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SYNTHESIS, BIOTRANSFORMATION AND STEREOCHEMISTRY OF 6β-SESQUITERPENE LACTONES: SYNTHESES OF 6β-ARTEPAULIN, 11,13-DIHYDRO-6β-TUBERIFERIN, 5,15-DIHYDRO-6β-OOPODIN, 4-EPI-6β-VULGARIN AND 6β-VULGARIN

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SUMMARY: 6β-Artepaulin, 11,13-dihydro-6β-tuberiferin, 4,15-dihydro-6β-oopodin, 4-epi-6β-vulgarin and 6β-vulgarin were obtained from α-santonin. Stereochemical studies showed that the configuration at C-6 is decisive in the chemical behaviour of the A ring. Biotransformation of 1-oxo-5,6αH,4,11βH-eudesm-2-en-6,12-olide with *Rhizopus nigricans* cultures probed to be a very efficient alternative way to obtain 4-*epi*-6β-vulgarin, which was then converted to 6β-vulgarin, a convenient starting material for biogenetical studies of pseudoguaianolides. A new 8ß-hydroxyl derivative obtained from this biotransformation constitutes a new approach to the synthesis of 8,12-eudesmanolides and other sesquiterpenolides. Molecular structures were determined mainly by mono- and bidimensional nmr experiments.

INTRODUCTION

The biogenesis and reactivity of 6α-eudesmanolides have been extensively studied and processes of chemical[1], photochemical[2], biomimetic syntheses[3] and biotransformation[4] have been reported. These structures, despite their limited size, show versatile reactivity. The stereochemistry and the presence or absence of functional groups are decisive in their chemical behaviour[5], which is of fundamental importance in the study of biomimetic processes. On the other hand the 6ß-sesquiterpene lactones, which are scarce in nature[6], have rarely been studied. The synthesis of these compounds offers an interesting approach to biogenetic problems such as the biogenesis of pseudoguaianolides and elemanolides. In this article we present the results of a study designed to establish some synthetic methods of obtaining 6ß-lactones, which yielded the 6ß-analogues of artepaulin[7], 11,13-dihydrotuberiferin[8], 5,15-dihydroopodin[9], 4-*epi*-vulgarin and vulgarin[10]. We also report a biotransformation method which may constitute an alternative to some familiar chemical routes.

RESULTS AND DISCUSSION

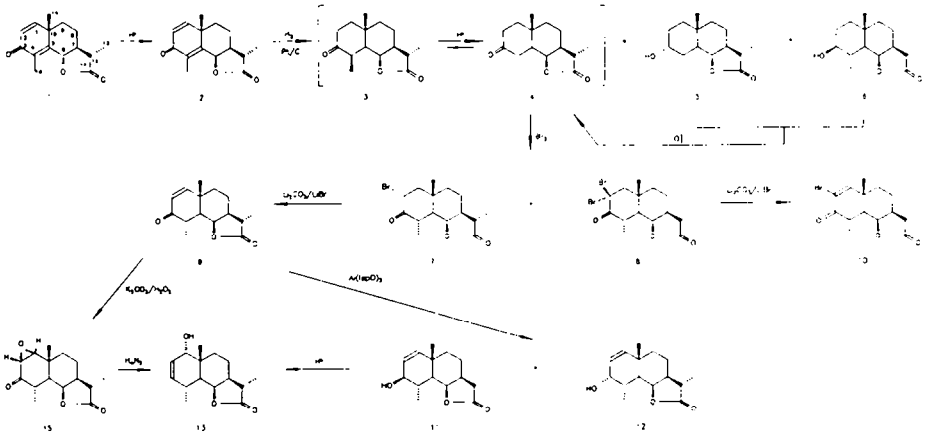
The epimerization at C-6 of (-)-α-santonin[11] (**1**) in an acidic medium has been described[12]. The catalytic hydrogenation of 6ß-santonin (**2**) thus obtained under the same conditions as described[13] for **1** was problematic and caused cleavage of the lactone ring. Furthermore, catalytic hydrogenation in CH_2Cl_2 (see Experimental section) yielded two ketone compounds (**3**, 60% and 6ß-artepaulin (**4**, 6%) and two alcohols (**5**, 6% and **6**, 14%). The configuration at C-5 of ketone **3** epimerized spontaneously to give **4** (3/4, 70/30). The higher ^{1}H-nmr chemical shifts of methyl groups at C-4 of **3** than **4**, and the relevant ^{13}C nmr γ-syn effect on C-2 in ketone **3** (see table II) allowed us to assign **3** to the 4R- configuration and **4** to the S-configuration. The alcohols **5** and **6** were also trans-decalin compounds, as can be appreciated from the C-6 proton signal of both products in their ^{1}H nmr spectra (see table I). The configuration at C-4 must be S because the H-4/H-15 coupling constants are similar to those described previously for **4** (see table I). Moreover, ^{13}C nmr spectra for **5** and **6** corroborated this configuration at C-4 due to C-6 chemical shifts (see table II). The oxidation of **5** and **6** with 2,2'-bipyridinium chlorochromate[14] yielded **4**. Thus, the alcohols **5** and **6** are epimeres at C-3 . The presence of the alcohols **5** and **6** indicated that the reduction took place through both sides of ketone **4**.

Treatment of **4** with bromine in carbon tetrachloride solution (see Experimental section) yielded monobromine (**7**, 62%) and dibromine (**8**, 9%) derivatives. The nmr spectra of **7** indicated that the halogen was equatorial at C-2 and that the two bromines were situated at C-2 in **8**. On the other hand, the configuration at C-4 was unaltered (see tables I and II) in both compounds. The dehydrobromation of **7**, as described previously [15], gave 11,13-dihydro-6ß-tuberiferin (**9**, 94%). A similar process in **8** gave **10**. The Meerwein-Pondorf reduction of **9** yielded the alcohols **11** (72%) and **12** (25%). In the case of 6α-lactones, a similar reduction gave a mixture of non-isolated alcohols[16]. Thus the reduction occurred preferably on the α-side to give the equatorial alcohol. However, alcohol **11** showed an ^{1}H nmr signal of the proton at C-3 with only one observable coupling constant (J=8.8 Hz, see table III) which could indicate that the functional group was situated at C-1 by means of allylic rearrangement. The irradiation at H-4 of **11** definitely indicated that the hydroxyl group was situated at C-3. By comparing the H-3/H-4 coupling constant for **11** and **12** (see table III), we were able to assign their configurations. The ^{13}C nmr spectra of both epimere compounds **11** and **12** were similar with the exception of the chemical shift of C-5, which presented a difference of 15 ppm. Evidently a γ-syn effect on C-5 was expected for the axial alcohol **12**, but such a large difference must be due to some conformational effect.

