36s | 1.22s | 1.50s | 1.50s | 1.47s | 1.66s | 1.48s | 1.50s | 1.50s | 1.50s | 1.55sa |
| Me | 0.90d | 0.89d J=7.0Hz | 0.87d J=6.9Hz | 0.87d J=7.0Hz | 0.92d J=7.1Hz | 1.28d J=7.7Hz | 1.28d J=7.6Hz | 1.21d J=6.9Hz | 1.29d J=7.7Hz | 1.29d J=7.7Hz | 1.18d J=7.2Hz | 1.29d J=7.4Hz |
| MeCOO | | 2.04s | 2.02s | 2.04s | | | | | | | | |
| MeCOO | | 2.01s | 2.04s | 2.05s | | | | | | | | |
| MeCOO | | | 2.09s | | | | | | | | | |
| $MeSO_2$ | | | | | | | | | 3.01s | | | |

## TABLE IV

| C | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 80.2 | 80.1 | 39.2 | 80.6 | 79.5 | 213.7 | 213.9 | 77.3 | 138.2 | 138.1 | 131.2 |
| 2 | 24.8 | 23.8 | 24.1 | 28.7 | 28.7 | 33.8 | 34.9 | 26.5 | 121.3 | 121.8 | 29.2 |
| 3 | 40.4 | 40.5 | 38.7 | 41.5 | 38.8 | 35.2 | 34.9 | 38.7 | 44.9 | 44.7 | 39.7 |
| 4 | 73.6 | 71.9 | 70.4 | 72.8 | 71.8 | 71.2 | 70.2 | 71.2 | 70.8 | 70.8 | 81.2 |
| 5 | 56.3 | 56.3 | 64.9 | 55.5 | 53.0 | 52.9 | 54.6 | 53.1 | 52.8 | 52.7 | 53.5 |
| 6 | 69.7 | 72.1 | 211.8 | 66.1 | 76.0 | 76.7 | 79.8 | 75.6 | 75.6 | 76.0 | 77.3 |
| 7 | 46.8 | 44.5 | 50.8 | 49.0 | 43.8 | 43.8 | 52.6 | 43.7 | 44.1 | 41.1 | 44.0 |
| 8 | 19.0 | 18.8 | 21.5 | 21.5 | 23.4 | 23.3 | 22.5 | 23.0 | 24.2 | 19.1 | 26.1 |
| 9 | 39.0 | 38.5 | 28.2 | 42.1 | 42.0 | 41.2 | 35.9 | 41.5 | 40.2 | 40.0 | 32.1 |
| 10 | 39.5 | 40.1 | 42.6 | 39.3 | 38.2 | 45.7 | 47.5 | 37.9 | 36.0 | 36.1 | 128.9 |
| 11 | 30.5 | 29.8 | 30.2 | 37.5 | 42.9 | 41.2 | 35.9 | 42.7 | 42.9 | 40.6 | 39.2 |
| 12 | 68.0 | 67.4 | 66.7 | 66.5 | 180.5 | 180.2 | 178.3 | 180.1 | 180.8 | 179.9 | 180.9 |
| 13 | 11.2 | 11.1 | 12.8 | 14.7 | 14.3 | 14.0 | 12.4 | 14.0 | 14.6 | 9.2 | 16.3 |
| 14 | 15.0 | 14.7 | 16.3 | 16.1 | 14.1 | 19.8 | 18.6 | 15.0 | 21.5 | 21.1 | 21.0 |
| 15 | 23.6 | 23.8 | 24.1 | 25.2 | 25.4 | 26.7 | 26.3 | 25.3 | 26.7 | 26.8 | 24.2 |
| $CH_3$ | 21.2 | 21.7 | 21.2 | | | | | 39.0 | | | |
| $CH_3$ | 21.1 | 21.3 | 21.0 | | | | | | | | |
| $CH_3$ | | 21.1 | | | | | | | | | |
| CO | 171.4 | 171.2 | 171.2 | | | | | | | | |
| CO | 170.8 | 170.7 | 170.9 | | | | | | | | |
| CO | | 170.3 | | | | | | | | | |