Allylic rearrangement of a mixture of alcohols **11** and **12** was performed in acidic medium (see experimental section) to give the 1α-hydroxyl derivative **13** (4,15-dihydro-6ß-oopodin, 71%). Moreover, 16% of equatorial alcohol **11** and 5% of the axial alcohol **12** were recovered unaltered from the reaction. The configuration at C-1 of **13** was not easy to determine. Oxidation of alcohol **13** gave the ketone **14**. The comparison of ^{13}C nmr spectra of **13** and **14** seemed to indicate that the hydroxyl group could be axial at C-1 in **13**, if we assumed that the configuration at C-4 was the same for both products, because a γ-syn effect on C-5 was eliminated in ketone **14** (see table IV). Nevertheless the configuration of C-4 for both products **13** and **14** was also difficult to elucidate because the ^{1}H nmr signal

of H-4 of **13** was not clear, and the coupling constant H-3/H-4 (measured on H-3 signal) was smaller (J = 1.3 Hz) than the allylic constant H-2/H-4 (J = 2.1 Hz). A NOESY experiment performed on ketone **14** indicated dipolar correlations between the lactone H-6, the C-15 methyl, C-13 methyl groups and H-5, hence all these groups were situated on the α-side. On the other hand, the coupling constant 3H-15/H-4 measured on the 3H-15 signal (J = 7.1 Hz) of **13** had the same value as the corresponding signal of ketone **14**. This ketone **14** had a coupling constant of H-4/H-5 = 10.3 Hz, which indicated a trans-disposition between both atoms. The coupling constant 3H-15/H-4 measured on the 3H-15 signal (J = 7.1 Hz) had the same value for both products **13** and **14**, and indicated that the C-4 configuration was the same for these products.

Alcohol **13** was also obtained by an alternative means. The epoxidation of ketone **9** with alkaline hydrogen peroxide[16] (see Experimental section) yielded the epoxide **15** (58%). Epoxidation probably occurs on the α-face, with a lower steric hindrance, and without epimerization at C-4. To elucidate the configuration of epoxide carbons, several monodimensional nOe experiments, after COSY and C/H correlation spectra, were carried out. Irradiation at the C-10 methyl group proton signal frequency enhanced the H-1 and H-4 signals, thus suggesting an α-disposition for the epoxide group and an axial disposition for the C-4 proton. The H-4 signal was observable in this experiment and its coupling constant H-4/H-5 (J = 11.9 Hz) indicated that they were trans-disposed



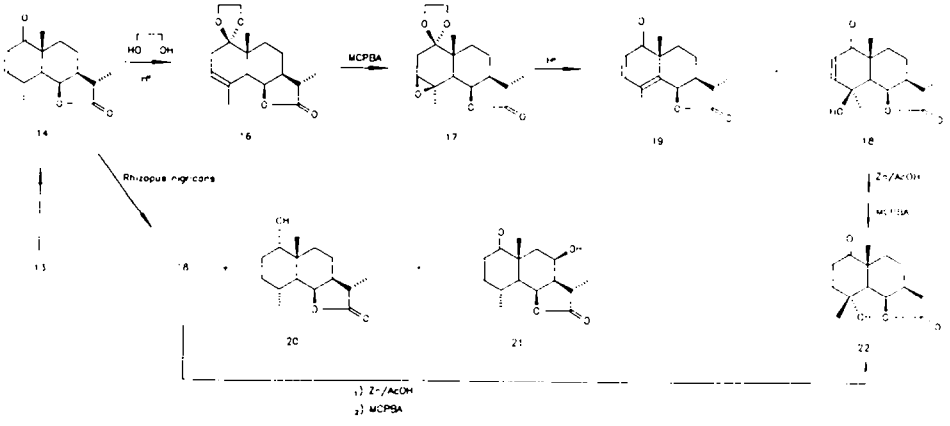
The reduction of **15** with hydrazine[8d,e] yielded **13** (28%). This route gave a lower yield than the route described above but was less time consuming and easier to perform. The oxidation of alcohol **13** with Jones' reagent yielded the ketone **14** (98%). In order to obtain similar vulgarin derivatives, the ketone **14** was treated with ethylene glycol in acidic medium to give the ethylenedioxy-derivative **16** (42%) in which migration of the C-C double bond occurred. Epoxidation of 6α-sesquiterpene lactones with similar functions was described as an α-epoxidation[17] after taking into account the α-oxygen directional effect of the C-1 ethylenedioxy group; soon afterwards this epoxide in basic medium evolved to the 3α-hydroxy-4(15)-ene derivative. However, a 3ß,4ß-epoxy-eudesmane gave a 3α-hydroxy -4(15)-ene derivative after treating the epoxy compound with a catalytic amount of pyridinium p-toluensulphonate[18]. Epoxidation of **16** with MCPBA for 24 h then yielded the 3ß,4ß-epoxide **17** (94%). Treatment of **17** in acidic medium (see Experimental section) gave **14** (46%), **18** (32%) and the diene compound **19** (13%). To determine the configuration at C-4 of **18**, (which must be the same as in the epoxide **17**) several ^1H and ^{13}C nmr mono- and bidimensional experiments about were performed. Dipolar coupling between the C-15 methyl group protons and the C-6 proton was observed in the NOESY experiment, thus supporting an equatorial disposition for this methyl group. This dipolar coupling was also corroborated in the monodimensional nOe-difference experiment. Thus, irradiation at the C-15 methyl group proton frequency gave nOe on H-6 and H-5 but not on C-14 methyl group. Irradiation at this C-14 methyl group did not modify the C-15 methyl group signal. These experiments indicated a 4ß-OH configuration for **18**, although irradiation at H-6 failed to enhance the C-15 methyl group signal, hence the epoxidation of **16** occurred on the ß-face. Thus, the directional effect of the ethylenedioxy group at C-1 seems not to be the determining factor in this epoxidation of eudesmanolides. Alternatively, the configuration at C-6 may be decisive in the stereochemistry of epoxidation if C-1 is a sp^3 carbon.

We have found an alternative route for obtaining 4-epi-6ß-vulgarin (**18**) from ketone **14**. Incubation of **14** with *Rhizopus nigricans* cultures for 6 days yielded the starting material **14** (48%), alcohol **20** (8%), 4-epi-6ß-vulgarin **18** (8%) and the new 8ß-hydroxyl derivative **21** (11%). Consistently, the obtention of **18** through our biotransformation route gave moderate yields approaching those of chemical approaches. A longer incubation period could improve the results, as a considerable quantity of unaltered starting material **14** was recovered. The metabolite **20** was the result of α,ß-unsaturated keto group reduction on the ß-face to give 1S-alcohol, as described in the biotransformation reported previously[4a,19].

The most polar metabolite isolated (**21**) maintained the functional groups of ketone **14**. The presence of a new hydroxyl group was deduced from MS, ^1H and ^{13}C nmr data (see experimental section and tables III and IV). A ^1H nmr double resonance experiment with irradiation at the proton geminal to the new hydroxyl group showed that this new hydroxyl group was situated at C-8; a large coupling constant (J= 9.9 Hz) seemed to indicate that this new hydroxyl group at C-8 was equatorial. However, after taking into account the ^1H nmr coupling constants (J_1=9.9,J_2=4.2,J_3=3.7 Hz) and the Dreiding models we believe that the metabolite **21** had an 8ß-hydroxyl group, although ring B did not show a chair conformation by the steric interaction between the C-14 methyl group and the ß-hydroxyl group at C-8. The coupling constants described above are totally consistent with a twist-boat conformation of the B ring and an 8ß-hydroxylation. The introduction of

hydroxyl groups at this position is not easy to obtain by chemical methods and may involve a new route to the synthesis of 8,12-sesquiterpene lactones.

The synthesis of 6ß-eudesmanolides as a step toward obtaining several types of 6ß-sesquiterpene lactones such as guaianolides, elemanolides, germacranolides and pseudoguaianolides has been a challenge, as these decaline compounds with an equatorial hydroxy group at C-1 can be rearranged into azulene compounds[20]. Hence 6ß-vulgarin, which can be easily transformed to its 1ß-hydroxy-2,3-dihydro derivative, is an adequate starting material to attempt the biogenetical formation of pseudoguaianolides, the configuration at C-4 of precursors being of key importance[21,3a,3f].



Treatment of **18** with AcOH/Zn[10] and subsequent epoxidation with MCPBA epimerized **18** at C-4 by means of the 1-keto-3-ene derivative[4a] to give **22** (see tables II and IV for ^1H and ^{13}C nmr data of **22**). This process occurs by the epoxidation of the double bond and subsequent rearrangement to **22**[4a]. As can be seen from the resulting configuration at C-4 of **22**, in this case epoxydation occurs on the α-face, in contrast to epoxidation of the ethylenedioxy derivative **16**.

TABLA I

	1	2	3	4	5	6	7	8	9	10
H-1	6.66 d	6.74 d	----	----	----	----	----	2.88 QAB	6.63 d	7.12 s
H-1α	----	----		1.66 ddd			1.86 dd		----	----
H-1β	----	----					2.30 dd		----	----
H-2	6.12 d	6.23 d	----	----	----	----	----	----	5.83 d	
H-2α	----	----	2.24 ddd	2.39 ddd			----			
H-2β	----	----	2.79 ddd	2.58 ddd			4.89 ddd			
H-3	----	----	----	----	----	----	----	----	----	----
H-3α					----	3.06 ddd				
H-3β					3.89 ddd	----				
H-4α		----	2.60 ddq	----	----	----	----	----	----	----
H-4β		----	----	2.70 dq			2.86 dq	3.49 dq	2.74 dq	2.91 dq
H-5α		----		1.27 dd			1.32 dd	1.48 dd	1.72 dd	
H-6α		5.52 d	4.50 dd	4.62 dd	4.59 dd	4.62 dd	4.59 dd	4.59 dd	4.68 dd	4.67 dd
H-6β	4.76 d	----	----	----	----	----	----	----	----	----
H-7		2.15 ddd	1.99 ddd	1.98 ddd			2.00 ddd	2.00 ddd	2.04 ddd	2.07 ddd
H-8α		1.86 dddd		1.75 dddd			1.77 dddd	1.75 dddd		
H-8β								1.47 dddd		
H-9α							1.15 ddd	1.06 ddd		
H-9β				1.57 ddd			1.59 ddd	1.62 ddd		
H-11	2.39 dq	2.52 q	2.33 q	2.39 q	2.33 q	2.29 q	2.40 q	2.41 q	2.40 q	2.42 q
3H-13	1.22 d	1.37 d	1.26 d	1.29 d	1.26 d	1.28 d	1.30 d	1.30 d	1.31 d	1.32 d
3H-14	1.28 s	2.03 s	1.28 s	1.84 s	0.93 s	0.94 s	1.23 s	1.38 s	1.17 s	1.23 s
3H-15	2.07 s	1.26 s	1.39 d	1.12 d	1.03 d	1.07 d	1.20 s	1.33 d	1.25 d	1.33 d

J(Hz) 1: 6,7=11; 7,11=11.9; 11,13=6.9. 3: 2α,4=1.6; 4,5=5.1; 4.15=7.7; 5,6=4. 4: 1α,1β=13.2. 3 and 4: 1α,2α=6.6; 1α,2β=14.1; 1β,2α=5; 1β,2β=6.6; 2α,2β=14.1. 5: 2α,3=2.6; 2β,3=5.3; 3,4=5.3. 6: 2α,3=5; 2β,3=10.5; 3,4=10.5. 7: 1α,2=13.4; 1β,2=6.3; 1α,1β=12.9; 2,4=0.7. 8: 1α,1β=15.7. 1,2 and 9; 1,2=9.8. 2-10: 6,7=4.6; 7,8α=6.8; 7,8β=11.4; 11,13=7.6. 4-10: 4,5 =12.8; 4,15=6.6; 5,6=4.1. 2,4,7 and 8: 8α,8β=13.8; 8α,9α= 8α,9β= 3.4. 4, 7 and 8: 8β,9β=6.6; 9α,9β=13.2. 7 and 8: 8β,9α=10.2.