## EXPERIMENTAL

Measurements of NMR spectra (300 MHz $^1H$ and 75.47 MHz $^{13}C$) were done in $CDCl_3$ (which also provided the lock signal) in a Bruker AM-300 spectrometer equipped with a process controller and an array processor. The assignments of $^{13}C$ chemical shifts were done with the aid of distortionless enhancement by polarization transfer (DEPT) using a flip angle of 135°. IR spectra were recorded on a Perkin-Elmer mod. 983 G spectrometer or on a Nicolet 20SX FT-IR spectrometer. Mass spectra were determined with CI (methane) or EI (70 eV) in a Hewlett-Packard mod. 5988 A spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 20°. Silica gel SDS 60 A CC (40-60 μm) was used for flash chromatography. $CH_2Cl_2$ or $CHCl_3$ containing increasing amounts of $Me_2CO$ were used as the eluent. Analytical plates (silica gel, Merck 60 G) were rendered visible by spraying with $H_2SO_4$/AcOH, followed by heating to 120°. The identity of compounds **10**, **11** and **13** were confirmed by direct comparison with authentic samples (IR, MS, NMR, etc.).

*Catalytic hydrogenation of α-santonin* (**1**)

A solution of product **1** (1 g) in $CH_2Cl_2$ (50 mL) was hydrogenated for 5 h with $H_2$ (4 atm) on $PtO_2$. The reaction mixture was filtered and the solvent was removed by distillation at reduced pressure, which yielded, after column chromatography, 750 mg of 3β-hydroxy-4α,5α,11β-H-eudesman-6α,12-olide (**2**, 75%); m.p.: 125 °C; $[\alpha]_D$= -62° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3460, 1767, 1237 $cm^{-1}$; $^1H$ nmr see Table I; $^{13}C$ nmr see Table II; ms, m/z (%): $[M+1]^+$ 253 (50), 235 (100); and 300 mg of 3α-hydroxy-4α,5α,11β-H-eudesman-6α,12-olide (**3**, 20%); m.p.: 116-8 °C; $[\alpha]_D$= -54° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3460, 1767 $cm^{-1}$; $^1H$ nmr see Table I; ms, m/z (%): $[M+1]^+$ 253 (49), 235 (100).

*Reduction of 3β-hydroxy-4α,5α,11β-H-eudesman-6α,12-olide* (**2**)

720 mg of product **2** were dissolved in 150 mL of dry THF and 270 mg of $LiAlH_4$ were added. The reaction mixtured was refluxed for 2 h, and diluted with aqueous ether, extracted with $CH_2Cl_2$, dried with anhydrous $Na_2SO_4$ and evaporated to dryness. Chromatography over silica gel yielded 610 mg of product **4**, a product characterized later as the triacetyl derivative **5**.

*Acetylation of product* **4**

Product **4** (580 mg) was dissolved in $Ac_2O$/Py (1:2) (30 mL) with stirring for 12 h at room temperature. The reaction mixture was diluted with water, extracted with $CH_2Cl_2$, washed with saturated aqueous $KHSO_4$ and dried with anhydrous $Na_2SO_4$. Chromatography over silica gel yielded 405 mg of 3β,12-diacetoxy-6α-hydroxy-4α,5α,11β-H-eudesmane (**6**, 75%); m.p.: 102 °C; $[\alpha]_D$= -20° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3460, 1733, 1245 $cm^{-1}$; $^1H$ nmr see Table I; $^{13}C$ nmr see Table II; ms, m/z (%): $[M+1]^+$ 341 (21), 323 (32), 263 (29), 221 (100); 85 mg of 6α,12-diacetoxy-3β-hydroxy-4α,5α,11β-H-eudesmane (**7**, 15%); Syrup; $[\alpha]_D$= -13° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3448, 1734, 1240 $cm^{-1}$; $^1H$ nmr see Table I; $^{13}C$ nmr see Table II; ms, m/z (%): $[M+1]^+$ 341 (1), 323 (12), 281 (61), 203 (100); and 30 mg of 3β,6α,12-triacetoxy-4α,5α,11β-H-eudesmane (**5**, 5%); m.p.: 115 °C; $[\alpha]_D$= -24° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 1732, 1246 $cm^{-1}$; $^1H$ nmr see Table I; $^{13}C$ nmr see Table II; ms, m/z (%): $[M+1]^+$ 383 (0.5), 323 (22), 281 (51), 263 (55), 221 (67), 203 (100).

***Oxidation of 3β,12-diacetoxy-6α-hydroxy-4α,5α,11β-H-eudesmane* (6)**

Jones' reagent was added dropwise to a stirred solution of product **6** (370 mg) in acetone at 0 °C until an orange-brown color persisted. Methanol was then added and the reaction mixture was diluted with water and extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and evaporated to dryness. Chromatography on a silica gel column yielded 350 mg of 3β,12-diacetoxy-4α,5α,11β-H-eudesman-6-one (**8**); Syrup; $[\alpha]_D$= +14° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 1734, 1243, 1700 $cm^{-1}$; $^1H$ nmr see Table I; $^{13}C$ nmr see Table II; ms, m/z (%): $[M+1]^+$ 339 (3), 279 (100), 219 (23).