TABLA II

	1	2	3	4	5	6	7	8	9	10
C-1	154.95	157.29	41.64	41.76	36.20	40.40	54.12	63.90	159.30	159.19
C-2	125.83	125.82	34.86	38.01	29.12	30.93	53.54	64.21	126.22	122.05
C-3	186.30	186.00	214.25	211.85	72.08	76.91	201.98	196.94	201.43	193.30
C-4	128.63	137.49	50.00	42.98	33.22	36.87	43.04	38.40	40.46	41.21
C-5	151.06	148.52	47.83	50.39	43.03	48.97	50.45	49.04	48.43	47.94
C-6	81.38	76.19	81.35	77.00	77.78	77.10	76.50	76.19	76.45	76.03
C-7	53.53	43.42	43.02	41.78	42.41	42.19	41.40	41.38	41.48	41.21
C-8	23.04	23.00	24.07	23.54	23.76	23.58	23.26	22.62	23.47	23.28
C-9	37.83	34.43	41.22	38.55	39.27	39.24	37.87	38.79	35.71	35.59
C-10	41.36	39.15	32.63	32.57	32.72	32.32	35.27	35.48	35.25	38.33
C-11	40.97	43.82	43.48	44.49	44.63	44.52	44.31	44.29	44.40	44.23
C-12	177.61	179.47	180.11	179.90	180.84	180.53	179.53	174.37	179.79	179.80
C-13	12.49	14.70	15.97	14.61	14.61	14.64	14.58	14.62	14.64	14.60
C-14	25.12	24.84	20.39	18.07	17.82	18.58	18.55	19.13	19.15	18.96
C-15	10.89	11.01	14.03	10.85	15.35	14.41	11.47	12.34	11.30	12.03

TABLA III

	11	12	13	14	15	16	17	18	20	21	22
H-1	5.48 QAB	5.58 d	----	----	----	----	----	----	----	----	----
H-1α	----	----	----		----	----	----	----	----	----	----
H-1β	----	----	3.39 d		3.16 d	----	----	----	3.34 bs	----	----
H-2	5.48 QAB	5.64 dd	5.77 m	5.85 dd	----		2.15 AB	6.66 d		5.88 dd	6.73 d
H-2α					----		----	----		----	----
H-2β					3.32 d		----	----		----	----
H-3	----	----	5.72 m	6.71 dd		5.38 bm	----	5.91 d		----	6.01 d
H-3α	3.80 d	----					----			----	----
H-3β	----	4.03 dd					----			----	----
H-4α	----	----		----	----		----			----	----
H-4β	1.96 dq	2.15 dq		2.86 dddq						2.85 m	----
H-5α				1.58 dd	1.92 dd	2.53 bm	2.34 dd	1.91 d		1.62 dd	2.74 d
H-6α	4.69 dd	4.71 dd	4.79 dd	4.73 dd	4.67 dd	4.87 dd	4.91 dd	5.04 dd	4.78 dd	4.46 dd	4.99 dd
H-6β	----	----	----	----	----	----	----	----	----	----	----
H-7		2.02 ddd	2.01 dd		2.02 ddd		1.97 ddd			1.86 dd	
H-8α					1.83 dddd		1.70 ddd	1.85 ddd		----	
H-8β										3.72 ddd	
H-9α										2.27 dd	
H-9β							2.00 ddd				
H-11	2.36 q	2.37 q		2.40 q	2.41 q		2.34 q	2.42 q	2.34 q	2.91 q	2.38 q
3H-13	1.29 d	1.29 d	1.30 d	1.30 d	1.29 d	1.30 d	1.29 d	1.34 d	1.29 d	1.37 d	1.31 d
3H-14	1.05 s	0.98 s	0.90 s	0.93 s	1.02 s	1.01 s	1.07 s	1.38 s	0.94 s	1.16 s	1.28 s
3H-15	1.18 d	1.14 d	1.11 d	1.23 d	1.22 d	1.83 bs	1.51 s	1.53 s	0.97 s	1.27 d	1.53 s

J (Hz) 11: 3,4=8.8. 12: 2,3=4.1; 3,4=3.9. 11 and 12: 1,2=9.8. 13: 1,2=4.6; 2,3=9.9; 2,4=2.1; 3,4=1.3. 14: 2,3=10.1; 2,4=2.8; 3,4=2;4,5=10.3. 13 and 14: 4,15=7.1. 15: 1,2=4.1. 16: H-3,Wh/2=9; H-5,Wh/2=7.5. 17: 2α,2β=15.7; 2α,3= 2β,3=2.9. 18 and 21: 2,3=10.2. 21: 7,8=4.2; 8,9α=9.9; 8,9β=3.7. 11-22: 5,6=4; 6,7=4.6; 11,13=7.6. 11,12,15 and 20: 4,5=12.6; 4,15=6.6. 12,13,15 and 18: 7,8α=6.8. 12,13,15 and 17: 7,8β=11.4. 15,17 and 18: 8α,8β=13.8; 8α,9α= 8α,9β=3.4. 18: 8β,9β=6.4; 9α,9β=12.8. 21: 2,4=2.8; 3,4=2; 4,5=10.4; 4,15=7.1; 7,8=4.2; 8,9α=9.9; 8,9β=3.7; 9α,9β=13.2. 22: 2,3=10.4; 5,6=2.6; 6,7=3.8.