***Reduction and saponification of 3β,12-diacetoxy-4α,5α,11β-H-eudesman-6-one* (8)**

320 mg of product **8** was dissolved in absolute EtOH (40 mL) and 45 mg of $NaBH_4$ was added slowly. The reaction was stirring for 2 h at room temperature. Then a solution of diluted NaOH was added dropwise until the reaction has finished (TLC). The reaction mixture was extracted with $CH_2Cl_2$, dried over $Na_2SO_4$ and evaporated in a vacuum, yielding 285 mg of 3β,6β,12-trihydroxy-4α,5α,11β-H-eudesmane (**9**, 90%); m.p.: 140 °C; $^1H$ nmr see Table I; $^{13}C$ nmr see Table II; ms, m/z (%): $[M+1]^+$ 257 (24), 239 (20), 221 (100), 203 (15).

***Lactonization of 3β,6β,12-trihydroxy-4α,5α,11β-H-eudesmane* (9) *with* $RuH_2(Ph_3P)_4$**

260 mg of product **9** was dissolved in 9 mL of dry toluene and 0.5 mL of acetone was added. $RuH_2(Ph_3P)_4$ (21 mg) was added to the solution, and the mixture was kept in a closed tube at 180 °C under an argon atmosphere for 6 h. The reaction mixture was cooled before the tube was opened, and was then concentrated in a vacuum. Chromatography on a silica gel column yielded 165 mg of 3β-hydroxy-4α,5α,11β-H-eudesma-6β,12-olide (**10**, 55%)[9b]; and 25 mg of 3-oxo-4α,5α,11β-H-eudesman-6β,12-olide (**11**, 10%)[9a].

***Lactonization of 3β,6β,12-trihydroxy-4α,5α,11β-H-eudesmane* (9) *with tetrapropylammoniun perrutenate***

Solid TPAP (18 mg) was added in a single portion to a stirred mixture of product **9** (140 mg), NMO (4-methylmorpholine N-oxide, 140 mg) and activated powdered molecular sieves (140 mg) in dry $CH_2Cl_2$ (30 mL) at room temperature under argon. On completion, the reaction mixture was concentrated in a vacuum. Purification by column chromatography on silica gel yielded 108 mg of product **10** (80%) and 13 mg of product **11** (10%).

***Catalytic hydrogenation of 4α-hydroxy-1-oxo-5α,11β-H-eudesm-2-en-6α,12-olide (vulgarin)* (12) *with Pt-charcoal***

A solution of product **1** (1 g) in EtOH (50 mL) was hydrogenated for 7 h with $H_2$ (4 atm) on Pt-charcoal. The reaction mixture was filtered and the solvent was removed by distillation at reduced pressure, which yielded, after column chromatography, 950 mg of 1β,4α-dihydroxy-5α,11β-H-eudesman-6α,12-olide (**13**)[17].

***Reduction of 1β,4α-dihydroxy-5α,11β-H-eudesman-6β,12-olide* (13)**

900 mg of product **13** was dissolved in 200 mL of dry THF and 320 mg of $LiAlH_4$ was added. The reaction mixtured was refluxed for 2 h, and then diluted with aqueous ether, extracted with $CH_2Cl_2$, dried with anhydrous $Na_2SO_4$ and evaporated to dryness. Chromatography over silica gel yielded 790 mg of

1β,4α,6α,12-tetrahydroxy-5α,11β-H-eudesmane (**14**, 85%); m.p.: 117-9 °C; $^1$H nmr see Table III; ms, m/z (%): $[M+1]^+$ 273 (3), 255 (60), 237 (100).