TABLA IV

	11	12	13	14	15	16	17	18	20	21	22
C-1	141.02	142.96	72.98	203.75	63.48	111.54	111.32	205.60	75.50	202.43	202.49
C-2	127.30	125.32	125.85	126.25	55.75	26.71	26.89	126.00	28.88	126.00	128.39
C-3	76.16	69.12	138.03	154.37	206.99	120.85	60.79	150.45	30.28	154.51	151.43
C-4	35.98	32.98	30.05	30.80	40.42	132.64	77.30	69.40	28.55	30.84	82.83
C-5	47.19	32.13	42.57	48.56	41.45	45.24	45.37	47.99	43.85	50.38	44.33
C-6	76.74	77.34	77.11	76.49	76.34	78.04	78.11	76.67	77.88	77.74	75.87
C-7	42.04	42.25	41.80	41.68	40.11	41.72	42.39	42.60	42.30	41.79	42.45
C-8	23.75	23.82	23.30	23.00	23.34	23.62	23.13	22.92	23.62	67.74	23.25
C-9	36.61	36.59	31.97	30.13	34.28	34.52	32.39	31.40	32.88	39.89	33.02
C-10	34.49	35.04	35.93	43.29	33.16	39.89	39.59	43.41	36.99	44.97	43.99
C-11	44.57	44.50	44.52	44.38	44.38	44.66	44.32	42.98	44.61	48.35	43.77
C-12	180.44	180.65	180.31	179.75	179.46	180.39	180.10	178.63	180.71	179.55	179.97
C-13	14.74	14.73	14.42	14.46	14.42	14.50	13.91	14.47	14.58	14.80	13.92
C-14	21.60	20.08	18.53	17.59	17.12	15.64	16.29	20.68	19.40	18.35	20.51
C-15	15.00	13.25	18.20	17.54	14.31	20.73	21.76	29.16	18.85	17.69	20.30
C-16						*65.73	65.53	----			
C-17						*65.06	65.15	----			

* (These values could be interchangeables)

EXPERIMENTAL

Melting points (Kofler apparatus) are uncorrected. The nmr spectra were obtained with a Bruker AM-300 spectrometer equipped with a process controller and an "array processor". Samples were solved in CDCl3 with SiMe4 as the internal standard. Bruker's programs were used for COSY (45°) NOESY, C/H correlation and CONOESY (90°). Monodimensional nOe difference experiments were performed by irradiation for 4 s in series of 8 scans with alternanting on-resonance and off- resonance. Distortionless enhancement by polarization transfer (DEPT) was made using a "flip angle" of 135°. The optical rotations were measured on a Perkin-Elmer 240 polarimeter. IR spectra were recorded with a FT-IR-Nicolet 20SX spectrophotometer. Mass spectra were carried out with a Hewlett-Packard 5988-A spectrometer. Merck 7729 silica gel (less than 0.08 mm) was used for flash chromatography. CH_2Cl_2 containing increasing amounts of acetone was used as the eluent. Analytical plates (Merck G silica gel) were visualized by spraying with H_2SO_4-AcOH, followed by heating for 5 min.

Conversion of (-)-α-santonin **1** *into the epimeric (-)-6-epi-α- santonin* **2** *by the Ishikawa procedure.-*

(-)-α-santonin (**1**)(10 g, 40 mmol) was dissolved in anhydrous N,N'-dimethylformamide (100 ml) containing 5% anhydrous hydrogen chloride. The solution was heated to 85°C for 3 h. The mixture was allowed to stand at room temperature overnight, then diluted with water and extracted with CH_2Cl_2. The organic layer was washed with sat NaCl aq, sat $NaHCO_3$ aq. and water. The solvent was removed under reduced pressure. The viscous red oil obtained was chromatographed over silica gel. Elution with $CHCl_3$ containing increasing amounts of acetone, yielded (-)-6-epi-α- santonin (**2**)(6g, 60%) as light-yellow blocks; m.p.:103-105°C; $[\alpha]_D$:-292.6° ($CHCl_3$, c 1); ir μ_{max} ($CHCl_3$): 1769, 1659 and 1628 cm-1; ^1H nmr (300 MHz): see table I; ^{13}C nmr: see table II; ms, m/z(%): 247(M^++1, 20%), 246(M^+)(100).

Catalytic hydrogenation of 3-oxo-6αH,11βH-eudesm-1,4-dien- 6,12-olide (**2**).-

A solution of 3-oxo-6αH,11βH-eudesm-1,4-dien-6,12-olide (**2**)(1 g, 4 mmol) in CH_2Cl_2(30 ml) was hydrogenated for 5 h with H_2 (5 atm) on Pt-charcoal (150 mg). The reaction mixture was filtered and the solvent was removed by distillation at reduced pressure, which yielded 890 mg of yellow oil which was chromatographed over silica gel and eluted with Cl_2CH_2-$(CH_3)_2CO$. The first run gave 3-oxo-4,5,6αH,11βH-eudesman- 6,12-olide (**3**)(610 mg, 60%), m.p.: 130-132°C; $[\alpha]_D$:-60° ($CHCl_3$, c 1); ir μ_{max} ($CHCl_3$): 1763 cm-1; ^1H nmr (300 MHz): see table I; ^{13}C nmr: see table II. Further elution yielded 3-oxo-5,6αH,4,11βH-eudesman- 6,12-olide (**4**)(65 mg, 6%); m.p.: 162-164°C; $[\alpha]_D$: -70.4°($CHCl_3$, c 1); ir μ_{max} ($CHCl_3$): 1760 cm-1; ^1H nmr (300 MHz): see table I; ^{13}C nmr: see table II; ms, m/z(%): 251 (M^++1, 16%) , 250 (100). The third run gave 3α-hydroxy-5,6αH,4,11βH- eudesman-6,12-olide (**5**)(60 mg, 5%); syrup; $[\alpha]_D$: -26.4° ($CHCl_3$, c 1); ir μ_{max} ($CHCl_3$): 3479 and 1765 cm-1; ^1H nmr (300 MHz): see table I; ^{13}C nmr: see table II; ms, m/z(%): 253(M^++1, 27%), 235 (M^+- 17)(100). Continued elution yielded 3β-hydroxy-5,6αH,4,11βH-eudesman-6,12-olide (**6**)(140 mg, 14%), syrup; $[\alpha]_D$: -121.4° ($CHCl_3$, c 1); ir μ_{max} ($CHCl_3$): 3241 and 1755 cm-1; ^1H nmr (300 MHz): see table I; ^{13}C nmr: see table II; ms, m/z(%): 253 (M^++1, 7%), 252 (M^+, 44%), 234 (M^+-17)(100).