*Acetylation of 1β,4α,6α,12-tetrahydroxy-5α,11β-H-eudesmane* (**14**)

Product **14** (750 mg) was dissolved in $Ac_2O$/Py (1:2) (45 mL) with stirring for 12 h at room temperature. The reaction mixture was diluted with water, extracted with $CH_2Cl_2$, washed with saturated aqueous $KHSO_4$ and dried with anhydrous $Na_2SO_4$. Chromatography over silica gel yielded 660 mg of 1β,12-diacetoxy-4α,6α-dihydroxy-5α,11β-H-eudesmane (**15**, 90%); m.p.: 109-1 °C; $[\alpha]_D$= -15° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3372, 1736, 1245 cm$^{-1}$; $^1$H nmr see Table III; $^{13}$C nmr see Table IV; ms, m/z (%): $[M+1]^+$ 357 (3), 321 (25) and 30 mg of 1β,6α,12-triacetoxy-4α-hydroxy-5α,11β-H-eudesmane (**16**, 5%); m.p.: 47-9 °C; $[\alpha]_D$= -13° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3514, 1734, 1240 cm$^{-1}$; $^1$H nmr see Table III; $^{13}$C nmr see Table IV; ms, m/z (%): $M^+$ 398 (0.16), 381 (70), 321 (16), 279 (36), 261 (100), 201 (35).

*Oxidation of 1β,12-diacetoxy-4α,6α-dihydroxy-5α,11β-H-eudesmane* (**15**)

Jones' reagent was added dropwise to a stirred solution of product **15** (630 mg) in acetone at 0 °C until an orange-brown color persisted. Methanol was then added and the reaction mixture was diluted with water and extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and evaporated to dryness. Chromatography on a silica gel column yielded 600 mg of 1β,12-diacetoxy-4α-hydroxy-5α,11β-H-eudesman-6-one (**17**); Syrup; IR $\nu_{max}$ ($CHCl_3$): 3200, 1736, 1374 cm$^{-1}$; $^1$H nmr see Table III; $^{13}$C nmr see Table IV; ms, m/z (%): $[M+1]^+$ 355 (0.33), 295 (20), 277 (100).

*Reduction and saponification of 1β,12-diacetoxy-4α-hydroxy-5α,11β-H-eudesman-6-one* (**17**)

570 mg of product **17** was dissolved in absolute EtOH (60 mL) and 80 mg of $NaBH_4$ was added slowly. The reaction was stirring for 2 h at room temperature. Then a solution of diluted NaOH was added dropwise until the reaction has finished (TLC). The reaction mixture was extracted with $CH_2Cl_2$, dried over $Na_2SO_4$ and evaporated in a vacuum, yielding 550 mg of 1β,4α,6β,12-tetrahydroxy-5α,11β-H-eudesmane (**18**, 90%); m.p.: 106-8 °C; $^1$H nmr see Table III; $^{13}$C nmr see Table IV; ms, m/z (%): $[M+1]^+$ 273 (3), 255 (99), 219 (100).

*Lactonization of 1β,4α,6β,12-tetrahydroxy-5α,11β-H-eudesmane* (**18**) *with* $RuH_2(Ph_3P)_4$

520 mg of product **18** was dissolved in 14 mL of dry toluene and 0.5 mL of acetone was added. $RuH_2(Ph_3P)_4$.(42 mg) was added to the solution and the mixture was kept in a closed tube at 180 °C under an argon atmosphere for 6 h. The reaction mixture was cooled before the tube was opened, and was then concentrated in a vacuum. Chromatography on a silica gel column yielded 300 mg of 1β,4α-dihydroxy-5α,11β-H-eudesman-6β,12-olide (tetrahydro-6β-vulgarin) (**19**, 58%); m.p.: 102-4 °C; $[\alpha]_D$= -54° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3428, 1759, 1232 cm$^{-1}$; $^1$H nmr see Table III; $^{13}$C nmr see Table IV; ms, m/z (%): $M^+$ 268 (0.15), 250 (8.2); and 40 mg of 4α-hydroxy-1-oxo-5α,11β-H-eudesman-6β,12-olide (dihydro-6β-vulgarin) (**20**, 8%); m.p.: 140-2 °C; $[\alpha]_D$= -59° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3354, 1769, 1708, 1259 cm$^{-1}$; $^1$H nmr see Table III; $^{13}$C nmr see Table IV; ms, m/z (%): $M^+$ 266 (8), 248 (6).

***Catalytic hydrogenation of 4α-hydroxy-1-oxo-5α,11β-H-eudesm-2-en-6α,12-olide (vulgarin)* (12) *with Pd-$BaSO_4$***

A solution of product **12** (50 mg) in EtOH (3 mL) was hydrogenated for 5 h with $H_2$ (4 atm) on Pd-$BaSO_4$. The reaction mixture was filtered and the solvent was removed by distillation at reduced pressure, which yielded, after column chromatography, 45 mg of 4α-hydroxy-1-oxo-5α,11β-H-eudesman-6α,12-olide (**21**); m.p.: 173-5 °C; $[\alpha]_D$= -39° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3525, 1770, 1710 $cm^{-1}$; $^1H$ nmr see Table III; $^{13}C$ nmr see Table IV; ms, m/z (%): $M^+$ 266, 248 (13).