Oxidation of 3α-hydroxy-5,6αH,4,11βH-eudesman-6,12-olide (5) and 3β-hydroxy-5,6αH,4,11βH-eudesman-6,12-olide (**6**).-

A solution of a mixture (**5** and **6**) (500 mg, 2 mmol) in CH_2Cl_2 (3 ml) was added to a stirred suspension of 2,2'- bipyridinium chlorochromate (870 mg, 3 mmol) in CH_2Cl_2 (4 ml). Stirring was continued at room temperature for 12 h. Ether was added and the reaction mixture was filtered through celite and washed with ether. The solvent was evaporated under reduced pressure to give a crude product (350 mg) which was chromatographed over silica gel. 290 mg (58%) of 3-oxo- 5,6αH,4,11βH-eudesman-6,12-olide (**4**) was isolated.

Bromation of 3-oxo-5,6αH,4,11βH-eudesman-6,12-olide(**9**).-

0.93 m bromine-carbon tetrachloride solution (4.5 ml) was added all at once to a solution of 3-oxo-5,6αH,4,11βH- eudesman-6,12-olide (**4**) (1 g, 4 mmol) in 30 ml $CHCl_3$. The mixture was stirred for 10 min at room temperature, after which water was added and extracted with $CHCl_3$. The extract was washed with sat. $NaHCO_3$ aq and sat NaCl aq, dried over Na_2SO_4 and concentrated to give 970 mg of crude crystalline material. Chromatographic separation yielded 2,2-dibromo-3-oxo-5,6αH,4,11βH-eudesman-6,12-olide (**8**)(140 mg, 8%), M.p.: 170- 171°C; $[\alpha]_D$: +8° ($CHCl_3$ c 1); ir μ_{max} ($CHCl_3$): 1771, 1729 and 1189 cm1; ^1H nmr: see table I; ^{13}C nmr: see table II; ms, m/z(%): 408 (M^++2, 66%), 406 (M^+, 42%), 328 (100%). The second band gave 2α-bromo-3-oxo-5,6αH,4,11βH- eudesman-6,12-olide (**7**) (800 mg, 61%) as a crystalline material; m.p.: 168-169°C; $[\alpha]_D$: -46.3° ($CHCl_3$, c 1); ir μ_{max} ($CHCl_3$: 1759, 1717, 1166 an 1205 cm-1; ^1H nmr (300 MHz): see table I; ^{13}C nmr: see table II; ms, m/z(%): 330 (M^++2, 63%), 329(M^++1, 15%), 78 (100).

Dehydrohalogenation of 2,2-dibromo-3-oxo-5,6αH,4,11βH- eudesman-6,12-olide(**8**).-

Lithium carbonate (75 mg) and lithium bromide (53 mg) were added to a solution of 2,2-dibromo-3-oxo-5,6αH,4,11βH-eudesman-6,12-olide (**8**) (140 mg, 0.34 mmol) in dry N,N'-di methylformamide. The suspension was stirred at 120°C under nitrogen for 90 min. The reaction mixture was cooled, poured into diluted acetic acid and extracted thoroughly with methylene chloride. The organic layer was washed with water and sat NaCl aq, dried over $MgSO_4$ and concentrated in vacuo to give a crude semisolid product which was chromatographed to yield 105 mg (92%) of 2-bromo-3-oxo-5,6αH,4,11βH-eudesm-1-en-6,12-olide (**10**); m.p.: 187-188°C; $[\alpha]_D$: -138° ($CHCl_3$, c 1); ir μ_{max}($CHCl_3$): 1771, 1684 and 1170 cm -1; ^1H nmr (300MHz): see table I; ^{13}C nmr: see table II; ms, m/z(%): 327 (M^++1)(100).

Dehydrohalogenation of 2-bromo-3-oxo-5,6αH,4,11βH-eudesman- 6,12-olide (**7**).-

Lithium carbonate (440 mg) and dry lithium bromide (330 mg) were added to a solution of 2-bromo-3-oxo-5,6αH,4,11βH- eudesman-6,12-olide (**7**)(800 mg, 2 mmol) in dry N,N'- dimethylformamide. The suspension was stirred at 120°C under nitrogen for 75 min. The reaction mixture was cooled, poured into diluted acetic acid and extracted thoroughly with methylene chloride. The organic layer was washed with water and sat. NaCl aq., dried over $MgSO_4$ and concentrated in vacuo. Chromatographic separation yielded 3-oxo-5,6αH,4,11βH-eudesm-1-en-6,12-olide (**9**)(570 mg, 94%). M.p.: 168-169°C; $[\alpha]_D$: -189.3° ($CHCl_3$, c 1); ir μ_{max} ($CHCl_3$): 1772 and 1667 cm-1; ^1H nmr (300 MHz): see table I; ^{13}C nmr: see table II; ms, m/z(%): 249 (M^++1, 17%), 248(M^+)(100).