***Lactonization of 1β,4α,6β,12-tetrahydroxy-5α,11β-H-eudesmane* (18) *with tetrapropylammoniun perrutenate (TPAP)***

Solid TPAP (25 mg) was added in a single portion to a stirred mixture of product **18** (200 mg), NMO (4-methylmorpholine N-oxide, 200 mg) and activated powdered molecular sieves (200 mg) in dry $CH_2Cl_2$ (30 mL) at room temperature under argon. On completion, the reaction mixture was concentrated in a vacuum. Purification by column chromatography on silica gel yielded 160 mg of product **19** (80%). Product **20** was not detected with this lactonization reagent.

***Mesylation of 1β,4α-dihydroxy-5α,11β-H-eudesman-6β,12-olide (tetrahydro-6β-vulgarin)* (19)**

2 mL of MsCl (methanesulfonyl chloride) was added to a solution of 200 mg of product **19** dissolved in 10 mL of pyridine. The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was diluted with $CH_2Cl_2$, washed with water and with saturated aqueous $KHSO_4$ and concentrated in a vacuum. Chromatography on a silica gel column yielded 215 mg of 4α-hydroxy-1β-mesyloxy-5α,11β-H-eudesman-6β,12-olide (**22**, 90%); m.p.: 148 °C; $[\alpha]_D$= -53° C ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3315, 1762, 1218 $cm^{-1}$; $^1H$ nmr see Table III; $^{13}C$ nmr see Table IV; ms, m/z (%): $[M+1]^+$ 347 (5), 329 (11), 251 (19), 233 (100).

***Solvolysis of 4α-hydroxy-1β-mesyloxy-5α,11β-H-eudesman-6β,12-olide* (22)**

200 mg of product **22** was dissolved in 8 mL of a solution of KOAc/HOAc (0.23 N) and refluxed for 72 h. The reaction mixture was then washed with saturated aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, dried over $Na_2SO_4$ and evaporated to dryness. Chromatography on a silica gel column yielded 28 mg of 4α-hydroxy-5α,11ß-H-eudesm-1-en-6β,12-olide (**23**, 20%); m.p.: 178 °C; $[\alpha]_D$= -62° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3428, 1763, 1453 $cm^{-1}$; $^1H$ nmr see Table III; $^{13}C$ nmr see Table IV; ms, m/z (%): $[M+1]^+$ 251 (40), 233 (100); 14 mg of 4α-hydroxy-5α,11α-H-eudesman-1-en-6β,12-olide (**24**, 10%); m.p.: 150 °C; $[\alpha]_D$= -135° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3452, 1762, 1457 $cm^{-1}$; $^1H$ nmr see Table III; $^{13}C$ nmr see Table IV; ms, m/z (%): $[M+1]^+$ 251 (27), 233 (100); and 55 mg of 4α-hydroxy-5α,11β-H-guai-1(10)-en-6β,12-olide (**25**, 40%); m.p.: 138 °C; $[\alpha]_D$= -45° ($CHCl_3$, c 1); IR $\nu_{max}$ ($CHCl_3$): 3428, 1763, 1453 $cm^{-1}$; $^1H$ nmr see Table III; $^{13}C$ nmr see Table IV; ms, m/z (%): $[M+1]^+$ 251 (6), 233 (100).

## ACKNOWLEDGEMENTS

This work was supported by a grant from the Dirección General de Investigación Científica y Técnica. We thank Karen Shashok for her assistance in the translation of the text.