Aluminum isopropoxide reduction of 3-oxo-5,6αH,4,11βH- eudesm-1-en-6,12-olide (**9**).-

A suspension of 3-oxo-5,6αH,4,11βH-eudesm-1-en-6,12- olide (**9**)(1g, 4 mmol) in dry isopropyl alcohol (60 ml) and aluminium isopropoxide (3.7 g, 17.6 mmol) was stirred and boiled gently in a flask fitted with a vigreaux column while the acetone vapor was allowed to escape. After 6 h the reaction mixture was poured over cold 2M HCl solution (57 ml) and extracted with chloroform. The combined extracts were washed with sat. $NaHCO_3$ aq and sat NaCl aq, dried over $MgSO_4$ and evaporated under reduced pressure to give 990 mg of an oily mixture which was chromatographed over silica gel. Elution of the column yielded 3α-hydroxy-5,6αH,4,11βH- eudesm-1-en-6,12-olide (**12**) (250 mg, 25%); syrup; $[\alpha]_D$: -183° ($CHCl_3$ c 1); ir μ_{max} ($CHCl_3$): 3436 and 1767 cm-1; ^1H nmr (300 MHz): see table III; ^{13}C nmr: see table IV; ms, m/z(%): 251 (M^++1, 54%), 250 (M^+, 7%), 233 (M^+-17)(100). Further elution yielded 3β-hydroxy-5,6αH,4,11βH-eudesm-1-en-6,12-olide (**11**) (370 mg, 72%), syrup;$[\alpha]_D$ -90° ($CHCl_3$, c 1; ir μ_{max} ($CHCl_3$): 3175 and 1754 cm-1; ^1H nmr (300 MHz): see table III; ^{13}C nmr: see table IV; ms, m/z(%): 251 (M^++1, 54%), 250 (M^+, 7%), 233 (M^+-17) (100).

Allylic rearrangement of 3α-hydroxy-5,6αH,4,11βH-eudesm-1- en-6,12-olide (**12**) and *3β-hydroxy-5,6αH,4,11βH-eudesm-1-en-6,12- olide* (**11**).-

A solution of mixture (**11** and **12**)(500 mg, 1.9 mmol) in THF (40 ml) and 2 M HCl solution (30 ml) were refluxed under nitrogen for 3 h. The cooled solution was poured over sat NaCl aq, extracted successively with $CHCl_3$, washed with sat $NaHCO_3$ aq and sat ClNa aq, dried over $MgSO_4$ and concentrated in vacuo. The crude oil was chromatographed to give 1α-hydroxy -5,6αH,4,11βH-eudesm-2-en-6,12-olide (**13**) (358 mg, 71%); syrup; $[\alpha]_D$: -29.4° ($CHCl_3$, c 1); ir μ_{max} ($CHCl_3$): 3455 and 1768 cm-1; ^1H nmr (300 MHz): see table III; ^{13}C nmr: see table IV; ms, m/z(%): 250 (M^++1, 32%), 232 (M^+-18)(100). The second run gave a starting material mixture: 3α-hydroxy- 5,6αH,4,11βH-eudesm-1-en-6,12-olide (**12**) (23 mg, 5%) and 3β-hydroxy-5,6αH,4,11βH-eudesm-1-en-6,12-olide (**11**) (82mg, 16%).

Oxidation of 1α-hydroxy-5,6αH,4,11βH-eudesm-2-en-6,12-olide (13).-

Jones reagent was added to a stirred solution of 1α- hydroxy-5,6αH,4,11βH-eudesm-2-en-6,12-olide (**13**) (500 mg, 2 mmol) in acetone (10 ml) at 0°C until an orange color persisted. Methanol was then added and the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with sat NaCl aq, dried over $MgSO_4$ and evaporated to dryness. Chromatographic separation yielded 1-oxo-5,6αH,4,11βH-eudesm-2-en- 6,12-olide (**14**)(487 mg, 98%). M.p.: 115-116°C; $[\alpha]_D$: -91.5° ($CHCl_3$, c 1); ir μ_{max} ($CHCl_3$): 1771 and 1677 cm-1; ^1H nmr (300 MHz): see table III; ^{13}C nmr: see table IV; ms, m/z(%): 249 (M^++1, 6%), 248 (M^+, 35%), 78(100).

Epoxidation of 3-oxo-5,6αH,4,11βH-eudesm-1-en-6,12-olide (9) with alkaline hydrogen peroxide.-

Anhydrous sodium carbonate (30 mg), 30% hydrogen peroxide (0.16ml) and water (0.73 ml) were added to a solution of 3-oxo-5,6αH,4,11βH-eudesm-1-en-6,12-olide (**9**)(200 mg, 0.8 mmol) in THF (10 ml). The mixture was heated to 35-40°C for 2 h. The solution was cooled, poured into water, and extracted with CH_2Cl_2. The organic layer was washed with diluted acetic acid and sat NaCl aq and dried over $MgSO_4$. The solvent was removed and the residue (180 mg) was chromatographed over silica gel. The first band gave 1α,2α-epoxy-3-oxo-5,6αH,4,11βH- eudesman-6,12-olide (**15**) (123 mg, 57%); m.p.: 123-124°C; $[\alpha]_D$: -42.8° ($CHCl_3$, c 1); ir μ_{max}($CHCl_3$):1767, 1707, 1190 and 1159 cm- 1; ^1H nmr (300 MHz): see table III; ^{13}C nmr: see table IV; ms, m/z(%): 264 (M^+)(100). Continued elution yielded the starting compound: 3-oxo-5,6αH,4,11βH-eudesm-1-en-6,12-olide (**9**) (42 mg, 21%).

Hydrazine reduction of 1α,2α-epoxy-3-oxo-5,6αH,4,11βH- eudesman-6,12-olide (15).-

100% hydrazine hydrate (0.045 mmol) was added dropwise to a solution of 1α,2α-epoxy-3-oxo-5,6αH-eudesman-6,12-olide (**15**) (100 mg, 0.37 mmol) in THF (5 ml). The mixture was heated refluxed for 5 min. while nitrogen evolved. After cooling, the reaction was diluted with water and extracted with chloroform. Evaporation of the dried solution furnished an oily crude material (36 mg). Chromatographic separation yielded 27 mg (28%) of 1α-hydroxy- 5,6αH,4,11βH-eudesm-2-en-6,12-olide (**13**).

Acetalization of 1-oxo-5,6αH,4,11βH-eudesm-2-en-6,12-olide (14).-

A mixture of 1-oxo-5,6αH,4,11βH-eudesm-2-en-6,12-olide (**14**)(250 mg, 1 mmol), pyridinium p-toluensulphonate (30 mg) and ethylene glycol (3 ml) in dry benzene was refluxed for 24 h under nitrogen. The reaction mixture was cooled and washed with sat NaCl aq and $NaHCO_3$ aq. The benzene layer was drawn off, and the aqueous layer was extracted with $CHCl_3$ and dried over $MgSO_4$. The extracts were evaporated under reduced pressure to give a crude material (220 mg) which was chromagraphied over silica gel: 125 mg (42%) of 1,1-ethylenedioxy-5,6αH,11βH-eudesm-3-en-6,12- olide (**16**), syrup, ir μ_{max}($CHCl_3$): 1769, 1680 and 893 cm-1; ^1H nmr (300 MHz): see table III; ^{13}C nmr: see table IV; ms, m/z(%): 293 (M^++1)(100).

Epoxidation of 1,1-ethylenedioxy-5,6αH,11βH-eudesm-3-en- 6,12-olide (16) with MCPBA.-

50 mg (0.28 mmol) of MCPBA was added to a solution of 1,1-ethylenedioxy-5,6αH,11βH-eudesm-3-en-6,12-olide (**16**) (89 mg, 0.27 mmol) in dry dichloromethane (3 ml), and the reaction mixture was stirred at room temperature and monitored by TLC. After 4 days, the reaction was complete An aqueous solution of $FeSO_4$ was then added and after extraction with CH_2Cl_2, the dried extract was washed with sat $NaHCO_3$ aq. The dried extract was concentrated to give a residue (82 mg) which was chromatographed over silica gel. Elution of the column yielded 3β,4β-epoxy-1,1 -ethylenedioxy-5,6αH,11βH-eudesman-6,12-olide (**17**) (80 mg, 94%), syrup, $[\alpha]_D$: -42.6° ($CHCl_3$, c 1); ir μ_{max} ($CHCl_3$): 1772. 1672, 1067. 909 and 835 cm-1; ^1H nmr (300 MHz): see table III; ^{13}C nmr see table IV; ms, m/z(%): 308 (M^++1)(100).

Deacetalization and epoxide ring opening of 3β,4β-epoxy-1,1- ethylene dioxy-5,6αH,11βH-eudesman-6,12-olide (17).-

A mixture of 3β,4β-epoxy-1,1-ethylenedioxy-5,6αH,11βH- eudesman-6,12-olide (**17**) (50 mg, 0.17 mmol), H_2O (0.5 ml) and a catalytic amount of pyridinium p-toluenesulphonate in THF (2 ml) was refluxed for 24 h under N_2, cooled, poured into sat NaCl aq and extracted successively with chloroform. After the combined extracts had been dried over anhydrous sodium sulphate, the chloroform was removed under reduced pressure, giving 47 mg of a crude material which was chromatographed over silica gel. The first run gave 1-oxo-5,6αH,11βH-eudesm-2-en- 6,12-olide (**14**) (20 mg, 46%) as a starting compound. The second band yielded 1-oxo-eudesm-2,4-dien-6,12- olide (**19**) (8 mg, 13%). Continued elution yielded 4β-hydroxy-1-oxo-5,6αH,11βH-eudesm-2-en-6,12-olide (**18**) (15 mg, 32%); m.p.: 150-151°C; $[\alpha]_D$: -32.6° ($CHCl_3$, c 1); ir μ_{max} ($CHCl_3$): 3464, 3433 3402 and 1771 cm-1; ^1H nmr (300 MHz): see table III; ^{13}C nmr: see table IV; ms, m/z(%): 265 (M^++1, 64%), 247 (M^+-17)(100).

Fermentation of 1-oxo-5,6αH,4,11βH-eudesm-2-en-6,12-olide (14) with Rhizopus nigricans *cultures.-*

Substrate (**14**) (25 mg) was dissolved in EtOH (1 ml), distributed in erlenmeyer flask and incubated for 6 days after which the culture was filtered and pooled; the cells were washed twice with water. The liquid was saturated with NaCl and extracted with CH_2Cl_2. Both extracts were dried over $MgSO_4$ and evaporated under reduced pressure to give a mixture which was chromatographed over silica gel. The first band gave a starting material (**14**) (12 mg, 48%). Further elution yielded 1α-hydroxy-5,6αH,4,11βH-eudesman- 6,12-olide (**20**) (2 mg, 7.8 %); ^1H nmr (300 MHz): see table III; ^{13}C nmr: see table IV; ms, m/z(%): 253 (M^++1, 62%), 235 (M^+-18)(100). The third band gave 4β-hydroxy-1-oxo-5,6αH,11βH-eudesm- 2-en-6,12-olide (**18**) (2 mg, 7.5%). Continued elution yielded 8β-hydroxy-1-oxo-5,6αH,4,11βH- eudesm-2-en-6,12-olide (**21**) (3 mg, 11.2%); ^1H nmr (300 MHz): see table III; ^{13}C nmr: see table IV; ms, m/z(%): 265 (M^++1, 50%), 79 (100).

Conversion of 4β-hydroxy-1-oxo-5,6αH,11βH-eudesm-2-en-6,12- olide (18) into 4α-hydroxy -1-oxo-5,6αH,11βH-eudesm-2-en-6,12- olide (22).-

4β-hydroxy-1-oxo-5,6αH,11βH-eudesm-2-en-6,12-olide (**18**) (40 mg) was dissolved in 3 ml of acetic acid. When the mixture was boiling, 90 mg of powdered zinc was added over a period of 20 min.. The solution was cooled and filtered, and the residue was washed with chloroform. The organic layer was subsequently washed with aq sodium bicarbonate and water, dried and evaporated to give 20 mg of material which was dissolved in dry dichloromethane (2 ml). MCPBA (14 mg, 0.08 mmol) was then added and the reaction mixture was stirred at room temperature for 48 h. An aqueous solution of $FeSO_4$ was added and extracted with CH_2Cl_2. The organic solution was washed with sat $NaHCO_3$ aq. The dried extract was evaporated to give a reaction product which was chromatographed over silica gel to give 4α-hydroxy-1-oxo-5,6αH,11βH-eudesm-2- en-6,12-olide (**22**) (22 mg, 55%); ^1H nmr (300 MHz): see table III; ^{13}Cnmr:see table IV; ms, m/z(%): 265 (M^++1)(100).

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