## REFERENCES

1. Adekenov, S.M.; Kagarlistskii, A.D.; Mukhametzhanov, M.N. and Kapriyanov, A.N.; *Khim. Prir. Soedin*, **1983**, 238.
2. Irwin, M.A. and Geissman, T.A.; *Phytochemistry*, **1969**, *8*, 2411.
3. Barrero, A.F.; Sánchez, J.F.; Molina, J.; Barrón, A. and Salas, M.M.; *Phytochemistry*, **1990**, *29*(11), 3575-3580.
4. Fischer, N.H.; Oliver, E.J. and Fischer, H.D.: "The Biogenesis and Chemistry of Sesquiterpene Lactones". In: "*Progress in the Chemistry of Organic Natural Products*". (Ed. Herz, W.; Grisebach, H. and Kirby, G.W.), Springer-Verlag, Wien, New York, **1979**, *38*, 47-390.
5. a) Ando, M.; Akahane, A. and Takase, K.; *Bull. Chem. Soc. Japan*, **1978**, *51*(1), 283.
   b) Jain, T.C. and Banks, C.M.; *Can. J. Chem.*, **1980**, *58*, 447.
   c) Ando, M.; Tajima, K. and Takase, K.; *J. Org. Chem.*, **1983**, *48*, 1210.
6. Lange, G.L. and Lee, M.; *J. Org. Chem.*, **1987**, *52*, 325.
7. a) Bordoloi, M.J.; Sharma, R.P. and Sarmah, J.C.; *Tetrahedron lett.*, **1986**, *27*, 4633.
   b) Parodi, F.J. and Fisher, N.H.; *J. Chem. Soc. Chem. Comm.*, **1986**, 1405.
   c) Gonzalez, A. G.; Galindo, A.; Alonso, M.M.; Mansilla, H. and López, H.; *Tetrahedron*, **1988**, *44*, 4585.
   d) Gonzalez, A. G.; Galindo, A.; Alonso, M.M.; Mansilla, H. and Palenzuela, J.A.; *Tetrahedron*, **1988**, *44*, 4575.
   e) Harapanhalli, R.S.; *J. Chem. Soc.* Perkin Trans I, **1988**, 2633.
   f) Bordoloi, M.J.; Sharma, R.P. and Sarmah, J.C.; *Tetrahedron*, **1989**, *45*, 289.
   g) Ortega, A. and Maldonado, E.; *Heterocycles*, **1989**, *29*, 635.
8. a) Yamakawa, K.; Nishitani, K.; Iida, M. and Mikami, A.; *Chem. Pharm. Bull.*, **1986**, *34*(3), 1319.
   b) Arias, J.M.; Bretón, J.L.; Gavin, J.A.; García-Granados, A.; Martínez, A. and Onorato, M.E.; *J. Chem. Soc.* Perkin Trans I, **1987**, 471-474.
   c) Naik, V.P.; Mavinkurve, S.; Naik, V.S. and Paknikar, S.K.; *Indian J. Chem., Sect. B.*, **1988**, *27B*(4), 381.
9. a) Amate, Y.; Bretón, J.L.; García-Granados, A.; Martínez, A.; Onorato, M.E. and Sáenz de Buruaga, A.; *Tetrahedron*, **1990**, *46*(19), 6939-6950.
   b) Amate, Y.; García-Granados, A.; Martínez, A.; Sáenz de Buruaga, A.; Bretón, J.L.; Onorato, M.E. and Arias, J.M.; *Tetrahedron*, **1991**, *47*(30), 5811-5818.
10. a) García-Granados, A.; Martínez, A.; Onorato, M.E.; Rivas, F. and Arias, J.M.; *Tetrahedron*, **1991**, *47*(1), 91-102.
    b) García-Granados, A.; Martínez, A.; Parra, A.; Rivas, F.; Onorato, M.E. and Arias, J.M.; *Tetrahedron*, **1993**, *49*(5), 1091-1102.
11. Ishikawa, H. and Zasshi, Y.; *J. Pharm. Soc., Japan*, **1956**, *76*, 500-504.
12. a) White, D.N.J. and Sim, G.A.; *Tetrahedron*, **1973**, *29*, 3933-3938.
    b) Calculation with an interactive molecular modelling program (PC-MODEL 3.0, Serena Software) of the difference between the *steric* energies for both lactones showed this energy to be 2.1 Kcal/mol greater for the 6α-lactone.
13. Curtis, R.G.; Heilbron, H.; Jones, E.H.R. and Woods, Q.F.; *J. Chem. Soc.*, **1953**, 457.
14. Murahashi, S.I.; Naota, T.; Ito, K.; Maeda, Y. and Taki, H.; *J. Org. Chem.*, **1987**, *52*, 4319-4327.
15. Bloch, R. and Brillet, C.; *Synlett.*, **1991**, 829-830.
16. Gonzalez, A. G.; Bermejo, J.; Bretón, J.L. and Fajardo, M.; *An. Quim.*, **1973**, *69*, 667.
17. Gonzalez, A. G.; Galindo, A. and Mansilla, H.; *Tetrahedron*, **1980**, *36*, 2015.

(*Received in UK* 4 *November* 1993; *revised* 3 *December* 1993; *accepted* 10 *December* 1993)